Studies on Application of Silyl Groups in
Ring-Closing Metathesis Reactions
and Fragment-Based Probe Discovery

Abstract

In efforts to search for tool compounds that are capable of probing normal and disease-associated biological processes, both quality and identity of the screening collection are very important. Towards this goal, diversity-oriented synthesis (DOS) has been explored for a decade, which aims to populate the chemical space with diverse sets of small molecules distinct from the traditional ones obtained via combinatorial chemistry.

In the practice of DOS, macrocyclic ring-closing metathesis (RCM) reactions have been widely used. However, the prediction and control of stereoselectivity of the reaction is often challenging; chemical transformation of the olefin moiety within the product is in general limited. Chapter I of this thesis describes a methodology that addresses both problems simultaneously and thus extends the utility of the RCM reactions.
By installing a silyl group at the internal position of one of the olefin termini, the RCM reaction could proceed with high stereoselectivity to afford the \((E)\)-alkenylsiloxane regardless of the intrinsic selectivity of the substrate. The resulting alkenylsiloxane can be transformed to a variety of functionalities in a regiospecific fashion. The conversion of the \((E)\)-alkenylsiloxanes to alkenyl bromides could proceed with inversion of stereochemistry for some substrates allowing the selective access of both the \(E\)- and \(Z\)-trisubstituted macrocyclic alkenes. It was also found that the silyl group could trap the desired mono-cyclized product by suppressing nonproductive pathways.

Chapter II of this thesis describes the application of the concept of DOS in the area of fragment-based drug discovery. Most fragment libraries used to date have been limited to aromatic heterocycles with an underrepresentation of chiral, enantiopure, \(sp^3\)-rich compounds. In order to create a more diverse fragment collection, the build/couple/pair algorithm was adopted. Starting from proline derivatives, a series of bicyclic compounds were obtained with complete sets of stereoisomers and high \(sp^3\) ratio. Efforts are also described toward the generation of diverse fragments using methodology described in Chapter I. The glycogen synthase kinase (GSK3\(\beta\)) was selected as the proof-of-concept target for screening the DOS fragments.
# Table of Contents

Acknowledgements.......................................................................................................................... vii

Abbreviations....................................................................................................................................... xii

Chapter I. Extending the Utility of Ring-Closing Metathesis Reactions through the Introduction of a Silyl Group................................................................................................................................. 1

  Chapter I-1. Introduction.................................................................................................................. 2

  Chapter I-2. Ring-Closing Metathesis of Vinysilanes and Vinylsiloxanes................................. 14

  Chapter I-3. Diversification of Alkenylsiloxanes and Alkenylsilanes........................................ 30

  Chapter I-4. Conversion of Macrocyclic (E)-Alkenylsiloxanes to the Corresponding (Z)-Alkenyl Bromides................................................................................................................................. 34

  Chapter I-5. Applications of the Silyl Group in Other Types of Metathesis Reactions......................... 40

  Chapter I-6. Conclusion and Future Directions............................................................................... 44

Experimental Section......................................................................................................................... 46

References............................................................................................................................................. 137

$^1$H and $^{13}$C NMR Spectra.................................................................................................................... 152

Chapter II. Synthesis of Diversity-Oriented Synthetic Fragment Library and Biological Screening against GSK3β............................................................................................................................................. 253

  Chapter II-1. Introduction.................................................................................................................. 254

  Chapter II-2. Design and Synthesis of Diversity-Oriented Synthetic Fragment Libraries.............................. 259
Chapter II-3. Screen the Synthetic Fragment Library against GSK3β.................268

Chapter II-4. Conclusion and Future Directions..................................................281

Experimental Section...........................................................................................283

References.............................................................................................................303

$^1$H and $^{13}$C NMR Spectra....................................................................................309
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ADP</td>
<td>adenosine diphosphate</td>
</tr>
<tr>
<td>ATP</td>
<td>adenosine triphosphate</td>
</tr>
<tr>
<td>B/C/P</td>
<td>build couple pair</td>
</tr>
<tr>
<td>bHLH</td>
<td>basic helix-loop-helix</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butoxycarbonyl</td>
</tr>
<tr>
<td>CM</td>
<td>cross metathesis</td>
</tr>
<tr>
<td>CyP450</td>
<td>cytochrome P450</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>DIPEA</td>
<td>N,N-diisopropylethylamine</td>
</tr>
<tr>
<td>DMEDA</td>
<td>N,N'-dimethylethylenediamine</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>DOS</td>
<td>diversity-oriented synthesis</td>
</tr>
<tr>
<td>DPPF</td>
<td>1,1'-bis(diphenylphosphino)ferrocene</td>
</tr>
<tr>
<td>EA</td>
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</tr>
<tr>
<td>EDC</td>
<td>1-ethyl-3-(3-dimethylaminopropyl) carbodiimide</td>
</tr>
<tr>
<td>FBDD</td>
<td>fragment-based drug discovery</td>
</tr>
<tr>
<td>Grubbs I (G-I)</td>
<td>Grubbs catalyst first generation</td>
</tr>
<tr>
<td>Grubbs II (G-II)</td>
<td>Grubbs catalyst second generation</td>
</tr>
<tr>
<td>GSK</td>
<td>glycogen synthase kinase</td>
</tr>
<tr>
<td>HDAC</td>
<td>histone deacetylase</td>
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<tr>
<td>Term</td>
<td>Definition</td>
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<tr>
<td>-----------</td>
<td>------------------------------------------------</td>
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<tr>
<td>HEPES</td>
<td>4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid</td>
</tr>
<tr>
<td>HFIP</td>
<td>hexafluoroisopropanol</td>
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<tr>
<td>HTS</td>
<td>high-throughput screening</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>ITC</td>
<td>isothermal titration calorimetry</td>
</tr>
<tr>
<td>LC-MS</td>
<td>liquid chromatography-mass spectrometry</td>
</tr>
<tr>
<td>NIS</td>
<td>n-iodosuccinimide</td>
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<td>NMR</td>
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</tr>
<tr>
<td>NOE</td>
<td>nuclear overhauser effect</td>
</tr>
<tr>
<td>Nosyl (Ns)</td>
<td>2-nitrophenylsulfonyl</td>
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<tr>
<td>PTFE</td>
<td>polytetrafluoroethylene</td>
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<tr>
<td>RCAM</td>
<td>ring-closing alkyne metathesis</td>
</tr>
<tr>
<td>RCM</td>
<td>ring-closing metathesis</td>
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<tr>
<td>SAR</td>
<td>structure-activity relationship</td>
</tr>
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<td>SFC</td>
<td>supercritical fluid chromatography</td>
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<td>surface plasmon resonance</td>
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<td>stereochemical structure-activity relationship</td>
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<td>Trypanosoma brucei</td>
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<td>TBAF</td>
<td>tetra-\textit{n}-butylammonium fluoride</td>
</tr>
<tr>
<td>TBS</td>
<td>\textit{tert}-butyldimethylsilyl</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>--------------</td>
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</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
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<td>TLC</td>
<td>thin-layer chromatography</td>
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<td>trimethylsilyl</td>
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<td>TMSOTf</td>
<td>trimethylsilyl triflate</td>
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<tr>
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<td>transition state</td>
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<tr>
<td>Ts</td>
<td>$p$-toluenesulfonyl</td>
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<tr>
<td>WaterLOGSY</td>
<td>water ligand optimized gradient spectroscopy</td>
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Chapter I.

Extending the Utility of Ring-Closing Metathesis Reactions through the Introduction of a Silyl Group
Chapter I-1. Introduction

1. Application and limitations of metathesis reactions in the build/couple/pair strategy for the generation of optimal small-molecule screening collections

One of the most challenging problems that organic chemists face is the need to generate optimal small-molecule screening collections capable of probing normal and disease-associated biological processes. As described in a recent review, a novel strategy in diversity-oriented synthesis (DOS) called build/couple/pair (B/C/P) has emerged, which may have the potential to achieve these goals.

Although such transformative chemistry has historically proven difficult to achieve, a novel strategy in diversity-oriented synthesis (DOS) called build/couple/pair (B/C/P) has emerged, which may have the potential to achieve these goals.

In the “build” phase (Scheme I-1), building blocks containing orthogonal sets of functional groups suitable for subsequent coupling and pairing reactions are bought or synthesized. For chiral building blocks, obtaining all possible stereoisomers in their enantiopure form is a requirement. In the “couple” phase, intermolecular coupling reactions are performed to join the building blocks together either without the creation of new stereogenic elements or with complete control of all possible stereochemical outcomes. In the “pair” phase, intramolecular functional-group-pairing reactions are
performed. In this strategy, molecular complexity is generated in pairing reactions and sometimes in coupling reactions as well. Stereochemical diversity is incorporated in the build and couple phases, while skeletal diversity is achieved through the different combinations of pairing reactions between polar and polar, polar and nonpolar, or nonpolar and nonpolar functional groups. Overall, this strategy integrates complexity-generating reactions with diversity-generating processes by focusing on making the product of one reaction the substrate of a diverse range of subsequent pairing reactions.

**Scheme I-1.** Illustration of the build/couple/pair strategy (adapted from ref. 1).

In practice, when applying the build/couple/pair strategy to generate diverse, small-molecule screening collections, it is necessary to consider the qualities of an ideal functional group pairing reaction. There are two criteria by which such a reaction can be
evaluated. First, the reaction used for pairing should be highly general over a wide range of substrates. By carefully studying previous works, we recognized that ring-closing metathesis (RCM) was widely used as a pairing reaction due to its generality and robustness. Besides forming cyclic structures with various ring sizes, metathesis reactions can provide skeletal diversity starting from different substrates (Scheme 1-2). RCM produces a cyclic alkene from a diene (eq. 1, eq. 2, eq. 3), a cyclic diene from an ene-yne (eq. 4, eq. 5, eq. 6) and a bicyclic diene from an ene-yne-ene (eq. 7). Moreover, a ring-opening/ring-closing cascade can generate polycyclic structures (eq. 8).

Scheme 1-2. Skeletal diversity generated from different types of RCM reactions.

In addition to substrate generality and diversity, reactions yielding products that are in turn poised for further transformations are also desired. The ideal situation arises when the functional group(s) created by a highly general reaction is itself a substrate for an
array of synthetic transformations. For example, a $\beta$-hydroxy carbonyl moiety generated from an aldol reaction can be dehydrated, alkylated, reduced, or oxidized to provide different functionalities and the potential for further transformations. The diversification potential of such intermediates allows the efficient generation of analogues that are useful for the study of structure-activity relationships. Moreover, this potential also facilitates the medicinal chemistry effort to tune the physicochemical properties of a hit compound. Following this criterion, we became conscious of the fact that RCM products offer relatively few opportunities for further modification. We therefore initiated several research projects with the goal of expanding the diversification potential of the RCM products to further increase the utility of this reaction.

2. RCM of dienes to build naturally occurring and novel macrocyclic compounds

We initially focused on macrocyclic RCM of diolefinic substrates. Macrocyclic compounds (with ring sizes larger than or equal to 8) are important naturally occurring small molecules produced by various organisms during the course of evolution. These macrocycles usually display interesting biological activities.13-33 A number of them and their analogues have been in use as therapeutics for years and include antibiotics (erythromycin,34 rifamycins,35,36 colistin37,38, daptomycin39, and vancomycin40-42), antifungals (amphotericin B43), immunosuppressants (sirolimus,44,45 and cyclosporine46,47), and cancer therapies (azaepothilone B48 and sirolimus49-51). Due to the biological activity and structural complexity of macrocyclic compounds, they represent an attractive and challenging class of compounds for organic chemists to synthesize.
There are indirect ways to form macrocycles, yet the most efficient method is macrocyclization. In theory, any reaction that couples two parts of a linear molecule together can be used as a macrocyclization reaction. However in practice, only a small number of reactions have been developed and extensively used by organic chemists in this respect. Typical macrocyclization reactions (Figure I-1) include lactonization, lactamization, alkylation, $\text{S}_{\text{N}}\text{Ar}$ reactions, Horner-Wadsworth-Emmons or Wittig reactions, transition metal-catalyzed coupling reaction, and alkene ring-closing metathesis. Other types of reactions such as ring-closing alkyne metathesis (RCAM), cycloaddition, oxidative lactonization, Prins-type reactions, and multicomponent cyclizations have also been recently explored. Among these transformations, RCM of diolefinic compounds is an attractive methodology for three major reasons. First, olefins are orthogonal to a number of common reactions and so rarely require protection. Second, reaction conditions of RCM are relatively mild, thus common functional groups (as well as protecting groups) are compatible under these conditions. Third, RCM is a catalyzed reaction that does not typically need any activating reagents. Therefore, since the commercialization of metathesis catalysts, the applications of RCM in synthesizing macrocyclic compounds have been extensively explored.
In addition to the total synthesis of macrocyclic natural products and their analogues, there has been interest in accessing non-naturally occurring macrocycles using RCM reactions in search for novel biological activities.\textsuperscript{98,99,101,107,109,111,114,132-136} Screening of such compounds has successfully yielded compounds that have novel antibiotic activities\textsuperscript{137-139} as well as activities against different types of biological targets including histone deacetylases\textsuperscript{8,140,141} and sonic hedgehog\textsuperscript{7} (Figure I-2). Moreover, macrocyclic RCM reactions have been extensively used in medicinal chemistry to cyclize precursors in order to improve target affinity and selectivity, as well as bioavailability and stability.\textsuperscript{142-150} Within our own laboratories, macrocyclic RCM has proven to be an enabling methodology toward the goal of assembling small-molecule screening collections to probe normal and disease-associated biological processes.\textsuperscript{7,8,12,151-153}

3. Limitations of ring-closing metathesis towards the generation of macrocyclic compounds and previous approaches to address them
In efforts to synthesize macrocyclic compounds via RCM reactions, we have recognized two major limitations: lack of control over the stereochemistry of olefin product and limited potential for further transformations on the olefin moiety (Scheme 1-3).

First, controlling the stereochemistry of the resulting olefin is often problematic. Under the circumstances when the olefin moiety is not required for further transformation or in the final compound, the stereoselectivity generally will not be an issue after reduction of the double bond. On the contrary when the olefin moiety is crucial, it is often challenging to separate the desired stereoisomer from the mixture at the cost of the undesired isomer. In some extreme cases when the RCM reactions only generated the undesired stereoisomers, extra synthetic steps to produce the desired alkene configuration are required or the synthetic route has to be redesigned. Since a variety of factors can determine the stereochemical outcome in RCM reactions, general strategies that give rise to either Z or E olefins remain a significant challenge.

**Scheme I-3.** Limitations in macrocyclic RCM of diolefinic compounds.

Two major advances that address the stereoselectivity of macrocyclic RCM reactions have been achieved. One approach involves ring-closing alkyne metathesis and selective reduction of the macrocyclic alkyne intermediate to yield Z or E olefins (Scheme I-4, A). However, this approach is only applicable to ring sizes of 12 and larger due to
the ring strains of cyclic alkynes.\textsuperscript{168,169} Another approach is based on the development of 
Z-selective catalysts that have been successfully applied in cross-metathesis (CM) 
reactions and macrocyclic RCM reactions (Scheme I-4, B),\textsuperscript{170-174} however, catalysts that 
yield the \textit{E} olefin product selectively have yet to be discovered.

\textbf{Scheme I-4.} Two approaches to solve the stereoselectivity issue of macrocyclic RCM 
reactions.

The second limitation of macrocyclic RCM is that, as mentioned above, there are few 
opportunities for further modification. The \textit{sp}^2 carbon atoms in a cyclic 1,2-disubstituted 
olefin (the typical RCM product) are not easily chemically differentiated. In the absence 
of a dominant steric or electronic bias within the substrate, achieving regioselectivity on 
such a product is problematic (e.g. in a hydroboration reaction). Due to this drawback, 
post-metathesis functionalizations have predominantly been confined to “symmetrical” 
transformations (Scheme I-3) such as hydrogenation, dihydroxylation,\textsuperscript{175-177} 
epoxidation,\textsuperscript{154,177,178} and aziridination.\textsuperscript{179,180}
4. Our proposed approach to address both the stereoselectivity and the post-RCM functionalization simultaneously by using a versatile silyl group (the major focus of this chapter)

To address both limitations, we investigated the introduction of a chemical handle at the internal position of one of the olefins. Such geminal-disubstituted olefins could generate cyclic trisubstituted alkenes upon the treatment with a RCM catalyst. First, the steric of the exocyclic chemical handle would be expected to favor formation of the E product (assuming it is larger than a methylene group). Second, it would allow subsequent functionalization of the product that is not limited to “symmetrical” transformations.

Aryl groups, carbonyl groups, silicon groups, boron groups, alkoxy groups, halogens, nitrogen, and phosphinate can be incorporated into the internal position of one of the olefins yielding a variety of trisubstituted alkenes. Yet to our knowledge, most of these precedents were limited to making small rings (5-, 6-, or 7-membered) and not macrocycles. It has been shown that alkyl groups (a methyl or ethyl group) can be installed to access trisubstituted macrocycles. However, they failed to control the stereoselectivity of the reaction.

Among these explorations, we are especially interested in the cases when a non-carbon substituent was employed (Scheme I-5). Advantages of having exocyclic silicon (eq. 9, eq. 10), bromide (eq. 11, eq. 12), or boron (eq. 13, eq. 14) attached to the alkenes in the product are due to the versatile nature of such groups. Ipsilo-protonation reactions (protodesilylation, protodebromination, protodeboronation) generate simple
disubstituted alkenes. Oxidation of alkenylsiloxanes and alkenylboronates yields ketones; of alkenyl bromide yields α-bromoketones. Most importantly, all of these functional groups can participate in transition-metal catalyzed coupling reactions, which enables diversification of the substituted alkenes in a regiospecific manner.

Scheme I-5. RCM of vinyl halides, vinylboronates, and vinylsilanes to make trisubstituted cyclic alkenes.

Our detailed proposal is described in Scheme I-6. Silyl groups were selected in our study owing to several reasons. First, the inclusion of a silyl group at the internal carbon of one of the olefins could be easily achieved via a regioselective hydrosilylation reaction of a terminal alkyne. A ruthenium-based catalyst developed in the Trost group is able to achieve this transformation with high chemo- and regio-selectivity, good functional group compatibility, and broad silyl group generality. Second, silylalkene groups are, in general, compatible with metathesis catalysts compared to bromoalkenes. Third, silyl groups are easier to handle and more stable than boryl groups. We also hypothesized that the steric bulk of the silyl group would likely control the stereoselectivity of the RCM reaction yielding the E product (Scheme I-6, the 1st goal). Moreover, if the (E)-alkenylsiloxane can be transformed to the Z-trisubstituted alkenyl bromide (the 2nd goal),
we would not only obtain both stereoisomers, but also introduce great potential for further diversification of both stereoisomers.

**Scheme I-6.** Expanding the scope of RCM reactions through silyl group incorporation.

5. **Applications of silyl groups in other types of RCM reactions**

Given the versatility of the silyl group, another research project was also launched in our group to explore its potential in ene-yne RCM reactions.

**Scheme I-7.** Extension of the ene-yne RCM reaction by the introduction of a silyl group.

Ene-yne RCM reactions are powerful transformations to generate cyclic dienes. Without a functional group on the resulting diene, the most common way of further transforming
it was a Diels-Alder reaction (Scheme I-7, A). The incorporation of a silyl group on the alkyne moiety for ene-yne RCM was already reported but not well studied. The silyl group that ends up on the diene can be oxidized to generate an enone moiety (Scheme I-7, B), which serves as a dienophile or hetero-diene as well as a Michael accepter. In addition, metal-catalyzed cross-coupling reactions can convert the silyl group to a variety of aromatic groups. The Diels-Alder reaction is still applicable but with the benefit of leaving a valuable alkenylsiloxane moiety for further transformations.

Concurrent with our studies of macrocyclic RCM of vinylsiloxanes, the Fürstner group demonstrated the use of silyl groups in macrocyclic diene-ene RCM. By installing the silyl group on the C3 position of a terminal butadiene (Scheme I-8, eq. 15), they were able to control the stereochemical outcome of the macrocyclic RCM reaction (in this case E-selective) and prevent ring contraction to form the 10-membered ring (the reaction with the internal alkene of the diene) observed in the absence of the silyl group.

Scheme I-8. An example of the use of silyl groups in macrocyclic diene-ene RCM.
Chapter I-2. Ring-Closing Metathesis of Vinylsilanes and Vinlysiloxanes

1. Initial attempt of RCM of vinylsilanes and vinylsiloxanes to form small rings and macrocycles

As shown in Table I-1, Dr. Masaaki Hirano pioneered the RCM of trimethylvinylsilane 1g’ to form a 5-membered ring. Mr. Miguel Jimenez and I explored the RCM of dimethylphenylsilanes 1e’ or 2e’ and tert-butyldimethylsilanes 1h’ or 2h’ to form 5- or 6-membered rings. In accordance with previous reports, all substrates were successfully closed although the yields of different substrates varied. However, 8-membered rings bearing either silyl group, substrate 3e’ and 3h’ failed to undergo ring-closing metathesis.

At the same time, Mr. Anders S. Hansen and Dr. Eun-Ang Raiber were attempting the RCM of vinylsilanes 6’ or 7’ to form 12- or 14-membered rings. Various reaction conditions were applied, but none of them were effective. Next they tried to introduce a rigidifying element to favour the ring closure. Substrates 8’ and 9’ were synthesized and subjected to various reaction conditions. However, no desired 15-membered products were observed under any condition. In most of the unsuccessful cases, incomplete conversion and decomposition of starting materials were observed.
Table I-1. Initial exploration on RCM of vinylsilanes and vinylsiloxanes to make small rings and macrocycles with various silyl groups and reaction conditions.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product Y. [b] (%)</th>
<th>Rxn cond. [a]</th>
<th>Substrate</th>
<th>Product Y. [b] (%)</th>
<th>Rxn cond. [a]</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Image" /></td>
<td>95</td>
<td>A</td>
<td><img src="image2" alt="Image" /></td>
<td>not observed</td>
<td>-</td>
</tr>
<tr>
<td><img src="image3" alt="Image" /></td>
<td>92</td>
<td>A</td>
<td><img src="image4" alt="Image" /></td>
<td>not observed</td>
<td>-</td>
</tr>
<tr>
<td><img src="image5" alt="Image" /></td>
<td>81</td>
<td>B</td>
<td><img src="image6" alt="Image" /></td>
<td>not observed</td>
<td>-</td>
</tr>
<tr>
<td><img src="image7" alt="Image" /></td>
<td>95</td>
<td>A</td>
<td><img src="image8" alt="Image" /></td>
<td>not observed</td>
<td>-</td>
</tr>
<tr>
<td><img src="image9" alt="Image" /></td>
<td>44</td>
<td>B</td>
<td><img src="image10" alt="Image" /></td>
<td>not observed</td>
<td>-</td>
</tr>
<tr>
<td><img src="image11" alt="Image" /></td>
<td>not observed</td>
<td>-</td>
<td><img src="image12" alt="Image" /></td>
<td>not observed</td>
<td>-</td>
</tr>
<tr>
<td><img src="image13" alt="Image" /></td>
<td>not observed</td>
<td>-</td>
<td><img src="image14" alt="Image" /></td>
<td>not observed</td>
<td>-</td>
</tr>
<tr>
<td><img src="image15" alt="Image" /></td>
<td>20[c]</td>
<td>B</td>
<td><img src="image16" alt="Image" /></td>
<td>27[c]</td>
<td>C</td>
</tr>
</tbody>
</table>

- **Substrate:** 95, A; 92, A; 81, B; 95, A; 44, B; not observed, B; not observed, B; 20[c], B; 27[c], C
- **Product Y. [b] (%)**:
  - 95
  - 92
  - 81
  - 95
  - 44
  - not observed
  - not observed
  - 20[c]
  - 27[c]
- **Rxn cond. [a]**:
  - A. Grubbs II 10 mol%, DCM (20 mM), r.t., 18 h; B. Grubbs II 20 mol%, DCM (3 mM), reflux, 18 h; C. Grubbs II 10 mol%, DCM (2 mM), reflux, 10 h; D. Hoveyda-Grubbs II 20 mol%, DCM (1.7 mM), reflux, 24 h; E. Grubbs II 10 mol%, toluene (2 mM), 65 °C, 18 h; F. Grubbs I 10 mol%, DCM (1.8 mM), reflux, 18 h; G. Grubbs II 20 mol%, toluene (3 mM), 300 W Microwave, 100 °C, 30 min/cycle, 3 cycles; H. Schrock’s Mo-based catalyst 50 mol%, DCM (2.6 mM), r.t., 18 h; I. Schrock’s Mo-based catalyst 50 mol%, toluene (2.6 mM), 45 °C, 18 h; J. Hoveyda-Grubbs II 20 mol%, toluene (1.7 mM), 60 °C, 24 h; K. Hoveyda-Grubbs II 20 mol%, toluene (1 mM), 300 W Microwave, 100 °C, 30 min/cycle, 3 cycles; L. the isolated homodimers were resubmitted to condition C with 6 mol% Grubbs II catalyst added in 2 times.
- **Isolated yield unless otherwise indicated.**
- **Yield determined by 1H NMR analysis.**
Table I-2. Influence of the silyl group in CM reactions.

\[
\begin{array}{ccc}
\text{Entry} & \text{[Si]} & \text{Yield (\%)} \\
1 & \text{Si(OEt)}_3 & \text{Ph} & 80 \\
2 & \text{SiCl}_3 & \text{Ph} & 83 \\
3 & \text{Si(OAc)}_3 & \text{Ph} & 75 \\
4 & \text{Si(OEt)}_2\text{Me} & \text{Ph} & 6 \\
5 & \text{Si(OEt)}\text{Me}_2 & \text{Ph} & 5 \\
6 & \text{SiMe}_3 & \text{Ph} & 0 \\
7 & \text{SiPh}_3 & \text{C}_4\text{H}_9 & 0 \\
8 & \text{Si(C}_6\text{H}_4\text{-Me}-\text{p})_3 & \text{C}_4\text{H}_9 & 0 \\
9 & \text{Si(C}_6\text{H}_4\text{-CF}_3\text{-p})_3 & \text{C}_4\text{H}_9 & 97 \\
\end{array}
\]

This result drew our attention the role of the silyl group. Although the influence of different silyl groups had not been extensively studied for RCM, there were ample precedents in the area of cross metathesis (CM). Pietraszuk et al. demonstrated that the influence of the silyl groups on CM largely originates from an electronic effect of the substituents on silicon (Table I-2). Silyl groups with electronegative substituents such as EtO-, AcO-, Cl- gave better yields than with Me- and/or Ph- groups (entry 1-3 versus 6, 7). The use of \((p\text{-CF}_3\text{Ph})_3\text{Si-}\) led to quantitative yield in the CM reaction with 1-hexene (entry 9) while the use of Ph₃Si- or \((p\text{-MePh})_3\text{Si-}\) did not produce any detectable product (entry 7 and 8). With this knowledge, we decided to pursue a substrate, that had been shown to undergo RCM to give a trisubstituted macrocycle (Scheme I-9), with alkoxy silyl groups (10a’ and 10b’) instead of the original methyl group (10-Me’).

The initial attempts to close substrate 10a’ and 10b’ were not successful under condition B and only homodimers were isolated. Through personal contact with Prof. Fürstner by Dr. Raiber, it was found out that in order to close substrate 10-Me’, homodimers needed to be separated and resubmitted to the RCM reaction using Grubbs II as catalyst.
However following this procedure (Table I-1, condition L), they were still unable to cyclize either substrate.

**Scheme I-9.** Reported RCM to form macrocyclic trisubstituted alkenes (adapted from ref 181).

Despite those unsuccessful attempts, Mr. Miguel Jimenez and I were able to obtain an 8-membered ring 4a with a triethoxysilyl group. In contrast, substrate 5’ failed to yield the 12-membered product. Dr. Eun-Ang Raiber and I decided to revisit the salicylate-based substrates. Compounds 11a’ and 11b’ were made separately and submitted to RCM reactions. However, both failed to give any cyclized products. We then increased the ring size from 12 to 14 by inserting an ethylene group into the substrates. Finally, substrate 12a’ with a triethoxysilyl group was successfully closed to generate the 14-membered macrocyclic alkenylsiloxane 12a under un-optimized reaction conditions with 27% $^1$H NMR yield. Surprisingly, the analogue 12b’ with a diethoxyphenylsilyl group yielded only 2% of the desired product 12b under the same reaction conditions.

This initial exploration taught us several lessons. First, macrocyclic RCM of vinylsiloxanes is possible. However, typical RCM conditions are not optimal. Second, ring sizes of the products seem to affect the outcome of the reaction, and so far only 8-
and 14-membered macrocycles were formed. Finally, the silyl groups played an important role in this reaction, which might be more complicated than a purely electronic effect in CM reactions. With this knowledge in mind, I decided to move forward to systematic optimization of the reaction conditions.

2. Screening catalysts and optimizing reaction conditions for RCM of vinylsiloxanes to make macrocycles

Substrate 13a’ (an analogue of 12a’ with an extra methylene group) was synthesized and subjected to the initial conditions. Not surprisingly, the yield of the 15-membered product 13a dropped to 3% (Table I-3, Entry 2). This demanding substrate was then used to optimize the reaction conditions.

Among commercially available ruthenium-based metathesis catalysts, catalyst A was able to increase the yield from 3% to 19% under the original reaction conditions. In contrast to the second-generation Grubbs catalyst, A bears one methyl group on the ortho-position of each phenyl ring, making it less sterically hindered and more reactive. After varying solvent, temperature, and concentration we found that optimal results (63%, 1H NMR yield) were obtained using benzene or toluene as solvent at 35 °C and with 20 mol% of catalyst A (Table I-3, Entry 11 and 12).

Under the optimal reaction conditions, unreacted starting material was still observed, indicating that the catalyst was deactivated before the reaction went to completion. It is very likely that C(sp^3)-H bond insertion of the N-aryl ring on the ligand by ruthenium can
lead to fast deactivation of catalyst A,\textsuperscript{237} in addition to the commonly observed
decomposition pathways of Grubbs II.\textsuperscript{238}

Table I-3. Catalysts screening and reaction condition optimization.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solv.</th>
<th>Temp. (°C)</th>
<th>Conc. (mM)</th>
<th>Yield (%)\textsuperscript{[a]}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Grubbs I</td>
<td>DCM</td>
<td>reflux</td>
<td>2</td>
<td>&lt; 2</td>
</tr>
<tr>
<td>2</td>
<td>Grubbs II</td>
<td>DCM</td>
<td>reflux</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>Hoveyda-Grubbs I</td>
<td>DCM</td>
<td>reflux</td>
<td>2</td>
<td>&lt; 2</td>
</tr>
<tr>
<td>4</td>
<td>Hoveyda-Grubbs II</td>
<td>DCM</td>
<td>reflux</td>
<td>2</td>
<td>&lt; 2</td>
</tr>
<tr>
<td>5</td>
<td>A</td>
<td>DCM</td>
<td>reflux</td>
<td>2</td>
<td>19</td>
</tr>
<tr>
<td>6</td>
<td>B</td>
<td>DCM</td>
<td>reflux</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>A</td>
<td>ClCH\textsubscript{2}CH\textsubscript{2}Cl</td>
<td>50</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>8</td>
<td>A</td>
<td>benzene</td>
<td>50</td>
<td>2</td>
<td>54</td>
</tr>
<tr>
<td>9</td>
<td>A</td>
<td>toluene</td>
<td>50</td>
<td>2</td>
<td>50</td>
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<tr>
<td>10</td>
<td>A</td>
<td>benzene</td>
<td>23</td>
<td>2</td>
<td>42</td>
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<tr>
<td>11</td>
<td>A</td>
<td>benzene</td>
<td>30</td>
<td>2</td>
<td>63</td>
</tr>
<tr>
<td>12</td>
<td>A</td>
<td>benzene</td>
<td>40</td>
<td>2</td>
<td>63</td>
</tr>
<tr>
<td>13</td>
<td>A</td>
<td>benzene</td>
<td>60</td>
<td>2</td>
<td>45</td>
</tr>
<tr>
<td>14</td>
<td>A</td>
<td>benzene</td>
<td>35</td>
<td>1</td>
<td>52</td>
</tr>
<tr>
<td>15</td>
<td>A</td>
<td>benzene</td>
<td>35</td>
<td>5</td>
<td>39</td>
</tr>
<tr>
<td>16</td>
<td>A</td>
<td>benzene</td>
<td>35</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>17</td>
<td>A</td>
<td>benzene</td>
<td>35</td>
<td>20</td>
<td>12</td>
</tr>
</tbody>
</table>

\textsuperscript{[a]}Yield determined by \textsuperscript{1}H NMR analysis.

3. Influence of silyl groups on the reaction outcome

We next examined the influence of different silyl groups on the yield of the RCM
reaction (Table I-4). The results are in alignment with those of CM reactions. Generally,
ethoxy substituents promote the formation of product and lead to higher yields compared
to alkyl and/or aryl substituents (compare a-d with e, f). More ethoxy substituents are
preferred over less (compare c with d). Pietraszuk \textit{et al.} noted that electron-withdrawing
substituents shut down an undesired pathway that leads to catalyst deactivation.\textsuperscript{228,230} We
suggest that these unproductive processes are operative in macrocyclization reactions as
well and require the appropriate siloxane group to suppress them. However, in contrast to the CM precedents, the sterics of the silyl group also influenced the yield of the reaction. This effect is seen with the more demanding substrates 13a'-13f', while substrates 12a'-12f' show the same trend but to a lesser degree. When one of the ethoxy substituents was changed to a methyl group (13a' versus 13c'), the yield was improved while a change to a phenyl group (13c' versus 13b') resulted in the yield being halved. Our results indicate that the diethoxymethylsilyl group delivers the best reaction outcomes by maintaining a balance between both steric and electronic effects.

**Table I-4. Influence of the silicon substituents on the yield of RCM.**

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Entry</th>
<th>Silyl group</th>
<th>12[a]</th>
<th>13[a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Si(OEt)₃</td>
<td>92</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>Si(OEt)₂Ph</td>
<td>69[b]</td>
<td>35[b]</td>
<td></td>
</tr>
<tr>
<td>c</td>
<td>Si(OEt)₂Me</td>
<td>95</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>d</td>
<td>Si(OEt)Me₂</td>
<td>81</td>
<td>62[b]</td>
<td></td>
</tr>
<tr>
<td>e</td>
<td>SiMe₂Ph</td>
<td>54 (71[b])</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>f</td>
<td>SiEt₃</td>
<td>10[b]</td>
<td>&lt; 2</td>
<td></td>
</tr>
</tbody>
</table>

*a* Isolated yield (%) unless otherwise indicated; *b* yield calculated based on ¹H NMR analysis of reaction mixtures.

Vinylsiloxanes and alkenylsiloxanes are stable toward column chromatography and can be stored at -20 °C for 6 months without significant decomposition.

4. **Substrate generality study and protodesilylation**

Using the diethoxymethylsilyl group, macrocyclic alkenyl siloxane products with a wide range of ring sizes were obtained in moderate to excellent yields (Scheme 1-10). Diastereomers gave differing yields of purified products. For some substrates, silyl groups were incorporated into each of the alkene termini of the diene substrates. The *trans*-cyclohexanediols with silyl groups on different termini behaved similarly (21 and
23); while the silyl regioisomers of cis-cyclohexanediols behaved differently (22 and 24). To test the generality of this method in more complex molecules, two substrates inspired by previous work were prepared, incorporating vinylsiloxanes on either alkene termini. The 16-membered rings were both formed in moderate yields (32 and 33).

Scheme 1-10. Isolated yields of the RCM of various substrates and protodesilylation of the alkenyl siloxane products (in parentheses).

All corresponding Z-disubstituted olefins were obtained by protodesilylation with good to excellent yields while maintaining the geometry of the olefins. As envisaged, the tri-substituted olefins in the macrocyclic products have the E configuration (except for 30 and 32 that are mixtures of both stereoisomers with high E selectivity).
Scheme I-11. Substrates that failed to be cyclized under sub-optimal reaction conditions with ring sizes of desired products (in parentheses).

Substrates with silyl groups that failed to be closed are listed in Scheme I-11. Although these substrates were not subjected to the optimum reaction conditions (50 °C for some substrates, and Si(OEt)₃ instead of Si(OEt)₂Me), the introduction of the silyl group did not result in productive RCM. We do not know whether the non-silylated analogues of these substrates are competent to undergo RCM to generate the desired macrocycles if the ring strains associated with the formation of the macrocycles are intrinsically high (see discussion in Chapter I-2-7). Regarding instances when the silyl group thwarts ring closure, it may result from transannular interactions introduced by the silyl group which disfavor the formation of the macrocycle. A more comprehensive mechanistic
investigation into the factors governing the outcomes of these reactions is warranted. In order to close these recalcitrant substrates, higher reaction temperature might be required. However, the catalyst decomposes faster at higher temperatures. Therefore, future work or collaboration should involve the development of more stable catalyst that can improve the generality of this methodology.

5. Role of silyl groups in controlling stereochemistry of the reaction

We next sought to understand the role of the silyl group in controlling the stereochemical outcome of the reaction. For comparison, most of the corresponding simple (non-silyl containing) RCM precursors were synthesized in order to determine the intrinsic stereoselectivity of the substrates (Table I-5). Upon treatment with the optimized reaction conditions as well as typical RCM conditions using Grubbs II, Z-selective, E-selective, and non-selective outcomes were all observed. For the Z-selective (33’, 34’, 38’, 39’, 40’, 43’, and 14’) or non-selective (42’) simple olefin substrates, the introduction of the silyl group was found to reinforce the intrinsic stereoselectivity. More dramatically, for the E-selective substrates (36’, 37’, 41’, 44’, and 45’), the introduction of silyl groups in the substrates (17’, 18’, 22’, 24’, 30’, 31’, and 32’) can completely override the intrinsic preferences and generate the E-trisubstituted products (with Z configuration after protodesilylation). This confirmed our initial hypothesis that a silyl group serves as an effective controlling group favoring the formation of the E product in macrocyclic RCM reactions. During this comparative study, it was noticed that the RCM of simple olefin substrate gave rise to complex mixture of products in some cases. This observation
promoted us to explore and understand another important role of the silyl group. For a
detailed explanation, see Chapter I-2-7.

