Exploring the Synthetic Application of Allylic Alcohol Isomerization

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Submitted to the Graduate Faculty of the

Dietrich School of Arts and Sciences in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh

2014

UNIVERSITY OF PITTSBURGH

DIETRICH SCHOOL OF ARTS AND SCIENCES

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University of Pittsburgh, 2014

Allylic alcohol transposition lacks a thermodynamic driving force and usually displays stereo-infidelity and poor regioselectivity. However, regio- and stereoselectivity can be achived by coupling allylic alcohol transposition to a subsequent step that is kinetically and thermodynamically favorable. Based on this rationale, the allylic alcohol transposition and capture sequence was delevoped and applied successfully in heterocycle synthesis. Regio- and stereoselectivity were achieved when a pre-existing stereogenic center in the substrates could induce significant thermodynamic difference between diastereomeric products and when the individual steps toward these diastereomeric products were reversible.

Epoxides were later used as ennantioenriched electrophiles in this transposition/trapping sequence for stereoselective synthesis of heterocycles. The mechanism for this transformation was elucidated and a cascade approach using epoxides as trapping agents in the transposition of allylic alcohols was developed and applied in the stereoselective formation of polycyclic ethers.

Finally, an improved sequence using “traceless trapping agents” was developed. This new method did not leave any vestige in the resulting product and offered much more freedom for the application of allylic alcohol transposition in heterocycle synthesis. Understanding the relative rates of the steps in this new sequence led to the design of reactions that created multiple stereogenic centers with good to excellent levels of control.

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PREFACE

First of all, I would like to thank my Ph.D supervisor, Professor Paul Floreancig, for accepting me into his group as a graduate student and providing me with these thought-provoking projects. He had always been encouraging and inspiring during my study in his group and I would not have gone so far in organic chemistry without his guidance.

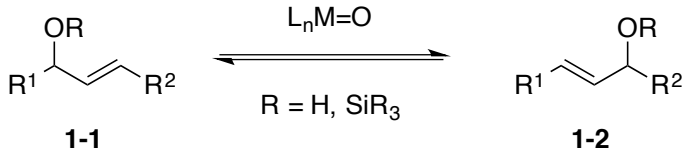
I would like to express my gratitude to Professor Arndt, Professor, Brummond and Professor Koide for being my Ph.D committee members. They provide useful guidance during my comprehensive examination, graduation proposal writing, and dissertation studies. I also want to thank Professor Horne for his patience in teaching me how to write individual research proposals.

Next, I would like to thank all Floreancig's group members, past and present, for all your help and cooperation in the past five years, I enjoy every moment we spent together. I want to thank all the staff and technicians in the Chemistry department, they work together to provide me an outstanding research environment and make my life here much easier.

Finally, I want to thank my father, my mother and my wife for all the love and care they had shown me throughout my life. I would never have gone so far in my career without their unconditional support.

1.0 INTRODUCTION

The direct metal-catalyzed [1,3]-transposition of allylic alcohols or allylic silyl ethers is a powerful atom- and step-economical transformation (Scheme 1.1). This method allows facile preparation of a less accessible isomer from a more readily available precursor in a single operation and obviates the need for substrate derivatization. As a result, it could potentially serve as a powerful tool in multistep synthesis of complex molecules. However, the development of synthetically useful methods that allow for a high level of regio- and stereoselectivity control have emerged only recently and their applications in organic synthesis are very limited even though [1,3]-transposition of allylic alcohols has been known since late 1960s.[1] The major reason for such a dilemma is the intrinsic low regio- and stereoselectivity of this method. Several groups have dedicated themselves to solving this problem yet a general solution is still lacking. In accord with our continued interest in the synthesis of heterocycles, we sought to develop a new protocol that uses the intrinsic low regio- and stereoselectivity to our advantage for the stereoselective syntheses of cyclic ethers.



1-1 **1-2**

Scheme 1.1 [1,3]-transposition of allylic alcohols or allylic silyl ethers catalyzed by metal-oxo complexes

1.1 ALLYLIC ALCOHOL ISOMERIZATION

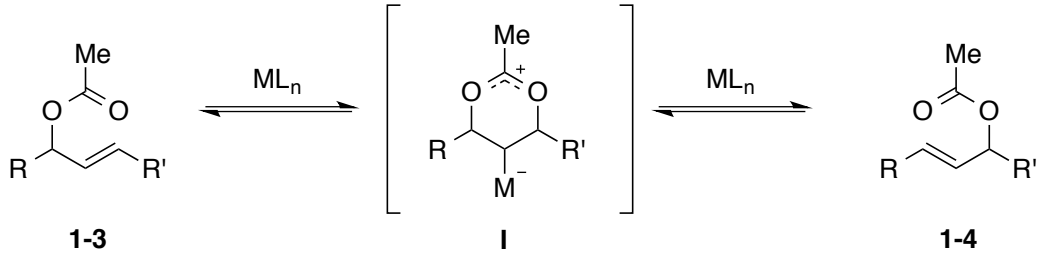
Allylic alcohols and their derivatives are useful chemical moieties because of their important roles in a variety of synthetic transformations such as Claisen and Cope rearrangements, directed epoxidations,[2] cyclopropanations,[3] carbonyl formations,[4] etc. Even though there are numerous synthetic strategies to prepare allylic alcohols, the [1,3]-isomerization offers unique opportunities to access regioisomers that are difficult to access directly through conventional strategies.

1.1.1 Allyl ester isomerization

The rearrangement of allylic esters, or the [1, 3]-dioxa-Cope rearrangement, is the first example of allylic alcohol isomerization and was first reported in the late 1960s, when Lewis and co-workers observed this transformations in the gas phase.[5] However, this transformation was not widely used at that time due to a lack of regioselectivity. When subjecting an allylic ester to the reaction conditions, a mixture of isomers was obtained in which the product distribution was determined by the thermodynamic stabilities of the two allylic isomers. In the mid 1970s, Brønsted acid catalyzed isomerizations of tertiary alcohols into the corresponding primary allylic esters were achieved selectively through an ionization-recombination process,[6] however the harsh reaction conditions limited their synthetic applications. Milder reaction conditions needed to be developed for this transformation in order to make it synthetically useful.

The quest for milder reaction conditions led to studies of catalytic version of these transformations in late 1970s. Late transition metal catalysts such as mercury(II)[7] and palladium(II)[8] were reported by Overman and co-workers to effect rearrangements of allylic

acetates and carbamates with moderate to high levels of selectivity, and when enantioenriched allylic acetates were used, high levels of chirality transfer could be obtained. Overman also postulated that this metal catalyzed isomerization of allylic acetates proceeded via a "cyclization-induced" process (Scheme 1.2), in which the electrophilic metal binds to the alkene and activates it toward nucleophilic attack by the pendant carbonyl oxygen. The resulting cyclic organometallic intermediate breaks down to yield the isomerized product. Late transition metal catalysts have been proven to be effective for promoting allylic acetate isomerizations and have been applied in the synthesis of several natural products.[9]

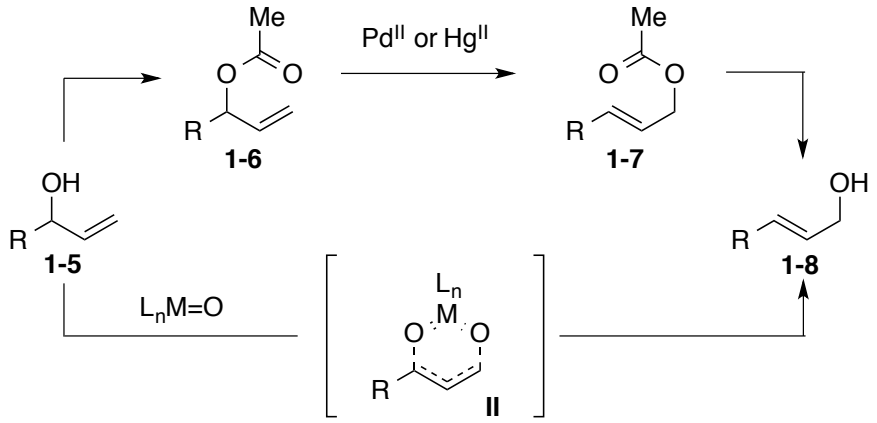


Scheme 1.2 Mechanism of "cyclization-induced" rearrangement

1.1.2 Allylic alcohol isomerization catalyzed by metal-oxo complexes

Despite the promising aspects of the allylic acetate isomerizations, the direct isomerization of allylic alcohols is a more attractive alternative since the two redundant steps of acylation and deacylation can be avoided. As shown in Scheme 1.3, it is proposed that the binding of a metal-oxo complex to the allylic alcohol can form a metalloester, which will subsequently undergo a [3,3]-rearrangement through a cyclic transition state (II) to yield the transposed allylic alcohol. This process is similar to the thermal rearrangement of allylic acetates catalyzed by late

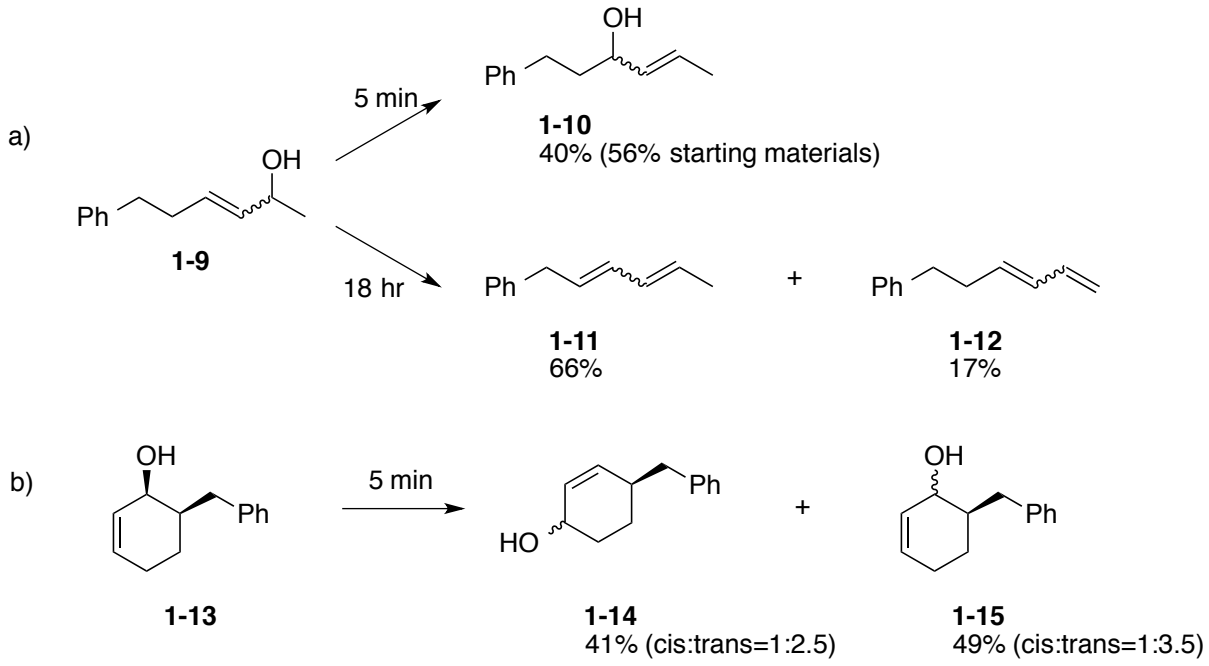
transition metals, but the metal-oxo complex catalyzed isomerization does not require two additional steps of acylation and deacylation and is completely atom-economic.



Scheme 1.3 Metal-oxo complex vs late transition metal-catalyzed isomerization

Metal-catalyzed allylic [1,3]-transposition was initially discovered by Chabardes using a vanadium-oxo complex in the late 1960s.[1] The catalysts suitable for this isomerization were later extended to several other high oxidation state transition metal-oxo complexes of vanadium,[1, 10-14] tungsten,[15] molybdenum,[16-18] and rhenium.[19-26] These early catalysts have several limitations such as the requirement of high reaction temperature for optimal catalytic activities, limited stability, poor functional group compatibility, etc. Vanadium- and tungsten-based catalysts such as $VO(OR)_3$[1, 10-12] and $WO(OSiEt_3)_3$•Py[15] show high catalytic efficiency only at temperatures between 140-200 ºC, even though a low catalyst loading (0.05-2 wt%) is sufficient to effect a fast equilibrium. Activation of metal-oxo complexes with TMSOOTMS obviates the need for high temperature so that the reaction could be performed at room temperature.[13-14] However, activation of $VO(acac)_2$ with TMSOOTMS yielded an ill-defined catalyst system that resulted in selective isomerization of primary allylic alcohols to the corresponding tertiary ones with noticeable side reactions[13] while the combination of $MoO_2(acac)_2$ and TMSOOTMS was shown

to be less effective.[14] Mo-based catalysts such as $MoO_2(Ot\text{-}Bu)_2$[16] and $MoCl_2(O)(O_2)(OPMePh_2)_2$[18] were reported to be more effective. However, due to the high oxidation state of molybdenum in these complexes, slow oxidation of the alcohol substrate becomes a problem and ultimately reduces the catalyst lifetime.[23] In comparison with the weak oxidizing capability of Mo- and W-based oxo-complexes, the strong oxidizing power of oxochromium(VI) complexes makes them unsuitable for the [1,3]-transposition of primary and secondary allylic alcohols although they have been used for oxidative [1,3]-transposition of tertiary allylic alcohols to α,β-unsaturated carbonyl compounds.[26-29] Another problem arising from the high oxidation states of metal-oxo complexes is the inherent Lewis acidity, which becomes more evident as the number of oxo ligands increases. As a consequence, side reactions such as dehydration, condensation, and racemization become significant and compete with the desired [1,3]-transposition.



Scheme 1.4 Examples of isomerizations catalyzed by Bu_4NReO_4/*p*TsOH•H_2O

More efficient and mild catalytic systems were developed subsequently for allylic [1,3]-transposition using oxorhenium complexes. It was initially discovered that Bu_4NReO_4/*p*TsOH•H_2O[19-20] catalyst system was superior compared to metal oxo-complexes in previous reports. However, the reaction selectivity was low and side reactions such as condensation and dehydration were still significant as a result of the Brønsted acidity of this catalyst system (Scheme 1.4). $MeReO_3$[21-23] was developed later as a more efficient and milder catalyst and has been applied for the equilibration between secondary and primary allylic alcohols in industry. However, water was found to inhibit the catalytic ability by reacting with $MeReO_3$ to form the inactive species $MeRe(O)_2(OH)_2$.[22] Triphenylsilyl perrhenate, $Ph_3SiOReO_3$,[30] has been identified as the most efficient and practically applicable catalyst for the [1,3]-transposition of allylic alcohols and allylic silyl ethers after investigations and mechanistic studies. Compared to previously known oxorhenium-based catalysts, $Ph_3SiOReO_3$ possesses a high catalytic activity at or below room temperature with negligible side reactions such as condensation, dehydration, oxidation, etc. As a result, this new catalyst has gradually evolved as the catalyst of choice for the [1,3]-transposition of allylic alcohols and allylic silyl ethers and has been applied extensively thereafter. The substrate scope of the reaction, the degree of chirality transfer, and the reaction selectivity have been established through subsequent investigations.[31-32]

Despite the improved catalytic efficiency of oxorhenium complexes, they can not tolerate basic functional groups such as amines. Imido complexes[33] are formed when oxorhenium complexes are reacted with amines. Although some imido complexes are still active, their catalytic efficiencies are significantly reduced, and therefore amines are widely used to quench oxorhenium catalysts. Hall and co-workers showed that boronic acid catalysis (BAC) could be applied to allylic alcohol isomerization. BAC not only tolerates both acid and base sensitive

functional groups, but also yields higher E/Z selectivity, especially when trisubstituted alkenes are formed from isomerization of tertiary allylic alcohols.[34] However, the application of this method is limited and oxorhenium complexes are still the catalysts of choice for [1,3]-transposition of allylic alcohols and allylic silyl ethers.

1.2 MECHANISM OF METAL-CATALYZED [1,3]-TRANSPOSITIONS OF ALLYLIC ALCOHOLS

[1,3]-transpositions of allylic alcohols catalyzed by metal-oxo complexes have been studied by several groups. In a general mechanism, formation of a metallo-ester is followed by [3,3]-sigmatropic rearrangement via a cyclic transition state (II in Scheme 1.3). This mechanism is useful in explaining the high E/Z selectivity of disubstituted alkenes, however, it does not provide reasonable explanation for several side reactions (observed in different extents) such as racemization, dehydration, condensation, etc. The real mechanism is much more complicated than initially proposed and can divert significantly from a concerted pathway, depending on the catalysts, substrates, and reaction conditions.

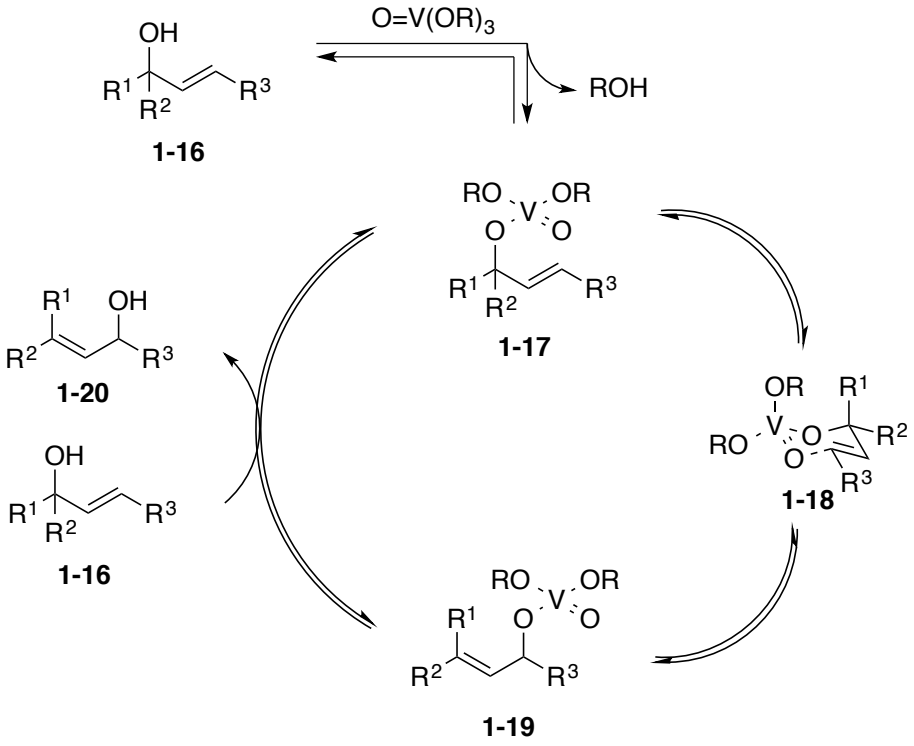
1.2.1 Mechanism of allylic isomerization catalyzed by oxovanadium complexes

In his seminal work, Chabardes proposed the first mechanism of metal-catalyzed [1,3]-transposition of allylic alcohols by oxovanadium complexes.[10] As shown in Scheme 1.5, the substrate alcohol **1-16** reacts with the catalyst by replacing one of its alkoxy ligands to generate vanadate ester **1-17**. A subsequent isomerization of **1-17** via [3,3]-sigmatropic rearrangement

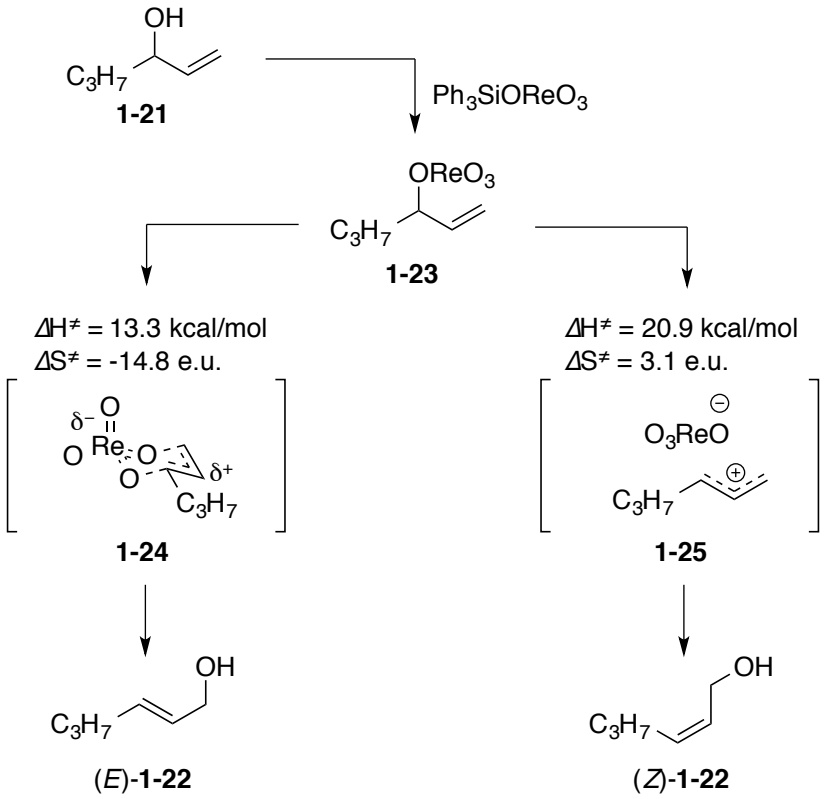
(intermediate **1-18**) delivers the transposed vanadate ester **1-19**. This intermediate will release product **1-20** and regenerate vanadate ester **1-17** for another catalytic cycle by ligand exchange with substrate **1-16**. In this mechanism, each individual step is reversible and the reaction product is a thermodynamic mixture of isomeric alcohols. This mechanism was initially proposed and supported by experiments.[25, 26] A few years later, Dedieu and co-workers conducted DFT calculations, in which they revealed the details of charge distribution in the transition state and its effects on the reaction selectivities.[35]

1.2.2 Mechanism of $Ph_3SiOReO_3$-catalyzed [1,3]-allylic alcohol transposition by Osborn

Osborn and coworkers[25, 32] conducted kinetic studies on $Ph_3SiOReO_3$-catalyzed [1,3]-allylic alcohol transposition and found that the formation of *cis* isomer product (*Z*)-**1-22** was extremely slow compared to the formation of *trans* isomer product (*E*)-**1-22**. This difference arises from the disparity in the transition states for the formation of each isomer. Isomerization of hex-1-en-3-ol **1-21** to (*E*)-hex-2-en-1-ol (*E*)-**1-22** has $\Delta H^{\neq}$ = 13.3 ± 0.3 kcal mol^{-1} and $\Delta S^{\neq}$ = -14.8 ± 1.0 e.u. The large negative activation entropy suggested a highly ordered polarized transition state **1-24** via a [1,3]-sigmatropic pathway. In this pathway, a partially negatively perrhenate group migrates intramolecularly across a partially positively charged allyl moiety. However, the formation of (*Z*)-**1-22** has activation enthalpy of 20.9± 0.3 kcal mol^{-1} and activation entropy of 3.1 ± 1.0 e.u. The positive activation entropy indicates a more disordered transition state, namely an ionization-recombination pathway with the solvent-separated allylic cation and perrhenate anion. This difference was also supported by the solvent study by the same group: polar solvents favor the more disordered ionic pathway and increase the formation of the *cis* isomer.[25]

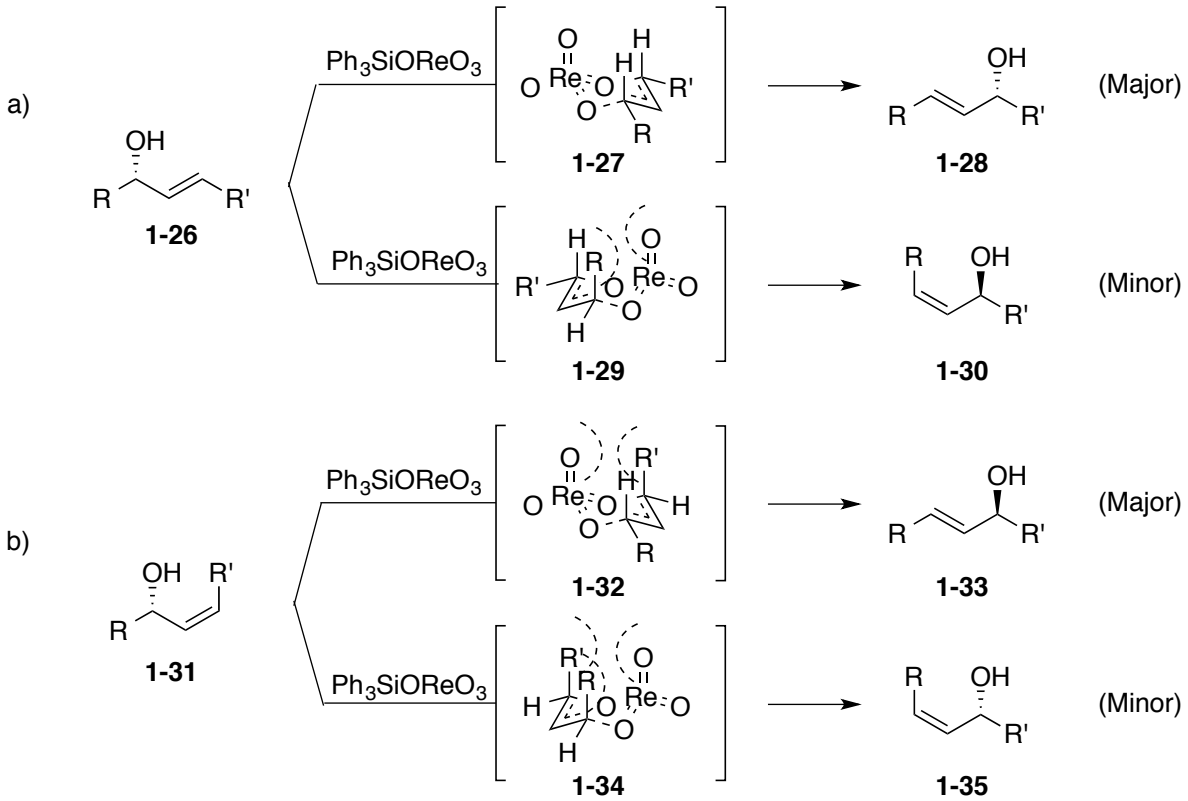


Scheme 1.5 Mechanism of the [1,3]-transposition of allylic alcohols proposed by Chabardes



Scheme 1.6 Mechanism of [1,3]-allylic alcohol transposition proposed by Osborn

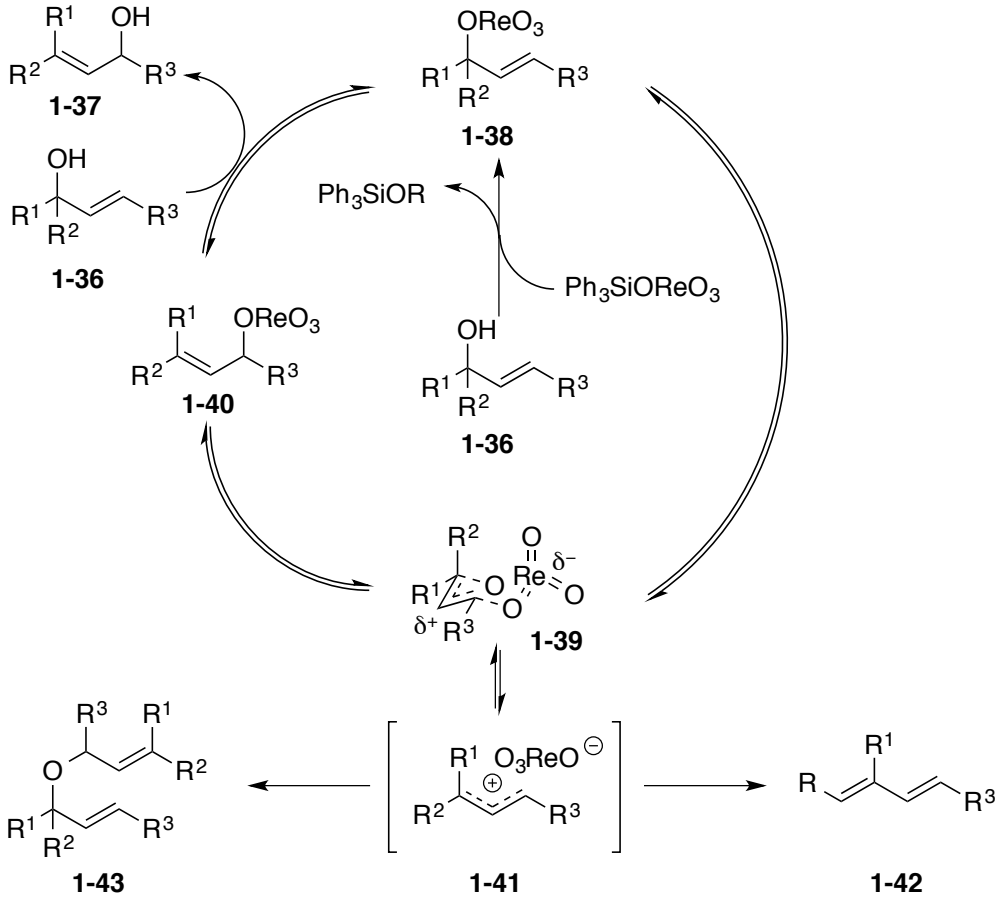
Osborn explained the observed selectivity for (*E*)-**1-22** [25, 32] based on the *trans*-diaxial interaction between an oxo ligand and the alkyl substituent on the migrating allyl group in the transition state, which will be greater for the *cis* isomer and lead to an increase in charge separation. However, whether an oxo ligand is large enough to have this steric effect is still in debate.[32, 35] Nonetheless, this *trans*-diaxial interaction can explain why allylic alcohols containing *Z*-alkenes also yield the corresponding *E*-products after isomerization. In the case of **1-26**, the transition structure leading to the *E*-isomer has no diaxial interactions while that leading to the *Z*-isomer isomer has one noticeable diaxial interaction (Scheme 1.7a). In the case of **1-31** the transition structure leading to the *E*-isomer has one diaxial interaction while that leading to the Z-isomer has one R, R interaction alongside two other diaxial R, O interactions.



Scheme 1.7 Consequence of *E*/*Z* isomerization on selectivity

1.2.3 Mechanism of $Ph_3SiOReO_3$-catalyzed [1,3]-transposition proposed by Grubbs

Grubbs and coworkers suggested a more detailed mechanism based on thorough studies of the reaction and limitations of the [1,3]-transposition of allylic alcohols. As shown in Scheme 1.8, this mechanism is similar to the one proposed by Osborn, in which the isomerization proceeds through an asynchronous [3,3]-sigmatropic rearrangement via a polarized chair-like transition state **1-39**. In this transition state, the C-O bond is highly polarized so that an ion pair intermediate **1-41** emerges and competes with the sigmatropic rearrangement. The existence of this ion pair intermediate is the reason for the undesirable side reactions such as elimination (**1-42**), condensation (**1-43**), and racemization of enantiomerically enriched substrates.



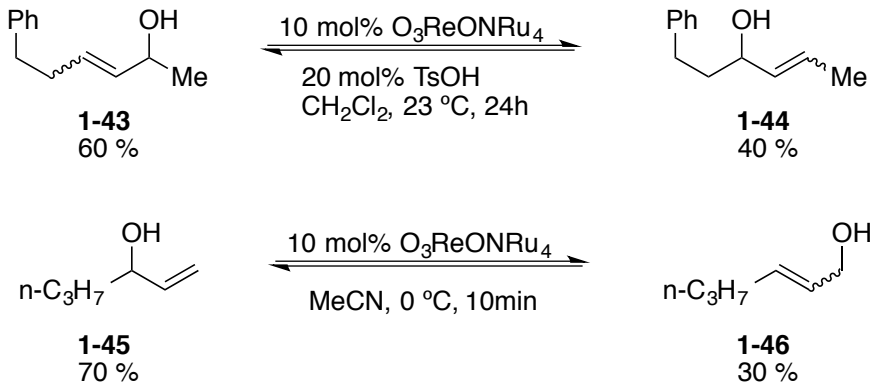
Scheme 1.8 Mechanism of allylic [1,3]-transposition proposed by Grubbs and coworkers

Similar to the mechanistic rationale suggested by Osborn, Grubbs and coworkers explained the selective formation of *E*-isomers from both (*E*)- and (*Z*)-allylic alcohols by the increased diaxial interactions in the transition state that led to the (*Z*)-configured product. Due to the high polarization of the transition state **1-39**, the electronic effects of substituents have a strong influence on the properties of the transition state and, as a result, the reaction outcome. Accordingly, more substituted alkenes or alkenes with electron donating substituents are capable of stabilizing a positive charge on the allylic moiety and favor the ionic pathway **1-41**. Although the reaction rate is fast in this case, the reaction selectivity is jeopardized due to several possible side reactions of the allyl cation. As a result, low reaction temperatures of –78 ºC to –50 ºC are required to suppress the formation of ion pairs. On the other hand, reactions of electron-poor allylic alcohols can be performed at room temperature even though the reaction rate is reduced compared to electron rich substrates. The degree of chirality transfer is also affected by the electronic nature of the substrates: higher electron-withdrawing capacity of the substituents results in higher degree of chirality transfer, and vice versa.

1.3 APPLICATION OF ALLYLIC ALCOHOL ISOMERIZATION

The most important application of allylic alcohol isomerization is to access regioisomers or diastereomers that are not easy to obtain by traditional methods such as the addition of nucleophiles to aldehydes,[36] kinetic resolution of racemic secondary alcohols,[37] stereoselective reduction of α,β-unsaturated ketones,[38] etc. However, poor stereoselectivity and a lack of regioselectivity greatly hamper its application in more complex settings. As a result, the application of allylic alcohol isomerization in complex molecule synthesis has been very limited,

with the first example reported in 2000,[39] more than three decades after its discovery. Ever since then, several groups have dedicated themselves toward improving both regio- and stereoselectivity of this method. As a result, allylic alcohol isomerization has been applied in the total synthesis of various complex molecules such as amphidinolide B1,[40] cladiell-11-ene-3,6,7-triol,[41] leucascandrolide A,[42] 6′-hydroxylarenarol,[43] (–)-apratoxin A,[44] (–)-dactylolide,[45] laulimalide,[46] (–)-amphidinolide V.[47]



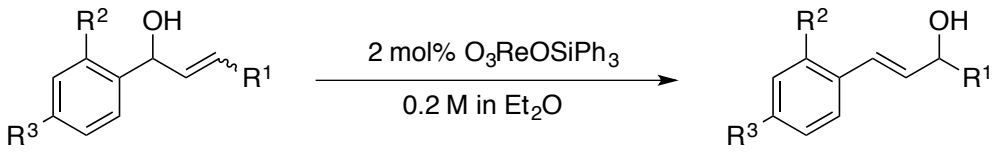
Scheme 1.9 Oxorhenium complex catalyzed allylic alcohol isomerization

1.3.1 Enhanced selectivity by extended conjugation

Rhenium oxo-complex catalyzed allylic alcohol isomerization is known for its poor regioselectivity. As shown in Scheme 1.9, a mixture of the starting material and the isomerized product is usually obtained with the ratio depending on the relative thermodynamic stability of each regioisomer. In order to obtain enhanced regioselectivity, significant differences between the thermodynamic stabilities of the isomers should be created during the design of the reaction substrate. Grubbs and coworkers were able to achieve a high level of reaction selectivity by introducing extended conjugation.[31, 32] As shown in Table 1.1, these products have extended

conjugation so that they are more thermodynamically stable than the corresponding starting substrates. High levels of selectivity were obtained for all substrates tested although the yield for electron rich systems (entry 5, 6, 11) are low due to the formation of byproducts resulting from increased stability of allyl cations. When enantioenriched substrates (not shown) are used, high levels of chirality transfer were observed for electron deficient systems while various degrees of racemization were observed for electron rich systems.[32]

Table 1.1 Isomerization of aryl secondary allylic alcohols



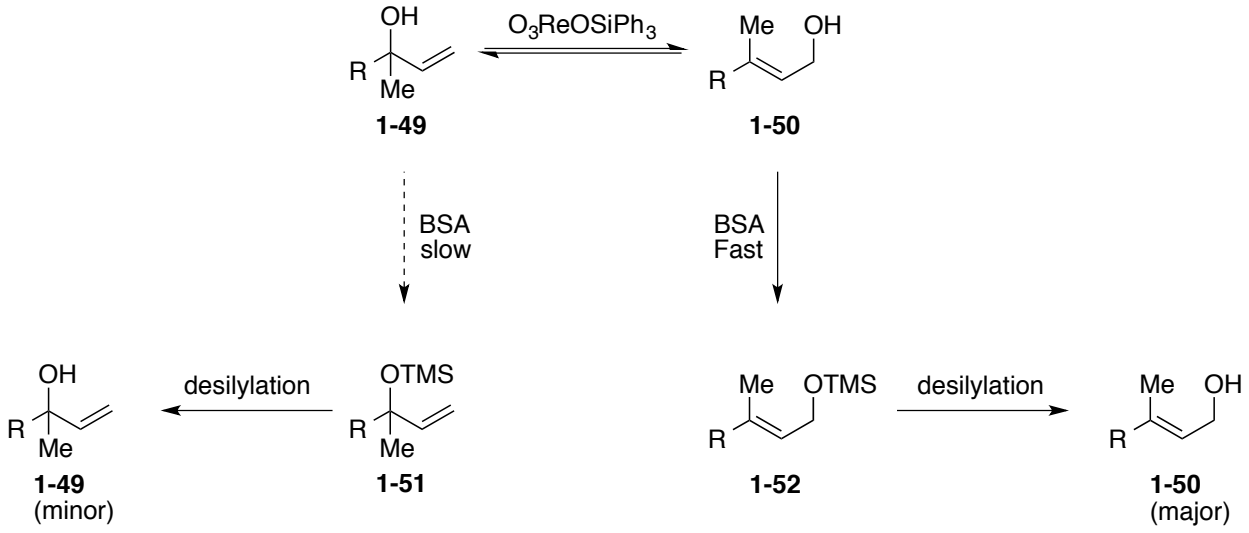
1-47 **1-48**

Entry	(*E*/*Z*)[a] ratio	R^1	R^2	R^3	Temp (°C)	Time (min)	Yield (%)[b]
1	10:1	n-hex	H	H	-50	30	98
2	10:1	n-hex	NO_2	H	23	30	98
3	<1:20	n-hex	H	NO_2	0	30	94
4[c]	>20:1	n-hex	H	CF_3	-50	60	98
5[d]	10:1	n-hex	OMe	H	-78	120	68
6[d]	>20:1	n-hex	H	OMe	-78	120	79
7	12:1[e]	c-C_6H_{11}	H	H	-50	30	95
8	1:12[e]	c-C_6H_{11}	H	H	-50	30	93
9		H	H	H	0	30	98
10		H	NO_2	H	23	30	98
11		H	OMe	H	-50	30	65

a) Determined by ^{1}H NMR; b) *E*/*Z*>20:1 as determined by ^{1}H NMR, c) use 3 mol% of catalyst; d) use 4 mol% of catalyst; e) Determined by GC; f) Reaction done in CH_2Cl_2.

1.3.2 Enhanced selectivity by consecutive transposition and silylation

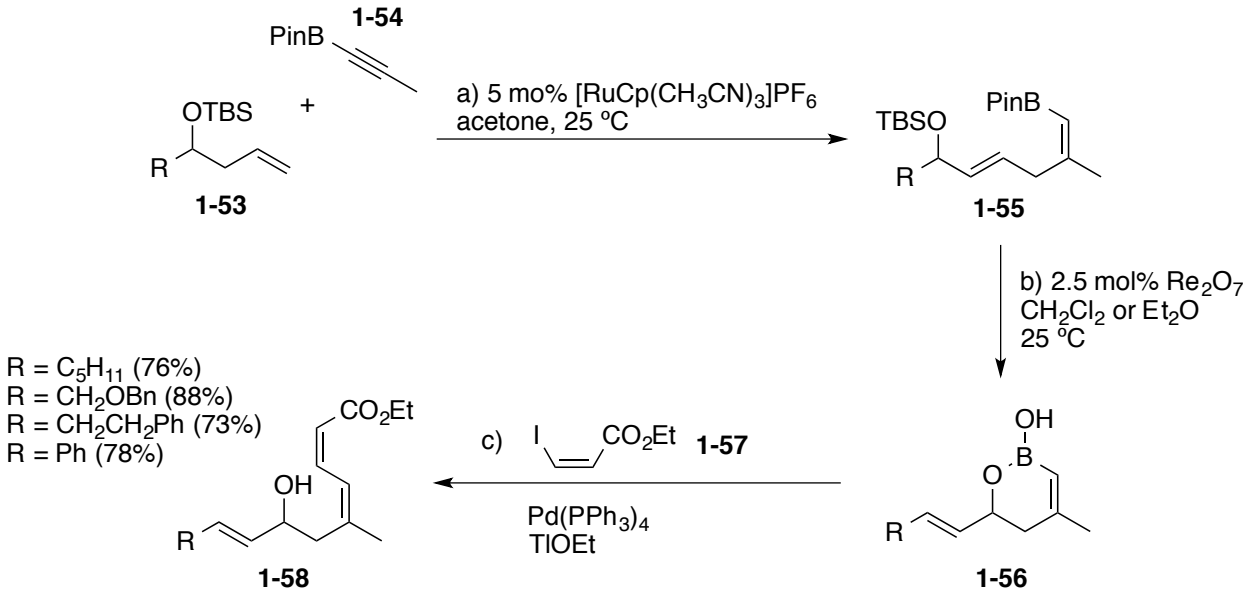
Another way to improve the regioselectivity is to couple the isomerization to a subsequent step that shows different reactivity toward the equilibrating isomers. By taking one isomer out of the equilibrating system, one can push the reaction to yield the desired product. For example, inspired by Osborn's observation that isomerization of allyl silyl ethers was slow relative to that of allylic alcohols[25] Grubbs and co-workers designed a unique silylation and desilylation sequence that selectively removed the primary alcohol from the equilibrating mixture by taking advantage of the fact that the silylation of primary alcohol (**1-50**) is much faster than that of tertiary alcohol (**1-49**). As shown in Scheme 1.10, after desilylation the primary allylic alcohol was obtained as major product with good selectivity.[32] However, selective isomerization of secondary allyl alcohol to primary allyl alcohol is ineffective using this method. This strategy was later applied successfully in the total synthesis of 6′-hydroxylarenarol[43] and (–)-apratoxin A.[44]



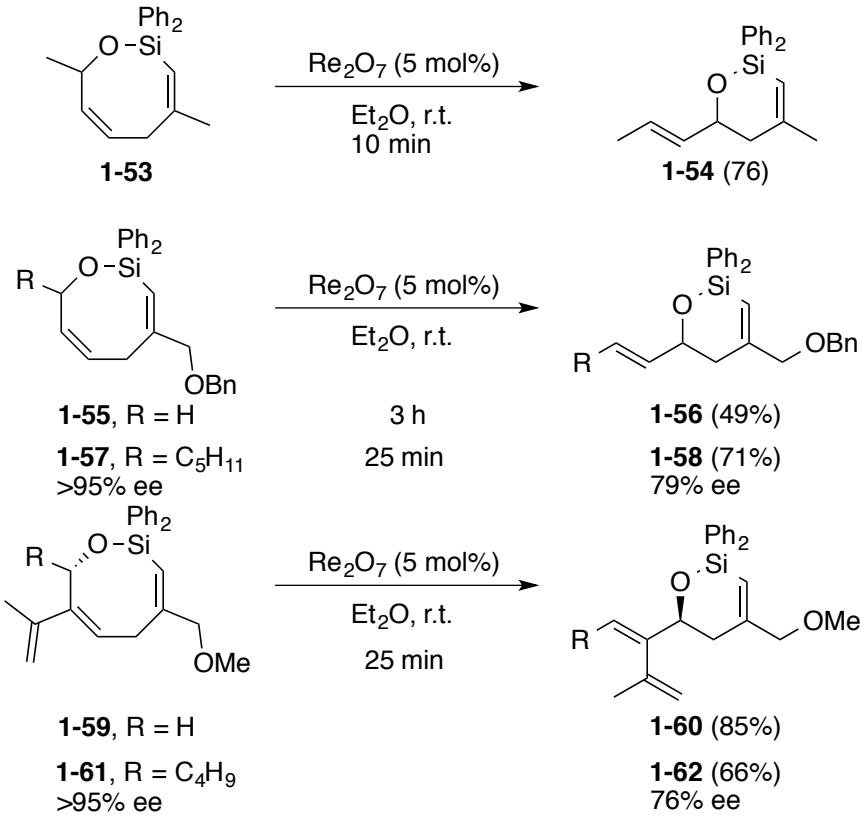
Scheme 1.10 Enhancing regioselectivity by selective silylation (BSA: N,O-Bis(trimethylsilyl)acetamide)

1.3.3 Enhanced selectivity by trapping with boronates

Lee and co-workers[48] were able to shift the equilibrium toward the desired direction by introducing an electrophilic boronate group within the molecule that can trap the isomerized hydroxyl group. The corresponding substrates are difficult to prepare, but the corresponding silylated substrates are much easier to prepare with an Alder-ene reaction (Scheme 1.11, step a). Isomerization of **1-55** and subsequent intramolecular trapping of the transposed allyl silyl ether moiety forms cyclic boronate **1-56** that serves as important intermediates for Suzuki coupling reactions (step c). This strategy offers an easy access to an important class of structures and has been applied successfully in the total synthesis of (–)-dactylolide.[45]



Scheme 1.11 Allylic transposition of silyl ethers and subsequent Suzuki coupling of cyclic vinyl boronic acid

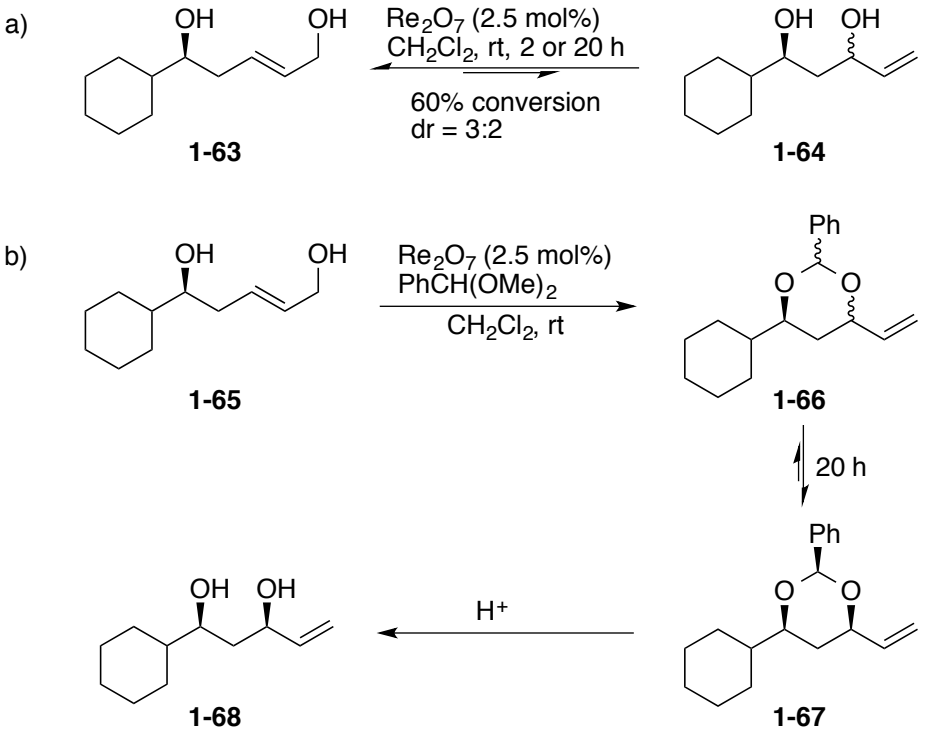


Scheme 1.12 Ring-contractive allylic transposition of cyclic silyl ethers

1.3.4 Enhanced selectivity by ring contraction

Lee and coworkers developed another approach for selective [1,3]-transposition of allyl silyl ethers by relieving ring strain of medium-sized rings.[49] In this protocol, eight membered ring siloxadienes undergo ring contractions to form the corresponding six-membered siloxenes bearing an endocyclic double bond and an exocyclic alkenyl substituent. This ring contraction also generates a *trans*-double bond from the internal *cis*-alkene, providing an additional driving force for the transformation. As shown in Scheme 1.12, in the presence of 5 mol% Re_2O_7, various silacyclodienes (**1-53**, **1-57**, **1-61**) undergo effective ring contractions to afford **1-54**, **1-58**, **1-62** respectively in good to high yields with *trans*-configuration of the exocyclic double

bonds. However, the rearrangement of substrate **1-55** derived from a primary allyl alcohol afforded product **1-56** with reduced efficiency and the rearrangement of enantioenriched substrate **1-61** afforded **1-62** with some degree of enantiomeric excess erosion. This method was later applied successfully in the total synthesis of (–)-amphidinolide V.[47]



Scheme 1.13 Regio- and stereocontrol of allylic alcohol isomerization by benzylidene acetal formation

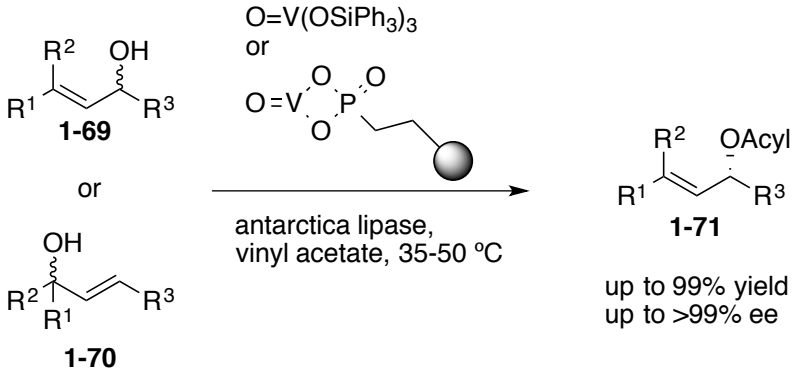
1.3.5 Enhanced selectivity via reversible trapping by benzylidene acetal

Zakarian and coworkers developed the ketalization-based trapping strategy for the transposed hydroxyl group to achieve high product selectivity for the synthesis of the most thermodynamically stable 1,3-diol benzylidene acetals. As shown in Scheme 1.13a, a traditional

isomerization of **1-63** gives a diastereomeric mixture of **1-64** in equilibration with the starting material. However, the mixture **1-64** possesses a 1,3-diol moiety and can be trapped by ketalization to form another mixture **1-66**. This mixture of acetals will then slowly equilibrate to selectively yield diastereomer **1-67**, which has the highest thermodynamic stability (scheme 1.13b). Subsequent hydrolysis of **1-67** gives syn-1,3-diol **1-68**, an important moiety in organic chemistry.