**Table I-5.** Influence of the silyl group on the specificity and stereoselectivity of RCM
reactions.

<table>
<thead>
<tr>
<th>Substrate #</th>
<th>R</th>
<th>Cond. I [a]</th>
<th>Cond. II [a]</th>
<th>Substrate #</th>
<th>R</th>
<th>Cond. I [a]</th>
<th>Cond. II [a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>4c'</td>
<td>[Si][b]</td>
<td>Z[c]</td>
<td>-</td>
<td>24'</td>
<td>Si</td>
<td>H</td>
<td>Z</td>
</tr>
<tr>
<td>33'</td>
<td>H</td>
<td>Z</td>
<td>Z</td>
<td>22'</td>
<td>H</td>
<td>Si</td>
<td>Z</td>
</tr>
<tr>
<td>15'</td>
<td>[Si]</td>
<td>Z</td>
<td>-</td>
<td>19'</td>
<td>[Si]</td>
<td>Z</td>
<td>-</td>
</tr>
<tr>
<td>34'</td>
<td>H</td>
<td>Z</td>
<td>-</td>
<td>38'</td>
<td>H</td>
<td>c. mix.</td>
<td>(Z)</td>
</tr>
<tr>
<td>16'</td>
<td>[Si]</td>
<td>Z</td>
<td>-</td>
<td>29'</td>
<td>[Si]</td>
<td>Z</td>
<td>-</td>
</tr>
<tr>
<td>35'</td>
<td>H</td>
<td>c. mix.</td>
<td>c. mix.</td>
<td>43'</td>
<td>H</td>
<td>c. mix.</td>
<td>(Z)</td>
</tr>
<tr>
<td>17'</td>
<td>[Si]</td>
<td>Z</td>
<td>-</td>
<td>12c'</td>
<td>[Si]</td>
<td>Z</td>
<td>-</td>
</tr>
<tr>
<td>36'</td>
<td>H</td>
<td>c. mix.</td>
<td>(24:76)</td>
<td>14'</td>
<td>H</td>
<td>81:19[f]</td>
<td>80:20[g]</td>
</tr>
<tr>
<td>18'</td>
<td>[Si]</td>
<td>Z</td>
<td>-</td>
<td>30'</td>
<td>[Si]</td>
<td>90:10</td>
<td>-</td>
</tr>
<tr>
<td>37'</td>
<td>H</td>
<td>E</td>
<td>E</td>
<td>44'</td>
<td>H</td>
<td>28:72</td>
<td>24:76</td>
</tr>
<tr>
<td>20'</td>
<td>[Si]</td>
<td>Z</td>
<td>-</td>
<td>13c'</td>
<td>[Si]</td>
<td>Z</td>
<td>-</td>
</tr>
<tr>
<td>39'</td>
<td>H</td>
<td>c. mix.</td>
<td>(Z)</td>
<td>42'</td>
<td>H</td>
<td>57:43[f]</td>
<td>54:46[g]</td>
</tr>
<tr>
<td>23'</td>
<td>Si</td>
<td>H</td>
<td>Z</td>
<td>31'</td>
<td>Si</td>
<td>H</td>
<td>Z</td>
</tr>
<tr>
<td>21'</td>
<td>H</td>
<td>Si</td>
<td>Z</td>
<td>32'</td>
<td>H</td>
<td>Si</td>
<td>86:14</td>
</tr>
<tr>
<td>40'</td>
<td>H</td>
<td>H</td>
<td>c. mix.</td>
<td>45'</td>
<td>H</td>
<td>H</td>
<td>36:64</td>
</tr>
</tbody>
</table>

[a] Cond. I: cat. A (20 mol%), toluene, 35 °C; Cond. II: Grubbs II (10 mol%), 1,4-benzoquinone (20 mol%),
toluene, 35 °C; [b] [Si] equals diethoxymethylsilyl. For silylated substrates, Z:E assignment is based on the
protodesilylated products; [c] Single stereoisomer reported for Z:E ratios >98:2, otherwise Z:E ratio was
determined by 1H NMR analysis of the crude mixture; [d] c. mix.: complex mixture of products (cyclized and
uncyclized oligomers); [e] stereochemistry of cyclized monomer reported in parentheses whenever its
proportion within the complex mixture was sufficient for determination; [f] reactions performed at room
temperature; [g] reactions performed in refluxing DCM.
6. Proposed models to explain the stereoselectivity controlled by the silyl group

Scheme I-12. Two proposed models to explain the stereoselectivity of the RCM reaction.

Based on previous studies on CM by Grubbs and coworkers\textsuperscript{239} as well as our own observations, the initiation of the reaction would most likely happen on the simple olefin (for detailed discussion, see Chapter I-2-7). After the formation of I, we propose metallocyclobutane intermediates II is preferably formed leading to the \textit{E} product (Scheme I-12). There are two models that can explain the high selectivity observed. As shown in model A, the allylic carbon in transition state (TS) IIa avoids steric interactions with the bulky silyl group as in TS IIIa. Thus the formation of intermediate II is favored. To support this model, CM of a geminal-disubstituted vinylsiloxane and a simple mono-substituted olefin was performed (see Chapter I-5-2). Without the influence imposed by the macrocycle, the stereoselectivity of the CM reaction will only reflect the interaction between the silyl group and the allylic carbon. Unfortunately, the CM reactions that we
performed so far were not successful. Therefore, we looked for evidence that is consistent or in conflict with what can be inferred from model A. No matter which olefin terminus the silyl group is installed on, the stereoselectivity should be the same according to model A. However, for the complex substrate, putting the silyl group on one side, 31’, yielded only the E isomer, yet putting the silyl group on the other side, 32’, yielded mixture of both stereoisomers with $E:Z$ ratio of 86:14 (see Table I-5). Based on this result, we concluded that the first model might be operative to some degree but not exclusive.

We then proposed model B that can explain the stereoselectivity of the reaction from a different perspective. Macrocycles are known to have transannular interactions especially when an alkene is present. Depending on the macrocyclic conformation of each substrate, the energy of transition states leading to both intermediates is differentiated by transannular interactions between the silyl group and the backbone or substituent of the macrocycle. The transition state IIIb leading to III is more likely to have transannular interactions than the transition state IIb leading to II because in transition state IIIb, the backbone has to connect the two allylic carbons which will be on opposite faces of the metallocyclobutane ring. If this model is operating, larger rings will be able to accommodate the transition state leading to the (Z)-macrocycle without having severe transannular interactions. This prediction is in accordance with the results. Substrates 30’ and 32’ that form 15- or 16-membered rings gave rise to little amount of the (Z)-macrocycle, although the dominant products are still the E isomer. This model also explains that silyl groups on different olefin termini resulted in different stereoselectivities. However, model B is dependent on the macrocyclic conformation that
varies with different substrates. The prediction of stereoselectivity for a novel substrate will therefore not be straightforward.

7. Role of silyl groups in trapping the desired product

It is also noteworthy that several of the simple substrates gave rise to a complex mixture of products (Table I-5, substrates 34', 36', 38', 39', 40', 41', and 43'), sometimes without a detectable level of cyclized monomer (substrate 35'). The LC-MS analysis of the crude reaction indicated the formation of cyclized dimers and other polymeric by-products. This is a general problem for macrocyclic RCM reactions of simple olefins.241-243 While the reaction conditions for the simple substrates were not optimized, these results point to the additional ability of the silyl group to suppress the formation of undesired products.

Scheme I-13. Possible reaction pathways of macrocyclic RCM with and without a 2-silyl group (A); route to compound 35 from RCM of the vinylsiloxane (B).

Based on our data, we propose a model for the reaction pathways depicted in Scheme I-13, A. Several unproductive pathways are involved in RCM reactions of simple olefins including re-opening of the monocyclized product (A'), CM to generate an acyclic dimer or oligomer (B, C), and potential cyclization at either of these stages (C, D). In contrast,
when the silyl group is incorporated in one of the olefins, pathway A leading to the desired product is no longer reversible. When we re-subjected the purified trisubstituted silylalkene product to the reaction conditions, no ring-opening product was observed. Pathway B exists to generate the acyclic dimers, but only through the CM between the simple olefins – the 2-silyl alkene remains a spectator to CM under our reaction conditions. However, when re-subjected to the reaction conditions, the purified acyclic cross-dimers (E and Z) of the silylated substrates 13a’ yielded macrocyclic products with 60% $^1$H NMR yield comparable to that starting from monomer (Scheme I-14). Additionally, since the 2-silyl alkene remains a spectator to CM, pathway C is shut down. Pathway D is also blocked because the formation of a tetrasubstituted alkene with two silyl groups is highly disfavored.

**Scheme I-14.** RCM of acyclic dimers of 13a’ compared to the reaction with monomer 13a’.

Overall, the silyl group is able to lower the reactivity of the attached olefin, thereby suppressing non-productive pathways while still allowing the pathways to yield the desired product. In agreement with this analysis, for the substrates that gave low yields, only unreacted starting material, the acyclic cross-dimers, and a styrene derivative were
observed along with the product. To explore the “trapping” role of the silyl group, the monocyclized (Z)-alkene 35 (not observed from the RCM of the simple olefin substrate 35', Scheme I-13, B) obtained from protodesilylation of compound 16 was subjected to reaction condition II. Not surprisingly, it was almost completely consumed to generate dimers and oligomers. Owing to the fact that the silyl group can be removed, this method offers a means to cyclize some recalcitrant substrates using RCM.
Chapter I-3. Diversification of Alkenylsiloxanes and Alkenylsilanes

1. Further transformation of macrocyclic alkenylsiloxanes

As a principle goal of this project, we aimed to demonstrate the synthetic versatility of alkenylsiloxanes by directly transforming them into a variety of different products (Scheme I-15). Alkenyl siloxanes are capable of undergoing a wide range of transformations. Accordingly, the simple Z-disubstituted olefin 46-Z was obtained by protodesilylation. This two-step process affords Z olefins selectively from RCM reactions. Oxidation of the alkenyl siloxane generated ketone 47 at the carbon bearing the siloxyl group. Ketones, which are found in many biologically active and naturally occurring small molecules, have not typically been obtained from metathesis products in the past except from the RCM product of enol ethers. Our methodology should permit the synthesis of ketones at either of the alkenyl carbons.


The direct synthesis of trisubstituted macrocyclic olefins using RCM is generally challenging. The siloxyl-substituted macrocycles provide an effective solution.
to this synthetic objective. An *ipso*-iodination of the alkenyl siloxane provided alkenyl iodide 48, a substrate with considerable synthetic potential in transition metal-catalyzed cross-coupling reactions. We also achieved several carbon-carbon bond-forming reactions using the macrocyclic alkenyl siloxane directly. A palladium-catalyzed cross-coupling enabled direct C-C bond formation with an aryl halide, affording the aryl-appended macrocycle 49. The alkenyl siloxane also underwent a conjugate addition to an α,β-unsaturated ketone in the presence of a rhodium catalyst to generate a C(sp²)-C(sp³) bond in compound 50 as a mixture of diastereomers.

2. An effective way to synthesize cyclic α-silyl carbonyl compounds via silapinacol rearrangement

Compounds containing α-silyl carbonyl moieties are versatile synthetic intermediates because the silyl group differentiates the two α-positions of a carbonyl moiety that are hard to be selectively transformed otherwise. Three conventional ways of accessing the α-silyl carbonyl moiety include α-silylation of carbonyl compounds, oxidation of β-silyl alcohols, and the addition of silyl-containing organolithium or organomagnesium to esters and acid chlorides. It was also reported that α,β-dihydroxysilanes can undergo “silapinacol” rearrangement upon the treatment of an acid to generate α-silyl ketones or aldehydes. Cunico reported that when α,β-dihydroxysilane 51 was dissolved in CDCl₃ (without the addition of extra acid), the intermediate α-silyl aldehyde 52 could be observed, coexisting with the starting material for some hours, but slowly collapsing to the desilylated aldehyde product 53 (Scheme I-16, A). If the appropriate silyl group was selected that is stable at the α position of a
carbonyl moiety under acidic conditions (a TBS group in contrast with a TMS group, Scheme I-16, B), α-silyl ketones, or aldehydes, can be obtained.

**Scheme I-16.** Silapinacol rearrangement of acyclic α,β-dihydroxysilanes.

Enabled by the RCM of vinylsilanes and the following syn-dihydroxylation catalyzed by OsO₄, cyclic α,β-dihydroxysilanes can be easily accessed. Mr. Miguel Jimenez and I explored the application of the silapinacol rearrangement in these cyclic substrates to obtain cyclic α-silyl ketones that serve as another versatile functionality for further diversification in addition to the direct transformation of vinylsilanes.

Precursors 56, 57, 61, and 62 with two silyl groups were synthesized. Upon treatment of an acid, only the 6-membered ring with a TBS group 62 was able to yield the desired α-silyl ketone 64. We speculate that the 5-membered ring is not flexible enough to provide the required conformation for the silyl group to migrate (assuming an antiperiplanar relationship between the migrating silyl group and the leaving protonated or borylated β-hydroxy group, Scheme I-18, C). Unlike the acyclic substrate, 1 equivalent of acid and higher reaction temperatures are required for the rearrangement to occur. Additionally,
stronger acid than TFA is required such as HCl or BF₃·Et₂O. Finally, the dimethylphenylsilyl group is not stable enough to stay at the α position of ketone.

Table I-6. Silapinacol rearrangement of 5- and 6-membered alkenylsilanes under different acids and reaction conditions.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product, yield (conversion)</th>
<th>TFA[a]</th>
<th>HCl[b]</th>
<th>BF₃·Et₂O[c]</th>
<th>Zn(OTf)₂[d]</th>
<th>TMSOTf[e]</th>
<th>MgBr₂[f]</th>
</tr>
</thead>
<tbody>
<tr>
<td>56</td>
<td>no rxn</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>(&gt;95%)</td>
<td>no rxn</td>
<td></td>
</tr>
<tr>
<td>57</td>
<td>no rxn</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>(&gt;95%)</td>
<td>no rxn</td>
<td></td>
</tr>
<tr>
<td>61</td>
<td>24%</td>
<td>65</td>
<td>65</td>
<td>decomposition</td>
<td>(&gt;95%)</td>
<td>no rxn</td>
<td></td>
</tr>
<tr>
<td>62</td>
<td>20%</td>
<td>64</td>
<td>64</td>
<td>decomposition</td>
<td>(&gt;95%)</td>
<td>no rxn</td>
<td></td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 1 eq. TFA, 80 °C for substrate 56 and 57, 50 °C for substrate 61 and 62, toluene (25 mM), 16 h.
[b] Reaction conditions: 1 eq. HCl (1 M solution in Et₂O), 80 °C for substrate 56 and 57, 50 °C for substrate 61 and 62, toluene (25 mM), 16 h.
[c] Reaction conditions: 1 eq. BF₃·Et₂O, 50 °C for substrate 56 and 57, toluene (25 mM); 0 °C for substrate 61 and 62, DCM (25 mM), 16 h.
[d] Reaction conditions: 1.1 eq. Zn(OTf)₂, 80 °C for substrate 56 and 57, 50 °C for substrate 61 and 62, dioxane (25 mM), 16 h.
[e] Reaction conditions: 1 eq. TMSOTf, 0 °C, toluene (25 mM), 2 h.
[f] Reaction conditions: 1.2 eq. MgBr₂, 80 °C for substrate 56 and 57, 50 °C for substrate 61 and 62, toluene (25 mM), 16 h.

We halted further exploration because we could not access tert-butyldimethylsilylalkenes with ring sizes larger than 6 by RCM reaction under our current reaction conditions. Nevertheless, this methodology would greatly increase the diversification potential of the product from RCM of vinylsilanes.
Chapter I-4. Conversion of Macrocyclic (E)-Alkenylsiloxanes to the Corresponding (Z)-Alkenyl Bromides

Inspired by early studies of Jarvie et al.\textsuperscript{277} and Miller et al.\textsuperscript{278} acyclic alkenylsilanes can be transformed to alkenyl bromides with inversion of stereochemistry. It is desirable to apply this transformation to the macrocyclic alkenylsiloxane obtained from RCM reactions because not only the stereochemistry can be inverted, but the alkenyl bromide also serves as a versatile synthetic intermediate.

Using substrate 12c, Mr. Miguel Jimenez and I tried some mild dihalogenation reagents such as pyridinium tribromide and phenyltrimethylammonium tribromide. None of them provided complete consumption of starting material or clean reaction without decomposition. We then turned our focus to bromine. Treatment of substrate 12c in DCM at -78 °C with dropwise addition of bromine solution showed complete consumption of starting material and formation of a dibromide intermediate along with a small amount of alkenyl bromide product suggested by LC-MS analysis. It was found that the dibromide intermediate could convert into the alkenyl bromide on silica gel when running TLC analysis. So instead of isolating the intermediate, a two-step, one-pot procedure was adopted. TBAF was chosen as the bromodesilylation reagent. Upon the addition of up to 4 equivalents of TBAF as solution in THF, the dibromide intermediate completely collapsed to the desired alkenyl bromide after warming up to room temperature. The E isomer was assigned by confirming the NOE effect between the two groups of allylic protons. The Z:E ratio was determined with \textsuperscript{1}H NMR analysis.
Table 1-7. Influence of reaction conditions on the stereoselectivity of converting alkenylsiloxane to alkenyl bromide.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time (min)</th>
<th>Reaction outcome</th>
<th>Stereoselectivity (E:Z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DCM</td>
<td>40</td>
<td>5</td>
<td>94%</td>
<td>15:85</td>
</tr>
<tr>
<td>2</td>
<td>DCM</td>
<td>0</td>
<td>5</td>
<td>91%</td>
<td>8:92</td>
</tr>
<tr>
<td>3</td>
<td>DCM</td>
<td>-78</td>
<td>5</td>
<td>95%</td>
<td>3:97</td>
</tr>
<tr>
<td>4</td>
<td>DCM</td>
<td>-100</td>
<td>15</td>
<td>95%</td>
<td>2:98</td>
</tr>
<tr>
<td>5</td>
<td>toluene</td>
<td>23</td>
<td>5</td>
<td>94%</td>
<td>17:83</td>
</tr>
<tr>
<td>6</td>
<td>toluene</td>
<td>0</td>
<td>5</td>
<td>94%</td>
<td>13:87</td>
</tr>
<tr>
<td>7</td>
<td>toluene</td>
<td>-78</td>
<td>5</td>
<td>98%</td>
<td>8:92</td>
</tr>
<tr>
<td>8</td>
<td>CS₂</td>
<td>23</td>
<td>5</td>
<td>94%</td>
<td>13:87</td>
</tr>
<tr>
<td>9</td>
<td>CS₂</td>
<td>0</td>
<td>5</td>
<td>73%</td>
<td>15:85</td>
</tr>
<tr>
<td>10</td>
<td>CS₂</td>
<td>-78</td>
<td>5</td>
<td>95%</td>
<td>3:97</td>
</tr>
<tr>
<td>11</td>
<td>THF</td>
<td>23</td>
<td>5</td>
<td>full conv., minor decomp.</td>
<td>31:69</td>
</tr>
<tr>
<td>12</td>
<td>THF</td>
<td>0</td>
<td>5</td>
<td>full conv., minor decomp.</td>
<td>22:78</td>
</tr>
<tr>
<td>13</td>
<td>THF</td>
<td>-78</td>
<td>5</td>
<td>incompl. conv., minor decomp.</td>
<td>67:33</td>
</tr>
<tr>
<td>14</td>
<td>THF</td>
<td>-100</td>
<td>15</td>
<td>incompl. conv., minor decomp.</td>
<td>84:16</td>
</tr>
<tr>
<td>15</td>
<td>Et₂O</td>
<td>23</td>
<td>5</td>
<td>&gt;95%[d]</td>
<td>20:80</td>
</tr>
<tr>
<td>16</td>
<td>Et₂O</td>
<td>0</td>
<td>5</td>
<td>92%</td>
<td>13:87</td>
</tr>
<tr>
<td>17</td>
<td>Et₂O</td>
<td>-78</td>
<td>5</td>
<td>30%</td>
<td>55:45</td>
</tr>
<tr>
<td>18</td>
<td>DMF</td>
<td>23</td>
<td>5</td>
<td>incompl. conv., decomp.</td>
<td>n. d.[e]</td>
</tr>
<tr>
<td>19</td>
<td>DMF</td>
<td>0</td>
<td>5</td>
<td>incompl. conv., decomp.</td>
<td>n. d.[e]</td>
</tr>
<tr>
<td>20</td>
<td>DMF</td>
<td>-78</td>
<td>5</td>
<td>incompl. conv., decomp.</td>
<td>n. d.[e]</td>
</tr>
</tbody>
</table>

*a* Time between addition of Br₂ and TBAF. *b* Isolated yield unless otherwise indicated. *c* Determined by ¹H NMR analysis of reaction mixture after workup. *d* Yield determined by ¹H NMR analysis. *e* Ratio not determined.

Next we explored the influence of solvent and temperature on the stereoselectivity of this transformation (Table 1-7). It was found that nonpolar solvents (DCM, CS₂, and toluene) generally favored inversion of stereochemistry leading to the desired (Z)-alkenyl bromide. In these solvents, lowering temperature could increase the selectivity towards the Z isomer, and reactions could reach complete conversion in most cases. On the
contrary, polar solvent such as DMF favored the retention of stereochemistry yielding the
$E$ isomer as the major product independent of reaction temperature. Also, side reactions
that led to decomposition became significant in DMF. Interestingly, when the reaction
was performed in ether or THF, the reaction proceeded slower at lower temperature (-100
°C to -78 °C) with higher $E$ selectivity. As temperature was elevated, both the conversion
and $Z$ selectivity were increased. Reaction mechanisms leading to the formation of either
stereoisomers and the role of solvents are not fully clear at this point.

**Table I-8.** Stereoselectivity of converting ($E$)-alkenylsiloxane substrates to the
corresponding alkenyl bromide.

<table>
<thead>
<tr>
<th>Substrate$^a$</th>
<th>Alkenyl bromide, ($E$:$Z$)$^b$</th>
<th>Substrate</th>
<th>Alkenyl bromide, ($E$:$Z$)</th>
</tr>
</thead>
</table>

$^a$ [Si] equals diethoxymethylsilyl. $^b$ Reaction condition: alkenylsiloxane (1 eq.), Br$_2$
(1.05 eq.), DCM (40 mM), -78 °C, 5 min; TBAF (4 eq.), warmed up to r.t., 15 min.
$E$:$Z$ ratio was determined by $^1$H NMR analysis of crude extract.

The stereoselectivity of the product is further complicated by the fact that macrocyclic
substrates may have intrinsic conformational constraints that affect stereochemistry of
each step in the reaction sequence. As shown in Table I-8, 11- or 12-membered rings gave retention of stereochemistry, while 14- and 15-membered rings yielded almost complete inversion.

**Scheme I-17.** Proposed reaction mechanism of dibromination/bromodesilylation leading to either stereoisomer.

A general model that explains the dependency of stereochemistry on the ring size of the macrocycle is proposed in Scheme I-17. In the ideal situation, once the bromonium ion I is formed, the bromide (Br⁻) attacks from the back to generate the *anti*-dibromide (pathway A). The issue of which carbon the bromide attacks (II or III) is inconsequential as long as the relative stereochemistry of the dibromide is *anti*. Upon treatment with
TBAF, bromodesilylation happens only when the β-bromo group is antiperiplanar to the silyl group via rotation about the C-C bond (transition state VI and VII) following an E₂ mechanism. The products from both intermediates are the same (Z)-alkenyl bromide (XI).

This explains the high selectivity observed for the 14- or 15-membered substrates when reactions are performed in nonpolar solvents at low temperature. However at higher temperatures, the Z selectivity decreases because the E₂ process is eroded by the E₁ process (pathway C via the fully formed carbocation or D via rearrangement of the bromonium ion). Additionally, at these temperatures syn-dibromination may occur also leading to the E product (pathway B).

In polar solvents the situation is reversed since the solvent can stabilize either the bromonium ion or the fully formed carbocation. When the reaction of substrate 12c was performed in solvents such as THF or ether, a critical temperature exists, below which pathways leading to the E product (B, C, or D) become dominant (observed at -100 °C) potentially because the solvent-stabilized cation does not easily undergo a back-side attack by another bromide; however above this critical temperature pathways leading to the Z product (A) become dominant (observed at 0 °C) because the desired anti dibromide can readily form as with nonpolar solvents but with lower selectivity.

For 11- or 12-membered substrates, pathway A becomes disfavored even in nonpolar solvent (Table I-8, substrate 17, 18, 21, 22, and 25). It is possible that in these smaller
ring-sizes, even though the reactivity of the bromonium ion is maintained, the back side of the bromonium ion is blocked by the backbone and the substituents of the macrocycle transannularly so that *anti*-dibromination is largely prohibited at the temperatures reported. Another possibility is that the *(E)*-alkenyl bromide product is higher in energy than the *Z* isomer. So even if the *anti*-dibromide is initially formed, it may revert to the bromonium ion and eventually form the *Z* product through the pathways mentioned above. Further mechanistic study is warranted to understand the stereoselectivity with different substrates.
Chapter I-5. Applications of the Silyl Group

in Other Types of Metathesis Reactions

1. Enyne RCM of alkynylsilanes and alkynylsiloxanes

Mr. Michele Melchiorre and Ms. Cinzia Botta initiated the enyne RCM study. They used a model substrate to show the importance of the silyl groups in the enyne metathesis (Table I-9). A number of silyl groups could be installed on the terminal alkyne with moderate to excellent yields. However, three silyl groups (Entry 1, 2, and 4) failed to afford the desired butadiene product under optimized reaction conditions.

Table I-9. Influence of the silyl group on the enyne RCM reactions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>[Si]</th>
<th>Silylation Product, Yield (%)</th>
<th>Enyne RCM Product, Yield (%)</th>
<th>Entry</th>
<th>R group</th>
<th>Silylation Product, Yield (%)</th>
<th>Enyne RCM Product, Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SiClMe₂</td>
<td>79', 80</td>
<td>no rxn</td>
<td>5</td>
<td>SiMe₂Ph</td>
<td>83', 72</td>
<td>83, 74</td>
</tr>
<tr>
<td>2</td>
<td>Si(OMe)Me₂</td>
<td>80', 32</td>
<td>no rxn</td>
<td>6</td>
<td>SiMe₂</td>
<td>84', 91</td>
<td>84, 77</td>
</tr>
<tr>
<td>3</td>
<td>Si(O'Bu)Ph₂</td>
<td>81', 95</td>
<td>81, 49</td>
<td>7</td>
<td>SiBnMe₂</td>
<td>85', 76</td>
<td>85, 93</td>
</tr>
<tr>
<td>4</td>
<td>SiHMe₂</td>
<td>82', 76</td>
<td>no rxn</td>
<td>8</td>
<td>SiMePh₂</td>
<td>86', 75</td>
<td>86, 96</td>
</tr>
</tbody>
</table>

Ms. Cinzia Botta and Mr. Brandon Silverman then studied the generality of the enyne RCM reaction to form different sized products. It was found that when the ring sizes become larger, the yield for the enyne RCM dropped significantly (Scheme I-18). Especially substrate 89’ and 90’ failed to generate any detectable amount of 7-membered ring products.
Scheme I-18. Reaction outcome of enyne RCM yielding products with different ring sizes.

Based on the initial study on this reaction and our understanding of the role of silyl groups in the RCM reaction, I explored the reaction to form the 7-membered product using a triethoxysilyl group (Scheme I-19). Initial efforts to separate the alkynylsiloxane failed because it decomposes on silica gel. Instead, a one-pot procedure was adopted. After silylation of the terminal alkyne 91, the reaction was concentrated and then a solution of Hoveyda-Grubbs second-generation catalyst in toluene was added. The resulting mixture was charged with ethylene gas and left at room temperature for 12 hours. The overall yield of desired silyl-diene 92 after workup and flash chromatography was 14% without any optimization. Further effort is required to find the optimal silyl group that is compatible with the enyne RCM reaction and at the same time suitable for following transformations especially the Fleming-Tamao oxidition.

Scheme I-19. Initial exploration on synthesis and enyne RCM of triethoxysilyl-containing substrate to form a 7-membered product.
2. Cross metathesis and relay cross metathesis of vinylsiloxanes

In order to understand the role of the silyl group in determining stereochemistry of the macrocyclic RCM reaction, CM of geminal-disubstituted silanes or siloxanes with a monosubstituted olefin was performed. Without any intrinsic preference toward Z or E imposed by macrocyclic conformation and transannular interactions, the stereoselectivity of the CM reaction would reflect the influence of the steric of the silyl group. However, we failed to observe any desired product forming in any of the reactions listed in Scheme 1-20. Difficulties in achieving CM of geminal-disubstituted siloxanes categorized them in the spectator class for CM reaction under current reaction conditions, which is in accordance with our analysis of the reaction pathway mentioned in Chapter I-2-7.

In order to overcome the low reactivity of sterically hindered geminal-disubstituted olefins, we have explored a strategy called relay metathesis used in RCM reaction.\textsuperscript{279-282} Compound 95e was synthesized and subjected to the CM reaction with allyl acetate. We failed to observe any desired product under these conditions (Scheme 1-20). Only homodimers of allyl acetate were observed. The effort to synthesize compound 95a with a Si(OEt)\textsubscript{3} group instead of a SiPhMe\textsubscript{2} was more challenging. An inseparable mixture of both regioisomers (95a and 96a) was obtained and the desired isomer is the minor product. Although we did not observe any desired CM product upon treatment of the mixture with catalyst A and allyl acetate, the result was inconclusive. Further investigation into the relay CM is warranted.
**Scheme I-20.** Attempted CM between geminal-disubstituted vinylsiloxanes and a monosubstituted olefin; attempted relay CM reactions.
Chapter I-6. Conclusion and Future Directions

In summary, the introduction of silyl groups into several types of metathesis reactions has been extensively explored. The macrocyclic RCM was the primary focus. Under optimized reaction conditions, a series of 8- to 16-membered macrocyclic rings containing trisubstituted olefins and other useful functionality, including rings having complex substitution patterns, can be accessed. The results demonstrated that the silyl group plays three roles: control of the stereoselectivity of the reaction favoring formation of the $E$ product, trapping the desired product by preventing the undesired reaction pathways, and providing the diversification potential with regiochemical control. However, introduction of the silyl group compromises the generality of the RCM reaction to some extent, which is compounded by the instability of the optimal catalyst. Future works on development of metathesis catalyst can be done to increase the generality of this methodology.

In addition, it has been shown that $(E)$-alkenyl siloxanes can be transformed to $(Z)$-alkenyl bromides with inversion of stereochemistry. The alkenyl bromide can also serve as a versatile chemical handle for further diversification. The stereoselectivity of this transformation is substrate-dependent, however, we have not fully understood the reaction mechanism. Both $Z/E$ isomers of a variety of trisubstituted macrocyclic alkenes are accessible for substrates that give complete inversion of stereochemistry from alkenylsiloxane to alkenyl bromide.
To utilize the diversification potential of the silyl group, enyne RCM of alkynylsiloxanes were studied yielding limited success thus far. Further exploration is required to understand the stability of the alkynylsiloxane, the compatibility of the silyl group in the RCM reaction, the optimal catalyst and reaction conditions, and substrate generality of this reaction.

Attempts to effect a CM between a vinylsiloxane and a simple alkene were made to understand the role of silyl groups in determining stereoselectivity of the RCM reaction. Different substrates and reaction conditions as well as the relay strategy were tried but failed to generate a detectable amount of products. It is likely that novel catalysts will be required for this transformation.
Experimental section

1. Material and Methods

Except as otherwise noted, reactions were carried out under argon. All reaction solvents except acetone and pyridine were dispensed from a solvent purification system wherein solvents are passed through a packed activated alumina column. Acetone was Aldrich 99.5+% histological grade. Pyridine was Aldrich 99.8% histological grade. NMR spectra were recorded at 500 MHz using a Varian I-500 instrument. Chemical shifts for proton NMR spectra are reported in parts per million downfield from tetramethylsilane and were referenced to residual protonated solvent (CHCl₃: d 7.26, C₆H₆: d 7.15). Chemical shifts for carbon NMR spectra are reported in parts per million downfield from tetramethylsilane and referenced to protonated solvent (CHCl₃: d 77.0, C₆H₆: d 128.0). Data are represented as follows: chemical shift (multiplicity [bs = broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet], coupling constants in Hertz, integration). High-resolution mass spectra were obtained through the Harvard University mass spectrometry facility. Infrared spectra were obtained with a Nicolet IR100 FTIR from Thermo Scientific. Optical rotations were obtained using digital polarimeter Autopol IV (Rudolph research Analytical) with a 1 mL cell and a 1 dm path length. All reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) using E. Merck silica gel 60 F254 precoated plates (0.25 mm). Flash chromatography was performed either with the indicated solvent on E. Merck silica gel 60 (230-400 mesh) or using a CombiFlash companion system (Teledyne ISCO, Inc.) with pre-packed FLASH silica gel columns (Teledyne ISCO, Inc.). SFC/MS chromatography was performed with a Berger analytic SFC (Waters ZQ Mass Spectometer) using CO₂ and isopropanol as the
mobile phase and using a Chiralpak® AD-H column purchased from Chiral Technology Inc. (column length: 4.6x250mm, particle size: 5um). HPLC purification was performed on a Waters mass-directed autopurification system. The system consisted of 2767 injection/collection sample manager, a 2525 binary gradient high pressure LC pump, two 515 pumps to deliver makeup and dilution flow, a column fluidic organizer (CFO), a 2996 photodiode array detector, and a ZQ quadropole MS equipped with an electrospray interface. All of the instrumentation was controlled by MassLynx and FractionLynx software versions 4.1. All reagents were obtained from commercial sources and used without further purification.

2. Experimental procedures

Note on compound numbering: ring-closed products are designated as the parent compound and numerated with just a number with or without a letter. Whenever necessary, Z or E is used to distinguish between both stereoisomers. Substrates (simple, silyl-containing, or enyne) for RCM reactions are designated with a prime after the compound name. The undesired regioisomer of the vinylsiloxane from the hydrosilylation reaction is designated with double primes after the name. The styrene derivative from the RCM reaction is labeled with ‘s’ after the name of the substrate. For the same scaffold that has different silyl groups, letters are used to differentiate: ‘a’ Si(OEt)₃; ‘b’ Si(OEt)₂Ph; ‘c’ Si(OEt)₂Me; ‘d’ Si(OEt)Me₂; ‘e’ SiMe₂Ph; ‘f’ SiEt₃; ‘g’ SiMe₃; ‘h’ Si’tBuMe₂.

A. Synthesis and RCM of vinylsilane
Scheme I-21. Synthetic route toward cyclic alkenylsilanes.

As shown in Scheme I-21, it takes three steps to access the silyl-containing diolefinic substrates for RCM reactions. According to the literature, the first step involves a dibromination and HBr elimination of a vinylsilane to generate the bromovinylsilane. The second step starts with a lithium-bromo exchange of the bromovinylsilane, which is subsequently quenched with paraformaldehyde. Then the allyl alcohol is subjected to a Mitsunobu reaction with tosylamine serving as a nucleophile. The general procedures of these three steps are described as follows.

Bromine (1 equiv.) in carbon tetrachloride (1.2 M) was added dropwise, via a cannula, to a stirred solution of vinylsilane (1 equiv.) in carbon tetrachloride (1.2 M) at 0 °C. The solution was stirred for 10 min at 0 °C, washed sequentially with saturated aqueous sodium hydrogen carbonate containing some sodium hydrogen sulfite (3 × 50 ml) and brine (50 ml), dried over magnesium sulfate and concentrated in vacuo to give the crude dibromide. This crude product was dissolved in diethylamine (0.6 M) and refluxed for 12 h. After cooling to room temperature, the dark brown reaction mixture was diluted with diethyl ether and washed with water. The organics were then washed with brine, dried over sodium sulfate and concentrated in vacuo, which was then purified by flash column chromatography (hexane) to give the bromovinylsilane.
To a stirred solution of bromovinylsilane in diethyl ether (0.3 M) at -78 °C, \textit{tert}-butyllithium (1.7 M solution in pentane, 2.1 equiv.) was added dropwise. After complete addition, the reaction was stirred for 1 h at -78 °C. A solution of paraformaldehyde (2 equiv.) in diethyl ether (2.5 M) was then added dropwise via a cannula. After stirring for 1 hour at -78 °C, the reaction was allowed to warm to room temperature. Water was added, the mixture was separated and the aqueous layer was extracted with diethyl ether for 3 times. The organics were then washed with brine, dried over sodium sulfate and concentrated \textit{in vacuo}, which was purified by flash column chromatography (5% ethyl acetate in hexane) to give the vinylsilane-containing alcohol.

The vinylsilane-containing alcohol was dissolved in THF (0.1 M). \textit{PPh}_3 (1.2 equiv.) was added to the solution. Then \textit{N}-alkenyl-4-methylbenzenesulfonamide (1.1 equiv.) was added. The reaction was cooled to 0 °C. DIAD (1.1 equiv.) was added dropwise. The reaction was warmed to r.t. and stirred for 12h. The reaction mixture was concentrated \textit{in vacuo}. The residue was purified via flash column chromatography (10% ethyl acetate in hexane) to give the RCM substrate.

\textit{Initial RCM reaction conditions}: substrate (1 equiv.) was dissolved in anhydrous DCM at a concentration of 20 mM (for compound 1\textit{e'}, and 2\textit{e'}) or 3 mM (for compound 1\textit{h'}, 2\textit{h'}, 3\textit{e'}, 3\textit{h'}, 4\textit{a'}, 5', 11\textit{a'}, and 11\textit{b'}) under argon. Grubbs II (10 mol\% for 1\textit{e'} and 2\textit{e'}; 20 mol\% for others) was added to the solution. The reaction was kept at room temperature for 18 hours (for 1\textit{e'} and 2\textit{e'}) or heated up to 40 °C for 18 hours (for other substrates). The resulting mixture was concentrated under reduced pressure and the residue was
analyzed by $^1$H NMR or purified by silica gel column chromatography using Hexanes/EtOAc as eluent.

\[
\text{N-allyl-N-(2-(dimethyl(phenyl)silyl)allyl)-4-methylbenzenesulfonamide (1e')}
\]
Yield 46% (colorless oil); $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 7.66-7.64 (m, 2 H), 7.61-7.49 (m, 2 H), 7.37-7.33 (m, 3 H), 7.27-7.25 (m, 2 H), 5.83-5.82 (m, 1 H), 5.54-5.53 (m, 1 H), 5.39-5.30 (m, 1 H), 4.96-4.94 (m, 1 H), 4.90-4.86 (m, 1 H), 3.83 (s, 2 H), 3.66 (d, $J = 7.0$ Hz, 2 H), 2.41 (s, 3 H), 0.41 (s, 6 H); $^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$ 144.1, 143.0, 137.3, 137.1, 133.9, 132.0, 129.6, 129.2, 128.1, 127.8, 127.2, 119.3, 51.0, 49.6, 21.5, -3.4.

\[
\text{3-(dimethyl(phenyl)silyl)-1-tosyl-2,5-dihydro-1H-pyrrole (1e)}
\]
Yield 92% (colorless oil); $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 7.67 (d, $J = 8.5$ Hz, 2 H), 7.39-7.26 (m, 7 H), 5.82 (t, $J = 1.0$ Hz, 1 H), 4.17-4.13 (m, 4 H), 2.43 (s, 3 H), 0.33 (s, 6 H); $^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$ 143.3, 138.9, 136.2, 135.3, 134.4, 133.6, 129.7, 129.5, 127.9, 127.3, 58.5, 56.6, 21.5, -3.4.

\[
\text{3-(tert-butyldimethylsilyl)-1-tosyl-2,5-dihydro-1H-pyrrole (1h)}
\]
Yield 86% (colorless oil); $^1$H-NMR (500 MHz, CDCl$_3$) δ 7.71 (d, $J$ = 8.5 Hz, 2 H), 7.31 (d, $J$ = 8.5 Hz, 2 H), 5.78 (t, $J$ = 1.3 Hz, 1 H), 4.20-4.18 (m, 2 H), 4.14-4.12 (m, 2 H), 2.42 (s, 3 H), 0.80 (s, 9 H), 0.01 (s, 6 H; $^{13}$C-NMR (125 MHz, CDCl$_3$) δ 143.3, 138.4, 135.1, 134.4, 129.7, 127.3, 59.4, 56.5, 26.3, 21.5, 16.6, -6.4.

![Structure](image)

$N$-(but-3-en-1-yl)-$N$-(2-(dimethyl(phenyl)silyl)allyl)-4-methylbenzenesulfonamide (2e')

Yield 69% (colorless oil); $^1$H-NMR (500 MHz, CDCl$_3$) δ 7.64 (d, $J$ = 8.0 Hz, 2 H), 7.52-7.50 (m, 2 H), 7.38-7.26 (m, 3 H), 7.26 (d, $J$ = 8.0 Hz, 2 H), 5.85-5.84 (m, 1 H), 5.55-5.47 (m, 2 H), 4.92-4.85 (m, 2 H), 3.83 (s, 2 H), 3.06-3.03 (m, 2 H), 3.41 (s, 3 H), 2.02-1.98 (m, 2 H), 0.43 (s, 6 H); $^{13}$C-NMR (125 MHz, CDCl$_3$) δ 144.5, 143.0, 137.1, 137.0, 134.7, 133.9, 129.6, 129.3, 128.2, 127.9, 127.1, 116.7, 52.3, 47.1, 32.1, 21.5, -3.4.

![Structure](image)

5-(dimethyl(phenyl)silyl)-1-tosyl-1,2,3,6-tetrahydropyridine (2e)

Yield 82% (colorless oil); $^1$H-NMR (500 MHz, CDCl$_3$) δ 7.61 (d, $J$ = 6.0 Hz, 2 H), 7.45-7.43 (m, 2 H), 7.39-7.32 (m, 3 H), 7.27 (d, $J$ = 8.0 Hz, 2 H), 6.03-6.01 (m, 1 H), 3.62-3.61 (m, 2 H), 3.16 (t, $J$ = 6.0 Hz, 2 H), 2.42 (s, 3 H), 2.25-2.22 (m, 2 H), 0.33 (s, 6 H); $^{13}$C-NMR (125 MHz, CDCl$_3$) δ 143.3, 136.7, 135.0, 133.8, 133.7, 133.5, 129.5, 129.2, 127.8, 127.5, 46.4, 42.2, 26.6, 21.4, -3.6.
\[
N-(\text{but-3-en-1-yl})-N-(2-(\text{tert-butyl}d\text{imethyl}silyl)\text{allyl})-4\text{-methylbenzenesulfonamide (2h')}
\]
Yield 76% (colorless oil); \(^{13}\text{C-NMR (125 MHz, CDCl}_3\) \(\delta\) 143.3, 143.0, 137.3, 134.7, 129.6, 127.4, 127.1, 116.9, 53.2, 47.5, 32.7, 26.7, 21.5, 16.9, -6.2.

\[
5-(\text{tert-Butyl}d\text{imethyl}silyl)-1\text{-tosyl-1,2,3,6-tetrahydropyridine (2h)}
\]
Yield 18% (colorless oil); \(^1\text{H-NMR (500 MHz, CDCl}_3\) \(\delta\) 7.67 (d, *J* = 8.5 Hz, 2 H), 7.31 (d, *J* = 8.5 Hz, 2 H), 5.99-5.97 (m, 1 H), 3.63 (dt, *J* = 2.3, 2.3 Hz, 2 H), 3.15 (t, *J* = 5.5 Hz, 2 H), 2.43 (s, 3 H), 2.28-2.24 (m, 2 H), 0.84 (s, 9 H), 0.02 (s, 6 H).

**B. Initial synthesis and RCM of vinylsiloxane**

*Hydrosilylation:* following the literature procedure\(^{197,198}\) to a solution of the alkyne substrate (1 equiv.) in DCM (0.5 M) was added the diethoxymethylsilane (1.1 equiv.). The flask was cooled to 0 °C and catalyst [Cp*Ru(MeCN)_3]PF_6 (5 mol%) was added. The ice bath was immediately removed and the solution was stirred for 30 min. The resulting mixture was concentrated *in vacuo* and the residue was purified by silica gel column chromatography using Hexanes/EtOAc as eluent to give the RCM substrate.
4-methyl-N-(pent-4-en-1-yl)-N-(3-(triethoxysilyl)but-3-en-1-yl)benzenesulfonamide (4a’)

Yield 68% (colorless oil); \(^1\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta 7.69 (d, J = 8.0 \text{ Hz}, 2 \text{ H}), 7.28 (d, J = 8.0 \text{ Hz}, 2 \text{ H}), 5.81-5.73 (m, 2 \text{ H}), 5.67-5.66 (m, 2 \text{ H}), 5.03-4.99 (m, 2 \text{ H}), 4.98-4.96 (m, 2 \text{ H}), 3.83-3.78 (m, 6 \text{ H}), 3.23-3.20 (m, 2 \text{ H}), 3.14 (t, J = 7.6 \text{ Hz}, 2 \text{ H}), 2.41 (s, 3 \text{ H}), 2.37-2.33 (m, 2 \text{ H}), 2.05 (dt, J = 7.0, 7.0 \text{ Hz}, 2 \text{ H}), 1.69-1.63 (m, 2 \text{ H}), 1.23-1.20 (m, 9 \text{ H}); \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)) \(\delta 142.9, 140.2, 137.5, 137.2, 131.7, 129.5, 127.1, 115.2, 58.6, 48.0, 47.9, 35.6, 30.8, 27.7, 21.5, 18.2.

\((E)\)-1-tosyl-6-(triethoxysilyl)-1,2,3,4,7,8-hexahydroazocine (4a)

Yield 71% (colorless oil); \(^1\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta 7.67 (d, J = 8.5 \text{ Hz}, 2 \text{ H}), 7.28 (d, J = 8.5 \text{ Hz}, 2 \text{ H}), 6.37 (t, J = 8.2 \text{ Hz}, 1 \text{ H}), 3.82-3.75 (m, 6 \text{ H}), 3.16 (bs, 2 \text{ H}), 3.04-3.02 (m, 2 \text{ H}), 2.44-2.30 (m, 7 \text{ H}), 1.79-1.75 (m, 2 \text{ H}), 1.21-1.18 (m, 9 \text{ H}).

5-(Triethoxysilyl)hex-5-en-1-yl 2-(pent-4-en-1-yloxy)benzoate (12a’)

53
Yield 72% (colorless oil); IR (neat, cm\(^{-1}\)) 3077, 2974, 2927, 2890, 2736, 1729, 1705, 1641, 1601, 1583, 1492, 1469, 1452, 1390, 1301, 1251, 1165, 1080, 1016, 958; \(^1\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.78-7.76 (m, 1 H), 7.44-7.40 (m, 1 H), 6.97-6.93 (m, 2 H), 5.85 (ddt, \(J = 17.0, 10.5, 6.8\) Hz, 1 H), 5.74-5.73 (m, 1 H), 5.65-5.65 (m, 1 H), 5.08-5.04 (m, 1 H), 4.99 (d, \(J = 10.0\) Hz, 1 H), 4.30 (t, \(J = 6.8\) Hz, 2 H), 4.04 (t, \(J = 6.5\) Hz, 2 H), 3.82 (q, \(J = 6.8\) Hz, 6 H), 2.28 (dt, \(J = 7.2, 7.2\) Hz, 2 H), 2.21 (t, \(J = 7.8\) Hz, 2 H), 1.93 (tt, \(J = 7.0, 7.0\) Hz, 2 H), 1.76 (tt, \(J = 7.2, 7.2\) Hz, 2 H), 1.65-1.59 (m, 2 H), 1.22 (t, \(J = 6.5\) Hz, 9 H); \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)) \(\delta\) 166.6, 158.5, 143.3, 137.7, 133.1, 131.5, 131.5, 129.4, 120.1, 120.0, 115.2, 113.1, 68.0, 64.8, 58.5, 35.6, 30.0, 28.5, 28.3, 25.1, 18.2; HRMS (ESI-TOF) calcd. for C\(_{24}\)H\(_{38}\)O\(_6\)Si [M+Na\(^+\)] 473.23299, found 473.23204.

![Image](image.png)

\((E)-6-(triethoxysilyl)-3,4,7,8,9,10-hexahydrobenzo[b][1,5]dioxacyclotetradecin-12(2H)-one (12a)\)

Yield 92% (pale yellow oil) with optimized reaction conditions; IR (neat, cm\(^{-1}\)) 3076, 2972, 2927, 2735, 1705, 1602, 1582, 1491, 1453, 1387, 1302, 1252, 1166, 1128, 1080, 1025, 996, 958; \(^1\)H-NMR (500 MHz, C\(_6\)D\(_6\)) \(\delta\) 7.79-7.77 (m, 1 H), 7.44-7.41 (m, 1 H), 6.97 (dd, \(J = 7.5, 7.5\) Hz, 1 H), 6.92 (d, \(J = 8.5\) Hz, 1 H), 6.21 (t, \(J = 8.0\) Hz, 1 H), 4.43 (t, \(J = 5.2\) Hz, 2 H), 4.06 (t, \(J = 5.0\) Hz, 2 H), 3.83 (q, \(J = 7.0\) Hz, 6 H), 2.43-2.38 (m, 2 H), 2.23-2.19 (m, 2 H), 1.90-1.85 (m, 2 H), 1.83-1.78 (m, 2 H), 1.71-1.65 (m, 2 H), 1.24 (t, \(J = 6.8\) Hz, 9 H); \(^{13}\)C-NMR (125 MHz, C\(_6\)D\(_6\)) \(\delta\) 168.1, 158.1, 145.2, 134.1, 132.9,
132.8, 122.1, 120.1, 112.1, 67.0, 63.5, 58.6, 30.1, 28.6, 27.7, 26.0, 25.5, 18.6; HRMS (ESI-TOF) calcd. for C_{22}H_{34}O_6Si [M+Na]^+ 445.20169, found 445.20168.

**C. Catalysts screening**

To a round-bottomed flask equipped with magnetic stir bar and armed with a condenser was added substrate 13a’ (1.0 equiv.) in anhydrous dichloromethane (2 mM) under argon. The catalyst (0.2 equiv.) was then added and the reaction was refluxed for 18 hours. The mixture was cooled to room temperature, concentrated under reduced pressure. The conversion was analyzed by crude proton NMR study using CDCl₃ as solvent (Table I-10). Representative NMR spectrum (olefinic proton area) of the RCM reaction of substrate 13a’ with catalyst A was shown in **Figure I-3**. The peak at 6.23 ppm (t) was the resonance of olefin proton within product 13a (the overlap of product peak with one of the styrene olefin proton was corrected by subtracting integration of the other styrene olefin proton (6.42-6.39 ppm) from the integration of 6.26-6.20 ppm). Unreacted starting material, acyclic cross-dimmers, and the styrene derivative share the common moiety of vinylsiloxane which gives two terminal olefin proton peaks at 5.73 and 5.65 ppm. Integration for one of them and the corrected integration of desired product were then used for determination of the conversion of the reaction. After catalyst A was discovered, reaction conditions for RCM of substrate 13a’ were then optimized (see Table I-3 in Chapter I-2-2).
Table I-10. Conversion of the RCM reaction of substrate 13a’ with various catalysts to desired product.

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<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Conversion to product (%)</th>
<th>Entry</th>
<th>Catalyst</th>
<th>Conversion to product (%)</th>
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<tr>
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<tr>
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Figure I-3. Representative crude proton NMR spectrum (olefinic proton area) of RCM reaction for catalysts screening, reaction condition optimization, and catalyst decomposition studies.

Reaction condition: substrate 13a’ with catalyst A, DCM, reflux, 18 hours.

Optimized reaction conditions for RCM of vinyl siloxane substrates: substrate (1 equiv.) was dissolved in anhydrous toluene (or other solvent when indicated) at a concentration of 2 mM under argon. Catalyst A (20 mol%) was added to the solution. High vacuum was applied to the reaction flask for 5 min and charged with argon. This operation cycle was repeated for 5 times. The reaction was then heated up to 35 °C and left for 12 hours. The resulting mixture was concentrated under reduced pressure and the residue was analyzed by 1H NMR or purified by silica gel column chromatography using Hexanes/EtOAc as eluent.
**5-(Triethoxysilyl)hex-5-en-1-y1 2-(hex-5-en-1-yloxy)benzoate (13a')**

Yield 72% (colorless oil); IR (neat, cm\(^{-1}\)) 3076, 2974, 2936, 1729, 1705, 1641, 1601, 1583, 1491, 1452, 1389, 1301, 1249, 1165, 1079, 995, 958; \(^1\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.76 (d, \(J = 8.0\) Hz, 1H), 7.44-7.40 (m, 1 H), 6.96-6.93 (m, 2 H), 5.82 (ddt, \(J = 17.0, 10.5, 6.5\) Hz, 1 H), 5.73-5.73 (m, 1 H), 5.65-5.65 (m, 1 H), 5.05-5.01 (m, 1 H), 4.97 (d, \(J = 10.5\) Hz, 1 H), 4.30 (t, \(J = 6.8\) Hz, 2 H), 4.03 (t, \(J = 6.2\) Hz, 2 H), 3.82 (q, \(J = 6.8\) Hz, 6 H), 2.21 (t, \(J = 7.5\) Hz, 2 H), 2.13 (dt, \(J = 7.2, 7.2\) Hz, 2 H), 1.84 (tt, \(J = 7.1, 7.1\) Hz, 2 H), 1.76 (tt, \(J = 7.1, 7.1\) Hz, 2 H), 1.64-1.57 (m, 4 H), 1.22 (t, \(J = 7.0\) Hz, 9 H); \(^1\)C-NMR (125 MHz, CDCl\(_3\)) \(\delta\) 166.6, 158.5, 143.3, 138.5, 133.1, 131.5, 129.4, 120.9, 119.9, 114.7, 113.0, 68.6, 64.8, 58.5, 35.5, 33.4, 28.6, 28.4, 25.2, 25.1, 18.2; HRMS (ESI-TOF) calcd. for C\(_{25}\)H\(_{40}\)O\(_6\)Si [M+Na]\(^+\) 487.24864, found 487.24889.

**\((E)\)-7-(Triethoxysilyl)-4,5,8,9,10,11-hexahydro-2H-benzo[b][1,5]dioxacyclopentadecin-13(3H)-one (13a)**

Yield 60% (pale yellow oil) with optimized reaction conditions; IR (neat, cm\(^{-1}\)) 2972, 2927, 1700, 1602, 1491, 1453, 1388, 1302, 1250, 1166, 1102, 1078, 1018, 958; \(^1\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.75-7.74 (m, 1 H), 7.42-7.39 (m, 1 H), 6.96 (dd, \(J = 7.5, 7.5\) Hz, 1
H), 6.91 (d, J = 8.5 Hz, 1 H), 6.23 (t, J = 7.5 Hz, 1 H), 4.40 (t, J = 5.5 Hz, 2 H), 4.07 (t, J = 5.0 Hz, 2 H), 3.80 (q, J = 6.8 Hz, 6 H), 2.27-2.21 (m, 4 H), 1.87-1.77 (m, 4 H), 1.68-1.58 (m, 4 H), 1.22 (t, J = 6.8 Hz, 9 H); \(^{13}\)C-NMR (125 MHz, C\(_6\)D\(_6\)) \(\delta\) 167.8, 158.2, 145.0, 134.9, 132.6, 132.2, 122.3, 120.1, 112.4, 68.1, 64.3, 58.6, 29.1, 28.9, 28.7, 27.1, 26.9, 18.5; HRMS (ESI-TOF) calcd. for C\(_{23}\)H\(_{36}\)O\(_6\)Si [M+Na]\(^+\) 459.21734, found 459.21736.

\section*{D. Study of influence of silyl groups}

Different vinyl silane or vinyl siloxane substrates were synthesized following general procedure for hydrosilylation using the respective silanes. The RCM reaction was then performed following the general procedure for RCM.

\begin{center}
\includegraphics[width=0.5\textwidth]{image}
\end{center}

5-(Diethoxy(phenyl)silyl)hex-5-en-1-yl 2-(pent-4-en-1-yloxy)benzoate (12b')

Yield 91% (colorless oil); IR (neat, cm\(^{-1}\)) 3071, 2973, 2940, 2881, 1728, 1704, 1641, 1601, 1583, 1491, 1469, 1452, 1430, 1389, 1301, 1251, 1164, 1119, 1101, 1079, 1016, 952; \(^1\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.76-7.74 (m, 1 H), 7.64-7.62 (m, 2 H), 7.44-7.33 (m, 4 H), 6.96-6.93 (m, 2 H), 5.88-5.79 (m, 2 H), 5.67-5.66 (m, 1 H), 5.06-5.03 (m, 1 H), 4.98 (d, J = 10.0 Hz, 1 H), 4.23 (t, J = 6.5 Hz, 2 H), 4.03 (t, J = 6.5 Hz, 2 H), 3.81 (q, J = 7.0 Hz, 4 H), 2.26 (dt, J = 7.2, 7.2 Hz, 2 H), 2.22 (t, J = 8.0 Hz, 2 H), 1.91 (tt, J = 6.9, 6.9 Hz, 2 H), 1.70 (tt, J = 7.2, 7.2 Hz, 2 H), 1.56 (tt, J = 7.6, 7.6 Hz, 2 H), 1.23 (t, J = 7.2 Hz, 6 H); \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)) \(\delta\) 166.6, 158.4, 145.5, 137.7, 134.6, 133.3, 133.1,
131.5, 130.0, 129.4, 127.7, 120.8, 120.0, 115.2, 113.1, 68.0, 64.8, 58.7, 35.2, 30.0, 28.4, 28.3, 25.1, 18.3; HRMS (ESI-TOF) calcd. for C_{28}H_{38}O_5Si [M+Na]^+ 505.23807, found 505.24127.

RCM reaction of compound 12b' gave rise to an inseparable mixture of product 12b and styrene derivative 12b'-s as well as acyclic dimer and unreacted starting material. The NMR yield was calculated to be 69% based on analysis of crude $^1$H NMR spectrum.

5-(Diethoxy(methyl)silyl)hex-5-en-1-yl 2-(pent-4-en-1-yloxy)benzoate (12c')

Yield 85% (colorless oil); IR (neat, cm$^{-1}$) 3077, 2972, 2943, 2879, 2763, 2735, 1728, 1705, 1641, 1601, 1583, 1491, 1452, 1389, 1301, 1253, 1164, 1130, 1103, 1079, 1016, 951; $^1$H-NMR (500 MHz, CDCl$_3$) δ 7.77 (d, J = 7.0 Hz, 1 H), 7.42 (dd, J = 7.2, 7.2 Hz, 1 H), 6.97-6.93 (m, 2 H), 5.85 (ddt, J = 17.2, 10.2, 7.0 Hz, 1 H), 5.69 (bs, 1 H), 5.57-5.56 (m, 1 H), 5.06 (d, J = 17.5 Hz, 1 H), 4.99 (d, J = 10.0 Hz, 1 H), 4.30 (t, J = 6.5 Hz, 2 H), 4.04 (t, J = 6.5 Hz, 2 H), 3.76 (q, J = 6.8 Hz, 4 H), 2.27 (dt, J = 7.0, 7.0 Hz, 2 H), 2.21 (t, J = 7.5 Hz, 2 H), 1.93 (tt, J = 6.9, 6.9 Hz, 2 H), 1.76 (tt, J = 7.2, 7.2 Hz, 2 H), 1.60 (tt, J = 7.6, 7.6 Hz, 2 H), 1.21 (t, J = 7.0 Hz, 6 H), 0.19 (s, 3 H); $^{13}$C-NMR (125 MHz, CDCl$_3$) δ 166.6, 158.4, 147.0, 137.7, 133.1, 131.5, 127.7, 120.8, 120.0, 115.2, 113.0, 67.9, 64.8,
58.2, 35.1, 30.0, 28.5, 28.3, 25.1, 18.3, -4.6; HRMS (ESI-TOF) calcd. for C$_{23}$H$_{36}$O$_5$Si [M+H]$^+$ 421.24048, found 421.24067.

(E)-6-(Diethoxy(methyl)silyl)-3,4,7,8,9,10-
hexahydrobenzo[b][1,5]dioxacyclotetradecin-12(2H)-one (12c)

Yield 95% (pale yellow oil); IR (neat, cm$^{-1}$) 3076, 2970, 2873, 1705, 1602, 1582, 1491, 1453, 1386, 1356, 1303, 1253, 1165, 1129, 1103, 1079, 1051, 1024, 995; $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 7.79-7.77 (m, 1 H), 7.44-7.41 (m, 1 H), 6.97 (dd, $J = 7.2$, 7.2 Hz, 1 H), 6.92 (d, $J = 8.0$ Hz, 1 H), 6.11 (t, $J = 8.0$ Hz, 1 H), 4.43 (t, $J = 5.2$ Hz, 2 H), 4.06 (t, $J = 5.0$ Hz, 2 H), 3.77 (q, $J = 7.0$ Hz, 4 H), 2.40 (dt, $J = 6.0$, 6.0 Hz, 2 H), 2.21-2.18 (m, 2 H), 1.90-1.84 (m, 2 H), 1.83-1.78 (m, 2H), 1.69-1.62 (m, 2 H), 1.23 (t, $J = 7.2$ Hz, 6 H), 0.19 (s, 3 H); $^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$ 168.5, 157.6, 143.5, 136.8, 133.1, 132.2, 121.1, 120.1, 112.0, 67.4, 63.8, 58.2, 29.9, 28.4, 26.9, 25.7, 25.3, 18.3, -4.9; HRMS (ESI-TOF) calcd. for C$_{21}$H$_{32}$O$_5$Si [M+H]$^+$ 393.20918, found 393.20943.

Hydrosilylation reaction gave rise to a 14.4:1 mixture of two regioisomers with the desired regioisomer 12d$'$ being the major one. Yield 84% (colorless oil).
(E)-6-(Ethoxydimethylsilyl)-3,4,7,8,9,10-hexahydrobenzo[b][1,5]dioxacyclotetradecin-12(2H)-one (12d)

Yield 81% (pale yellow oil); IR (neat, cm⁻¹) 2959, 2926, 2865, 1704, 1602, 1491, 1453, 1386, 1303, 1250, 1164, 1131, 1102, 1080, 1049, 1023, 993; ¹H-NMR (500 MHz, CDCl₃) δ 7.79-7.77 (m, 1 H), 7.44-7.41 (m, 1 H), 6.97 (dd, J = 7.5, 7.5 Hz, 1 H), 6.92 (d, J = 8.5 Hz, 1 H), 5.97 (t, J = 8.0 Hz, 1 H), 4.43 (t, J = 5.2 Hz, 2 H), 4.06 (t, J = 5.0 Hz, 2 H), 3.65 (q, J = 7.0 Hz, 2 H), 2.42-2.36 (m, 2 H), 2.22-2.18 (m, 2 H), 1.89-1.84 (m, 2 H), 1.83-1.78 (m, 2 H), 1.67-1.61 (m, 2 H), 1.19 (t, J = 7.0 Hz, 3 H), 0.19 (s, 6 H); ¹³C-NMR (125 MHz, CDCl₃) δ 168.5, 157.7, 141.7, 139.8, 133.1, 132.3, 121.1, 120.1, 112.1, 67.5, 63.8, 58.4, 30.1, 28.5, 27.2, 25.8, 25.5, 18.5, -2.4; HRMS (ESI-TOF) calcd. for C₂₀H₃₀O₄Si [M+Na]⁺ 385.18056, found 385.19580.

5-(Dimethyl(phenyl)silyl)hex-5-en-1-yl 2-(pent-4-en-1-yloxy)benzoate (12e’)

Yield 93% (colorless oil); IR (neat, cm⁻¹) 3069, 2949, 1728, 1641, 1601, 1491, 1452, 1430, 1387, 1302, 1251, 1164, 1133, 1078, 1050, 1015; ¹H-NMR (500 MHz, CDCl₃) δ 7.75-7.73 (m, 1 H), 7.51-7.49 (m, 2 H), 7.44-7.40 (m, 1 H), 7.34-7.32 (m, 3 H), 6.97-6.93 (m, 2 H), 5.84 (ddt, J = 17.0, 10.0, 6.8 Hz, 1 H), 5.70-5.69 (m, 1 H), 5.42-5.42 (m, 1 H),
5.06-5.03 (m, 1 H), 4.99 (d, J = 10.5 Hz, 1 H), 4.21 (t, J = 7.0 Hz, 2 H), 4.03 (t, J = 6.5 Hz, 2 H), 2.26 (dt, J = 7.2, 7.2 Hz, 2 H), 2.17 (t, J = 7.5 Hz, 2 H), 1.91 (tt, J = 6.9, 6.9 Hz, 2 H), 1.68 (tt, J = 7.1, 7.1 Hz, 2 H), 1.52-1.46 (m, 2 H), 0.36 (s, 6 H); $^{13}$C-NMR (125 MHz, CDCl$_3$) δ 166.6, 158.4, 149.8, 138.2, 137.7, 133.8, 133.1, 131.5, 128.9, 127.7, 126.0, 120.8, 120.0, 115.2, 113.0, 67.9, 64.7, 35.4, 30.0, 28.4, 28.3, 25.1, -3.0; HRMS (ESI-TOF) calcd. for C$_{26}$H$_{34}$O$_3$Si [M+H]$^+$ 423.23500, found 423.23601.

(E)-6-(Dimethyl(phenyl)silyl)-3,4,7,8,9,10-hexahydrobenzo[b][1,5]dioxacyclotetradecin-12(2H)-one (12e)

RCM reaction of the previous compound (18e’) gave rise to an inseparable mixture of product and styrene derivative together with unreacted starting material. The NMR yield was calculated to be 71% based on analysis of crude $^1$H NMR spectrum. After the first column chromatography to get rid of the unreacted starting materials, the mixture of product and styrene derivative was subjected to HPLC separation that gave rise to 25 mg pure product (54% yield) as pale yellow oil. HPLC conditions: compound was dissolved in a 1 ml volume of DMSO. The separation was executed on an XBridge 19x100 mm 5 μm columns at a flow rate of 44 ml/min. Aqueous mobile phase A consisted of 0.1% formic acid in water, and organic mobile phase B was 0.1% formic acid in acetonitrile. Purification fractions were immediately frozen at -50°C and lyophilized for 24hrs using the Genesis Virtis. After lyophilization the compound was transferred to a preweighed vial using dichloromethane. IR (neat, cm$^{-1}$) 3067, 2954, 2860, 1703, 1602,
1490, 1452, 1429, 1383, 1302, 1250, 1165, 1131, 1050, 1023, 992; $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 7.78-7.76 (m, 1 H), 7.53-7.51 (m, 2 H), 7.44-7.40 (m, 1 H), 7.36-7.33 (m, 3 H), 6.97 (dd, $J = 7.5$, 7.5 Hz, 1 H), 6.92 (d, $J = 7.5$ Hz, 1 H), 5.91 (t, $J = 8.0$ Hz, 1 H), 4.38 (t, $J = 5.2$ Hz, 2 H), 4.06 (t, $J = 5.0$ Hz, 2 H), 2.42-2.37 (m, 2 H), 2.18-2.15 (m, 2 H), 1.89-1.84 (m, 2 H), 1.73-1.68 (m, 2 H), 1.59-1.52 (m, 2 H), 0.35 (s, 6 H); $^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$ 168.5, 157.7, 141.7, 139.4, 138.8, 134.0, 133.1, 132.2, 128.8, 127.7, 121.1, 120.0, 112.1, 67.5, 63.8, 30.1, 28.4, 28.2, 25.9, 25.7, -3.1; HRMS (ESI-TOF) calcd. for C$_{24}$H$_{30}$O$_3$Si [M+Na]$^+$ 417.18564, found 417.18593.

![Structure Diagram]

5-(Triethylsilyl)hex-5-en-1-yl 2-(pent-4-en-1-yloxy)benzoate (12f')

Yield 38% (colorless oil); IR (neat, cm$^{-1}$) 3077, 3048, 2951, 2911, 2875, 1729, 1704, 1641, 1601, 1582, 1491, 1453, 1416, 1385, 1301, 1250, 1164, 1133, 1078, 1050, 1013; $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 7.78-7.76 (m, 1 H), 7.44-7.41 (m, 1 H), 6.97-6.94 (m, 2 H), 5.85 (ddt, $J = 17.0$, 10.0, 6.8 Hz, 1 H), 5.65-5.64 (m, 1 H), 5.32-5.31 (m, 1 H), 5.08-5.04 (m, 1 H), 4.99 (d, $J = 10.0$ Hz, 1 H), 4.30 (t, $J = 6.5$ Hz, 2 H), 4.04 (t, $J = 6.5$ Hz, 2 H), 2.27 (dt, $J = 7.2$, 7.2 Hz, 2 H), 2.14 (t, $J = 7.8$ Hz, 2 H), 1.93 (tt, $J = 7.0$, 7.0 Hz, 2 H), 1.76 (tt, $J = 7.1$, 7.1 Hz, 2 H), 1.60-1.54 (m, 2 H), 0.92 (t, $J = 8.0$ Hz, 6 H), 0.60 (q, $J = 8.0$ Hz, 9 H); $^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$ 166.6, 158.4, 148.5, 137.7, 133.1, 131.5, 125.3, 120.8, 120.0, 115.2, 113.1, 68.0, 64.8, 35.7, 30.0, 28.6, 28.3, 25.1, 21.7, 3.9; HRMS (ESI-TOF) calcd. for C$_{24}$H$_{38}$O$_3$Si [M+H]$^+$ 403.26630, found 403.26630.
RCM reaction of compound \(12f^*\) gave rise to an inseparable mixture of product \(12f\) and styrene derivative. Unreacted starting material and acyclic dimer were also observed. The NMR yield was calculated to be 10% based on analysis of crude \(^1\)H NMR spectrum.

\[
\begin{align*}
\text{5-(Diethoxy(phenyl)silyl)hex-5-en-1-yl 2-(hex-5-en-1-yloxy)benzoate (13b')} \\
\text{Yield 76% (colorless oil); IR (neat, cm}^{-1}\text{) 3071, 2973, 2938, 1729, 1704, 1640, 1601, 1583, 1491, 1470, 1453, 1430, 1389, 1301, 1250, 1164, 1119, 1102, 1079, 997, 952; }^{1}\text{H-NMR (500 MHz, CDCl}_3\text{) }\delta \text{ 7.75-7.73 (m, 1 H), 7.64-7.62 (m, 2 H), 7.44-7.33 (m, 4 H), 6.96-6.93 (m, 2 H), 5.85-5.77 (m, 2 H), 5.67-5.66 (m, 1 H), 5.04-5.00 (m, 1 H), 4.96 (d, } J = 10.0 \text{ Hz, 1 H), 4.22 (t, } J = 7.0 \text{ Hz, 2 H), 4.02 (t, } J = 6.2 \text{ Hz, 2 H), 3.81 (q, } J = 7.0 \text{ Hz, 4 H), 2.22 (t, } J = 7.8 \text{ Hz, 2 H), 2.11 (dt, } J = 5.5, 5.5 \text{ Hz, 2 H), 1.83 (tt, } J = 7.0, 7.0 \text{ Hz, 2 H), 1.70 (tt, } J = 7.2, 7.2 \text{ Hz, 2 H), 1.62-1.52 (m, 4 H), 1.23 (t, } J = 7.2 \text{ Hz, 6 H); }^{13}\text{C-NMR (125 MHz, CDCl}_3\text{) }\delta \text{ 166.6, 158.5, 145.5, 138.5, 134.6, 133.3, 133.1, 131.5, 130.0, 129.4, 127.7, 120.9, 119.9, 114.7, 113.0, 68.6, 64.8, 58.7, 35.2, 33.4, 28.6, 28.4, 25.2, 25.1, 18.3; HRMS (ESI-TOF) calcd. for C}_{29}H_{40}O_5Si [M+Na]^+ 519.25372, found 519.25541.}
\end{align*}
\]
RCM reaction of compound 13b’ gave rise to an inseparable mixture of product 13b and styrene derivative 13b'-s as well as acyclic dimers and unreacted starting material. The NMR yield was calculated to be 35% based on analysis of crude ¹H NMR spectrum.

5-(Diethoxy(methyl)silyl)hex-5-en-1-yl 2-(hex-5-en-1-yloxy)benzoate (13c’)

Yield 79% (colorless oil); IR (neat, cm⁻¹) 3076, 2972, 2940, 1729, 1705, 1641, 1601, 1491, 1452, 1389, 1301, 1252, 1164, 1103, 1079, 996, 951; ¹H-NMR (500 MHz, CDCl₃) δ 7.78-7.76 (m, 1 H), 7.44-7.40 (m, 1 H), 6.96-6.93 (m, 2 H), 5.82 (ddt, J = 17.0, 10.5, 6.5 Hz, 1 H), 5.57-5.69 (m, 1 H), 5.05-5.01 (m, 1 H), 4.30 (t, J = 6.8 Hz, 2 H), 4.03 (t, J = 6.5 Hz, 2 H), 3.76 (q, J = 7.0 Hz, 4 H), 2.21 (t, J = 7.5 Hz, 2 H), 2.13 (dt, J = 7.2, 7.2 Hz, 2 H), 1.84 (tt, J = 7.1, 7.1 Hz, 2 H), 1.76 (tt, J = 7.2, 7.2 Hz, 2 H), 1.63-1.57 (m, 4 H), 1.21 (t, J = 7.0 Hz, 6 H), 0.19 (s, 3 H); ¹³C-NMR (125 MHz, CDCl₃) δ 166.6, 158.5, 147.1, 138.5, 133.1, 131.5, 127.6, 120.8, 119.9, 114.7, 113.0, 68.6, 64.8, 58.2, 35.1, 33.4, 28.6, 28.5, 25.2, 25.1, 18.3, -4.6; HRMS (ESI-TOF) calcd. for C₂₄H₃₈O₃Si [M+Na]⁺ 457.23807, found 457.24010.
(E)-7-(Diethoxy(methyl)silyl)-4,5,8,9,10,11-hexahydro-2H-
benzo[b][1,5]dioxacyclopentadecin-13(3H)-one (13c)

Yield 76% (pale yellow oil); IR (neat, cm\(^{-1}\)) 2969, 2928, 1700, 1602, 1491, 1452, 1387, 1302, 1251, 1165, 1130, 1078, 1016, 952; \(^1\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.76-7.74 (m, 1 H), 7.42-7.39 (m, 1 H), 6.96 (dd, \(J = 7.5, 7.5\) Hz, 1 H), 6.92 (d, \(J = 7.5\) Hz, 1 H), 6.13 (t, \(J = 7.5\) Hz, 1 H), 4.40 (t, \(J = 5.5\) Hz, 2 H), 4.08 (t, \(J = 5.0\) Hz, 2 H), 3.74 (q, \(J = 6.8\) Hz, 4 H), 2.25-2.21 (m, 4 H), 1.87-1.76 (m, 4 H), 1.68-1.56 (m, 4 H), 1.21 (t, \(J = 6.8\) Hz, 6 H), 0.17 (s, 3 H); \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)) \(\delta\) 168.2, 157.7, 143.5, 137.5, 132.9, 131.7, 121.2, 120.0, 112.3, 68.3, 64.6, 58.1, 28.9, 28.8, 28.6, 28.0, 26.9, 26.7, 18.3, -4.6; HRMS (ESI-TOF) calcd. for C\(_{22}\)H\(_{34}\)O\(_5\)Si [M+Na]\(^+\) 429.20677, found 429.20692.

Hydrosilylation reaction gave rise to a 14.3:1 mixture of two regioisomers with the desired regio isomer \(19d''\) being the major one. Yield 89% (colorless oil).
RCM reaction of the mixture 13d' and 13d'' gave rise to an inseparable mixture of product 13d and styrene derivative as well as acyclic dimer and unreacted starting material. The NMR yield was calculated to be 62% based on analysis of crude $^1$H NMR spectrum.