1.3.6 Enhanced selectivity by dynamic kinetic resolution (DKR)

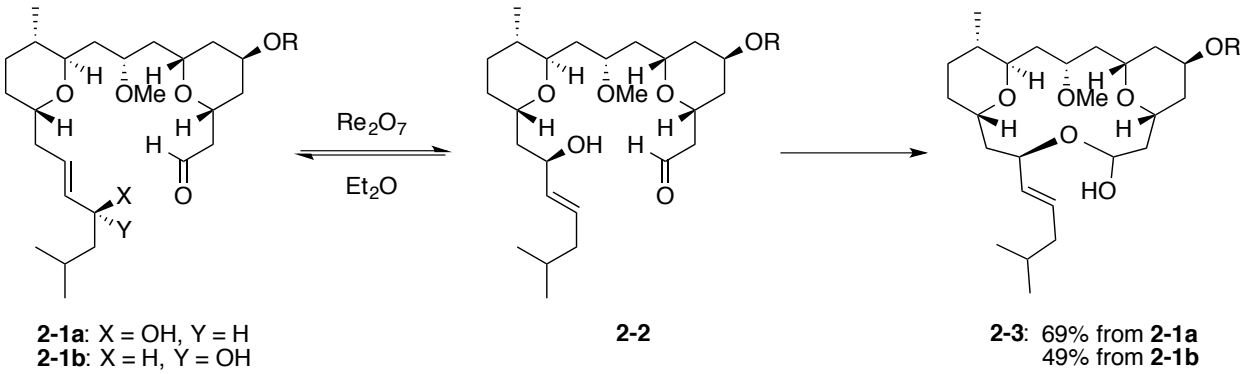
Akai and coworkers developed an elegant DKR (dynamic kinetic resolution) approach[51, 52] in which a free or polymer-bound vanadium-oxo complex was used to catalyze the rapid and continuous racemization of the alcohols as well as the allylic transposition of the hydroxyl groups, while the lipase was used to effect the chemo- and enantioselective esterification of allylic alcohols. As shown in scheme 1.14, regardless of which equilibrating isomer is used, the same final product will be obtained with high yield and enatiopurity. This approach is impressive since it provides great flexibility to substrate synthesis, as one can simply choose to start with the isomer that is easiest to synthesize.



Scheme 1.14 Synthesis of optically active allyl esters via Lipase-Vanadium combo catalysis

2.0 STEREOSELECTIVE HETEROCYCLE SYNTHESIS THROUGH A REVERSIBLE ALLYLIC ALCOHOL TRANSPOSITION AND NUCLEOPHILIC ADDITION SEQUENCE

Our interest in allylic alcohol isomerization arose from our studies in the total synthesis of leucascandrolide A,[42] where allylic alcohol **2-1a** or **2-1b** was subjected to Re_2O_7 to effect the reversible conversion to **2-2** followed by the thermodynamically driven formation of macrolactol **2-3** (See Scheme 2.1). The same final product was obtained regardless of which starting isomer was used, indicating that dynamic thermodynamic stereocontrol can be achieved under these reversible conditions due to the lack of stereochemical fidelity in the transposition process. The stereochemical infidelity, often viewed as undesirable, was used in this case to our benefit to obviate the need for an additional step of preparing a stereochemically defined allylic alcohol, which could be labor and material intensive considering the complexity of **2-2**.



2-1a: X = OH, Y = H
2-1b: X = H, Y = OH

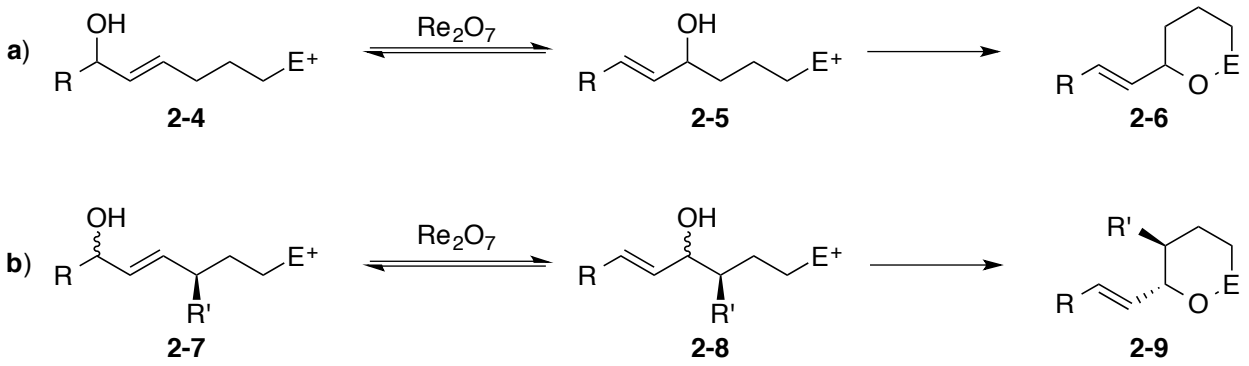
2-2

2-3: 69% from **2-1a**
49% from **2-1b**

Scheme 2.1 Allylic alcohol transposition and capture in the total synthesis of leucascandrolide A

2.1 RESEARCH OBJECTIVES AND SUBSTRATE DESIGN

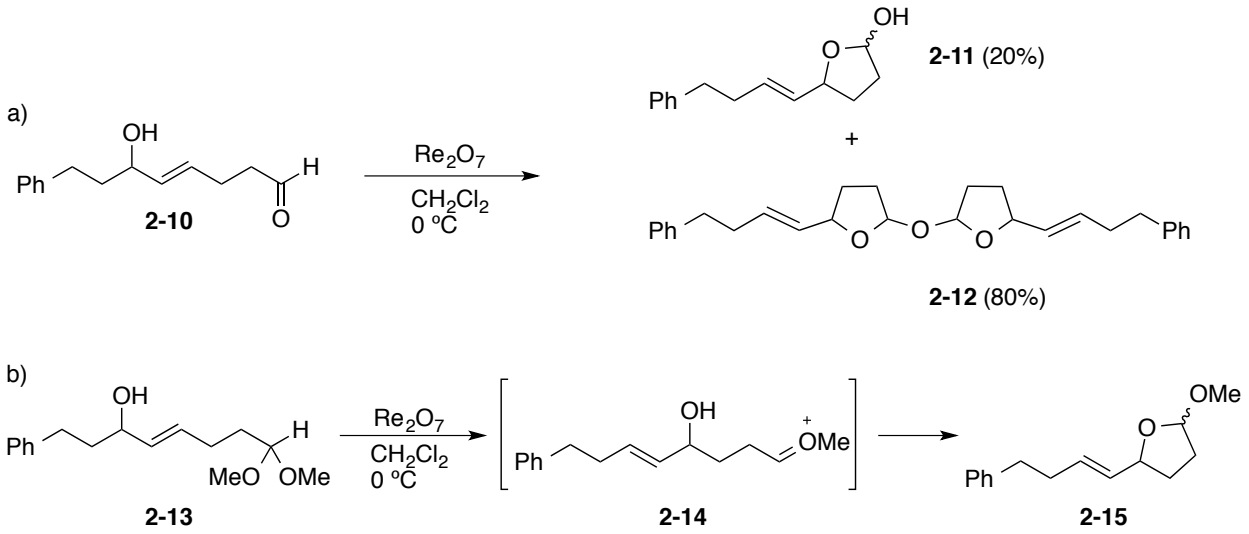
Our previous synthesis of leucascandrolide A indicated that a mixture of diastereomers could be equilibrated to a single product with proper substrate design, which highlighted the possibility of applying non-stereoselective allylic alcohol transposition to stereoselective syntheses of complex molecules through thermodynamic equilibration. This strategy, if proved viable, will provide great freedom and flexibility to substrate preparation and minimize the need for reagent-controlled asymmetric transformations during synthetic endeavors. We begin to explore this strategy by studying its applicability in the preparation of some simpler structures such as small heterocycles.



Scheme 2.2 Proposed transposition and trapping sequence catalyzed by Re_2O_7

We propose that transposed allylic alcohols can be trapped by preinstalled electrophiles for the syntheses of small cyclic ethers.[53] (Scheme 2.2, equation a) Pre-installed stereogenic centers might be able to affect the overall stereochemical outcome by thermodynamically driven equilibration processes (Scheme 2.2, equation b), facilitating the stereoselective syntheses of these small cyclic ethers, which are ubiquitous and important moieties in organic chemistry.

2.2 RESEARCH RESULTS AND DISCUSSIONS

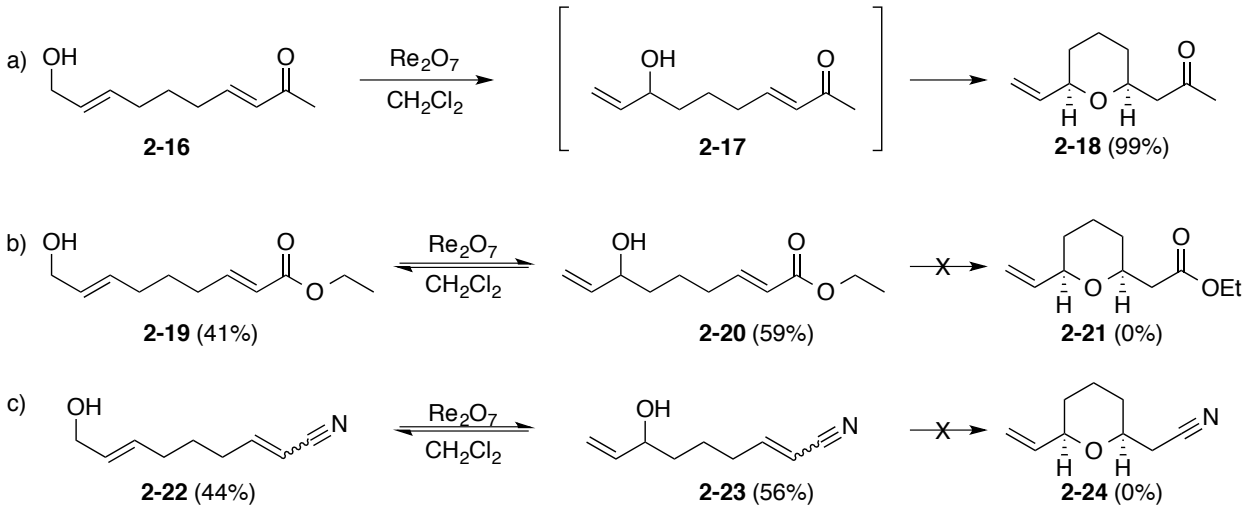


Scheme 2.3 Initial cyclization studies

2.2.1 Application to the synthesis of medium-sized cyclic ethers

We tested the applicability of the transposition/hemicacetal formation to form small rings (Scheme 2.3) by subjecting alcohol **2-10** to 5 mol% Re_2O_7 in CH_2Cl_2. After stirring at room temperature for 30 min, we observed complete consumption of the starting material and the formation of lactol **2-11**, but the yield was only 20%. The major product **2-12** resulted from dehydrative coupling reactions of **2-11** via tetrahydrofuryl oxocarbenium ion formation[50, 54] and nucleophilic addition. This pathway could be suppressed by conducting the reaction with acetal **2-13**, whereby the Lewis acidity of Re_2O_7 acted to form oxocarbenium ion **2-14**, which trapped the transposed alcohol to form **2-15** in 83% yield. No stereocontrol was observed in this reaction,

which is consistent with our expectations based on thermodynamic considerations. Enone **2-16** was also exposed to the reaction conditions to explore the viability of an allylic alcohol transposition and oxa-Michael reaction[55] sequence and tetrahydropyran **2-18** was formed as a single stereoisomer in nearly quantitative yield within 10 min at room temperature. α,β-Unsaturated esters and nitriles are not sufficiently electrophilic for these reactions. These substrates only equilibrate with the corresponding transposed allylic alcohols when exposed to the standard reaction conditions (Scheme 2.4, equation b and c).

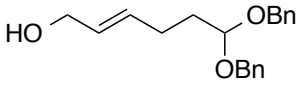
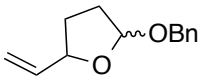
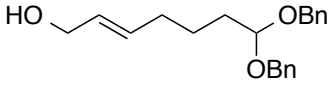
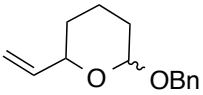
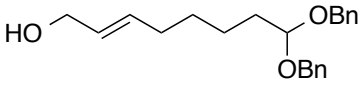
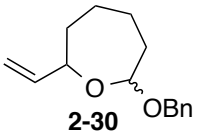
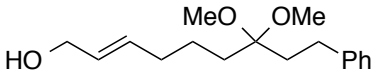
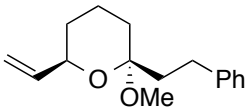
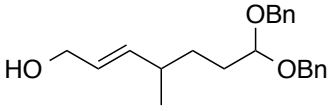
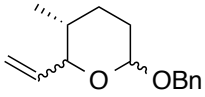
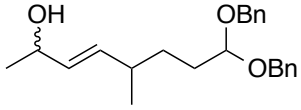
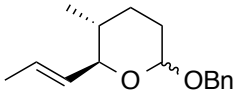
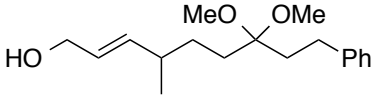
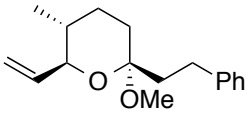
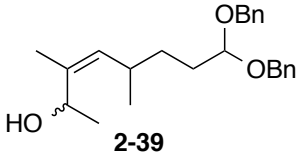
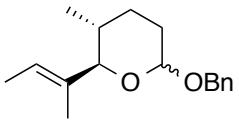
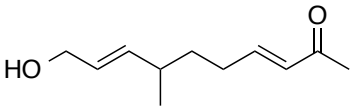
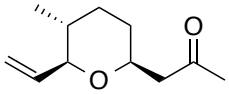
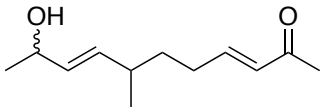
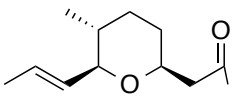


Scheme 2.4 Trapping transposed allylic alcohol with Michael acceptors

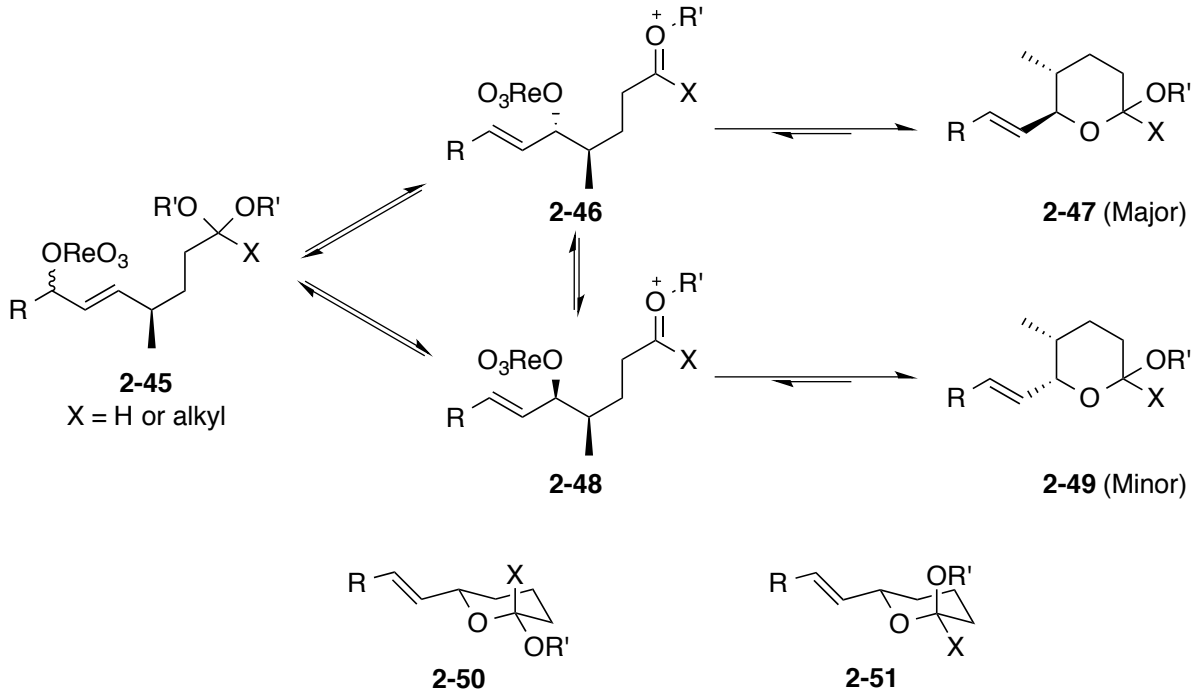
The scope of these monocyclization reactions is shown in Table 2.1. Entries 1-3 show that acetals containing primary allylic alcohols are suitable substrates, and the formation of five-, six-, and seven-membered rings proceeds smoothly with nearly equivalent efficiency. As shown in Scheme 2.3, no stereoselectivity was observed in these reactions, which is consistant with the fact that no significant difference in thermodynamic stability exists between the corresponding isomers. Ketals react with even greater efficiency, as shown in entry 4, where **2-32** was formed as a single stereoisomer within 10 min at lowered temperature. In fact when the reaction was

performed at room temperature, a low yield was observed resulting from the generation of a significant amount of byproducts, perhaps forming via the carbocation intermediates.

Table 2.1 Exploration of the reaction scope

Entry	Substrate	Product	Time	%Yield
1	 **2-25**	 **2-26**	30 min	84
2	 **2-27**	 **2-28**	30 min	81
3	 **2-29**	 **2-30**	30 min	81
4	 **2-31**	 **2-32**	10 min	85
5	 **2-33**	 **2-34**	30 min	99 dr = 1:1
6	 **2-35**	 **3-36**	30 min	86 dr>10:1
7	 **2-37**	 **2-38**	20 min	81 dr = 10:1
8	 **2-39**	 **2-40**	30 min	91
9	 **2-41**	 **2-42**	48 h	88
10	 **2-43**	 **2-44**	60 min	90

No stereocontrol is observed in acetal substrates that contain a stable stereocenter and a primary allylic alcohol (entry 5), but excellent stereocontrol arises from subjecting the corresponding secondary alcohol to the reaction conditions (entry 6). Ketal substrates that contain a stereocenter and primary alcohol group show high stereocontrol (entry 7), with **2-28** being formed as nearly a single stereoisomer from **2-37** within 30 min. Trisubstituted alkene substrates are also viable participants in this reaction, as shown by the conversion of **2-39** to **2-40** (entry 8). Stereoselective transformations can also be achieved with enone electrophiles, as seen in entries 9 and 10. Equilibration is much faster for secondary allylic alcohol **2-43** in comparison to primary alcohol **2-41**.

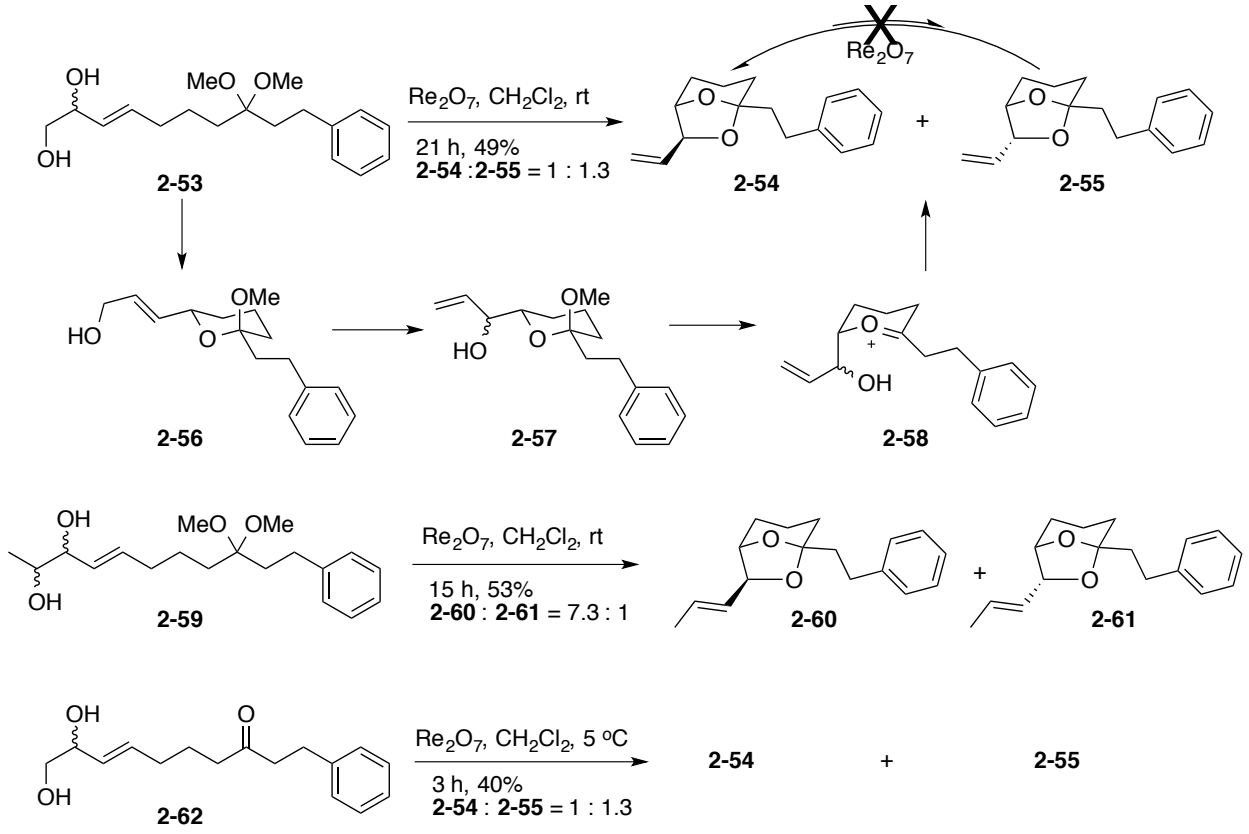


Scheme 2.5 Pathways for stereochemical isomerization

Scheme 2.5 provides a consistent explanation based on fundamental principles for the results shown in Table 1. Rearrangement of the initially formed perrhenate ester **2-45** proceeds with little or no stereocontrol to form a mixture of esters **2-46** and **2-48**. Cyclization follows

oxocarbenium ion formation to yield **2-47** and **2-49**, respectively, as the kinetic products. Ring formation is reversible, however, leading to thermodynamic equilibration in some cases. The equilibration most likely results from perrhenate ester ionization to form an allylic cation followed by ion-pair collapse to yield a mixture of stereoisomers. Secondary allylic alcohols ionize more readily than primary allylic alcohols due to the cation-stabilizing effect of the additional alkyl group. Thus, the superior stereocontrol in the cyclization of **2-35** relative to **2-33** (enties 5 and 6 in Table 2.1**)** can be ascribed to the greater potential for the stereomutation in the short-lived acyclic intermediate. The heightened stability of the oxocarbenium ion from the ionization of ketals rather than acetals promotes ring opening and enhances opportunities for stereochemical editing by conferring a longer lifetime to the acyclic intermediate. This difference accounts for the excellent level of stereocontrol that was observed in the cyclization of **2-37** (entry 7). Trisubstituted alkene substrates can yield products with a single alkene geometry when sufficient energetic preference exists (entry 8). The cyclization of **2-39** is also noteworthy because the dehydrooxecane that would form via a direct cyclization of the starting alcohol into the intermediate oxocarbenium ion is not observed. The corresponding primary alcohol yields a mixture of tetrahydropyran and dehydrooxecane products (not shown), again highlighting the benefits of utilizing secondary alcohols on isomerization kinetics. Thermodynamics dictate the stereochemical orientation of the anomeric centers, with isomer **2-50** and **2-51** having similar energies when X = H, and **2-50** being significantly less stable than **2-51** when X = alkyl. The same products are observed when secondary alcohol substrates are single stereoisomers or diastereomeric mixtures, confirming that stereocontrol arises from thermodynamic control rather than kinetical control. Ketone products equilibrate through retro oxa-Michael reactions. Again,

additonal alkyl substituent facilitates ionization and leads to a more rapid equilibration. This is the reason why the formation of **2-44** took only 60 minutes while that of **2-42** took two days.



Scheme 2.6 Double isomerization/cyclization route to bridged structures

2.2.2 Application to the synthesis of bridged bicyclic acetals

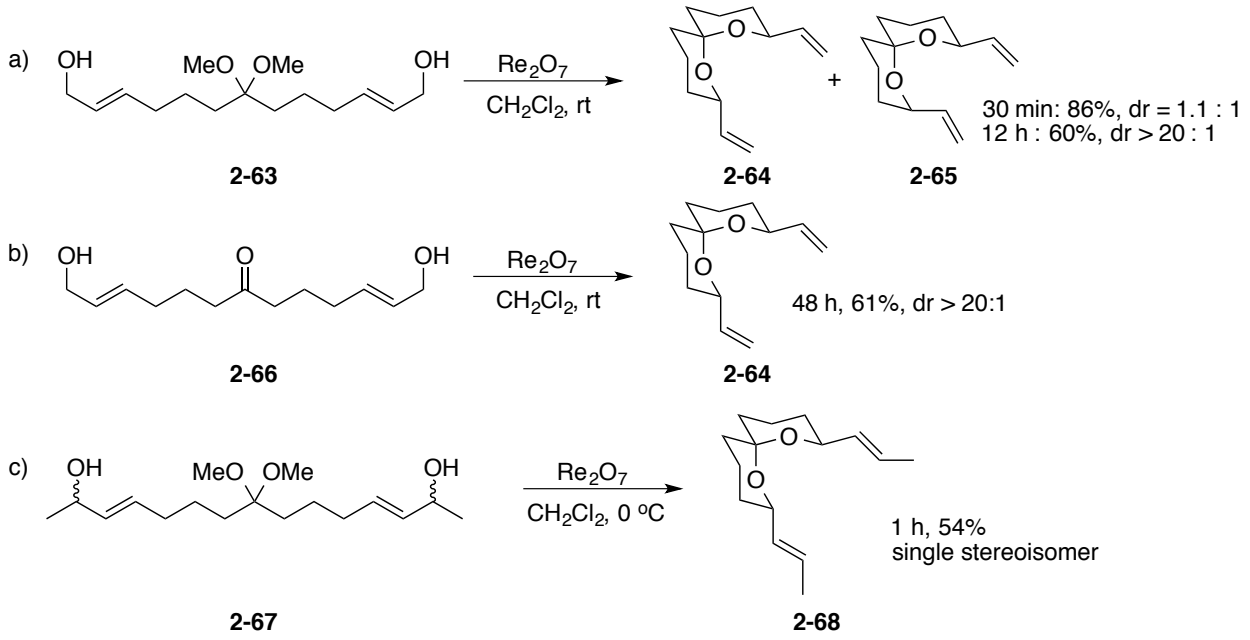
Upon establishing the basic reactivity patterns of the process, we turned our attention toward its application to the construction of more complex bicyclic structures. In these reactions, the acetal group serves as an electrophile for consecutive nucleophilic additions. Bridged bicyclic structures of this type that are found in a number of biologically active compounds such as the didemniserinolipids[56] and the pinnatoxins.[57] The reaction of diol acetal **2-53** with Re_2O_7 provides

diastereomeric bicycles **2-54** and **2-55** as a separable 3:4 mixture after 21 h. This reaction proceeded through an initial isomerization/cyclization to form **2-56**, which underwent a second isomerization to yield **2-58** as a mixture of diastereomers. Ring closure provided the observed products. Resubmitting pure **2-55** to the reaction conditions yielded only a minimal amount of **2-54**, indicating that the product ratio can be attributed to kinetic rather than thermodynamic factors. Diol **2-59** was prepared as a mixture of stereoisomers in an effort to facilitate equilibration. Exposing **2-59** to the standard conditions resulted in the formation of bicycles **2-60** and **2-61** in 53% yield as a 7.3:1 mixture, indicating that the increased substitution in the allylic system promotes thermodynamic equilibration in accord with prior results. Resubjecting **2-61** to the reaction conditions provided a similar ratio of **2-60** and **2-61**. This ratio is consistent with the energetic difference between the isomers that was calculated by Spartan.[58] We also examined the cyclization of ketone **2-62** based on our supposition that intramolecular addition into the oxocarbenium ion that formed from ionization of the initial lactol would be faster than the bimolecular addition that was observed in the reaction of **2-10**. While **2-62** proceeded through the sequence with slightly lower efficiency than **2-53**, the reaction yielded **2-54** and **2-55** in the same ratio.

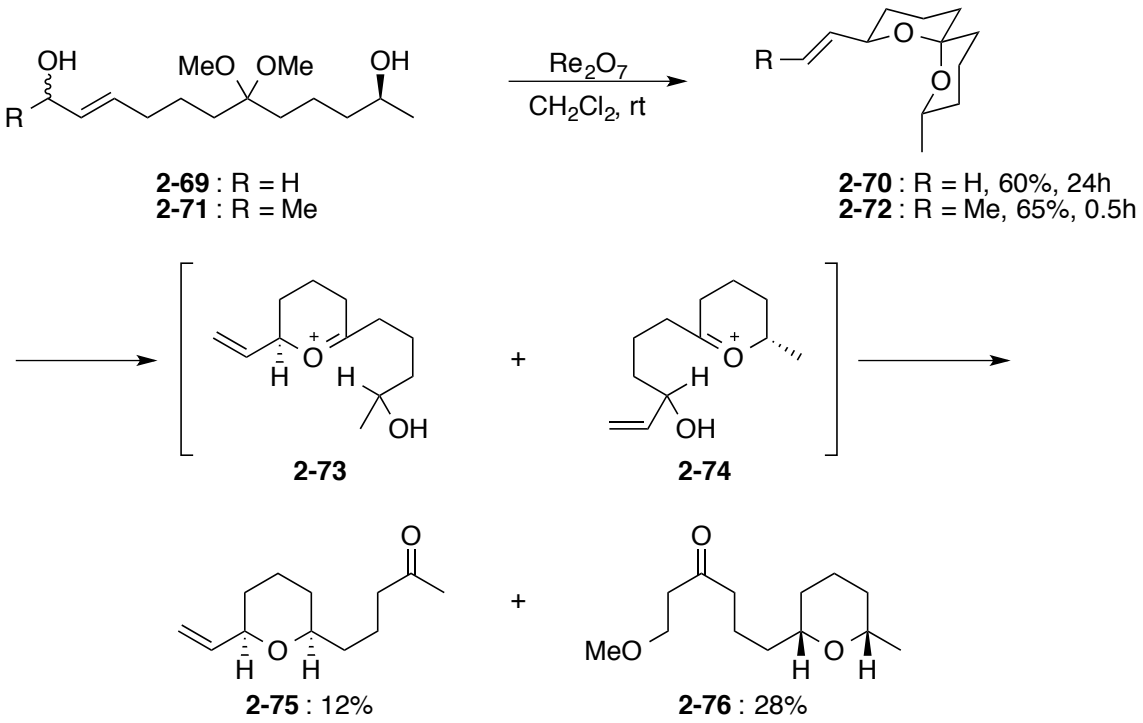
2.2.3 Application to the synthesis of bicyclic spiroketals

This strategy can also be applied to the synthesis of spirocyclic structures[59] as shown in Scheme 2.7. Diol acetal **2-63** reacted with Re_2O_7 under standard condition to provide a 1.1:1 mixture of spiroketals **2-64** and **2-65** within 30 min at rt. Allowing the reaction to proceed for 12 h improved the ratio of **2-64** and **2-65** to > 20: 1 in which the major product has the anomerically preferred stereochemical orientation at the ketal center, and both vinyl groups have equatorial

alignments. Ketones also serve as useful substrates for the process though the isomerization process is slower, with **2-66** providing **2-64** in 61% yield after 48 h. Notably, equilibration in this reaction required the addition of MeOH. We postulate that the addition of MeOH facilitates the ring-opening event to a greater degree than water, or water suppresses the catalytic efficiency of Re_2O_7[2c] because the cyclization of the ketone substrate will generate one equivalent of water. As expected, secondary diol **2-67** equilibrated more rapidly, providing **2-68** as a single stereoisomer within 1 h at 0 °C. Reaction of the secondary diol substrate at higher temperature results in decomposition, this is again due to the increased stability of the allylic cation when an additional alkyl group is introduced.



Scheme 2.7 Synthesis of spiroketals



Scheme 2.8 Remote stereoinduction and intramolecular redox isomerization

Next, diol acetals **2-69** and **2-71** were prepared to study the influence of a non-equilibrating secondary alcohol on remote stereochemical induction. These compounds proceeded through the cyclization reactions (Scheme 2.8) efficiently to form spiroketals **2-70** and **2-71** in 60% and 65% yield, respectively. Consistent with previous studies, the reaction of secondary alcohol **2-71** converged to a single stereoisomer much more rapidly (30 min *vs.* 24 h) than the cyclization of primary alcohol **2-69**. When enantiomerically pure **2-69** was used in the reaction, minimal racemization (~2%) was observed by HPLC detection (Figure 2.1). Thus this transformation demonstrates that a high level of relayed 1,9-stereoinduction can be obtained based on thermodynamic control. The isolation of tetrahydropyranyl ketones **2-75** and **2-76** as minor products from the cyclization of **2-69** is also noteworthy. These products arise from the ionization of the spiroketal to form oxacarbenium ions **2-73** and **2-74**. Reduction of these ions by

intramolecular hydride transfer leads to the tetrahydropyranyl ketones, with conjugate addition of MeOH to the intermediate enone ultimately providing **2-76**. These transformations, while not resulting from predominant pathways, are nonetheless mechanistically intriguing because the stereocenter that directs the creation of the two stereocenters in the product is ultimately destroyed in this process.

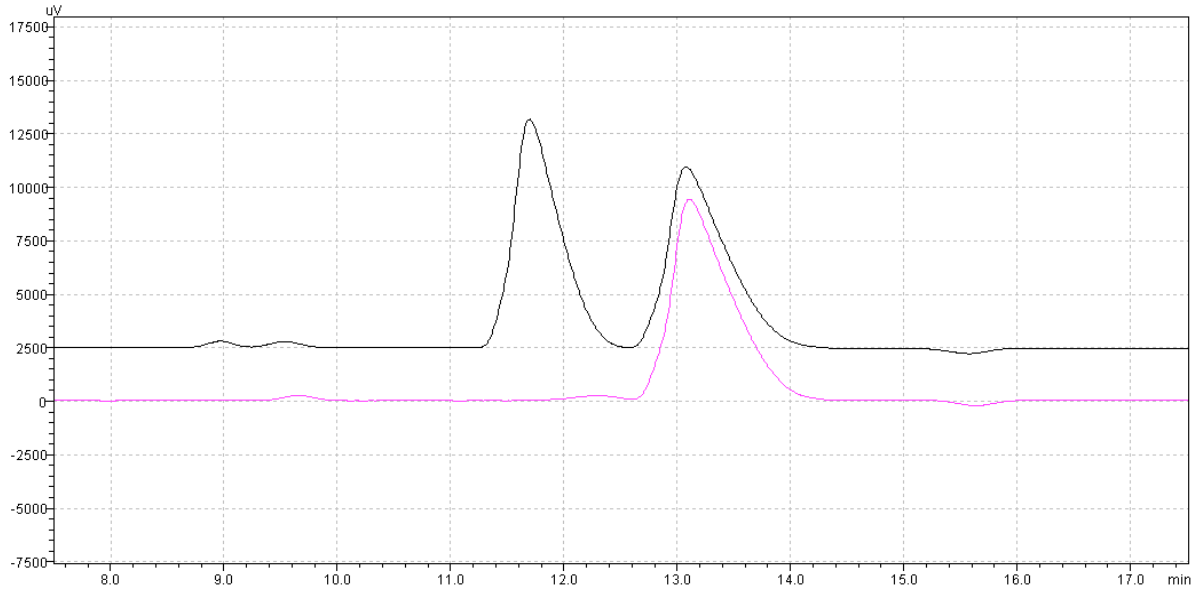
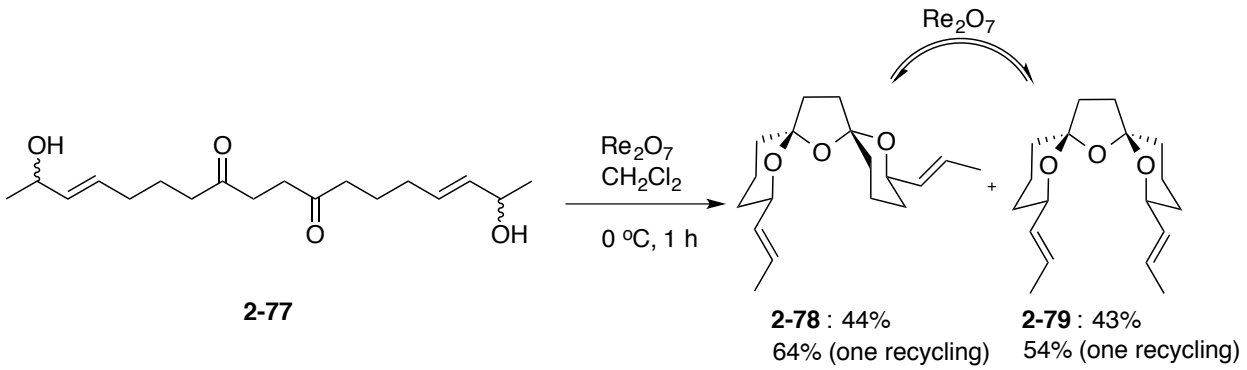


Figure 2.1 HPLC traces of racemic (black) and enantioenriched (pink) **2-70** from racemic and enantioenriched substrate **2-69** using a chiral stationary phase

2.2.4 Application to the synthesis of spirotricycles



Scheme 2.9 Synthesis and equilibration of spirotricycles

We explored the capacity for remote stereochemical induction across a spirotricyclic system by preparing diketone diol **2-77** through an oxidative enolate coupling reaction[60] (see experimental details). Exposing **2-77** to Re_2O_7 at 0 °C for 1 h provided spirotricycles **2-78** and **2-79** in 44% and 43% yield, respectively (see Scheme 2.9). Confirmation for these structures was provided by HPLC experiments (see Figure 2.2) where racemic **2-78** showed 2 peaks of equal intensities when a chiral stationary phase was employed while *meso* isomer **2-79** showed only one peak. The formation of a diastereomeric mixture is a result of the lack of a strong thermodynamic preference for either compound that results from the numerous low energy conformations of the central tetrahydrofuran unit.[61] Re-subjecting either of the products to the reaction conditions quickly resulted in the formation of the thermodynamic mixture of diastereoisomers. Therefore one recycling of **2-79** provided **2-78** in an overall yield of 64% While one recycling of **2-78** provided **2-79** in 54% overall yield. The ratio of products that was formed in the equilibration

reaction was slightly different from the ratio that was observed in the initial cyclization. We postulate that the liberation of water in the initial cyclization reaction could have a subtle influence on the rate of equilibration since water was excluded from the equilibration protocol. The important conclusion from this study is that either stereoisomer can be accessed in reasonable yield through a rapid sequence of reactions. The stereochemical arrangement around the tetrahydrofuran ring in **2-78** matches the orientation that is seen in azaspiracid-1[62] while the arrangement in **2-79** matches the pinnatoxins.[57] Multiple studies have shown[63] that the thermodynamic preferences in these spirotricycles can be manipulated by subtle structural changes, indicating that this protocol could be broadly applicable to the synthesis of this molecular class, particularly in the consideration of the improved access to 1,4-diketones that has resulted from advances in oxidative enolate heterocoupling reactions.[64] This sequence produced compounds in which stereocenters in the product arose from prochiral sites that had a 1,12-relationship in the starting material.

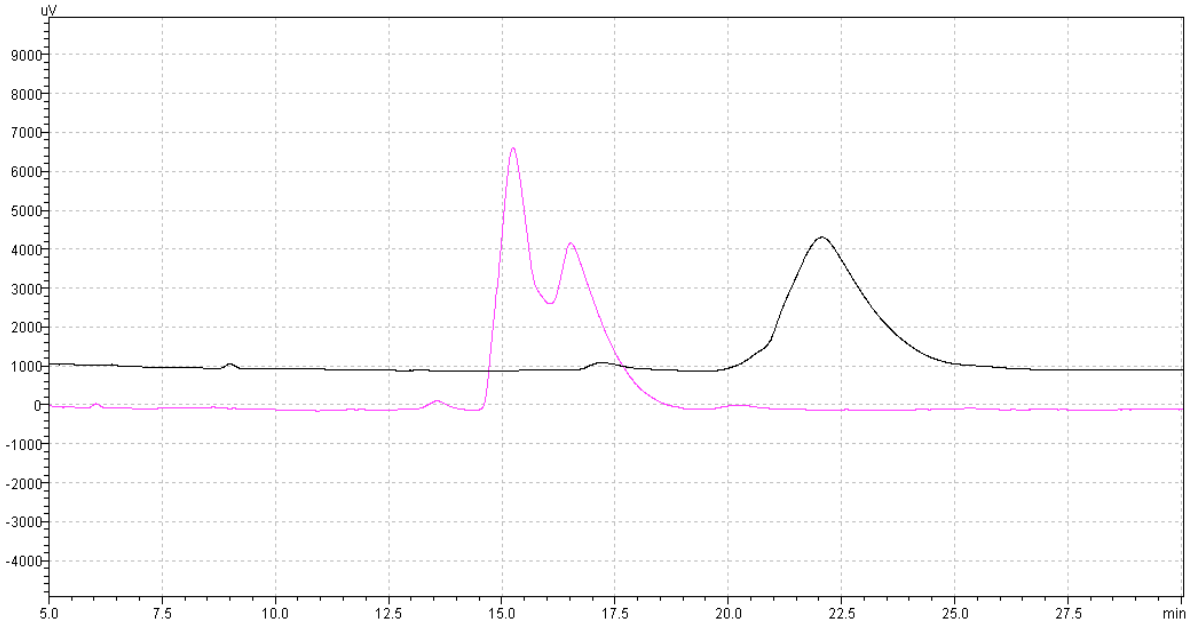


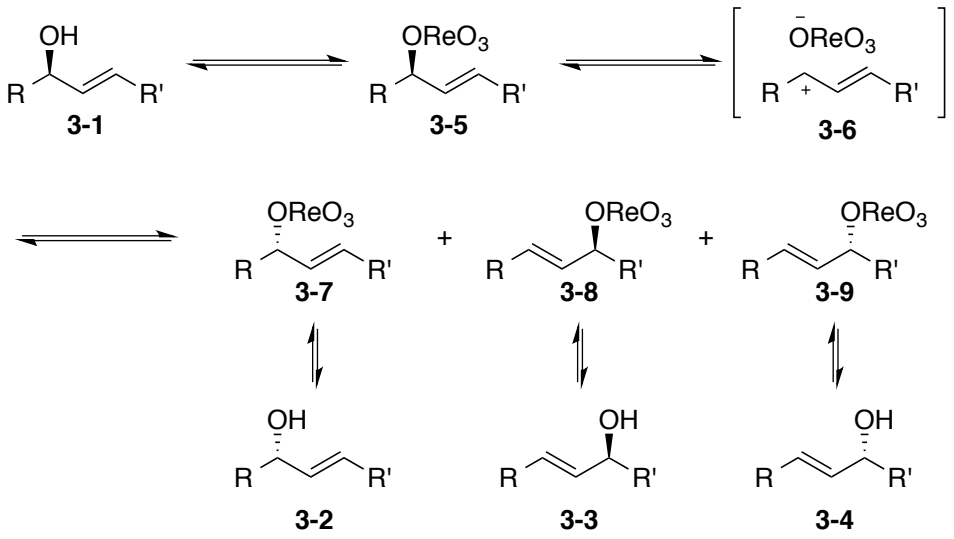
Figure 2.2 HPLC traces of **2-78** (pink) and **2-79** (black) using chiral stationary phase

2.3 CONCLUSION

It has been demonstrated that the experimentally facile sequence of Re_2O_7-mediated allylic alcohol isomerization followed by nucleophilic addition into an oxocarbenium ion can be used to generate stereocenters with high levels of diastereocontrol. Stereocontrol is maximized when the energetic difference between diastereomeric products is sufficient to create a strong preference, when reversibility in the cyclization reaction is facilitated by increasing the stability of the oxocarbenium ion intermediate and when stereochemical scrambling is promoted by increasing the substitution on the intermediate allyl cation. Application of these principles in more complex substrates lead to the syntheses of bridged and spirocyclic ketals with good to excellent levels of stereocontrol. This method is particularly effective for setting remote stereocenters in spirocycle synthesis, where a relayed 1,9- and 1,12-stereoinduction was demonstrated. Applying thermodynamic equilibration to establish remote stereocenters alleviates the need for labor- and material-intensive reagent-controlled asymmetric transformations, thereby enhancing the overall efficiency of complex molecule synthesis.

3.0 CASCADE APPROACH TO STEREOSELECTIVE POLYCYCLIC ETHER FORMATION: EPOXIDES AS TRAPPING AGENTS FOR TRANSPOSING ALLYLIC ALCOHOLS

In the previous chapter, Re_2O_7-catalyzed allylic alcohol transposition reactions and their application in the stereoselective ring-forming processes were studied. These reactions proceeded through intramolecular trapping of the hydroxyl group with an pendent electrophile, followed by thermodynamically controlled equilibration.[53] These initial studies employed achiral electrophiles such as ketals and enones, therefore requiring a stereogenic center in the tether between the nucleophile and the electrophile in order to control the stereochemical outcome. However, trapping transposed alcohols with chiral electrophiles offers significant advantages for the preparation of enantiomerically pure molecules via this isomerization/cyclization sequence. Epoxide groups are particularly attractive for this sequence because they are easily incorporated into a molecule and there are several well-documented methods to prepare epoxides in enantiomerically pure form.[65] Moreover, epoxides can act as electrophiles to liberate nucleophilic hydroxyl groups upon opening,[66] or as nucleophiles to create electrophilic epoxonium ions upon reacting with a cation.[67] These features have led to the development of numerous epoxide-opening cascade reactions and have been applied commonly in natural product synthesis.[68] In this chapter, the application of epoxides as trapping agents for allylic alcohols in rhenium oxide-mediated transposition reactions is studied.