5-(Dimethyl(phenyl)silyl)hex-5-en-1-yl 2-(hex-5-en-1-yloxy)benzoate (13e')

Yield 74% (colorless oil); IR (neat, cm$^{-1}$) 3069, 2945, 1728, 1703, 1641, 1601, 1491, 1452, 1430, 1388, 1301, 1250, 1164, 1133, 1077, 1049, 996; $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 7.75-7.73 (m, 1 H), 7.51-7.49 (m, 2 H), 7.44-7.40 (m, 1 H), 7.34-7.31 (m, 3 H), 6.96-6.93 (m, 2 H), 5.81 (ddt, $J$ = 16.8, 10.2, 6.5 Hz, 1 H), 5.70-5.69 (m, 1 H), 5.43-5.42 (m, 1 H), 5.04-5.00 (m, 1 H), 4.96 (d, $J$ = 9.5 Hz, 1 H), 4.21 (t, $J$ = 6.5 Hz, 2 H), 4.02 (t, $J$ = 6.2 Hz, 2 H), 2.17 (t, $J$ = 7.8 Hz, 2 H), 2.11 (dt, $J$ = 7.2, 7.2 Hz, 2 H), 1.83 (tt, $J$ = 7.0, 7.0 Hz, 2 H), 1.67 (tt, $J$ = 7.0, 7.0 Hz, 2 H), 1.58 (tt, $J$ = 7.5, 7.5 Hz, 2 H), 1.52-1.46 (m, 2 H), 0.37 (s, 6 H); $^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$ 166.6, 158.5, 149.9, 138.5, 138.2, 133.8, 133.1, 131.5, 128.9, 127.7, 126.0, 120.8, 119.9, 114.7, 113.0, 68.6, 64.7, 35.4, 33.4, 28.6, 28.4, 25.2, 25.1, -3.0; HRMS (ESI-TOF) calcd. for C$_{27}$H$_{36}$O$_3$Si [M+H]$^+$ 437.25065, found 437.25057.
(E)-7-(dimethyl(phenyl)silyl)-4,5,8,9,10,11-hexahydro-2H-
benzo[b][1,5]dioxacyclopentadecin-13(3H)-one (13e)

Yield 32% (pale yellow oil); IR (neat, cm<sup>-1</sup>) 3067, 2952, 2859, 1698, 1601, 1490, 1429, 1383, 1302, 1249, 1165, 1132, 1108, 1049, 1015, 963; <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 7.77-7.75 (m, 1 H), 7.51-7.49 (m, 2 H), 7.43-7.39 (m, 1 H), 7.34-7.33 (m, 3 H), 6.95 (dd, <i>J</i> = 7.8, 7.8 Hz, 1 H), 6.92 (d, <i>J</i> = 9.0 Hz, 1 H), 5.94 (t, <i>J</i> = 7.2 Hz, 1 H), 4.34 (t, <i>J</i> = 5.5 Hz, 2 H), 4.08 (t, <i>J</i> = 5.2 Hz, 2 H), 2.25-2.18 (m, 4 H), 1.87-1.82 (m, 2 H), 1.70-1.61 (m, 4 H), 1.46 (tt, <i>J</i> = 7.9 Hz, 2 H), 0.34 (s, 6 H); <sup>13</sup>C-NMR (125 MHz, C<sub>6</sub>D<sub>6</sub>) δ 168.2, 157.7, 142.2, 139.8, 139.0, 134.0, 133.0, 131.8, 128.8, 127.6, 121.1, 120.0, 112.3, 68.3, 64.6, 29.0, 28.9, 28.9, 28.8, 27.0, 27.0, -2.6; HRMS (ESI-TOF) calcd. for C<sub>25</sub>H<sub>32</sub>O<sub>3</sub>Si [M+Na]<sup>+</sup> 431.20129, found 431.20247.

5-(Triethylsilyl)hex-5-en-1-yl 2-(hex-5-en-1-yloxy)benzoate (13f’)

Yield 56% (colorless oil); IR (neat, cm<sup>-1</sup>) 3076, 3047, 2951, 2911, 2874, 1730, 1704, 1641, 1601, 1583, 1491, 1453, 1416, 1385, 1301, 1249, 1164, 1132, 1077, 1049, 1017, 959; <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 7.78-7.76 (m, 1 H), 7.44-7.41 (m, 1 H), 6.97-6.94 (m, 2 H), 5.82 (ddt, <i>J</i> = 17.0, 10.0, 6.8 Hz, 1 H), 5.65-5.64 (m, 1 H), 5.32-5.31 (m, 1 H), 5.05-5.01 (m, 1 H), 4.98-4.96 (m, 1 H), 4.30 (t, <i>J</i> = 6.8 Hz, 2 H), 4.03 (t, <i>J</i> = 6.8 Hz, 2 H), 2.16-2.11 (m, 4 H), 1.85 (tt, <i>J</i> = 7.0, 7.0 Hz, 2 H), 1.76 (tt, <i>J</i> = 7.0, 7.0 Hz, 2 H), 1.63-1.54 (m, 4 H), 0.92 (t, <i>J</i> = 8.0 Hz, 6 H), 0.60 (q, <i>J</i> = 8.0 Hz, 9 H); <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>) δ 166.7, 158.5, 148.6, 138.5, 133.1, 131.5, 125.3, 120.8, 120.0, 114.7, 113.1,
68.6, 64.8, 35.7, 33.4, 28.6, 28.6, 25.2, 25.1, 7.3, 2.9; HRMS (ESI-TOF) calcd. for C\textsubscript{25}H\textsubscript{40}O\textsubscript{3}Si [M+Na]\textsuperscript{+} 439.26389, found 439.26459.

RCM reaction of compound 13f' gave rise to less than 2% product based on analysis of crude \textsuperscript{1}H NMR spectrum. Styrene derivative 13f'-s, unreacted starting material and acyclic dimer were observed.

**E. RCM of various vinylsiloxane substrates and protodesilylation of the alkenyl siloxane products**

The RCM reactions were performed under optimized reaction conditions (see before).

*Protodesilylation:* adapted from the literature procedure\textsuperscript{165} the alkenyl siloxane product (1 equiv.) from the RCM reaction was dissolved in a anhydrous THF to a final concentration of 0.25 M. AgF (0.5 equiv.) was added to the solution immediately followed by acetic acid (1.5 equiv.) and TBAF (2.5 equiv., 1 M solution in THF). The reaction was kept in dark and stirred for 2 hours. The resulting mixture was filtered with celite, concentrated in vacuo and the residue was purified by silica gel column chromatography using Hexanes/EtOAc as eluent.
N-(3-(Diethoxy(methyl)silyl)but-3-enyl)-4-methyl-N-(pent-4-enyl)benzenesulfonamide (4c’)

Yield 70% (colorless oil); IR (neat, cm\(^{-1}\)) 3051, 2974, 2926, 2878, 1641, 1599, 1494, 1444, 1390, 1342, 1206, 1258, 1159, 1103, 1079, 955; \(^{1}\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.70 (d, \(J = 7.8\) Hz, 2 H), 7.28 (d, \(J = 7.8\) Hz, 2 H), 5.77 (ddt, \(J = 17.2, 10.2, 6.5\) Hz, 1 H), 5.70 (d, \(J = 1.2\) Hz, 1 H), 5.58 (d, \(J = 1.2\) Hz, 1 H), 5.01 (d, \(J = 17.2\) Hz, 1 H), 4.97 (d, \(J = 10.2\) Hz, 1 H), 3.74 (q, \(J = 7.0\) Hz, 4 H), 3.22-3.19 (m, 2 H), 3.14 (t, \(J = 7.8\) Hz, 2 H), 2.41 (s, 3 H), 2.35 (t, \(J = 8.0\) Hz, 2 H), 2.06 (dt, \(J = 7.0, 7.0\) Hz, 2 H), 1.69-1.63 (m, 2 H), 1.20 (t, \(J = 7.0\) Hz, 6 H), 0.18 (s, 3 H); \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)) \(\delta\) 144.1, 142.9, 137.5, 137.2, 130.0, 129.5, 127.1, 115.2, 58.3, 48.0, 47.8, 35.1, 30.8, 27.7, 21.4, 18.3, -4.9; HRMS (ESI-TOF) calcd. for C\(_{21}\)H\(_{35}\)NO\(_4\)SSi [M+Na]\(^{+}\) 448.19483, found 448.19573.

\(\text{(E)}\)-6-(Diethoxy(methyl)silyl)-1-tosyl-1,2,3,4,7,8-hexahydroazocine (4c)

Yield 75% (pale yellow oil); IR (neat, cm\(^{-1}\)) 2972, 2926, 1615, 1455, 1389, 1338, 1292, 1257, 1158, 1079, 1050, 1017, 995; \(^{1}\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.68 (d, \(J = 8.2\) Hz, 2 H), 7.28 (d, \(J = 8.2\) Hz, 2 H), 6.28 (t, \(J = 8.2\) Hz, 1 H), 3.72 (q, \(J = 7.2\) Hz, 4 H), 3.15 (bs, 2 H), 3.02 (t, \(J = 5.5\) Hz, 2 H), 2.44 (t, \(J = 5.0\) Hz, 2 H), 2.41 (s, 3 H), 2.32 (dt, \(J = 6.8, 6.8\) Hz, 2 H), 1.79-1.74 (m, 2 H), 1.19 (t, \(J = 7.0\) Hz, 6 H), 0.15 (s, 3 H); \(^{13}\)C-NMR (125
MHz, CDCl$_3$) δ 143.8, 142.8, 137.0, 137.0, 129.6, 126.8, 58.2, 50.8, 48.2, 29.2, 29.1, 24.8, 21.4, 18.3, -4.9; HRMS (ESI-TOF) calcd. for C$_{19}$H$_{31}$NO$_4$SSi [M+H]$^+$ 398.18159, found 398.27160.

(Z)-1-tosyl-1,2,3,4,7,8-hexahydroazocine (33-Z)

Yield 72% (colorless oil); IR (neat, cm$^{-1}$) 3018, 2933, 2858, 1598, 1494, 1456, 1369, 1333, 1304, 1289, 1157, 1112, 1091, 1060, 1038, 991; $^1$H-NMR (500 MHz, CDCl$_3$) δ 7.67 (d, $J = 8.5$ Hz, 2 H), 7.27 (d, $J = 8.5$ Hz, 2 H), 5.74-5.66 (m, 2 H), 3.14 (t, $J = 5.0$ Hz, 2 H), 3.08 (t, $J = 5.5$ Hz, 2 H), 2.40 (s, 3 H), 2.31-2.28 (m, 2 H), 2.22 (dt, $J = 6.9$, 6.9 Hz, 2 H), 1.76-1.72 (m, 2 H); $^{13}$C-NMR (125 MHz, CDCl$_3$) δ 142.9, 136.9, 131.3, 129.5, 128.2, 126.8, 50.8, 48.2, 29.4, 28.1, 23.3, 21.4; HRMS (ESI-TOF) calcd. for C$_{14}$H$_{19}$NO$_2$S [M+H]$^+$ 266.12093, found 266.12097.

Diethoxy(methyl)(3-((1S,2S)-2-(pent-4-enyloxy)cyclohexyloxy)prop-1-en-2-yl)silane

and its enantiomer (15’)

Yield 62% (colorless oil); IR (neat, cm$^{-1}$) 3077, 2974, 2934, 2865, 1641, 1449, 1390, 1366, 1295, 1257, 1164, 1104, 1083, 992, 951; $^1$H-NMR (500 MHz, CDCl$_3$) δ 6.00-5.98 (m, 1 H), 5.82 (ddddd, $J = 17.0$, 10.0, 6.5, 6.5 Hz, 1 H), 5.64-5.63 (m, 1 H), 5.03-4.99 (m, 1 H), 4.96-4.93 (m, 1 H), 4.24-4.23 (m, 2 H), 3.77 (q, $J = 7.0$ Hz, 4 H), 3.59-3.50 (m, 2
H), 3.26-3.18 (m, 2 H), 2.14-2.10 (m, 2 H), 1.97-1.94 (m, 2 H), 1.68-1.62 (m, 4 H), 1.35-1.19 (m, 10 H), 0.22 (s, 3 H); $^{13}$C-NMR (125 MHz, CDCl$_3$) δ 144.8, 138.5, 126.9, 114.5, 81.1, 80.6, 72.4, 69.1, 58.3, 30.4, 29.8, 29.8, 29.5, 23.3, 23.3, 18.3, -4.3; HRMS (ESI-TOF) calcd. for C$_{19}$H$_{36}$O$_4$Si [M+Na]$^+$ 379.22751, found 379.22440.

((8a$S$,12a$S$,E)-2,5,6,7,8a,9,10,11,12,12a-Decahydrobenzo[b][1,4]dioxecin-3-yl)diethoxy(methyl)silane and its enantiomer (15)

Yield 87% (pale yellow oil); IR (neat, cm$^{-1}$) 2972, 2932, 2862, 1615, 1451, 1390, 1364, 1256, 1165, 1113, 1082, 1009, 952; $^1$H-NMR (500 MHz, CDCl$_3$) δ 6.22 (dd, $J$ = 10.2, 6.8 Hz, 1 H), 4.33 (d, $J$ = 10.5 Hz, 1 H), 4.26 (d, $J$ = 10.5 Hz, 1 H), 3.81-3.76 (m, 4 H), 3.72-3.68 (m, 1 H), 3.62-3.57 (m, 1 H), 3.22-3.17 (m, 1 H), 3.02-2.97 (m, 1 H), 2.68-2.60 (m, 1 H), 2.18-2.12 (m, 1 H), 2.00-1.98 (m, 1 H), 1.94-1.92 (m, 1 H), 1.90-1.82 (m, 1 H), 1.66-1.65 (m, 2 H), 1.54-1.48 (m, 1 H), 1.26-1.12 (m, 10 H), 0.21 (s, 3 H); $^{13}$C-NMR (125 MHz, CDCl$_3$) δ 146.8, 136.6, 83.2, 83.1, 67.6, 66.7, 58.3, 31.8, 28.6, 25.1, 24.7, 24.5, 18.3, -4.4; HRMS (ESI-TOF) calcd. for C$_{17}$H$_{32}$O$_4$Si [M+Na]$^+$ 351.19621, found 351.19793.
(8aS,12aS,Z)-2,3,4,7,8a,9,10,11,12,12a-decahydrobenzo[b][1,4]dioxecine and its enantiomer (34-Z)

Yield 86% (colorless oil); IR (neat, cm⁻¹) 3012, 2930, 2858, 1451, 1360, 1315, 1239, 1206, 1117, 1086, 1051, 1026, 970; ¹H-NMR (500 MHz, CDCl₃) δ 5.79 (ddd, J = 10.0, 10.0, 5.0 Hz, 1 H), 5.55 (ddd, J = 10.7, 10.7, 6.5 Hz, 1 H), 4.31 (dd, J = 10.5, 10.5 Hz, 1 H), 4.19 (dd, J = 10.7, 5.2 Hz, 1 H), 3.70-3.67 (m, 1 H), 3.53-3.49 (m, 1 H), 3.20-3.15 (m, 1 H), 2.96-2.92 (m, 1 H), 2.65-2.59 (m, 1 H), 1.94-1.80 (m, 4 H), 1.64-1.63 (m, 2 H), 1.43-1.37 (m, 1 H), 1.22-1.10 (m, 4 H); ¹³C-NMR (125 MHz, CDCl₃) δ 131.7, 128.8, 84.7, 83.2, 67.3, 66.9, 32.2, 31.6, 28.1, 24.6, 24.5, 22.6; HRMS (ESI-TOF) calcd. for C₁₂H₂₀O₂ [M+H]⁺ 197.15361, found 197.15343.

![Image](image_url)

Diethoxy(3-((1S,2S)-2-(hex-5-enyloxy)cyclohexyloxy)prop-1-en-2-yl)(methyl)silane and its enantiomer (16’)

Yield 64% (colorless oil); IR (neat, cm⁻¹) 3076, 2974, 2934, 2863, 1641, 1451, 1390, 1366, 1295, 1257, 1164, 1104, 1083, 993, 951; ¹H-NMR (500 MHz, CDCl₃) δ 5.99-5.98 (m, 1 H), 5.80 (dddd, J = 17.0, 10.5, 7.0, 7.0 Hz, 1 H), 5.64-5.62 (m, 1 H), 5.01-4.98 (m, 1 H), 4.94-4.92 (m, 1 H), 4.23-4.23 (m, 2 H), 3.77 (q, J = 7.0 Hz, 4 H), 3.58-3.49 (m, 2 H), 3.25-3.18 (m, 2 H), 2.08-2.04 (m, 2 H), 1.97-1.93 (m, 2 H), 1.65-1.62 (m, 2 H), 1.60-1.54 (m, 2 H), 1.48-1.42 (m, 2 H), 1.35-1.19 (m, 10 H), 0.22 (s, 3 H); ¹³C-NMR (125 MHz, CDCl₃) δ 144.8, 138.8, 126.9, 114.4, 81.1, 80.6, 72.4, 69.6, 58.3, 33.6, 29.8, 29.8,
25.6, 23.3, 23.3, 18.3, -4.3; HRMS (ESI-TOF) calcd. for C_{20}H_{38}O_{4}Si \ [M+Na]^+ 393.24316, found 393.24372.

\((9aS,13aS,E)-5,6,7,8,9a,10,11,12,13,13a-\text{Decahydro-2H-benzo}[b][1,4]\text{-dioxacycloundecin-3-yl} \text{diethoxy(methyl)silane and its enantiomer (16)}\)

Yield 36% (pale yellow oil); IR (neat, cm\(^{-1}\)) 2971, 2929, 2860, 1618, 1450, 1389, 1371, 1255, 1191, 1165, 1104, 1044, 1003, 951; \(^1\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta\) 6.23 (dd, \(J = 10.0, 6.0\) Hz, 1 H), 4.24 (d, \(J = 10.2\) Hz, 1 H), 4.14 (d, \(J = 10.2\) Hz, 1 H), 3.85-3.82 (m, 1 H), 3.77 (q, \(J = 7.0\) Hz, 4 H), 3.54-3.51 (m, 1 H), 3.14-3.09 (m, 1 H), 3.00-2.97 (m, 1 H), 2.66-2.58 (m, 1 H), 2.24-2.18 (m, 1 H), 2.10-2.08 (m, 1 H), 2.00-1.98 (m, 1 H), 1.75-1.66 (m, 4 H), 1.59-1.52 (m, 1 H), 1.44-1.39 (m, 1 H), 1.23-1.08 (m, 10 H), 0.19 (s, 3 H); \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)) \(\delta\) 149.7, 133.4, 84.1, 82.2, 71.9, 66.2, 58.2, 31.5, 31.1, 28.4, 27.2, 27.0, 24.5, 24.3, 18.3, -4.6; HRMS (ESI-TOF) calcd. for C\(_{18}\)H\(_{34}\)O\(_4\)Si \([M+Na]^+\) 365.21186, found 365.21302.

\((9aS,13aS,Z)-3,4,5,8,9a,10,11,12,13,13a-\text{Decahydro-2H-benzo}[b][1,4]\text{-dioxacycloundecine and its enantiomer (35-Z)}\)
Yield 90% (colorless oil); IR (neat, cm⁻¹) 3012, 2930, 2858, 1450, 1370, 1312, 1243, 1188, 1130, 1102, 999; ¹H-NMR (500 MHz, CDCl₃) δ 5.65 (ddd, J = 9.5, 9.5, 5.0 Hz, 1 H), 5.56 (ddd, J = 10.0, 10.0, 5.0 Hz, 1 H), 4.28 (dd, J = 10.0, 10.0 Hz, 1 H), 4.06 (dd, J = 10.0, 5.0 Hz, 1 H), 3.70 (dd, J = 10.0, 8.0 Hz, 1 H), 3.47 (dd, J = 11.5, 6.5 Hz, 1 H), 3.14 (ddd, J = 9.0, 9.0, 5.0 Hz, 1 H), 2.98 (ddd, J = 9.5, 9.5, 5.0 Hz, 1 H), 2.63-2.56 (m, 1 H), 2.04-2.00 (m, 3 H), 1.73-1.64 (m, 4 H), 1.51-1.45 (m, 1 H), 1.42-1.37 (m, 1 H), 1.19-1.07 (m, 4 H); ¹³C-NMR (125 MHz, CDCl₃) δ 135.0, 126.1, 84.3, 82.1, 71.0, 66.4, 31.9, 30.7, 28.2, 26.7, 26.1, 24.5, 24.2; HRMS (ESI-TOF) calcd. for C₁₃H₂₂O₂ [M+H]⁺ 211.16926, found 211.16944.

(1S,2S)-2-((2-(Diethoxy(methyl)silyl)allyl)oxy)cyclohexyl hex-5-enoate and its enantiomer (17')

Yield 65% (colorless oil); IR (neat, cm⁻¹) 3077, 2973, 2938, 2866, 1736, 1641, 1452, 1389, 1365, 1254, 1168, 1103, 1080, 1009, 951; ¹H-NMR (500 MHz, CDCl₃) δ 5.93-5.93 (m, 1 H), 5.78 (dddd, J = 17.0, 10.5, 6.5, 6.5 Hz, 1 H), 5.62-5.62 (m, 1 H), 5.04-5.00 (m, 1 H), 4.98 (d, J = 10.0 Hz, 1 H), 4.81 (ddd, J = 8.5, 8.5, 4.5 Hz, 1 H), 4.20 (d, J = 13.0 Hz, 1 H), 4.10 (d, J = 13.0 Hz, 1 H), 3.76 (q, J = 7.0 Hz, 4 H), 3.32 (ddd, J = 8.5, 8.5, 4.0 Hz, 1 H), 2.31 (dd, J = 8.0, 8.0 Hz, 2 H), 2.09 (ddd, J = 7.0, 7.0, 7.0 Hz, 2 H), 2.03-1.97 (m, 2 H), 1.76-1.64 (m, 4 H), 1.44-1.33 (m, 3 H), 1.30-1.20 (m, 7 H), 0.20 (s, 3 H); ¹³C-NMR (125 MHz, CDCl₃) δ 172.9, 144.4, 137.8, 127.1, 115.2, 78.7, 74.7, 72.0, 58.3, 58.3,
33.9, 33.0, 29.6, 29.5, 24.1, 23.1, 23.0, 18.3, 4.3; HRMS (ESI-TOF) calcd. for C$_{20}$H$_{36}$O$_5$Si [M+Na]$^+$ 407.22242, found 407.22435.

(9aS,13aS,E)-7-(Diethoxy(methyl)silyl)-3,4,5,8,9a,10,11,12,13,13a-decahydro-2H-benzo[b][1,4]dioxacycloundecin-2-one and its enantiomer (17)

Yield 43% (pale yellow oil); IR (neat, cm$^{-1}$) 2971, 2932, 2865, 1736, 1614, 1450, 1389, 1365, 1256, 1225, 1196, 1152, 1084, 1055, 983, 952; $^1$H-NMR (500 MHz, CDCl$_3$) δ 6.20-6.17 (m, 1 H), 4.75 (ddd, $J = 10.0, 10.0, 5.0$ Hz, 1 H), 4.22 (d, $J = 12.8$ Hz, 1 H), 3.99 (d, $J = 12.8$ Hz, 1 H), 3.81-3.73 (m, 4H), 3.21 (ddd, $J = 10.0, 10.0, 4.5$ Hz, 1 H), 2.85-2.76 (m, 1 H), 2.37-2.26 (m, 2 H), 2.16-2.12 (m, 2 H), 2.06-1.99 (m, 1 H), 1.95-1.93 (m, 1 H), 1.83-1.70 (m, 3 H), 1.34-1.16 (m, 10 H), 0.20 (s, 3 H); $^{13}$C-NMR (125 MHz, CDCl$_3$) δ 173.4, 150.2, 135.5, 79.4, 75.0, 63.3, 58.2, 58.2, 33.3, 30.6, 30.1, 27.1, 24.1, 23.6, 18.4, 18.3, 4.9; HRMS (ESI-TOF) calcd. for C$_{18}$H$_{32}$O$_5$Si [M+H]$^+$ 357.20918, found 357.20950.

(9aS,13aS,Z)-3,4,5,8,9a,10,11,12,13,13a-decahydro-2H-benzo[b][1,4]dioxacycloundecin-2-one and its enantiomer (36-Z)
Yield 83% (colorless oil); IR (neat, cm$^{-1}$) 3011, 2936, 2862, 1735, 1451, 1364, 1322, 1217, 1153, 1087, 1032, 984; $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 6.63-6.59 (m, 1 H), 5.47-5.48 (ddd, $J$ = 10.5, 8.0, 8.0 Hz, 1 H), 4.73-4.68 (m, 1 H), 4.20 (dd, $J$ = 13.2, 4.8 Hz, 1 H), 3.94 (dd, $J$ = 13.2, 7.2 Hz, 1 H), 3.24-3.19 (m, 1 H), 2.50-2.43 (m, 1 H), 2.36-2.26 (m, 2 H), 2.16-2.03 (m, 2 H), 1.97-1.85 (m, 2 H), 1.82-1.67 (m, 3 H), 1.33-1.13 (m, 4 H); $^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$ 173.2, 134.6, 127.3, 80.1, 75.8, 64.3, 33.9, 30.9, 30.5, 25.9, 24.0, 23.9, 23.8; HRMS (ESI-TOF) calcd. for C$_{13}$H$_{20}$O$_3$ [M+Na]$^+$ 247.13047, found 247.13070.

(1R,2S)-2-((2-(Diethoxy(methyl)silyl)allyl)oxy)cyclohexyl hex-5-enoate and its enantiomer (18')

Yield 69% (colorless oil); IR (neat, cm$^{-1}$) 3077, 2973, 2939, 2869, 1733, 1641, 1449, 1388, 1364, 1255, 1170, 1104, 1082, 951; $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 5.94-5.93 (m, 1 H), 5.78 (dddd, $J$ = 16.8, 10.2, 6.8, 6.8 Hz, 1 H), 5.64-5.63 (m, 1 H), 5.08-5.07 (m, 1 H), 5.04-5.00 (m, 1 H), 4.98 (d, $J$ = 10.0 Hz, 1 H), 4.14 (d, $J$ = 13.0 Hz, 1 H), 4.10 (d, $J$ = 13.0 Hz, 1 H), 3.79-3.75 (m, 4 H), 3.49-3.48 (m, 1 H), 2.34 (dd, $J$ = 7.5, 7.5 Hz, 2 H), 2.09 (ddd, $J$ = 7.0, 7.0, 7.0 Hz, 2 H), 1.93-1.88 (m, 1 H), 1.85-1.78 (m, 1 H), 1.76-1.65 (m, 3 H), 1.62-1.47 (m, 3 H), 1.43-1.29 (m, 2 H), 1.23-1.20 (m, 6 H), 0.22 (s, 3 H); $^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$ 173.1, 144.4, 137.8, 127.4, 115.2, 76.5, 71.6, 58.3, 33.9, 33.0,
27.8, 27.8, 24.2, 22.0, 21.8, 18.3, -4.3; HRMS (ESI-TOF) calcd. for C_{20}H_{36}O_{5}Si [M+Na]^+ 407.22242, found 407.22426.

(9aS,13aR,E)-7-(Diethoxy(methyl)silyl)-3,4,5,8,9a,10,11,12,13,13a-decahydro-2H-benzo[b][1,4]dioxacycloundecin-2-one and its enantiomer (18)

Yield 36% (pale yellow oil); IR (neat, cm^{-1}) 2970, 2931, 2870, 1730, 1614, 1450, 1390, 1360, 1246, 1225, 1162, 1110, 1080, 1049, 949; \(^1\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta\) 6.24 (dd, \(J = 9.8, 6.2\) Hz, 1 H), 4.67 (ddd, \(J = 11.0, 3.8, 3.8\) Hz, 1 H), 4.29 (d, \(J = 11.5\) Hz, 1 H), 3.89 (bs, 1 H), 3.86 (d, \(J = 11.5\) Hz, 1 H), 3.80-3.75 (m, 4 H), 2.45 (ddd, \(J = 13.2, 8.2, 4.8\) Hz, 1 H), 2.25-2.13 (m, 3 H), 1.94-1.88 (m, 2 H), 1.86-1.78 (m, 2 H), 1.72-1.70 (m, 1 H), 1.59-1.48 (m, 2 H), 1.42-1.17 (m, 9 H), 0.21 (s, 3 H); \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)) \(\delta\) 173.6, 147.9, 134.7, 75.6, 74.0, 65.8, 58.3, 34.7, 28.6, 27.6, 26.5, 24.9, 23.7, 19.9, 18.3, -4.6; HRMS (ESI-TOF) calcd. for C\(_{18}\)H\(_{32}\)O\(_5\)Si [M+H]^+ 357.20918, found 357.21015.

(9aS,13aR,Z)-3,4,5,8,9a,10,11,12,13,13a-decahydro-2H-benzo[b][1,4]dioxacycloundecin-2-one and its enantiomer (37-Z)
Yield 92% (colorless oil), inseparable mixture with styrene derivative; IR (neat, cm\(^{-1}\)) 3010, 2937, 2862, 1729, 1448, 1359, 1243, 1212, 1155, 1083, 1051, 1014; \(^1\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.61-5.52 (m, 2 H), 4.66-4.62 (m, 1 H), 4.50 (dd, \(J = 12.2, 7.8\) Hz, 1 H), 4.05 (bs, 1 H), 3.93 (dd, \(J = 12.2, 5.0\) Hz, 1 H), 2.33-2.29 (m, 2 H), 2.24-2.10 (m, 2 H), 1.93-1.79 (m, 4 H), 1.74-1.72 (m, 1 H), 1.59-1.50 (m, 2 H), 1.47-1.27 (m 3 H); \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)) \(\delta\) 173.5, 133.7, 127.6, 75.5, 72.3, 64.8, 35.0, 30.1, 26.3, 26.1, 24.9, 24.1, 19.7; HRMS (ESI-TOF) calcd. for C\(_{13}\)H\(_{20}\)O\(_3\) [M+Na]\(^+\) 247.13047, found 247.13029.

(±)-1-(2-(((2-(Diethoxy(methyl)silyl)allyl)oxy)methyl)piperidin-1-yl)hept-6-en-1-one (19’)

Yield 54% (pale yellow oil); IR (neat, cm\(^{-1}\)) 3075, 2973, 2930, 2865, 1644, 1425, 1390, 1365, 1257, 1166, 1103, 1081, 1029, 952; \(^1\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.89 and 5.87 (pair of bs due to rotamers, 1 H), 5.80 (dddd, \(J = 17.0, 10.0, 6.8, 6.8\) Hz, 1 H), 5.64 (bs, 1 H), 5.01-4.98 (m, 1 H), 4.93 (d, \(J = 10.0\) Hz, 1 H), 4.57 and 3.66 (pair of d due to rotamers, \(J = 13.0\) Hz, 1 H), 4.14-4.04 (m, 3 H), 3.76 (q, \(J = 6.8\) Hz, 4 H), 3.61-3.46 (m, 2 H), 3.11 and 2.57 (pair of dd due to rotamers, \(J = 13.0, 13.0\) Hz, 1 H), 2.43-2.29 (m, 2 H), 2.07 (dddd, \(J = 7.2, 7.2, 7.2\) Hz, 2 H), 1.86-1.80 (m, 1 H), 1.71-1.49 (m, 6 H), 1.46-1.33 (m, 3 H), 1.21 (t, \(J = 7.0\) Hz, 6 H), 0.20 (s, 3H); \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)) \(\delta\) 172.4 and 171.8 (due to rotamers), 144.0 and 143.8 (due to rotamers), 138.7, 127.7,
114.4, 74.0 and 73.8 (due to rotamers), 68.7 and 68.4 (due to rotamers), 58.3, 52.4, 46.8, 42.2, 37.0, 33.6 and 33.2 (due to rotamers), 33.6, 28.7, 26.5 and 25.9 (due to rotamers), 25.2 and 25.1 (due to rotamers), 24.9 and 24.8 (due to rotamers), 19.6 and 19.4 (due to rotamers), 18.3, -4.5; HRMS (ESI-TOF) calcd. for C_{21}H_{39}NO_{4}Si [M+H]^+ 398.27211, found 398.27371.

(±)-(E)-4-(Diethoxy(methyl)silyl)-1,6,7,8,9,12,13,14,15,15a-decahydropyrido[2,1-c][1,4]oxaazacyclododecen-10(3H)-one (19)

Yield 33% (colorless oil); IR (neat, cm\(^{-1}\)) 2970, 2928, 2865, 1634, 1444, 1389, 1366, 1256, 1165, 1106, 1079, 952; \(^1\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta\) 6.15 (dd, \(J = 9.5, 5.5\) Hz, 1 H), 4.65 (d, \(J = 13.0\) Hz, 1 H), 4.40 (bs, 1 H), 4.29 (d, \(J = 11.2\) Hz, 1 H), 3.95 (d, \(J = 11.2\) Hz, 1 H), 3.79 (dd, \(J = 9.8, 9.8\) Hz, 1 H), 3.73 (q, \(J = 6.9\) Hz, 4 H), 3.33 (dd, \(J = 11.0, 4.5\) Hz, 1 H), 2.85-2.82 (m, 1 H), 2.59-2.55 (m, 2 H), 1.96-1.92 (m, 2 H), 1.74-1.58 (m, 6 H), 1.48-1.35 (m, 4 H), 1.19 (dd, \(J = 6.8, 6.8\) Hz, 6 H), 0.16 (s, 3 H); \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)) \(\delta\) 173.7, 148.0, 132.9, 67.6, 67.4, 58.3 52.0, 36.6, 29.3, 27.3, 27.0, 26.9, 25.3, 23.8, 19.7, 18.3, 18.3, -4.6; HRMS (ESI-TOF) calcd. for C_{19}H_{35}NO_{4}Si [M+Na]^+ 392.22276, found 392.22352.
(±)-(Z)-1,6,7,8,9,12,13,14,15,15a-decahydropyrido[2,1-c][1,4]oxaazacyclododecine-10(3H)-one (38-Z)

Yield 90% (colorless oil); IR (neat, cm⁻¹) 3010, 2934, 2861, 1631, 1444, 1419, 1367, 1327, 1266, 1125, 1078, 1029; ¹H-NMR (500 MHz, CDCl₃) δ 5.59-5.49 (m, 2 H), 4.61-4.59 (m, 1 H), 4.36 (bs, 1 H), 4.24-4.20 (m, 1 H), 3.84-3.82 (m, 1 H), 3.76 (dd, J = 9.8, 9.8 Hz, 1 H), 3.43-3.40 (m, 1 H), 2.74 (bs, 1 H), 2.53 (dd, J = 12.2, 12.2 Hz, 1 H), 2.38 (bs, 1 H), 1.93-1.92 (m, 2 H), 1.73-1.60 (m, 6 H), 1.44-1.30 (m, 4 H); ¹³C-NMR (125 MHz, CDCl₃) δ 173.3, 134.9, 125.4, 67.3, 65.5, 51.1, 36.8, 29.5, 26.8, 26.4, 25.2, 25.1, 23.6, 19.4; HRMS (ESI-TOF) calcd. for C₁₄H₂₃NO₂ [M+Na]⁺ 260.16210, found 260.16176.

Diethoxy(3-(((1S,2S)-2-(hept-6-en-1-yloxy)cyclohexyl)oxy)prop-1-en-2-yl)(methyl)silane and its enantiomer (20‘)

Yield 59% (colorless oil); IR (neat, cm⁻¹) 3076, 2974, 2933, 2862, 1641, 1451, 1390, 1366, 1295, 1257, 1164, 1104, 1083, 994, 952; ¹H-NMR (500 MHz, CDCl₃) δ 5.99-5.98 (m, 1 H), 5.80 (dddd, J = 17.0, 10.5, 6.8, 6.8 Hz, 1 H), 5.64-5.63 (m, 1 H), 5.01-4.97 (m, 1 H), 4.94-4.92 (m, 1 H), 4.23-4.23 (m, 2 H), 3.77 (q, J = 7.0 Hz, 4 H), 3.57-3.48 (m, 2 H)
(10aS,14aS,E)-2,5,6,7,8,9,10a,11,12,13,14,14a-
Dodecahydrobenzo[b][1,4]dioxacyclododecin-3-yl)diethoxy(methyl)silane and its
enantiomer (20)

Yield 59% (pale yellow oil); IR (neat, cm⁻¹) 2970, 2930, 2859, 1616, 1450, 1389, 1365, 1254, 1166, 1135, 1111, 1083, 1024, 950; ¹H-NMR (500 MHz, CDCl₃) δ 6.33 (dd, J = 8.8, 6.8 Hz, 1 H), 4.35 (d, J = 8.8 Hz, 1 H), 4.07 (d, J = 8.8 Hz, 1 H), 3.92-3.89 (m, 1 H), 3.79-3.74 (m, 4 H), 3.16-3.12 (m, 1 H), 3.09-3.05 (m, 2 H), 2.62-2.55 (m, 1 H), 2.08-2.03 (m, 2 H), 2.00-1.94 (m, 1 H), 1.68-1.59 (m, 4 H), 1.56-1.46 (m, 4 H), 1.22-1.08 (m, 10 H), 0.19 (s, 3 H); ¹³C-NMR (125 MHz, CDCl₃) δ 149.7, 133.7, 84.2, 81.4, 70.0, 66.5, 58.2, 58.2, 31.2, 30.7, 27.7, 27.4, 27.2, 25.8, 24.5, 24.2, 18.3, -4.5; HRMS (ESI-TOF) calcd. for C₁₉H₃₆O₄Si [M+Na]⁺ 379.22751, found 379.22910.
(10aS,14aS,Z)-2,3,4,5,6,9,10a,11,12,13,14,14a-dodecahydrobenzo[b][1,4]dioxacyclododecine and its enantiomer (39-Z)

Yield 88% (colorless oil), inseparable mixture with styrene derivative; IR (neat, cm\(^{-1}\)) 3014, 2930, 2858, 1451, 1361, 1334, 1313, 1244, 1190, 1130, 1047, 983, 962; \(^1\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.73-5.65 (m, 2 H), 4.47 (dd, \(J = 9.0, 9.0\) Hz, 1 H), 3.96 (dd, \(J = 9.2, 4.2\) Hz, 1 H), 3.93-3.90 (m, 1 H), 3.16-3.08 (m, 3 H), 2.45-2.38 (m, 1 H), 2.08-2.07 (m, 1 H), 2.00-1.98 (m, 1 H), 1.90-1.86 (m, 1 H), 1.70-1.60 (m, 3 H), 1.52-1.45 (m, 4 H), 1.28-1.13 (m, 5 H); \(^1\)C-NMR (125 MHz, CDCl\(_3\)) \(\delta\) 135.4, 126.3, 84.8, 80.8, 69.6, 66.0, 31.5, 30.6, 28.1, 27.3, 24.9, 24.6, 24.1, 24.0; HRMS (ESI-TOF) calcd. for C\(_{14}\)H\(_{24}\)O\(_2\) [M+Na]\(^+\) 247.16685, found 247.16800.

(1S,2S)-2-((2-(Diethoxy(methyl)silyl)allyl)oxy)cyclohexyl hept-6-enoate and its enantiomer (21’)

Yield 60% (colorless oil); IR (neat, cm\(^{-1}\)) 3075, 2973, 2865, 1736, 1641, 1452, 1389, 1257, 1166, 1103, 1080, 1008, 952; \(^1\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.93-5.93 (m, 1 H), 5.79 (ddddd, \(J = 17.0, 10.5, 6.5, 6.5\) Hz, 1 H), 5.62-5.62 (m, 1 H), 5.02-4.98 (m, 1 H), 4.95 (d, \(J = 10.0\) Hz, 1 H), 4.81 (dd, \(J = 8.2, 8.2, 4.5\) Hz, 1 H), 4.21 (d, \(J = 13.2\) Hz, 1 H), 1.28-1.13 (m, 5 H); HRMS (ESI-TOF) calcd. for C\(_{14}\)H\(_{24}\)O\(_2\) [M+Na]\(^+\) 247.16685, found 247.16800.
H), 4.10 (d, J = 13.2 Hz, 1 H), 3.76 (q, J = 7.0 Hz, 4 H), 3.32 (ddd, J = 8.5, 8.5, 4.0 Hz, 1 H), 2.30 (dd, J = 8.0, 8.0 Hz, 2 H), 2.08-1.96 (m, 4 H), 1.71-1.61 (m, 4 H), 1.45-1.39 (m, 3 H), 1.34 (dd, J = 9.5, 9.5 Hz, 2 H), 1.30-1.20 (m, 7 H), 0.21 (s, 3 H); 13C-NMR (125 MHz, CDCl3) δ 173.0, 144.4, 138.4, 127.1, 114.6, 78.7, 74.6, 72.0, 58.3, 58.3, 34.5, 33.4, 29.6, 29.5, 28.3, 24.4, 23.1, 23.0, 18.3, -4.3; HRMS (ESI-TOF) calcd. for C21H36O5Si [M+Na]+ 421.23807, found 421.23885.

(10aS,14aS,E)-8-(Diethoxy(methyl)silyl)-3,4,5,6,10a,11,12,13,14,14a-decahydrobenzo[b][1,4]dioxacyclododecin-2(9H)-one and its enantiomer (21)

Yield 82% (pale yellow oil); IR (neat, cm⁻¹) 2971, 2936, 2866, 1734, 1617, 1451, 1389, 1360, 1338, 1256, 1225, 1189, 1150, 1104, 1082, 1036, 996, 950; 1H-NMR (500 MHz, CDCl3) δ 6.37 (dd, J = 10.2, 5.8 Hz, 1 H), 4.61 (ddd, J = 10.2, 10.2, 4.5 Hz, 1 H), 4.10 (d, J = 9.0 Hz, 1 H), 4.04 (d, J = 9.0 Hz, 1 H), 3.76-3.71 (m, 4 H), 3.22 (ddd, J = 10.0, 10.0, 4.5 Hz, 1 H), 2.66 (dddd, J = 11.3, 11.3, 11.3, 4.0 Hz, 1 H), 2.47 (ddd, J = 12.5, 12.5, 4.5 Hz, 1 H), 2.35 (ddd, J = 13.2, 4.8, 4.8 Hz, 1 H), 2.16-2.15 (m, 1 H), 2.07-2.06 (m, 1 H), 1.96-1.90 (m, 1 H), 1.85-1.78 (m, 1 H), 1.74-1.69 (m, 2 H), 1.65-1.56 (m, 2 H), 1.33-1.18 (m, 11 H), 0.17 (s, 3 H); 13C-NMR (125 MHz, CDCl3) δ 173.8, 151.1, 132.6, 80.4, 76.5, 65.4, 58.3, 58.2, 33.3, 31.0, 30.2, 27.9, 27.7, 24.9, 24.1, 24.0, 18.3, -4.9; HRMS (ESI-TOF) calcd. for C19H34O5Si [M+H]+ 371.22483, found 371.22556.
(10αS,14αS,Z)-3,4,5,6,10a,11,12,13,14,14a-decahydrobenzo[b][1,4]dioxacyclododecin-2(9H)-one and its enantiomer (40-Z)

Yield 91% (colorless oil); IR (neat, cm\(^{-1}\)) 3019, 2937, 2862, 1732, 1451, 1354, 1278, 1222, 1150, 1107, 1085, 1034, 989; \(^1\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.84 (ddd, \(J = 10.0, 10.0, 5.5\) Hz, 1 H), 5.65 (ddd, \(J = 10.0, 7.0, 7.0\) Hz, 1 H), 4.62 (ddd, \(J = 10.0, 10.0, 5.0\) Hz, 1 H), 4.06 (dd, \(J = 8.5, 8.5\) Hz, 1 H), 3.98 (dd, \(J = 9.5, 6.5\) Hz, 1 H), 3.22 (ddd, \(J = 10.0, 10.0, 4.0\) Hz, 1 H), 2.55 (ddddd, \(J = 11.5, 11.5, 11.5, 4.0\) Hz, 1 H), 2.46 (dd, \(J = 12.5, 12.5, 4.0\) Hz, 1 H), 2.35 (dd, \(J = 13.0, 5.0, 5.0\) Hz, 1 H), 2.11-2.06 (m, 2 H), 1.94-1.87 (m, 1 H), 1.76-1.67 (m, 3 H), 1.65-1.55 (m, 2 H), 1.34-1.17 (m, 5 H); \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)) \(\delta\) 173.6, 138.1, 124.6, 80.6, 76.7, 65.2, 33.1, 30.9, 30.6, 28.2, 25.9, 24.6, 24.2, 23.9; HRMS (ESI-TOF) calcd. for C\(_{14}\)H\(_{22}\)O\(_3\) [M+Na]\(^+\) 261.14612, found 261.14610.

(1R,2S)-2-((2-(Diethoxy(methyl)silyl)allyl)oxy)cyclohexyl hept-6-enoate and its enantiomer (22’)

Yield 66% (colorless oil); IR (neat, cm\(^{-1}\)) 3076, 2972, 2938, 2866, 1734, 1641, 1449, 1388, 1364, 1257, 1169, 1104, 1081, 992, 951; \(^1\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.94-5.93
(m, 1 H), 5.79 (dddd, $J = 17.0, 10.5, 6.5, 6.5$ Hz, 1 H), 5.64-5.63 (m, 1 H), 5.08-5.06 (m, 1 H), 5.02-4.98 (m, 1 H), 4.94 (d, $J = 10.0$ Hz, 1 H), 4.14 (d, $J = 13.0$ Hz, 1 H), 4.10 (d, $J = 13.0$ Hz, 1 H), 3.79-3.75 (m, 4 H), 3.49-3.48 (m, 1 H), 2.33 (dd, $J = 7.2, 7.2$ Hz, 2 H), 2.06 (ddd, $J = 7.2, 7.2, 7.2$ Hz, 2 H), 1.93-1.87 (m, 1 H), 1.85-1.78 (m, 1 H), 1.70-1.47 (m, 6 H), 1.46-1.29 (m, 4 H), 1.21 (dd, $J = 7.0, 7.0$ Hz, 6 H), 0.22 (s, 3 H); $^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$ 173.2, 144.4, 138.5, 127.4, 114.6, 76.5, 71.6, 58.3, 34.5, 33.4, 28.3, 27.8, 27.8, 24.5, 22.0, 21.9, 18.3, -4.3; HRMS (ESI-TOF) calcd. for C$_{21}$H$_{38}$O$_5$Si [M+Na]$^+$ 421.23807, found 421.23931.

(10a$S$,14a$R$,E)-8-(Diethoxy(methyl)silyl)-3,4,5,6,10a,11,12,13,14,14a-decahydrobenzo[b][1,4]dioxacyclocdecin-2(9H)-one and its enantiomer (22)

Yield 46% (pale yellow oil); IR (neat, cm$^{-1}$) 2970, 2935, 2864, 1730, 1616, 1449, 1389, 1353, 1256, 1224, 1156, 1105, 1079, 984, 952; $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 6.26 (dd, $J = 8.2, 6.8$ Hz, 1 H), 5.02-5.00 (m, 1 H), 4.06-4.01 (m, 2 H), 3.78-3.73 (m, 4 H), 3.61-3.60 (m, 1 H), 2.40-2.28 (m, 2 H), 2.27-2.15 (m, 2 H), 1.96-1.90 (m, 1 H), 1.88-1.78 (m, 2 H), 1.75-1.68 (m, 1 H), 1.67-1.54 (m, 6 H), 1.40-1.29 (m, 2 H), 1.22-1.19 (m, 6 H), 0.18 (s, 3 H); $^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$ 174.3, 149.6, 133.3, 75.0, 71.9, 63.6, 58.3, 58.2, 34.9, 29.7, 28.6, 27.9, 27.7, 27.6, 24.4, 22.1, 21.7, 18.3, -4.8; HRMS (ESI-TOF) calcd. for C$_{19}$H$_{34}$O$_5$Si [M+Na]$^+$ 393.20677, found 393.20690.
(10aS,14aR,Z)-3,4,5,6,10a,11,12,13,14,14a-decahydrobenzo[b][1,4]dioxacyclododecin-2(9H)-one and its enantiomer (41-Z)

Yield 97% (colorless oil); IR (neat, cm⁻¹) 2935, 2859, 1729, 1449, 1352, 1219, 1147, 1081, 1047; ¹H-NMR (500 MHz, CDCl₃) δ 5.71 (ddd, J = 10.5, 8.0, 8.0 Hz, 1 H), 5.61 (ddd, J = 10.5, 6.5, 6.5 Hz, 1 H), 5.07-5.06 (m, 1 H), 4.09-4.00 (m, 2 H), 3.65-3.63 (m, 1 H), 2.43-2.38 (m, 1 H), 2.34-2.29 (m, 1 H), 2.26-2.18 (m, 1 H), 2.10-2.03 (m, 1 H), 1.99-1.94 (m, 1 H), 1.83-1.72 (m, 3 H), 1.71-1.50 (m, 6 H), 1.42-1.28 (m, 2 H); ¹³C-NMR (125 MHz, CDCl₃) δ 174.3, 136.3, 125.4, 74.3, 71.9, 62.8, 34.6, 28.7, 28.3, 27.5, 26.1, 23.9, 22.2, 21.6; HRMS (ESI-TOF) calcd. for C₁₄H₂₂O₃ [M+Na]⁺ 261.14612, found 261.14045.

(1S,2S)-2-(Allyloxy)cyclohexyl 6-(diethoxy(methyl)silyl)hept-6-enoate and its enantiomer (23’)

Yield 82% (colorless oil); IR (neat, cm⁻¹) 3075, 2973, 2937, 2865, 1736, 1641, 1452, 1389, 1364, 1257, 1166, 1102, 1080, 1008, 994, 952; ¹H-NMR (500 MHz, CDCl₃) δ 5.91-5.84 (m, 1 H), 5.67 (bs, 1 H), 5.55-5.55 (m, 1 H), 5.25 (d, J = 17.5 Hz, 1 H), 5.13 (d, J = 10.0 Hz, 1 H), 4.80-4.76 (m, 1 H), 4.09 (dd, J = 12.8, 5.2 Hz, 1 H), 4.01 (dd, J = 12.8,
5.2 Hz, 1 H), 3.76 (q, J = 7.0 Hz, 4 H), 3.32-3.28 (m, 1 H), 2.31 (dd, J = 7.8, 7.8 Hz, 2 H), 2.16 (dd, J = 7.8, 7.8 Hz, 2 H), 2.00-1.97 (m, 2 H), 1.71-1.62 (m, 4 H), 1.52-1.46 (m, 2 H), 1.41-1.20 (m, 10 H), 0.19 (s, 3 H); $^{13}$C-NMR (125 MHz, CDCl$_3$) \(\delta\) 173.0, 147.1, 135.4, 127.5, 116.2, 78.4, 74.7, 70.4, 58.2, 35.1, 34.6, 29.9, 29.7, 28.2, 24.9, 23.2, 23.2, 18.3, -4.6; HRMS (ESI-TOF) calcd. for C$_{21}$H$_{38}$O$_5$Si [M+Na]$^+$ 421.23807, found 421.24013.

(10aS,14aS,E)-7-(Diethoxy(methyl)silyl)-3,4,5,6,10a,11,12,13,14,14a-decahydrobenzo[b][1,4]dioxacyclododecin-2(9H)-one and its enantiomer (23)

Yield 79\% (pale yellow oil); IR (neat, cm$^{-1}$) 2971, 2937, 2866, 1733, 1450, 1390, 1353, 1339, 1256, 1227, 1146, 1103, 1081, 1036, 996, 951; $^1$H-NMR (500 MHz, CDCl$_3$) \(\delta\) 6.21 (dd, J = 7.0, 7.0 Hz, 1H), 4.65-4.60 (m, 1 H), 4.20 (dd, J = 8.5, 8.5 Hz, 1 H), 3.98 (dd, J = 9.0, 6.0 Hz, 1 H), 3.76-3.72 (m, 4 H), 3.23 (ddd, J = 10.0, 10.0, 4.0 Hz, 1 H), 2.58 (ddd, J = 12.5, 12.5, 3.5 Hz, 1 H), 2.54-2.48 (m, 1 H), 2.34 (ddd, J = 13.0, 5.0, 5.0 Hz, 1 H), 2.10 (bs, 2 H), 1.95-1.87 (m, 2 H), 1.76-1.69 (m, 3 H), 1.64-1.57 (m, 1 H), 1.33-1.18 (m, 11 H), 0.18 (s, 3 H); $^{13}$C-NMR (125 MHz, CDCl$_3$) \(\delta\) 173.7, 146.5, 136.5, 80.7, 77.1, 65.8, 58.2, 58.2, 33.4, 31.0, 30.7, 29.0, 27.8, 25.5, 24.3, 23.9, 18.3, 18.3, -4.7; HRMS (ESI-TOF) calcd. for C$_{19}$H$_{34}$O$_5$Si [M+H]$^+$ 371.22483, found 371.22591.

Protodesilylation of 23 generated 40-Z with 52\% yield.
(1R,2S)-2-(Allyloxy)cyclohexyl 6-(diethoxy(methyl)silyl)hept-6-enoate and its enantiomer (24*)

Yield 80% (colorless oil); IR (neat, cm⁻¹) 3051, 2971, 2938, 2866, 1733, 1449, 1388, 1365, 1257, 1238, 1168, 1104, 1081, 950; ¹H-NMR (500 MHz, CDCl₃) δ 5.92-5.84 (m, 1 H), 5.68-5.67 (m, 1 H), 5.55-5.54 (m, 1 H), 5.28-5.24 (m, 1 H), 5.15-5.12 (m, 1 H), 5.09-5.08 (m, 1 H), 4.05 (dd, J = 13.0, 5.8 Hz, 1H), 3.98 (dd, J = 13.2, 5.8 Hz, 1 H), 3.76 (q, J = 7.0 Hz, 4 H), 3.49-3.47 (m, 1 H), 2.35 (dd, J = 7.5, 7.5 Hz, 2 H), 2.16 (dd, J = 7.5, 7.5 Hz, 2 H), 1.91-1.86 (m, 1 H), 1.83-1.76 (m, 1 H), 1.71-1.62 (m, 3 H), 1.60-1.46 (m, 5 H), 1.43-1.29 (m, 2 H), 1.21 (dd, J = 7.0, 7.0 Hz, 6 H), 0.18 (s, 3 H); ¹³C-NMR (125 MHz, CDCl₃) δ 173.3, 174.1, 135.3, 127.5, 116.5, 76.0, 71.0, 69.7, 58.2, 35.1, 34.6, 28.2, 27.9, 27.8, 24.9, 22.1, 21.7, 18.3, -4.6; HRMS (ESI-TOF) calcd. for C₂₁H₃₈O₅Si [M+Na]⁺ 421.23807, found 421.23908.

(10aS,14aR,E)-7-(Diethoxy(methyl)silyl)-3,4,5,6,10a,11,12,13,14,14a-decahydrobenzo[b][1,4]dioxacyclobdecin-2(9H)-one and its enantiomer (24)
Yield 14% (colorless oil); IR (neat, cm$^{-1}$) 2970, 2935, 2865, 1731, 1449, 1390, 1354, 1256, 1226, 1149, 1103, 1079, 986, 952; $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 6.14 (dd, $J = 6.5$, 6.5 Hz, 1 H), 5.06-5.05 (m, 1H), 4.19 (dd, $J = 10.8$, 6.5 Hz, 1 H), 4.03 (dd, $J = 10.8$, 6.5 Hz, 1 H), 3.77-3.72 (m, 4 H), 3.60-3.59 (m, 1 H), 2.46-2.40 (m, 2 H), 2.34 (ddd, $J = 13.0$, 5.5, 5.5 Hz, 1 H), 2.08 (ddd, $J = 12.2$, 12.2, 5.0 Hz, 1 H), 1.98-1.92 (m, 1 H), 1.84-1.71 (m, 3 H), 1.68-1.54 (m, 5 H), 1.50-1.28 (m, 3 H), 1.20 (dd, $J = 7.5$, 7.5 Hz, 6 H), 0.18 (s, 3 H); $^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$ 174.0, 144.2, 137.3, 74.8, 72.3, 63.9, 58.2, 34.0, 29.7, 28.3, 28.1, 28.0, 27.4, 25.1, 22.3, 21.4, 18.3, -4.6; HRMS (ESI-TOF) calcd. for C$_{19}$H$_{34}$O$_5$Si [M+H]$^+$ 371.22483, found 371.22603.

Protodesilylation of 24 generated 41-Z with 54% yield.

Hydrosilylation reaction gave rise to a 6.1:1 mixture of two regioisomers with the desired regio isomer 25$^*$ being the major one. Yield 75% (colorless oil).
(E)-3-(diethoxy(methyl)silyl)-10-methyl-5,6,7,8-tetrahydro-2H-
benzo[b][1,4]oxaazacyclododecin-9(10H)-one (25)

Yield 64% (colorless oil); \(^1\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.34-7.30 (m, 1 H), 7.14-7.12 (m, 1 H), 7.04-7.02 (m, 1 H), 6.99-6.95 (m, 1 H), 4.42-6.38 (m, 1 H), 3.80-3.75 (m, 4 H), 3.14 (s, 3 H), 2.32-2.26 (m, 1 H), 2.16-2.08 (m, 1 H), 2.00-1.92 (m, 1 H), 1.89-1.83 (m, 2 H), 1.70-1.62 (m, 1 H), 1.47-1.40 (m, 1 H), 1.33-1.25 (m, 1 H), 1.23-1.20 (m, 6 H), 0.22 (s, 3 H); \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)) \(\delta\) 173.6, 154.4, 153.1, 132.6, 130.0, 129.1, 128.9, 120.9, 112.5, 64.1, 58.4, 58.3, 36.5, 29.6, 27.5, 26.1, 23.7, 18.3, -5.0.

(\(E\))-6-(diethoxy(methyl)silyl)-2,3,4,5,9,10-hexahydrobenzo[b][1,5]dioxacyclopentadecin-12(8H)-one (26)

Yield 78% (colorless oil); IR (neat, cm\(^{-1}\)) 2970, 1704, 1601, 1489, 1453, 1300, 1252, 1164, 1101, 1078, 1020, 951; \(^1\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.75-7.73 (m, 1 H), 7.43-7.40 (m, 1 H), 7.01-6.96 (m, 2 H), 6.02 (t, \(J = 7.5\) Hz, 1 H), 4.34 (t, \(J = 5.2\) Hz, 2 H), 4.17 (t, \(J = 5.5\) Hz, 2 H), 3.77-3.73 (m, 6 H), 2.40-2.35 (m, 2 H), 2.22-2.19 (m, 2 H), 1.86-1.77 (m, 4 H), 1.66-1.61 (m, 2 H), 1.22 (t, \(J = 6.7\) Hz, 6 H), 1.22 (t, \(J = 6.7\) Hz, 6 H), 0.18 (s, 3 H); \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)) \(\delta\) 168.2, 157.4, 143.0, 137.7, 132.9, 131.6, 121.9, 120.2, 113.1, 66.9 64.1, 58.1, 28.7, 28.4, 27.4, 26.0, 25.0, 18.3, -4.7; HRMS (ESI-TOF) calcd. for C\(_{21}\)H\(_{32}\)O\(_3\)Si [M+H]\(^+\) 393.20918, found 393.21212.
Hydrosilylation reaction gave rise to a 14.3:1 mixture of two regioisomers with the desired regio isomer 27' being the major one. Yield 82% (colorless oil).

\[(E)-6-(diethoxy(methyl)silyl)-4,5,8,9,10,11-hexahydro-2H-benzo[b][1,5]dioxacyclopentadecin-13(3H)-one (27)\]

Yield 58% (colorless oil); IR (neat, cm\(^{-1}\)) 2969, 1700, 1602, 1492, 1453, 1388, 1302, 1253, 1165, 1130, 1078, 952; \(^1\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.75-7.73 (m, 1 H), 7.42-7.38 (m, 1 H), 6.95 (dd, \(J = 7.2, 7.2\) Hz, 1 H), 6.90 (d, \(J = 8.0\) Hz, 1 H), 6.11 (t, \(J = 7.5\) Hz, 1 H), 4.41 (t, \(J = 5.7\) Hz, 2 H), 4.02 (t, \(J = 5.2\) Hz, 2 H), 3.76-3.72 (m, 4 H), 2.22-2.17 (m, 4 H), 1.85-1.78 (m, 4 H), 1.68-1.57 (m, 4 H), 1.21 (t, \(J = 6.2\) Hz, 6 H), 0.17 (s, 3 H); \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)) \(\delta\) 168.4, 157.7, 144.0, 136.6, 132.9, 131.6, 121.0, 119.8, 112.0, 67.9, 64.3, 58.1, 29.4, 28.4, 28.1, 28.1, 27.7, 26.0, 18.3, -4.8; HRMS (ESI-TOF) calcd. for C\(_{22}\)H\(_{34}\)O\(_5\)Si [M+H]\(^+\) 407.22483, found 407.22437.
(15S,2S)-2-(Hex-5-en-1-yl oxy)cyclohexyl 5-(diethoxy(methyl)silyl)hex-5-enoate and its enantiomer (29')

Yield 73% (colorless oil); IR (neat, cm⁻¹) 3076, 2972, 2866, 1735, 1641, 1452, 1389, 1256, 1165, 1109, 1082, 953; ¹H-NMR (500 MHz, CDCl₃) δ 5.79 (dddd, J = 17.2, 10.2, 7.0, 7.0 Hz, 1 H), 5.69-5.69 (m, 1 H), 5.58-5.58 (m, 1 H), 5.01-4.97 (m, 1 H), 4.94 (d, J = 10.0 Hz, 1 H), 4.78-4.74 (m, 1 H), 3.76 (q, J = 7.0 Hz, 4 H), 3.56-3.52 (m, 1 H), 3.44-3.39 (m, 1 H), 3.24-3.19 (m, 1 H), 2.30 (dd, J = 7.5, 7.5 Hz, 2 H), 2.19 (dd, J = 7.5, 7.5 Hz, 2 H), 2.05 (ddd, J = 7.0, 7.0, 7.0 Hz, 2 H), 1.98-1.96 (m, 2 H), 1.82-1.76 (m, 2 H), 1.70-1.64 (m, 2 H), 1.56-1.50 (m, 2 H), 1.45-1.40 (m, 2 H), 1.36-1.31 (m, 3 H), 1.28-1.20 (m, 7 H), 0.20 (s, 3 H); ¹³C-NMR (125 MHz, CDCl₃) δ 172.9, 146.6, 138.8, 128.1, 114.4, 78.9, 74.6, 69.3, 58.2, 34.9, 34.2, 33.5, 29.8, 29.7, 29.6, 25.5, 24.1, 23.2, 18.3, 4.6; HRMS (ESI-TOF) calcd. for C₂₃H₄₂O₅Si [M+Na]⁺ 449.26937, found 449.27061.

(12aS,16aS,E)-6-(Diethoxy(methyl)silyl)-4,5,8,9,10,11,12a,13,14,15,16,16a-dodecahydrobenzo[b][1,4]dioxacyclotetradecin-2(3H)-one and its enantiomer (29)

Yield 76% (pale yellow oil); IR (neat, cm⁻¹) 2930, 2865, 2733, 1731, 1612, 1452, 1389, 1367, 1338, 1293, 1252, 1212, 1191, 1165, 1110, 1080, 1020, 989, 951; ¹H-NMR (500 MHz, CDCl₃) δ 6.08 (dd, J = 7.0, 7.0 Hz, 1H), 4.76 (ddd, J = 10.0, 10.0, 4.5 Hz, 1 H), 3.80-3.71 (m, 5 H), 3.28-3.22 (m, 2 H), 2.38-2.12 (m, 6 H), 2.07-1.99 (m, 2 H), 1.88-1.82
(m, 1 H), 1.74-1.52 (m, 6 H), 1.43-1.36 (m, 1 H), 1.32-1.18 (m, 10 H), 0.16 (s, 3 H); $^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$ 173.2, 145.5, 135.4, 79.8, 75.2, 67.7, 58.1, 33.4, 30.9, 29.6, 28.5, 28.3, 27.4, 27.1, 24.4, 24.1, 24.0, 18.3, -4.4; HRMS (ESI-TOF) calcd. for C$_{21}$H$_{38}$O$_5$Si [M+H]$^+$ 399.25613, found 399.25752.

(12a$S,16aS,Z$)-4,5,8,9,10,11,12a,13,14,15,16,16a-dodecahydrobenzo[b][1,4]dioxacyclotetradecin-2(3H)-one and its enantiomer (43-Z)

Yield 60% (colorless oil), inseparable mixture with styrene; IR (neat, cm$^{-1}$) 3002, 2936, 2861, 1731, 1452, 1368, 1246, 1207, 1162, 1111, 1022; $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 5.51 (ddd, $J = 8.5, 8.5, 8.5$ Hz, 1H), 5.24 (ddd, $J = 10.0, 10.0, 6.5$ Hz, 1H), 4.80 (ddd, $J = 10.0, 10.0, 5.0$ Hz, 1H), 3.78-3.75 (m, 1 H), 3.25-3.20 (m, 2 H), 2.38-2.04 (m, 6 H), 1.99-1.83 (m, 3 H), 1.76-1.57 (m, 3 H), 1.55-1.37 (m, 4 H), 1.32-1.17 (m, 4 H); $^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$ 173.1, 131.6, 128.9, 79.8, 74.9, 66.9, 32.1, 30.9, 29.7, 28.3, 26.7, 26.6, 25.6, 24.1, 23.9, 23.7; HRMS (ESI-TOF) calcd. for C$_{16}$H$_{26}$O$_3$ [M+Na]$^+$ 289.17742, found 289.17804.
(1S,2S)-2-(Hept-6-en-1-yloxy)cyclohexyl 5-(diethoxy(methyl)silyl)hex-5-enoate and its enantiomer (30')

Yield 79% (colorless oil); IR (neat, cm⁻¹) 3077, 2973, 2865, 1736, 1641, 1452, 1389, 1256, 1166, 1110, 1082, 995, 953; ¹H-NMR (500 MHz, CDCl₃) δ 5.80 (dddd, J = 17.0, 10.0, 6.8, 6.8 Hz, 1 H), 5.69-5.69 (m, 1 H), 5.58-5.58 (m, 1 H), 5.01-4.97 (m, 1 H), 4.93 (d, J = 10.0 Hz, 1 H), 4.76 (dd, J = 8.5, 8.5, 4.5 Hz, 1 H), 3.76 (q, J = 7.0 Hz, 4 H), 3.53 (ddd, J = 9.0, 6.5, 6.5 Hz, 1 H), 3.41 (ddd, J = 9.5, 7.0, 7.0 Hz, 1 H), 3.21 (ddd, J = 8.5, 8.5, 4.0 Hz, 1 H), 2.30 (dd, J = 7.2, 7.2 Hz, 2 H), 2.19 (dd, J = 7.8, 7.8 Hz, 2 H), 2.04 (ddd, J = 7.2, 7.2, 7.2 Hz, 2 H), 1.98-1.96 (m, 2 H), 1.83-1.77 (m, 2 H), 1.70-1.64 (m, 2 H), 1.55-1.49 (m, 2 H), 1.42-1.20 (m, 14 H), 0.20 (s, 3 H); ¹³C-NMR (125 MHz, CDCl₃) δ 172.9, 146.6, 138.9, 128.1, 114.2, 78.9, 74.6, 69.5, 58.2, 34.9, 34.3, 33.7, 30.0, 29.8, 29.7, 28.7, 25.6, 24.1, 23.2, 18.3, -4.6; HRMS (ESI-TOF) calcd. for C₂₄H₄₄O₅Si [M+H]⁺ 441.30308, found 441.30151.

![Structure](image)

(13aS,17aS,E)-6-(Diethoxy(methyl)silyl)-3,4,5,8,9,10,11,12,13a,14,15,16,17,17a-tetradecahydro-2H-benzo[b][1,4]dioxacyclopentadecin-2-one and its enantiomer (30)

Yield 43% (pale yellow oil), Z:E = 8:92, E product was purified and characterized.; IR (neat, cm⁻¹) 2935, 2861, 1735, 1613, 1452, 1414, 1365, 1311, 1255, 1218, 1188, 1162, 1111, 1080, 1017, 988, 952; ¹H-NMR (500 MHz, CDCl₃) δ 6.08 (dd, J = 10.5, 5.0 Hz, 1
H), 4.72 (dd, J = 10.0, 10.0, 4.3 Hz, 1 H), 3.74 (q, J = 7.0Hz, 4 H), 3.68-3.65 (m, 1 H), 3.40-3.36 (m, 1 H), 3.15 (ddd, 9.5, 9.5, 4.5 Hz, 1 H), 2.55-2.49 (m, 1 H), 2.38-2.20 (m, 3 H), 2.12-2.07 (m, 2 H), 2.02-1.89 (m, 3 H), 1.72-1.62 (m, 4 H), 1.40-1.14 (m, 15 H), 0.17 (s, 3 H); \textsuperscript{13}C-NMR (125 MHz, CDCl\textsubscript{3}) \textsuperscript{\delta} 173.3, 145.5, 135.3, 80.1, 76.4, 68.9, 58.1, 58.1, 32.4, 31.1, 31.0, 29.2, 28.8, 27.8, 27.3, 25.5, 24.2, 24.0, 23.5, 18.3, -4.3; HRMS (ESI-TOF) calcd. for C\textsubscript{22}H\textsubscript{40}O\textsubscript{5}Si [M+H]\textsuperscript{+} 413.27178, found 413.27159.

Protodesilylation of 30 (mixture of Z and E isomers with a ratio of 8:92) gave rise to 44 as an inseparable mixture of Z and E isomers with a ratio of 90:10 determined by \textsuperscript{1}H NMR analysis.

\textbf{(Z)-3,4,7,8,9,10-Hexahydrobenzo[\textit{b}][1,5]dioxacyclotetradecin-12(2\textit{H})-one (14-Z)}

Protodesilylation of 91 mg 12c (0.22 mmol) followed by column chromatography (gradient 0 – 20% ethyl acetate/hexane) gave rise to 35 mg of the title compound. Yield 64% (colorless oil); IR (neat, cm\textsuperscript{-1}) 3009, 2935, 2865, 1703, 1601, 1581, 1490, 1453, 1384, 1354, 1302, 1250, 1165, 1132, 1097, 1049, 1015, 975; \textsuperscript{1}H-NMR (500 MHz,
CDCl$_3$) $\delta$ 7.78-7.76 (m, 1 H), 7.44-7.40 (m, 1 H), 6.98-6.93 (m, 2 H), 5.68 (dt, $J = 10.0$, 8.2 Hz, 1 H), 5.48 (dt, $J = 10.0$, 8.2 Hz, 1 H), 4.43 (t, $J = 6.0$ Hz, 2 H), 4.09 (t, $J = 5.2$ Hz, 2 H), 2.29 (dt, $J = 7.8$, 7.8 Hz, 2 H), 2.13-2.08 (m, 2 H), 1.85-1.79 (m, 4 H), 1.69-1.63 (m, 2 H); $^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$ 168.5, 157.5, 133.1, 132.2, 130.1, 130.0, 121.3, 120.0, 112.2, 66.9, 63.8, 29.8, 27.6, 25.7, 25.4, 23.5; HRMS (ESI-TOF) calcd. for C$_{16}$H$_{20}$O$_3$ [M+H]$^+$ 261.14852, found 261.14455.

\[
\begin{align*}
&\text{(Z)-4,5,8,9,10,11-Hexahydro-2H-benzo[\text{b}]\text{[1,5]}dioxacyclopentadecin-13(3H)-one (42-Z)}
\end{align*}
\]

Protodesilylation of 13c (60 mg, 0.14 mmol) followed by column chromatography (gradient 0 – 20% ethyl acetate/hexane) gave rise to 17 mg of the title compound. Yield 46% (colorless oil); IR (neat, cm$^{-1}$) 3007, 2936, 2862, 1698, 1601, 1491, 1452, 1384, 1300, 1249, 1164, 1131, 1097, 1050, 958; $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 7.71-7.69 (m, 1 H), 7.42-7.38 (m, 1 H), 6.97-6.94 (m, 1 H), 6.91 (d, $J = 8.0$ Hz, 1 H), 5.55 (dt, $J = 10.8$, 7.4 Hz, 1 H), 5.50 (dt, $J = 10.8$, 7.4 Hz, 1 H), 4.40 (t, $J = 6.0$ Hz, 2 H), 4.04 (t, $J = 5.2$ Hz, 2 H), 2.14-2.09 (m, 4 H), 1.85-1.77 (m, 4 H), 1.65-1.59 (m, 2 H), 1.58-1.52 (m, 2 H); $^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$ 168.3, 157.6, 132.7, 131.2, 130.3, 129.8, 121.5, 120.0, 112.3, 68.3, 64.5, 28.6, 27.9, 27.1, 26.9, 26.4, 26.0; HRMS (ESI-TOF) calcd. for C$_{17}$H$_{22}$O$_3$ [M+Na]$^+$ 297.14612, found 297.14667.
F. Synthesis of compound 31 and 32 and determination of stereoselectivity

Following the reported procedure, the alkyne substrates were synthesized. Hydrosilylation of the alkynes gave rise to the corresponding alkenyl siloxane 31' and 32', which were subjected to the RCM reaction.

Note: The $^1$H and $^{13}$C NMR spectra of many of these compounds were extremely complicated owing to the various combinations of rotamers, and conformers. Efforts to completely coalesce the resonances through variable temperature NMR (up to 110 °C) were unsuccessful. Despite their complexity, all spectra are for single compounds that were larger than 95% pure by LC/MS.

![Chemical Structure](image)

*tert*-Butyl (2R,3R)-2-(2-(diethoxy(methyl)silyl)allyloxy)-4-(2-(hex-5-enyloxy)-N-((S)-1-(4-methoxybenzyloxy)propan-2-yl)-5-nitrobenzamido)-3-methylbutyl(methyl)carbamate (31')

Yield 69% (pale yellow oil); IR (neat, cm$^{-1}$) 2973, 2932, 1693, 1640, 1612, 1588, 1516, 1458, 1391, 1365, 1272, 1251, 1160, 1078, 1036, 952; HRMS (ESI-TOF) calcd. for C$_{43}$H$_{67}$N$_3$O$_{11}$Si [M+Na]$^+$ 852.44371, found 852.44396; [$\alpha$]$_D^{21}$ = -25.5 (c = 2.2, CHCl$_3$).
tert-Butyl ((10R,11R,E)-7-(diethoxy(methyl)silyl)-13-((S)-1-(4-methoxybenzyloxy)propan-2-yl)-11-methyl-16-nitro-14-oxo-2,3,4,5,8,10,11,12,13,14-decahydrobenzo[b][1,9,5]dioxaazacycloc hexadecin-10-yl)methyl(methyl)carbamate (31)

Z/E ratio is less than 1:99. Yield 47% (pale yellow oil); IR (neat, cm⁻¹) 2972, 2934, 1692, 1633, 1614, 1588, 1516, 1468, 1392, 1365, 1341, 1302, 1271, 1251, 1159, 1105, 1080, 1036, 1010, 986, 953; HRMS (ESI-TOF) calcd. for C₄₁H₆₃N₃O₁₁Si [M+Na]⁺ 824.41241, found 824.41263; [α]D²¹ = -16.4 (c = 7.6, CHCl₃).

tert-Butyl ((2R,3R)-2-(allyloxy)-4-(2-((5-(diethoxy(methyl)silyl)hex-5-en-1-yl)oxy))-N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-5-nitrobenzamido)-3-methylbutyl)(methyl)carbamate (32’)

Yield 69% (pale yellow oil); IR (neat, cm⁻¹) 2973, 2934, 1694, 1940, 1612, 1588, 1516, 1457, 1391, 1365, 1340, 1272, 1252, 1162, 1078, 1036, 952; HRMS (ESI-TOF) calcd.
for C_{43}H_{67}N_{3}O_{11}Si [M+Na]^+ 852.44371, found 852.44378; [α]_D^{20} = -32.3 (c = 2.4, CHCl_3).

**tert**-Butyl (((10R,11R,E)-6-(diethoxy(methyl)silyl)-13-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-11-methyl-16-nitro-14-oxo-2,3,4,5,8,10,11,12,13,14-decahydrobenzo[b][1,9,5]dioxazacyclododecacin-10-yl)methyl)(methyl)carbamate (32)

Z/E ratio is 14:86. Yield 44% (pale yellow oil); IR (neat, cm\(^{-1}\)) 2972, 2934, 1689, 1636, 1612, 1588, 1515, 1463, 1391, 1365, 1340, 1273, 1252, 1164, 1104, 1078; HRMS (ESI-TOF) calcd. for C_{41}H_{63}N_{3}O_{11}Si [M+H]^+ 802.43046, found 802.42662; [α]_D^{22} = -29.8 (c = 3.2, CHCl_3).

The simple diolefinic substrate was synthesized and subjected to RCM reaction using catalyst A. A mixture of both stereoisomers was obtained. The Z/E ratio was analyzed to be 36:64 using SFC/MS chromatography (Figure I-4, first trace). SFC: Chiralpak® AD-H column; 25% iPrOH, 75% sfCO_2, 10 minutes run length, t_R^{(Z)} = 3.77 min, area = 36%, t_R^{(E)} = 5.12 min, area = 64%.
First trace: RCM of simple diolefinic substrate; second trace: protodesilylation of compound 32; third trace: protodesilylation of compound 31.