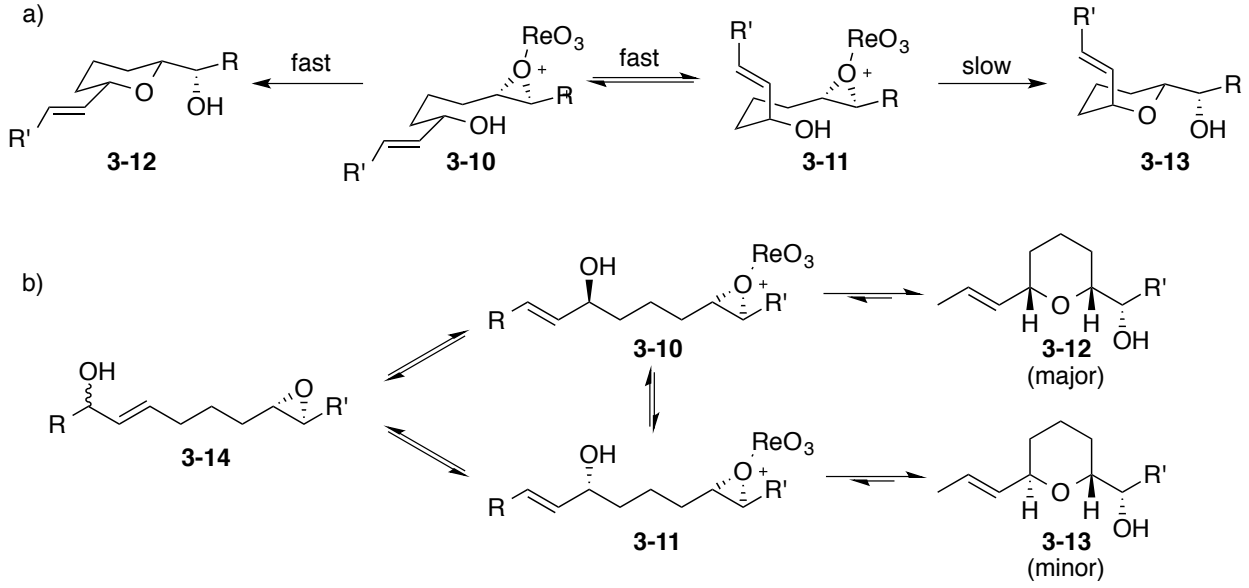


Scheme 3.1 Adjustment of regio- and stereochemistry in rhenium oxide-catalyzed allylic alcohol transposition

3.1 RESEARCH DESIGN AND OBJECTIVES

Rhenium oxide-mediated allylic alcohol transposition can be applied in the design of thermodynamically controlled reactions due to its capacity to adjust regiochemistry and stereochemistry (Scheme 3.1) in response to structural influences. This has been demonstrated in its increased applications in complex molecule synthesis[40-47] as well as chapter 2. Here we propose that coupling this reaction to a trapping by epoxides offer an another opportunity for stereoselective synthesis.[69] As shown in Scheme 3.2, stereoselective synthesis of tetrahydropyran will be realized if either one of the two proposed pathways can work. In pathway a, a fast equilibration is established between two diastereomeric intermediates **3-10** and **3-11**, the formation of **3-12** is faster compared to that of **3-13** due to pseudoaxial vinyl group in the transition state for the conversion of **3-11** to **3-13**, leading to the selective formation of **3-12**. In pathway b, the cyclization of **3-10** and **3-11** to **3-12** and **3-13** is much faster compared to the

equilibration between **3-10** and **3-11**, however the cyclization is a reversible process and the thermodynamically less stable isomer **3-13** undergoes ring opening, and stereoinversion followed by ring closure to deliver the thermodynamically more stable isomer **3-12**. This approach is studied and its application in complex structure synthesis is detailed in the following sections.



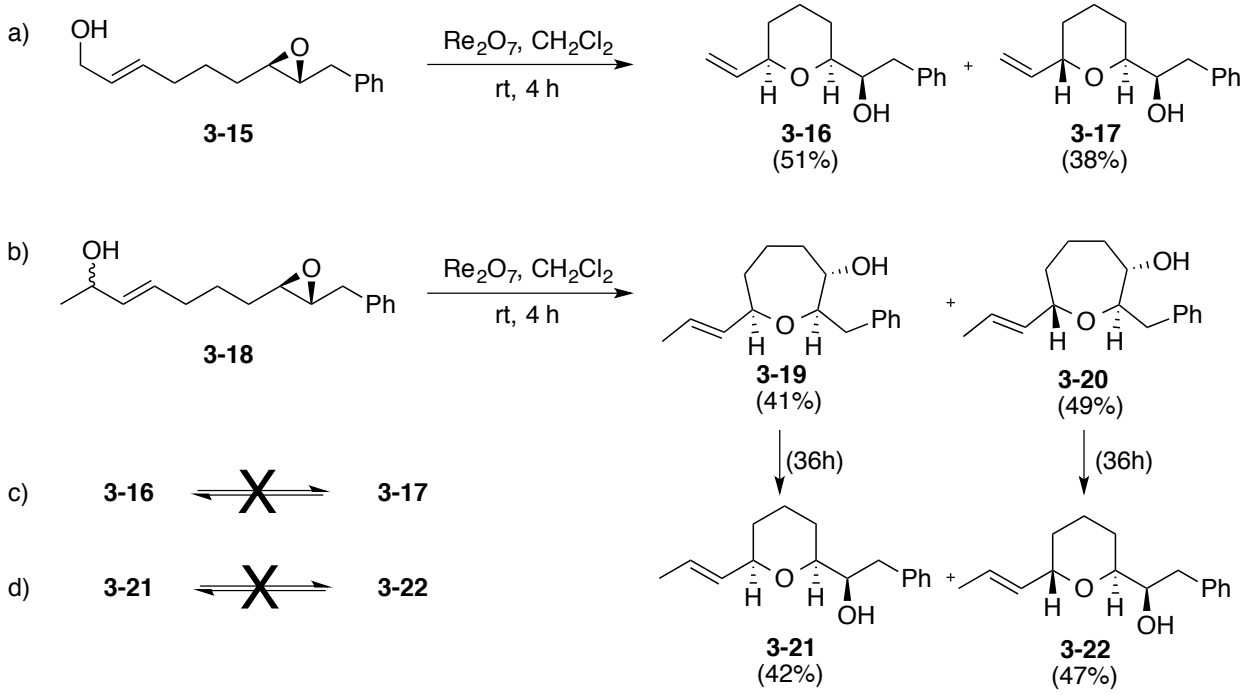
Scheme 3.2 Stereoselective tetrahydropyran formation using epoxides as trapping electrophiles (Same molecules are drawn from different perspective for a and b)

3.2 INITIAL RESULTS ON MONOCYCLIZATION AND DISCUSSIONS

3.2.1 Results for monocyclization

The general applicability of epoxides as trapping agents was demonstrated with substrates **3-15** and **3-16**. When exposing **3-15** to Re_2O_7 (5 mol%) for 4 h at rt, tetrahydropyrans **3-16** and **3-17** were produced in 51% and 38% yields, respectively. This result showed that the reaction exhibits

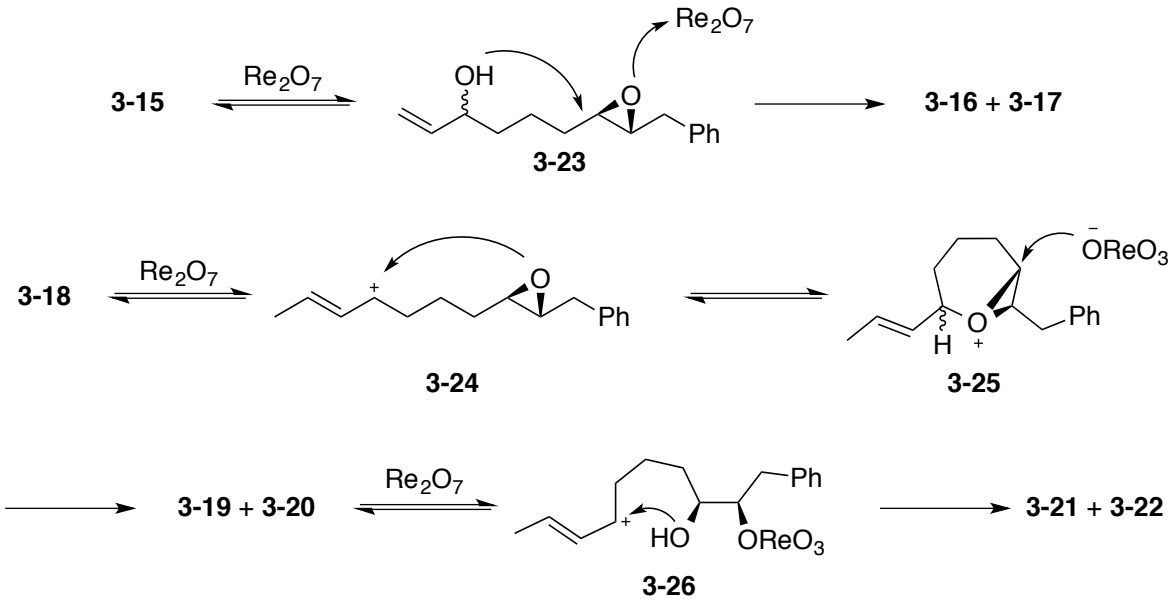
a slight preference for the formation of the thermodynamically more stable isomer **3-16**. Resubjecting either isomer to the reaction conditions resulted in no change, thereby establishing that this result does not arise from thermodynamic equilibration. The reaction of secondary alcohol **3-18** proved to be much more complicated than that of **3-15**. A mixture of oxepanes **3-19** and **3-20** was produced after a reaction time of 45 min. However, prolonged exposure with increased catalyst loading (15 mol%) resulted in the formation of tetrahydropyrans **3-21** and **3-22** in a nearly 1:1 ratio. Resubjection of **3-19** to the reaction conditions yields predominantly **3-21** while resubjection of **3-20** provides predominantly **3-22**. Similar to **3-16** and **3-17**, **3-21** and **3-22** interconvert extremely slowly when resubjected the reaction condition.



Scheme 3.3 Epoxides as the trapping agent in alcohol transposition reactions

These studies showed that primary and secondary allylic alcohols react via different pathways although both produced similar final products when given sufficient reaction time. As shown in

Scheme 3.4, primary allylic alcohol **3-15** undergoes isomerization to form a diastereomeric mixture of secondary alcohols **3-23**. The secondary alcohols then undergo nucleophilic attack toward the Re_2O_7 activated epoxide group to deliver the tetrahydropyran products. On the other hand, secondary allylic alcohol **3-18** reacts with Re_2O_7 to form allyl cation **3-24** due to the stabilization by the additional alkyl group. The epoxide then undergoes nucleophilic attack toward the allyl cation to form epoxonium ion **3-25**, which reacts with perrhenate anion via a kinetically preferred[67e] endo-pathway to provide an oxepanyl perrhenate ester that decomposes to deliver the initially observed oxepanyl alcohol products. Another possible explanation for the formation of these oxepanyl alcohol products is the direct nucleophilic attack of the transposed allylic alcohol toward the Re_2O_7 activated epoxide group via a 7-endo-pathway, and the corresponding products from this mechanism have the opposite stereochemistry compared to those from the former mechanism. However, crystallographic[70] and Mosher ester[71] analysis of the products from enantiomerically enriched substrates showed that the absolute stereochemistry at the distal carbon of the epoxide (with respect to the allylic alcohol) was retained while absolute stereochemistry at the proximal carbon was inverted, providing strong evidence for the first pathway. Oxepanyl alcohol products **3-19** and **3-20** then undergo Re_2O_7-mediated ionization to yield allyl cations **3-26**, then **3-26** react with the pendant free hydroxyl groups to yield the tetrahydropyrans as the thermodynamic products which appear to be inert toward further ionization. The process proceeds predominantly with stereochemical retention, as the isomerization of **3-19** gives **3-21** while that of **3-20** gives **3-22**. Racemization in these processes is minimal, indicating that the allylic ethers undergo ionization at much faster rates than aliphatic ethers.



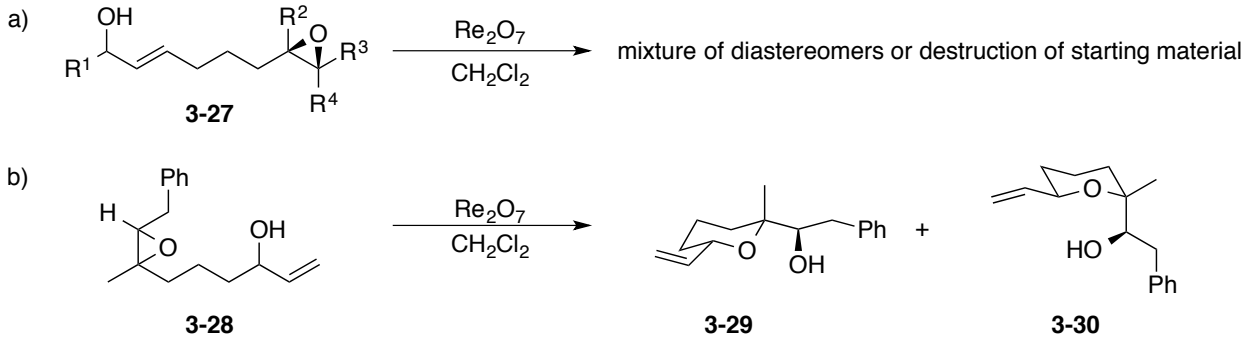
Scheme 3.4 Mechanistic details

3.2.2 Efforts toward understanding the lack of selectivity

Although epoxides can act as effective trapping agents for the transposed allylic alcohol, there is almost no stereoselectivity for such a transposition/cyclization sequence. Many expreriments were conducted in order to confirm either one of the two pathways in Scheme 3.2. For example, to validate the first pathway, substrates **3-27** with different substituents at the epoxide or/and allylic alcohol moiety were synthesized in order to create a larger energetic difference between the two transition states, so that the cyclization of the less energetically favorable intermediate is hampered. However, in all these substrates, the cyclization was much faster than the interconversion of the two intermediate structures and a near 1:1 mixture of diastereomers were obtained for most substrates tested (equation a in talbe 3.1). Lowering the reaction temperature resulted in the increased selectivity at the expense of a reduced yield. This is because the low temperature created a larger energetic difference for cyclization, however, reduced

stereoinversion of the allylic alcohol (e.g. **3-28**) also significantly slowed down and the diastereomer that lead to the minor isomer is enriched over time without converting to the other isomer, supported by of the recovery of starting material. For example, ^{1}H and ^{13}C NMR of the recovered starting material from entry 7 showed that only one diastereomer remained. This result provides strong evidence that the increased selectivity is a result of intramolecular kinetic resolution rather than thermodynamic equilibration, and explains why the overall yield decreased as the diastereoselectivity increased.

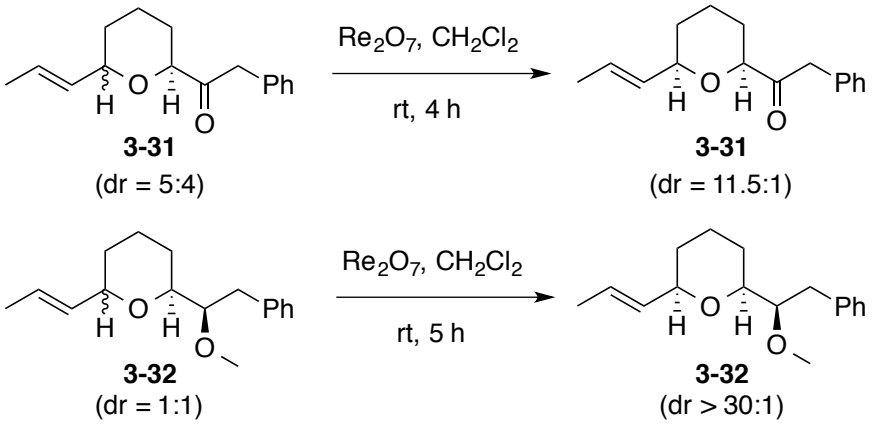
Table 3.1 Efforts toward improving the diastereoselectivity in the epoxide opening



Entry	Temperature	Time	Yield	dr
1	25 ºC	3 h	92%	1.5:1
2	0 ºC	18 h	88%	1.5:1
3	25 ºC	15 min	63%	2.6:1
4	0 ºC	30 min	54%	3.7:1
5	-25 ºC	30 min	31%	6.0:1
6	-78 ºC	6 h	38%	11.0:1
7	-78 ºC	10 h	58%	5.6:1

The failure of the first pathway (Scheme 3.2a) left the second one (Scheme 3.2b) as the only option. However, unlike the products arising from other trapping agents such as ketals and enones in the previous chapter, the cyclization products using epoxides as trapping agents do not

undergo thermodynamic equilibration, which was proved after extensive screening of substrates and reaction conditions. The slowed isomerization of **3-21** and **3-22** compared to that of **3-19** and **3-20** led to the speculation that the exocyclic hydroxyalkyl group suppresses the allyl cation formation, an important step for post cyclization equilibration. To test this hypothesis, ketone **3-31** was prepared as a 5:4 ratio of stereoisomers by oxidation of a crude mixture of **3-21** and **3-22**. When subjecting **3-231** to Re_2O_7 at rt for 4 h, a significant enhancement (11.5:1) of the thermodynamically favored *cis*-isomer was observed (Scheme 3.5). However, a similar substrate with terminal alkene showed little isomerization after extended exposure to the reaction conditions, confirming the importance of cation stabilization in stereochemical equilibration. Another substrate, **3-32,** with the free hydroxyl group protected as methyl ether was prepared in a 1:1 mixture of stereoisomers in order to determine whether the enhancement of ionization rate resulted from the absence of hydroxyl group or from an increased inductive effect. This mixture, when exposed to the standard reaction conditions for 5 h, produced the *cis*-isomer as nearly exclusive product, thereby confirming the role of hydrogen bonding in suppressing ionization-based isomerization.



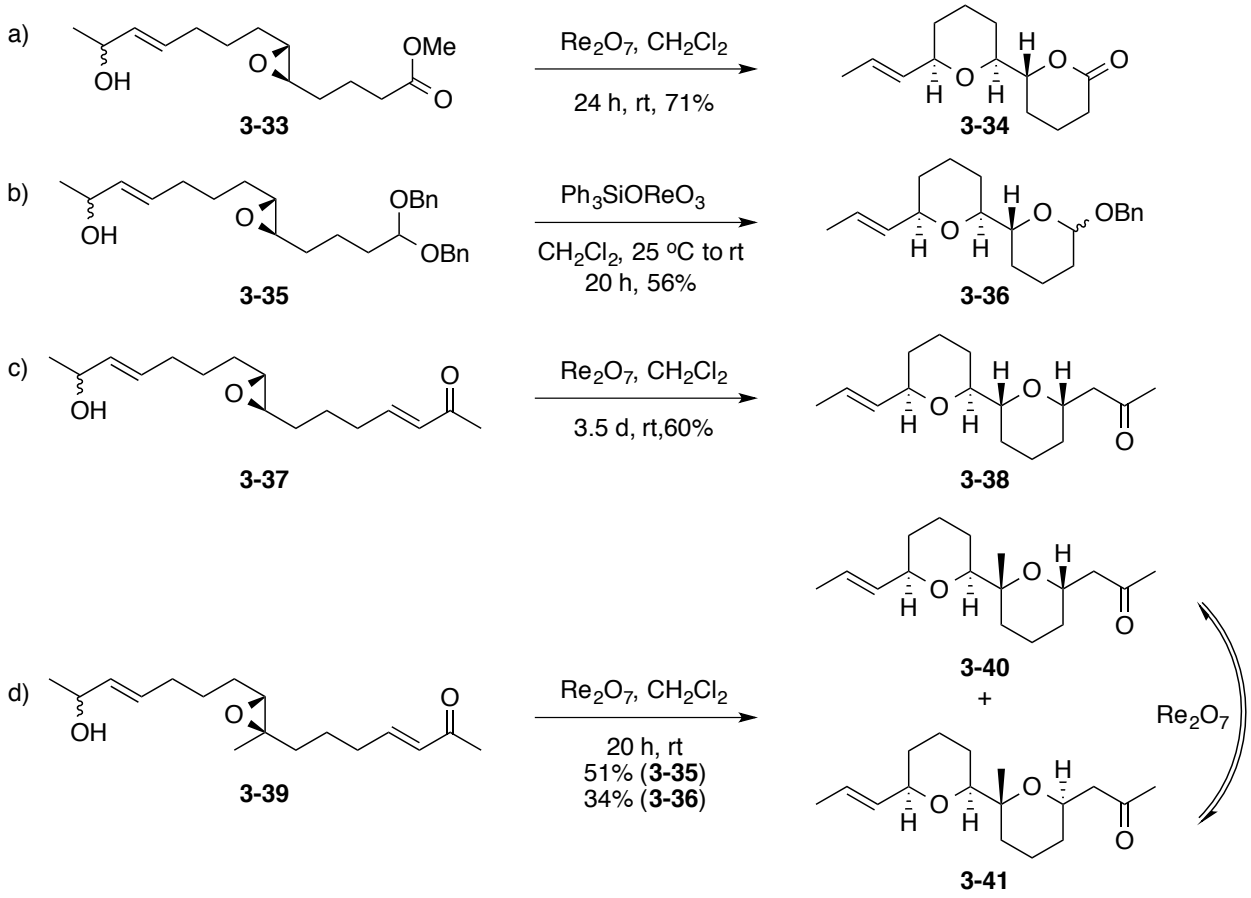
Scheme 3.5 Stereochemical isomerization

3.3 INCORPORATION OF EPOXIDE OPENING INTO A CASCADE PROCESS

When epoxides were used as trapping agents in the transposition/cyclization sequence, no selectivity was observed in tetrahydropyran formations. Studies showed that the free hydroxyl group after the epoxide opening is responsible for this lack of selectivity. However, these results indicated that these processes have the capability to provide stereochemically pure products if the hydroxyl group that results from epoxide opening is consumed in a subsequent step in a cascade process.

3.3.1 Trapping the hydroxyl group following epoxide opening

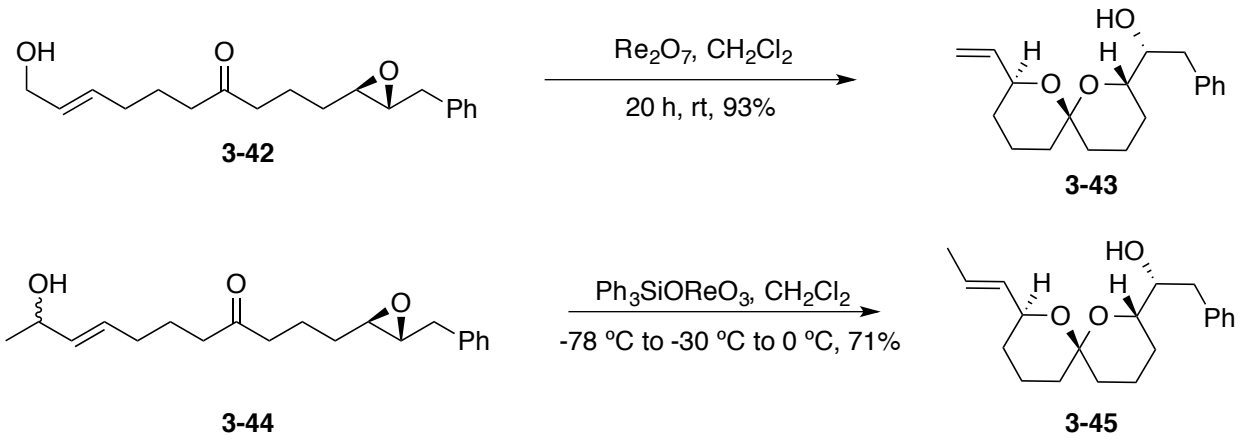
To test the validity of this cascade process, substrates were synthesized with electrophiles or pro-electrophiles incorporated at their termini in order to trap the hydroxyl groups after epoxide opening. When exposing epoxy ester **3-33** to Re_2O_7, lactone **3-34** was produced as a single stereoisomer in 71% yield, although removal of MeOH proved to be important for equilibration. Epoxy acetal **3-35** was prepared to study the capability of rhenium oxide to promote the formation of oxocarbenium ion[53, 72-73] as trapping group. Exposing **3-35** to Re_2O_7 at room temperature lead to decomposition of the starting materials without any production of the desired product, and lowering the reaction temperature only gave a low yield of **3-36**. However, when switching to the more soluble catalyst, $Ph_3SiOReO_3$ and initiating the reaction at -25 ºC followed by warming to room temperature to effect the stereochemical equilibration, **3-36** was isolated as a single stereoisomer and as a 5:2 mixture at the anomeric site. More stereoisomeric products were observed if the reaction was stopped early, confirming that equilibration follows the initial cyclization.



Scheme 3.6 Cascade reactions

Enones could also be used as trapping agents for this cascade reaction, as shown by the conversions of **3-37** to **3-38** and **3-39** to **3-40** and **3-41**. The reaction of **3-37** yielded a diastereomeric mixture of bis-tetrahydropyrans after 20 hours and required 3.5 days at room temperature for the mixture to converge and provide the product as a single stereoisomer. The reaction of **3-39** proceeded to completion within 20 h to provide a mixture of **3-40** and **3-41** in a ratio of 1.5:1. Reexposing either **3-40** or **3-41** to the reaction conditions lead to the production of the same 1.5:1 ratio of product, thereby confirming the thermodynamic ratio of the product mixture. This observation led to the somewhat surprising conclusion that axial tetrahydropyranyl groups are only modestly disfavored relative to axial methyl groups. The reactions with enones

as electrophiles are significant because they have demonstrated bidirectional stereogenesis, in which the introduction of new stereogenic centers from distal prochiral units are directed by the stereochemistry of the epoxide group. Additionally, these transformations with enone substrates proceed with perfect atom economy.[74]

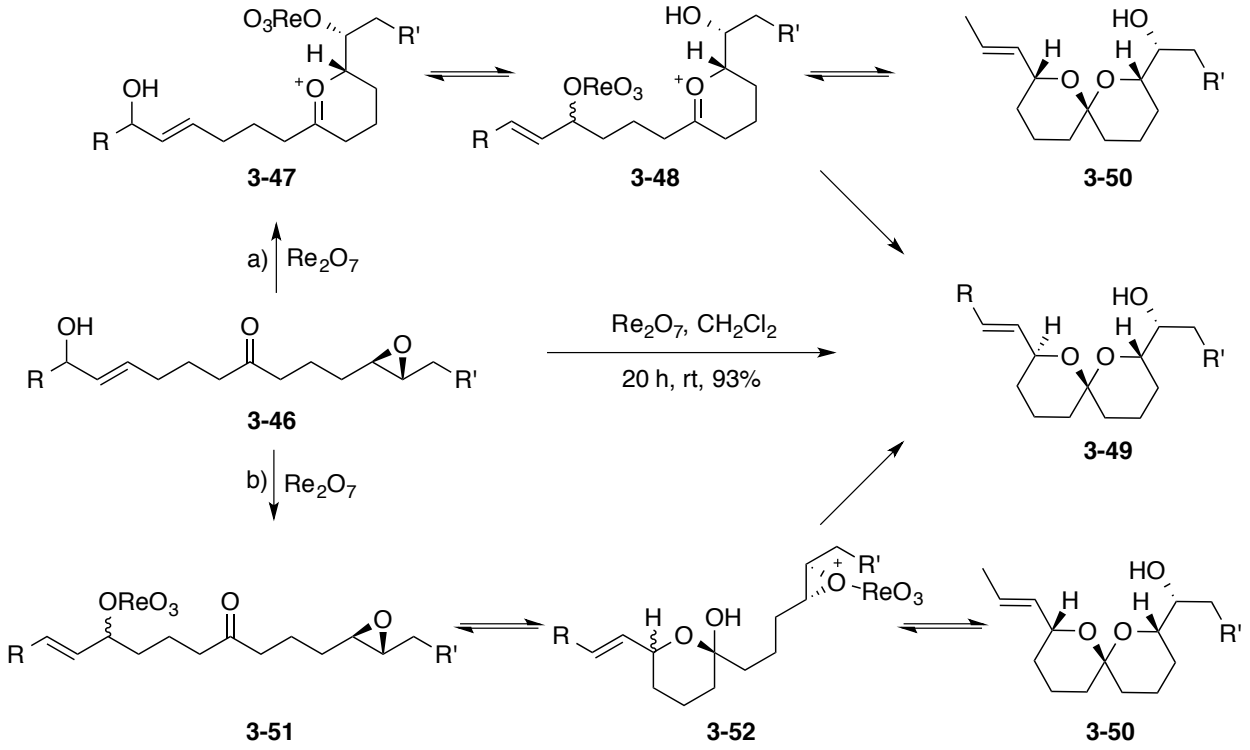


Scheme 3.7 Ketones as stereochemical conduits

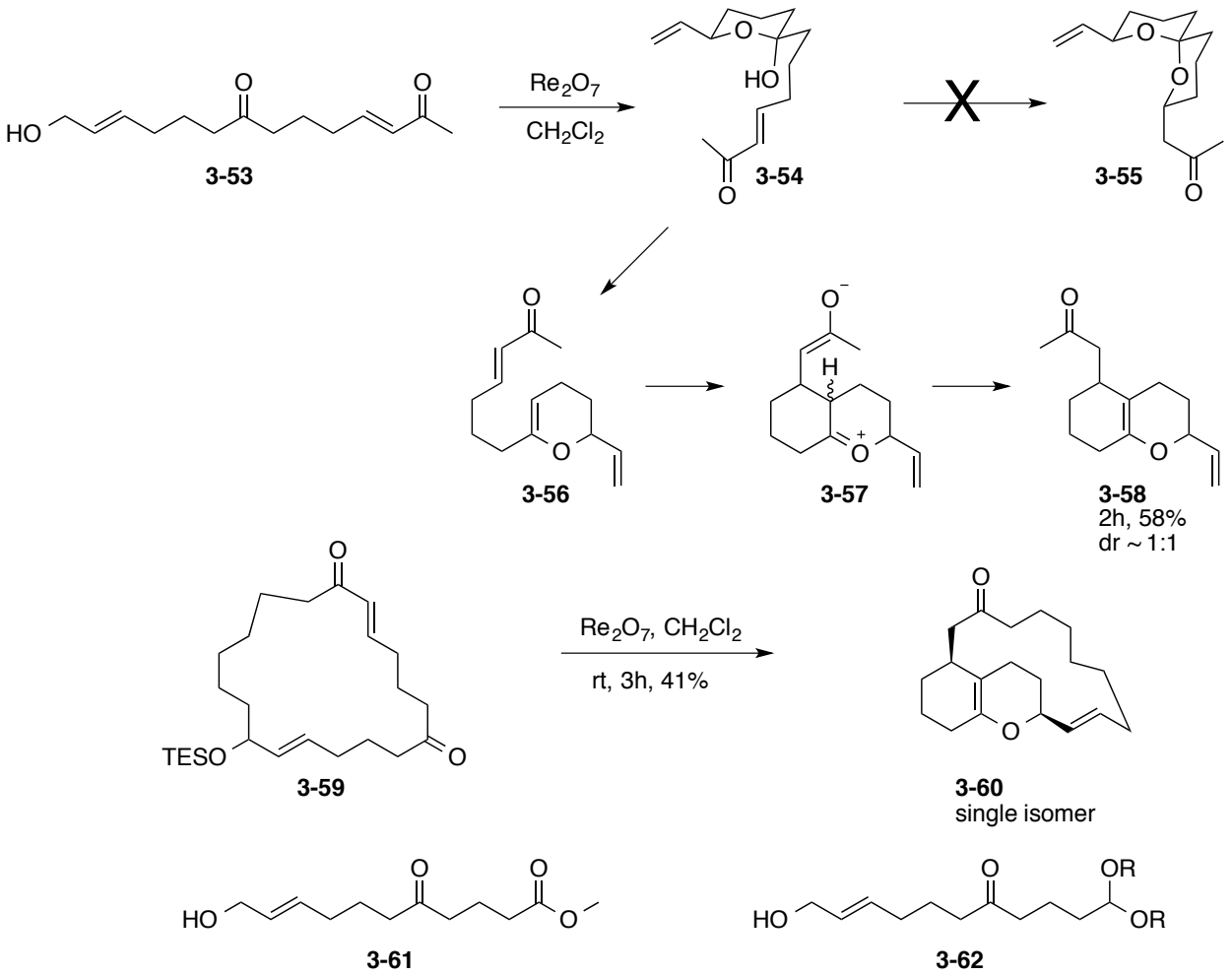
3.3.2 Cascade reactions using ketones as stereochemical conduits

Consumption of the free hydroxyl group from epoxide opening with a trapping agent eradicates the influence of hydrogen bonding on the ionization-based equilibration, thereby allowing stereoselective synthesis through post-cyclization equilibration. Another way to overcome influence of the hydroxyl group is to separate it from the stereogenic center that needs to be edited through thermodynamic equilibration. In such an approach, a ketone group is chosen as a nucleophile to open the epoxide, thereby generating a chiral oxocarbenium ion that acts as an electrophile to trap the transposed allylic alcohol. This product of this process is a spiroketal with a hydroxyl group that is far from the allylic system, as a result, stereochemical editing through

acetal ionization and allylic alcohol transposition without the influence from the free hydroxyl group is possible. Additionally, ketones can act as stereochemical conduits and provide an alternate strategy to transfer the chirality of epoxide groups to remote sites. As shown in Scheme 3.7, this approach is demonstrated by the reaction of **3-42** with Re_2O_7, which gives spiroketal **3-43** as a single stereoisomer in 93% yield within 20 h at room temperature. Secondary alcohol substrate **3-44** decomposed under these reaction conditions, presumably due to the various pathways that are possible upon the formation of an allylic cation intermediate. However, success was achieved by using $Ph_3SiOReO_3$ and initializing the reaction at -78 ºC followed by a slow and controlled process of warming. This improved protocol resulted in 71% yield of **3-45** from **3-44**. A minor diastereomer was isolated in 4% yield, but the overall yield of **3-45** was compromised if the reaction was allowed to run to complete equilibration.



Scheme 3.8 Possible reaction pathways with ketones as stereochemical conduits



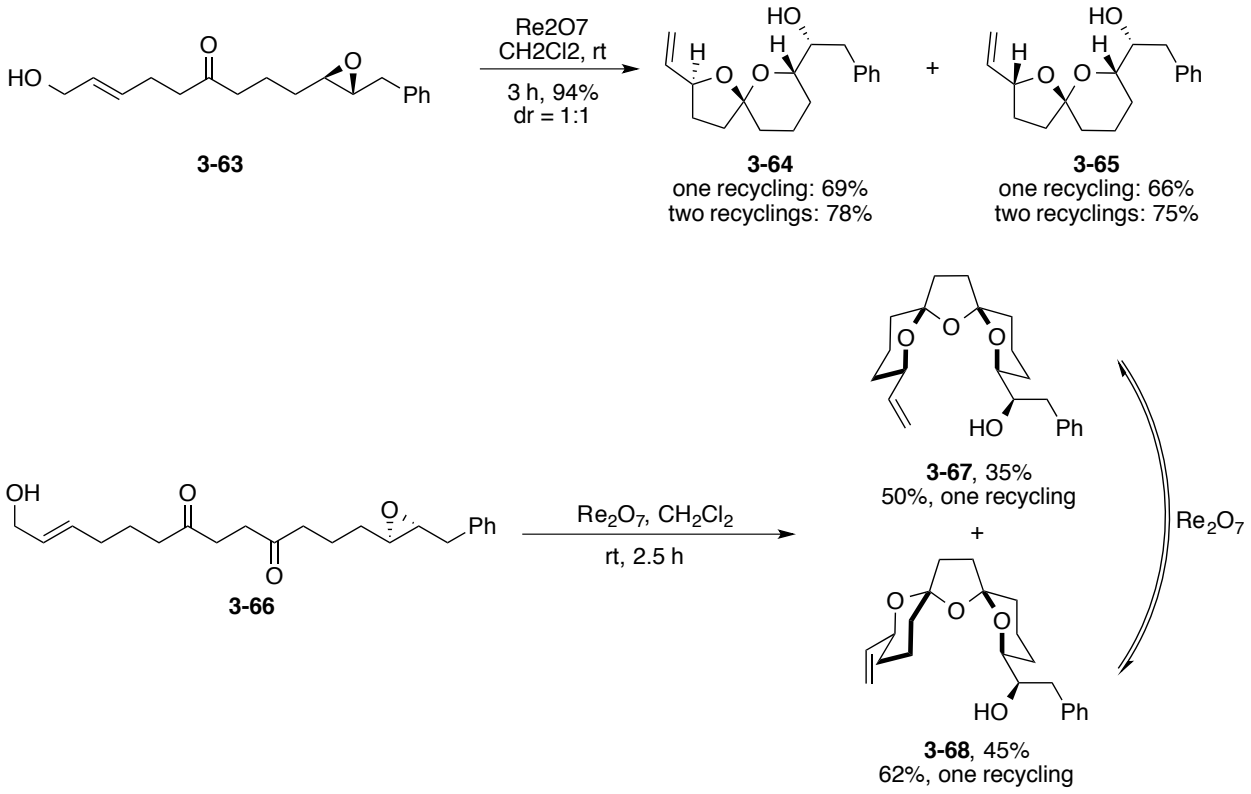
Scheme 3.9 Additional studies of hemiacetals as nucleophiles

A plausible mechanism for this transformation is shown in Scheme 3.8 (pathway a). When subjecting **3-46** to Re_2O_7, it undergoes Lewis acid-mediated opening of the epoxide by the oxygen of the ketone to yield oxocarbenium ion **3-47**. The allylic alcohol reversibly transposes to form a mixture of secondary allylic alcohols **3-48**, which add to the oxocarbenium ion to form **3-49** and **3-50**. This mixture will finally converge to yield the thermodynamically preferred spiroketal **3-49** as the sole product of this transformation because the thermodynamically less stable **3-50** can revert to a single diastereomer **3-48**, which undergoes stereochemical editing through ionization/recombination. An alternative mechanism is shown as pathway b, in which

the transposing alcohols add into ketone to form a mixture of hemiacetals that add into epoxide to form **3-49** and **3-50** followed by stereochemical editing to provide exclusively **3-49**. However, this second mechanism is less likely due to the information gained from studies using intermediate hemiacetals as nucleophiles in cascade reactions (Scheme 3.9). Substrate **3-53**, when exposed to Re_2O_7, undergoes allylic alcohol transposition followed by nucleophilic addition to ketone to deliver intermediate hemiacetal **3-54**, which could give spiroketal **3-55** if hemiacetal underwent 1,4-addition into the enone. However, an interesting compound **3-58** was the only product isolated, and no trace of **3-55** was detected. The compound **3-58** is generated through the dehydration of hemiacetal **3-54** to form **3-56**, and then the cyclic enol ether undergoes a Michael addition followed by proton transfer to deliver the product **3-58** as a mixture of 1:1 diastereomers. A cyclic substrate **3-59** undergoes a similar process to give **3-60** as a single diastereomer as a result of the constraint the macrocycle imposes on the system. Efforts to form spiroketals by using other electrophile or pre-electrophiles such as ester (**3-61**) and acetal (**3-62**) also did not lead to any success. These results lead to the speculation that hemiacetals might not be good nucleophiles in the current system. As a result, pathway b in scheme 3.8 is less likely to be the true mechanism because a step using a hemiacetal as a nucleophile is included.

Lower homologs are also suitable substrates for these cascade reactions, however stereocontrol of the product is lost in these transformations due to the greater conformational freedom of the tetrahydrofurans in comparision to tetrahydropyrans. As shown in Scheme 3.10, exposing **3-63** to Re_2O_7 lead to a combined 94% yield of **3-64** and **3-65** in a 1:1 mixture after 3 h at room temperature. Despite the failure to deliver a major product under thermodynamic control, the yield of either isomer could be increased to useful levels through a simple recycling protocol.

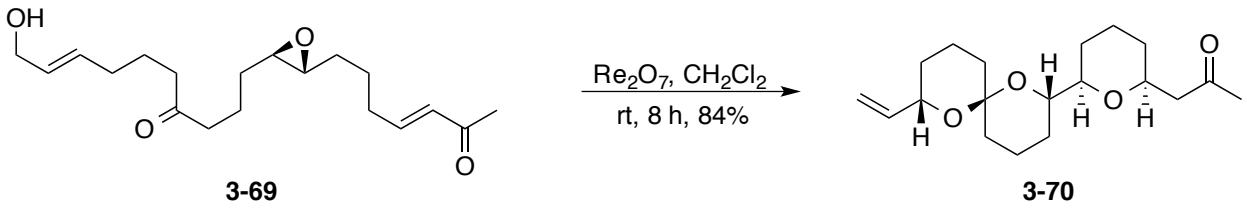
As a result, **3-64** can be isolated in 69% yield by resubjecting **3-65** to the reaction conditions and in 78% yield after two recyclings. On the other hand, **3-65** can be obtained in 66% yield after subjecting **3-64** to one recycling and in 76% yield after two recyclings. The stereochemical relay can also be conducted through two ketone groups. When diketone epoxide substrate **3-66** was subjected to the reaction conditions, spirotricycles **3-67** and **3-68** were produced in 35% and 45% yields, respectively. The lack of selectivity was, again, due to the thermodynamic freedom of the central tetrahydrofurans. As in previous examples, improved yields of each isomer can be accessed via recycling, with **3-67** being isolated in 50% yield upon resubjecting **3-68** to the reaction conditions and **3-68** being isolated in 62% yield after resubjecting **3-67** to the reaction conditions.



Scheme 3.10 Formation and equilibration of spirocyclic tetrahydrofurans

3.3.3 Combined use of a ketone as a stereochemical conduit and an enone as a trapping agent

The use of ketone as stereochemical conduits can be combined with enones as terminal electrophiles to provide structures with impressive molecular complexity through bidirectional stereogenesis. As shown in scheme 3.11, when a judiciously designed substrate **3-69** was subjected to the standard reaction conditions for 8 h, a single isomer **3-70** was isolated in 84% yield with complete stereocontrol. This transformation is impressive in that a compound with one ring and two stereogenic centers is converted to a structure with three rings and five stereogenic centers. The overall stereochemistry is determined by a single epxoide and the reaction is completely atom economical.



Scheme 3.11 Bidirectional stereogenesis with ketone conduit

3.4 DEVELOPMENT OF A EASILY USABLE CATALYST

During our research with Re_2O_7 as a catalyst for allylic alcohol transformation, difficulty was encountered while delivering small amounts of this catalyst. While no precautions were required

to prevent Re_2O_7 from being exposed to air or moisture, and most reactions can be performed under air without any special handling needed, the Re_2O_7 quickly liquefies in ambient condition, which makes it difficult to precisely measure small amounts of the catalyst. This led us to explore an alternative reagent preparation protocol. We found that a supported catalyst could be prepared simply by stirring a mixture of Re_2O_7 and silica gel in anhydrous Et_2O for several hours, followed by solvent removal under vacuum. By using this protocol, we prepared a 10% (w/w) mixture of Re_2O_7 on SiO_2, which was shown to be a competent catalyst for the transformations developed previously. There is no significant difference in yields or reactions times when either immobilized or free catalysts were employed. For example, when immobilized catalyst was used instead of a free catalyst, **3-42** was converted to **2-43** in 93% yield after 12 h, **3-66** was converted to **3-67** and **3-68** in 82% yield after 2.5 h and **3-69** was converted to **3-70** in 76% yield after 24h. More notably, the immobilized catalyst could effect the conversion of **3-35** to **3-36** in 60% yield, which indicated that the more expensive $Ph_3SiOReO_3$ could be replaced by this easily accessible catalyst. This immobilized catalyst can be easily weighed, even in humid environments which causes the free catalyst to liquefy, and can be stored without any loss of reactivity for at least six months. Moreover, the immobilized catalyst yields superior dispersion of the Re_2O_7, eliminating the need for an induction period as often observed for the free catalyst. Reuse of the immobilized catalyst by filtering of the catalyst from the reaction resulted in diminished activity, indicating that partial leaching of Re_2O_7 occurs during the reaction. Although this protocol does not provide a completely reusable catalyst, it significantly facilitates the transformations from an operational perspective, particularly for reactions that utilize high molecular weight substrates that only require small amounts of catalyst.

3.5 CONCLUSION

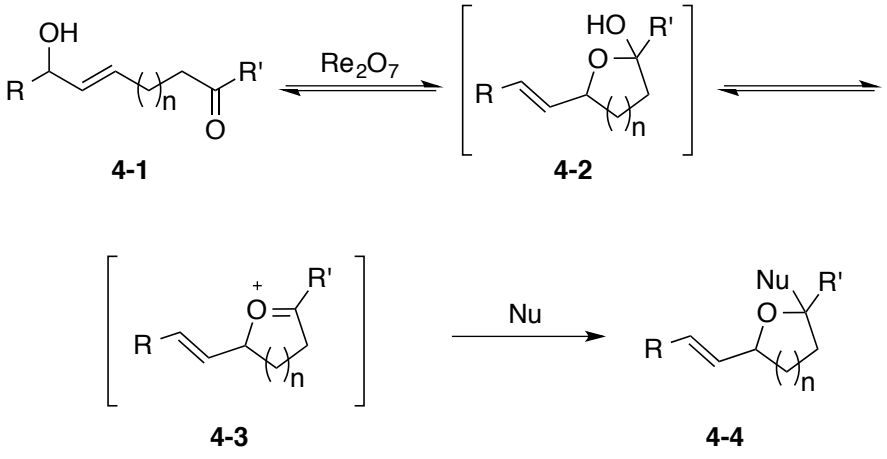
The application of epoxides as trapping agents has been studied, and the mechanistic details of this transformation have been unveiled. Based on this information, epoxide cascade reactions initiated by rhenium oxide mediated allylic alcohol transposition have been realized. The success of these transformations are due to the roles of rhenium oxide as both a transposition catalyst and an acid that enhances the electrophilicity of the epoxide to promote product ionization, thereby enabling thermodynamically controlled stereochemical equilibration. This approach for diastereoselective synthesis relies on the functionalization of prochiral carbons rather than the generation of stereochemically defined nucleophiles for epoxide opening. Reactions proceed either via direct addition of transposed alcohol to the activated epoxide or by using ketones as conduits that relay the stereochemical information from the epoxide to distal sites of the product. Molecular complexity could be maximized when an electrophile is present for the trapping of the hydroxyl group that is generated upon epoxide opening. When enones are used in this strategy, bidirectional stereogenesis could be achieved, in which the stereochemical information in the epoxide is transferred to opposite ends of the product. This reaction is atom-ecnomical.

4.0 HETEROCYCLE SYNTHESIS BASED ON ALLYLIC ALCOHOL TRANSPOSITION USING TRACELESS TRAPPING GROUPS

In previous chapters, the use of allylic alcohols for stereocontrolled heterocycle syntheses has been explored.[53, 69] An isomerization/cyclization sequence has been developed in which Re_2O_7 has been employed as a catalyst to initiate reversible allylic alcohol isomerization and promote ring formation through nucleophilic addition of the transposed hydroxyl group to a pendant electrophile. A variety of electrophiles are capable of trapping the transposed hydroxyl group, and thermodynamically controlled stereochemical editing can be achieved if there is significant energetic difference among different products, and if the reactions leading to these products are reversible. This new strategy allows for fast access to functionalized cyclic and polycyclic ethers, and minimizes the need for reagent-based stereoselective protocols. In this chapter, the application of allylic alcohols in the stereoselective synthesis of cyclic ethers is further expanded by the development of a new sequence of allylic alcohol transposition, intramolecular trapping, oxocarbenium ion formation, and intermolecular nucleophilic addition.

4.1 RESEARCH DESIGN AND OBJECTIVES

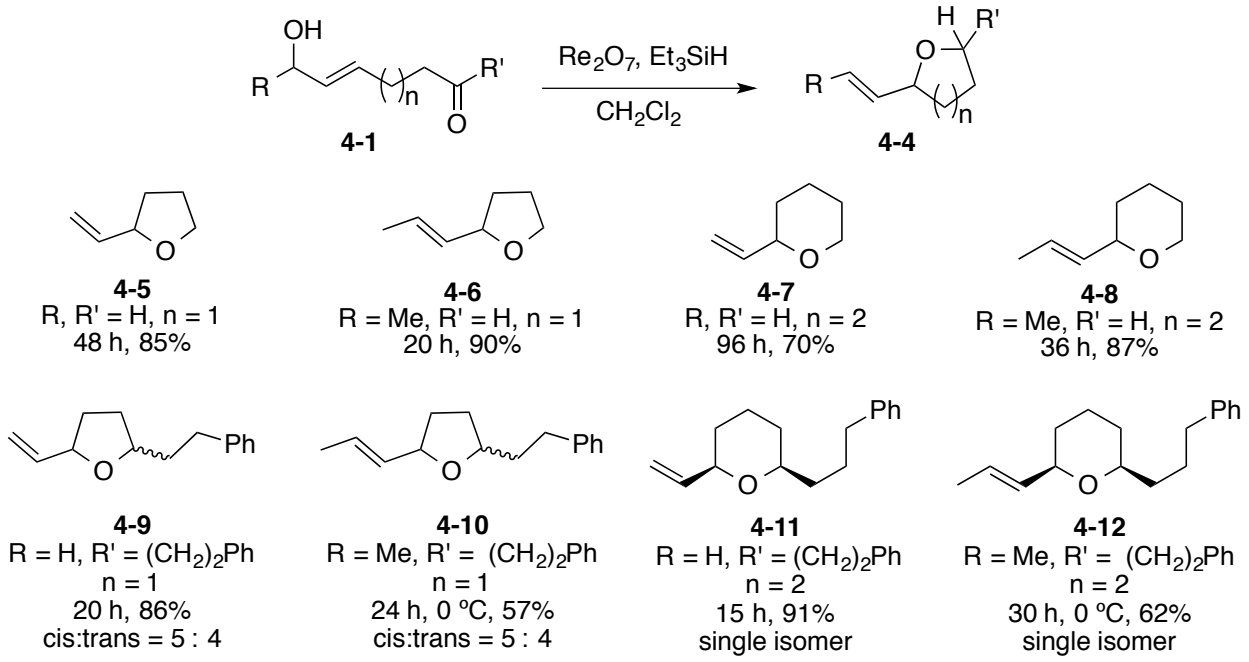
The previously discussed isomerization/cyclization sequences required preinstalled electrophiles as trapping groups, and generally contained a vestige of the electrophile. While the presence of vestige provided the opportunity for further elaboration of the resulting product, more freedom could be provided to this methodology if this process was achieved using a traceless trapping group.[75] As shown in Scheme 4.1, it is proposed that this approach can be realized by adding the transposed allylic alcohol to a carbonyl group to form a cyclic hemiacetal **4-2**, which subsequently can undergo ionization to form an oxocarbenium ion **4-3**, and followed by trapping with an additional nucleophile to terminate the sequence, product **4-4** can be produced. This sequence, once proved valid, could significantly expand the scope of products that can be accessed via this method by utilizing different nucleophiles in the termination step, and eliminate the remnant of the original trapping group.