In order to confirm the geometry of the double bond within alkenyl siloxane products 31 and 32, protodesilylation reaction was performed to generate the simple olefins. The Z/E ratio of desilylated product 45-Z from compound 31 was larger than 99:1 (Figure I-4, third trace, $t_R^{(Z)} = 3.70$ min, area = 100%). Due to highly rotameric nature of compound 45-Z, VT NMR was performed in C$_6$D$_6$ at 80 °C. The coupling constant was measured to be 10.5 Hz, characteristic of Z olefin. Since the protodesilylation reaction is stereospecific, the configuration of compound 31 was E. The Z/E ratio of desilylated product from compound 32 was 86:14 (Figure I-4, second trace, $t_R^{(Z)} = 3.83$ min, area = 86%, $t_R^{(E)} = 5.33$ min, area = 14%), which indicated that the Z/E ratio of compound 32 is 14:86. In both cases, the siloxyl group was able to overcome the intrinsic selectivity
focusing the formation of the \( E \) olefin. However, the positions of the siloxyl group had different influences on the selectivity of the olefin geometry within the product.

\[
\text{\textit{tert-Butyl (((10R,11R,Z)-13-(S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-11-methyl-16-nitro-14-oxo-2,3,4,5,8,10,11,12,13,14-decahydrobenzo[\textit{b}][1,9,5]dioxaazacyclodecan-10-yl)methyl)(methyl)carbamate (45-Z)}
\]

Yield 86% (pale yellow oil); IR (neat, cm\(^{-1}\)) 2936, 2862, 1690, 1633, 1588, 1515, 1464, 1392, 1366, 1341, 1272, 1250, 1159, 1104, 1036, 979; HRMS (ESI-TOF) calcd. for \( C_{36}H_{51}N_{3}O_9 \) [M+Na]\(^+\) 692.35175, found 692.35064; [\( \alpha \)]\(_D\)\(^{21} \) = -9.9 (c = 4.6, CHCl\(_3\)).

Protodesilylation of 32 generated 45 with 60% yield

**G. Influence of the silyl group on the specificity and stereoselectivity of RCM reactions**

\( \text{RCM of simple di-olefinic substrates} \): substrate (1 equiv.) was dissolved in anhydrous toluene (or other solvent when indicated) at a concentration of 2 mM under argon. Catalyst A (20 mol\%) or Grubbs II 10 mol\%, and 20 mol\% 1,4-benzoquinone was added to the solution. High vacuum was applied to the reaction flask for 5 min and charged with
argon. This operation cycle was repeated for 5 times. The reaction was then heated up to 35 °C and left for 12 hours. The resulting mixture was concentrated in vacuo and the residue was analyzed by $^1$H NMR or purified by silica gel column chromatography using Hexanes/EtOAc as eluent.

Simple di-olefinic substrates were synthesized and subjected to two different reaction conditions: I, 20 mol% cat. A, 20 mol% 1,4-benzoquinone, toluene, 2 mM, 35 °C, 12 hours; II, 10 mol% Grubbs II, 20 mol% 1,4-benzoquinone, toluene, 2 mM, 35 °C, 12 hours. The reaction outcome was analyzed by proton NMR study of the crude mixture using CDCl₃ or C₆D₆ as solvent. Since the outcomes under both conditions are very similar, only expanded region of the proton NMR spectrum from condition II was shown here. The resonance of the olefinic proton corresponding to the cis olefin was known from the protodesilylation of alkenyl siloxane intermediate. The resonance of the olefinic proton corresponding to the trans olefin was rigorously analyzed when the reaction is trans selective.

![N-(but-3-en-1-yl)-4-methyl-N-(pent-4-en-1-yl)benzenesulfonamide (33')](image)

IR (neat, cm⁻¹) 3077, 2977, 2929, 2869, 1641, 1599, 1494, 1458, 1340, 1158, 1091, 993, 958; $^1$H-NMR (500 MHz, CDCl₃) δ 7.68 (d, $J = 8.0$ Hz, 2 H), 7.28 (d, $J = 8.0$ Hz, 2 H), 5.80-5.66 (m, 2 H), 5.06-4.96 (m, 4 H), 3.16 (t, $J = 7.5$ Hz, 2 H), 3.11 (t, $J = 7.5$ Hz, 2 H), 2.41 (s, 3 H), 2.28 (dt, $J = 7.3$, 7.3 Hz, 2 H), 2.04 (dt, $J = 7.1$, 7.1 Hz, 2 H), 1.63 (tt, $J = 7.5$, 7.5 Hz, 2 H); $^{13}$C-NMR (125 MHz, CDCl₃) δ 143.0, 137.4, 136.9, 134.6, 129.6,
127.1, 117.0, 115.2, 47.9, 47.7, 33.3, 30.7, 27.8, 21.4; HRMS (ESI-TOF) calcd. for C_{16}H_{23}NO_2S [M+Na]^+ 316.13417, found 316.13501.

(1S,2S)-1-(allyloxy)-2-(pent-4-en-1-yloxy)cyclohexane and its enantiomer (34')

IR (neat, cm^{-1}) 3078, 2934, 2861, 1640, 1366, 1315, 1271, 1243, 1208, 1161, 1106, 993; ^1H-NMR (500 MHz, CDCl_3) δ 5.97-5.89 (m, 1 H), 5.86-5.78 (m, 1 H), 5.29-5.26 (m, 1 H), 5.14-5.12 (m, 1 H), 5.04-5.00 (m, 1 H), 4.96-4.94 (m, 1 H), 4.16-4.10 (m, 2 H), 3.60-3.52 (m, 2 H), 3.23-3.14 (m, 2 H), 2.15-2.11 (m, 2 H), 1.98-1.95 (m, 2 H), 1.68-1.62 (m, 4 H), 1.31-1.17 (m, 4 H); ^13C-NMR (125 MHz, CDCl_3) δ 138.5, 135.8, 116.1, 114.5, 81.5, 80.8, 71.0, 69.2, 30.4, 30.2, 29.5, 23.6, 23.6; HRMS (ESI-TOF) calcd. for C_{14}H_{24}O_2 [M+Na]^+ 247.16685, found 247.16675.
Figure I-5. $^1$H NMR spectrum (expansion of 3.0 to 6.5ppm) of reaction mixture of 33’ under condition II.

Figure I-6. $^1$H NMR spectrum (expansion of 3.0 to 6.5ppm) of reaction mixture of 34’ under condition II.
(1S,2S)-1-(allyloxy)-2-(hex-5-en-1-yloxy)cyclohexane and its enantiomer (35’)

IR (neat, cm$^{-1}$) 3077, 2933, 1642, 1366, 1244, 1098; $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$
5.97-5.89 (m, 1 H), 5.85-5.77 (m, 1 H), 5.29-5.26 (m, 1 H), 5.14-5.12 (m, 1 H), 5.01-4.98
(m, 1 H), 4.95-4.93 (m, 1 H), 4.16-4.08 (m, 2 H), 3.59-3.51 (m, 2 H), 3.22-3.14 (m, 2 H),
2.06 (ddd, $J = 7.0$, 7.0, 7.0 Hz, 2 H), 1.97-1.95 (m, 2 H), 1.64-1.55 (m, 4 H), 1.49-1.43
(m, 2 H), 1.31-1.17 (m, 4 H); $^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$ 138.9, 135.8, 116.1, 114.4,
81.5, 80.8, 71.1, 69.8, 33.4, 30.4, 30.2, 29.8, 25.5, 23.6, 23.6; HRMS (ESI-TOF) calcd.
for C$_{15}$H$_{26}$O$_2$ [M+Na]$^+$ 261.18250, found 261.18388.

Figure I-7. $^1$H NMR spectrum (expansion of 3.0 to 6.5ppm) of reaction mixture of 35’
under condition II.
The monocyclized Z-alkene compound 35-Z (corresponding to what would be the monocyclized product of the RCM of 35*) obtained from protodesilylation of compound 16 was subjected to reaction condition II using second generation Grubbs catalyst. It was almost completely consumed to generate dimers and oligomers (Figure I-8).

**Figure I-8.** $^1$H NMR spectrum (expansion of 3.0 to 6.5ppm) of reaction mixture of 35-Z under condition II.

(1S,2S)-2-(allyloxy)cyclohexyl hex-5-enoate and its enantiomer (36*)
IR (neat, cm\(^{-1}\)) 3078, 2938, 2863, 1734, 1453, 1367, 1246, 1175, 1101, 994; \(^1\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.90-5.74 (m, 2 H), 5.26-5.23 (m, 1 H), 5.13-5.11 (m, 1 H), 5.04-4.96 (m, 2 H), 4.80-4.75 (m, 1 H), 4.10-4.06 (m, 1 H), 4.02-3.98 (m, 1 H), 3.29 (ddd, \(J = 8.5, 8.5, 4.0\) Hz, 1 H), 2.31 (dd, \(J = 7.2, 7.2\) Hz, 2 H), 2.09 (ddd, \(J = 7.0, 7.0, 7.0\) Hz, 2 H), 2.00-1.97 (m, 2 H), 1.76-1.63 (m, 4 H), 1.40-1.20 (m, 4 H); \(^13\)C-NMR (125 MHz, CDCl\(_3\)) \(\delta\) 172.9, 137.8, 135.3, 116.2, 115.2, 78.4, 74.8, 70.4, 33.9, 33.0, 29.9, 29.8, 24.1, 23.2; HRMS (ESI-TOF) calcd. for C\(_{15}\)H\(_{24}\)O\(_3\) [M+Na]\(^+\) 275.16177, found 275.16271.

**Figure I-9.** \(^1\)H NMR spectrum (expansion of 3.0 to 6.5 ppm) of reaction mixture of 36’ under condition II.
Figure I-10. $^1$H NMR spectrum of purified monocyclized product mixture from reaction of 36’ for ratio determination.

(1R,2S)-2-(allyloxy)cyclohexyl hex-5-enoate and its enantiomer (37’)

IR (neat, cm$^{-1}$) 3078, 2939, 2861, 1732, 1642, 1500, 1363, 1247, 1175, 1089, 994; $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 5.91-5.83 (m, 1 H), 5.80-5.73 (m, 1 H), 5.27-5.23 (m, 1 H), 5.14-5.11 (m, 1 H), 5.10-5.08 (m, 1 H), 5.03-4.96 (m, 2 H), 4.04 (dd, $J = 13.0$, 5.5 Hz, 1 H), 3.97 (dd, $J = 13.0$, 5.7 Hz, 1 H), 3.47-3.46 (m, 1 H), 2.34 (dd, $J = 7.5$, 7.5 Hz, 2 H), 2.11-2.07 (m, 2 H), 1.90-1.85 (m, 1 H), 1.81-1.64 (m, 4 H), 1.60-1.46 (m, 3 H), 1.42-1.27 (m, 2 H); $^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$ 173.1, 137.8, 135.2, 116.5, 115.2, 76.0, 70.9,
69.6, 33.9, 33.0, 27.9, 27.8, 24.2, 22.1, 21.6; HRMS (ESI-TOF) calcd. for C_{15}H_{24}O_{3} [M+Na]^+ 275.16177, found 275.16316.

\[ \text{(9aR,13aS,E)-3,4,5,8,9a,10,11,12,13,13a-decahydro-2H-benzo[b][1,4]dioxacycloundecin-2-one and its enantiomer (37-E)} \]

Yield 73% (colorless oil); IR (neat, cm\(^{-1}\)) 2934, 2858, 1725, 1443, 1363, 1256, 1210, 1159, 1139, 1109, 1089, 1073, 1047, 980; \(^1\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.64 (ddd, \(J = 15.0, 10.5, 4.0\) Hz, 1 H), 5.42 (ddd, \(J = 15.0, 10.2, 5.5\) Hz, 1 H), 4.44-4.40 (m, 1 H), 4.23-4.20 (dd, \(J = 13.0, 4.2\) Hz, 1 H), 3.77 (bs, 1 H), 3.40 (dd, \(J = 12.5, 11.0\) Hz, 1 H), 2.38-2.29 (m, 2 H), 2.12-2.07 (m, 1 H), 1.99-1.70 (m, 6 H), 1.56-1.47 (m, 2 H), 1.41-1.23 (m, 3 H); \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)) \(\delta\) 174.9, 132.0, 132.0, 75.1, 74.9, 72.2, 34.4, 33.6, 30.6, 25.8, 24.5, 24.2, 19.4; HRMS (ESI-TOF) calcd. for C_{13}H_{20}O_{3} [M+H]^+ 225.14852, found 225.16079.
Figure I-11. $^1$H NMR spectrum (expansion of 3.0 to 6.5ppm) of reaction mixture of 37’ under condition II (the major product was purifiable and is reported as $37^\text{-E}$).

(1S,2S)-1-(allyloxy)-2-(hept-6-en-1-yloxy)cyclohexane and its enantiomer (39’)

IR (neat, cm$^{-1}$) 3077, 2932, 2859, 1642, 1365, 1314, 1270, 1244, 1161, 1107, 994; $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 5.97-5.89 (m, 1 H), 5.84-5.76 (m, 1 H), 5.29-5.25 (m, 1 H), 5.14-5.12 (m, 1 H), 5.01-4.97 (m, 1 H), 4.94-4.91 (m, 1H), 4.16-4.08 (m, 2 H), 3.59-3.50 (m, 2 H), 3.22-3.13 (m, 2 H), 2.07-2.03 (m, 2 H), 1.96-1.95 (m, 2 H), 1.65-1.54 (m, 4 H), 1.44-1.33 (m, 4 H), 1.30-1.15(m, 4 H); $^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$ 139.0,
135.8, 116.0, 114.2, 81.6, 80.8, 71.1, 69.9, 33.7, 30.4, 30.2, 28.8, 25.7, 23.6, 23.6;
HRMS (ESI-TOF) calcd. for C_{16}H_{28}O_{2} \text{[M+Na]}^{+} 275.19815, \text{found} 275.19975.

**Figure I-12.** $^1$H NMR spectrum (expansion of 3.0 to 6.5ppm) of reaction mixture of 39’ under condition II.

(1S,2S)-2-(allyloxy)cyclohexyl hept-6-enoate and its enantiomer (40’)

IR (neat, cm$^{-1}$) 3078, 2937, 2863, 1735, 1641, 1453, 1353, 1174, 1101, 994; $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 5.90-5.74 (m, 2 H), 5.26-5.23 (m, 1 H), 5.13-5.11 (m, 1 H), 5.01-4.98 (m, 1 H), 4.95-4.93 (m, 1 H), 4.77 (ddd, $J = 8.5$, 8.5, 5.0 Hz, 1 H), 4.08 (dd, $J = 7.8,$
5.0 Hz, 1 H), 4.00 (dd, J = 7.8, 5.0 Hz, 1 H), 3.29 (ddd, J = 8.5, 8.5, 4.0 Hz, 1 H), 2.30 (dd, J = 7.2, 7.2 Hz, 2 H), 2.08-2.04 (m, 2 H), 1.99-1.97 (m, 2 H), 1.70-1.61 (m, 4 H), 1.46-1.20 (m, 6 H); $^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$ 173.0, 138.4, 135.3, 116.2, 114.6, 78.5, 74.8, 70.4, 34.5, 33.4, 29.9, 29.8, 28.3, 24.5, 23.2; HRMS (ESI-TOF) calcd. for C$_{16}$H$_{26}$O$_3$ [M+Na]$^+$ 289.17742, found 289.17766.

Figure I-13. $^1$H NMR spectrum (expansion of 3.0 to 6.5ppm) of reaction mixture of 40’ under condition II.

(1R,2S)-2-(allyloxy)cyclohexyl hept-6-enoate and its enantiomer (41’)

(1R,2S)-2-(allyloxy)cyclohexyl hept-6-enoate and its enantiomer (41’)

114
IR (neat, cm⁻¹) 3078, 2938, 2860, 1732, 1642, 1450, 1362, 1236, 1174, 1089, 994; ¹H-NMR (500 MHz, CDCl₃) δ 5.91-5.75 (m, 2 H), 5.27-5.23 (m, 1 H), 5.14-5.08 (m, 2 H), 5.02-4.98 (m, 1 H), 4.95-4.93 (m, 1 H), 4.04 (dd, J = 8.0, 5.5 Hz, 1 H), 3.98 (dd, J = 8.0, 5.5 Hz, 1 H), 3.48-3.46 (m, 1 H), 2.34 (dd, J = 7.2, 7.2 Hz, 2 H), 2.08-2.04 (m, 2 H), 1.90-1.85 (m, 1 H), 1.81-1.75 (m, 1 H), 1.70-1.28 (m, 10 H); ¹³C-NMR (125 MHz, CDCl₃) δ 173.2, 138.5, 135.2, 116.5, 114.6, 76.0, 71.0, 69.6, 34.5, 33.4, 28.3, 27.9, 27.8, 24.5, 22.1, 21.7; HRMS (ESI-TOF) calcd. for C₁₆H₂₆O₃ [M+Na]⁺ 289.17742, found 289.17867.

**Figure I-14.** ¹H NMR spectrum (expansion of 3.0 to 6.5ppm) of reaction mixture of 41’ under condition II.
Figure I-15. $^1$H NMR spectrum of purified monocyclized product mixture from reaction of 41’ for identification of trans isomer.

(±)-1-(2-((allyloxy)methyl)piperidin-1-yl)hept-6-en-1-one (38’)

IR (neat, cm$^{-1}$) 3076, 2934, 2859, 1642, 1426, 1357, 1243, 1178, 1134, 1104, 1057, 1028, 992; The $^1$H and $^{13}$C NMR spectra of many of this compound was complicated owing to the combination of rotamers. HRMS (ESI-TOF) calcd. for C$_{16}$H$_{27}$NO$_2$ [M+Na]$^+$ 288.19340, found 288.19396.
Figure I-16. $^1$H NMR spectrum (expansion of 3.0 to 6.5ppm) of reaction mixture of 38’ under condition II.

(1S,2S)-2-(hex-5-en-1-yloxy)cyclohexyl hex-5-enoate and its enantiomer (43’)

IR (neat, cm$^{-1}$) 3077, 2936, 2862, 1734, 1641, 1453, 1369, 1175, 1111; $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 5.83-5.74 (m, 2 H), 5.04-4.92 (m, 4 H), 4.75 (ddd, $J = 9.0$, 9.0, 4.5 Hz, 1 H), 3.54 (ddd, $J = 9.0$, 6.5, 6.5 Hz, 1 H), 3.40 (ddd, $J = 9.0$, 6.5, 6.5 Hz, 1 H), 3.21 (ddd, $J = 8.5$, 8.5, 4.0 Hz, 1 H), 3.32-2.29 (m, 2 H), 2.11-2.02 (m, 4 H), 2.00-1.95 (m, 2 H), 1.76-1.63 (m, 4 H), 1.56-1.50 (m, 2 H), 1.46-1.38 (m, 2 H), 1.37-1.19(m, 4 H); $^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$ 172.9, 138.8, 137.8, 115.2, 114.4, 79.0, 74.7, 69.3, 33.9, 33.5, 33.0, 29.8,
29.6, 25.5, 24.2, 23.3; HRMS (ESI-TOF) calcd. for $\text{C}_{18}\text{H}_{30}\text{O}_3 [\text{M+Na}]^+$ 317.20872, found 317.20928.

**Figure I-17.** $^1\text{H}$ NMR spectrum (expansion of 3.0 to 6.5ppm) of reaction mixture of 43’ under condition II.

![NMR Spectrum](image)

**Hex-5-en-1-yl 2-(pent-4-en-1-yloxy)benzoate (14’)**

IR (neat, cm$^{-1}$) 3077, 2976, 2940, 2870, 1728, 1704, 1641, 1601, 1583, 1491, 1469, 1452, 1416, 1386, 1302, 1251, 1164, 1133, 1080, 1049, 1013, 995; $^1\text{H}$-NMR (500 MHz, CDCl$_3$) $\delta$ 7.78-7.76 (m, 1 H), 7.44-7.41 (m, 1 H), 6.98-6.94 (m, 2 H), 5.89-5.77 (m, 2 H), 5.08-4.95 (m, 4 H), 4.30 (t, $J = 7.0$ Hz, 2 H), 4.04 (t, $J = 6.5$ Hz, 2 H), 2.30-2.25 (m, 2 H),
2.14-2.09 (m, 2 H), 1.96-1.90 (m, 2 H), 1.80-1.74 (m, 2 H), 1.58-1.52 (m, 2 H); $^{13}\text{C}$-NMR (125 MHz, CDCl$_3$) δ 166.7, 158.4, 138.4, 137.7, 133.1, 131.5, 120.9, 120.0, 115.2, 114.8, 113.1, 68.0, 64.7, 33.3, 30.0, 28.3, 28.2, 25.3; HRMS (ESI-TOF) calcd. for C$_{18}$H$_{24}$O$_3$ [M+Na]$^+$ 311.16177, found 311.16440.

**Figure I-18.** $^1$H NMR spectrum of purified monocyclized product mixture from reaction of 43’ for ratio determination.
Figure I-19. $^1$H NMR spectrum (expansion of 3.0 to 6.5ppm) of reaction mixture of 14’ under condition II.

(1S,2S)-2-(hept-6-en-1-yloxy)cyclohexyl hex-5-enoate and its enantiomer (44’)

IR (neat, cm$^{-1}$) 3077, 2934, 2861, 1734, 1641, 1452, 1417, 1369, 1247, 1175, 1111, 1026, 994; $^1$H-NMR (500 MHz, CDCl$_3$) δ 5.83-5.74 (m, 2 H), 5.04-4.91 (m, 4 H), 4.75 (ddd, $J$ = 9.0, 9.0, 4.5 Hz, 1 H), 3.53 (ddd, $J$ = 9.5, 6.5, 6.5 Hz, 1 H), 3.39 (ddd, $J$ = 9.0, 7.0, 7.0 Hz, 1 H), 3.20 (ddd, $J$ = 9.0, 9.0, 4.0 Hz, 1 H), 2.32-2.29 (m, 2 H), 2.11-2.07 (m, 2 H), 2.05-2.01 (m, 2 H), 1.99-1.95 (m, 2 H), 1.76-1.63 (m, 4 H), 1.54-1.49 (m, 2 H), 1.41-1.19 (m, 8 H); $^{13}$C-NMR (125 MHz, CDCl$_3$) δ 172.9, 138.9, 137.8, 115.2, 114.2, 79.0, 74.8,
69.5, 33.9, 33.7, 33.0, 30.0, 29.8, 28.7, 25.6, 24.2, 23.3; HRMS (ESI-TOF) calcd. for C_{19}H_{32}O_{3} [M+H]^+ 309.24242, found 309.24229.

**Figure I-20.** $^1$H NMR spectrum (expansion of 3.0 to 6.5ppm) of reaction mixture of 44' under condition II.

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\text{Hex-5-en-1-yl 2-(hex-5-en-1-yl)oxybenzoate (42')} \]

IR (neat, cm$^{-1}$) 3076, 2937, 2862, 1728, 1704, 1640, 1601, 1583, 1491, 1469, 1453, 1386, 1302, 1250, 1164, 1133, 1079, 1049, 995, 953; $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 7.78-7.76
(m, 1 H), 7.44-7.41 (m, 1 H), 6.97-6.94 (m, 2 H), 5.87-5.78 (m, 2 H), 5.05-5.01 (m, 2 H), 4.98-4.96 (m, 2 H), 4.30 (t, \( J = 6.8 \) Hz, 2 H), 4.03 (t, \( J = 6.5 \) Hz, 2 H), 2.15-2.10 (m, 4 H), 1.85 (tt, \( J = 7.1, 7.1 \) Hz, 2 H), 1.77 (tt, \( J = 7.2, 7.2 \) Hz, 2 H), 1.63-1.52 (m, 4 H); \( ^{13}\text{C}-\text{NMR} \) (125 MHz, CDCl\(_3\)) \( \delta \) 166.7, 158.4, 138.5, 138.4, 133.1, 131.5, 120.8, 120.0, 114.8, 114.7, 113.0, 68.6, 64.7, 33.4, 33.3, 28.6, 28.2, 25.3, 25.2; HRMS (ESI-TOF) calcd. for \( \text{C}_{19}\text{H}_{26}\text{O}_3 \) [M+Na\(^+\)] 325.17742, found 325.17910.

**Figure I-21.** \(^1\text{H} \) NMR spectrum (expansion of 3.0 to 6.5 ppm) of reaction mixture of 42’ under condition II.
H. Further transformation of macrocyclic alkenylsiloxanes

![Chemical Structure](image)

*tert*-Butyl (((10-*R*,11-*R*)-13-(((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-11-methyl-16-nitro-7,14-dioxo-2,3,4,5,6,7,8,10,11,12,13,14-dodecahydrobenzo[*b*][1,9,5]dioxazacyclohexadecin-10-y1)methyl)(methyl)carbamate (47)

Adapted from the reported procedure,\textsuperscript{244} to a stirred solution of compound 31 (78.0 mg, 0.097 mmol) in tetrahydrofuran/methanol (1:1, 2.0 mL, 50 mM), was added anhydrous potassium fluoride (17.0 mg, 0.29 mmol), potassium bicarbonate (29.0 mg, 0.15 mmol), and 30% hydrogen peroxide (110 mg, 0.97 mmol). The reaction was stirred at 23 °C for 3 h. The suspension was then filtered through a Celite pad and the filtrate was dried with sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography (gradient 40 – 60% ethyl acetate/hexane) to give compound 47 as a white solid (50.0 mg, 0.073 mmol).

Yield 75%; IR (neat, cm\(^{-1}\)) 3055, 2936, 2870, 1729, 1689, 1634, 1613, 1588, 1516, 1489, 1462, 1392, 1366, 1340, 1302, 1271, 1152, 1109, 1035; HRMS (ESI-TOF) calcd. for C\(_{36}\)H\(_{51}\)N\(_3\)O\(_{10}\) [M+Na]\(^+\) 708.34667, found 708.34659; \([\alpha]_D^{19} = -17.5\) (c = 2.2, CHCl\(_3\)).
tert-Butyl (((10R,11R,E)-7-ido-13-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-11-methyl-16-nitro-14-oxo-2,3,4,5,8,10,11,12,13,14-decahydrobenzo[b][1,9,5]dioxazacyclohexadecin-10-yl)methyl)(methyl)carbamate (48)

To a stirred solution of compound 31 (60.0 mg, 0.075 mmol) in dimethylformamide (3.7 mL, 20 mM), was added anhydrous potassium fluoride (8.7 mg, 0.15 mmol), potassium carbonate (15.0 mg, 0.15 mmol), and iodine (95.0 mg, 0.37 mmol). The reaction was heated to 50 °C and left for 18 hours. Then another portion of potassium fluoride (8.7 mg, 0.15 mmol), potassium carbonate (15.0 mg, 0.15 mmol), and iodine (95.0 mg, 0.37 mmol) was added. The resulting mixture was allowed to react at 50 °C for another 18 hours before quenched with 20 mL solution of 10% sodium bisulfite and 10% sodium bicarbonate. The aqueous solution was extracted with dichloromethane (15 mL x 3). The combined extracts were dried with sodium sulfate and concentrated in vacuo. Purification by column chromatography (gradient 20 – 50% ethyl acetate/hexane) gave compound 48 as yellow oil (42.0 mg, 0.053 mmol).

Yield 70%; IR (neat, cm⁻¹) 2968, 2935, 2866, 1687, 1631, 1613, 1588, 1515, 1466, 1392, 1365, 1341, 1302, 1272, 1250, 1158, 1110, 1083, 1034; HRMS (ESI-TOF) calcd. for C₃₆H₅₀N₅O₉I [M+H]+ 796.26645, found 796.26655; [α]D24 = -33.1 (c = 4.1, CHCl₃).
tert-Butyl (((10R,11R,Z)-13-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-11-methyl-16-nitro-14-oxo-7-(3-oxo-1-phenylbutyl)-2,3,4,5,8,10,11,12,13,14-decahydrobenzo[b][1,9,5]dioxazacyclohexadecin-10-yl)methyl)(methyl)carbamate (50, mixture of diastereomers)

Adapted from the reported procedure, to a round bottom flask armed with a condenser, was added compound 31 (77.0 mg, 0.096 mmol), anhydrous tetrahydrofuran (4.8 mL, 20 mM), trans-4-phenyl-3-buten-2-one (28.1 mg, 0.192 mmol), cyclooctadiene rhodium chloride dimer (9.5 mg, 0.019 mmol), and tetra-n-butylammonium fluoride (1.0 M solution in tetrahydrofuran, 144 µl, 0.14 mmol). The reaction was stirred under reflux for 3 h. The suspension was then concentrated in vacuo and purified by column chromatography (gradient 20 – 50% ethyl acetate/hexane) to give compound 50 as yellow oil (38.0 mg, 0.047 mmol).

Yield 48%; IR (neat, cm⁻¹) 2971, 2935, 2866, 1690, 1613, 1588, 1515, 1482, 1468, 1454, 1393, 1365, 1341, 1302, 1271, 1250, 1157, 1108, 1079, 1035; HRMS (ESI-TOF) calcd. for C₄₆H₆₁N₃O₁₀ [M+H]⁺ 816.44297, found 816.44253; [α]D²² = -31.1 (c = 4.5, CHCl₃).
Adapted from the reported procedure, to a stirred solution of compound 31 (55.0 mg, 0.069 mmol) in anhydrous tetrahydrofuran (1.4 mL, 20 mM), was added 1-(4-iodophenyl)ethanone (21.9 mg, 0.089 mmol), palladium(II) acetate (1.5 mg, 0.007 mmol), triphenylphosphine (3.6 mg, 0.014 mmol), and tetra-n-butylammonium fluoride (1.0 M solution in tetrahydrofuran, 103 µl, 0.10 mmol). The reaction was stirred at 23 °C for 5 h. The suspension was then concentrated in vacuo and purified by column chromatography (gradient 20 – 50% ethyl acetate/hexane) to give compound 49 as yellow oil (46.0 mg, 0.058 mmol).

Yield 85%; IR (neat, cm⁻¹) 2970, 2935, 2869, 1681, 1632, 1611, 1589, 1515, 1467, 1393, 1365, 1341, 1270, 1157, 1081, 1036, 984, 954; HRMS (ESI-TOF) calcd. for C₄₄H₅₇N₃O₁₀ [M+Na]⁺ 810.39362, found 810.39373; [α]D²² = -65.1 (c = 3.4, CHCl₃).

I. Conversion of alkenyl silanes to α-silyl ketones

Dihydroxylation: to a solution of vinylsilane (1 equiv.) and 4-methylmorpholine 4-oxide (2 equiv.) in mixed solvent (acetone, water, and tert-butyl alcohol, 20:1:1, 0.1 M) was
added 0.7% of a 2.5% solution (w/v) of osmium tetroxide in tert-butyl alcohol. The reaction mixture was warmed up to 50 °C for 24 h and cooled to room temperature, and then aqueous NaHSO₃ (20%), was added. The resulting mixture was concentrated on the rotary evaporator (room temperature) to remove most of the tert-butyl alcohol and acetone, saturated with NaCl, and extracted five times with EA. The extract was then concentrated *in vacuo* and purified by column chromatography (gradient 50 – 100% ethyl acetate/hexane).

*General procedure for silapinacol rearrangement*: to a stirred solution of dihydroxysilane (1 equiv.) in solvent (DCM, toluene or 1,4-dioxane, 25 mM) at 0 °C or r.t. was added the corresponding acid (1.2 equiv.). The resulting mixture was warmed up to the desired temperature and stirred for 16 hours. The reaction was then quenched with aqueous NaHCO₃ (saturated), extracted with EA, concentrated *in vacuo* and purified by column chromatography (gradient 20 – 50% ethyl acetate/hexane).

(3R,4R)-3-(dimethyl(phenyl)silyl)-1-tosylpyrrolidine-3,4-diol and its enantiomer(56)
Yield 99% (colorless oil); ¹H-NMR (500 MHz, CDCl₃) δ 7.65 (d, *J* = 8.0 Hz, 2 H), 7.52-7.51 (m, 2 H), 7.44-7.36 (m, 3 H), 7.28 (d, *J* = 8.0 Hz, 2 H), 7.05 (dd, *J* = 8.0, 15.5 Hz, 1 H), 3.46 (dd, *J* = 7.0, 14.5 Hz, 1 H), 3.40 (d, *J* = 12.5 Hz, 1 H), 3.33 (d, *J* = 12.5 Hz, 1 H), 3.02 (dd, *J* = 8.0, 9.5 Hz, 1 H), 2.42 (s, 3 H), 2.04 (d, *J* = 8.0 Hz, 1 H), 1.73 (s, 1 H), 0.39
(s, 3 H), 0.38 (s, 3 H); $^{13}$C-NMR (125 MHz, CDCl$_3$) δ 143.6, 134.3, 134.1, 133.6, 130.0, 129.7, 128.2, 127.4, 73.3, 72.2, 56.2, 51.2, 21.5, -5.9, -5.9.

(3$R$,4$R$)-3-(tert-butyldimethylsilyl)-1-tosylpyrrolidine-3,4-diol and its enantiomer (57)

Yield 94% (colorless oil); $^1$H-NMR (500 MHz, CDCl$_3$) δ 7.70 (d, $J$ = 8.5 Hz, 2 H), 7.33 (d, $J$ = 7.5 Hz, 2 H), 4.11(dd, $J$ = 8.0, 16.0 Hz, 1 H), 3.50-3.44 (m, 2 H), 3.37 (d, $J$ = 11.5 Hz, 1 H), 3.05 (dd, $J$ = 7.5, 10.0 Hz, 1 H), 2.55 (d, $J$ = 8.5 Hz, 1 H), 2.43 (s, 3 H), 1.88 (s, 1 H), 0.93 (s, 9 H), 0.03 (s, 3 H), -0.04 (s, 3 H); $^{13}$C-NMR (125 MHz, CDCl$_3$) δ 143.8, 133.6, 129.7, 127.5, 74.0, 73.4, 57.0, 51.1, 27.2, 21.5, 17.5, -7.5, -7.6.

1-Tosylpyrrolidin-3-one (60)

$^1$H-NMR (500 MHz, CDCl$_3$) δ 7.72 (d, $J$ = 8.5 Hz, 2 H), 7.38 (d, $J$ = 8.0 Hz, 2 H), 3.54 (d, $J$ = 7.5 Hz, 2 H), 3.49 (s, 2 H), 2.50 (t, $J$ = 7.5 Hz, 2 H), 2.45 (s, 3 H).
(3R,4R)-3-(dimethyl(phenyl)silyl)-1-tosylpiperidine-3,4-diol and its enantiomer (61)

Yield 82% (colorless oil); $^1$H-NMR (500 MHz, CDCl$_3$) δ 7.58-7.54 (m, 4 H), 7.42-7.26 (m, 5 H), 3.53-3.51 (m, 1 H), 3.46-3.41 (m, 2 H), 2.46-2.43 (m, 4 H), 2.36-2.31 (m, 1 H), 2.14 (s, 1 H), 2.03 (d, $J$ = 9.5 Hz, 1 H), 1.86-1.73 (m, 2 H), 0.46 (s, 3 H), 0.44 (s, 3 H);

$^{13}$C-NMR (125 MHz, CDCl$_3$) δ 143.9, 135.2, 134.4, 132.9, 129.8, 129.7, 127.9, 127.6, 70.4, 66.6, 52.0, 44.2, 28.8, 21.5, -4.6, -5.1.

(3R,4R)-3-(tert-butyldimethylsilyl)-1-tosylpiperidine-3,4-diol and its enantiomer (62)

Yield 92% (colorless oil); $^1$H-NMR (500 MHz, CDCl$_3$) δ 7.64-7.62 (m, 2 H), 7.35-7.33 (m, 2 H), 3.80-3.77 (m, 1 H), 3.69-3.64 (m, 1 H), 3.53-3.48 (m, 1 H), 2.51 (d, $J$ = 12.0 Hz, 1 H), 2.45 (s, 3 H), 2.20 (s, 1 H), 1.99 (d, $J$ = 11.0 Hz, 1 H), 1.87-1.80 (m, 2 H), 0.95 (s, 9 H), 0.13-0.08 (m, 6 H).

1-Tosylpiperidin-3-one (65)

$^1$H-NMR (500 MHz, CDCl$_3$) δ 7.67 (d, $J$ = 9.0 Hz, 2 H), 7.35 (d, $J$ = 8.0 Hz, 2 H), 3.60 (s, 2 H), 3.29 (t, $J$ = 6.7 Hz, 2 H), 2.44 (s, 3 H), 2.36 (t, $J$ = 6.7 Hz, 2 H), 2.04-1.99 (m, 2 H).
Racemic 4-(tert-butyldimethylsilyl)-1-tosylpiperidin-3-one (64)

$^1$H-NMR (500 MHz, CDCl$_3$) δ 7.65 (d, $J = 8.0$ Hz, 2 H), 7.35 (d, $J = 8.5$ Hz, 2 H), 3.62 (d, $J = 17.0$ Hz, 2 H), 3.46-3.39 (m, 2 H), 2.99-2.94 (m, 2 H), 2.44-2.42 (m, 4 H), 2.22-2.06 (m, 2 H), 0.91 (s, 9 H), 0.11 (s, 3 H), 0.01 (s, 3 H).

J. Conversion of alkenylsiloxanes to alkenyl halides

Dibromination/bromodesilylation: to a stirred solution of alkenylsiloxane (1 equiv.) in the corresponding solvent (50 mM) was added Br$_2$ (1.05 equiv.) at -78 °C. After 5 min at -78 °C, TBAF (1 M solution in THF, 4 equiv.) was added and the reaction was allowed to warm up to r.t. over 15 min and stirred at r.t. for another 15 min. The reaction was then quenched with aqueous Na$_2$S$_2$O$_3$ (10 %), extracted with EA. The extract was concentrated in vacuo and purified by column chromatography (gradient 0 – 10% ethyl acetate/hexane).

Iodination: adapted from reported procedure,$^{284}$ to a stirred solution of alkenylsiloxane (1 equiv.) in HFIP (50 mM) was added NIS (1.5 equiv.) at 0 °C. After 40 min at 0 °C, the reaction was then quenched with aqueous Na$_2$S$_2$O$_3$ (10 %), extracted with EA. The extract was concentrated in vacuo and purified by column chromatography (gradient 0 – 10% ethyl acetate/hexane).
(Z)-6-bromo-3,4,7,8,9,10-hexahydrobenzo[b][1,5]dioxacyclotetradecin-12(2H)-one

Yield 89% (colorless oil); IR (neat, cm\(^{-1}\)) 2940, 1698, 1601, 1491, 1452, 1384, 1300, 1244, 11166, 1133, 1097, 1053; \(^1\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.82-7.80 (m, 1 H), 7.46-7.43 (m, 1 H), 7.00-6.94 (m, 1 H), 6.26 (t, \(J = 6.7\) Hz, 1 H), 4.38 (t, \(J = 5.2\) Hz, 2 H), 4.16 (t, \(J = 5.0\) Hz, 2 H), 2.56-2.53 (m, 2 H), 2.44-2.40 (m, 2 H), 2.00-1.96 (m, 2 H), 1.89-1.84 (m, 2 H), 31.75-1.70 (m, 2 H); \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)) \(\delta\) 167.8, 157.6, 133.2, 132.1, 128.7, 125.6, 1206, 120.1, 112.1, 70.7, 65.0, 38.9, 31.7, 27.7, 25.6, 24.0.

(E)-6-iodo-3,4,7,8,9,10-hexahydrobenzo[b][1,5]dioxacyclotetradecin-12(2H)-one (76-E)

Yield 93% (colorless oil); IR (neat, cm\(^{-1}\)) 2953, 1702, 1601, 1490, 1452, 1384, 1354, 1302, 1251, 1193, 1164, 1132, 1097, 1052, 979; \(^1\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.77-7.75 (m, 1 H), 7.44-7.40 (m, 1 H), 6.99-6.92 (m, 2 H), 6.23 (t, \(J = 7.8\) Hz, 1 H), 4.40 (t, \(J = 5.0\) Hz, 2 H), 4.08 (t, \(J = 5.2\) Hz, 2 H), 2.65-2.62 (m, 2 H), 2.27-2.23 (m, 2 H), 1.84-1.80 (m, 6 H); \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)) \(\delta\) 168.3, 157.1, 140.1, 133.1, 132.2, 121.2, 120.2, 112.2, 101.6, 66.1, 63.7, 38.7, 28.9, 27.1, 26.6, 24.4.
(E)-3-bromo-10-methyl-5,6,7,8-tetrahydro-2H-benzo[b][1,4]oxaazacyclododecino-9(10H)-one (71-E)

Yield 79% (colorless oil); $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 7.35-7.31 (m, 1 H), 7.18-7.16 (m, 1 H), 7.03-7.00 (m, 1 H), 6.93-6.92 (m, 1 H), 6.23-6.19 (m, 1 H), 4.96 (d, $J = 12.5$ Hz, 1 H), 4.73 (d, $J = 13.0$ Hz, 1 H), 3.20 (s, 3 H), 2.26-2.20 (m, 1 H), 2.01-1.84 (m, 4 H), 1.54-1.37 (m, 3 H).

(Z)-6-bromo-4,5,8,9,10,11-hexahydro-2H-benzo[b][1,5]dioxacyclopentadecino-13(3H)-one (74-Z)

Yield 97% (colorless oil); $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 7.69-7.67 (m, 1 H), 7.43-7.40 (m, 1 H), 7.00-6.97 (m, 2 H), 5.73 (t, $J = 7.0$ Hz, 1 H), 4.30 (t, $J = 5.5$ Hz, 2 H), 4.02 (t, $J = 7.0$ Hz, 2 H), 2.50 (t, $J = 6.0$ Hz, 2 H), 2.27-2.24 (m, 2 H), 1.91-1.85 (m, 2 H), 1.94-1.78 (m, 2 H), 1.74-1.69 (m, 2 H), 1.64-1.59 (m, 2 H).
(E)-6-iodo-4,5,8,9,10,11-hexahydro-2H-benzo[b][1,5]dioxacyclopentadecin-13(3H)-one (77-E)

Yield 87% (colorless oil); $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 7.73-7.71 (m, 1 H), 7.43-7.40 (m, 1 H), 6.97 (dd, $J$ = 8.0, 8.0 Hz, 1 H), 6.91 (d, $J$ = 8.0 Hz, 1 H), 6.27 (t, $J$ = 8.2 Hz, 1 H), 4.38 (t, $J$ = 6.0 Hz, 2 H), 4.06 (t, $J$ = 5.2 Hz, 2 H), 2.57 (t, $J$ = 7.8 Hz, 2 H), 2.11-2.07 (m, 2 H), 1.92-1.86 (m, 2 H), 1.83-1.75 (m, 4 H), 1.60-1.54 (m, 2 H); $^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$ 168.2, 157.5, 140.7, 132.9, 131.5, 121.2, 120.1, 112.3, 101.9, 67.8, 64.5, 39.4, 30.2, 27.9, 27.7, 26.3, 25.7.

K. Enyne RCM reactions

Alkyne silylation and enyne RCM (un-optimized conditions): to a stirred solution of 91 (100 mg, 0.27 mmol) in 2.7 mL THF (0.1 M) at -78 °C was added 0.14 mL butyllithium (2 M in hexane, 0.28 mmol) followed by chlorotriethoxysilane (108 mg, 0.54 mmol). The reaction was stirred for 1 hour at -78 °C and warmed up to room temperature. THF was removed on the rotary evaporator (room temperature). Without workup or purification, the crude reaction mixture was charged with anhydrous toluene (2.7 mL) and 51 mg (0.082 mmol) HG-II, purged with ethylene gas, and left at room temperature for overnight. The reaction was then quenched with aqueous NaHCO$_3$ (saturated), extracted with EA, concentrated in vacuo and purified by column chromatography (gradient 20 –
50% ethyl acetate/hexane) to give compound 92 as yellow oil (20 mg, 0.038 mmol, 20% yield).

\[
(\mathbf{EtO}_3\mathbf{Si})\mathbf{N}^+\mathbf{Bn}^-\mathbf{Ts}\]

(R)-2-benzyl-1-tosyl-6-(1-(triethoxysilyl)vinyl)-2,3,4,7-tetrahydro-1H-azepine (92)

Yield 20% (colorless oil); \(^1\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.68 (d, \(J = 8.5\) Hz, 2 H), 7.30-7.27 (m, 2 H), 7.24-7.17 (m, 5 H), 5.91-5.90 (m, 1 H), 5.78-5.78 (m, 1 H), 5.72-5.71 (m, 1 H), 4.63 (d, \(J = 18.5\) Hz, 1 H), 4.01-3.95 (m, 1 H), 3.80 (q, \(J = 7.0\) Hz, 7 H), 3.03 (dd, \(J = 13.0, 3.5\) Hz, 1 H), 2.75 (dd, \(J = 13.0, 4.5\) Hz, 1 H), 2.37 (s, 3 H), 2.03-1.96 (m, 1 H), 1.70-1.58 (m, 2 H), 1.45-1.39 (m, 1 H), 1.22 (t, \(J = 7.0\) Hz, 9 H).

L. CM reactions

*General reaction conditions for cross metathesis:* to a stirred solution of vinylsiloxane or alkenylsiloxane (1 equiv.) in toluene (0.1 M) was added the simple olefin (allyl acetate, methyl acrylate, or methylvinylketone, 1 to 5 equiv.) and the catalyst (Cat. A, G-I, G-II, or HG-II, 20 mol%). The resulting mixture was warmed up to 50 °C and stirred for 16 hours. The crude reaction was then concentrated *in vacuo* and analyzed by \(^1\)H NMR.

\[
\text{Ph}^+\mathbf{OSi(OEt}_3^-\mathbf{O}
\]

Benzyl 5-(triethoxysilyl)hex-5-enoate (94a)
Yield 58% (colorless oil); $^1$H-NMR (300 MHz, CDCl$_3$) δ 7.36-7.31 (m, 5 H), 5.72-5.71 (m, 1 H), 5.67-5.66 (m, 1 H), 5.12 (s, 2 H), 3.81 (q, $J$ = 6.9 Hz, 6 H), 2.37 (t, $J$ = 7.2 Hz, 2 H), 2.19 (t, $J$ = 7.5 Hz, 2 H), 1.84 (tt, $J$ = 6.9, 6.9 Hz, 2 H), 1.22 (t, $J$ = 6.9 Hz, 9 H).

Benzyl 5-(diethoxy(methyl)silyl)hex-5-enoate (94c)

Yield 52% (colorless oil); $^1$H-NMR (300 MHz, CDCl$_3$) δ 7.36-7.31 (m, 5 H), 5.68-5.66 (m, 1 H), 5.58-5.57 (m, 1 H), 5.12 (s, 2 H), 3.75 (q, $J$ = 7.2 Hz, 4 H), 2.37 (t, $J$ = 7.8 Hz, 2 H), 2.18 (t, $J$ = 7.8 Hz, 2 H), 1.82 (tt, $J$ = 7.8, 7.8 Hz, 2 H), 1.20 (t, $J$ = 6.9 Hz, 6 H), 0.19 (s, 3 H).

Scheme I-22. Synthesis of 95e and 95a.

The synthesis of 95e started from hydrosilylation of oct-2-yn-1-ol (Scheme I-22). Following the general hydrosilylation procedure with acetone as solvent instead of DCM, compound 97 was obtained with 85% yield. Allylation of 97 gave rise to compound 95e with moderate yield. Surprisingly, hydrosilylation with HSi(OEt)$_3$ did not work. Instead, 1-(allyloxy)oct-2-yne was subjected to the hydrosilylation reaction. However, the reaction yielded the undesired regioisomer 96a as the major product that is not separable.
from the desired product 95a. Cross metathesis reactions with 95e or mixture of 95a and 96a were performed following the general procedure, but failed to generate any detectable amount of products.

(Z)-(1-(allyloxy)oct-2-en-3-yl)dimethyl(phenyl)silane (95e)

Yield 65% (colorless oil); \(^1\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.53-7.50 (m, 2 H), 7.36-7.32 (m, 3 H), 6.20 (t, \(J = 6.5\) Hz, 1 H), 5.82-5.75 (m, 1 H), 5.18-5.14 (m, 1 H), 5.11-5.08 (m, 1 H), 3.82 (d, \(J = 7.0\) Hz, 2 H), 3.74-3.73 (m, 2 H), 2.15 (t, \(J = 8.5\) Hz, 2 H), 1.40-1.34 (m, 2 H), 1.31-1.23 (m, 4 H), 0.87 (t, \(J = 7.0\) Hz, 3 H), 0.39 (s, 6 H).
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150


$^1$H and $^{13}$C NMR Spectra
165
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**Spectral Data**

- **Date:** 09/2019
- **Sample Code:** 012
- **Method:** 012

**Chemical Structures**

1. **(±)** Si(OEt)$_2$Me
2. 40-Z

**Spectral Details**

- **n/a:** Not applicable
- **ms:** Mass spectrometry
- **nm:** NMR spectrometry
- **mp:** Melting point
- **Rf:** Retention factor

**Peak Analysis**

- **ppm:** Parts per million
- **Area:** Area under the peak
- **Area R:** Area ratio

**Notes**

- **Wd:** Used
- **Wd:** Not used

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**Additional Information**

- **Si(OEt)$_2$Me**
- **40-Z**
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**Spectrum 22:**

- Compound: \(\pm\) Si(OEt)\(_2\)Me
- Peak: 22 ppm

**Spectrum 41-Z:**

- Compound: \(\pm\) 41-Z
- Peak: 41-Z ppm

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Note: The spectra are not labeled with specific chemical shifts or peak assignments, and the image quality is insufficient to provide detailed analysis.
(-) 41-Z

23°

Si(OEt)$_2$Me
Ts
N
33'

224
Chapter II.

Synthesis of Diversity-Oriented Synthetic Fragment Library and Biological Screening against GSK3β
Chapter II-1. Introduction

The use of small-molecule probes to shed light on both normal and disease-associated biological phenomena is a powerful approach in chemical biology.\textsuperscript{1-4} With respect to disease biology, such probes serve as useful starting points to produce new medicines. Technological advances have made high-throughput screening (HTS) the predominant mechanism through which these probes are discovered.\textsuperscript{5-11} The success of such an approach is inextricably linked to the identity and the quality of the screening collection.\textsuperscript{12,13} Synthetic organic chemistry has played a pivotal role in generating large collections of small molecules to be screened in various HTS campaigns. However, even the largest conceivable compound collections have fallen far short of sampling the chemical diversity space (an estimated to be upward of $10^{60}$ molecules containing up to 30 non-hydrogen atoms).\textsuperscript{14} Compounding the problem is the fact that most small molecule screening collections have substantial overlap, leading to a dearth of new chemical entities being discovered.\textsuperscript{15,16} Clearly, sources of chemicals with greater diversity are needed and alternative approaches toward probe development are warranted.

Fragment-based drug discovery (FBDD) is a complementary strategy to HTS, and is a well-validated approach toward generating small-molecule leads.\textsuperscript{17-23} The central theme underlying FBDD is the screening of a library of low molecular weight compounds (typically less than 250 g/mol),\textsuperscript{24} or “fragments,” against a specific biological target. The number of potential fragments with up to 12 heavy atoms (not including three- and four-membered ring structures) has been estimated at $10^7$.\textsuperscript{25} As a result, fragment libraries though substantially smaller, are still able to sample a higher percentage of the chemical
space compared to HTS screening collections.\textsuperscript{24-26} Because fragment molecules are small in size, they typically bind with lower affinity to a target protein (micromolar to millimolar range) compared with drug-like molecules (nanomolar to micromolar range). Consequently, the binding of a fragments is mostly captured by very sensitive biophysical techniques capable of picking up such weak interactions.\textsuperscript{27} Although the binding affinity of a fragment is low, it usually has high ligand efficiency which makes it a good starting point.\textsuperscript{21} After an appropriate fragment hit has been identified, it then serves as a constructive chemical anchor for the generation of a more potent ligand. This can be achieved by synthetically “growing” or “linking” the bound fragments.\textsuperscript{28-35} FBDD approaches are most efficiently executed when an X-ray or NMR structure of the target is available, giving critical binding information.\textsuperscript{36-45} With structural information in hand, follow-up chemistry is guided in a rational manner requiring fewer analogs to be made toward a potent lead compound.

The increasing popularity of fragment-based screening has led to an increase in the number of commercial vendors selling fragments. However, most fragment libraries used to date have been limited to aromatic heterocycles with an underrepresentation of chiral, enantiopure $sp^3$-rich compounds.\textsuperscript{46} These traditional planar $sp^2$-rich fragments have undoubtedly led to the generation of unique and high-quality starting points.\textsuperscript{22,47,48} In order to explore more difficult biological targets without well-defined binding pockets (\textit{e.g.} transcription factors), more emphasis should be placed upon developing compounds with different structural motifs.
Additionally, there have been several recent studies demonstrating the benefits of increasing the saturation content in drug-like compounds. The increased $sp^2$ content of a molecule was found to negatively correlate with the aqueous solubility, while positively correlating with lipophilicity, serum albumin binding, and CyP450 inhibition, suggesting that drug candidates with fewer aromatic rings were more “developable” than the lead compounds with more aromatic rings. The importance of $sp^3$-rich lead compounds in these studies can be extended to fragments, which support the hypothesis that $sp^3$-rich fragments can serve as higher-quality starting points in terms of physicochemical properties.

In addition to insufficient chemical diversity, buying fragments from various commercial vendors does not allow for efficient structure-activity relationship (SAR) determination. Because compounds were not selected on the basis of synthetic availability of their analogs, the chemistry to optimize hits from commercial collections can often be challenging and problematic. However, through proactively synthesizing a fragment collection, analogues with different regiochemical, stereochemical, and skeletal properties can be easily accessed to facilitate a rapid optimization after the primary screen.

The modification of fragments is another important step in the entire FBDD process. Guided by the structural information of the fragment binding against the macromolecule, positions and directions for “growing” or “linking” can be determined. The growth vector from $sp^2$ atoms (carbon or nitrogen) of traditional planar fragments is confined to the
plane of the ring. On the contrary, \( sp^3 \) atoms provide different geometric vectors off of a fragment, which enables orientation-dependent modifications of fragments into pockets of an active site that might otherwise be inaccessible to planar aromatic fragments. Researchers at Eli Lilly have recently demonstrated this notion (Figure II-1) by showing that the rigid bicyclic scaffold benzothiazine failed to afford optimal vectors for fragment growth into an adjacent pocket.\(^{52}\) The problem was solved by deplanarizing the aminothiazine, and introducing a quaternary methyl group to both exploit this topology and enhance chemical stability.

**Figure II-1.** Deplanarization of bicyclic fragment to enhance occupancy of S1 pocket of BACE1 and provide vector for introduction of an S3 binding element to increase affinity.\(^{52}\)

![Deplanarization of bicyclic fragment](image)

Taken together, these examples sufficiently show the benefits of putting an upfront effort into the synthesis of a diverse fragment collection. A fragment collection comprised of molecules that can be accessed using modular syntheses would circumvent downstream challenges. In an effort to generate such a library, a diversity-oriented synthesis (DOS) approach was undertaken.

After several years of exploration in the area of DOS, a build/couple/pair strategy (B/C/P) has recently emerged, which has been proven successful in producing molecules suitable
for HTS. In a recent paper, Dr. Alvin W. Hung, Mr. Alex Ramek, and I have demonstrated the application of this concept toward the generation of low molecular weight fragments. Short and efficient synthetic pathways following the logic of B/C/P were used to generate fragments that were structurally diverse and rich in \( sp^3 \)-content.

In addition to shape diversity and higher \( sp^3 \) content, the notion of synthetic accessibility of analogues was also incorporated into the design of fragments. In an ideal situation, one would like to have the ability of making modifications at every single atom of the scaffold. To achieve this goal, special attention was paid toward the synthetic accessibility and commercial availability of derivatives of the starting building blocks. Functional groups that have the potential to be diversified are also incorporated (see Chapter II-2-2). Another advantage of generating DOS fragments from the B/C/P strategy is the potential access to all possible stereoisomers including enantiomers and diastereomers in their enantiopure forms. Such a fragment library would enable the exploration of stereochemical structure-activity relationships, and more importantly allow for the differentiation between specific binders versus nonspecific binders. Such information is not included in commercial vendor collections.
Chapter II-2. Design and Synthesis of Diversity-Oriented Synthetic Fragment Libraries

1. Proline-based fragment library

Together with Dr. Alvin Hung, we designed a synthetic pathway starting with proline building blocks 1-3 (Scheme II-1). One factor for selecting these compounds was the readily available enantiomerically pure versions of all stereoisomers.\textsuperscript{70-72} Another benefit of using proline building blocks includes the extensive amount of chemistry focusing on the generation of pyrrolidine-based scaffolds.\textsuperscript{73} This information is constructive given that, if binders are found, numerous substituted pyrrolidines can be generated in the follow-up chemistry phase from a variety of known methods.

Scheme II-1. Application of a B/C/P approach to make bicyclic compounds starting from building blocks 1-3.

With compounds 1-3 in hand, we proceeded to the couple and pair phases of our
pathway. Scheme II-1 illustrates the implementation of this strategy. Intermolecular coupling reactions based around the building blocks yielded more densely functionalized pyrrolidine molecules (compounds 4'-11'),\textsuperscript{70,74,75} which were then paired under various conditions such as RCM, lactam formation, Michael addition, etc. Skeletally diverse bicyclic fragments that have 5,5, 5,6, 5,7, 5,8, and 5,9 fused ring systems were generated.

**Scheme II-2.** Using a B/C/P approach to obtain the full matrix of all possible diastereomeric products.

The devised B/C/P strategy not only created a small library of fragments of diverse skeletal structures, but also one rich in stereochemical variation. The mixing and matching of various stereogenic building blocks followed by versatile RCM pairing reactions generated a complete set of all possible diastereomers (Scheme II-2). The difference between various stereoisomers might be significantly large enough to completely obliterate binding. Therefore having a complete set of stereoisomers would facilitate the identification of the more potent stereoisomer and provided insights on
further design of a better inhibitor.

**Scheme II-3.** Reducing the olefin groups in a post-pairing phase to generate a new set of fragments.

In addition to structural and stereochemical diversity, we designed a third diversity element into our library: a “postpairing phase”. Fragments, because of their low molecular weight usually display weak binding affinities. Consequently, the particular functional groups within a given fragment are critical to the observation of a binding event. Subtle changes in functionalities and shape of fragments can result in significant changes to binding affinities. Accordingly, we determined that it would be imperative to take the scaffolds that were assembled in the B/C/P strategy and perform functional group interconversion reactions on them to produce new fragments (Scheme II-3). The result of these modifications would be to generate “functional group diversity” within the fragment library. Methyl esters were hydrolyzed to the carboxylic acids to give fragments 32, 33, and 34. These functional interconversions would have a significant impact on the
overall electronic properties of the fragments. The reduction of olefins in the fragments was also performed (Scheme II-3), resulting in increased $sp^3$ carbon atom content and a different conformational profile for the reduced fragments.

**Scheme II-4.** Synthesis of spirocyclic compounds.

Besides the design of the proline-based fragment library, my contribution to the execution of the synthesis was focused on the generation of spirocyclic fragments. Commercially available starting material 3’ (derivative of compound 3, see Scheme II-1) was coupled with allylamine (Scheme II-4). The RCM of 35 failed to generate the cyclized product because the thermodynamically favored rotamer of the secondary amide causes the two allyl groups to be positioned away from each other. To overcome this problem, 35 was methylated yielding the tertiary amide 36, which allowed for the two rotamers to be isothermic and interconvertible. The subsequent RCM of 36 gave rise to two enamides, a major product 37 and a minor product 38. In both products, migration of the double bond was observed, which is indicative of isomerization during the RCM reaction, presumably catalyzed by ruthenium hydride species.$^{76,77}$ Formation of the 6-
memed enamide 38 can be rationalized on grounds that the migration of the double bond occurred before the RCM releasing propene (instead of ethylene) to generate 38. However, migration of the double bond in situ could happen in the RCM of tertiary amide 42, but was not extensively studied. The desired spirocyclic product 43 was obtained with moderate yield (Scheme II-4).

2. Fragment library based on RCM of vinylsiloxanes

In addition to the proline-based fragment library mentioned above, a fragment library focusing on nitrogen-containing heterocycles was designed taking advantages of the RCM of vinylsiloxanes. The synthetic pathway (Scheme II-5) started from both enantiomers of allylglycine and propargylglycine, which are commercially available. Coupling of the Boc-protected amino acids with the corresponding propargylamine or allylamine gave rise to the tertiary amide with both alkene and alkyne functionality in it. After hydrosilylation of the alkyne, the vinylsiloxanes were subjected to the optimized RCM conditions described in Chapter I-2-2. The R group must be an alkyl group or sulfonyl group for the RCM reaction to occur. The presence of a N-aryl group did not permit RCM. It is rational that the N,N-phenylalkyl amide will adopt a different conformation than a N,N-bisalkyl amide, which may cause the dramatic change in the rates of the ring-closing reaction. If a m-nitrophenylsulfonyl (nosyl) group is used, it can be removed to release the secondary amide that has different hydrogen bonding ability compared to the sulfonamide or the tertiary amide. The switch between the alkene and alkyne enables the incorporation of silyl groups at either of the two $sp^2$-olefinic carbons in the RCM product so that both regioisomers are accessible.
Scheme II-5. Proposed synthetic pathway towards a 7-membered nitrogen-containing fragment library starting from amino acids and preliminary results.

Once the RCM product was obtained, a one-step transformation of the alkenylsiloxane moiety yielded either the ketone, alkenyl iodide, or the aryl-substituted alkene. Furthermore, an additional step would generate different functionalities from the parent fragments such as the secondary alcohol, substituted oxazole, or the saturated version of the 7-membered ring. Preliminary results have shown that both regioisomers 45 and 52
can be closed successfully with similar reaction outcome (Scheme II-5). Subsequent cross-coupling reactions can be executed from product 46 directly using Hiyama coupling\textsuperscript{79} or from the alkenyl iodide 48 using Suzuki coupling.\textsuperscript{80} In addition, the nosyl-protected amide 50 afforded the cyclized product with good yield. The synthesis of this library is currently being performed by Mr. Evan Liang.

**Figure II-2.** Substrates that failed to be closed under optimal RCM conditions (ring sizes of the desired products in parentheses).

To understand the generality of building up libraries around alkene- or alkyne-containing amino acids and amino alcohols, several other substrates were also prepared and subjected to the optimal RCM conditions. However, proline-based vinylsiloxanes failed to generate the 7- to 9-membered products with a conversion larger than 5% (Figure II-2, first row). Substrates based on protected allyl glycines or amino alcohols to provide 8-membered products also failed to be cyclized (Figure II-2, second row). This reflects the challenge of cyclizing medium size rings from 7- to 9-members due to high intrinsic ring strain as well as the constraint of the introduction of the silyl group.
Scheme II-6. Proposed synthetic pathway towards a nitrogen-containing fragment library starting from chiral amines.

Although the RCM of vinylsiloxanes to form rings larger than 7 is dependent on the nature of the substrates, it has been shown that the reaction is quite general towards the
formation of 5- and 6-membered rings in Chapter I-1-4 and I-2-1. We designed another pathway to access a diverse set of linked-bicyclic compounds and cyclic ketones with different ring sizes, stereoisomers, regioisomers, and various aromatic groups (Scheme II-6). Though the complete set of proposed 7-membered rings may not be fully accessible, I have explored the synthesis of 59 to test the feasibility of this approach (Scheme II-7). Starting with the (S)-amino alcohol 54, the tosyl-protected aziridine 55 was obtained in a one-pot transformation. The aziridine 55 was then opened with allylcyanocuprate reagent to install the terminal alkene. Propargylation of compound 56 gave rise to the alkenyl alkyne 57 with excellent yield. Hydrosilylation and RCM of 57 completed the synthesis of 7-membered alkenylsiloxane 59 in acceptable yields. The other starting chiral amines shown in Scheme II-6 are either commercially available or easily accessible from ring opening of chiral aziridines following the similar route to compound 56.

Scheme II-7. Preliminary results on RCM to form a 7-membered product.
Chapter II-3. Screen the Synthetic Fragment Library against GSK3β

1. Initial biophysical screening using thermal shift assay

The glycogen synthase kinase (GSK3β) was selected as the proof-of-concept target for screening the DOS fragments. GSK3β is a well-characterized target that is involved in a range of developmental and homeostatic cellular biology. Signaling abnormalities in the pathway involving this protein have been linked to a variety of human diseases. Pertaining to neuropsychiatric disease, growing evidence from human genetic studies implicates aberrant GSK3β signaling, including the discovery of the schizophrenia risk gene DISC1 as a direct binder and inhibitor of GSK3β,\textsuperscript{81} and the bHLH transcription factor TCF4 (ITF-2) as a GSK3β/B-catenin target gene\textsuperscript{82} making it a target of interest within the Stanley Center for Psychiatric Disease at the Broad Institute. To convincingly portray the role of GSK3β in neuropsychiatric disorders, a small-molecule ligand with exquisite potency and selectivity is required. To date, it has been difficult to obtain a small-molecule with such properties based on HTS. Therefore, a fragment-based approach has the potential to be impactful in an area where more conventional methods have not succeeded.

A florescence thermal shift assay\textsuperscript{83} was used to screen the entire fragment library against GSK3β. This method of screening has the advantage of robust throughput (96 well per 0.5 hour), enabling it for use as a primary screen against GSK3β. Our collaborator Dr. Steve Haggarty, of the Stanley Center and the Chemical Biology Platform had extensive
experience on using thermal shift with GSK3β. Accordingly, significant thermal shifts of 6-8 °C had been observed by them for known (nonselective) inhibitors of GSK3β. This would be beneficial, as it would translate into higher sensitivity when screening for fragments.

Optimization of the thermal shift assay against GSK3β was performed together with Dr. Alvin W. Hung and Mr. Alexander Ramek. Different combinations of protein concentration and dye concentration were tested until a good fluorescence curve was obtained with minimal amount of protein. Next the DMSO tolerance of GSK3β was determined. Given that high concentrations of fragment are required for the initial screening, we wanted to use a high percentage of DMSO in order to solubilize the ligand. However, higher concentration of DMSO can also interfere with the protein and eventually denature it. After several experiments, the optimal condition was determined to be 0.12 mg/mL GSK3β, 1:400 dilution of Sypro Orange from the original stock, and 2.5% DMSO. The assay was performed in 384-well plate format with final volume of 5 µL using a buffer solution containing 50 mM HEPES (pH 7.5) and 150 mM NaCl.

Next, known binders of the protein were tested under the optimized assay conditions to determine whether the assay was working as well as its sensitivity. In the GSK3β case, several known inhibitors were tested and all were discovered to give a positive thermal shift (Figure II-3). GW8510, an inhibitor of cyclin-dependent kinase-2, also inhibits T. brucei GSK-3 short protein with an IC₅₀ of 1 nM.²⁴ When tested at 20 µM, it showed a 6
°C positive thermal shift. Another inhibitor BRD4003 found by our collaborators, which has a $K_D$ of 130 nM (measured by SPR) also showed a shift around 3 °C. It will be interesting to note the correlation of thermal shift with $K_D$ in future experiments, when the whole set of data is collected.

Figure II-3. Thermal shift experiments on GSK3β with positive controls.

![Graph showing thermal shift experiments on GSK3β with positive controls.](image)

Top traces: fluorescence level over temperature; bottom traces: first derivative of fluorescence level over temperature. Blue: DMSO control; green: compound BRD4003; pink: compound GW8510.

ATP is a cofactor of GSK3β and can also bind to the protein. As an additional control, we desired to determine whether the binding of ATP would stabilize the protein or not. To our surprise, when tested at 240 µM of ATP, the melting point of the protein was unchanged, suggestive of no interaction. By checking our assay conditions carefully, we found out that the assay buffer did not contain Mg(II), which is required for the activity of the protein. We then retested ATP in the presence of 10 mM MgCl₂, and a 2.0 °C
thermal shift was observed. Therefore, Mg(II) is required for ATP binding but not for the positive controls we had tested. We decided to screen our compound collection with and without Mg(II) in order to compare the results.

The screening of our fragment collection without Mg(II) yield 6 compounds that showed a positive thermal shift value larger than 0.4 °C (Figure II-4). Compound 60, 61, and 62 gave no shift when the assay was performed in the presence of Mg(II). However compound 63, 64, and 65 showed slight increases in their shift values when Mg(II) was present. We speculate that Mg(II) binding causes a conformational change of the protein that disfavors the binding of the first 3 compounds but favors the binding of others. This suggests to us that the first three compounds have distinct binding modes that might be interesting to study. However, we decided to follow up with the compounds that bind to the protein both with and without Mg(II).

Figure II-4. Hits from thermal shift assays against GSK3β in the absence (red value) or presence (blue value) of Mg(II).
2. Initial SAR of several analogues and their inhibitory activities

Compounds 63-65 were synthesized via a tandem Ullmann reaction/cyclodehydration sequence\textsuperscript{85} from different starting materials (Scheme II-8). Specifically, the sequence involves a one-pot reaction involving an intermolecular cross-coupling reaction between an amino group of the amino acid and an aryl bromide, followed by an intramolecular cyclization reaction that forms the amide bond. There are several desirable features of this reaction. First, aryl bromides with different substitutions can be used including the pyridyl bromide. Second, the other building block of this reaction is an amino acid. Various amino acids, either naturally occurring or non-naturally occurring, are commercially available with both enantiomers. Rapid access to analogues and stereoisomers will enable efficient growth of the fragment once a hit is identified, which also facilitates the study of (stereochemical) structure-activity relationships. Third, the free amine group can be easily modified, and the secondary amide moiety can be reduced to the corresponding amine. Last, starting with a secondary amine ($R_2^2 = \text{alkyl}$), the tertiary amide can be accessed that has totally different hydrogen bonding ability and steric compared to the secondary amide.

Scheme II-8. Versatility of the Ullmann reaction/cyclodehydration sequence.

However, there are several notable problems associated with this reaction. First, the
reaction is performed at 120 °C. Under such harsh conditions, epimerization of the chiral center within the amino acid occurs potentially at any stage of the reaction. Second, the use of aryl-substituted glycines leads to serious decomposition without isolation of desired product. Third, certain products can be further oxidized to the imine in solution at room temperature, eliminating the chiral center and posing challenges for storage of such compounds in a stock solution. To overcome the third limitation, small aliquots of each compound (mostly crystalline powders) were prepared and stored at -20 °C. Before running the assays, each compound was made freshly and discarded at the end of the day.

Enabled by the efficient Ullmann reaction, analogues were easily accessed. Thermal shifts of these compounds were obtained and listed in Figure II-5. At this point, we were interested in whether these compounds will inhibit the kinase activity of GSK3β. An ADP-Glo™ assay was adopted for this purpose. We measured the inhibitory activity of the compounds at a single concentration of 1 mM whenever soluble. The results are shown in Figure II-5.

**Figure II-5.** Results of thermal shift assay and inhibition assay with several analogues.
If the inhibitory activity is caused by non-specific aggregation of the compound, both enantiomers will have the same activity since enantiomers have the same physicochemical properties. Our results showed that the (\(R\))-enantiomer 66 is more active than the (\(S\))-enantiomer 65, which suggests the binding interaction and inhibitory activity are real and not due to promiscuous interactions. Other results also showed that the position of the pyridyl nitrogen matters. Among the four regioisomers 66-69, compound 66 with nitrogen atom adjacent to the amide yielded the optimal scaffold. Interestingly, when the pyridyl nitrogen is adjacent to the amine, the (\(R\))-enantiomer 69 is less active than the (\(S\))-enantiomer 70. The reversion of stereochemical SAR indicated that the binding modes of the two scaffolds (65, 66 versus 69, 70) are probably different from each other.

3. Identification of the key binding motif of a particular scaffold

We chose to follow up with the enantiomeric pair 65 and 66 first. It has been reported that a pyridylamide moiety is able to form a hydrogen-bonding network with the backbone carbonyl and amide hydrogen of the peptide through the amide hydrogen and pyridyl nitrogen.\(^{86-88}\) We hypothesized that this moiety is a key interaction for the small fragment. To test our hypothesis, perturbations of the moiety or the pattern were achieved synthetically (Figure 11-6). The secondary amide of compound 65 was reduced to generate the secondary amine 76, thereby deleting the carbonyl oxygen that previously served as a hydrogen bond accepter, and abolishing the binding interaction. Starting from N-methyl bromopyridylamine, tertiary amide 77 was obtained which not only removed the hydrogen bond donor ability but also increase the steric hindrance of the amide; and
again the binding interaction was abolished. A 7-membered analogue 79 was made to disturb the dihedral angle between the pyridyl group and the amide moiety, and it is also inactive compared to the parent compound. However, changes that have little interference with the key binding motif retain activity to some degree such as compound 75 (commercially available) and 78 (accessed via oxidation of 65).

**Figure II-6.** Key binding interaction probed by perturbations of compound 65 and 66.

4. Growth of the fragment to improve potency and confirmation by NMR and ITC

After the recognition of the key binding motif, we pursued the question of where to grow compound 66 to increase potency (Figure II-7). Increased potency of compound 73 and 74 indicated that there might be a pocket at the position where the substituent is pointing.

**Figure II-7.** Growth of fragment 66 to increase potency.
The geminal-dimethyl analogue 80 and cyclobutenyl analogue 81 were synthesized and shown to be less potent. The oxidized product 78 also displays less potency. Taken all together, these results indicated that the orientation of the substituent is important for picking up the favorable interactions, and there might be a hydrophobic pocket. Therefore, several analogues containing substituted alkyl, gem-dialkyl, benzyl, hydroxybenzyl, and heteroaromatic substituents from the corresponding amino acids were synthesized and tested using the thermal shift assay. Generally speaking, compounds that have heteroaromatic groups increase the binding interaction, among which the indole analogue 91 was found to be the most potent one.

STD and WaterLOGSY experiments41,44 were performed to confirm the binding interaction between compounds 66, 74, and 91 with GSK3β. The results are shown in Figure II-8. Using 5 µM of GSK3β and 500 µM of compound 74 or 91 for the NMR experiment, binding interactions of both were clearly shown in either experiment indicated by the increase of ligand signal in the presence of GSK3β. For compound 66, the binding interaction was also observed at 5 µM of GSK3β. However, the results shown in Figure II-8 were performed with 20 µM of GSK3β and 500 µM ligand in order to increase the signal/noise ratio. Next, an ATP competition assay was performed to determine whether compound 66 is an ATP-competitive binder or not. When ATP was added to the solution with both protein and compound 66 at a final concentration of 500 µM in the presence of 10 mM MgCl₂, signals corresponding to ATP were observed, which can be more clearly seen in the WaterLOGSY experiment. Interestingly, decreases of ligand signals in both experiments were observed indicating that ATP was competing
with compound 66.

**Figure II-8.** STD and WaterLOGSY NMR experiment of compound 74 (top left), 91 (top right), and 66 (bottom two).

ITC experiments were then performed to measure the binding constant of compounds 66, 74, and 91 (Figure II-9). The $K_d$ of each compound was determined to be 0.9 mM, 80 µM, 14 µM respectively, which correlate well with their thermal shift values.
Figure II-9. ITC results of compound 66 (top left), 74 (top right), and 91 (bottom).
5. Current exploration and future directions

X-Ray crystallography studies are being performed in Prof. Steve Almo’s group, which will help us to capture the binding interactions and guide further optimization of the inhibitor in a rational way.

Until all the experiments mentioned above were completed, the enantiopurity of some compounds was measured by chiral SFC analysis. The enantiomeric excess (ee) of compound 66 is 62%, of 67 is 98%, of 68 is 98%, of 69 is 80%, of 70 is 28%, of 91 is 34%. These results indicate that the racemization of the chiral center during the Ullmann reaction is a serious problem. Without enantiomerically pure forms of these compounds, the comparison between them is invalid, and Kd or IC50 values of the grown fragments are not accurate.

We explored ways to make the enantiopure compounds either by recrystallization or via a different synthetic route for compounds that cannot be easily recrystallized. It was found that the ee of compound 66 was improved by about 5-10% after one round of recrystallization from an initial ee of around 50%. At the same time, a different synthetic route was explored according to a reported procedure. As shown in Scheme II-9, 3-fluoro-2-nitropyridine underwent a S_NAr reaction with an amino ester to generate compound 93. The one-pot reduction/cyclization under transfer-hydrogenation conditions was low yielding. Nevertheless, the ee of isolated product 66n is determined to be 98%. To improve yield of this reaction, classical hydrogenation condition with H2 and Pd/C was adopted. The reduction of the nitro group in compound 94 was finished after 3 hours.
However, the cyclization did not proceed efficiently. Ammonium formate was then added to the reaction mixture after removal of H₂ from the flask. The reaction went to completion after 12 hours at 40 °C, yielding the desired product 65n with 55% yield and 98% ee. This new route did lead to a remarkable improvement of enantiopurity compared to the Ullmann reaction. Patrick Sheehan is currently resynthesizing several key compounds with high enantiopurity so that a valid comparison can be made and accurate binding affinities can be determined.