Scheme 4.1 Transposition, trapping, ionization, and nucleophilic termination (R, R' = H or alkyl, Nu = nucleophile)

4.2 RESULTS AND DISCUSSIONS

4.2.1 Validation of the new method and initial substrate reactivity studies



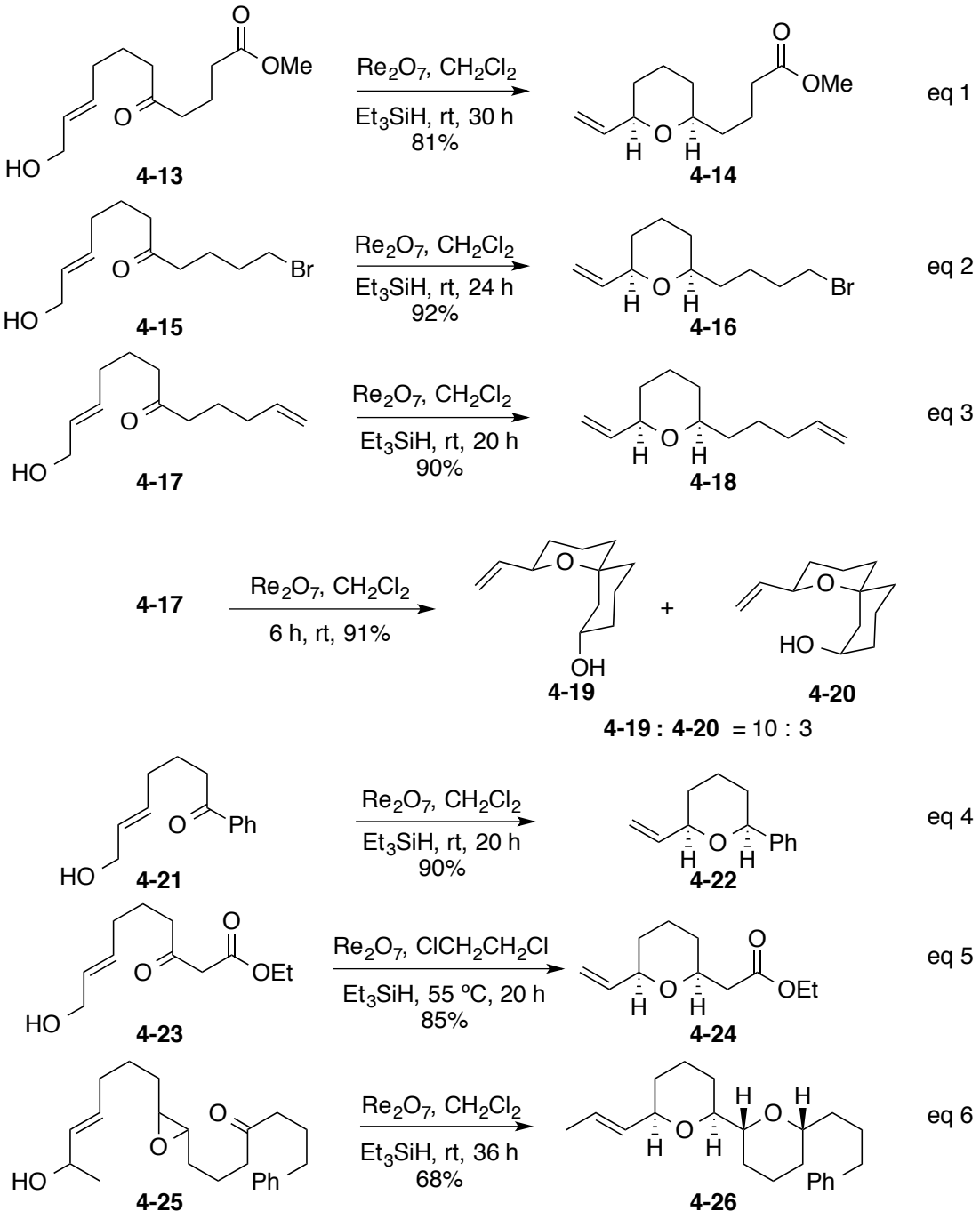
Scheme 4.2 Reactivity in tetrahydrofuran and tetrahydropyran formation

In order to demonstrate the feasibility of this approach, triethylsilane was chosen as the terminating reagent based on its proven ability in the reduction of oxocarbenium ions.[76] As shown in Scheme 4.2, several substrates with the general structure **4-1** were synthesized to test this approach. These reactions were conducted with 3 mol% Re_2O_7, and two equivalents of Et_3SiH at room temperature. Most of these reactions proceeded in excellent yield, although prolonged reaction time was required for completion. This was a result of the initial products arising from alcohol addition to the intermediate oxocarbenium ion, which was consistent with observations made by Dussault and coworkers.[77] The rate for the formation of these initial acetal

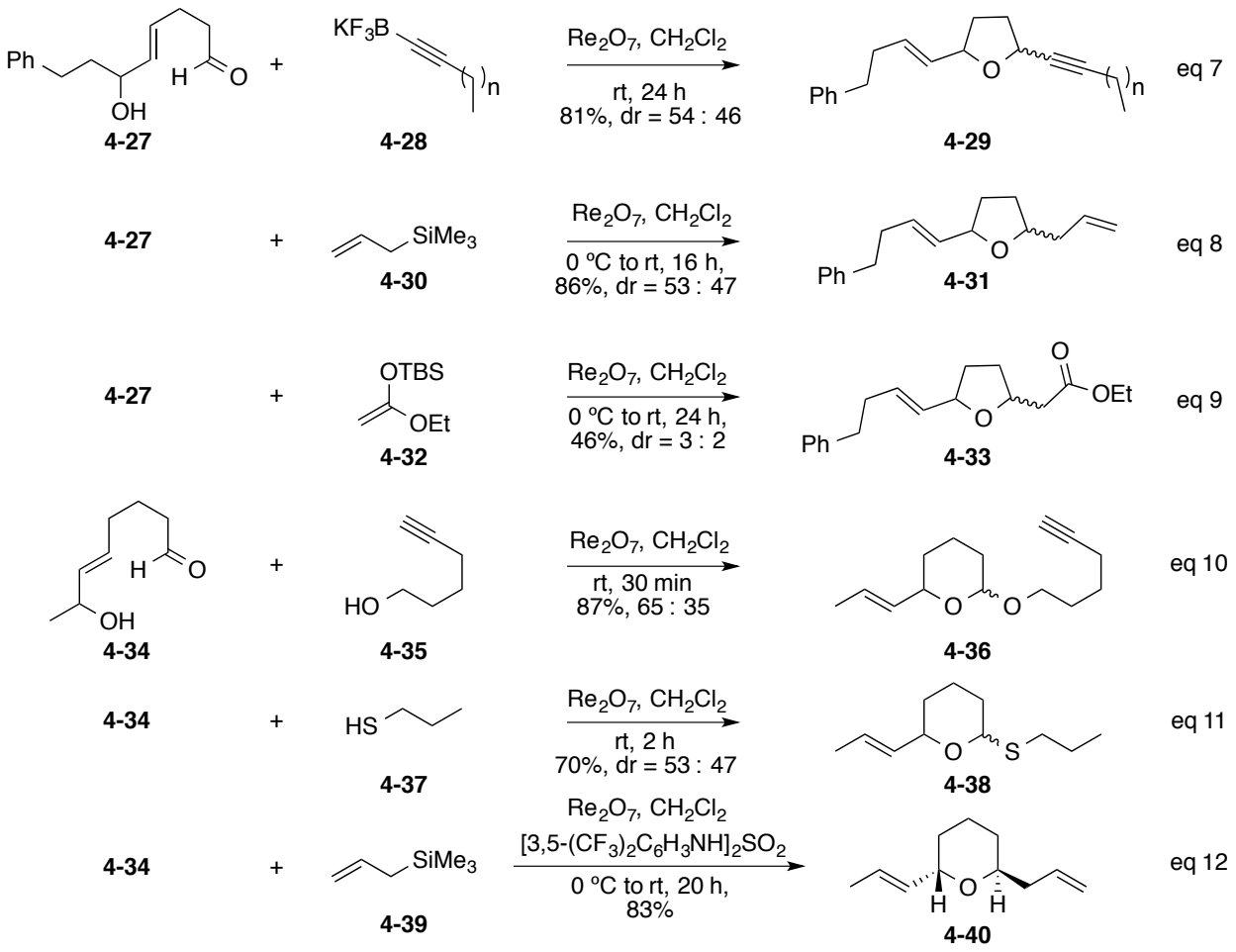
products is fast, and the final products are formed via the ionization of the intermediate acetals followed by oxocarbenium ion reduction. This second step is rate determining, and requires a much longer time to finish.

Although various factors can influence the rates of these reactions, several trends become apparent after analyzing the results from Scheme 4.2. Reaction rates for secondary allylic alcohols are usually faster than those of primary allylic alcohol substrates (**4-6** and **4-8** versus **4-5** and **4-7**). This result might arise from the increased access to the oxocarbenium ions, since the increased steric interactions in the intermediate mixed acetals from secondary allylic alcohol substrate can promote ionization, and as a result, reduction. Tetrahydrofurans form more quickly than tetrahydropyrans with similar substitution patterns (**4-5**, **4-6**, **4-9**, and **4-10** versus **4-7**, **4-8**, **4-11**, and **4-12**). This also arises from the increased access to the oxocarbenium ion intermediates because the tetrahydrofuranyl ethers ionize faster than tetrahydropyranyl ethers.[78] Reactions of ketone substrates are faster than aldehyde substrates (**4-9**, **4-10**, **4-11**, and **4-12** versus **4-5**, **4-6**, **4-7**, and **4-8**). This is again a result of the increased accessibility of the corresponding oxocarbenium ions due to the extra stabilization of the additional alkyl groups in ketone substrates. However, dehydration becomes a competitive side reaction for ketone substrates with secondary allylic alcohols. This might be because the relative stability of ketone-derived oxocarbenium ions reduces the rate of trapping, and increased substitution augments the potential for allylic cation formation, and as a result, enhances opportunities for dehydration via an E1 pathway. Acceptable yields could still be achieved for these substrates, however, by simply lowering the reaction temperature. For ketone substrates, stereocontrol was perfect for tetrahydropyran formation, but was poor for tetrahydrofuran formation, which agrees with established models for nucleophilic additions to cyclic oxocarbenium ions.[79]

4.2.2 Establishment of the reaction scope



Scheme 4.3 Reaction scope



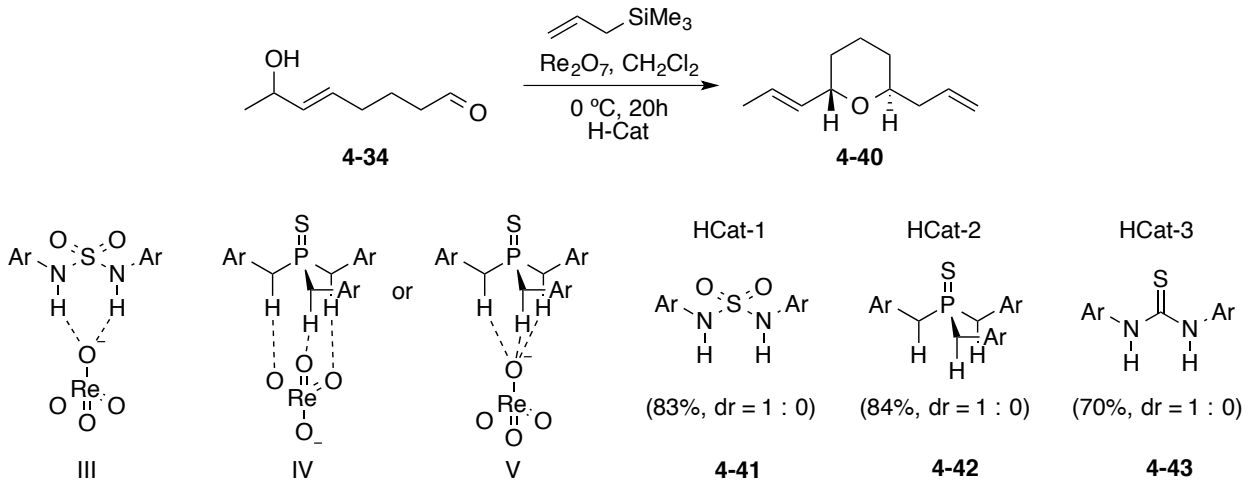
Scheme 4.4 Reaction scope (continued)

The scope of this reaction was established by variations in the substrate, through the use of different ketones as trapping groups (Scheme 4.3), or through the use of different nucleophiles (Scheme 4.4). As shown in Scheme 4.3, various functional groups were well tolerated by this method, including esters (**4-13**, **4-23**), bromides (**4-15**), alkenes (**4-17**), and phenyl groups (**4-21**), which can stabilize the carbonyl group via conjugation. Substrate **4-17**, when exposed to Re_2O_7 without the addition of Et_3SiH, delivered a combined yield of 90% of **4-18** and **4-19** in a 10:4 ratio through Prins cyclization.[73] However, when the reaction was conducted with the presence of Et_3SiH, **4-18** was isolated as the major product in 90% yield, while the combined yield of **4-18**

and **4-19** was reduced to less than 10%. This is an interesting observation because it shows that the intermolecular trapping by Et_3SiH is 10 times faster than intramolecular trapping by an alkene. Another interesting substrate is **4-23,** which contains a β-keto ester moiety; the presence of a second carbonyl group slows down the reaction by destabilizing the intermediate oxocarbenium ion via induction, the reaction of this substrate needed either elevated reaction temperature or extended reaction time. This product of this substrate is **4-24**, which is an apparent product of isomerization/cyclization sequence, however, previous studies have shown that α,β-unsaturated esters are not good trapping agents for transposed allylic alcohols (Scheme 2.4). This lends further justification for the development of a traceless trapping agent. Utilizing an epoxide (**4-25**) as the trapping group provides the opportunity for cascade cyclizations[68a, 75] in which stereochemical information from the epxoide is transferred to both ends of the product (**4-26**).

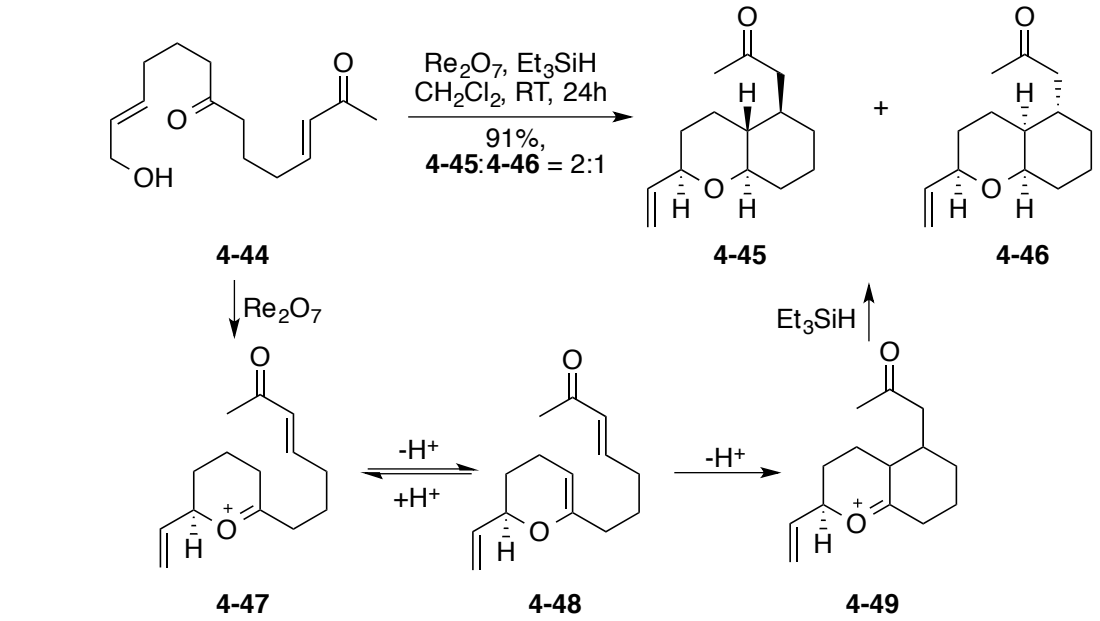
A limited number of nucleophiles have been studied to explore the potential application of this protocol in fragment coupling reactions. Potassium alkynyltrifluoroborate (**4-28**),[80] allylsilane (**4-30**),[77] and silyl ketene acetal (**4-32**) add to the tetrahydrofuranyl oxocarbenium ions to yield **4-29**, **4-31** and **4-33**, respectively. No stereocontrol was observed, which is consistent with the reductive quenching experiments of tetrahydrofuranyl oxocarbenium ions. Although heteroatom-based nucleophiles such as alcohol (**4-35**) and thiol (**4-37**) add successfully to tetrahydropyranyl oxocarbenium ions, carbon-based allyl trimethylsilane does not, presumably because these reaction conditions do not induce a sufficient level of ionization to promote reactions with weak π-nucleophiles. However, this problem could be circumvented by adding an anion-binding catalyst into the reaction. A quick screening revealed that several common anion-binding catalysts[81] showed enhancement effects, with both **4-41** and **4-42** giving more than 80%

yield. Literature precedent[82] suggests that the enhanced reactivity was due to the increased Lewis acidity of Re_2O_7 or $HReO_4$ by binding of the perrhenate anion to hydrogen bonding catalysts via adducts III, IV or V. This result is significant because it shows that thermodynamically disfavored isomers can be accessed by using this newly developed method, and that reductive and alkylative oxocarbenium ion quenching can provide complementary 2,6-stereochemical relationship in the products.



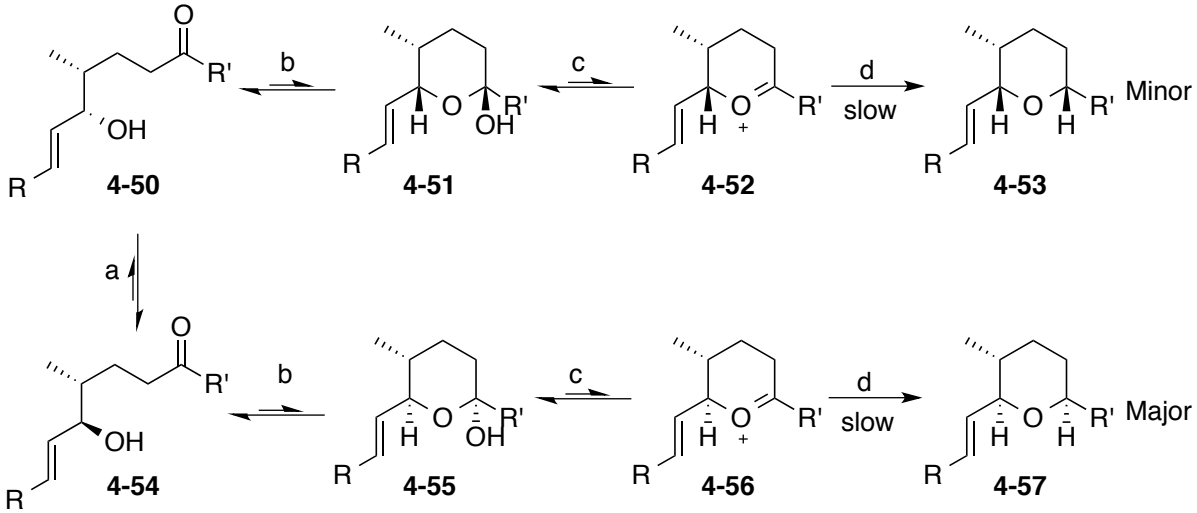
Scheme 4.5 Enhancement effect of hydrogen-bonding catalyst (Ar = 3,5-trifluoromethylphenyl)

A limitation of this reaction emerges when a π nucleophile is incorporated into the substrate, as shown in Scheme 4.6 for the conversion **4-44** to **4-45** and **4-46**. The intermediate oxocarbenium ion **4-47** exists in equilibrium with the enol ether **4-48**. Intramolecular Michael addition of the enol ether into the enone is faster than the reduction by Et_3SiH, thereby generating a second oxocarbenium ion **4-49**, which exists in the form of a diastereomeric mixture. Subsequent reduction of **4-49** delivers a combined 91% yield of **4-45** and **4-46** in a 2:1 ratio. This pathway is interesting because it suggests the possibility of developing a reaction that utilizes the trapping group first as an electrophile, and then as a nucleophile.



Scheme 4.6 Reaction in the presence of a π nucleophile

4.2.3 Development of a reaction with diastereocontrol



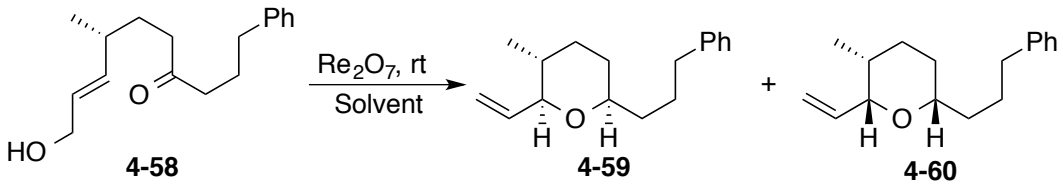
Scheme 4.7 An analysis of competitive processes for relative diastereocontrol

After the establishment of the general substrate scope, attention was turned to the study of the impact of a pre-existing stereogenic center on the stereochemical outcome of the reaction.[50, 53, 69] Unlike examples shown in previous chapters, in which cyclization is reversible and a thermodynamically driven stereochemical editing is possible, the final step in this new sequence is irreversible and the stereochemical editing will need the cyclic ether to ionize at the allylic carbon. While this is possible for internal alkenes, it is less likely to happen for terminal alkenes. Success in stereoselective synthesis is, however, achievable if a proper balance between the rates of equilibration with the rates of oxocarbenium ion formation and trapping. As shown in Scheme 4.7, stereoselective synthesis could be achieved if the equilibration between **4-50** and **4-54** is rapid, if the equilibrium between the hydroxyl carbonyl compound (**4-50**, **4-54**) and the cyclic hemiacetal (**4-51**, **4-55**) does not strongly favor the cyclic hemiacetal, if the ionization step is readily reversible (step c), and if the nucleophilic trapping step is slow (step d). In order to achieve high stereocontrol in this protocol, there should be sufficient energetic difference between the equilibrating lactols, so that one isomer is more thermodynamically favored over the other.

Further studies were carried out to show the relationship between the allylic alcohol structure, trapping group, product substitution pattern, and termination agent on reaction disastereocontrol. As shown in table 4.1, substrate **4-58** was chosen to study the influence of each step in scheme 4.7 on the stereochemical outcome of the reaction. When subjecting **4-58** to the standard reaction conditions with Et_3SiH as the termination agent, a combined 96% yield of **4-59** and **4-60** was obtained, although the diastereoselectivity was only 3:1 (entry 1). Adding Et_3SiH slowly over a period of 24 hours otherwise increased the diastereoselectivity to 6.5:1 despite the concomitant decrease in the total yield (entry 2). This outcome is consistent with

ionization being reversible and slowed termination allowing greater opportunity for stereochemical equilibration. This result also led to the study of the relationship between the silane reactivity and stereoselectivity. Less reactive silanes such as benzyldimethylsilane (entry 3) and triphenylsilane (entry 5) usually provided a greater degree of stereocontrol compared to more reactive silanes (entry 4, 6-7).[83] A brief solvent screening also showed that chlorinated solvents such as dichloromethane and 1,2-dichloroethane gave the best diastereoselectivity.

Table 4.1 Factors that influence the diastereoselectivity

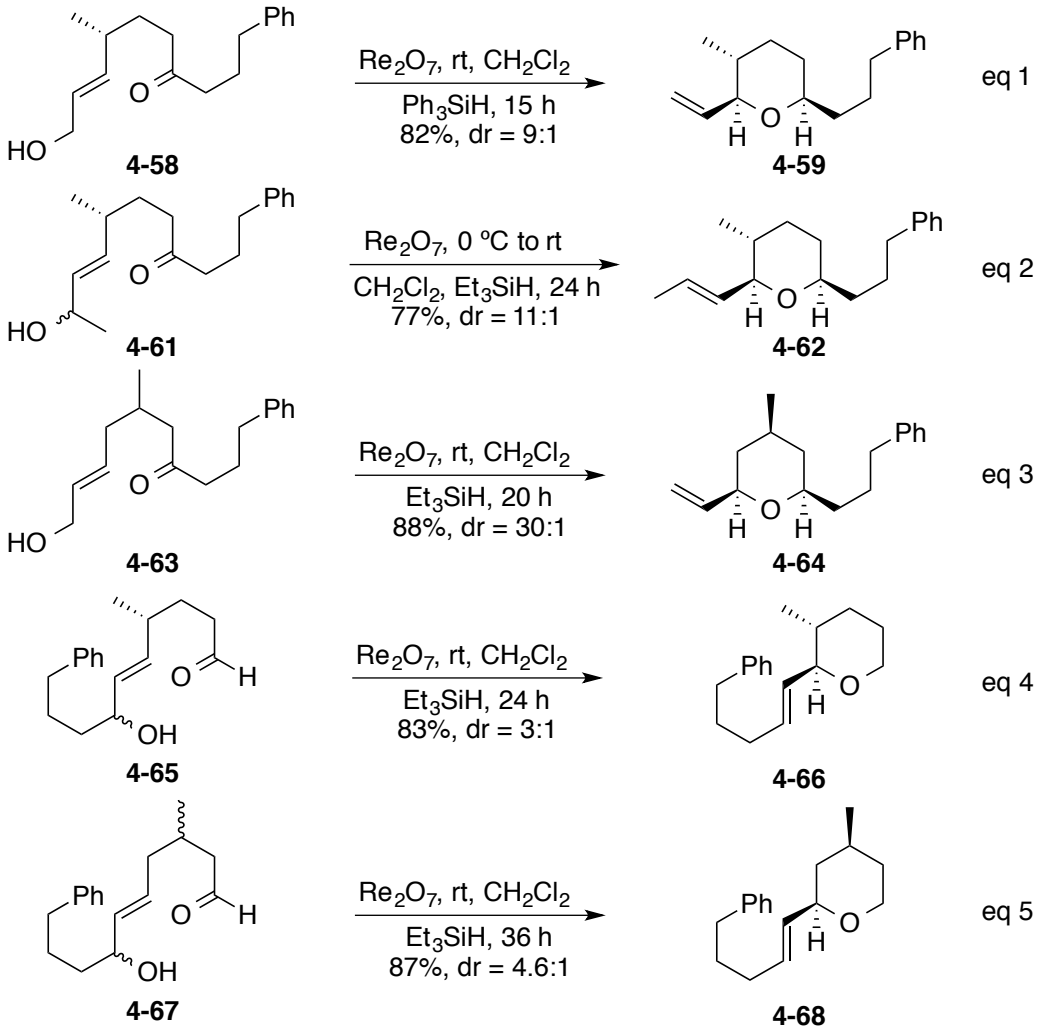


Entry	Solvent	Silane	Time	Yield	dr
1	CH_2Cl_2	Et_3SiH	20 h	96%	3.0:1
2[a]	CH_2Cl_2	Et_3SiH	24 h	59%	6.5:1
3[b]	CH_2Cl_2	Benzyldimethylsilane	6 h	96%	6.2:1
4[b]	CH_2Cl_2	Phenyldimethylsilane	6 h	94%	1.7:1
5[b]	CH_2Cl_2	Triphenylsilane	6 h	95%	9.1:1
6[b]	CH_2Cl_2	Ethoxydimethylsilane	6 h	95%	1.2:1
7[b]	CH_2Cl_2	Triethoxysilane	6 h	0 %	N.A
8[b]	CH_2Cl_2	2-thiophenyldimethylsilane	6 h	93%	2.1:1
9[b]	Toluene	Triphenylsilane	24 h	0%	N.A
10[b]	$ClCH_2CH_2Cl$	Triphenylsilane	12 h	96%	9:1
11[b]	Et_2O	Triphenylsilane	24 h	0%	N.A
12[b]	THF	Triphenylsilane	24 h	0%	N.A
13[b]	CH_3CN	Triphenylsilane	12 h	88%	5.9:1

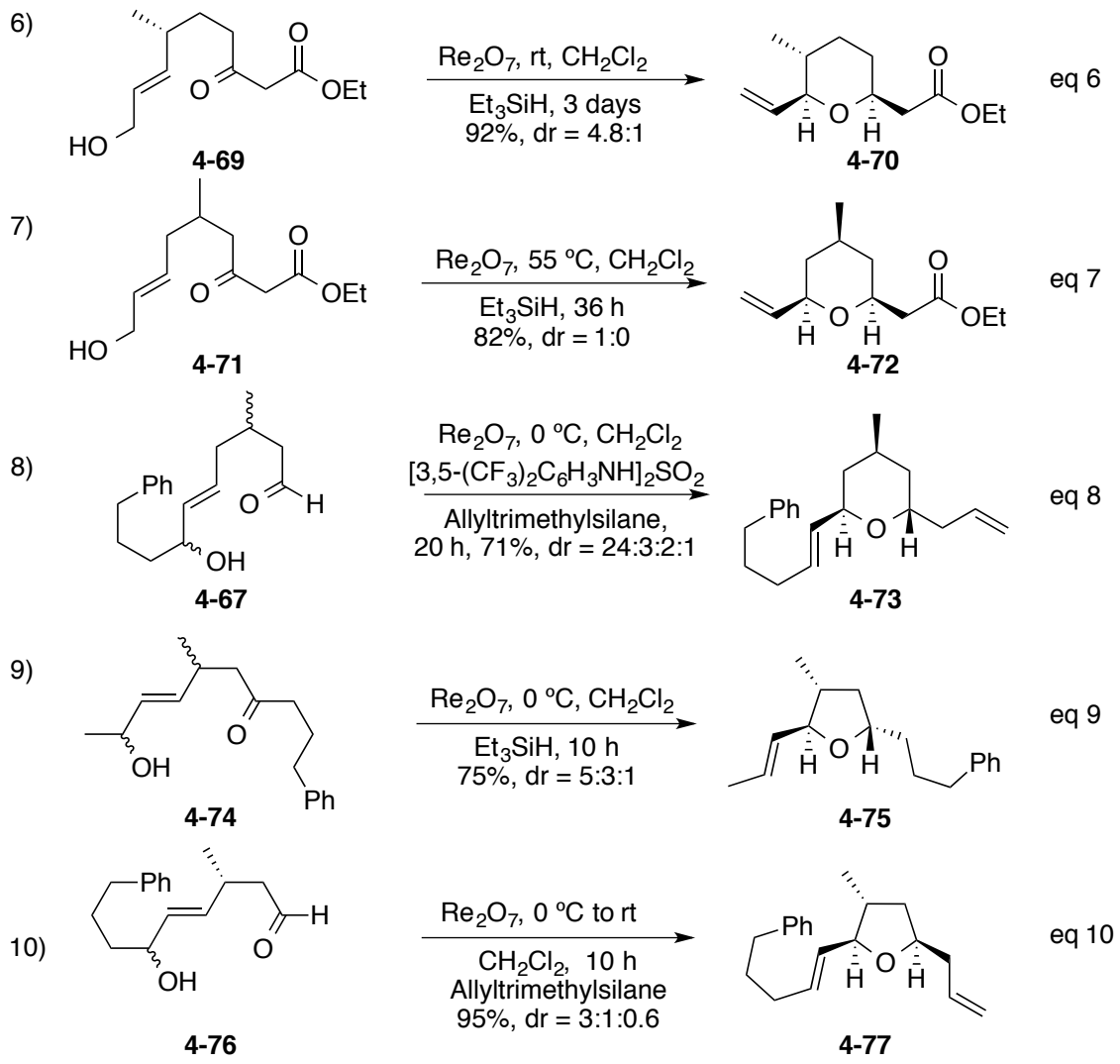
Reaction was conducted at room temperature with 2 equivalents of silane, 3 mol% Re_2O_7 unless otherwise mentioned: a) slow addition of silane over 24 hrs; b) reaction was performed at 5.0 mg scale with 5 mol% Re_2O_7, yield and dr were determined by taking the ^1H NMR of the crude with an internal standard (DMAP).

As shown in scheme 4.8 and 4.9, all tetrahydropyran-forming reactions provided a 2,6-*cis*-stereochemical relationship, which is consistent with previous studies. Several trends become

apparent after analyzing these results. Substrates with secondary allylic alcohols show higher selectivity than similarly substituted primary alcohol substrates (equation 2 in Scheme 4.8). This difference is attributed to the higher rate of stereochemical equilibration via a cationic intermediate (step a in Scheme 4.7). The equilibrium of the cyclization step (step b in Scheme 4.7) also influences the stereocontrol: aldehydes are more prone to exist in the lactol form than ketones, thus limiting the concentration of the stereochemically labile allylic alcohol, and leading to diminished level of 2,3-stereocontrol (equations 4, 5 vs equations 2, 3, Scheme 4.8)



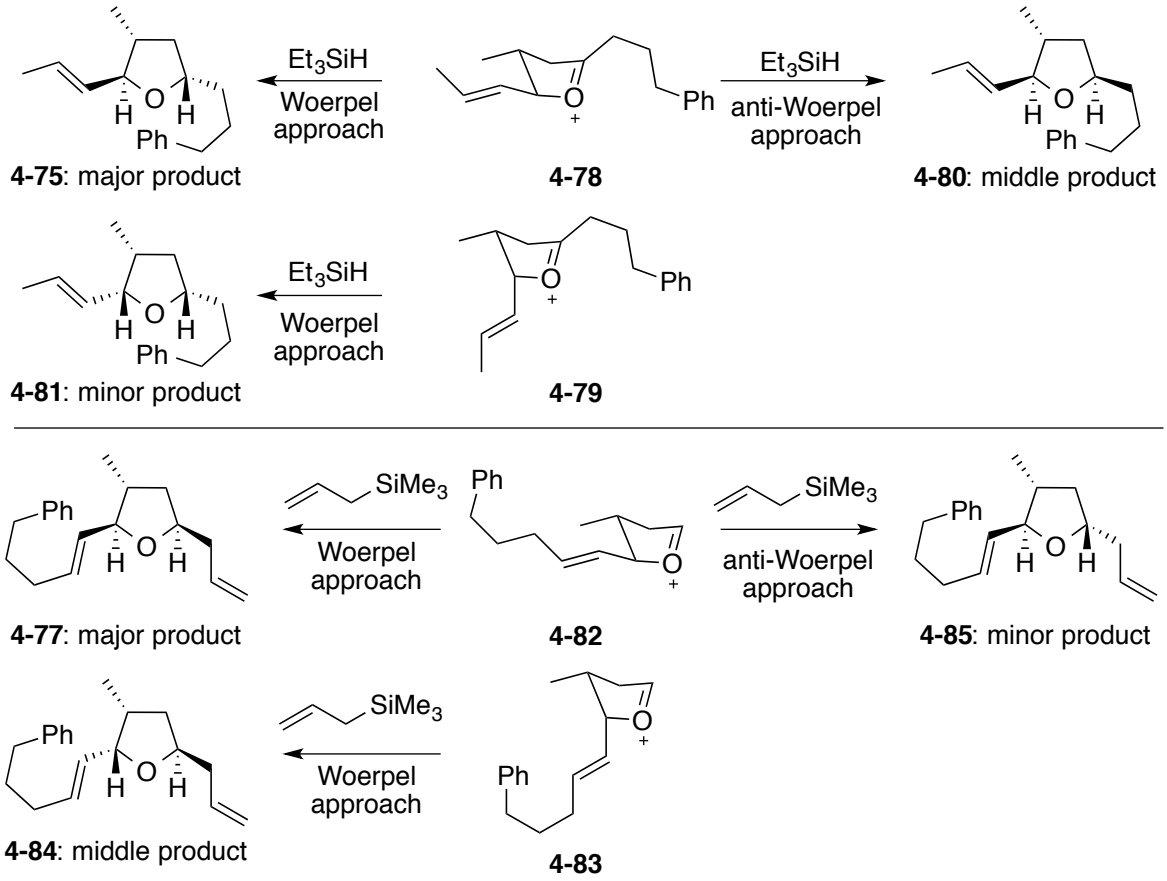
Scheme 4.8 Stereocontrolled synthesis



Scheme 4.9 Stereocontrolled synthesis (continued)

Substrates bearing a β-keto ester moiety showed increased diastereoselectivity compared to those containing simple ketone moieties (equations 6, 7 vs equations 1, 3). This is because the ionization step is slowed down, allowing longer time for stereochemical editing (step a and step b, scheme 4.7). Stereocontrol is enhanced for reactions that establish a 2,4-stereochemical relationship in the product (equations 3, 5, 7 versus equations 1, 4, 6). A significant steric interaction between an axially oriented substituent and the silane is present in the termination step, which leads to the minor product in these reactions. This steric interaction effectively slows

down the reduction, and allows for equilibration to the more reactive precursor, yielding the major product. Allytrimethylsilane can also add to tetrahydropyranyl oxocarbenium ion with good diastereocontrol (equation 8).



Scheme 4.10 Stereocontrol in tetrahydrofuran formation

Lower levels of stereocontrol were observed in tetrahydrofuran formation compared to that in tetrahydropyran formation. However, interesting trends were observed after analyzing the data. For example, ketone **4-74** underwent reductive cyclization to give a combined 75% yield of three isomers in a 5:3:1 ratio, with isomer **4-75** being the major product. As shown in Scheme 4.10, this reaction proceeds via the oxocarbenium ions **4-78** and **4-79**, with the 2,3-*trans*-isomer

4-78 being the dominant intermediate, avoiding eclipsing interactions in the ionization step.[84] Approach of the silane shows modest selectivity for the concave face, opposite the methyl group, which is consistent with the model developed by Woerpel and coworkers.[79c] Allylative cyclization of aldehyde **4-76** also delivers a mixture of three isomers, with **4-77** being the major product and stereochemical complementarity being observed for the two major products. The stereochemical preference for **4-82** over **4-83** is diminished compared to the preference of **4-78** over **4-79**, as was observed in the tetrahydropyran series. However, the Woerpel selectivity in the termination step was higher in this process, probably due to the reduced reactivity of the nucleophile, thereby leading to a 58% yield of the major product. Resubjecting the product mixture to Re_2O_7 in refluxing CH_2Cl_2 lead to the increased selectivity for the formation of **4-77**, with the ratio of **4-77**:**4-84**:**4-85** changing to 8.7:1:1.3 from 3:1:0.6. This increased selectivity results from the ionization of **4-84** to form an allylic cation intermediate, which undergoes stereochemical equilibration and subsequent ring closure to give the more stable 2,3-*trans*-isomer.

4.3 CONCLUSION

A new sequence of allylic alcohol transposition, intramolecular trapping, ionization, and intermolecular termination was developed and applied successfully to heterocycle synthesis. This protocol renders the initial trapping group traceless, thereby greatly increasing the reaction substrate scope. In this new sequence, primary and secondary allylic alcohols can be used as substrates, ketones and aldehydes are suitable trapping groups, and silanes, π-nucleophiles, and alcohols serve as terminating agents in the formation of cyclic ethers. Reactivity can be mediated

by controlling the concentration of the intermediate oxocarbenium ion, and by using trapping agents of appropriate nucleophilicity. It was found that the substitution patterns of the allylic alcohol, the trapping group, and the nucleophile influence the rate of this process. Relative stereocontrol is achievable through rational tuning of each step in this sequence, and complementary stereoisomers can be accessed via reductive and alkylative terminations. High stereocontrol can be achieved when the rate of the termination is low, while the rates for all other steps are high for sufficient thermodynamic equilibration of the reaction intermediates. Successful coupling ring formation with equilibrating stereocenter generation provides a useful alternative to reagent-based method for stereocontrol in the synthesis of stereochemically rich cyclic or polycyclic structures.

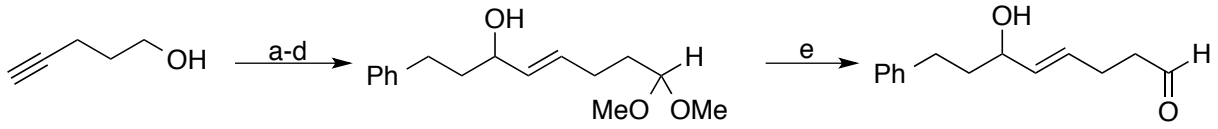
APPENDIX A

STEREOSELECTIVE HETEROCYCLE SYNTHESIS THROUGH A REVERSIBLE ALLYLIC ALCOHOL TRANSPOSITION AND NUCLEOPHILIC ADDITION SEQUENCE

General Information ^{1}H NMR and ^{13}C NMR spectra were taken on a Bruker Avance 300 spectrometer at 300 MHz and 75 MHz respectively, a Bruker Avance 400 spectrometer at 400 MHz and 100 MHz, or a Bruker Avance 500 spectrometer at 500 MHz and 125 MHz, as specified. The chemical shifts are reported in parts per million (ppm) on the delta (δ) scale. The solvent peak was used as a reference value, for ^{1}H NMR: $CDCl_3$ = 7.27 ppm, CD_2Cl_2 = 5.31 ppm, C_6D_6 = 7.16 ppm, for ^{13}C NMR: $CDCl_3$ = 77.23, $CDCl_3$ = 53.52, C_6D_6 = 128.37. Data are reported as follows: m = multiplet, s = singlet; d = doublet; t = triplet; q = quartet; p = pentet; dd = doublet of doublets; dt = doublet of triplets; br = broad. High resolution mass spectra were recorded on a Micromass UK Limited Q-Tof Ultima API or a Fissions VG Autospec spectrometer. Infrared (IR) spectra were taken on a Mattson Cygnus 100 spectrometer. Samples for IR were prepared as thin films on a NaCl plates by dissolving the corresponding compounds in CH_2Cl_2 followed by evaporation of the CH_2Cl_2. Methylene chloride was distilled under N_2 from CaH_2. Analytical TLC was performed on E. Merck pre-coated (25 mm) silica gel 60F-254

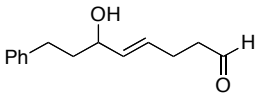
plates. Visualization was done under UV (254 nm). Flash chromatography was done using ICN SiliTech 32-63 60 Å silica gel. Reagent grade ethyl acetate, diethyl ether, pentane and hexanes (commercial mixture) were purchased from EM Science and used as is for chromatography. All reactions were performed in oven or flame-dried glassware under a positive pressure of N_2 with magnetic stirring unless otherwise noted.

General procedure for the Re_2O_7-mediated cyclization To a solution of the substrate in freshly distilled CH_2Cl_2 (~0.05-0.10M) was added Re_2O_7 (Used as received, 0.05 equiv). The reaction mixture was stirred at rt (unless otherwise mentioned) until the starting was completely consumed as determined by TLC, then the reaction was quenched with a few drops of pyridine or triethylamine and the solvent was removed under vacuum The final products were isolated after purification by flash chromatography or preparative TLC.



Reagents and conditions
a) DIBAL-H, THF, -78 ºC, then I_2, 52%; b)IBX, DMSO, 84%; c) $(MeO)_3CH$, PPTS, MeOH, 88%;
d) *t*BuLi, THF, -78 ºC, then $PhCH_2CH_2CHO$, 50%; e)HOAc, H_2O, 100%.

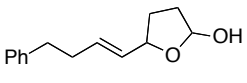
Scheme A1 Synthesis of substrates **2-10** and **2-13**



(*E*)-6-hydroxy-8-phenyloct-4-enal (2-10)

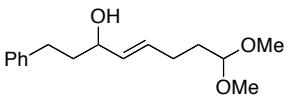
^{1}H NMR (400 MHz, CD_2Cl_2) δ 9.73 (t, *J* = 1.2 Hz, 1H), 7.26-7.29 (m, 2H), 7.15-7.21 (m, 3H), 5.65 (dtd, *J* = 0.4, 6.4, 15.6 Hz, 1H), 5.54 (tdd, *J* = 1.2, 6.4, 15.6 Hz, 1H), 4.04 (app q, *J* = 5.6 Hz, 1H), 2.59-2.73 (m, 2H), 2.51 (t, *J* = 8.0 Hz, 2H), 2.35 (q, *J* = 4.8 Hz, 2H), 1.70-1.87 (m, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 202.3, 142.6, 134.7, 129.8, 128.8,

128.7, 126.1, 72.3, 43.5, 39.3, 32.1, 25.1; IR (neat) 3439, 3063, 3031, 2954, 2925, 2867, 1605, 1496, 1453, 1375, 1179, 1121,1024 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{18}O_2Na$ $[M+Na]^+$ 241.1204, found 241.1211.



5-(4-phenylbut-1-en-1-yl)tetrahydrofuran-2-ol (2-11)

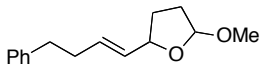
The general cyclization procedure was followed with **2-10** (50 mg, 0.23 mmol), Re_2O_7 (5.5 mg, 0.011 mmol), and CH_2Cl_2 (3 mL). The reaction was stirred at rt for 30 min and then was quenched with pyridine (25 mL). After evaporation of the solvent, the crude mixture was purified by flash chromatography (10-20% ethyl acetate in hexanes) to give the product (10 mg, 20%, dr = 1.2:1). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.24-7.28 (m, 2H), 7.14-7.19 (m, 3H), 5.70 (app q, *J* = 6.4 Hz, 0.45H), 5.67 (app q, *J* = 6.4 Hz, 0.55H), 5.54 (dt, *J* = 1.2, 7.6 Hz, 0.45H), 5.49-5.52 (m, 0.55H), 5.44 (dt, *J* = 1.2, 7.2, Hz 0.45H), 5.39-5.41 (m, 0.55H), 4.54 (q, *J* = 6.8 Hz, 0.55H), 4.33 (q, *J* = 6.8, 0.45H), 2.65-2.72 (m, 2H), 2.57-2.63 (m, 1H), 2.30-2.43 (m, 2H), 1.82-2.16 (m, 2.4H), 1.70-1.82 (m, 1H), 1.46-1.55 (m, 0.6H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 141.9, 133.0, 131.6, 131.4, 131.0, 128.4, 128.2, 125.7, 98.5, 98.4, 81.4, 78.8, 35.5, 34.2, 34.0, 33.8, 33.2, 30.4, 30.0; IR (neat) 3402, 3060, 3025, 2933, 2857, 1603, 1495, 1453, 1191, 1018; HRMS (ESI) calcd for $C_{14}H_{18}O_2Na$ $[M+Na]^+$ 241.1204, found 241.1228.



(*E*)-8,8-dimethoxy-1-phenyloct-4-en-3-ol (2-13)

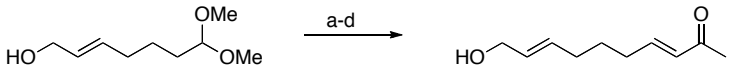
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.32 (m, 2H), 7.18-7.22 (m, 3H), 5.68 (ddt, *J* = 0.4, 6.4 Hz, 15.2, 1H), 5.55 (ddt, *J* = 1.2, 6.8, 15.2 Hz, 1H), 4.40 (t, *J* = 5.6 Hz, 1H), 4.09 (q, *J* = 5.7 Hz, 2H), 3.34 (s, 6H), 2.64-2.77 (m, 2H), 2.10-2.15 (q, *J* = 7.1 Hz, 2H), 1.77-1.94 (m, 2H), 1.74 (br, 1H), 1.70-1.70 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0,

133.4, 131.2, 128.5, 128.4, 125.8, 103.9, 72.2, 52.76, 53.74, 38.8, 32.0, 31.8, 27.3; IR (neat) 3426, 3060, 3025, 2941, 2857, 2831, 1669, 1602, 1495, 1452, 1385, 1190, 1127, 1058 969, 913, 747 cm^{-1}; HRMS (APCI) calcd for $C_{16}H_{24}O_3Na$ $[M+Na]^+$ 287.1623, found 287.1632.



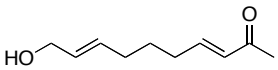
2-methoxy-5-(4-phenylbut-1-en-1-yl)tetrahydrofuran (2-15)

The general cyclization procedure was followed with **2-13** (50 mg, 0.19 mmol), Re_2O_7 (4.6 mg, 0.010 mmol), DCM (3 mL), the reaction was stirred at rt for 30 min, then was quenched with pyridine (25 mL). After evaporation of the solvent, the crude mixture was purified by flash chromatography (1%-3% ethyl acetate in hexanes) to give the product (36 mg, 83%, dr = 3:2). ^1H NMR (400 MHz, $CDCl_3$) δ. 7.28-7.35 (m, 2H), 7.18-7.25 (m, 3H), 5.69-5.84 (m, 1H), 5.43-5.65 (m, 1H), 5.08 (dd, *J* = 2.0, 5.2 Hz, 0.6H), 4.99 (d, *J* = 4.4 Hz, 0.4H), 4.50 (q, *J* = 7.1 Hz, 0.6H), 4.45 (q, *J* = 7.7 Hz, 0.4H), 3.39 (s, 1.8H), 3.37 (s, 1.2H), 2.62-2.82 (m, 2H), 2.26-2.53 (m, 2H), 1.70-2.20 (m, 3.4H), 1.50-1.62 (m, 0.6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.8, 132.8, 132.3, 131.8, 130.6, 128.5, 128.4,128.32, 128.30, 125.9, 125.8, 105.3, 105.0, 81.5, 78.7, 54.9, 54.5, 35.53, 35.49, 34.1, 34.0, 33.5, 32.4, 30.3, 30.1; IR (neat) 3061, 3026, 2984, 2928, 2828, 1684, 1603, 1495, 1453, 1363, 1203, 1098, 1034, 966, 746 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{20}O_2Na$ $[M+Na]^+$ 255.1361, found 255.1374.