Another way of solving the enantiopurity issue is to run the Ullmann reaction with α-disubstituted amino acids. By having an α-methyl group instead of the α-H in compound 91, both the epimerization and oxidation can be prevented at the same time.

**Scheme II-9.** Synthetic route towards enantiopure aza-quinoxalinone.
Chapter II-4. Conclusion and Future Directions

The concept of DOS was applied to the synthesis of novel fragment libraries to expand into the chemical space not covered by traditional fragments. The DOS fragment library was designed to have higher $sp^3$ content and more stereochemical and skeletal diversity compared to commercial fragment libraries. Modular synthetic pathways following the logic of B/C/P has enabled the access of all possible stereoisomers in their enantiopure forms. The inclusion of all stereoisomers provided primary SSAR information that was used to distinguish between specific binders from nonspecific binders and guide modification of the initial hit. Synthetic accessibility of derivatives of building blocks and pre-imbedded versatile functional groups allowed rapid access of analogues to gain SAR information and optimization of the initial hit. Such efforts can be made to increase the potency of the initial hit prior to the gathering of structural information from X-Ray crystallography studies.

To evaluate the DOS fragments that have been synthesized, GSK3β was selected as the proof-of-concept target. After initial hits were identified by thermal shift screenings, analogues were made efficiently via the Ullmann reaction and evaluated by thermal shift assays and biochemical assays. The $K_D$ was rapidly improved from 0.9 mM to 14 µM as determined by ITC experiments. However, the enantiopurity of analogues accessed by the Ullmann reaction are not consistently high, which complicated the comparison between different analogues and the determination of binding affinities of these compounds. The experience so far taught us that the design of synthetic pathways and the quality of the compounds within a library are very important for the success and
efficiency of the fragment-based approach and are worth the proactive effort. Progress is currently being made to solve the enantiopurity issue of the analogues. In addition, various DOS fragments from different synthetic pathways including the ones mentioned before are being made to increase the size of our library. These novel libraries will be screened against a broad array of biological targets to evaluate their biological activities.
Experimental Section

1. Material and Methods

Except as otherwise noted, reactions were carried out under argon. All reaction solvents except acetone and pyridine were dispensed from a solvent purification system wherein solvents are passed through a packed activated alumina column. Acetone was Aldrich 99.5+% histological grade. Pyridine was Aldrich 99.8% histological grade. NMR spectra were recorded at 500 MHz or 300 MHz using a Varian I-500 or M-300 instrument. Chemical shifts for proton NMR spectra are reported in parts per million downfield from tetramethylsilane and were referenced to residual protonated solvent (CHCl₃: d 7.26, C₆H₆: d 7.15, CH₃OH: 3.34, DMSO: 2.54). Chemical shifts for carbon NMR spectra are reported in parts per million downfield from tetramethylsilane and referenced to protonated solvent (CHCl₃: d 77.0, C₆H₆: d 128.0, CH₃OH: 49.9, DMSO: 39.5). Data are represented as follows: chemical shift (multiplicity [bs = broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet], coupling constants in Hertz, integration). High-resolution mass spectra were obtained through the Harvard University mass spectrometry facility. Infrared spectra were obtained with a Nicolet IR100 FTIR from Thermo Scientific. Optical rotations were obtained using digital polarimeter Autopol IV (Rudolph research Analytical) with a 1 mL cell and a 1 dm path length. All reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) using E. Merck silica gel 60 F254 precoated plates (0.25 mm). Flash chromatography was performed either with the indicated solvent on E. Merck silica gel 60 (230-400 mesh) or using a CombiFlash companion system (Teledyne ISCO, Inc.) with pre-packed FLASH silica gel columns (Teledyne ISCO, Inc.). SFC/MS chromatography was performed with
a Berger analytic SFC (Waters ZQ Mass Spectometer) using CO$_2$ and isopropanol as the mobile phase and using a Chiralpak® AD-H column purchased from Chiral Technology Inc. (column length: 4.6x250mm, particle size: 5um).

2. Experimental procedures

A. Synthesis of proline-based fragment library

The syntheses and characterizations of compounds 1-34 can be found in the paper (Proc. Natl. Acad. Sci. U.S.A. 2011, 108, 6799). The synthetic procedures of compounds 35-44 (Scheme II-4) are described as followings.

To a stirred solution of proline derivative 3’ (0.200 g, 0.78 mmol), allylamine (0.067 g, 1.18 mmol), ethyl(hydroxyimino)cyanoacetate (0.167 g, 1.18 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.225 g, 1.18 mmol) in dichloromethane (16 mL) was added triethylamine (0.328 mL, 2.35 mmol). The reaction was stirred for 4 h at 23 °C. Saturated aqueous sodium bicarbonate (15 mL) was added to the reaction mixture and the aqueous phase was extracted with dichloromethane (3 x 15 mL). The combined extracts were dried over sodium sulfate and concentrated in vacuo. Purification by column chromatography (gradient 20 – 30% ethyl acetate/hexane) gave the ally amide 35 as colourless oil (0.210 g, 91%).

To a stirred solution of ally amide 35 (0.066 g, 0.22 mmol) in anhydrous dimethylformamide (4.5 mL), methyl iodide (0.64 g, 4.5 mmol) was added. The resulting solution was cooled to 0 °C and sodium hydride (60% in mineral oil, 26.9 mg,
0.67 mmol) was added. The reaction was stirred for 4 h at 0 °C. Saturated aqueous ammonium chloride (20 mL) was added to the reaction mixture and the aqueous phase was extracted with dichloromethane (3 x 15 mL). The combined extracts were dried over sodium sulfate and concentrated in vacuo. Purification by column chromatography (gradient 20 – 30% ethyl acetate/hexane) gave 36 as colourless oil (0.050 g, 72%).

To a stirred mixture of 36 (0.070 g, 0.23 mmol) in anhydrous toluene (23 mL) was added Grubbs 2nd generation catalyst (0.019 g, 0.02 mmol). The reaction mixture was heated to 50 °C for 4 h followed by the addition of another portion of Grubbs 2nd generation catalyst (0.019 g, 0.02 mmol). After another 12 hours at 50 °C, ethylvinylether (0.327 g, 4.5 mmol) was added to the reaction and then the solvent was removed in vacuo. Purification by column chromatography (gradient 25 – 60% ethyl acetate/hexane) gave product 37 as yellow oil (0.038 g, 60%) and product 38 (0.005 g, 8%) as yellow oil. Deprotection of the Boc group on either product was performed in 2 ml neat trifluoroacetic acid for 5 minutes. The reaction was then concentrated in vacuo. The remaining TFA was quenched with anhydrous Na₂CO₃. The extracts were extracted with DCM and concentrated in vacuo respectively to give product 39 and 40 (quantitative).

\[(S)-7\text{-methyl-1,7-diazaspiro[4.6]undec-8-en-6-one (39)}\]

$^1$H-NMR (500 MHz, CDCl₃) δ 5.86 (d, $J = 9.5$ Hz, 1 H), 5.36 (ddd, $J = 9.5, 4.5, 4.5$ Hz, 1 H), 3.65-3.60 (m, 1 H), 3.42-3.37 (m, 1 H), 3.17 (s, 3 H), 2.65-2.61 (m, 1 H), 2.51-2.46
(m, 1 H), 2.40-2.22 (m, 4H), 2.19-2.14 (m, 1 H), 1.87-1.79 (m, 1 H); $^{13}$C-NMR (125 MHz, CDCl$_3$) δ 170.8, 128.4, 117.1, 73.0, 45.5, 37.9, 31.9, 31.9, 23.8, 23.6; HRMS (ESI-TOF) calcd. for C$_{10}$H$_{16}$N$_2$O $[M+H]^+$ 181.13354, found 181.13419.

(R)-7-methyl-1,7-diazaspiro[4.5]dec-8-en-6-one (40)

$^1$H-NMR (500 MHz, CDCl$_3$) δ 6.00-5.98 (m, 1 H), 5.16-5.12 (m, 1 H), 3.25-3.21 (m, 1 H), 3.09 (s, 3 H), 3.08-3.04 (m, 1 H), 2.53-2.49 (m, 1 H), 2.33 (dd, $J = 17.0$, 6.0 Hz, 1 H), 1.93-1.80 (m, 4 H); $^{13}$C-NMR (125 MHz, CDCl$_3$) δ 167.6, 130.5, 104.7, 66.9, 46.8, 35.0, 34.5, 29.7, 23.3; HRMS (ESI-TOF) calcd. for C$_9$H$_{14}$N$_2$O $[M+Na]^+$ 189.09983, found 189.09997.

(S)-7-methyl-1,7-diazaspiro[4.6]undecan-6-one (22)

A solution of 39 (0.007 g, 0.039 mmol) and palladium hydroxide (20 wt.% Pd on carbon, wet, 0.011 g) in methanol (8 mL) was stirred at 25 °C under an atmosphere of hydrogen gas for 16 h. The suspension was then filtered through a Celite pad and the filtrate was concentrated in vacuo to give compound 22 as a yellow solid (0.006 g, 90%). $^1$H-NMR (500 MHz, CDCl$_3$) δ 9.46 (bs, 1H), 3.60-3.54 (m, 2H), 3.36-3.31 (m, 1H), 3.29-3.25 (m, 1H), 3.08 (s, 3H), 2.35-2.30 (m, 2H), 2.25-2.15 (m, 2H), 2.03-1.85 (m, 4H), 1.72-1.63
(m, 1H), 1.53-1.45 (m, 1H); $^{13}$C-NMR (125 MHz, CDCl$_3$) δ 171.7, 73.4, 51.1, 45.1, 39.0, 32.0, 31.8, 26.9, 25.0, 24.6; HRMS (ESI-TOF) calcd. for C$_{10}$H$_{18}$N$_2$O [M+H]$^+$ 183.14919, found 183.14985.

To a stirred solution of proline derivative 3’ (0.110 g, 0.43 mmol), (S)-methyl 2-aminopent-4-enoate trifluoroacetic acid (0.125 g, 0.52 mmol), ethyl(hydroxyimino)cyanoacetate (0.092 g, 0.65 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.124 g, 0.65 mmol) in dichloromethane (16 mL) was added triethylamine (0.240 mL, 1.72 mmol). The reaction was stirred for 4 h at 25 °C. Saturated aqueous sodium bicarbonate (15 mL) was added to the reaction mixture and the aqueous phase was extracted with dichloromethane (15 mL, 3 times). The combined extracts were dried over sodium sulfate and concentrated in vacuo. Purification by column chromatography (gradient 20 – 30% ethyl acetate/hexane) gave the ally amide 41 as colourless oil (0.140 g, 89%).

To a stirred solution of the secondary amide 41 (0.140 g, 0.38 mmol) in anhydrous dimethylformamide (7.6 mL), methyl iodide (2.17 g, 15.3 mmol) was added. The resulting solution was cooled to 0 °C and sodium hydride (60% in mineral oil, 45.8 mg, 1.15 mmol) was added. The reaction was stirred for 4 h at 0 °C. Saturated aqueous ammonium chloride (20 mL) was added to the reaction mixture and the aqueous phase was extracted with dichloromethane (15 mL, 3 times). The combined extracts were dried over sodium sulfate and concentrated in vacuo. Purification by column chromatography
(gradient 20 – 30% ethyl acetate/hexane) gave the tertiary amide 42 as colourless oil (0.129 g, 89%).

To a stirred mixture of 42 (0.129 g, 0.34 mmol) in anhydrous dichloromethane (16 mL) was added Grubbs 2nd generation catalyst (0.058 g, 0.07 mmol). The reaction mixture was heated to reflux for 16 h. The solvent was removed in vacuo. Purification by column chromatography (gradient 25 – 45% ethyl acetate/hexane) gave product 43 as a white solid (0.012 g, 34%). Deprotection of the Boc group on either product with 2 ml neat trifluoroacetic acid followed by concentration in vacuo gave the product 44 as yellow oil (quantitative).

\[
(5R,8S,Z)\text{-methyl 7-methyl-6-oxo-1,7-diazaspiro[4.7]dodec-10-ene-8-carboxylate (44)}
\]

\(^1\text{H-NMR (500 MHz, CDCl}_3\text{)} \delta 5.75-5.68 (m, 2 H), 5.20 (dd, J = 10.2, 6.2 Hz, 1 H), 3.78 (s, 3 H), 3.49 (bs, 2 H), 3.17-3.13 (m, 1 H), 2.87-2.83 (m, 5 H), 2.78-2.71 (m, 1 H), 2.51-2.47 (m, 1 H), 2.17-2.08 (m, 2 H), 2.03-1.98 (m, 1 H); \(^{13}\text{C-NMR (125 MHz, CDCl}_3\text{)} \delta 169.7, 168.9, 129.8, 125.1, 73.0, 59.6, 52.9, 45.8, 36.9, 35.0, 33.9, 28.0, 22.4; HRMS (ESI-TOF) calcd. for C\text{13}H\text{20}N\text{2}O\text{3} [M+H]^+ 253.15467, found 253.15519.
(5S,8S)-methyl 7-methyl-6-oxo-1,7-diazaspiro[4.7]dodecane-8-carboxylate (27)

A solution of 44 (0.019 g, 0.075 mmol) and palladium hydroxide (20 wt.% Pd on carbon, wet, 0.011 g) in methanol (8 mL) was stirred at 25 °C under an atmosphere of hydrogen gas for 2 h. The suspension was then filtered through a Celite pad and the filtrate was concentrated in vacuo to give compound 27 as yellow oil (0.016 g, 84%). \(^1\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta\) 4.80 (dd, \(J = 7.5, 7.5\) Hz, 1 H), 3.80 (s, 3 H), 3.50-3.43 (m, 2 H), 2.95 (s, 3 H), 2.63-2.60 (m, 1 H), 2.26-2.16 (m, 2 H), 2.11-2.01 (m, 4 H), 1.98-1.92 (m, 1 H), 1.83-1.79 (m, 1 H), 1.70-1.61 (m, 2 H), 1.36-1.28 (m, 1H); \(^13\)C-NMR (125 MHz, CDCl\(_3\)) \(\delta\) 172.7, 171.8, 74.7, 61.6, 53.3, 47.8, 39.5, 36.8, 28.6, 23.5, 23.4, 22.5; HRMS (ESI-TOF) calcd. for C\(_{13}\)H\(_{22}\)N\(_2\)O\(_3\) [M+H]\(^+\) 255.17032, found 255.17059.

B. Synthesis of alkenylsiloxane-based fragment library

Following the general hydrosilylation and RCM procedures described in Chapter 1-7-2, compounds 46, 51, and 53 were efficiently synthesized.

(R)-tert-butyl (6-(diethoxy(methyl)silyl)-1-methyl-2-oxo-2,3,4,7-tetrahydro-1H-azepin-3-yl)carbamate (46)

Yield 62% (colorless oil); \(^1\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta\) 6.18-6.17 (m, 1 H), 5.79 (d, \(J = 5.5\) Hz, 1 H), 4.99-4.94 (m, 1 H), 4.43-4.39 (m, 1 H), 3.78-3.69 (m, 4 H), 3.52 (d, \(J = 17.5\) Hz, 1 H), 3.01 (s, 3 H), 2.79-2.73 (m, 1 H), 2.26-2.20 (m, 1 H), 1.42 (s, 9 H), 1.19 (t,
\[ J = 7.0 \text{ Hz}, 6 \text{ H}, 0.15 (s, 3 \text{ H}); \] 
\[ ^{13}\text{C-NMR} (125 \text{ MHz, CDCl}_3) \delta 172.0, 155.1, 142.2, 133.3, 79.5, 58.4, 49.2, 48.0, 35.7, 35.2, 28.3, 18.2, -5.5. \]

(R)-tert-butyl (6-(diethoxy(methyl)silyl)-1-((2-nitrophenyl)sulfonyl)-2-oxo-2,3,4,7-tetrahydro-1H-azepin-3-yl)carbamate (51)

Yield 70% (colorless oil); \(^1\text{H-NMR} (500 \text{ MHz, CDCl}_3) \delta 8.46-8.44 (m, 1 \text{ H}), 7.80-7.75 (m, 3 \text{ H}), 6.32 (dd, \( J = 2.7, 2.7 \text{ Hz}, 1 \text{ H}), 5.40 (d, \( J = 7.0 \text{ Hz}, 1 \text{ H}), 5.10-5.06 (m, 1 \text{ H}), 4.86 (d, \( J = 17.0 \text{ Hz}, 1 \text{ H}), 4.51-4.47 (m, 1 \text{ H}), 3.82-3.75 (m, 1 \text{ H}), 2.88-2.84 (m, 1 \text{ H}), 2.48-2.42 (m, 1 \text{ H}), 1.38 (s, 9 \text{ H}), 1.27-1.22 (m, 6 \text{ H}), 0.26 (s, 3 \text{ H}); \(^{13}\text{C-NMR} (125 \text{ MHz, CDCl}_3) \delta 172.5, 154.5, 147.9, 141.7, 134.7, 134.7, 1333.3, 132.9, 132.0, 124.6, 81.1, 58.6, 58.6, 51.1, 44.2, 35.4, 28.2, 18.2, -5.0. \)

(R)-tert-butyl (6-iodo-1-methyl-2-oxo-2,3,4,7-tetrahydro-1H-azepin-3-yl)carbamate (48)

To a stirred solution of compound 46 (155 mg, 0.42 mmol) in HFIP (6 mL) was added NIS (281 mg, 1.25 mmol) at room temperature. The resulting mixture was warmed up to 50 °C, and stirred for 3 hours. The reaction was then quenched with aqueous Na\(_2\)S\(_2\)O\(_3\) (10 %), extracted with EA. The extract was concentrated \( \text{in vacuo} \) and purified by column
chromatography (gradient 10 – 40% ethyl acetate/hexane) to give compound 48 as yellowish oil (0.060 g, 61%). $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 6.38-6.35 (m, 1 H), 5.73 (d, $J = 5.7$ Hz, 1 H), 4.90-4.72 (m, 2 H), 3.71 (d, $J = 18.6$ Hz, 1 H), 3.08 (s, 3 H), 2.64-2.54 (m, 1H), 2.25-2.19 (m, 1 H), 1.39 (s, 9 H).

(R)-tert-butyl (6-(2-chloropyridin-3-yl)-1-methyl-2-oxo-2,3,4,7-tetrahydro-1H-azepin-3-yl) carbamate (49)

Following the procedure described in ref. 80, to a stirred solution of compound 48 (80 mg, 0.22 mmol) in DMF (8 mL) was added (2-chloropyridin-3-yl)boronic acid (52 mg, 0.33 mmol), DPPF (8.5 mg, 15 $\mu$mol), and sodium carbonate solution (0.65 mL, 1 M). The resulting mixture was warmed up to 70 °C and stirred for 3 hours. The reaction was then cooled to room temperature after 2 hours, quenched with water, extracted with EA (3 times). The extract was washed with brine, dried with sodium sulfate, concentrated in vacuo and purified by column chromatography (25-55% EA in hexane) to afford the title compound as yellowish solid (65 mg, 63%). $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 8.31-8.29 (m, 1 H), 7.48-7.45 (m, 1 H), 7.23-7.19 (m, 1 H), 5.87 (d, $J = 6.3$ Hz, 1 H), 5.73-5.71 (m, 1 H), 5.07-4.99 (m, 1 H), 4.87-4.78 (m, 1 H), 3.52 (d, $J = 17.4$ Hz, 1 H), 3.11 (s, 3 H), 2.88-2.78 (m, 1 H), 2.39-2.27 (m, 1 H), 1.42 (s, 9 H).

C. Synthesis of GSK3β inhibitors
The syntheses and characterizations of compounds 60 and 61 can be found in the paper (*Org. Lett.* 2011, 13, 5556).

**General procedure for Ullmann reaction/cyclodehydration sequence:** adapted from the reported procedure, in a pressure tube, a suspension of 2-bromoaniline (1 equiv.), amino acid (2 equiv.), K$_3$PO$_4$ (2 equiv.), cuprous (I) chloride (2 mol%), and $N,N'$-dimethylethylenediamine (DMEDA) (20 mol%) in dry DMSO (0.3 M) was deoxygenated with argon and sealed with PTFE plug. The reaction mixture was then stirred at 120$^\circ$C for 24 h. The mixture was treated with water (20 mL) and the mixture was extracted three times with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate. After filtration, solvent was evaporated to give the crude product, which was subjected to chromatography on silica gel (hexanes/EtOAc or DCM/MeOH) providind the desired compound.

![Chemical structure](image)

**(S)-2-methyl-1,2-dihydropyrido[2,3-b]pyrazin-3(4H)-one (65)**

Yield 24% (yellowish solid); $^1$H-NMR (500 MHz, d$_6$-DMSO) $\delta$ 10.7 (s, 1 H), 7.61-7.59 (m, 1 H), 7.01-7.00 (m, 1 H), 6.84-6.81 (m, 1 H), 6.28 (s, 1 H), 3.92-3.88 (m, 1 H), 1.30 (d, $J = 7.0$ Hz, 3 H); $^{13}$C-NMR (125 MHz, d$_6$-DMSO) $\delta$ 169.1, 140.7, 136.1, 130.2, 118.9, 118.6, 50.7, 17.7.
(R)-2-methyl-1,2-dihydropyrido[2,3-b]pyrazin-3(4H)-one (66)

Yield 46% (yellowish solid); $^1$H-NMR (500 MHz, d$_6$-DMSO) $\delta$ 10.7 (s, 1 H), 7.61-7.59 (m, 1 H), 7.01-7.00 (m, 1 H), 6.84-6.81 (m, 1 H), 6.28 (s, 1 H), 3.92-3.88 (m, 1 H), 1.30 (d, $J = 7.0$ Hz, 3 H); $^{13}$C-NMR (125 MHz, d$_6$-DMSO) $\delta$ 169.1, 140.7, 136.1, 130.2, 118.9, 118.6, 50.7, 17.7.

(R)-2-methyl-1,2-dihydropyrido[3,4-b]pyrazin-3(4H)-one (67)

Yield 6% (brown solid); $^1$H-NMR (500 MHz, CD$_3$OD) $\delta$ 7.79 (d, $J = 5.5$ Hz, 1 H), 7.75 (s, 1 H), 6.63(d, $J = 5.5$ Hz, 1 H), 4.59 (s, 2 H), 4.10 (q, $J = 7.0$ Hz, 1 H), 1.40 (d, $J = 7.0$ Hz, 3 H).

(R)-3-methyl-3,4-dihydropyrido[3,4-b]pyrazin-2(1H)-one (68)

Yield 14% (brown solid); $^1$H-NMR (500 MHz, CD$_3$OD) $\delta$ 7.88 (s, 1 H), 7.79 (d, $J = 4.0$ Hz, 1 H), 6.76 (d, $J = 5.0$ Hz, 1 H), 3.97 (q, $J = 6.5$ Hz, 1 H), 3.34 (s, 1 H), 1.38 (d, $J = 6.0$ Hz, 3 H); $^{13}$C-NMR (125 MHz, CD$_3$OD) $\delta$ 168.7, 139.7, 134.6, 132.4, 130.9, 109.1, 50.7, 17.5.
(R)-3-methyl-3,4-dihydropyrido[2,3-b]pyrazin-2(1H)-one (69)

Yield 33\% (yellowish solid); $^1$H-NMR (500 MHz, d$_6$-DMSO) $\delta$ 10.4 (s, 1 H), 7.66-7.65 (m, 1 H), 6.97-6.96 (m, 1 H), 6.85 (s, 1 H), 6.62-6.59 (m, 1 H), 4.05-4.01 (m, 1 H), 1.33 (d, $J = 7.0$ Hz, 2 H).

(S)-3-methyl-3,4-dihydropyrido[2,3-b]pyrazin-2(1H)-one (70)

Yield 18\% (yellowish solid); $^1$H-NMR (500 MHz, d$_6$-DMSO) $\delta$ 10.4 (s, 1 H), 7.66-7.65 (m, 1 H), 6.97-6.96 (m, 1 H), 6.85 (s, 1 H), 6.62-6.59 (m, 1 H), 4.05-4.01 (m, 1 H), 1.33 (d, $J = 7.0$ Hz, 2 H); $^{13}$C-NMR (125 MHz, d$_6$-DMSO) $\delta$ 167.5, 147.0, 141.0, 120.8, 119.9, 113.3, 50.8, 18.5.

(R)-2-isopropyl-1,2-dihydropyrido[2,3-b]pyrazin-3(4H)-one (73)

Yellowish solid; $^1$H-NMR (500 MHz, CD$_3$OD) $\delta$ 7.56 (d, $J = 5.0$ Hz, 1 H), 7.02 (d, $J = 7.5$ Hz, 1 H), 6.81 (dd, $J = 7.0$, 5.0 Hz, 1 H), 3.76 (d, $J = 5.0$ Hz, 1 H), 2.13-2.07 (m, 1
H), 1.00 (d, $J = 7.0$ Hz, 3 H), 0.92 (d, $J = 7.0$ Hz, 3 H); $^{13}$C-NMR (125 MHz, CD$_3$OD) δ 170.5, 140.6, 136.6, 131.8, 120.6, 120.1, 62.8, 33.4, 19.1, 17.8.

(R)-2-(4-hydroxybenzyl)-1,2-dihydropyrido[2,3-b]pyrazin-3(4H)-one (74)

Yellowish solid; $^1$H-NMR (500 MHz, d$_6$-DMSO) δ 10.6 (s, 1 H), 9.15 (s, 1 H), 7.47-7.46 (m, 1 H), 6.95-6.93 (m, 3 H), 6.74-6.72 (m, 1 H), 6.61 (d, $J = 8.0$ Hz, 2 H), 6.04 (s, 1 H), 4.04-4.01 (m, 1 H), 2.82 (dd, $J = 13.5$, 4.5 Hz, 1 H), 2.75 (dd, $J = 13.5$, 7.0 Hz, 1 H); $^{13}$C-NMR (125 MHz, d$_6$-DMSO) δ 167.8, 155.8, 139.9, 135.5, 130.6, 129.5, 126.8, 118.7, 118.6, 56.9, 37.4.

(R)-2,4-dimethyl-1,2-dihydropyrido[2,3-b]pyrazin-3(4H)-one (77)

Yield 79% (yellowish solid); $^1$H-NMR (500 MHz, d$_6$-DMSO) δ 7.75-7.74 (m, 1 H), 7.08-7.06 (m, 1 H), 6.92-6.89 (m, 1 H), 6.38 (s, 1 H), 3.98 (q, $J = 6.5$ Hz, 1 H), 3.35 (s, 3 H), 1.32 (d, $J = 7.0$ Hz, 3 H).
2,2-Dimethyl-1,2-dihydropyrido[2,3-b]pyrazin-3(4H)-one (80)

Yellowish solid; $^1$H-NMR (500 MHz, d$_6$-DMSO) δ 10.6 (s, 1 H), 7.62-7.61 (m, 1 H), 7.01-7.00 (m, 1 H), 6.85-6.82 (m, 1 H), 6.25 (s, 1 H), 1.27 (s, 6 H).

1'H-spiro[cyclopentane-1,2'-pyrido[2,3-b]pyrazin]-3'(4'H)-one (81)

Yellowish solid; $^1$H-NMR (500 MHz, d$_6$-DMSO) δ 10.6 (s, 1 H), 7.62-7.61 (m, 1 H), 7.05-7.03 (m, 1 H), 6.84-6.82 (m, 1 H), 6.34 (s, 1 H), 2.08-2.03 (m, 2 H), 1.82-1.75 (m, 2 H), 1.70-1.56 (m, 4 H).

(R)-2-((1H-indol-3-yl)methyl)-1,2-dihydropyrido[2,3-b]pyrazin-3(4H)-one (91)

Yellowish solid; $^1$H-NMR (500 MHz, d$_6$-DMSO) δ 10.8 (s, 1 H), 10.6 (s, 1 H), 7.50 (d, $J$ = 8.0 Hz, 1 H), 7.47-7.46 (m, 1 H), 7.30 (d, $J$ = 8.0 Hz, 1 H), 7.10-7.09 (m, 1 H), 7.04 (dd, $J$ = 7.0, 7.0 Hz, 1 H), 6.96-6.91 (m, 2 H), 6.71 (dd, $J$ = 7.5, 5.0 Hz, 1 H), 6.05-6.04 (m, 1 H), 4.15-4.12 (m, 1 H), 3.09 (dd, $J$ = 15.0, 4.0 Hz, 1 H), 2.98 (dd, $J$ = 15.0, 7.5 Hz, 1 H); $^{13}$C-NMR (125 MHz, d$_6$-DMSO) δ 168.2, 140.0, 136.1, 135.5, 129.5, 127.5, 124.1, 120.8, 118.7, 118.6, 118.3, 118.3, 111.3, 109.1, 56.2, 28.3.
2-Methylpyrido[2,3-b]pyrazin-3(4H)-one (78)

To a solution of 8% aqueous sodium hydroxide (1.0 mL) was added compound 65 (48 mg, 0.3 mmol) followed by a solution of 30 wt% hydrogen peroxide in water (0.6 mL). The reaction mixture was slowly heated to 80 °C and maintained at this temperature for 4 h. The heating source was removed, and acetic acid (0.5 mL) was added dropwise. The suspension was stirred overnight at room temperature and the precipitated solid was collected by filtration to afford the desired product 78 as white solid. $^1$H-NMR (500 MHz, d$_6$-DMSO) δ 12.7 (bs, 1 H), 8.46 (s, 1 H), 8.10 (d, $J$ = 7.5 Hz, 1 H), 7.33-7.31 (m, 1 H), 2.40 (s, 3 H); $^{13}$C-NMR (125 MHz, d$_6$-DMSO) δ 160.7, 156.2, 149.1, 144.0, 135.8, 126.8, 119.5, 20.5.

2,3-Dihydro-1H-pyrido[2,3-b][1,4]diazepin-4(5H)-one (79)

A pressure tube was charged with CuI (19 mg, 0.1 mmol), 2-bromoaniline (0.35 g, 2 mmol), 2-azetidinone (0.17 g, 2.4 mmol), and K$_2$CO$_3$ (0.86 g, 4.1 mmol), evacuated, and backfilled with argon. $N,N'$-Dimethylethylenediamine (DMEDA) (18 mg, 0.10 mmol) and DMF (10 mL) were added under argon. The pressure tube was sealed with a PTFE plug and the reaction mixture was stirred at 110 °C for 24 h in a preheated oil bath. The resulting brown-black suspension was allowed to reach room temperature, filtered
through a silica gel plug eluting with 10:1 CH$_2$Cl$_2$/MeOH (50 mL), and the red filtrate was concentrated. The oily residue was transferred to a pressure tube, which was then evacuated, backfilled with argon, and sealed with a rubber septum. Ti(OiPr)$_4$ (0.2 g, 0.7 mmol) and toluene (6 mL) was added to the pressure tube and the septum was replaced with a PTFE plug under a stream of argon. The sealed pressure tube was placed in an oil bath preheated to 120 °C. After being stirred at 120 °C for 24 h, the reaction mixture was allowed to reach room temperature and then filtered through a silica gel plug eluting with 10:1 CH$_2$Cl$_2$/MeOH (50 mL). The filtrate was concentrated, and the residue was purified by column chromatography on silica gel (CH$_2$Cl$_2$/MeOH) to provide the desired product as yellowish solid. $^1$H-NMR (500 MHz, d$_6$-DMSO) δ 9.49 (s, 1 H), 7.66-7.53 (m, 1 H), 7.09 (d, $J = 8.0$ Hz, 1 H), 6.88-6.86 (m, 1 H), 5.98 (s, 1 H), 3.40 (dt, $J = 5.0$, 5.0 Hz, 2 H), 2.56 (t, $J = 5.0$ Hz, 2 H); $^{13}$C-NMR (125 MHz, d$_6$-DMSO) δ 172.1, 138.8, 136.6, 135.2, 125.3, 119.7, 42.6, 37.5.

![Chemical structure](image)

(S)-2-methyl-1,2,3,4-tetrahydropyrido[2,3-b]pyrazine (76)

To a stirred solution of compound 65 (22 mg, 0.14 mmol) in THF (1 mL) was added BH$_3$-THF solution (1 M, 0.67 mL) dropwise. The reaction was monitored by TLC until the disappearance of starting materials and then quenched with NaHCO$_3$ solution (saturated), extracted with EA (3 times). The extract was washed with brine, dried with sodium sulfate, concentrated in vacuo and purified by column chromatography (MeOH/DCM) to afford 76 as brown oil (10 mg, 48% yield). $^1$H-NMR (500 MHz,
CDCl₃) δ 7.47 (d, J = 5.0 Hz, 1 H), 6.63 (d, J = 7.5 Hz, 1 H), 6.46 (dd, J = 7.5, 5.0 Hz, 1 H), 4.87 (bs, 1 H), 3.52-3.49 (m, 1 H), 3.43 (dd, J = 11.0, 2.5 Hz, 1 H), 3.17 (dd, J = 10.5, 8.5 Hz, 1 H), 1.20 (d, J = 6.5 Hz, 3 H).

D. Revised synthetic route

Adapted from ref. 89.

General procedure for SₕAr: to a stirred solution of 2-Nitro-3-fluoropyridine (1 equiv.) and methyl amino ester (or its hydrochloride salt, 2 equiv.) in DMSO (0.5 M) was added DIPEA (4 equiv.) at room temperature. The resulting mixture was warmed up to 50 °C and stirred for 18 hours. The reaction was then cooled to room temperature, quenched with NaHCO₃ solution (saturated), extracted with EA (3 times). The extract was washed with brine, dried with sodium sulfate, concentrated in vacuo and purified by column chromatography (EA/hexane or MeOH/DCM) to afford the uncyclized product.

General procedure for cyclization: a solution of unyclized nitro-containing compound (1 equiv.) and palladium on carbon (10 wt.% Pd on carbon, wet, 0.05 equiv.) in solvent mixture of EA and ethanol (1:1, 0.1 M) was stirred at 25 °C under an atmosphere of hydrogen gas for 4 hours. The reaction flask was then purged with argon to replace hydrogen followed by the addition of ammonium formate (1 equiv.). The resulting mixture was warmed up to 40 °C and stirred for 18 hours. The suspension was then filtered through a Celite pad and the filtrate was concentrated in vacuo and purified by column chromatography (EA/hexane or MeOH/DCM) to afford the cyclized product.
E. Biochemical and biophysical assays

*Thermal shift Assay:*

Florescence thermal shift experiments were performed on a 480 Roche Lightcycler in a 384 well format. The fragments were tested at 2.5 mM with 2.5 % DMSO. The optimal condition was determined to be 0.12 mg/mL GSK3β and 1:400 dilution of Sypro Orange from the original stock. The assay was performed with final volume of 5 µL using a buffer solution containing 50 mM HEPES (pH 7.5) and 150 mM NaCl. Fragments that gave a thermal shift greater 0.5 °C were considered hits.

*Isothermal Titration Calorimetry:*

ITC experiments were performed on an ITC200 instruments from Microcal Inc. (GE Healthcare) at 25 °C. ITC cell was loaded with GSK3β in concentrations of 50-85 µM with 2-5 % DMSO solution. Ligands were tested at 0.5-2 mM concentrations. Typically, 18 injections of 2.4 µL ligand were performed over a period of 30 min with stirring at 1000 rpm.

*Biochemical assay:*

The assay kit was acquired from Promega V9103, ADP Glo.

First, 4 µL/well of CABPE, 2 µL of ATP (Promega V9103 component, in AB, 125 mM concentration), and 4 µL of ligand (2.5 mM in AB with 5% DMSO), DMSO (5% in AB), or positive control (GW8510, 20 µM in AB with 5% DMSO) was dispensed into respective wells of a 384-well plate (Corning 3572) to start the reaction. The reaction was
incubated at room temperature for 20 minutes. Second, 10 µL/well of ADP-Glo reagent was added to terminate the reaction. The plate was incubated at room temperature for 40 minutes. Last, 20 µL/well of kinase detection reagent was added. After 30 minutes incubation at room temperature, luminescence was read on an Envision (PerkinElmer) plate reader.

Buffer conditions: AB: 25 mM tris(hydroxymethyl)aminomethane, 10 mM magnesium chloride, pH adjusted to 7.5. CABPE (in AB): 12.5 mM dithiothreitol (Sigma 43816), 0.25 mg/mL bovine serum albumin (Sigma A4503), 0.5 U/mL heparin (Baxter NDC 0641-2440-41), 8 µM GSM (GSK3 substrate peptide, Millipore 12-533), 9 nM GSK3beta (XTAL Biostructures).

NMR experiments:
All spectra were recorded at 298 K on a Bruker Avance 600 MHz NMR spectrometer equipped with z-axis gradients. The data were collected with a sweep width of 12019 Hz and 8192 complex points. For each sample 1D 1H, STD, and WaterLOGSY spectra were collected with water suppression using excitation sculpting. The 1D 1H spectrum was acquired with 128 scans and a relaxation delay of 1.5s. The STD experiment was acquired with a 3s saturation period (50ms Gaussian shaped pulse), a recycle delay of 0.5s and 256 scans each for the on-resonance (0.8ppm) and off-resonance (-25ppm). The WaterLOGSY experiment was acquired with 512 scans, a mixing time of 2.3s, and a recycle delay of 1.3s. The relaxation-edited experiment was acquired with 256 scans, a recycle delay of 2s and a 300ms CPMG spin-lock period. All spectra were processed
using nmrPipe\textsuperscript{93} and prior to Fourier transformation the data were multiplied by and shifted sine-bell weighting function and an exponential function with a line broadening of 0.5Hz.
References


(2) Schreiber, S. L. *Nat. Chem. Biol.* 2005, 1, 64.


(73) Huang, P. Q. *Synlett* 2006, 1133.


$^1$H and $^{13}$C NMR Spectra
Me\(\text{N}^{}\)\(\text{Si(\text{OEt})_2Me}\)

\[46\]

Me\(\text{N}\)

\[\text{Si(\text{OEt})_2Me}\]

\[46\]