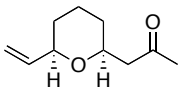
Reagents and conditions
a) HOAc, H_2O. b) TBDPSCl, imidazole, DMAP, DMF. c) $(EtO)_2P(O)CH_2C(O)CH_3$, NaH, THF. d) HF•pyridine, THF.

Scheme A2 Synthesis of substrate **2-16**



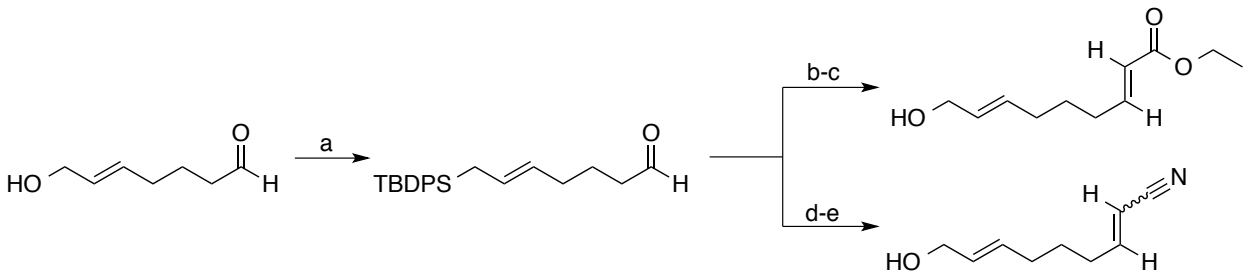
(3*E*,8*E*)-10-hydroxydeca-3,8-dien-2-one (2-16)

^{1}H NMR (400 MHz, CH_2Cl_2) δ 6.77 (dt, *J* = 7.2, 16.0 Hz, 1H), 6.03 (dt, *J* = 1.4, 16.0 Hz, 1H), 5.59-5.70 (m, 2H), 4.04 (d, *J* = 3.6 Hz, 2H), 2.22 (dt, *J* = 1.4, 7.2 Hz, 2H), 2.19 (s, 3H), 2.03-2.11 (m, 2H), 1.56 (p, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, CH_2Cl_2) δ 198.3, 147.9, 131.7, 131.4, 130.1, 63.4, 31.8, 31.6, 27.6, 26.6; IR (neat) 3427, 3004, 2928, 2857, 1672, 1625, 1431, 1362, 1431,1362, 1257, 1089, 972 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{16}O_2Na$ $[M+Na]^+$ 191.1048, found 191.1066.



1-((2S,6R)-6-vinyltetrahydro-2H-pyran-2-yl)propan-2-one (2-18)

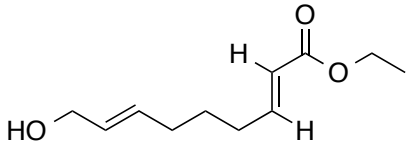
The general rearrangement procedure was followed with **2-16** (14.2 mg, 0.084 mmol), Re_2O_7 (2.1 mg, 0.004 mmol), and CD_2Cl_2 (1.5 mL). The reaction was stirred at 20 °C for 10 min, after which the catalyst was removed by filtration through a small pad of Celite. ^{1}H NMR was taken directly to show a quantative conversion. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 5.90 (ddd, J = 5.2, 10.4, 17.2 Hz, 1H), 5.16 (dt, J = 1.6, 17.2 Hz, 1H), 5.02 (dt, J = 1.6, 10.4 Hz, 1H), 3.75-3.85 (m, 2H), 2.63 (dd, J = 7.6, 15.6 Hz, 1H), 2.42 (dd, J = 5.2, 15.6 Hz, 1H), 2.13 (s, 3H), 1.79-1.87 (m, 1H), 1.51-1.65 (m, 3H), 1.13-1.29 (m, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2) 207.1, 139.6, 113.7, 78.1, 74.1, 50.3, 31.19, 31.16, 30.6, 20.3; IR (neat) 2934, 2857, 1717, 1438, 1358, 1199, 1089, 1045, 989, 916 cm^{-1}; HRMS (EI) calcd for $C_{10}H_{15}O_2$ $[M–H]^+$ 167.1072, found 167.1100.



Reagents and conditions:

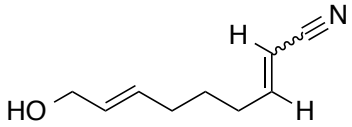
a) TBDPSCl, imidazole, CH_2Cl_2, rt, 67%; b) ethyl 2-(diethoxyphosphoryl)acetate, NaH, THF, 0 ºC, 32%; c) HF•pyridine, pyridine, Et_2O, rt, 81%, d) diethyl (cyanomethyl)phosphonate, NaH, THF, 0 ºC; e) HF•pyridine, pyridine, Et_2O, RT, 28% for two steps.

Scheme A3 Synthesis of substrates **2-16** and **2-22**



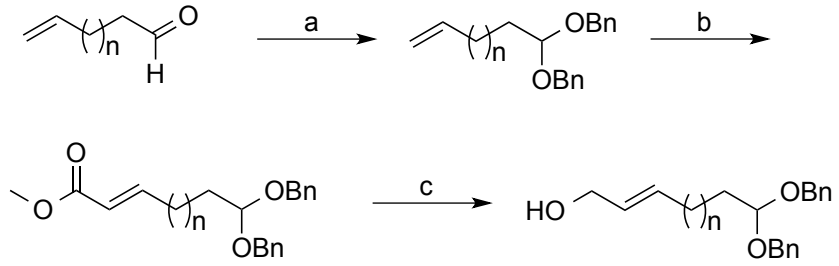
Ethyl (2*E*,7*E*)-9hydroxynona-2,7-dienoate (2-19)

^{1}H NMR (300 MHz, CD_2Cl_2) δ 6.92 (dt, *J* = 7.2, 15.6 Hz, 1H), 5.79 (dt, *J* = 1.5, 15.6, 1H), 5.55-5.71 (m, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 4.02 (d, *J* = 3.6 Hz, 2H), 2.20 (dq, *J* = 1.5, 7.2 Hz, 2H), 2.00-2.10 (m, 2H), 1.95 (br, 1H), 1.53 (p, *J* = 7.5 Hz, 2H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 166.5, 148.9, 131.6, 130.1, 121.4, 63.3, 60.1, 31.54, 31.53, 27.5, 14.0; IR (neat) 3424, 2982, 2932, 28591718, 1652, 1443, 1368, 1269, 1188, 1153, 1092, 1042, 972 cm^{-1}.



(7*E*)-9-hydroxynona-2,7-dienenitrile (2-22)

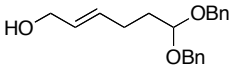
^{1}H NMR (300 MHz, CD_2Cl_2) δ 6.71 (dt, J = 6.9, 16.2 Hz, 0.48H), 6.48 (dt, J = 7.8, 10.8, 0.52H), 5.55-5.71 (m, 2H), 5.28-5.40 (m, 1H), 2.36-2.48 (m, 1H), 2.17-2.27 (m, 1H), 2.00-2.16 (m, 2H), 1.67 (br, 1H), 1.47-1.63 (m, 2H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 155.8, 154.9, 131.16, 131.11, 130.5, 130.3, 99.8, 99.7, 60.3, 60.2, 32.6, 31.3, 31.1, 27.5, 27.1; IR (neat) 3414, 2932, 2860, 2222, 1670, 1631, 1438, 1088, 999, 970, 740 cm^{-1}.



Reaction Conditions:

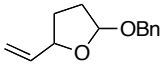
a) BnOH, PTSA.H_2O, Na2SO4, DCM, RT, 64% (n=1), 51% (n=2), 52% (n=3). b) Hoveyda-Grubbs 2nd, Methyl Acrylate, DCM, reflux, 89% (n=1), 97% (n=2), 99% (n=3). c) DIBAL,DCM, -78 °C, 90% (n=1), 89% (n=2), 86% (n=3).

Scheme A4 Synthesis of substrates **2-25**, **2-22**, **and 2-29**



(*E*)-6,6-bis(benzyloxy)hex-2-en-1-ol (2-25)

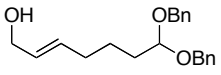
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.45 (m, 10H), 5.62-5.76 (m, 2H), 4.83 (t, *J* = 6.0 Hz, 1H), 4.74 (d, *J* = 12.0 Hz, 2H), 4.64 (d, *J* = 12.0 Hz, 2H), 4.07 (d, *J* = 4.8 Hz, 2H), 2.40 (br, 1H), 2.24 (q, *J* = 7.0 Hz, 2H), 1.93 (q, *J* = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 131.6, 129.8, 128.6, 127.9, 127.8, 101.6, 67.4, 63.4, 32.8, 27.6; IR (neat) 3401, 3087, 3062, 3030, 2930-2868, 1670, 1605, 1496, 1453, 1385, 1353, 1208, 1124, 1023,737 cm^{-1}; HRMS (APCI) calcd for $C_{20}H_{24}O_3Na$ $[M+Na]^+$ 355.1623, found 355.1608.



2-(Benzyloxy)-5-vinyltetrahydrofuran (2-26)

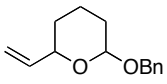
The general cyclization procedure was followed with **2-25** (100 mg, 0.32 mmol), Re_2O_7 (7.8 mg, 0.016 mmol), and CH_2Cl_2 (5 mL). The reaction was stirred at rt for 30 min and then was quenched with pyridine (25 mL). After evaporation of the solvent, the crude mixture was purified by flash chromatography (1%-3% ethyl acetate in hexanes) to give the product (55 mg, 84%, dr = 3:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.40 (m, 5H), 5.95 (ddd, *J* = 7.2, 10.0, 17.2 Hz, 0.4H), 5.90 (ddd, *J* = 6.8, 10.4, 17.2 Hz, 0.6H), 5.23-5.33 (m, 2H), 5.13-5.18

(m, 1H), 4.82 (d, J = 12.0 Hz, 0.4H), 4.81 (d, J = 12.0 Hz, 0.6H), 4.81 (q, J = 6.8 Hz, 0.6H), 4.50-4.55 (m, 1.4H), 2.20-2.30 (m, 0.6H), 2.08-2.16 (m, 1.5H), 1.88-2.04 (m, 1.5H), 1.61-1.70 (m,0.8H); ^{13}C NMR (100 MHz, $CDCl_3$) 140.5, 138.5, 138.34, 138.32, 128.4, 127.94, 127.88, 127.5, 115.7, 115.6, 103.5, 103.2, 81.8, 78.9, 69.0, 68.6, 33.5, 32.1, 30.02, 30.0; IR (neat) 3064,3030, 2924, 2853, 1605, 1455,1273, 1205, 1025, 733 cm^{-1}; HRMS (APCI) calcd for $C_{13}H_{16}O_2Na$ $[M+Na]^+$ 227.1048, found 227.1049.



(*E*)-7,7-bis(benzyloxy)hept-2-en-1-ol (2-27)

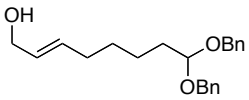
^{1}H NMR (300 MHz, $CDCl_3$) 7.33-7.44 (m, 10H), 5.62-5.76 (m, 2H), 4.83 (t, J = 6.0 Hz, 1H), 4.75 (d, J = 11.7 Hz, 2H), 4.65 (d, J = 11.7 Hz, 2H), 2.14 (q, J = 6.5 Hz, 2H), 1.86 (q, J = 7.2 Hz, 2H), 1.95 (p, J = 7.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 132.1, 129.8, 128.6, 127.9, 127.8, 102.1, 67.3,63.4, 32.9, 32.1, 24.4; IR 3403, 3062, 3030, 2932, 2865, 1669, 1605,1496, 1454,1384, 1351, 1208, 1124, 1023, 736 (neat) cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{26}O_3Na$ $[M+Na]^+$ 349.1780, found 349.1754.



2-(benzyloxy)-6-vinyltetrahydro-2H-pyran (2-28)

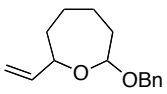
The general rearrangement procedure was followed with **2-27** (100 mg, 0.31 mmol), Re_2O_7 (7.4 mg, 0.015 mmol), and DCM (5 mL). The reaction was stirred at rt for 30 min and then was quenched with pyridine (25 mL). After evaporation of the solvent, the crude mixture was purified by flash chromatography (1%-3% ethyl acetate in hexanes) to give the product (55 mg, 81%, dr = 7:3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.41 (m, 5H), 5.95 (ddd, J = 5.2, 10.4, 17.2 Hz, 0.3H), 5.88 (ddd, J = 6.0, 10.8, 17.2 Hz, 0.7), 5.31 (dt, J = 1.6, 17.2 Hz, 0.3H), 5.26 (dt, J = 1.6, 17.6 Hz, 0.7H), 5.14 (dt, J = 1.4, 10.8 Hz, 0.3H), 5.13 (dt, J = 1.4, 10.4

Hz, 0.7H), 5.00 (d, *J* = 1.6 Hz, 0.7H), 4.95 (d, *J* = 12.0 Hz, 0.3H), 4.76 (d *J* = 12.0 Hz, 0.7H), 4.65 (d, *J* = 12.0 Hz, 0.3H), 4.55 (dd, *J* = 2.0, 9.2 Hz, 0.3H), 4.52 (d, *J* = 12.0 Hz, 0.7H), 4.31(ddddd, *J* = 1.6, 1.6, 1.6, 5.6, 10.4 Hz, 0.7H), 3.93 (ddddd, *J* = 1.2, 1.6, 2.4, 5.2, 11.2 Hz, 0.3H), 1.25-2.05 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 138.6, 138.4, 138.1, 128.4, 128.0, 127.8, 127.6, 127.5, 114.8, 114.6, 101.0, 96.7, 76.5, 69.8, 69.7, 68.5, 31.1, 31.0, 30.8, 29.5, 22.0, 18.0; IR (neat) 3065, 3030, 2940, 2867, 1646, 1604, 1496, 1454, 1357, 1261, 1205, 1121, 1023, 736 cm^{-1}; HRMS (APCI) calcd for $C_{14}H_{18}O_2Na$ $[M+Na]^+$ 241.1204, found 241.1184.



(*E*)-8,8-bis(benzyloxy)oct-2-en-1-ol (2-29)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.46 (m, 10H), 5.64-5.76 (m, 2H), 4.83 (t, *J* = 5.6 Hz, 1H), 4.74 (d, *J* = 12.0 Hz, 2H), 4.65 (d, *J* = 12.0 Hz, 2H), 4.09 (d, *J* = 4.8 Hz, 2H), 2.64 (br, 1H), 2.12 (q, *J* = 6.1 Hz, 2H), 1.86 (q, *J* = 6.8 Hz, 2H), 1.41-1.58 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 132.5, 129.5, 128.5, 127.9, 127.7, 102.2, 67.3, 63.4, 33.2, 32.2, 29.0, 24.3; IR (neat) 3406, 3062, 3030, 2932, 2861, 1669, 1605, 1494, 1454, 1384, 1351, 1205, 1125, 1022, 736 cm^{-1}; HRMS (APCI) calcd for $C_{22}H_{28}O_3Na$ $[M+Na]^+$ 363.1936, found 363.1925.



2-(Benzyloxy)-7-vinyloxepane (2-30)

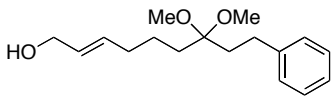
The general rearrangement procedure was followed with **2-29** (100 mg, 0.29 mmol), Re_2O_7 (7.1 mg, 0.015 mmol), and CH_2Cl_2 (5 mL). The reaction was stirred at rt for 30 min and then was quenched with pyridine (25 mL). After evaporation of the solvent, the crude mixture was purified by flash chromatography (1%-3% ethyl acetate in hexanes) to give the product (55 mg, 81%, dr = 9:1).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.40 (m, 5H), 5.94 (ddd, *J* =

5.2, 10.4, 17.2 Hz, 1H), 5.34 (dt, *J* = 1.6, 17.2 Hz, 1H), 5.14 (dt, *J* = 1.6, 10.4 Hz, 0.1H), 5.13 (dt, *J* = 1.6, 10.4 Hz, 0.9H), 4.93 (dd, *J* = 5.6, 8.8 Hz, 0.9H), 4.88 (d, *J* = 12.0 Hz, 0.1H), 4.81 (d, *J* = 11.6 Hz, 0.9H), 4.70 (dd, *J* = 3.6, 7.6 Hz, 0.1H), 4.57 (d, *J* = 12.0 Hz, 0.1H), 4.52 (d, *J* = 11.6 Hz, 0.9H), 4.45 (dd, *J* = 5.2, 9.6 Hz, 0.9H), 4.01-4.04 (m, 0.1H), 2.13-2.22 (m, 1H), 1.88-1.98 (m, 1H), 1.65-1.87 (m, 3H), 1.36-1.60 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.3, 139.5, 138.4, 138.1, 128.4, 128.1, 128.0, 127.5, 113.6, 103.3, 100.3, 77.8, 71.1, 69.2, 69.1, 36.5, 35.9, 35.7, 35.4, 29.5, 24.7, 23.3, 22.5; IR (neat) 3064, 3030, 2931, 2856, 1645, 1605, 1496, 1452, 1356, 1206, 1131, 1055, 1024, 735 cm^{-1}; HRMS (APCI) calcd for $C_{15}H_{20}O_2Na$ $[M+Na]^+$ 255.1361, found 255.1359.

Reagents and conditions:

a) Pentenylmagnesium bromide, THF, 0 ºC, 89%; b) PCC, Celite, CH_2Cl_2, 96%; c) *p*-TsOH, $(MeO)_3CH$, MeOH, 50 ºC, 93%; d) Ethyl acrylate, Grubbs-Hoveyda metathesis catalyst 2nd CH_2Cl_2, reflux; e) DIBAL-H, CH_2Cl_2, -78 ºC.

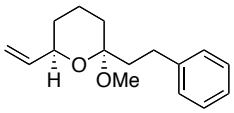
Scheme A5 Synthesis of substrate **2-31**



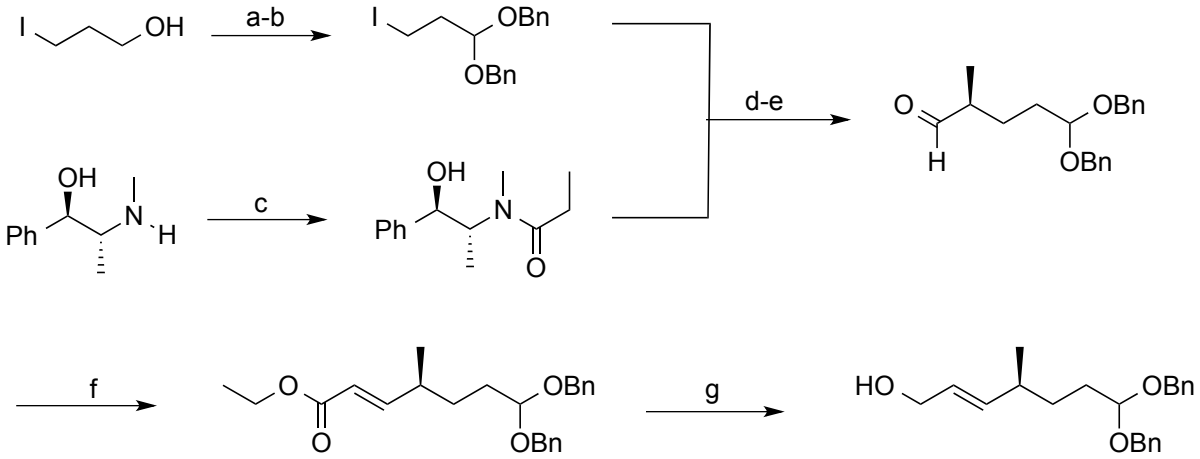
(*E*)-7,7-Dimethoxy-9-phenylnon-2-en-1-ol (2-31)

^{1}H NMR (400 MHz, C_6D_6) δ 7.04-7.18 (m, 5H), 5.47-5.57 (m, 2H), 3.87 (br, 2H), 3.05 (s, 6H), 2.58-2.63 (m, 2H), 1.94 -2.01 (m, 2H), 1.89-1.93 (m, 2H), 1.66-1.71 (m, 2H), 1.40 (p, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, C_6D_6) δ 142.1, 131.1, 130.3, 128.4, 128.2, 125.8, 102.8, 63.1, 47.2, 34.7, 32.3, 32.2, 30.4, 23.5; IR (neat) 3400, 3025, 2949, 2829, 1669, 1603, 1495, 1454, 1368, 1181, 1054, 971, 743 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{26}O_3Na$ $[M+Na]^+$ 301.1780, found 301.1811.

(±)-(2*S*, 6*R*)-2-methoxy-2-phenethyl-6-vinyltetrahydro-2H-pyran (2-32)



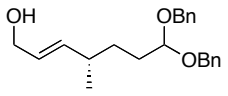
The general rearrangement cyclization procedure was followed with **2-31** (11 mg, 0.039 mmol), Re_2O_7 (2.0 mg, 0.004 mmol), and CD_2Cl_2 (1.0 mL). The reaction was stirred at 0 °C for 2 min, after which the cold bath was removed, and the reaction was stirred for another 8 min and then was quenched with pyridine (25 mL). $Me_2(Bn)SiH$ (5 µl) was added as an internal standard and crude NMR was used to determine the yield of 85%. ^1H NMR (400 MHz, C_6D_6) δ 7.12-7.19 (m, 2H), 7.04-7.11 (m, 3H), 5.88 (ddd, *J* = 5.6, 9.8, 17.2 Hz, 1H), 5.29 (dt, *J* = 1.8, 17.2 Hz, 1H), 5.03 (dt, *J* = 1.6, 17.2 Hz, 1H), 4.08 (ddddd, *J* = 1.2, 1.6, 2.4, 5.2, 11.6 Hz, 1H), 3.07 (s, 3H), 2.53-2.69 (m, 2H), 1.99-2.09 (m, 1H), 1.81-1.98 (m, 2H), 1.72 (dddd, *J* = 1.6, 1.6, 1.6, 12.8 Hz, 1H) 1.36-1.51 (m, 2H), 1.19-1.30 (m, 2H); ^{13}C NMR (100 MHz, C_6D_6) δ 142.3, 139.8, 128.4, 128.3, 125.7, 113.3, 99.1, 70.7, 46.7, 38.4, 32.2, 31.0, 30.0 18.9; IR (neat) 3063, 3026, 2941, 2867, 1646, 1603, 1496, 1454, 1367, 1273, 1216, 1104, 1024, 924, 755, 738 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{22}O_2Na$ $[M+Na]^+$ 269.1517, found 269.1548.



Reaction Conditions:

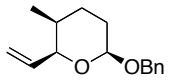
a) IBX, DMSO, DCM. b) BnOH, PTSA.H_2O, Na_2SO_4, DCM, rt, 27% for 2 steps. c) Propionic Anhydride, Et_3N, DCM, 0 °C, 73%. d) nBuLi, iPr_2NH, $BH_3.NH_3$, THF. e) IBX, DMSO, rt, 73% for 2 steps. f) NaH in Mineral Oil,Triethyl phosphonoacetate,THF, 0 °C, 99%. g) DIBAL, DCM, -78 °C, 92%.

Scheme A6 Synthesis of substrate **2-33**



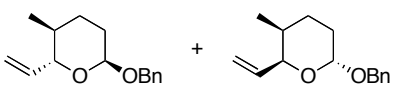
(*S*,*E*)-7,7-Bis(benzyloxy)-4-methylhept-2-en-1-ol (2-33)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.45 (m, 10H), 5.53-5.66 (m, 2H), 4.79 (t, *J* = 5.7 Hz, 1H), 4.73 (d, *J* = 11.7 Hz, 2H), 4.63 (d, *J* = 11.7 Hz, 2H), 4.10 (d, *J* = 4.2 Hz, 2H), 2.19 (heptet, *J* = 6.6 Hz, 1H), 1.94 (br, 1H), 1.74-1.88 (m, 2H), 1.40-1.54 (m, 2H), 1.06 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3, 138.1, 128.5, 127.9, 127.7, 102.3, 67.28, 67.26, 67.23, 63.6, 36.3, 31.7, 31.2, 20.5; IR (neat) 3403, 3063, 3030, 2926, 2867, 1667, 1605, 1493, 1454, 1380, 1349, 1208, 1122, 1022, 736 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{28}O_3Na$ $[M+Na]^+$ 363.1936, found 363.1973.



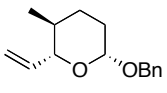
(2*S*,3*S*,6*S*)-6-(Benzyloxy)-3-methyl-2-vinyltetrahydro-2H-pyran (2-34)

The general rearrangement procedure was followed with **2-33** (50 mg, 0.16 mmol), Re_2O_7 (2 mg, 0.004 mmol), and CH_2Cl_2 (5 mL). The reaction was stirred at rt for 20 min and then was quenched with pyridine (25 mL). After evaporation of the solvent, the crude mixture was purified by flash chromatography (1%-3% ethyl acetate in hexanes) to give the product (33 mg, 100%, dr = 3:3:1:1). ^{1}H NMR (400 MHz, C_6D_6) δ 7.29-7.34 (m, 2H), 7.16-7.20 (m,2H), 7.07-7.12 (m, 1H), 5.74 (ddd, *J* = 4.8, 10.8, 17.2 Hz, 1H), 5.39 (dt, *J* = 2.0, 17.2 Hz, 1H), 5.10 (dt, *J* = 2.0, 10.8 Hz, 2H), 4.85 (d, *J* = 3.2 Hz, 1H), 4.70 (d, *J* = 12.0 Hz, 1H), 4.51(dddd, *J* = 0.5, 1.4, 1.6, 2.4 Hz, 1H), 4.37 (d, *J* = 12.0 Hz, 1H), 2.13 (dddd, *J* = 4.6, 4.6, 13.6, 13.6 Hz, 1H), 1.68 (dddd, *J* = 4.4, 4.4, 14.0, 14.0 Hz, 1H), 1.54 (m, 1H), 1.45 (dddd, *J* = 1.2, 2.8, 4.4, 14.0 Hz, 1H), 1.21 (dddd, *J* = 2.4, 2.8, 5.2, 13.6 Hz, 1H), 0.93 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 138.7,138.4, 128.2, 127.8, 127.3, 113.6, 96.4, 70.8, 68.3, 31.3, 25.3, 24.2, 11.4; IR (neat) 3065, 3030, 2938, 2892, 1645, 1606, 1453, 1351, 1211, 1126, 1019, 729 cm^{-1}; HRMS (APCI) calcd for $C_{15}H_{20}O_2Na$ $[M+Na]^+$ 255.1361, found 255.1372.



(2*R*, 3*S*, 6*S*)-6-(Benzyloxy)-3-methyl-2-vinyltetrahydro-2H-pyran and (2*S*, 3*S*, 6*R*)-6-(benzyloxy)-3-methyl-2-vinyltetrahydro-2H-pyran

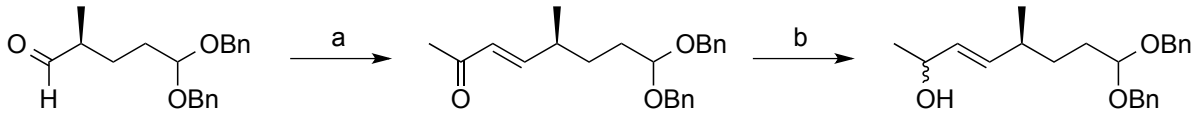
^{1}H NMR (400 MHz, C_6D_6) δ 7.28-7.36 (m, 2H), 7.13-7.19 (m, 2H), 7.05-7.11 (m, 1H), 5.87 (ddd, *J* = 6.8, 10.4, 17.2 Hz, 0.75H), 5.81 (ddd, *J* = 5.2, 10.8, 17.2 Hz, 0.25H), 5.35 (dt, *J* = 2, 17.2 Hz, 0.25H), 5.27 (ddd *J* = 0.8, 2.0, 17.2 Hz, 0.75H), 5.06-5.11 (m, 1H), 4.96 (d, *J* = 12.0 Hz, 0.25H), 4.89 (d, *J* = 3.2 Hz, 0.75H), 4.73 (d, *J* = 12.0 Hz, 0.75H), 4.53 (d, *J* = 12.0 Hz, 0.25H), 4.41 (dd, *J* = 2.8, 8.4 Hz, 0.25H), 4.40 (d, *J* = 12.0 Hz, 0.75H), 3.91 (dd, *J* = 7.2, 9.6 Hz, 0.75H), 3.84 (dddd, *J* = 1.6, 1.6, 3.8, 5.8 Hz, 0.25H), 1.45-1.85 (m, 3H), 1.25-1.45 (m, 2H), 0.87 (d, *J* = 6.4 Hz, 0.75H), 0.71 (d, *J* = 6.4 Hz, 2.25H); ^{13}C NMR (100 MHz, C_6D_6) δ 138.8, 138.7, 138.2, 137.7, 128.21, 128.17, 127.8, 127.3, 116.0, 114.3, 100.9, 95.9, 69.3, 68.2, 35.1, 31.4, 30.2, 28.3, 26.8, 26.7, 17.7, 12.5; IR (neat) 3066, 3030, 2930, 2876, 1645, 1604, 1455, 1376, 1232, 1123, 1023, 923, 730 cm^{-1}; HRMS (APCI) calcd for $C_{15}H_{20}O_2Na$ $[M+Na]^+$ 255.1361, found 255.1377.



(2*R*, 3*S*, 6*R*)-6-(Benzyloxy)-3-methyl-2-vinyltetrahydro-2H-pyran

^{1}H NMR (400 MHz, C_6D_6) δ 7.33-7.37 (m, 2H), 7.13-7.20 (m, 2H), 7.06-7.12 (m, 2H), 5.89 (ddd, *J* = 6.8, 10.4, 17.2 Hz, 1H), 5.29 (ddd, *J* = 1.2, 2.0, 17.2 Hz, 1H), 5.09 (ddd, *J* = 0.8, 2.0, 10.4 Hz, 1H), 4.98 (d, *J* = 12.0 Hz, 1H), 4.57 (d, *J* = 12.0 Hz, 1H), 4.37 (dd, *J* = 2.8, 8.8 Hz, 1H), 3.25 (dd, *J* = 2.8，10.0 Hz, 1H), 1.60-1.75 (m, 2H), 1.41-1.48 (dt, *J* = 3.6, 13.6 Hz, 2H), 1.15-1.28 (m, 2H), 0.80-0.91 (m, 2H), 0.61 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 138.8, 137.6, 128.2, 127.8, 127.3, 115.8, 100.7, 82.7, 69.5, 34.7, 31.7, 31.1, 16.8;

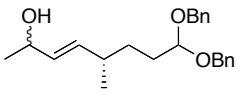
IR (neat) 3065, 3029, 2952, 2929, 2873, 2853, 1645, 1606, 1496, 1362, 1146, 1055, 1091, 920, 736 cm^{-1}; HRMS (APCI) calcd for $C_{15}H_{20}O_2Na$ $[M+Na]^+$ 255.1361, found 255.1342.



Reaction Conditions:

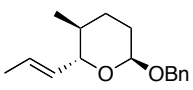
a) 60 % NaH in Mineral Oil, Diethyl (2-Oxopropyl) Phosphonate, THF, 83%. b) (*R*) or (*S*)-CBS, BH_3, THF, -25 °C, 80%. (Either (*R*) or (*S*)-CBS give a dr of 2:1, however this mixture, even with different major isomer, gave same cyclization product)

Scheme A7 Synthesis of substrate **2-35**



(5*S*,*E*)-8,8-Bis(benzyloxy)-5-methyloct-3-en-2-ol (2-35)

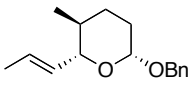
^1H NMR (400 MHz, $CDCl_3$) δ 7.29-7.44 (m, 10H), 5.44-5.56 (m, 2H), 4.76 (t, *J* = 5.6 Hz, 1H), 4.69 (d, *J* = 12.0 Hz, 2H), 4.59 (d, *J* = 12.0 Hz, 2H), 4.26 (p, *J* = 5.6 Hz, 1H), 2.07-2.18 (m, 1H), 1.72-1.82 (m, 2H), 1.65 (br, 1H) 1.37-11.49 (m, 2H), 1.27 (d, *J* = 6.4 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 1H) 1.01 (d, *J* =6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 136.1, 136.0, 133.08, 133.04, 128.5, 127.8, 127.7, 102.27, 102.25, 68.9, 68.8, 67.24, 67.15, 67. 13, 36.2, 36.1, 31.7, 31.6, 31.1, 23.6, 23.5, 20.6, 20.5 IR (neat) 3417, 3063, 3030, 2958, 2869, 1666, 1605, 1496, 1453, 1369, 1207, 1124, 1023, 972, 736 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{30}O_3Na$ $[M+Na]^+$ 377.2093, found 377.2063.



(2*S*, 3*S*, 6*S*)-6-(Benzyloxy)-3-methyl-2-((*E*)-prop-1-en-1-yl)tetrahydro-2H-pyran (2-36)

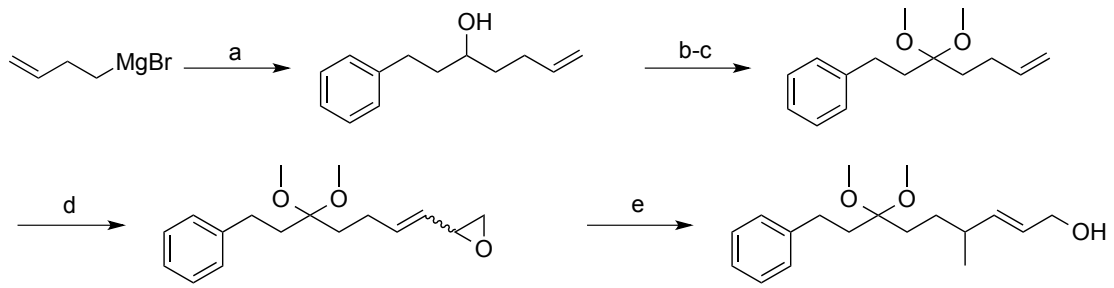
The general cyclization procedure was followed with **2-35** (50 mg, 0.14 mmol), Re_2O_7 (3 mg, 0.007 mmol), and CH_2Cl_2 (3 mL). The reaction was stirred at rt for 30 min and then was

quenched with pyridine (25 mL). After evaporation of the solvent, the crude mixture was purified by flash chromatography (1%-3% ethyl acetate in hexanes) to give the product (30 mg, 86%, dr = 3:1, *trans*: *cis* > 10:1 as determined by the ^{1}H NMR spectrum of the crude mixture). ^{1}H NMR (400 MHz, CD_2Cl_2) δ7.24-7.36 (m, 5H), 6.66 (dq, *J* = 6.4, 15.2 Hz, 1H), 5.39 (ddq, *J* = 1.6, 8, 15.2 Hz, 1H), 4.88 (dd, *J* = 2.0, 2.4 Hz, 1H), 4.67 (d, *J* = 12.0 Hz, 1H), 4.42 (d, *J* = 12.0 Hz, 1H), 3.74 (dd, *J* = 8.8, 9.2 Hz, 1H) 1.66-1.75 (m, 2H), 1.70 (dd, *J* = 1.6, 6.4 Hz, 3H), 1.48-1.58 (m, 2H), 1.35-1.47 (m, 1H), 0.77 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 138.8, 131.2, 128.8, 128.2, 127.8, 127.3, 96.4, 76.4, 68.3, 35.0, 30.2, 26.7, 17.8, 17.5. IR (neat) 3063, 3030, 2929, 2876, 1676, 1604, 1454, 1376, 1230, 1049, 1022, 972, 920, 730 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{22}O_2Na$ $[M+Na]^+$ 269.1517, found 269.1558 .



(2*S*, 3*S*, 6*R*)-6-(Benzyloxy)-3-methyl-2-((*E*)-prop-1-en-1-yl)tetrahydro-2H

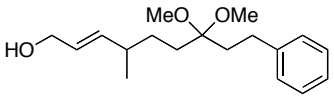
^{1}H NMR (400 MHz, C_6D_6) δ 7.35-7.38 (m, 2H), 7.14-7.19 (m, 2H), 7.05-7.11 (m, 1H), 5.67 (ddq, *J* = 0.8, 6.0, 15.2 Hz, 1H), 5.58 (ddq, *J* = 1.6, 6.8, 15.2 Hz, 1H), 5.01 (d, *J* =12.0 Hz, 1H), 4.59 (d, *J* = 12.0 Hz, 1H), 4.40 (dd, *J* = 2.8, 8.8 Hz, 1H), 3.28 (dd, *J* = 6.8, 9.6 Hz, 1H), 1.63-1.79 (m, 2H), 1.59 (d, *J* = 6.4 Hz, 3H), 1.49 (dq, *J* = 3.6, 13.2 Hz, 1H), 1.19-1.33 (m, 1H), 0.83-0.95 (m, 1H), 0.65 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 138.8, 131.3, 128.2, 127.8, 127.4, 127.2, 100.7, 82.6, 69.4, 34.9, 31.8, 31.2, 17.5, 17.1; IR (neat) 3030, 2950, 2929, 2853, 1676, 1606, 1454, 1365, 1146, 1102, 1078, 1031, 966, 735 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{22}O_2Na$ $[M+Na]^+$ 269.1517, found 269.1529.



Reaction Conditions:

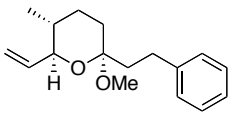
a) Hydrocinnamaldehyde, THF, 0 °C, 68%. b) PCC, Celite, DCM, rt, 81%. c) PTSA.H_2O, $CH(OMe)_3$, MeOH, 50 °C, 92%. d) 2-Vinyloxirane, Hoveyda-Grubbs 2nd, DCM, reflux, 25%. e) 6 equiv MeCuCNLi, THF, -78 °C to rt, 60 %.

Scheme A8 Synthesis of substrate **2-37**



(*E*)-7,7-dimethoxy-4-methyl-9-phenylnon-2-en-1-ol (2-37)

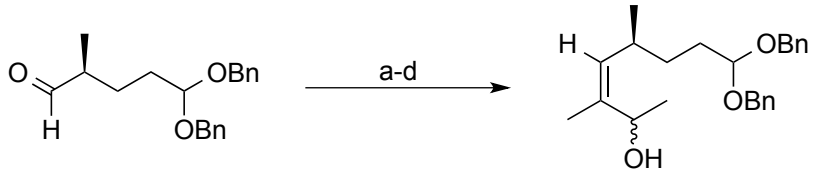
^{1}H NMR (500 MHz, C_6D_6) δ 7.05-7.21 (m, 5H), 5.48 (dt, *J* = 5.5, 15.5, 1H), 5.42 (ddt, *J* = 1.0, 7.5, 15.5 Hz, 1H), 3.86 (br, 2H), 3.07 (s, 3H), 3.06 (s, 3H), 2.62-2.66 (m, 2H), 1.95-2.04 (m, 3H), 1.65-1.80 (m, 2H), 1.34 (q, *J* = 7.0 , 2H), 0.95 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 142.1, 136.8, 128.6, 128.4, 128.3, 125.8, 102.9, 63.1, 47.2, 36.7, 34.6, 30.9, 30.4, 30.3, 20.4; IR (neat) 3403, 3025, 2955, 2869, 1667, 1603, 1454, 1374, 1299,1185, 1058, 972, 741 cm^{-1}; HRMS (APCI) calcd for $C_{18}H_{29}O_3$ $[M+H]^+$ 293.2117, found 293.2088.



(±)-(2*S*, 5*R*, 6*S*)-2-Methoxy-5-methyl-2-phenethyl-6-vinyltetrahydro-2H-pyran (2-38)

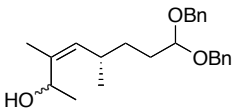
The general rearrangement procedure was followed with **2-37** (50 mg, 0.17 mmol), Re_2O_7 (4 mg, 0.008 mmol), and CD_2Cl_2 (3.0 mL). The reaction was stirred at 0 °C for 30 min, after which the cold bath was removed, the reaction was stirred for another 10 min, then was quenced with pyridine (25 mL). $BnMe_2SiH$ (5 µl) was added as an internal standard, and a ^{1}H NMR spectrum was taken of the crude mixture to determine the yield (81%, dr = 10:1). ^{1}H NMR (500 MHz,

CD_2Cl_2) δ 7.24-7.29 (m, 2H), 7.14-7.22 (m, 2H), 5.78 (ddd, *J* = 7.5, 10.0, 17.5 Hz, 1H), 5.23 (dd, *J* = 17.5, 2.0 Hz, 1H), 5.14 (dd, *J* = 10.0, 17.5 Hz, 1H), 3.60 (dd, *J* = 7.5, 10.0 Hz, 1H), 2.61 (m, 2H), 1.97 (ddd, *J* = 5.0, 12.0, 14.0 Hz, 2H), 1.81-1.85 (m, 1H), 1.76 (ddd, *J* = 4.5, 12.5, 14.0 Hz, 2H), 1.50-1.62 (m, 3H), 1.31-1.38 (m, 1H), 0.82 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, CD_2Cl_2) 142.4, 138.1,128.3, 128.2, 125.7, 116.5, 98.8, 78.1, 47.1, 38.0, 34.5, 32.9, 29.8, 27.6, 17.5; IR 3063, 3026, 2953, 2875, 1645, 1605, 1496, 1455, 1368, 1236, 1079, 1041, 932, 740 (neat) cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{24}O_2Na$ $[M+Na]^+$ 283.1674, found 283.1700.



Reagents and conditions:
a) Diethyl phosphonopropionate, NaH, THF, 0 ºC, 65%; b) DIBAL-H, CH_2Cl_2, -78 ºC, 95%; c) IBX, DMSO, 100%; d) MeMgBr, THF, 0 ºC, 100%, dr = 2.2 :1.

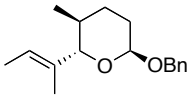
Scheme A9 Synthesis of substrate **2-39**



(5*S*, *Z*)-8,8-Bis(benzyloxy)-3,5-dimethyloct-3-en-2-ol (2-39)

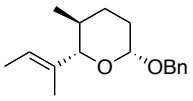
Major isomer: ^{1}H NMR (400 MHz, C_6D_6) δ 7.31-7.36 (m, 2H), 7.16-7.21 (m, 2H), 7.09-7.12 (m, 1H), 4.83 (d, *J* = 10.0 Hz, 1H), 4.71 (t, *J* = 5.6 Hz, 1H), 4.61 (dd, *J* = 4.8, 12.0 Hz, 2 H), 4.52-4.58 (m, 1H), 4.49 (d, *J* = 12.0 Hz, 2H), 2.27-2.39 (m, 1H), 1.70-1.87 (m, 2H), 1.70 (d, *J* = 0.8 Hz, 3H), 1.38-1.46 (m, 1H), 1.22-1.34 (m, 1H), 1.13 (dd, *J* = 2.8, 6.4 Hz, 3H), 0.84 (d, *J* =6.4 Hz, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 138.62, 138.58, 137.2, 132.5, 128.3, 127.8, 127.9,127.50, 127.49, 102.55, 67.4, 67.2, 65.6, 32.5, 31.4, 31.3, 21.52, 21.49, 16.8; IR (neat) 3439, 3063, 3030, 2954, 2867, 1605, 1496, 1453, 1375, 1121, 1024, 736 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{32}O_3Na$ $[M+Na]^+$ 391.2249, found 391.2263. Minor isomer: ^{1}H NMR (400

MHz, C_6D_6) δ 7.29-7.35 (m, 2H), 7.14-7.21 (m, 2H), 7.07-7.13 (m, 1H), 4.85 (d, *J* = 9.6 Hz, 1H), 4.68 (t, *J* = 5.6 Hz, 1H), 4.60 (dd, *J* = 3.6, 12.0 Hz, 2H), 5.53-4.60 (br, 1H), 4.47 (d, *J* = 12.0 Hz, 2H), 2.25-2.40 (m, 1H), 1.60-1.80 (m, 2H), 1.70 (s, 3H), 1.35-1.45 (m, 1H), 1.23-1.34 (m, 1H), 1.50 (dd, *J* = 1.2, 6.4 Hz, 3H), 0.60 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 138.8, 137.4, 132.2, 128.3, 127.6, 127.4, 102.1, 66.9, 66.8, 65.4, 32.6, 31.5, 31.4, 21.6, 21.5, 17.1; IR (neat) 3415, 3063, 3030, 2920, 1605, 1496, 1453, 1376, 1119, 1024, 898, 735 cm^{-1}; HRMS (APCI) calcd for $C_{24}H_{32}O_3Na$ $[M+Na]^+$ 391.2249, found 391.2242.



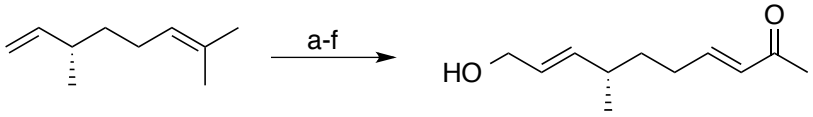
(2*S*, 3*S*, 6*S*)-6-(Benzyloxy)-2-((*E*)-but-2-en-2-yl)-3-methyltetrahydro-2H-pyran (2-40)

The general cyclization procedure was followed with **2-39** (50 mg, 0.14 mmol), Re_2O_7 (3 mg, 0.007 mmol), and CH_2Cl_2 (1.5 mL), the reaction was stirred at rt for 30 min and then was quenched with pyridine (25 mL). After evaporation of the solvent, the crude mixture was purified by flash chromatography (1%-3% ethyl acetate in hexanes) to give the product (32 mg, 91%, dr = 3:1). ^{1}H NMR (400 MHz, C_6D_6) δ 7.34-7.37 (m, 2H), 7.14-7.20 (m, 2H), 7.06-7.11 (m, 1H), 5.44 (qq, *J* = 1.2, 6.8 Hz, 1H), 4.92 (d, *J* = 3.2 Hz, 1H), 4.79 (d, *J* = 12.4 Hz, 1H), 4.43 (d, *J* = 12.4 Hz, 1H), 3.92 (d, *J* = 10.4 Hz, 1H), 1.66-1.78 (m, 2H), 1.71 (d, *J* = 1.2 Hz, 3H), 1.52-1.63 (m, 2H), 1.53 (dq, *J* = 1.2, 6.4 Hz, 3H), 1.39-1.46 (m, 1H), 0.68 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 139.0, 135.2, 128.2, 127.6, 127.2, 122.8, 96.1, 91.8, 68.1, 32.1, 20.4,27.0, 17.8, 12.7, 10.8; IR (neat) 3030, 2950, 2927, 2888, 1671, 1604, 1485, 1376, 1231, 1123, 1020, 920, 727 cm^{-1}; HRMS (APCI) calcd for $C_{17}H_{24}O_2Na$ $[M+Na]^+$ 283.1674, found 283.1665.



(2*S*, 3*S*, 6*R*)-6-(Benzyloxy)-2-((*E*)-but-2-en-2-yl)-3-methyltetrahydro-2H-pyran

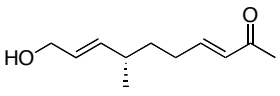
^{1}H NMR (400 MHz, C_6D_6) δ 7.32-7.37 (m, 2H), 7.13-7.19 (m, 2H), 7.05-7.10 (m, 1H), 5.42 (q, *J* = 6.4 Hz, 1H), 4.97 (d, *J* = 12.o Hz, 1H), 4.57 (d, *J* = 12.0 Hz, 1H), 4.20 (dd, *J* = 2.4, 9.2 Hz, 1H), 1.62-1.79 (m, 2H), 1,72 (s, 3H), 1.53 (d, *J* = 6.8 Hz, 3H), 1.48-1.56 (m, 1H), 1.37-1.48 (m, 1H), 0.85-0.97 (m, 1H), 0.58 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 138.9, 135.2, 128.1, 127.8, 127.2, 122.4, 101.0, 88.5, 69.4, 31.9, 31.7, 31.2, 17.0, 12.7, 12.7, 11.1; IR (neat) 3063, 3029, 2950, 2926 2854, 1672, 1607, 1454, 1375, 1308, 1148, 1056, 1021, 734 cm^{-1}; HRMS (APCI) calcd for $C_{17}H_{24}O_2Na$ $[M+Na]^+$ 283.1674, found 283.1685.



Reagents and conditions:

a) O_3, CH_2Cl_2, -78 ºC, then Me_2S, 33%; b) $(MeO)_3CH$, *p*-TsOH, MeOH, 50 ºC, 52%; c) Methyl acrylate, Grubbs-Hoveyda second generation metathesis catalyst, CH_2Cl_2; reflux, 85%; d) DIBAL-H, CH_2Cl_2, -78ºC, 58%; e) HOAc, H_2O, 95%; f) NaH, THF, 0 ºC $(EtO)_2P(O)CH_2C(O)CH_3$, 58%.

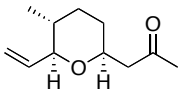
Scheme A10 Synthesis of substrate **2-41**



(7*S*,3*E*,8*E*)-10-hydroxy-7-methyldeca-3,8-dien-2-one (2-41)

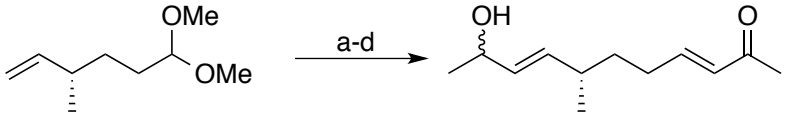
^{1}H NMR (300 MHz, CD_2Cl_2) δ 6.77 (dt, *J* = 6.9, 15.9 Hz, 1H), 6.01 (dt, *J* = 1.5, 15.9 Hz, 1H), 5.45-5.64 (m, 2H), 4.03 (d, *J* = 5.1 Hz, 2H), 2.08-2.26 (m, 4H), 2.18 (s, 3H), 1.39-1.49 (m, 2H), 0.99 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 198.6, 148.5, 137.1, 131.2, 128.5, 63.2, 36.0, 35.0, 30.2, 26.6, 20.2; IR (neat) 3426, 2957, 2924, 2868,

1672, 1625, 1427, 1363, 1256, 975 (neat) cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{18}O_2Na$ $[M+Na]^+$ 205.1204, found 205.1235.



1-((2R,5S,6R)-5-methyl-6-vinyltetrahydro-2H-pyran-2-yl)propan-2-one (2-42)

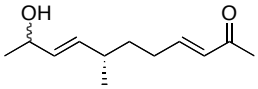
The general rearrangement procedure was followed with **2-41** (26.5 mg, 0.145 mmol), Re_2O_7 (3.5 mg, 0.007 mmol), and CH_2Cl_2 (1.5 mL). The reaction was stirred at rt for 24hr and then quenched with pyridine (25 mL). $Me_2(Bn)SiH$ (5 µl) was added as an internal standard and crude NMR was used to determine the yield of 88%. ^1H NMR (400 MHz, CH_2Cl_2) δ 5.75 (ddd, *J* = 6.8, 10.4 Hz, 17.2, 1H), 5.18 (ddd, *J* = 1.2, 2.0, 17.2 Hz, 1H), 5.11 (ddd, *J* = 0.8, 2.0, 10.4 Hz, 1H) 3.71-3.78 (m, 1H) 3.36 (dd, *J* = 7.2, 8.8 Hz, 1H), 2.62 (dd, *J* = 7.6, 15.6 Hz, 1H), 2.42 (dd, *J* = 5.2, 15.6 Hz, 1H), 2.12 (s, 3H), 1.77-1.82 (m, 1H), 1.60-1.65 (m, 1H), 1.17-1.36 (m, 3H), 0.78 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, CH_2Cl_2) δ 207.0, 137.9, 116.2, 85.1, 73.7, 50.2, 34.9, 32.3, 31.8, 30.5, 17.4; IR (neat) 3079, 2927, 2873, 2851,1716, 1457, 1425, 1356, 1225, 1152, 1072, 1018, 991, 923 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{18}O_2Na$ $[M+Na]^+$ 205.1204, found 205.1224.



Reagents and conditions:

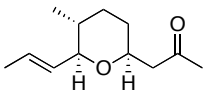
a) Methyl vinyl ketone, Grubbs-hoveyda second generation metathesis catalyst, CH_2Cl_2, reflux, 85%; b) DIBAL-H, CH_2Cl_2, -78 ºC, 45%, two steps; c) HOAc, H_2O, 82%, d) NaH, THF, $(EtO)_2P(O)CH_2C(O)CH_3$, 85%.

Scheme A11 Synthesis of substrate **2-43**



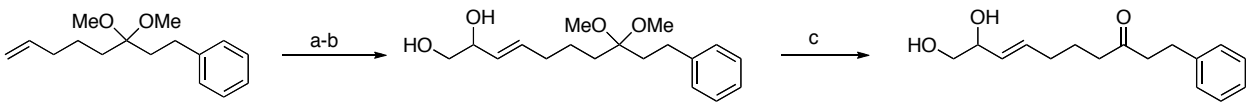
(3*E*,7*S*,8*E*)-10-hydroxy-7-methylundeca-3,8-dien-2-one (2-43)

^{1}H NMR (300 MHz, CD_2Cl_2) δ 6.76 (dt, *J* = 6.9, 15.9 Hz, 1H), 6.03 (dd, *J* = 1.2, 15.9 Hz, 1H), 5.38-5.52 (m, 2H), 4.26 (q, *J* = 6.0 Hz, 2H), 2.21 (s, 3H), 2.04-2.21 (m, 3H), 1.38-1.47 (m, 2H), 1.23 (d, *J* = 6.3 Hz, 3H), 0.98 (d, *J* = 6.6 Hz, 1.5H), 0.97 (d, *J* = 6.6 Hz, 1.5H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 198.8, 148.47, 148.42, 135.4, 135.3, 133.5, 131.2, 68.7, 68.6, 35.89, 35.87, 35.0, 30.2, 26.9, 23.6, 23.56, 20.4; IR (neat) 3431, 2966, 2925, 2870, 1672, 1625, 1453, 1364, 1255, 1140, 1059, 975 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{20}O_2Na$ $[M+Na]^+$ 219.1361, found 219.1392.



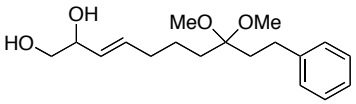
1-((2*R*,5*S*,6*S*)-5-methyl-6-((*E*)-prop-1-en-1-yl)tetrahydro-2H-pyran-2-yl) propan-2-one (2-44)

The general rearrangement procedure was followed with **2-43** (20.0 mg, 0.102 mmol), Re_2O_7 (2.5 mg, 0.005 mmol), and CH_2Cl_2 (1.5 mL). The reaction was stirred at rt for 50 min and then was quenched with pyridine (25 mL). $Me_2(Bn)SiH$ (5 μl) was added as an internal standard. Crude ^{1}H NMR was used to determine the yield of 90%. ^{1}H NMR (400 MHz, CH_2Cl_2) δ 5.68 (ddq, *J* = 0.8, 6.4, 15.2 Hz, 1H), 5.40 (ddq, *J* = 1.6, 7.6, 15.2 Hz, 1H), 3.77 (dddd, *J* = 2.4, 2.4, 6.4, 10.8 Hz, 1H) 3.35 (dd, *J* = 8.4, 8.8 Hz, 1H), 2.74 (dd, *J* = 6.4, 15.6 Hz, 1H), 2.47 (dd, *J* = 6.0, 15.6 Hz, 1H), 2.17 (s, 3H), 1.78-1.84 (m, 1H), 1.70 (dd, *J* = 1.6, 6.4 Hz, 3H), 1.64-1.69 (m, 1H), 1.20-1.37 (m, 3H), 0.78 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, CH_2Cl_2) δ 207.5, 130.9, 129.0, 85.1, 73.6, 50.3, 35.0, 32.3, 31.9, 31.0, 17.9, 17.8; IR (neat) 2925, 2872, 2852, 1716, 1676, 1453, 1357, 1224, 1186, 1169, 1151, 1069, 1014, 965 cm^{-1}; HRMS (APCI) calcd for $C_{12}H_{20}O_2Na$ $[M+Na]^+$ 219.1361, found 219.1383.



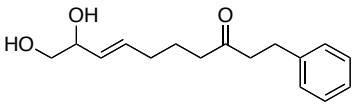
Reagents and conditions
a) Butenediol bis(triethylsilyl) ether, Grubbs-Hoveyda metathesis catalyst, CH_2Cl_2, reflux, 42%. b) Bu_4NF, THF, 97%. c) HOAc, H_2O, 85%.

Scheme A12 Synthesis of substrates **2-53** and **2-62**



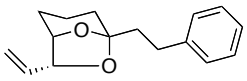
(*E*)-8,8-Dimethoxy-10-phenyldec-3-ene-1,2-diol (2-53)

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.23-7.29 (m, 2H), 7.14-7.21 (m, 3H), 5.76 (ddt, *J* = 2.0, 7.0, 15.5 Hz, 1H), 5.47 (ddt, *J* = 1.2, 6.5, 5.0 Hz, 1H), 4.11-4.18 (m, 1H), 3.54-3.60 (m, 1H), 3.39-3.45 (m, 1H), 3.24 (s, 6H), 2.51-2.56 (m, 2H), 2.24 (br, 1H), 2.04-2.10 (q, *J* = 7.0 Hz, 2H), 2.04-2.10 (br, 1H), 1.81-1.86 (m, 2H), 1.59-1.64 (m, 2H), 1.34-1.41 (m, 2H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 142.2, 133.2, 129.4, 128.3, 128.2, 125.8, 102.8, 73.1, 66.6, 47.5, 34.2, 32.3, 31.8, 30.1, 23.2; IR (neat) 3399, 3061, 3025, 2949, 2828, 1669, 1603, 1495, 1454, 1303, 1182, 1072, 971, 742 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{28}O_4Na$ $[M+Na]^+$ 331.1885, found 331.1889.



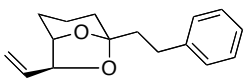
(*E*)-9,10-Dihydroxy-1-phenyldec-7-en-3-one (2-62)

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.23-7.30 (m, 2H), 7.14-7.20 (m, 3H), 5.69 (ddt, *J* = 1.2, 6.8, 15.2 Hz, 1H), 5.43 (ddt, *J* = 1.4, 6.4, 15.2 Hz, 1H), 4.09-4.17 (m, 1H), 3.56 (dd, *J* = 2.0, 10.8 Hz, 1H), 3.41 (dd, *J* = 7.4, 11.2 Hz, 1H), 2.85 (t, *J* = 7.4 Hz, 2H), 2.85 (br, 1H), 2.71 (t, *J* = 7.4 Hz, 2H), 2.71 (br, 1H), 2.38 (t, *J* = 7.4 Hz, 2H), 2.01 (q, *J* = 7.4 Hz, 2H), 1.62 (p, *J* = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 210.0, 141.4, 132.5, 129.6, 128.4, 128.3, 126.0, 73.0, 66.6, 44.1, 42.0, 31.6, 29.6, 23.0; IR (neat) 3378, 3030, 2929, 1709, 1603, 1495, 1453, 1408, 1372, 1074, 1029, 972, 748 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{22}O_3Na$ $[M+Na]^+$ 285.1467, found 285.1470.



(±)-(1*R*, 5*S*, 7*S*)-5-Phenethyl-7-vinyl-6,8-dioxabicyclo[3.2.1]octane (2-55)

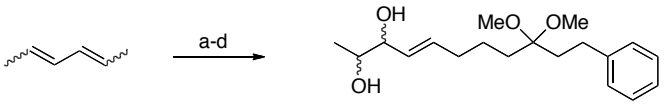
The general rearrangement procedure was followed with **2-53** (100 mg, 0.32 mmol), Re_2O_7 (8 mg, 0.02 mmol), and CH_2Cl_2 (5.0 mL). The reaction was stirred at rt for 21 h then was quenched with pyridine (25 mL). The crude material was purified by flash chromatography (1%-3% ethyl acetate in hexanes) to give the product (39 mg, 49%, dr = 4:3, for substrate **2-62**, 40%, dr = 4:3). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.22-7.29 (m, 2H), 7.18-7.22 (m, 2H), 7.12-7.18 (m, 1H), 6.05 (ddd, *J* = 6.8, 10.4, 17.2 Hz, 1H), 5.42 (dt, *J* = 1.6, 17.2 Hz, 1H), 5.29 (ddd, J = 1.2, 1.6, 10.4, 1H), 4.49 (ddq, J = 1.2, 4.4, 6.8, 1H), 4.30 (t, J = 4.0), 2.73-2.79 (m, 2H), 1.94-2.00 (m, 2H), 1.90-2.00 (m, 1H), 1.72-1.83 (m, 1H), 1.63-1.79 (m, 2H), 1.53-1.63 (m, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 142.7, 133.3, 128.34, 128.25, 125.6, 118.4, 108.7, 81.6, 77.7, 39.9, 33.4, 29.0, 24.6, 17.1; IR (neat) 3062, 2954, 2915, 1603, 1496, 1456, 1373, 1253, 1236, 1099, 1028, 988, 862,749 cm^{-1}; HRMS (APCI) calcd for $C_{16}H_{21}O_2$ $[M+H]^+$ 245.1442, found 245.1521.



(±)-(1*R*, 5*S*, 7*R*)-5-Phenethyl-7-vinyl-6,8-dioxabicyclo[3.2.1]octane (2-54)

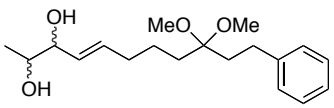
^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.23-7.28 (m, 2H), 7.13-7.21 (m, 3H), 5.88 (ddd, *J* = 7.2, 10.0, 17.2 Hz, 1H), 5.24 (ddd, *J* = 1.2, 1.6, 17.2 Hz, 1H), 5.10 (ddd, *J* = 0.8, 1.6, 10.0 Hz, 1H), 4.44 (dd, *J* = 0.4, 3.6 Hz, 1H), 4.20 (br, 1H), 2.72-2.78 (m, 2H), 1.94-2.00 (m, 2H), 1.85-1.94 (m, 1H), 1.75-1.84 (m, 1H), 1.61-1.69 (m, 3H), 1.54-1.61 (m, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 142.6, 139.0, 128.32, 128.27, 125.6, 115.3, 109.3, 80.8, 79.8, 39.6, 33.9, 29.4, 28.1, 17.1; IR (neat) 3062, 3026, 2925, 2871, 1728, 1607, 1496, 1457, 1374, 1343, 1278, 1234, 1179, 1111,

1085, 1032, 1004, 924, 750 cm^{-1}; HRMS (APCI) calcd for $C_{16}H_{21}O_2$ $[M+H]^+$ 245.1442, found 245.1581.



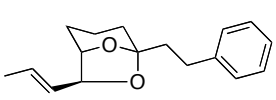
Reagents and conditions
a) AD-Mix β, $CH_3SO_2NH_2$, *t*BuOH, H_2O, 0 °C. b) TESCl, imidazole, DMAP, DMF, 74% (two steps). c) Alkenyl ketal, Grubbs-Hoveyda metathesis catalyst, CH_2Cl_2, reflux, 27%. d) Bu_4NF, THF, 75%,

Scheme A13 Synthesis of substrate **2-59**



(*E*)-9,9-dimethoxy-11-phenylundec-4-ene-2,3-diol (2-59)

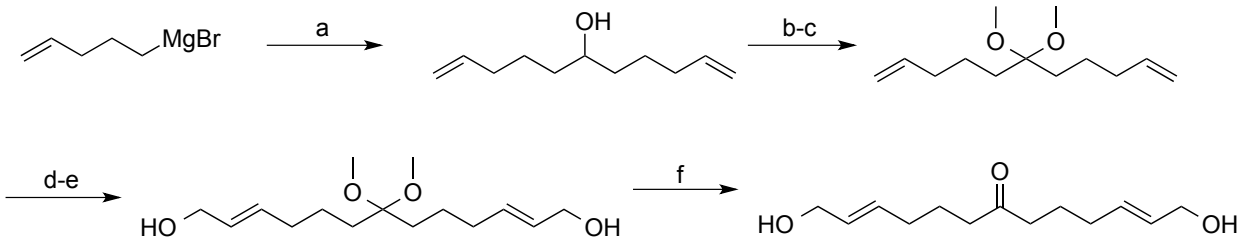
^1H NMR (400 MHz, CD_2Cl_2) δ 7.25-7.30 (m, 2H), 7.15-7.21 (m, 3H), 5.75 (ddt, *J* = 0.8, 6.8, 15.2 Hz, 1H), 5.46 (ddt, *J* = 1.4, 7.2, 15.2 Hz, 1H), 3.74 (t, *J* = 6.8 Hz, 1H), 3.60 (t, *J* = 6.4 Hz, 1H), 3.15 (s, 6H), 2.51-2.56 (m, 2H), 2.08 (q, *J* = 6.8 Hz, 2H), 1.82-1.88 (m, 2H), 1.60-1.65 (m, 2H), 1.35-1.43 (m, 2H), 1.12 (d, *J* =6.0 Hz, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 142.2, 133.9, 130.0, 128.4, 128.2, 125.8, 102.9, 77.8, 70.8, 47.5, 34.2, 32.4, 31.9, 30.1, 23.2, 18.8; IR (neat) 3411, 3061, 3025, 2951, 2829, 1669, 1603, 1495, 1454, 1368, 1266, 1181, 1055, 972, 742 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{30}O_4Na$ $[M+Na]^+$ 345.2042, found 345.2051.



(1*R*, 5*S*, 7*R*)-5-Phenethyl-7-((*E*)-prop-1-en-1-yl)-6,8-dioxabicyclo[3.2.1]octane (2-60)

The general cyclization procedure was followed with **2-59** (50 mg, 0.16 mmol), Re_2O_7 (4 mg, 0.008 mmol), and CH_2Cl_2 (5.0 mL). The reaction was stirred at rt for 15 h and then was quenched with pyridine (25 mL). The crude mixture was purified by flash chromatography (1%-

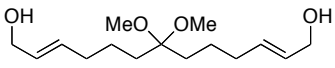
3% ethyl acetate in hexanes) to give the product (21 mg, 53%, dr = 7.5 : 1). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.23-7.29 (m, 2H), 7.18-7.22 (m, 2H), 7.12-7.18 (m, 1H), 5.67 (ddt, *J* = 0.4, 6.4, 15.2 Hz, 1H), 5.52 (ddt, *J* = 1.4, 8.0, 15.2 Hz, 1H), 4.40 (d, *J* = 8.0 Hz, 1H), 2.72-2.78 (m, 2H), 1.91-1.98 (m, 2H), 1.83-1.91 (m, 1H), 1.73-1.81 (m, 1H), 1.69 (dd, *J* = 1.6, 6.4 Hz, 3H), 1.59-1.66 (m, 3H), 1.52-1.58 (m, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 142.7, 132.1, 128.33, 128.25, 127.3, 125.6, 108.9, 80.7, 79.9, 39.6, 34.0, 29.4, 28.1, 17.3, 17.1; IR (neat) 3061, 3026, 2950, 1671, 1603, 1496, 1453, 1373, 1344, 1175, 1067, 1024, 990, 906, 751 cm^{-1}; HRMS (APCI) calcd for $C_{17}H_{23}O_2$ $[M+H]^+$ 259.1698, found 259.1673.



Reaction Conditions:

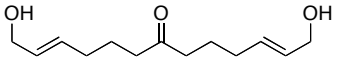
a) Ethyl Formate , THF, 0 °C, 82%. b) PCC, Celite, DCM, rt, 81%. c) PTSA.H_2O, $CH(OMe)_3$, MeOH, 50 °C, 92%. d) Methyl Acrylate, Hoveyda-Grubbs 2nd, DCM, reflux, 68.2%. e) DIBAL, DCM, -78 °C, 77%. f) 50% HOAc, rt, 84%.

Scheme A14 Synthesis of substrates **2-63** and **2-66**



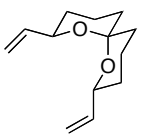
(2*E*,11*E*)-7,7-dimethoxytrideca-2,11-diene-1,13-diol (2-63)

^{1}H NMR (400 MHz, C_6D_6) δ 5.53-5.75 (m, 4H), 4.06 (br, 4H), 3.22-3.38 (br, 2H), 3.07 (s, 6H), 2.00 (q, *J* = 3.2 Hz, 4H), 1.65-1.71 (m, 4H), 1.42 (p, *J* = 7.6 Hz, 4H); ^{13}C NMR (100 MHz, C_6D_6) δ 131.2, 130.3, 103.3, 62.9, 47.2, 32.3, 32.1, 23.5; IR (neat) 3384, 2946, 1710, 1670, 1457, 1369, 1314, 1180, 1088, 970 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{28}O_4Na$ $[M+Na]^+$ 295.1885, found 295.1860.



(2*E*,11*E*)-1,13-dihydroxytrideca-2,11-dien-7-one (2-66)

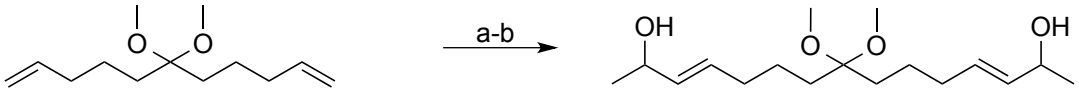
^{1}H NMR (400 MHz, CD_2Cl_2) δ 5.60-5.70 (m, 4H), 4.06 (br, 4H), 2.42 (t, *J* = 7.2 Hz, 4H), 2.25-2.35 (br, 2H), 2.02-2.09 (m, 4H), 1.66 (p, *J* = 7.2 Hz, 4H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 211.0, 131.5, 130.1, 63.2, 41.8, 31.5, 23.1; IR (neat) 3250, 3052, 3011, 2933, 2865, 1698, 1457, 1415, 1371, 1266, 1088, 1016, 970 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{22}O_3Na$ $[M+Na]^+$ 249.1467, found 249.1451.



(±)-(2*R*, 6*R*, 8*R*)-2,8-Divinyl-1,7-dioxaspiro[5.5]undecane (2-64)

The general rearrangement procedure was followed with **44** (14 mg, 0.051 mmol), Re_2O_7 (1.2 mg, 0.0025 mmol), and CD_2Cl_2 (1.0 mL). The reaction was stirred at rt for 30 min. $BnMe_2SiH$ (5 µl) was added as an internal standard, and a ^{1}H NMR spectrum was taken of the crude mixture to show an 88% yield and 1:1 ratio of two stereoisomers. Additional stirring (>12 h) resulted in the mixture giving essentially a single diastereomer (dr > 20:1) with a decrease in overal yield (60%). The general rearrangement cyclization procedure was also followed with **2-66** (50 mg, 0.221 mmol), Re_2O_7 (5.4 mg, 0.011 mmol), and CD_2Cl_2 (3.0 mL). The reaction was stirred at rt for 30 min. $BnMe_2SiH$ (5 µl) was added as an internal standard, and a ^{1}H NMR spectrum was taken of the crude mixture to show a 94% yield and 1:1 ratio of two stereoisomers. Additional stirring (48 h) with the addition of MeOH showed isomerization of the mixture to give essentially a single stereoisomer with a decrease in overall yield (61%). ^{1}H NMR (400 MHz, C_6D_6) δ 5.89 (ddd, *J* = 5.2, 10.4, 17.2 Hz, 2H), 5.30 (dt, *J* = 1.6, 17.2 Hz, 2H), 5.02 (dt, *J* = 1.6, 10.4 Hz, 2H), 4.17 (ddddd, *J* = 1.2, 1.6, 2.4, 5.6, 11.2 Hz, 2H), 2.03 (dq, *J* = 4.0, 13.2 Hz, 2H), 1.63 (dddd, *J* = 1.6, 2.4, 4.0, 13.2 Hz, 2H), 1.41-1.49 (m, 2H), 1.34-1.41 (m, 2H), 1.17-

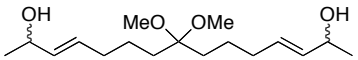
1.34 (m, 4H); ^{13}C NMR (100 MHz, C_6D_6) δ 140.0 113.2, 95.9, 69.7, 35.2, 31.1, 18.8; IR 3012, 2927, 2854, 1646, 456, 1374, 1279, 1220, 981, 917 (neat) cm^{-1}; HRMS (APCI) calcd for $C_{13}H_{21}O_2$ $[M+H]^+$ 209.1542, found 209.1567.



Reagents and conditions:

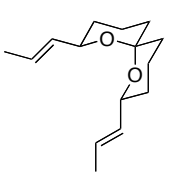
a) Methyl vinyl ketone, Grubbs-Hoveyda metathesis catalyst, CH_2Cl_2, reflux, 44%; b) DIBAL-H, CH_2Cl_2, -78 ºC, 81%.

Scheme A15 Synthesis of substrate **2-67**



(3*E*, 12*E*)-8,8-dimethoxypentadeca-3,12-diene-2,14-diol (2-67)

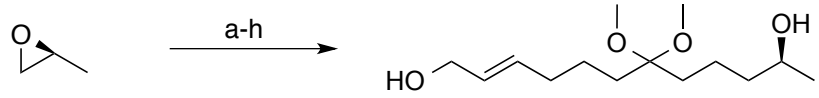
^{1}H NMR (400 MHz, C_6D_6) δ 5.52-5.62 (m, 4H), 4.21 (p, *J* = 5.2 Hz, 2H), 3.07 (s, 6H), 2.89 (br, 2H), 1.94-2.0 (m, 4H), 1.65-1.70 (m, 4H), 1.37-1.45 (m, 4H), 1.25 (d, *J* = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, C_6D_6) δ 135.5, 129.1, 103.2, 68.1, 47.1, 32.1, 32.0, 23.6, 23.5; IR (neat) 3388, 2950, 1711, 1670, 1455, 1368, 1294, 1181, 1060, 969, 941, 864 cm^{-1}; HRMS (APCI) calcd for $C_{17}H_{32}O_4Na$ $[M+Na]^+$ 323.2198, found 323.2199.



(±)-(2*R*, 6*R*, 8*R*)-2,8-Di((*E*)-prop-1-en-1-yl)-1,7-dioxaspiro[5.5]undecane (2-68)

The general rearrangement procedure was followed with **2-67** (44 mg, 0.15 mmol), Re_2O_7 (4 mg, 0.007 mmol), and CD_2Cl_2 (3.0 mL). The reaction was stirred at 0 °C for 60 min. $BnMe_2SiH$ (5 µl) was added as an internal standard, and a ^{1}H NMR spectrum was taken of the crude mixture to show a 54% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 (ddq, *J* = 1.2, 6.4, 15.2 Hz, 2H), 5.52 (ddq, *J* = 1.6, 6.4, 15.2 Hz, 2H), 4.04 (ddp, *J* = 1.2, 6.4, 11.6 Hz, 2H), 1.94

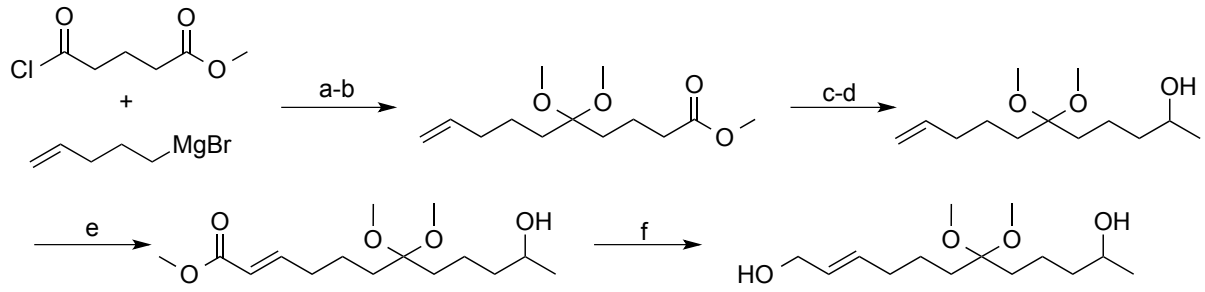
(tq, J = 4.0, 13.2 Hz, 2H), 1.71 (dd, J = 1.6, 6.4 Hz, 6H), 1.52-1.67 (m, 6H), 1.36-1.45 (m, 2H), 1.25-1.36 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.7, 126.4, 96.4, 69.6, 35.1, 31.0, 18.8, 17.9; IR 2937, 2867, 1731, 1676, 1452, 1438, 1377, 1279, 1219, 1201,1036, 979, 964 (neat) cm^{-1}; HRMS (APCI) calcd for $C_{15}H_{25}O_2$ $[M+H]^+$ 237.1855, found 237.1837.



Reagents and conditions:

a) Butenylmagnesium bromide, CuCN, Et_2O, 0 ºC, 30%; b) $Me_3CC(O)Cl$, Et_3N, DMAP, CH_2Cl_2; c) O_3, CH_2Cl_2, -78 ºC, then Me_2S, 27%, 2 steps; d) Pentenylmagnesium bromide, Et_2O, 0 ºC, 56%; e) PCC, Celite, CH_2Cl_2, 86%; f) $(MeO)_3CH$, *p*-TsOH, MeOH, 100%; g) Methyl acrylate, Grubbs-Hoveyda second generation metathesis catalyst, CH_2Cl_2, reflx, 96%; h) DIBAL-H, CH_2Cl_2, -78 ºC, 66%.

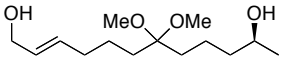
Scheme A16 Synthesis of substrate **2-69**



Reaction Conditions:

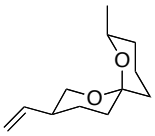
a) THF, -78 °C to rt, 77%. b) PTSA•H_2O, $CH(OMe)_3$, MeOH, 50 °C, 95%. c) DIBAL, DCM, -78 °C, 74%. d) MeMgBr, Et_2O, 0 °C to rt, 90%. e) Methyl Acrylate, Hoveyda-Grubbs 2nd, DCM, reflux. 82%. f) DIBAL, DCM, -78 °C, 72%.

Scheme A17 Synthesis of substrate *rac*-**2-69**



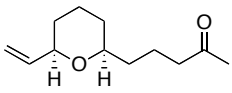
(*S, E*)-7,7-dimethoxydodec-2-ene-1,11-diol (2-69)

^{1}H NMR (400 MHz, C_6D_6) δ 5.58-5.71 (m, 2H), 4.04 (br, 2H), 3.63-3.70 (m, 1H), 3.09 (s, 3H), 3.08 (s, 3H), 1.95-2.05 (m, 2H), 1.62-1.76 (m, 4H), 1.28-1.60 (m, 6H), 1.12 (d, *J* = 6.0, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 131.1, 130.5, 103.4, 67.2, 62.9, 47.2, 39.4, 32.6, 32.1, 31.8, 23.6, 23.4, 20.1; IR (neat) 3396, 2949, 2871, 1669, 1458, 1372, 1131, 1041, 971 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{28}O_4Na$ $[M+Na]^+$ 283.1885, found 283.1915; $[\alpha]_D$ = + 6.26 (c 0.91, $CHCl_3$); ee>99% as determined by Mosher ester analysis.



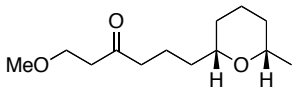
(2*S*, 6*R*, 8*R*)-2-methyl-8-vinyl-1,7-dioxaspiro[5.5]undecane (2-70)

The general rearrangement procedure was followed with **2-69** (50 mg, 0.19 mmol) and Re_2O_7 (5 mg, 0.01 mmol) in CD_2Cl_2 (3.0 mL), the reaction was stirred at rt for 24 h. $BnMe_2SiH$ (5 μl) was added as an internal standard, and a ^{1}H NMR spectrum was taken of the crude mixture to show a 61% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (ddd, *J* = 5.2, 10.4, 17.2 Hz, 1H), 5.26 (dt, *J* = 1.6, 17.2 Hz, 1H), 5.09 (dt, *J* = 1.6, 10.4 Hz, 1H), 4.08 (ddddd, *J* = 1.2, 1.6, 2.4, 5.2, 10.4 Hz, 1H)，3.72 (ddddd, *J* = 2.0, 6.0, 6.0, 6.0, 8.0 Hz, 1H), 1.86-2.02 (m, 2H), 1.49-1.70 (m, 6H), 1.35-1.46 (m 2H), 1.18-1.35 (m, 2H), 1.15 (d, *J* = 6.4, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8, 114.0, 96.3, 69.5, 65.2, 35.2, 35.1 32.7, 30.8, 21.9, 18.9, 18.8; IR (neat) 2924, 2853, 1658, 1459, 1377, 1224, 1087, 992 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{20}O_2Na$ $[M+Na]^+$ 219.1361, found 219.1387. $[\alpha]_D$ = – 43.2 (c 0.31, $CHCl_3$); ee: 96% as determined by HPLC analysis using a Phenomenex Lux 5m Cellulose-3 column (250 x 4.60 mm) with MeOH/H_2O (60/40, v/v) as the mobile phase.



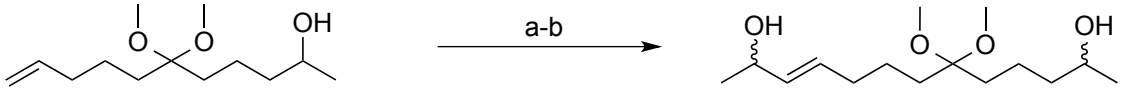
5-((2*S*, 6*R*)-6-vinyltetrahydro-2H-pyran-2-yl)pentan-2-one (2-75)

^{1}H NMR (400 MHz, CD_2Cl_2) δ 5.82 (ddd, *J* = 5.2, 10.4, 17.2 Hz, 1H), 5.18 (dt, *J* = 1.6, 17.2 Hz, 1H), 5.02 (dt, *J* = 1.6, 10.4 Hz, 1H), 3.77 (ddddd, *J* = 1.2, 1.6, 2.4, 5.2, 10.8 Hz, 1H), 3.30 (dddd, *J* = 2.0, 5.2, 7.6, 10.8 Hz, 1H), 2.41 (t, *J* = 7.2 Hz, 2H), 2.08 (s, 3H), 1.78-1.85 (m, 2H), 1.35-1.70 (m, 6H), 1.08-1.27 (m, 4H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 208.7, 140.0, 113.5, 78.0, 77.3, 43.5, 35.8, 31.6, 31.3, 29.6, 23.5, 20.0; IR 3080, 2933, 2857, 1715, 1647, 1440, 1410, 1364, 1201, 1167, 1090, 1046, 990,919 (neat) cm^{-1}; HRMS (APCI) calcd for $C_{12}H_{21}O_2$ $[M+H]^+$ 197.1542, found 197.1566.



1-methoxy-6-((2S,6S)-6-methyltetrahydro-2H-pyran-2-yl)hexan-3-one (2-76)

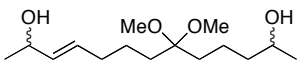
^{1}H NMR (400 MHz, CD_2Cl_2) δ 3.58 (t, *J* = 6.4, 2H), 3.36 (ddddd, *J* = 2.0, 6.0, 6.0, 6.0, 11.2, 1H), 3.22 (dddd, *J* = 2.0, 5.2, 7.2, 10.8, 1H), 1.72-1.81 (m, 1H), 1.58-1.78 (m, 1H), 1.47-1.58 (m, 4H), 1.27-1.47 (m, 3H), 1.09 (d, *J* = 6.4, 3H), 1.05-1.15 (m, 1H). ^{13}C NMR (100 MHz, CD_2Cl_2) δ 209.0, 77.3, 73.6, 67.6, 58.5, 43.1, 42.7, 35.9, 33.4, 31.3, 23.7, 22.0, 19.8. IR (neat) 2967, 2930, 2860, 1714, 1452, 1387, 1373, 1322, 1202, 1118, 1083, 1041, 963 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{24}O_3Na$ $[M+Na]^+$ 251.1623, found 251.1637.



Reagents and conditions:

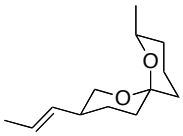
a) Methyl vinyl ketone, Grubbs-Hoveyda metathesis catalyst, CH_2Cl_2, reflux, 53%; b) DIBAL-H, CH_2Cl_2, -78 ºC, 61%.

Scheme A18 Synthesis of substrate **2-71**



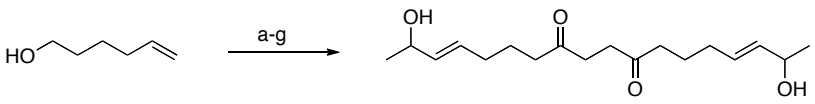
(*E*)-8,8-dimethoxytridec-3-ene-2,12-diol (2-71)

^{1}H NMR (400 MHz, C_6D_6) δ 5.48-5.64 (m, 2H), 4.20 (p, *J* = 6.0 Hz, 2H), 3.65 (q, *J* = 5.2 Hz, 1H), 3.091 (s, 3H), 3.087 (s, 3H), 2.79 (d, *J* = 14.8 Hz, 1H), 2.52 (d, *J* = 15.6 Hz, 1H), 1.95-2.02 (q, *J* = 7.2 Hz, 2H), 1.66-1.77 (m, 3H), 1.27-1.59 (m, 6H), 1.24 (d, *J* = 6.4 Hz, 3H), 1.10 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 135.73, 135.68, 129.1, 103.3, 68.12,68.09, 67.16, 67.10, 47.1, 39.4, 32.61, 32.59, 32.0, 31.8, 31.7, 23.7, 23.53. 23. 48, 23.44, 20.12, 20.08 IR (neat) 3391, 2952, 2830, 1170, 1670, 1457, 1370, 1313, 1126, 1064, 969, 941 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{30}O_4Na$ $[M+Na]^+$ 297.2042, found 297.2065.



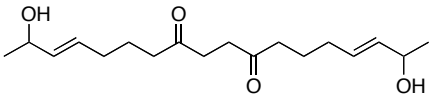
(2*S*, 6*R*, 8*R*)-2-methyl-8-((*E*)-prop-1-en-1-yl)-1,7-dioxaspiro[5.5]undecane (2-72)

The general cyclization procedure was followed with **2-71** (50 mg, 0.18 mmol) and Re_2O_7 (4 mg, 0.009 mmol) in $CDCl_3$ (3.0 mL). The mixture was stirred at rt for 30 min after which the reaction was quenched with pyridine (25 mL). $BnMe_2SiH$ (5 μl) was added as an internal standard, and a ^{1}H NMR spectrum was taken of the crude mixture to show a 65% yield. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 5.69 (ddq, *J* = 1.2, 6.4, 15.2 Hz, 1H), 5.51 (ddq, *J* = 1.6, 6.0, 15.2 Hz, 1H), 4.02 (ddp, *J* = 1.2, 6.0, 11.6 Hz, 1H), 3.72 (ddq, *J* = 2.0, 6.4, 11.2 Hz, 1H), 1.85-1.99 (m, 2H), 1.71 (dd, *J* = 2.4, 6.4, 3H), 1.49-1.66 (m, 6H), 1.41 (ddd, *J* = 4.4, 8.4, 13.2, 2H), 1.28-1.36 (m, 1H), 1.18-1.28 (m, 1H), 1.15 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.8, 126.2, 96.3, 69.5, 65.1, 35.21., 35.16, 32.8, 31.0, 21.9, 18.9, 18.8, 17.9; IR (neat) 2936, 2869, 1676, 1440, 1383, 1280, 1224, 1204,1087, 991, 964 cm^{-1}; HRMS (APCI) calcd for $C_{13}H_{23}O_2$ $[M+H]^+$ 211.1698, found 211.1716.



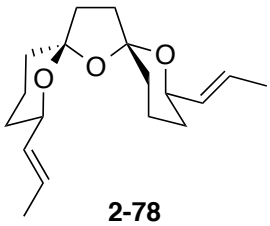
Reagents and conditions
a) PCC, Celite, CH_2Cl_2. b) MeMgBr, THF, 0 °C, 58% (two steps). c) PCC, Celite, CH_2Cl_2. d) (*Z*)-Hex-3-ene-2,5-diol, Grubbs-Hoveyda 2nd generation metathesis catalyst, CH_2Cl_2. e) TBDMSCl, imidazole, DMAP, DMF, 50% (three steps). f) LDA, THF, 0 °C, then $CuCl_2$, 26%. g) Bu_4NF, THF.

Scheme A19 Synthesis of substrate **2-77**

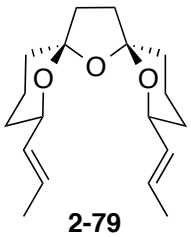


(*3E,15E*)-2,17-dihydroxyoctadeca-3,15-diene-8,11-dione (2-77)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.48-5.61 (m, 4H), 4.25 (q, *J* = 6.0 Hz, 2H), 2.65 (s, 4H), 2.46 (t, *J* = 7.2 Hz, 4H), 2.02 (q, *J* = 6.8 Hz, 4H), 1.67 (p, *J* = 7.2 Hz, 4H), 1.24 (d, *J* = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.6, 135.2, 129.7, 68.8, 41.9, 36.1, 31.5, 23.4, 22.9; IR (neat) 3406, 2968, 2928, 1707, 1639, 1450, 1369, 1139, 1062, 970, 938 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{30}O_4Na$ $[M+Na]^+$ 333.2042, found 333.2075.



2-78



2-79

Spirotricycles 2-78 and 2-79

The general rearrangement procedure was followed with **2-77** (110 mg, 0.354 mmol), Re_2O_7 (8.6 mg, 0.018 mmol), and CH_2Cl_2 (3.0 mL). The reaction was stirred at 0 °C for 2 h and then was quenched with pyridine (25 mL). After evaporation of the solvent, the crude mixture was purified by flash chromatography 1%-3% ethyl acetate in hexanes) to give the product (87 mg, 84%, dr = 1:1, **2-78**: 43 mg, **2-79**: 44 mg).

Faster eluting major isomer **2-78**: ^{1}H NMR (400 MHz, CD_2Cl_2) δ 5.60 (ddq, *J* = 0.8, 6.4, 15.2 Hz, 2H), 5.40 (ddq, *J* = 1.6, 6.8, 15.2 Hz, 2H), 4.21 (dd, *J* = 7.2, 11.2 Hz, 2H), 1.85-1.98 (m,

4H), 1.79-1.83 (m, 2H), 1.65 (d, J = 6.4 Hz, 6H), 1.54-1.70 (m, 8H), 1.20-1.31 (m, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 133.0, 125.8, 106.8, 71.4, 36.7, 34.8, 31.2, 20.3, 17.5; IR (neat) 3023, 2981, 2937, 2864, 1731, 1676, 1452, 1439, 1375, 1314, 1266, 1231,1072, 1028, 968, 874 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{28}O_3Na$ $[M+Na]^+$ 315.1936, found 315.1919. The stereochemical arrangement was established by HPLC analysis using a Phenomenex Lux 5m Cellulose-3 column (250 x 4.60 mm) with MeOH/H_2O (Black line: 60/40 or Purple Line: 70/30, v/v) as the mobile phase.

Slower eluting minor isomer **2-79**: ^{1}H NMR (400 MHz, CD_2Cl_2) δ 5.58 (ddq, J = 0.8, 6.4, 15.6 Hz, 2H), 5.41 (ddq, J = 1.6, 6.8, 15.6 Hz, 2H), 4.28 (dd, J = 7.2, 10.8 Hz, 2H), 2.01-2.07 (m, 2H), 1.81-1.91 (m, 2H), 1.73-1.79 (m, 2H), 1.65 (d, J = 6.4 Hz, 6H), 1.48-1.63 (m, 8H), 1.22-1.33 (m, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 133.0, 126.2, 107.2, 72.6, 37.4, 34.8, 31.1, 20.1, 17.5; IR (neat) 3022, 2936, 2864, 1676, 1453, 1439, 1377, 1301, 1233, 1165, 1073, 1028, 964, 866 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{28}O_3Na$ $[M+Na]^+$ 315.1936, found 315.1918.

The two stereoisomers were resubjected to the following isomerization condition: 7.2 mg Re_2O_7 (0.015 mmol) and 1.5 ml CD_2Cl_2. After stirring at 0 °C for 4 h, the isomerizations were quenched with pyridine (25 mL). $BnMe_2SiH$ (5 µl) was added as an internal standard to each isomerization mixture, and a ^{1}H NMR spectrum was taken of the crude mixture to show that the equilibration of **2-78** provided 51% of **2-78** and 27% of **2-79**. The equilibration of **2-79** provided 52% of **2-78** and 29 % of **2-79**. Thus, after one cycle of isomerization: a total yield of 64% could be obtained for **2-78** and a total yield of 54% could be obtained for **2-79**.

APPENDIX B

CASCADE APPROACH TO STEREOSELECTIVE POLYCYCLIC ETHER FORMATION: EPOXIDES AS TRAPPING AGENTS FOR TRANSPOSING ALLYLIC ALCOHOL

General Information ^{1}H NMR and ^{13}C NMR spectra were taken on a Bruker Avance 300 spectrometer at 300 MHz and 75 MHz respectively, a Bruker Avance 400 spectrometer at 400 MHz and 100 MHz, a Bruker Avance 500 spectrometer at 500 MHz and 125 MHz if specified. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. The solvent peak was used as a reference value, for ^{1}H NMR: $CDCl_3$ = 7.27 ppm, CD_2Cl_2 = 5.31 ppm, C_6D_6 = 7.16 ppm, for ^{13}C NMR: $CDCl_3$ = 77.23, $CDCl_3$ = 53.52, C_6D_6 = 128.37. Data are reported as follows: m=multiplet, s = singlet; d = doublet; t = triplet; q = quartet; p = pentet; h = hexet; dd = doublet of doublets; dt = doublet of triplets; br = broad. High resolution and low resolution mass spectra were collected on a VG 7070 spectrometer. Infrared (IR) spectra were taken on a Mattson Cygnus 100 spectrometer. Samples for IR were prepared as thin films on a NaCl plates by dissolving the corresponding compounds in CH_2Cl_2 followed by evaporation of the CH_2Cl_2. Methylene chloride was distilled under N_2 from CaH_2. Analytical TLC was performed on E. Merck pre-coated (25 mm) silica gel 60F-254 plates. Visualization was done under UV (254 nm).

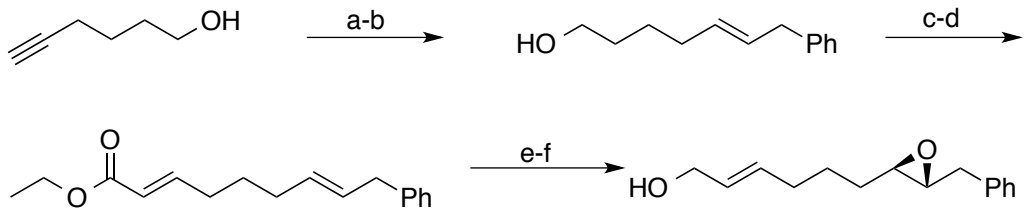
Flash chromatography was done using Silicycle SiliaFlash P60 40-63 μm silica gel (230-400 mesh). Reagent grade ethyl acetate, diethyl ether, pentane and hexanes (commercial mixture) were purchased from EM Science and used as is for chromatography. All reactions were performed in oven or flame-dried glassware under a positive pressure of N_2 with magnetic stirring unless otherwise noted.

Preparation of Re_2O_7 supported on SiO_2

A slurry of 1.8 g of SiO_2 and 200mg of Re_2O_7 in Et_2O was stirred at rt for 3 h, followed by removal of Et_2O under reduced pressure, the obtained powder was dried under vacuum overnight. The catalyst was stored in dessicator and shielded from light by wrapping the sample container with aluminium foil.

General procedure for rearrangement cyclization catalyzed by Re_2O_7

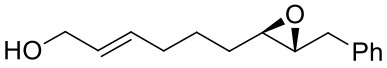
To a solution (~10 mM) of corresponding substrate in CH_2Cl_2 was added 0.05 equivalent of Re_2O_7, the reaction mixture was stirred at rt (unless otherwise mentioned in the substrate tables) and monitored by TLC until complete consumption of the starting material, then the reaction was quenched with a few drops of pyridine or triethylamine and the solvent was removed under vacuum, followed by purification by flash chromatography or preparation TLC to give the product.



Reaction Conditions:

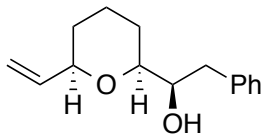
a) DIBAL, hexanes, then I_2, THF, -78 ºC, 51%; b) $PhCH_2MgCl$, $Cl_2Pd(dppf)_2$, THF, 20 ºC, 95%; c) PCC, celite, DCM, 20 ºC; d) 60% NaH dispersed in mineral oil, triethyl phosphonoacetate, THF, 0 ºC,77% for two steps; e) Shi ketone derived from D-fructose, oxone, $Na_2B_4O_7$, $Na_2(EDTA)$, K_2CO_3, Nu_4NHSO_4, MeCN, H_2O, 0 ºC, 39%; f) DIBAL, DCM, -78 ºC, 91%.

Scheme B1 Synthesis of substrate **3-15**



(*E*)-6-((2*R*,3*R*)-3-benzyloxiran-2-yl)hex-2-en-1-ol (3-15)

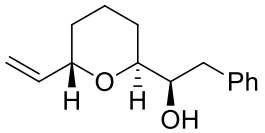
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.38 (m, 2H), 7.23-7.30 (m, 3H), 5.57-5.72 (m, 2H), 4.08 (d, *J* = 5.2, 2H), 2.90-2.98 (m, 2H), 2.77-2.86 (m, 2H), 2.03-2.13 (m, 2H), 1.83 (br, 1H), 1.45-1.65 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) 137.4, 132.3, 129.6, 128.9, 128.6, 126.6, 63.5, 58.8, 58.6, 38.5, 31.8, 31.3; IR (neat) 3407, 3027, 2973, 2929, 2857, 1669, 1604, 1494, 1370, 1088, 1001, 971, 932, 743 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{20}O_2Na$ $[M + Na]^+$ 255.1361, found 255.1387.



(*R*)-2-phenyl-1-((2*S*,6*R*)-6-vinyltetrahydro-2H-pyran-2-yl)ethanol (3-16)

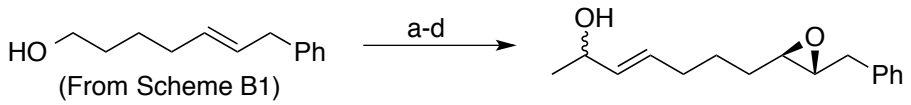
The general rearrangement procedure was followed with **3-15** (28.0 mg, 0.121 mmol), Re_2O_7 (2.9 mg, 0.006 mmol), and CH_2Cl_2 (12 mL). The reaction was stirred at 20 °C for 4 h and then quenched with five drops of pyridine. After evaporation of the solvent, the crude mixture was purified by flash chromatography (10%-20% ethyl acetate in hexanes) to give the product (25.0 mg, 89%, dr = 59:44). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.35 (m, 2H), 7.21-7.28 (m, 3H), 5.89 (ddd, *J* = 5.2, 10.8, 17.2, 1H), 5.26 (dt, *J* = 1.6, 17.2, 1H), 5.12 (dt, *J* = 1.6, 10.8, 1H), 3.94 (h, *J*

= 4.0, 1H), 3.88 (ddddd, *J* = 1.2, 1.6, 2.8, 5.2, 10.8, 1H), 3.35 (ddd, *J* = 2.0, 4.4, 10.8, 1H), 2.89 (dd, *J* = 4.8, 13.6, 1H), 2.80 (dd, *J* = 8.4, 13.2, 1H), 2.04 (d, *J* = 4.0, 1H), 1.92-1.99 (m, 1H), 1.62-1.77 (m, 2H), 1.41-1.62 (m, 2H), 1.28-1.39 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 139.4, 138.5, 129.4, 128.5, 126.3, 114.4, 79.5, 78.4, 74.7, 38.7, 31.6, 25.1, 23.0; IR (neat) 3446, 3027, 2934, 2855, 1646, 1603, 1495, 1453, 1306, 1201, 1077, 1046, 915, 748; HRMS (ESI) calcd for $C_{15}H_{20}O_2Na$ $[M + Na]^+$ 255.1361, found 255.1378.



(*R*)-2-phenyl-1-((2*S*,6*S*)-6-vinyltetrahydro-2H-pyran-2-yl)ethanol (3-17)

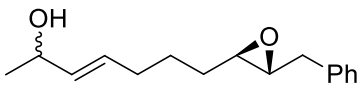
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.34 (m, 2H), 7.21-7.28 (m, 3H), 5.92-6.02 (m, 1H), 5.25-5.27 (m, 1H), 5.21-5.24 (m, 1H), 4.45-4.51 (m, 1H), 3.89 (h, *J* = 4.4, 1H), 3.63 (ddd, *J* = 2.0, 5.2, 9.2, 1H), 2.93 (dd, *J* = 4.0, 14.0, 1H), 2.69 (dd, *J* = 8.8, 14.0, 1H), 1.91 (d, *J* = 3.6, 1H), 1.77-1.88 (m, 1H), 1.63-1.75 (m, 4H), 1.52-1.63 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 138.6, 138.1, 129.4, 128.5, 126.4, 116.4, 74.1, 73.3, 73.0, 39.0, 28.6, 25.5, 18.3; IR (neat) 3439, 3027, 2930, 2858, 1669, 1603, 1494, 1453, 1407, 1338, 1203, 1121, 1048, 1039, 921, 891, 748 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{20}O_2Na$ $[M + Na]^+$ 255.1361, found 255.1376.



Reaction Conditions:

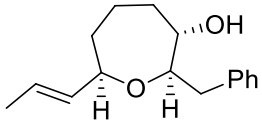
a) PCC, celite, DCM, 20 ºC; b) 60% NaH dispersed in Mineral oil, Diethyl (2-oxopropyl)phosphonate, THF, 0 ºC, 66% for two steps; c) Shi ketone derived from D-fructose, oxone, $Na_2B_4O_7$, $Na_2(EDTA)$, K_2CO_3, Bu_4NHSO_4, MeCN, H_2O, 0 ºC, 58%; f) DIBAL, DCM, -78 ºC, 91%.

Scheme B2 Synthesis of substrate **3-18**



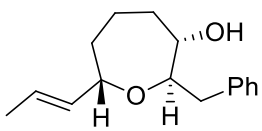
(*E*)-7-((2*R*, 3*R*)-3-benzylloxiran-2-yl)hept-3-en-2-ol (3-18)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.38 (m, *2*H), 7.23-7.30 (m, 3H), 5.46-5.66 (m, 2H), 4.26 (p, *J* = 6.3, 1H), 2.90-2.98 (m, 2H), 2.77-2.85 (m, 2H), 2.05 (q, *J* = 6.6, 2H), 1.78 (br, 1H), 1.46-1.62 (m, 4H), 1.26 (d, *J* = 6.3, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.4, 134.8, 130.0, 128.9, 128.5, 126.6, 68.7, 58.8, 58.6, 38.5, 31.7, 31.3, 25.5, 23.5; IR (neat) 3412, 3027, 2971, 2925, 2857, 1604, 1494, 1453, 1367,1145, 1063, 969, 798, 743 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{22}O_2Na$ $[M + Na]^+$ 269.1517, found 269.1529.



(2*R*,3*S*,7*R*)-2-benzyl-7-((*E*)-prop-1-en-1-yl)oxepan-3-ol (3-19)

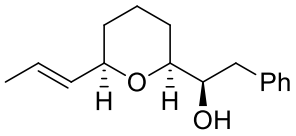
The general rearrangement procedure was followed with **3-18** (25.0 mg, 0.102 mmol), Re_2O_7 (2.5 mg, 0.005 mmol), and CH_2Cl_2 (10.2 mL). The reaction was stirred at 20 °C for 45 min and then quenched with five drops of pyridine. After evaporation of the solvent, the crude mixture was purified by flash chromatography (20%-30% ethyl acetate in hexanes) to give the product (22.3 mg, 89%, dr = 6:7). ^{1}H NMR (400 MHz, $C6D_6$) δ 7.35-7.37 (m, 2H), 7.18-7.22 (m, 2H), 7.08-7.12 (m, 1H), 5.39-5.51 (m, 2H), 3.62-3.67 (m, 1H), 3.42-3.45 (m, 1H), 3.38 (dt, *J* = 3.2, 8.4, 1H), 3.04 (dd, *J* = 3.0, 13.8, 1H), 2.78 (dd, *J* = 8.6, 13.8, 1H), 1.70-1.79 (m, 1H), 1.49-1.58 (m, 2H), 1.53 (d, *J* = 5.2, 3H), 1.35-1.48 (m, 3H). 0.78 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 139.5, 132.3, 129.5, 128.1, 126.0, 125.8, 86.2, 82.4, 75.3, 40.7, 36.2, 35.8, 19.4, 17.8; IR (neat) 3415, 3027, 2926, 2857, 1672, 1604, 1495, 1452, 1133, 1101, 1037, 999, 966, 750 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{22}O_2$ $[M]^+$ 246.1620, found 246.1629.



(2*R*,3*S*,7*S*)-2-benzyl-7-((*E*)-prop-1-en-1-yl)oxepan-3-ol (3-20)

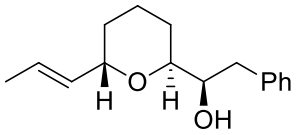
^{1}H NMR (400 MHz, C_6D_6) δ 7.29-7.33 (m, 2H), 7.17-7.22 (m, 2H),

7.07-7.12 (m, 1H), 5.24 (ddq, *J* = 1.2, 6.4, 15.6, 1H), 4.91 (ddq, *J*= 1.6, 5.6, 15.6, 1H), 3.92 (p, *J* = 5.2, 1H), 3.46 (dt, *J* = 2.8, 9.2, 1H), 3.12 (dt, *J* = 4.4, 9.2, 1H), 3.17 (dd, *J* = 2.8, 13.6, 1H), 2.64 (dd, *J* = 9.2, 13.6, 1H), 1.79-1.87 (m, 1H), 1.48-1.56 (m, 1H), 1.35-1.47 (m, 2H), 1.39 (d, *J* = 6.4, 3H), 1.18-1.35 (m, 3H), 0.90 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 139.4, 132.3, 130.0, 128.0, 125.9, 125.7, 78.3, 75.6, 75.3, 39.4, 38.4, 33.9, 21.5, 17.8; IR (neat) 3307, 3034, 2926, 2855, 1605, 1495, 1451, 1354, 1123, 1091, 1036, 970, 744 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{22}O_2Na$ $[M + Na]^+$ 269.1517, found 269.1509.



(*R*)-2-phenyl-1-((2*S*,6*R*)-6-((*E*)-prop-1-en-1-yl)tetrahydro-2H-pyran-2-yl)ethanol (3-21)

The general rearrangement procedure was followed with **3-18** (29.5 mg, 0.120 mmol), Re_2O_7 (2.9 mg, 0.006 mmol), and CH_2Cl_2 (12.0 mL). The reaction was stirred at 20 °C for 36 hrs (5% more catalyst added at 12 h and 24 h respectively) and then quenched with five drops of pyridine. After evaporation of the solvent, the crude mixture was purified by flash chromatography (10%-20% ethyl acetate in hexanes) to give the product (27.4 mg, 93%, dr = 10:11). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.37 (m, 2H), 7.23-7.30 (m, 3H), 5.72 (ddt, *J* = 0.8, 6.4, 15.6, 1H), 5.55 (ddt, *J* = 1.6, 6.0, 15.6, 1H), 3.96 (h, *J* = 4.0, 1H), 3.84 (dd, *J* = 6.2, 10.2, 1H), 3.34 (ddd, *J* = 1.8, 4.2, 10.6, 1H), 2.88 (dd, *J* = 5.0, 13.8, 1H), 2.81 (dd, *J* = 8.2, 13.8, 1H), 2.01-2.04 (m, 1H), 1.92-1.98 (m, 1H), 1.73 (d, *J* = 6.4, 3H), 1.72 (br, 1H), 1.58-1.67 (m, 1H), 1.41-1.58 (m, 2H), 1.36 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 138.5, 132.4, 129.4, 128.5, 126.5, 126.3, 79.4, 78.5, 74.6, 38.7, 31.9, 24.9, 23.0, 17.9; IR (neat) 3360, 3029, 2960, 2928, 2912, 2839, 1677, 1495, 1453, 1379, 1293, 1196, 1078, 1037, 748 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{22}O_2Na$ $[M + Na]^+$ 269.1517, found 269.1535.



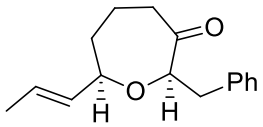
(*R*)-2-phenyl-1-((2*S*,6*S*)-6-((*E*)-prop-1-en-1-yl)tetrahydro-2H-pyran-2-yl)ethanol (3-22)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.38 (m, 2H), 7.23-7.31 (m, 3H), 5.64-5.75 (m, 2H), 4.40-4.46 (m, 1H), 3.87-3.93 (m, 1H), 3.64 (ddd, *J* = 2.2, 5.2, 9.0, 1H), 3.95 (dd, *J* = 3.6, 14.0, 1H), 2.72 (dd, *J* = 9.0, 14.0, 1H), 1.92 (br, 1H), 1.78-1.86 (m, 1H), 1.76 (d, *J* = 4.8, 3H), 1.68-1.74 (m, 3H), 1.56-1.67 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 138.7, 130.6, 129.5, 128.5, 127.9, 126.4, 73.9, 73.2, 72.8, 39.0, 29.2, 25.5, 18.4, 18.0; IR (neat) 3434, 3026, 2934, 2859, 1668, 1603, 1494, 1452, 1202, 1077, 1035, 966, 890, 748 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{22}O_2Na$ [M + Na]$^+$ 269.1517, found 269.1496.

The absolute configuration of the secondary alcohols in structures **3-19** to **3-22** were determined by Mosher ester analysis.[71] Typically, 5-6 mg of each alcohol was divided into two parts, these two parts were treated with R and S Mosher acid respectively: 2-3 mg alcohol, 5 equiv Mosher acid (R or S), 5.5 equiv DCC, 5.5 equiv DMAP in 1ml DCM. The reactions were stirred at 20 °C and monitored by TLC, when the starting alcohol was completely consumed, filter the reaction mixture through a short column of silica gel to remove the insoluble salts, then flush the column with DCM until all ester products are eluted. After the removal of the solvents under reduced pressure, ^{1}H NMR and ^{19}F NMR were taken to determine the confituration and enantiopurity of the conrresponding alcohols.

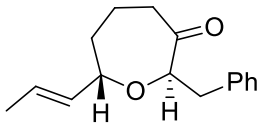
Structures **3-19** and **3-20**, **3-21** and **3-22** were difficult to differentiate by ^{1}H NMR , ^{14}C NMR, COSY and NOESY. But it became easier to differentiate them once they are oxidized to the corresponding ketones since they have very different chemical shifts and splitting patterns for

those benzylic hydrogens. The ketone products were obained by submitting the corresponding alcohols to the PCC oxidation conditions: typically, 2-7 mg of alcohol was treated with 5-10 equiv PCC and celite in DCM until complete consumption of the alcohol, then the reaction mixture was filtered through a short column of silica gel to give the pure ketones. (yield: 92%-97%) The sturctures **3-20** and **3-21** were also confirmed by X-ray crystallography.



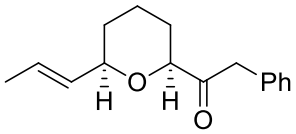
(2*R*,7*R*)-2-benzyl-7-((*E*)-prop-1-en-1-yl)oxepan-3-one

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-7.32 (m, 5H), 5.40-5.56 (m, 2H), 4.03 (dd, *J* = 4.0, 8.4, 1H), 3.66 (d, *J* = 9.4, 1H), 3.06 (dd, *J* = 3.6, 14.0, 1H), 2.89 (dd, *J* = 9.0, 14.0, 1H), 2.69 (dt, *J* = 2.4, 12.4, 1H), 2.32 (dd, *J* = 6.4, 12.0, 1H), 1.90-1.99 (m, 1H), 1.80-1.88 (m, 1H), 1.64 (d, *J* = 6.0, 3H), 1.58-1.69 (m, 1H), 1.41-1.54 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 216.3, 137.6, 131.8, 129.6, 128.1, 126.4, 125.7, 87.1, 83.2, 41.6, 39.2, 36.2, 23.3, 17.4; IR (neat) 3061, 3029, 2931,2859, 1711, 1603, 1495, 1452, 1434, 1319, 1173, 1107, 966, 735 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{20}O_2Na$ $[M + Na]^+$ 267.1361, found 267.1350.



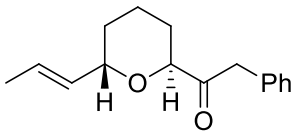
(2*R*,7*S*)-2-benzyl-7-((*E*)-prop-1-en-1-yl)oxepan-3-one

^{1}H NMR (400 MHz, C_6D_6) δ 7.19-7.23 (m, 2H), 7.12-7.15 (m, 2H), 7.04-7.09 (m, 1H), 5.11-5.27 (m, 2H), 4.08 (dd, *J* = 3.6, 8.8, 1H), 3.91 (m, 1H), 3.23 (dd, *J* = 3.6, 14.4, 1H), 2.79 (dd, *J* = 8.8, 14.4, 1H), 2.46-2.54 (m, 1H), 2.27-2.36 (m, 1H), 1.41 (d, *J* = 5.6, 3H), 1.32-1.37 (m, 3H), 1.22-1.32 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6) 212.9, 138.5, 130.9, 129.8, 127.6, 126.5, 126.1, 81.3, 76.4, 40.2, 37.0, 33.1, 21.3, 17.4; IR (neat) 3061, 3028, 2933, 2863, 1711, 1604, 1459, 1452, 1324, 1180, 1093, 968, 785 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{20}O_2Na$ $[M + Na]^+$ 267.1361, found 267.1379.



2-phenyl-1-((2*S*,6*R*)-6-((*E*)-prop-1-en-1-yl)tetrahydro-2H-pyran-2-yl)ethanone (3-31cis)

^{1}H NMR (400 MHz, C_6D_6) δ 7.22-7.28 (m, 2H), 7.12-7.17 (m, 2H), 7.03-7.09 (m, 1H), 5.65 (ddq, *J* = 0.8, 6.4, 15.2, 1H), 5.53 (ddq, *J* = 1.6, 5.6, 15.2, 1H), 3.92 (d, *J* = 15.2, 1H), 3.84 (d, *J* = 15.2, 1H), (3.61 (dd, *J* = 2.4, 11.2, 1H), 3.51 (ddt, *J* =1.2, 5.6, 10.2, 1H), 1.70-1.76 (m, 1H), 1.60 (dt, *J* = 1.2, 6.4, 3H), 1.43-1.49 (m, 1H), 1.25-1.30 (m, 1H), 1.02-1.21 (m, 3H); ^{13}C NMR (100 MHz, C_6D_6) 206.7, 134.7, 132.5, 130.0, 128.3, 126.5, 125.5, 82.0, 78.0, 44.7, 31.4, 27.5, 22.9, 17.6; IR (neat) 3061, 3029, 2936, 2855, 1722, 1601, 1495, 1452, 1299, 1199, 1095, 1034, 965, 742, 702 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{20}O_2Na$ $[M + Na]^+$ 267.1361, found 267.1406.



2-phenyl-1-((2*S*,6*S*)-6-((*E*)-prop-1-en-1-yl)tetrahydro-2H-pyran-2-yl)ethanone (3-31trans)

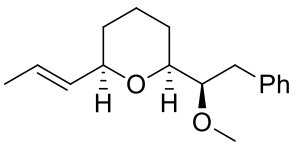
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.35 (m, 2H), 7.22-7.28 (m, 3H), 5.72 (ddt, *J* = 1.2, 6.4, 15.2, 1H), 5.56 (ddt, *J* = 1.6, 5.6, 15.2, 1H), 4.30 (t, *J* = 5.0, 1H), 4.11 (t, *J* = 5.6, 1H), 3.95 (d, *J* = 15.2, 1H), 3.85 (d, *J* = 15.2, 1H), 1.83-1.91 (m, 1H), 1.74 (dt, *J* = 1.2, 6.4, 3H), 1.64-1.72 (m, 3H), 1.44-1.62 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 209.6, 134.2, 131.0, 128.5, 128.0, 126.8, 77.3, 74.4, 45.3, 30.2, 25.2, 19.3, 17.9; IR (neat) 3029, 2936, 2854, 1717, 1601, 1495, 1453, 1260, 1202, 1084, 1028, 965, 797 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{20}O_2Na$ $[M + Na]^+$ 267.1361, found 267.1359.

Isomerization of **3-31cis** and **3-31trans**: to of a mixture of **3-31cis** and **3-31trans** (14.9 mg, 0.061 mmol, dr = 5:4) in 5 ml DCM was added Re_2O_7 (1.5 mg, 0.003 mmol), reaction was

stirred at 20 °C for 4 h before quenched with 5 drops of pyridine (measured by pipet). After evaporation of the solvent, the crude mixture was purified by flash chromatography (5%-10% ethyl acetate in hexanes) to give the product (11.5 mg, 73%, dr = 11.5:1).

Synthesis of **3-32cis** and **3-32trans**: at 0 °C, to a mixture of **3-21** and **3-22** (27.4 mg, 0.111 mmol, dr = 1:1) in 3ml THF was added 60% NaH dispersed in mineral oil (8.9 mg, 0.222 mmol) followed by addtion of MeI (31.6 mg, 0.222 mmol), then stirred at 20 °C for 6h and quenched with saturated NH_4Cl solution (10 ml). Then the mixture was extracted by ether (3*20 ml), the organic layer was combined and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (5%-10% ethyl acetate in hexanes) to give the product (25.6 mg, 88%, dr = 1:1).

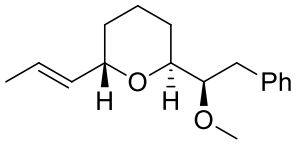
Isomerization of **3-32cis** and **3-32trans**: to of a mixture of **3-32cis** and **3-32trans** (12.4 mg, 0.048 mmol, dr = 1:1) in 2 ml DCM was added Re_2O_7 (1.2 mg, 0.0023 mmol), reaction was stirred at 20 °C for 5 h before quenched with 5 drops of pyridine. After evaporation of the solvent, the crude mixture was purified by flash chromatography (5%-10% ethyl acetate in hexanes) to give the product (11.2 mg, 90%, dr > 30:1).



(2*S*,6*R*)-2-((*R*)-1-methoxy-2-phenylethyl)-6-((*E*)-prop-1-en-1-yl) tetrahydro-2H-pyran (3-32cis)

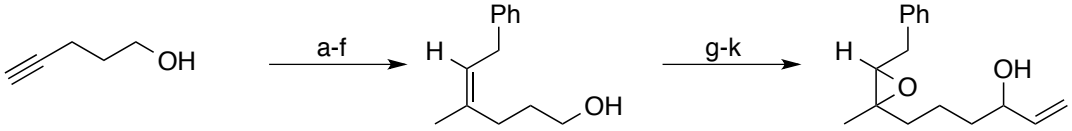
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-7.35 (m, 5H), 5.73 (dt, *J* = 6.4, 15.6, 1H), 5.56 (dd, *J* = 4.4, 15.6, 1H), 3.74 (dd, *J* = 5.6, 10.4, 1H), 3.41 (q, *J* = 6.0, 1H), 3.36 (s, 3H), 3.23 (ddd, *J* = 1.8, 5.8, 11.0, 1H), 2.95 (dd, *J* = 4.4, 14.0, 1H), 2.85 (dd, *J* = 6.8, 14.0, 1H), 1.86-1.94 (m, 1H), 1.76-1.82

(m, 1H), 1.74 (d, J = 6.4, 3H), 1.59-1.66 (m, 1H), 1.44-1.56 (m, 1H), 1.28-1.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 139.0, 132.7, 129.7, 128.1, 126.0, 125.9, 84.8, 78.7, 78.2, 58.8, 36.7, 31.9, 26.7, 23.3, 17.9; IR (neat) 3061, 3027, 2932, 2855, 1603, 1495, 1453, 1352, 1301, 1196, 1103, 1037, 964, 749 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{24}O_2Na$ $[M + Na]^+$ 283.1674, found 283.1684.



(2*S*,6*S*)-2-((*R*)-1-methoxy-2-phenylethyl)-6-((*E*)-prop-1-en-1-yl) tetrahydro-2H-pyran (3-32trans)

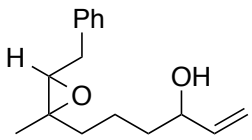
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.33 (m, 4H), 7.18-7.24 (m, 1H), 5.55-5.69 (m, 2H), 3.58 (ddd, J = 2.4, 6.0, 9.6, 1H), 3.41 (ddd, J = 4.0, 6.8, 7.2, 1H), 3.27 (s, 3H), 3.98 (dd, J = 3.6, 14.0, 1H), 3.75 (dd, J = 7.2, 14.0, 1H), 1.62-1.82 (m, 4H), 1.71 (d, J = 5.2, 3H), 1.46-1.60 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 139.3, 130.9, 129.7, 128.1, 127.6, 125.9, 83.8, 72.9, 71.9, 58.7, 36.8, 29.5, 26.5, 18.8, 18.0; IR (neat) 3061, 3027, 2932, 2824, 1603, 1494, 1453, 1378, 1352, 1200, 1105, 1036, 966, 887, 749 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{24}O_2Na$ $[M + Na]^+$ 283.1674, found 283.1678.



Reaction conditions:

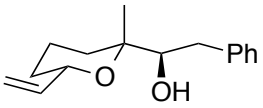
a) BuLi, THF, TMSCl, -78 ºC to rt, then 1.0N HCl, 91%; b) Cp_2ZrCl_2, $AlMe_3$, $(CH_2Cl)_2$, then I_2, THF; c) MeOH, NaOMe, 65 ºC, 39% for two steps; d) TBSCl, imidazole, DMAP, CH_2Cl_2, 95%; e) $Ni(PPh_3)_2Cl_2$, Et_2O, Benzylmagnesium bromide, rt, quantitive; f) TBAF, THF, rt, quantitive; g) TsCl, pyridine, DCM, 0 ºC, 94%; h) NaCN, DMSO, 90 ºC, 93%; i) DIBAL-H, DCM, -78 ºC to 0 ºC, 97%; j) Vinylmagnesium bromide, THF, 83%; k) MCPBA, DCM, $NaHCO_3$, 0 ºC, 87%.

Scheme B3 Synthesis of substrate **3-28**



6-(3-benzyl-2-methyloxiran-2-yl)hex-1-en-3-ol (3-28)

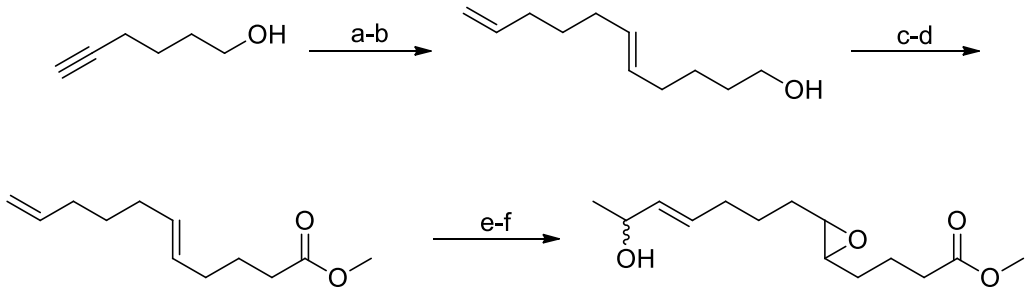
^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.28-7.35 (m, 2H), 7.19-7.28 (m, 3H), 5.88 (ddd, *J* = 6.0, 10.2, 17.1, 1H), 5.24-5.26 (m, 0.5H), 5.18-5.20 (m, 0.5H), 5.10-5.12 (m, 0.5H), 5.07-5.09 (m, 0.5H), 4.05-4.15 (m, 1H), 2.90-2.96 (m, 1H), 2.77-2.88 (m, 2H), 1.78 (br, 1H), 1.50-1.70 (m, 6H), 1.28 (s, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2) 155.8, 154.9, 131.2, 131.1, 130.5, 130.3, 99.8, 99.7, 63.3, 63.2, 32.6, 31.3, 31.1, 27.54, 27.1; IR (neat) 3428, 3063, 3028, 2920, 2864, 1643, 1604, 1494, 1453, 1428, 1380, 1129, 1074, 1029, 993, 920, 737 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{22}O_2Na$ $[M + Na]^+$ 269.1517, found 269.1541.



***rac*-(*R*)-1-((2*R*,6*S*)-2-methyl-6-vinyltetrahydro-2*H*-pyran-2-yl)-2-phenylethan-1-ol (3-29)**

The general rearrangement procedure was followed with **3-28,** the resulting products are non-separable mixturex of two isomers, the ratio of which are shown in scheme 3.5 under different conditions. The following is the result for entry 7, in which the genera procudure was followed with **3-28** (21.3 mg, 0.0865 mmol), Re_2O_7, DCM (8.5 ml), the reaction was conducted at -78 ºC for 10 hours, followed by quenching with 5 drops of pyridine. After removal of solvent under reduced pressure, flash chromatography (5%-10% ethyl acetate in hexanes) give 12.4 mg **3-29** (58%, dr = 5.6 :1), 7.7 mg (36%) starting material was recoverd, ^{1}H and ^{13}C NMR of this recoverd material showed that only one isomer is left. The reaction was stirred at 20 °C for 12 hrs. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.23-7.30 (m, 4H), 7.16-7.21 (m, 1H), 5.82 (ddd, *J* = 5.2, 10.4, 17.2, 1H), 5.17 (dt, *J* = 1.6, 17.2, 1H), 5.04 (dt, *J* = 1.6, 10.4, 0.15H), 5.02 (dt, *J* = 1.6, 10.4, 0.75H), 4.28 (dd, *J* = 2,8, 9.6, 0.15H), 4.09 (ddddd, *J* = 0.8, 1.2, 1.6, 4.0, 11.6, 1H), 3.58 (dt, *J* = 2.8, 10.4, 0.85H), 2.76-2.83 (m, 1H), 2.50-2.65 (m, 2H), 1.71-1.79 (m, 2H), 1.62-1.70 (m, 1H),

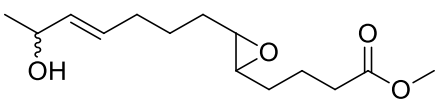
1.45-1.51 (m, 2H), 1.27-1.32 (m, 0.15H), 1.24 (s, 3H), 1.14-1.24 (m, 0.85H); ^{13}C NMR (100 MHz, CD_2Cl_2) 140.2, 129.3, 128.1, 125.9, 113.5, 80.5, 76.2, 71.0, 37.0, 31.7, 31.0, 19.3, 14.8; IR (neat) 3428, 3063, 3028, 2920, 2864, 1643, 1604, 1494, 1453, 1428, 1380, 1320, 1129, 1074, 1029, 993, 920, 737 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{22}O_2Na$ [M + Na]$^+$ 269.1517, found 269.1533.



Reaction Conditions:

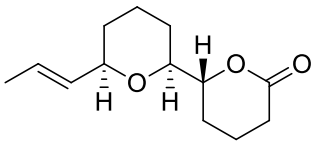
a) DIBAL, Hesanes then I_2, THF, -78 °C, 51%. b) Pent-4-en-1-ylmagnesium bromide, $Cl_2Pd(dppf)_2$, Et_2O, 20 °C, 65%. c) Jones reagent, 0-5 °C, 64%. d) K_2CO_3, MeI, DMF, 0-20 °C 99%.e) MCPBA, $NaHCO_3$, DCM, 0 °C, 67%. f) (*Z*)-hex-3-ene-2,5-diol, Hoveyda-Grubbs 2nd, DCM, 20 °C, 57%.

Scheme B4 Synthesis of substrate **3-33**



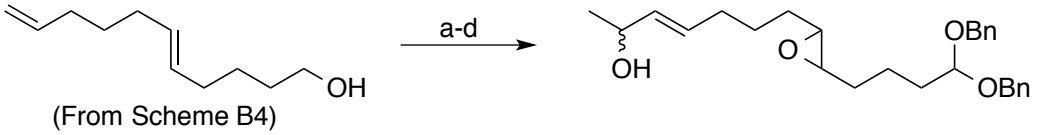
(*E*)-methyl 4-(3-(6-hydroxyhept-4-en-1-yl)oxiran-2-yl) butanoate (3-33)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.58 (dt, *J* = 6.4, 15.2, 1H), 5.49 (dd, *J* = 6.4, 15.2, 1H), 4.22 (p, *J* = 6.0, 1H), 3.64 (s, 3H), 2.62-2.67 (m, 2H), 2.34 (dt, *J* = 1.4, 7.2, 2H), 2.01-2.08 (m, 2H), 1.82 (br, 1H), 1.68-1.80 (m, 2H), 1.42-1.62 (m, 6H), 1.22 (d, *J* = 6.4, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 173.7, 134.8, 130.0, 68.7, 58.4, 58.2, 51.6, 33.6, 31.8, 31.40, 31.37, 25.5, 23.4, 21.5; IR (neat) 3433, 2928, 2860, 1737, 1438, 1367, 1248, 1169, 1117, 1061, 970, 893 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{24}O_4Na$ [M + Na]$^+$ 279.1572, found 279.1552.



(2*R*,2'*S*,6'*R*)-6'-((*E*)-prop-1-en-1-yl)hexahydro-2H,2'H-[2,2'-bipyran]-6(3H)-one (3-34)

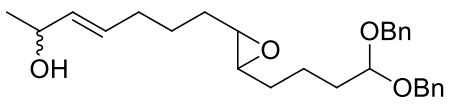
The general rearrangement procedure was followed with **3-33** (32.0 mg, 0.125 mmol), Re_2O_7 (3.0 mg, 0.006 mmol), and CH_2Cl_2 (12.5 mL). The reaction was stirred at 20 °C for 12 hrs. The solvent was then removed under reduced pressure and the reaction mixture was kept at high vaccum for 1hr, after which the reaction mixture was redispersed in CH_2Cl_2 (12.5 mL) and 5% more catalyst was added. The reaction mixture was stirred at 20 °C for another 12 hrs before quenched with 5 drops of pyridine. After the removal of solvent under reduced pressure, the crude mixture was purified by flash chromatography (20%-30% ethyl acetate in hexanes) to give the product (23.0 mg, purity: 87%, 71% with respect to the desired product). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66 (ddq, J = 0.8, 6.4, 15.2, 1H), 5.46 (ddq, J = 1.2, 6.0, 15.2, 1H), 4.17 (ddd, J = 3.6, 6.4, 10.4, 1H), 3.79 (dd, J = 6.0, 10.4, 1H), 3.42 (ddd, J = 2.0, 6.0, 11.2, 1H), 2.52-2.62 (m, 1H), 2.41-2.51 (m, 1H), 2.06-2.14 (m, 1H), 1.75-1.98 (m, 4H), 1.68 (d, J = 6.4, 3H), 1.57-1.72 (m, 2H), 1.46-1.56 (m, 1H), 1.20-1.37 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.5, 132.2, 126.4, 82.5, 78.8, 78.3, 31.6, 29.8, 27.2, 24.0, 22.9, 18.1, 17.9; IR (neat) 2935, 2855, 1738, 1440, 1346, 1240, 1203, 1169, 1089, 1049, 965, 933 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{21}O_3$ $[M + H]^+$ 225.1491, found 225.1481.



Reaction Conditions:

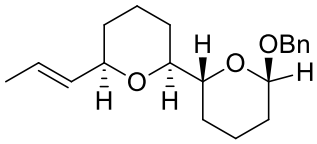
1) PCC, celite, rt; b) BnOH, PTSA•H_2O, DCM, Na_2SO_4, rt, 67% for two steps; c) MCPBA, $NaHCO_3$, DCM, 0 ºC, 57%; d) (*Z*)-hex-3-ene-2,5-diol, Hoveyda-Grubbs 2nd, DCM, rt, 73%.

Scheme B5 Synthesis of substrate **3-35**



(*E*)-7-(3-(4,4-bis(benzyloxy)butyl)oxiran-2-yl)hept-3-en-2-ol (3-35)

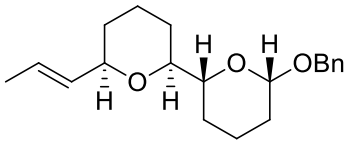
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.40 (m,8H), 7.28-7.34 (m, 2H), 5.63 (dt, *J* = 6.4, 15.2, 1H), 5.54 (dd, *J* = 6.4, 15.2, 1H), 4.76 (t, *J* = 6.0, 1H), 4.68 (dd, *J* = 0.8, 12.0, 2H), 4.58 (d, *J* = 12.0, 2H), 4.26 (p, *J* = 6.4, 1H), 2.62-2.70 (m, 2H), 2.03-2.13 (m, 2H), 1.76-1.86 (m, 2H), 1.64 (br, 1H), 1.45-1.62 (m, 8H), 1.26 (d, *J* = 6.4, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 138.2, 134.8, 130.2, 128.5, 127.8, 127.7, 101.9, 68.8, 67.33, 67.28, 58.6, 33.1, 31.9, 31.8, 31.5, 25.6, 23.5, 21.4; IR (neat) 3444, 3030, 2929, 2863, 1605, 1496, 1454, 1366, 1307, 1207, 1123, 1046, 970, 737 cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{36}O_4Na$ $[M + Na]^+$ 447.2511, found 447.2531.



(2*R*,2'*S*,6*R*,6'*R*)-6-(benzyloxy)-6'-((*E*)-prop-1-en-1-yl)octahydro-2H,2'H-2,2'-bipyran (3-36a)

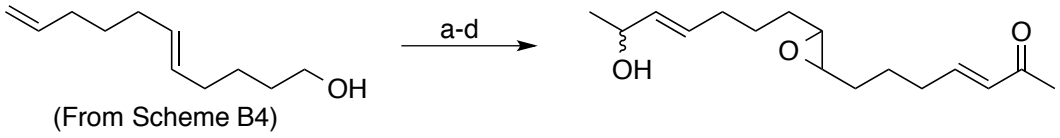
The general rearrangement procedure was followed with **3-35** (25.0 mg, 0.059 mmol), 10% Re_2O_7 on SiO_2 (14.3 mg, 0.003 mmol), and CH_2Cl_2 (12.0 mL). The reaction was stirred at -25 °C for 8 hrs (when all starting materials was consumed) and then 20 °C for another 10 hrs before quenched with five drops of pyridine. After evaporation of the solvent, the crude mixture was purified by flash chromatography (2%-5% ethyl acetate in hexanes) to give the product (11.5 mg, 62%, dr = 5:2). ^{1}H NMR (400 MHz, C_6D_6) δ 7.35-7.39 (m, 2H), 7.16-7.21 (m, 2H), 7. 07-7.13 (m, 1H), 5.69 (ddq, *J* = 0.8, 6.4, 15.2, 1H), 5.59 (ddq, *J* = 1.2, 5.2, 15.2, 1H), 4.88 (d, *J* = 2.8, 1H), 4.80 (d, *J* = 12.0, 1H), 4.39 (d, *J* = 12.0, 1H), 3.91 (ddd, *J* = 2.0, 6.8, 10.8, 1H), 3.74 (dd, *J* = 5.2, 9.6, 1H), 3.33 (ddd, *J* = 2.0, 6.8, 10.4, 1H), 2.00-2.07 (m, 1H), 1.88-1.99 (m, 2H), 1.61-1.75 (m, 2H), 1.58 (dt, *J* = 1.2, 6.4, 3H), 1.27-1.54 (m, 7H); ^{13}C NMR (100 MHz, C_6D_6) 138.8, 133.3, 128.2, 127.9, 127.3, 124.6, 96.2, 80.3, 77.9, 71.8, 68.8,

32.2, 30.0, 27.9, 27.8, 23.3, 18.0, 17.6; IR (neat) 3029, 2932, 2854, 1496, 1453, 1440, 1360, 1302, 1195, 1126, 1079, 1036, 964, 734 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{28}O_3Na$ $[M + Na]^+$ 339.1936, found 339.1923.



(2*R*,2'*S*,6*S*,6'*R*)-6-(benzyloxy)-6'-((*E*)-prop-1-en-1-yl) octahydro -2H,2'H-2,2'-bipyran (3-36b)

^1H NMR (400 MHz, C_6D_6) δ 7.36-7.40 (m, 2H), 7.17-7.21 (m, 2H), 7.08-7.12 (m, 1H), 5.55-5.70 (m, 2H), 4.95 (d, *J* = 12.0, 1H), 4.55 (d, *J* = 12.0, 1H), 4.33 (dd, *J* = 2.0, 9.2, 1H), 3.72 (dd, *J* = 4.8, 10.0, 1H), 3.38 (ddd, *J* = 2.0, 7.2, 10.4, 1H), 5.25 (ddd, *J* = 2.0, 7.2,10.4, 1H), 1.96-2.02 (m, 1H), 1.88-1.94 (m, 1H), 1.64-1.76 (m, 2H), 1.58 (d, *J* = 6.0, 3H), 1.50-1.61 (m, 2H), 1.41-1.49 (m, 1H), 1.14-1.40 (m, 5H); ^{13}C NMR (100 MHz, C_6D_6) 138.7, 133.2, 128.2, 127.6, 127.3, 124.8, 101.3, 80.2, 78.9, 77.9, 69.4, 32.3, 31.5, 28.2, 27.8, 23.2, 21.8, 17.6; IR (neat) 3030, 2933, 2854, 1496, 1453, 1439, 1360, 1305, 1261, 1199, 1123, 1086, 1024, 964, 732 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{28}O_3Na$ $[M + Na]^+$ 339.1936, found 339.1945.

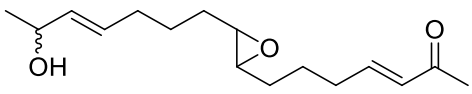


(From Scheme B4)

Reaction Conditions:

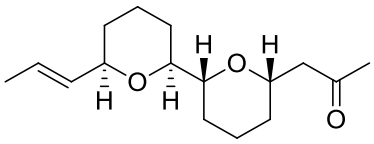
1) PCC, celite, rt; b) 60% NaH on Mineral oil, Diethyl (20oxopropyl)Phosphonate, THF, 0 C,78% for two steps; c) MCPBA, $NaHCO_3$,DCM, 0 ºC,66%; d) (*Z*)-hex-3-ene-2,5-diol, Hoveyda-Grubbs 2nd, DCM, RT,56%.

Scheme B6 Synthesis of substrate **3-37**



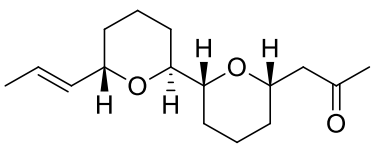
(*E*)-7-(3-((*E*)-6-hydroxyhept-4-en-1-yl)oxiran-2-yl)hept-3-en-2-one (3-37)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (dt, *J* = 6.8, 16.0, 1H), 6.08 (d, *J* = 16.0, 1H), 5.62 (dt, *J* = 6.4, 15.2, 1H), 5.52 (dd, *J* = 6.4, 15.2, 1H), 5.26 (p, *J* = 6.4, 1H), 2.64-2.69 (m, 2H), 2.28 (q, *J* = 6.8, 2H), 2.24 (s, 3H), 2.03-2.10 (m, 2H), 1.57-1.70 (m, 4H), 1.45-1.57 (m, 5H), 1.25 (d, *J* = 6.4, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 198.7, 147.6, 134.8, 131.6, 130.1, 68.8, 58.5, 58.3, 32.1, 31.8, 31.5, 31.4, 27.0, 25.5, 24.6, 23.5; IR (neat) 3446, 2969, 2930, 2859, 1673, 1626, 1454, 1363, 1255, 1145, 1062, 974, 894 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{26}O_3Na$ $[M + Na]^+$ 289.1780, found 289.1795.



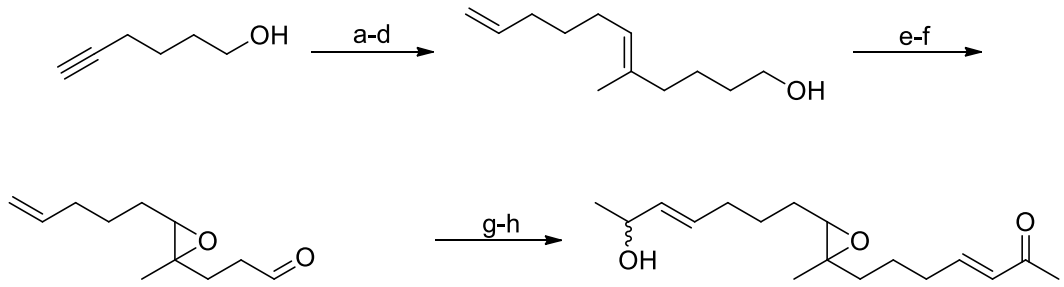
1-((2*R*,2'*S*,6*S*,6'*R*)-6'-((*E*)-prop-1-en-1-yl)octahydro-2H,2'H-[2,2'-bipyran]-6-yl)propan-2-one (3-38)

The general rearrangement procedure was followed with **3-37** (22.0 mg, 0.083 mmol), Re_2O_7 (2.0 mg, 0.004 mmol), and CH_2Cl_2 (8.3 mL). The reaction was stirred at 20 °C for 3.5 days and then quenched with five drops of pyridine. Me_2(Bn)SiH (5 μl) was added as an internal standard and crude NMR was used to determine the yield of 59% (dr >20:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66 (ddq, *J* = 0.8, 6.4, 15.2, 1H), 5.49 (ddq, *J* = 1.6, 6.0, 15.2, 1H), 3.72-3.81 (m, 2H), 3.15-3.25 (m, 2H), 2.64 (dd, *J* = 8.2, 15.0, 1H), 2.42 (dd, *J* = 4.6, 15.0, 1H), 2.18 (s, 3H), 1.76-1.95 (m, 2H), 1.68 (d, *J* = 6.4, 3H), 1.55-1.64 (m, 2H), 1.42-1.55 (m, 2H), 1.11-1.34 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) 207.9, 132.6, 126.2, 80.8, 80.3, 78.1, 74.7, 50.5, 31.9, 31.7, 30.8, 28.0, 27.9, 23.1, 23.0, 17.9; IR (neat) 2928, 2846, 1707, 1439, 1405, 1379, 1360, 1319, 1305, 1194, 1170, 1091, 1042, 963 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{26}O_3$ $[M]^+$ 289.1780, found 289.1766.



1-((2*R*,2'*S*,6*S*,6'S)-6'-((*E*)-prop-1-en-1-yl)octahydro-2H,2'H-[2,2'-bipyran]-6-yl)propan-2-one

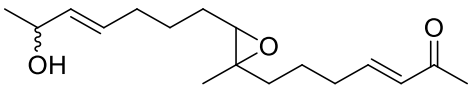
Minor product obtained when quenched before isomerization is complete: the general rearrangement procedure was followed with **3-37** (23.0 mg, 0.086 mmol), Re_2O_7 (2.1 mg, 0.004 mmol), and CH_2Cl_2 (8.6 mL). The reaction was stirred at 20 °C for 12hrs and then quenched with five drops of pyridine. $Me_2(Bn)SiH$ (5 µl) was added as an internal standard and crude NMR was used to determine the yield of 67% (dr = 3:1). ^1H NMR (400 MHz, $CDCl_3$) δ 5.65 (ddq, *J* = 0.8, 6.4, 15.2, 1H), 5.53 (ddq, *J* = 1.6, 5.2, 15.2, 1H), 4.18-4.25 (m, 1H), 3.78 (dddd, *J* = 2.4, 4.8, 8.4, 10.4, 1H), 3.54 (dt, *J* = 3.2, 7.6, 1H), 3.39 (ddd, *J* = 1.6, 7.6, 11.2, 1H), 2.67 (dd, *J* = 8.4, 15.2, 1H), 2.42 (dd, *J* = 4.4, 15.2, 1H), 2.18 (s, 3H), 1.80-1.91 (m, 2H), 1.71 (d, *J* = 6.4, 3H), 1.41-1.69 (m, 8H), 1.13-1.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 207.7, 131.4, 127.3, 78.6, 74.8, 73.7, 72.5, 50.3, 31.6, 30.9, 29.8, 27.6, 26.6, 23.1, 18.6, 17.9; IR (neat) 2932, 2857, 1716, 1440, 1357, 1262, 1198, 1090, 1044 965, 889 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{26}O_3$ $[M]^+$ 289.1780, found 289.1776.



Reaction Conditions:

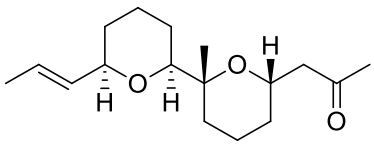
a) Imidazole, DMAP, DCM, TBSCl, 20 °C, 95%, b) $AlMe_3$, Cp_2ZrCl_2, DCM, then I_2 and THF, 0 °C, 59%. c) Pent-4-en-1-ylmagnesium bromide, $Cl_2Pd(dppf)_2$, Et_2O, 20 °C. d) 2.0M HCl, THF, 91% for two steps. e) PCC,celite, DCM, 20 °C, 62%. f) MCPBA, $NaHCO_3$, DCM, 0 °C, 50%. g) (*Z*)-hex-3-ene-2,5-diol, Hoveyda-Grubbs 2nd, DCM, 20 °C, 58%. h) 60% NaH on Mineral oil, diethyl (2-oxopropyl)phosphonate, THF, 0°C, 80%.

Scheme B7 Synthesis of substrate **3-30**



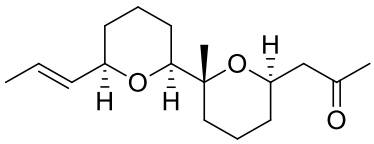
(*E*)-7-(3-((*E*)-6-hydroxyhept-4-en-1-yl)-2-methyloxiran-2-yl)hept-3-en-2-one (3-39)

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.75 (dt, *J* = 6.9, 15.9, 1H), 6.04 (dt, *J* = 1.5, 15.9, 1H), 5.46-5.65 (m, 2H), 4.23 (p, *J* = 6.3, 1H), 2.64-2.70 (m, 1H), 2.16-2.26 (m, 2H), 2.21 (s, 3H), 2.01-2.10 (m, 2H), 1.87 (br, 1H), 1.41-1.65 (m, 8H), 1.22 (d, *J* = 6.3, 3H), 1.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 198.7, 147.6, 134.9, 131.5, 130.0, 68.7, 63.3, 60.5, 60.4, 38.1, 32.3, 31.8, 28.1, 26.9, 26.0, 23.7, 23.5, 16.5; IR (neat) 3447, 2928, 2861, 1673, 1626, 1457, 1363, 1255, 1145, 1063, 974, 865 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{27}O_3$ $[M-H]^+$ 279.1960, found 279.1962.



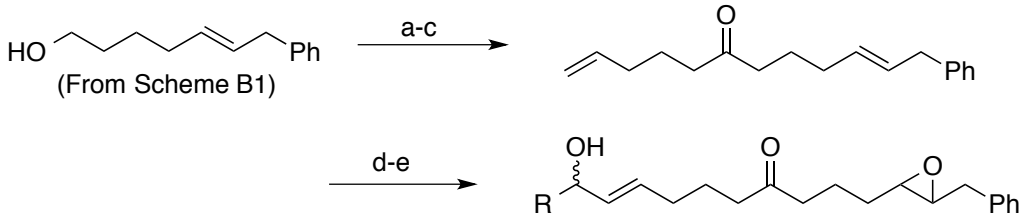
1-((2*R*,2'*S*,6*S*,6'*R*)-2-methyl-6'-((E)-prop-1-en-1-yl)octahydro-2H,2'H-[2,2'-bipyran]-6-yl)propan-2-one (3-40)

The general rearrangement procedure was followed with **3-39** (44.5 mg, 0.159 mmol), Re_2O_7 (3.8 mg, 0.008 mmol), and CH_2Cl_2 (8.6 mL). The reaction was stirred at 20 °C for 20hrs and then quenched with five drops of pyridine. Me_2(Bn)SiH (5 µl) was added as an internal standard and crude NMR was used to determine the yield of 85% (**3-40**:**3-41** = 3:2) ^{1}H NMR (400 MHz, CD_2Cl_2) δ 5.61 (ddq, *J* = 1.2, 6.4, 15.2, 1H), 5.44 (ddq, *J* = 1.6, 5.2, 15.2, 1H), 3.97 (dddd, *J* = 2.4,4.4, 8.4, 11.2, 1H), 3.72 (dd, *J* = 5.6, 11.2, 1H), 3.04 (dd, *J* = 1.6, 11.2, 1H), 2.45 (dd, *J* = 8.4, 14.8, 1H), 2.34 (dd, *J* = 4.4, 14.8, 1H), 2.10 (s, 3H), 1.78-1.85 (m, 1H), 1.60-1.71 (m, 3H), 1.65 (d, *J* = 6.4, 3H), 1.50-1.60 (m, 3H), 1.40-1.49 (m, 1H), 1.05-1.29 (m, 4H), 1.12 (s, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2) 207.5, 133.1, 125.0, 85.6, 78.3, 75.2, 67.1, 50.9, 33.0, 32.3, 31.8, 30.3, 24.1, 23.5, 19.2, 17.5, 14.9; IR (neat) 2932, 2854, 1716, 1439, 1369, 1281, 1206, 1187, 1102, 1050, 963 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{27}O_3$ $[M-H]^+$ 279.1960, found 279.1962.



1-((2*R*,2'*S*,6*R*,6'*R*)-2-methyl-6'-((*E*)-prop-1-en-1-yl)octahydro -2H,2'H-[2,2'-bipyran]-6-yl)propan-2-one (3-41)

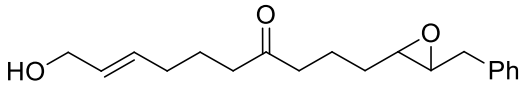
^{1}H NMR (400 MHz, CD_2Cl_2) δ 5.61 (ddq, *J* = 1.2, 6.4, 15.2, 1H), 5.44 (ddq, *J* = 1.6, 5.2, 15.2, 1H), 3.90 (dddd, *J* = 2.0,4.4, 7.6, 12.0, 1H), 3.79 (dd, *J* = 1.6, 11.2, 1H), 3.73 (dd, *J* = 5.6, 11.2, 1H), 2.53 (dd, *J* = 8.0, 15.2, 1H), 2.29 (dd, *J* = 4.4, 15.6, 1H), 2.10 (s, 3H), 1.96-2.03 (m, 1H), 1.84-1.91 (m, 1H), 1.45-1.73 (m, 5H), 1.65 (dt, J = 1,2, 6.4, 3H), 1.16-1.28 (m, 5H), 1.01 (s, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2) 207.4, 135.1, 125.0, 78.5, 75.3, 74.9, 67.2, 50.7, 32.2, 31.7, 31.2, 31.1, 23.7, 23.6, 23.3, 18.9, 17.5; IR (neat) 2933, 2857, 1718, 1441, 1359, 1206, 1075, 1046, 965, 837 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{29}O_3$ $[M+H]^+$ 281.2117, found 281.2124.



Reaction Conditions:

a) PCC, celite, DCM, 20 ºC; b) Pent-4-en-1-ylmagnesium bromide, Et_2O, 0 ºC, 70% for two steps; c) PCC celite, DCM, 20 ºC, 93%; d) MCPBA, $NaHCO_3$, DCM, 0 ºC, 52%; e) But-2-ene-1,4-diol (R = H) or *(Z)*-hex-3-ene-2,5-diol (R = CH_3), Hoveyda-Grubbs 2nd, DCM, 20 ºC, 59% (R = H, dr = 9 :1) or 75% (R = CH_3)

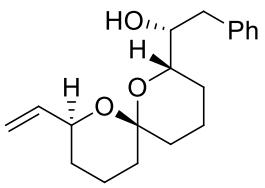
Scheme B8 Synthesis of substrates **3-42** (R = H) and **3-44** (R = CH_3)



(*E*)-1-(3-benzyloxiran-2-yl)-10-hydroxydec-8-en-4-one (3-42)

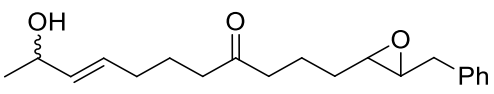
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.35 (m, 2H), 7.22-7.27 (m, 3H), 5.59-5.69 (m, 2H), 4.08 (d, *J* = 2.0, 2H), 2.88-2.96 (m, 2H), 2.75-2.83 (m, 2H), 2.41 (d, *J* = 7.2, 2H), 2.37 (d, *J* = 7.2, 2H), 2.01-2.11 (m, 2H), 1.92 (br, 1H), 1.56-1.77 (m, 5H), 1.49 (p, *J* = 7.2, 1H); ^{13}C NMR (100 MHz,

$CDCl_3$) 210.6, 137.3, 131.8, 130.0, 128.9, 128.6, 126.6, 63.5, 58.6, 58.4, 42.0, 41.9, 38.4, 31.6, 31.2, 23.0, 20.2; IR (neat) 3443, 3027, 2934, 2863, 1709, 1604, 1494, 1453, 1410, 1089, 1001, 972, 744 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{27}O_3$ $[M + H]^+$ 303.1960, found 303.1942.



(*R*)-2-phenyl-1-((2*S*,6*S*,8*S*)-8-vinyl-1,7-dioxaspiro[5.5]undecan-2-yl) ethanol (3-43)

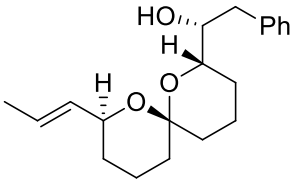
The general rearrangement procedure was followed with **3-42** (33.9 mg, 0.112 mmol), Re_2O_7 (2.7 mg, 0.006 mmol), and CH_2Cl_2 (11.2 mL). The reaction was stirred at 20 °C for 20 hrs and then quenched with five drops of pyridine. After evaporation of the solvent, the crude mixture was purified by flash chromatography (10%-15% ethyl acetate in hexanes) to give the product (31.5 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-7.37 (m, 5H), 5.85 (ddd, *J* = 5.6, 10.4, 17.2, 1H), 5.20 (dt, *J* = 1.6, 17.2, 1H), 5.09 (dt, *J* = 1.6, 10.4, 1H), 4.04 (ddddd, *J* = 0.8, 1.2, 2.6, 5.6, 11.2, 1H), 3.86 (p, *J* = 4.4, 1H), 3.00 (dd, *J* = 4.0, 14.0, 1H), 2.68 (dd, *J* = 9.2, 14.0, 1H), 1.86-2.04 (m, 3H), 1.74-1.82 (m, 1H), 1.57-1.73 (m, 5H), 1.41-1.51 (m, 2H), 1.27-1.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 139.4, 138.9 129.3, 128.5, 126.4, 114.5, 96.6, 75.1, 71.7, 70.0, 39.3, 35.5, 35.0, 30.6, 24.9, 18.7, 18.2; IR (neat) 3470, 3062,2938, 2868, 1646, 1603, 1495, 1453, 1438, 1373, 1279, 1222, 1142, 1059, 980, 915, 747 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{27}O_3$ $[M + H]^+$ 303.1960, found 303.1979.



(*E*)-1-(3-benzyloxiran-2-yl)-10-hydroxyundec-8-en-4-one (3-44)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.33 (m, 2H), 7.20-7.26 (m, 3H), 5.48-5.61 (m, 2H), 4.24 (p, *J* = 6.4, 1H), 2.87-2.93 (m, 2H), 2.73-2.82 (m, 2H), 2.39 (t, *J* = 7.6, 2H), 2.35 (t, *J* = 7.6, 2H),

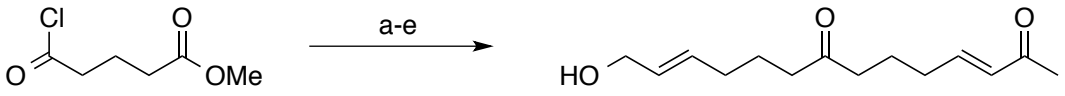
2.06 (br, 1H), 2.00 (q, J = 6.8, 2H), 1.54-1.74 (m, 5H), 1.48 (p, J = 7.2, 1H), 1.24 (d, J = 6.4, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 210.5, 137.3, 135.2, 129.6, 128.9, 128.6, 126.6, 68.6, 58.6, 58.4, 42.0, 41.9, 38.4, 31.5, 31.2, 23.5, 23.1, 20.2; IR (neat) 3450, 3061, 2968, 2930, 1709, 1604, 1494, 1452, 1409, 1370, 1138, 1063, 970, 743 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{29}O_3$ $[M + H]^+$ 317.2117, found 317.2095.



(*R*)-2-phenyl-1-((2*S*,6*S*,8*S*)-8-((*E*)-prop-1-en-1-yl)-1,7-dioxaspiro [5.5]undecan-2-yl)ethanol (3-45)

The general rearrangement procedure was followed with **3-44** (12.0 mg, 0.038 mmol), $O_3ReOSiPh_3$ (1.0 mg, 0.002 mmol), and CH_2Cl_2 (3.8 mL). The reaction was initiated at -78 °C followed by warming to -30 °C, stir at -30 °C (90 min) until complete consumption of starting compound, then the reaction mixture was warmed up to 0 °C and strred at 0 °C for 4 hrs. The final isomerization was monitored closely by TLC, the reaction was quenched immediately with five drops of pyridine when the mixture of isomers change to one major with tiny amount of minor product (Longer reaction time increase the ration between major and minor products with the price of reduced yield). After evaporation of the solvent, the crude mixture was purified by flash chromatography (10%-15% ethyl acetate in hexanes) to give the product (8.5 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21-7.35 (m, 5H), 5.55 (ddq, J = 0.8, 6.4, 15.6, 1H), 5.46 (ddq, J = 1.2, 6.4, 15.6, 1H), 3.94 (dd, J = 6.0, 11.6, 1H), 3.85 (p, J = 4.4, 1H), 3.58 (ddd, J = 2.4, 4.8, 11.6, 1H), 2.98 (dd, J = 4.4, 13.6, 1H), 2.68 (dd, J = 9.2, 13.6, 1H), 1.97 (br, 1H), 1.88 (tq, J = 4.0, 12.8, 2H), 1.72-1.80 (m, 1H), 1.69 (d, J = 6.4, 3H), 1.54-1.66 (m, 5H), 1.35-1.48 (m, 3H), 1.25-1.34 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 138.8, 132.3, 129.3, 128.5, 126.9, 126.3, 96.6, 75.1, 71.5, 70.0, 39.3, 35.5, 35.0,30.8, 24.8, 18.8, 18.3, 17.9; IR (neat)

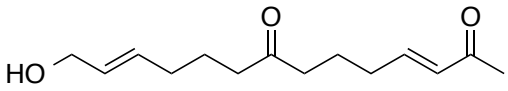
3464, 3060, 2937, 2868, 1603, 1495, 1453, 1439, 1377, 1279, 1221, 1203, 1142, 1042, 979, 746 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{29}O_3$ $[M + H]^+$ 317.2117, found 317.2141.



Reaction Cconditions:

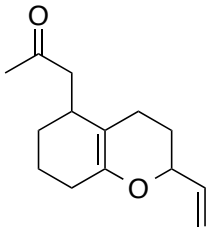
a) Pent-4-en-1-ylmagnesium bromide, Et_2O, 0 ºC, 74%; B) DIBAL-H, CH_2Cl_2, -78 ºC, 88%; c) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2; d) Diethyl (2-oxopropyl)phosphonate, NaH, THF, 79% for two steps; e) (*Z*)-2-Butene-1,4-diol, Grubbs-Hoveyda 2nd generation matathesis catalyst, CH_2Cl_2, 68%.

Scheme B9 Synthesis of substrate **3-53**



(3*E*, 12*E*)-14-Hydroxytetradeca-3, 12-diene-2, 8-dione (3-53)

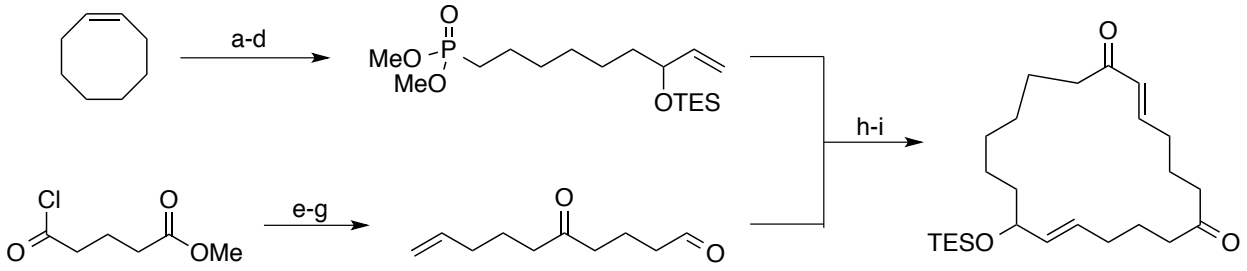
^1H NMR (400 MHz, $CDCl_3$) δ 6.74 (dt, *J* = 6.8, 16.0 Hz, 1H), 6.06 (dt, *J* = 1.6, 16.0 Hz, 1H), 5.44-5.68 (m, 2H), 4.04-4.17 (m, 2H), 2.36-2.45 (m, 4H), 2.18-2.26 (m, 2H), 2.23 (s, 3H), 1.99-2.09 (m, 2H), 1.75 (p, *J* = 7.6 Hz, 2H), 1.66 (p, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.1, 198.7, 147.3, 131.8, 130.0, 63.5, 42.1, 41.7, 31.8, 31.5, 26.9, 23.0, 21.9; IR (neat) 3445, 3000, 2935, 1709, 1672, 1626, 1413, 1363, 1256, 1186, 1090, 974 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{22}O_3$ $[M]^+$ 238.1569, found 238.1595.



1-(2-vinyl-3,4,5,6,7,8-hexahydro-2*H*-chromen-5-yl)propan-2-one (3-58)

The general rearrangement procedure was followed with **3-53** (25.0 mg, 0.105 mmol), Re_2O_7 (2.5 mg, 0.005 mmol), and CH_2Cl_2 (2.5 mL). The reaction was stirred at 20 °C 2h and then quenched with five drops of pyridine. After evaporation of the solvent, the crude mixture was purified by flash chromatography (5%-10%

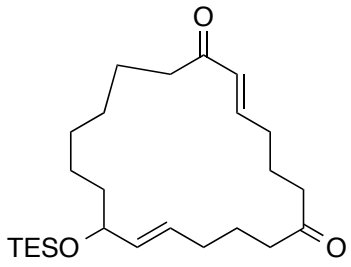
ethyl acetate in hexanes) to give the product (12.9 mg, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84-5.96 (m, 1H), 5.29 (dt, *J* = 1.6, 17.2, 0.55H), 5.26 (dt, *J* = 1.6, 17.2, 0.45H), 5.13-5.19 (m, 1H), 4.29-4.34 (m, 0.45H), 4.17-4.23 (m, 0.55H), 2.65 (dd, *J* = 4.0, 15.6, 0.55H), 2.51-2.61 (m, 1.45H), 2.26-2.40 (m, 1H), 2.16 (d, *J* = 6.4, 3H), 2.08-2.12 (m, 2.45H), 1.85-1.98 (m, 2H), 1.50-1.80 (m, 5H), 1.35-1.45 (m, 0.55). ^{13}C NMR (100 MHz, $CDCl_3$) 209.2, 209.1, 147.8, 147.3, 138.2, 137.9, 115.7, 115.5, 106.2, 105.6, 75.4, 75.0, 48.1, 47.5, 34.7, 33.2, 30.63, 30.56, 28.9, 28.3, 27.9, 27.63, 27.55, 23.4, 22.2, 20.4, 19.0; IR (neat) 2929, 2860, 1713, 1682, 1446, 1408, 1360, 1241, 1167, 1080, 991, 925 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{21}O_2$ $[M+H]^+$ 221.1536, found 221.1530.



Reaction conditions:

a) O_3, Na_2CO_3, DCM, MeOH,-78 ºC, then Et_3N, Ac_2O, DCM, 0 ºC, 81%; b) Vinylmagnesium bromide, THF, -78 ºC to rt, 49%; c) TESCl, DMAP, imidazole, DCM, rt, 89%; d) dimethyl methylphosphonate, nBuLi, THF, -78 ºC to rt, 62%; e) Pent-4-en-1-ylmagnesium bromide, Et_2O, 0 ºC, 74%; f) DIBAL-H, -78 ºC, DCM, 88%; g) DMSO, $(COCl)_2$, Et_3N, DCM, -78 ºC to rt; h) NaH, THF, 0 ºC, 65% for two steps; i) Grubbs-Hoveyda 2nd generation matathesis catalyst, toluene, 110 ºC.

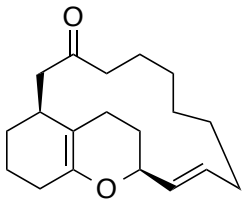
Scheme B10 Synthesis of substrate **3-59**



Macrocycle (3-59)

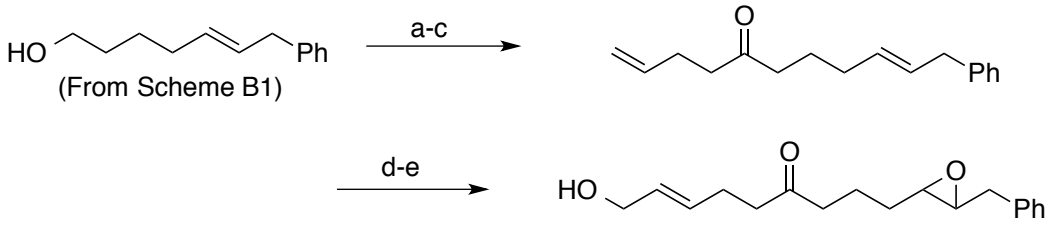
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (dt, *J* = 7.6, 15.6, 1H), 6.13 (dt, *J* = 1.2, 15.6, 1H), 5.28-5.43 (m, 2H), 4.98-4.04 (m, 1H), 2.48 (t, *J* = 6.8, 2H), 2.25-2.36 (m, 6H), 2.08-2.20 (m, 1H), 1.92-2.02 (m, 1H), 1.78-1.85 (m, 2H), 1.59-1.72 (m, 4H), 1.39-1.59 (m, 2H), 1.22-1.34 (m, 4H), 1.12-1.22 (m,

2H), 0.93 (t, J = 8.0, 9H), 0.57 (q, J = 8.0, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.2, 201.8, 146.8, 135.1, 131.8, 129.8, 73.5, 41.7, 40.9, 40.2, 38.3, 31.3, 31.2, 29.7, 29.5, 26.3, 25.1, 22.6, 21.3, 6.8, 4.9.



Macrocycle (3-60)

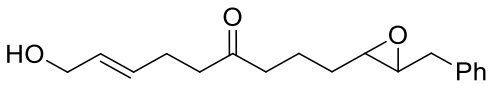
The general rearrangement procedure was followed with **3-60** (10.0 mg, 0.024 mmol), Re_2O_7 (1.2 mg, 0.002 mmol), and CH_2Cl_2 (6.0 mL). The reaction was stirred at 20 °C 3h and then quenched with five drops of pyridine. After evaporation of the solvent, the crude mixture was purified by flash chromatography (5%-10% ethyl acetate in hexanes) to give the product (2.8 mg, 41%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.43-5.52 (m, 1H), 5.33-5.37 (m, 1H), 4.65-4.70 (m, 1H), 2.73 (dd, J = 3.2, 15.2, 1H), 2.27-2.47 (m, 4H), 1.95-2.23 (m, 5H), 1.85-1.95 (m, 1H), 1.77-1.84 (m, 1H), 1.66-1.77 (m, 3H), 1.50-1.65 (m, 4H), 1.21-1.59 (m, 5H), 1.12-1.21 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) 211.0, 146.3, 130.6, 130.5, 105.0, 72.0, 46.3, 42.8, 36.1, 31.2, 29.1, 27.7, 27.2, 26.6, 25.8, 25.6, 21.6, 21.4, 20.6; IR (neat) 2926, 2855, 1709, 1676, 1444, 1409, 1375, 1244, 1170, 1139, 1085, 1012, 967 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{29}O_2$ $[M+H]^+$ 289.2168, found 289.2220.



Reaction Conditions:

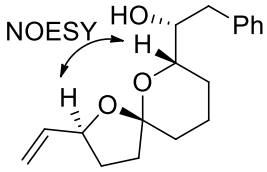
a) PCC, celite, DCM, 20 ºC; b) But-3-en-1-ylmagnesium bromide, Et_2O, 0 ºC, 77% for two steps; c) PCC celite, DCM, 20 ºC, 86%; d) MCPBA, $NaHCO_3$, DCM, 0 ºC, 49%; e) But-2-ene-1,4-diol, Hoveyda-Grubbs 2nd, DCM, 20 ºC,71% (dr = 9 :1).

Scheme B11 Synthesis of substrate **3-63**



(*E*)-1-(3-benzyloxiran-2-yl)-9-hydroxynon-7-en-4-one (3-63)

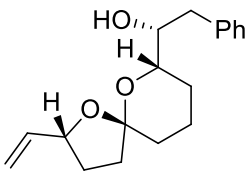
^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.27-7.33 (m, 2H), 7.19-7.26 (m, 3H), 5.57-5.68 (m, 2H), 4.01 (br, 2H), 2.76-2.89 (m, 3H), 2.73 (t, J = 5.6, 1H), 2.43 (t, J = 7.2, 2H), 2.39 (t, J = 7.2, 2H), 2.22-2.30 (m, 2H), 1.60-1.73 (m, 3H), 1.41-1.59 (m, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2) 209.9, 138.1, 131.1, 130.5, 129.3, 128.8, 126.9, 63.6, 58.8, 58.6, 42.4, 42.3, 38.8, 31.6, 26.6, 20.5; IR (neat) 3433,3027, 2929, 2862, 1710, 1494, 1453, 1410, 1373, 1089, 1007, 972, 745 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{25}O_3$ $[M + H]^+$ 289.1804, found 289.1829.



(*R*)-2-phenyl-1-((2*S*,5*R*,7*S*)-2-vinyl-1,6-dioxaspiro[4.5]decan-7-yl) ethanol (3-64)

The general rearrangement procedure was followed with **3-63** (29.0 mg, 0.101 mmol), Re_2O_7 (2.4 mg, 0.005 mmol), and CH_2Cl_2 (10.0 mL). The reaction was stirred at 20 °C for 3 hrs and then quenched with five drops of pyridine. After evaporation of the solvent, the crude mixture was purified by flash chromatography (10%-15% ethyl acetate in hexanes) to give the product (27.5 mg, 95%, **32**:**33** = 50:49). ^{1}H NMR (400 MHz, C_6D_6) δ 7.19-7.23 (m, 2H), 7.13-7.19 (m, 2H), 7.05-7.10 (m, 1H), 5.82 (ddd, J = 6.4, 10.4, 16.8, 1H), 5.22 (dt, J = 1.6, 16.8, 1H), 4.98 (dt, J = 1.6, 10.4, 1H), 4.49 (q, J = 6.4, 1H), 3.85 (ddd, J = 2.4, 5.2, 11.6, 1H), 3.75-3.83 (m, 1H), 2.83 (dd, J = 3.6, 14.0, 1H), 2.66 (dd, J = 9.2, 14.0, 1H), 1.87-2.19 (m, 2H), 1.77-1.87 (m, 1H), 1.59-1.67 (m, 3H), 1.47-1.59 (m, 3H), 1.31-1.47 (m, 2H); ^{13}C NMR (100 MHz, C_6D_6) 135.4, 129.5, 128.3, 127.6, 126.1, 114.0, 106.4, 78.7, 74.9, 73.3, 39.3, 37.5, 33.6, 30.3, 25.0, 19.8; IR (neat) 3463, 3027, 2945, 2872, 1644, 1603, 1495, 1454, 1439, 1370, 1271, 1222,

1071,1036, 988, 874, 748 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{25}O_3$ $[M + H]^+$ 289.1804, found 289.1828.



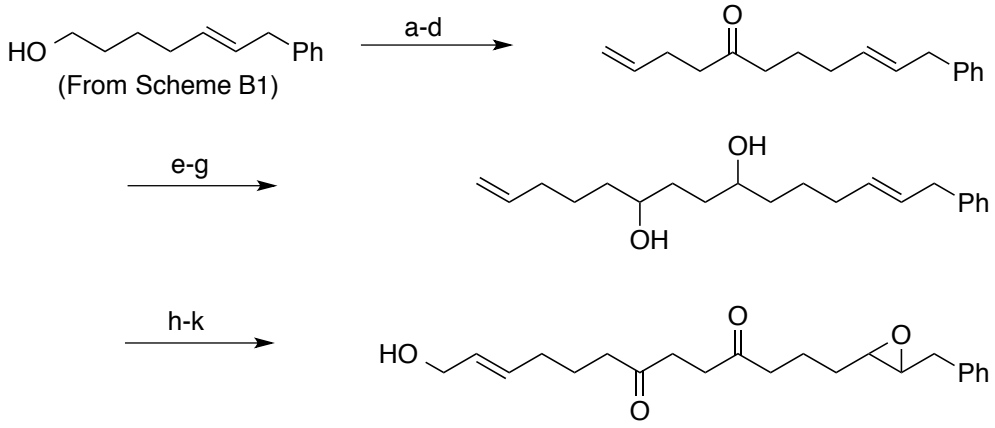
(*R*)-2-phenyl-1-((2*R*,5*R*,7*S*)-2-vinyl-1,6-dioxaspiro[4.5]decan-7-yl) ethanol (3-65)

^1H NMR (300 MHz, C_6D_6) δ 7.12-7.23 (m, 4H), 7.04-7.11 (m, 1H), 5.91 (ddd, *J* = 7.2, 10.2, 17.4, 1H), 5.10 (ddd, *J* = 1.2, 1.8, 17.2, 1H), 4.95 (ddd, *J* = 0.9, 1.8, 10.4, 1H), 4.35 (q, *J* = 7.2, 1H), 3.96 (ddd, *J* = 2.4, 5.1, 11.4, 1H), 3.74-3.83 (m, 1H), 2.88 (dd, *J* = 3.9, 13.8, 1H), 2.69 (dd, *J* = 9.3, 13.8, 1H), 1.78-2.05 (m, 3H), 1.56-1.76 (m, 4H), 1.30-1.55 (m, 5H); ^{13}C NMR (100 MHz, C_6D_6) 141.1, 139.4, 129.4, 128.3, 126.0, 114.4, 106.2, 81.6, 75.1, 73.0, 39.5, 38.9, 33.6, 30.6, 25.1, 19.8; IR (neat) 3463, 3026, 2943, 2870, 1643, 1603, 1495, 1454, 1370, 1296, 1220, 1034, 988, 875, 747 cm^{-1}; HRMS (ESI) calcd for for $C_{18}H_{25}O_3$ $[M + H]^+$ 289.1804, found 289.1832.

The relative stereochemistry was determined by a combination of ^1H NMR, ^{13}C NMR, COSY, NOESY. While both **3-65** and **3-65** showed similar ^1H NMR, ^{13}C NMR and COSY spectra, only structure **3-64** showed a NOESY coupling of the two ethereal hydrogens as indicated because of their spacial proximity.

The two stereoisomers were resubmitted to the following isomerization conditions: ~20mM solution, 5% Re_2O_7, stirred at 20 °C for 18 hrs (no obvious change after 12hrs) then quenched with 5 drops of pyridine. After After evaporation of the solvent, the crude mixture was purified by flash chromatography (10%-15% ethyl acetate in hexanes) to give the product (yield for each

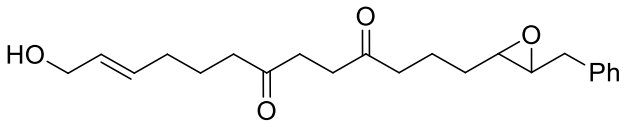
isomerization: ~90%-95%, dr = 11:9). Isomerization of **3-64** gave additional 19% of **3-65** while isomerization of **3-64** gave additional 22% of **3-65**. Thus after one recycling of isomerization: a total yield of 69% could be obtained for **3-64** and a total yield of 63% could be obtained for **3-65**. A second recycling gave a total yield of 78% for **3-64** and a total yield of 75% for **3-65**.



Reaction Conditions:

a) PCC, celite, DCM, 20 ºC; b)Allylmagnesium bromide, Et_2O, 0 ºC, 69% for two steps; c) TBSCl, DMAP, imidazole, DCM, 20 ºC; d) 9-BBM, THF, then 3.0 M NaOH and 30% H_2O_2, 0 ºC, 72%; e) Py•SO_3, DMSO, Et_3N, DCM, 0-20 ºC,; f) Pent-4-en-1-ylmagnesium bromide, Et_2O, 0 ºC; g) TBAF, THF, 20 ºC, 76% for three steps; h) PCC, celite, DCM, 20 ºC, 84%; i) MCPBA, $NaHCO_3$, DCM, 0 ºC, 49%; i) But-2-ene-1,4-diol, Hoveyda-Grubbs 2nd, DCM, 20 ºC, 81% (dr = 9 :1).

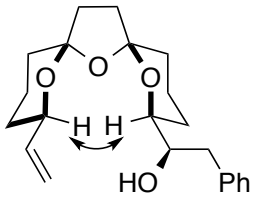
Scheme B12 Synthesis of substrate **3-66**



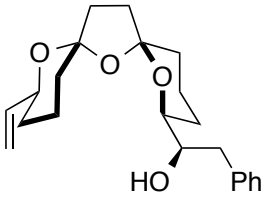
(*E*)-1-(3-benzyloxiran-2-yl)-13-hydroxytrid-ec-11-ene-4,7-dione (3-66)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.33 (m, 2H), 7.20-7.26 (m, 3H), 5.57-5.68 (m, 2H), 4.07 (d, *J* = 3.6, 2H), 2.87-2.93 (m, 2H), 2.72-2.81 (m, 2H), 2.59-2.68 (m, 4H), 2.43-2.49 (m, 4H), 2.02-2.09 (m, 2H), 1.83 (br, 1H), 1.62-1.75 (m, 4H), 1.47-1.63 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 209.3, 209.2, 137.4, 131.9, 130.1, 128.9, 128.6, 126.6, 63.6, 58.6, 58.4, 42.0, 41.9, 38.5, 36.1, 36.0, 31.6, 31.1, 22.9, 20.2; IR (neat) 3463, 3026, 2940, 2869, 1711, 1603, 1495, 1454, 1438,

1365, 1236, 1164, 1076, 1028, 970, 752 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{30}O_4Na$ $[M + Na]^+$ 381.2042, found 381.2014.



3-67



3-68

Spirotricycles 3-67 and 3-68

The general rearrangement procedure was followed with **3-66** (32.0 mg, 0.089 mmol), 10% Re_2O_7 supported on SiO_2 (21.6 mg, 0.0045 mmol), and CH_2Cl_2 (8.9 mL). The reaction was stirred at 20 °C for 2.5 hrs and then quenched with five drops of pyridine. After evaporation of the solvent, the crude mixture was purified by flash chromatography (10%-15% ethyl acetate in hexanes) to give the product (26.2 mg, 82%, **3-67**:**3-68** = 4:5).

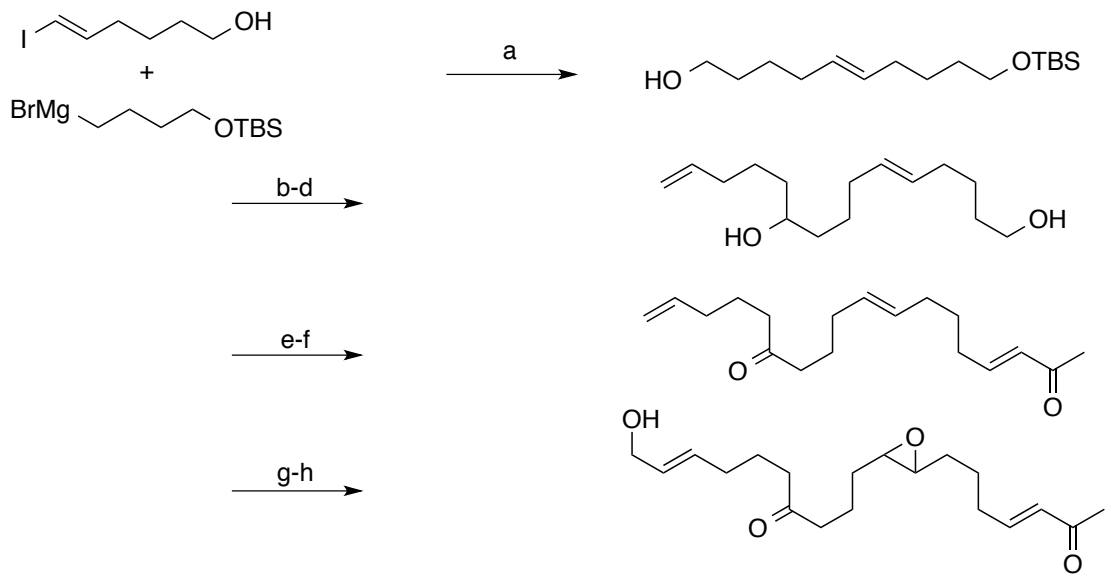
Faster eluting major isomer **3-68**: ^1H NMR (400 MHz, C_6D_6) δ 7.12-7.21 (m, 4H), 7.05-7.11 (m, 1H), 5.90 (ddd, *J* = 5.2, 10.4, 17.2, 1H), 5.27 (dt, *J* = 1.6, 17.2, 1H), 5.01 (dt, *J* = 1.6, 10.4, 1H), 4.42 (ddddd, *J* = 2.0, 2.8, 3.6, 5.2, 11.2, 1H), 3.85 (ddd, *J* = 2.0, 5.2, 11.6, 1H), 3.77 (h, *J* = 4.4, 1H), 2.87 (dd, *J* = 4.0, 14.0, 1H), 2.72 (dd, *J* = 8.4, 14.0, 1H), 1.80-2.06 (m, 6H), 1.45-1.71(m, 9H), 1.20-1.42 (m, 2H); ^{13}C NMR (100 MHz, C_6D_6) 140.1, 139.2, 129.5, 128.3, 126.1, 113.2, 107.1, 106.8, 74.9, 73.3, 71.3, 39.4, 36.7, 36.6, 35.0, 34.7, 31.0, 25.1, 20.3, 20.0; IR (neat) 3466, 3062, 2942, 2867, 1646, 1603, 1495, 1453, 1438, 1366, 1265, 1232, 1123, 1073, 1034, 969, 877, 747 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{30}O_4Na$ $[M + Na]^+$ 381.2042, found 381.2051.

Slower eluting minor isomer **3-67**: ^1H NMR (300 MHz, C_6D_6) δ 7.23-7.29 (m, 2H), 7.16-7.20 (m, 2H), 7.05-7.11 (m, 1H), 5.91 (ddd, *J* = 5.2, 10.8, 17.2, 1H), 5.32 (dt, *J* = 1.6, 17.2, 1H), 5.02 (dt, *J* = 1.6, 10.4, 1H), 4.40 (ddddd, *J* = 1.2, 1.6, 2.8, 5.2, 11.6, 1H), 3.94 (ddd, *J* = 2.0, 5.2, 11.6, 1H),

3.84 (h, J = 4.4, 1H), 3.03 (dd, J = 3.6, 14.0, 1H), 2.77 (dd, J = 9.6, 14.0, 1H), 2.22-2.29 (m, 1H), 2.12-2.19 (m, 1H), 1.84-1.98 (m, 2H), 1.78 (d, J = 4.0, 1H), 1.66-1.73 (m, 1H), 1.34-1.62 (m, 10H), 1.20-1.31 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6) ; IR (neat) 140.0, 139.8, 129.5, 128.3, 126.0, 113.3, 107.3, 107.2, 75.0, 74.8, 72.3, 39.7, 37.5, 37.4, 34.8, 30.9, 25.4, 20.1, 19.9 cm^{-1}; HRMS (ESI) calcd for for $C_{22}H_{30}O_4Na$ $[M + Na]^+$ 381.2042, found 381.2043.

The relative stereochemistry was determined by a combination of ^{1}H NMR, ^{13}C NMR, COSY, NOESY. While both **3-67** and **3-68** showed similar ^{1}H NMR, ^{13}C NMR and COSY spectra, only structure **3-67** showed a NOESY coupling of the two ethereal hydrogens as indicated because of their spacial proximity.

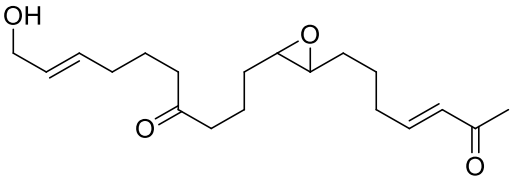
The two stereoisomers were resubmitted to the following isomerization conditions: ~10mM solution, 5% Re_2O_7, stirred at 20 °C for 12 hrs then quenched with 5 drops of pyridine. After After evaporation of the solvent, the crude mixture was purified by flash chromatography (10%-20% ethyl acetate in hexanes) to give the product (yield for each isomerization: ~80%, dr = 5:4). Isomerization of **3-68** gave additional 15% of **3-67** while isomerization of **3-67** gave additional 16% of **3-68**. Thus after one recycling of isomerization: a total yield of 50% could be obtained for **3-67** and a total yield of 62% could be obtained for **3-68**.



Reaction Conditions:

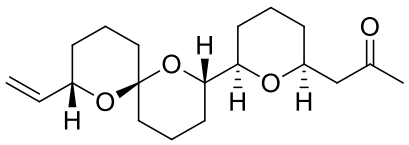
a) $Cl_2Pd(dppf)_2$, Et_2O, 20 ºC, 79%; b) Py•SO_3, DMSO, Et_3N, DCM, 0-20 ºC, 86%; c) Pent-4-en-1-ylmagnesium bromide, Et_2O, 0 ºC, 85%; d) TBAF, THF, 20 ºC, 69%; e) PCC, celite, DCM, 20 ºC, 66%; f) 60% NaH dispersed in mineral oil, diethyl (2-oxopropyl)phosphonate, THF, 0 ºC, 87%; g) MCPBA, $NaHCO_3$, DCM, 0 ºC, 70%; h) But-2-ene-1,4-diol, Hoveyda-Grubbs 2nd generation alkene metathesis catalyst, DCM, 20 ºC, 69% (dr = 1:1).

Scheme B13 Synthesis of substrate **3-69**



(*E*)-10-hydroxy-1-(3-((*E*)-6-oxohept-4-en-1-yl) oxiran-2-yl)dec-8-en-4-one (3-69)

^{1}H NMR (400 MHz, CD_2Cl_2) δ 6.76 (dt, *J* = 6.8, 16.0, 1H), 6.03 (dt, *J* = 1.6, 16.0, 1H), 5.56-5.67 (m, 2H), 4.02 (br, 2H), 2.60-2.65 (m, 2H), 2.43 (t, *J* = 7.2, 2H), 2.38 (t, *J* = 7.2, 2H), 2.26 (dq, *J* = 1.6, 7.2, 2H), 2.19 (s, 3H), 1.99-2.07 (m, 2H), 1.39-1.70 (m, 11H); ^{13}C NMR (100 MHz, CD_2Cl_2) 210.1, 198.2, 147.5, 131.6, 131.5, 130.1, 63.3, 58.1, 57.9, 42.1, 41.8, 32.1, 31.53, 31.46, 31.4, 26.6, 24.6, 23.1, 20.2; IR (neat) 3451, 2934, 2862, 11708, 1672, 1626, 1431, 1364, 1256, 1089, 976, 893 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{30}O_4Na$ $[M + Na]^+$ 345.2042, found 345.2071.



1-((2*S*,6*R*)-6-((2*S*,6*S*,8*S*)-8-vinyl-1,7-dioxaspiro[5.5]undecan-2-yl) tetrahydro-2H-pyran-2-yl)propan-2-one (3-70)

The general rearrangement procedure was followed with **3-69** (25.2 mg, 0.078 mmol), Re_2O_7 (1.9 mg, 0.004 mmol), and CH_2Cl_2 (7.8 mL). The reaction was stirred at 20 °C for 8 hrs and then quenched with five drops of pyridine. After evaporation of the solvent, the crude mixture was purified by flash chromatography (10%-15% ethyl acetate in hexanes) to give the product (21.2 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (ddd, *J* = 5.2, 10.4, 17.2, 1H), 5.23 (dt, *J* = 1.6, 17.2, 1H), 5.07 (dt, *J* = 1.6, 10.4, 1H), 4.04 (ddddd, *J* = 1.2, 1.6, 2.8, 5.2, 11.6, 1H), 3.77 (dddd, *J* = 1.2, 4.4, 8.8, 10.4, 1H), 3.42 (ddd, *J* = 2.0, 8.0, 10.4, 1H), 3.18 (ddd, *J* = 2.0, 8.0, 10.4, 1H), 2.64 (dd, *J* = 8.8, 14.8, 1H), 2.41 (dd, *J* = 4.4, 14.8, 1H), 2.18 (s, 3H), 1.95-2.03 (m, 1H), 1.78-1.94 (m, 4H), 1.49-1.69 (m, 7H), 1.33-1.44 (m, 2H), 1.21-1.32 (m, 2H), 1.05-1.21 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 207.8, 139.5, 114.3, 96.1, 80.9, 74.8, 71.8, 69.7, 50.4, 35.6, 35.2, 31.7, 30.9, 30.7, 28.3, 27.8, 23.0, 18.8, 18.3; IR (neat) 3078, 2936, 2861, 1716, 1646, 1438, 1371, 1279, 1224, 1202, 1134, 1089, 1040, 981, 914, 861 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{30}O_4Na$ [M + Na]$^+$ 345.2042, found 345.2007.

APPENDIX C

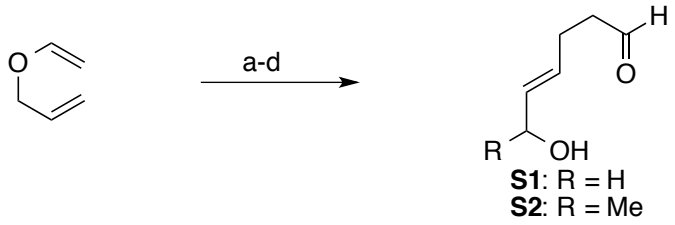
HETEROCYCLE SYNTHESIS BASED ON ALLYLIC ALCOHOL TRANSPOSITION USING TRACELESS TRAPPING GROUPS

General Information ^{1}H NMR and ^{13}C NMR spectra were taken on a Bruker Avance 300 spectrometer at 300 MHz and 75 MHz respectively, a Bruker Avance 400 spectrometer at 400 MHz and 100 MHz, a Bruker Avance 500 spectrometer at 500 MHz and 125 MHz if specified. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. The solvent peak was used as a reference value, for ^{1}H NMR: $CDCl_3$ = 7.27 ppm, CD_2Cl_2 = 5.31 ppm, C_6D_6 = 7.16 ppm, for ^{13}C NMR: $CDCl_3$ = 77.2, CD_2Cl_2 = 53.52, C_6D_6 = 128.37 . Data are reported as follows: m=multiplet, s = singlet; d = doublet; t = triplet; q = quartet; p = pentet; dd = doublet of doublets; dt = doublet of triplets; br = broad. High resolution and low-resolution mass spectra were collected on a VG 7070 spectrometer. Infrared (IR) spectra were taken on a Mattson Cygnus 100 spectrometer. Samples for IR were prepared as thin films on a NaCl plates by dissolving the corresponding compounds in CH_2Cl_2 followed by evaporation of the CH_2Cl_2. Methylene chloride was distilled under N_2 from CaH_2. Analytical TLC was performed on E. Merck pre-coated (25 mm) silica gel 60F-254 plates. Visualization was done under UV (254 nm). Flash chromatography was done using ICN SiliTech 32-63 60 Å silica gel. Reagent grade

ethyl acetate, diethyl ether, pentane and hexanes (commercial mixture) were purchased from EM Science and used as is for chromatography. All reactions were performed in oven or flame-dried glassware under a positive pressure of N_2 with magnetic stirring unless otherwise noted. Product volatility dictated yield determination by NMR in many cases. NMR-based yield determinations were conducted in accord with a validated protocol that was previously reported.[53] Primary data for these analyses are included with the spectra. When possible products were purified and characterized following yield determination.

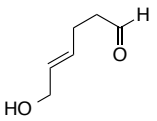
General procedure for Re_2O_7- catalyzed cyclization

To a solution (~20 mM) of corresponding substrate and Et_3SiH or nucleophile (2 equiv) in CH_2Cl_2 (DCM) or CH_2ClCH_2Cl (DCE) was added Re_2O_7 (0.03 equiv). The reaction mixture was stirred at rt (unless otherwise noted) and monitored by TLC until complete consumption of the starting material, after which the reaction was quenched by adding a few drops of pyridine or triethylamine. The solvent was removed under vacuum and the crude product was purified by flash chromatography or preparative TLC to give the product.



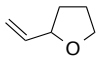
Reagents and conditions
a) 150 °C, quantitative. b) BnOH, *p*-TsOH, Na_2SO_4, 64%. c) (*Z*)-2-Butene-1,4-diol or (Z)-hex-3-ene-2,5-diol, Grubbs-Hoveyda 2nd generation metathesis catalyst, CH_2Cl_2. d) CF_3CO_2H, CH_2Cl_2, H_2O, 30% (R = H) or 57% (R = Me) (two steps).

Scheme C1 Synthesis of substrates **S1** and **S2**



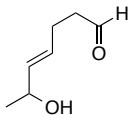
(*E*)-6-Hydroxyhex-4-enal (S1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (t, *J* = 1.2 Hz, 1H), 5.51-5.73 (m, 2H), 4.06 (d, *J* = 3.2 Hz, 2H), 2.53 (dt, *J* = 1.2, 6.8 Hz, 2H), 2.32-2.40 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.1, 130.4, 130.2, 63.2, 43.0, 24.6; IR (neat) 3371, 2924, 2856, 2730, 1721, 1671, 1443, 1411, 1362, 1245, 1179, 1110, 1026, 971 cm^{-1}; LRMS calcd for C_6H_8O $[M\text{-}H_2O]^+$ 96, found 96. Note: HRMS was not possible for this compound due to its low molecular weight. GC evidence for purity is included in the spectra section.



2-Vinyltetrahydrofuran (4-5)

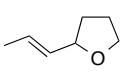
The general reductive cyclization procedure was followed with **S1** (22 mg, 0.19 mmol), Et_3SiH (44 mg, 0.38 mmol), Re_2O_7 (2.7 mg, 0.0057 mmol), and DCM (9.4 mL). The reaction was stirred at rt for 48 h, then was quenched with 5 drops of pyridine. After evaporation of the solvent under slightly reduced presssure, 5 μl of benzyldimethylsilane was added into the crude as an internal standard. The mixture was dissolved in $CDCl_3$ and ^{1}H NMR showed a yield of 85%. ^{1}H NMR data for this compound matched those from a prior study.[85]



(*E*)-6-Hydroxyhept-4-enal (S2)

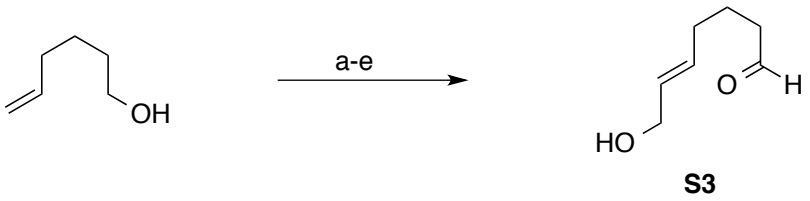
^{1}H NMR (300 MHz, CD_2Cl_2) δ 9.72 (t, *J* = 1.5 Hz, 1H), 5.49-5.66 (m, 2H), 4.20 (p, *J* = 6.3 Hz, 1H), 2.46-2.53 (m, 2H), 2.28-2.36 (m, 2H), 1.91 (br, 1H), 1.19 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 202.29, 136.0, 128.4, 68.7, 43.5, 25.0, 23.6; IR (neat) 3393, 2970, 2925, 2850, 2725, 1725, 1443, 1409, 1389, 1369, 1313, 1186, 1141, 1107, 1057, 969, 871 cm^{-1}; LRMS calcd for $C_7H_{10}O$ $[M\text{-}H_2O]^+$ 110, found 110. Note: HRMS was not possible for

this compound due to its low molecular weight. GC evidence for purity is included in the spectra section.



(*E*)-2-(Prop-1-en-1-yl)tetrahydrofuran (4-6)

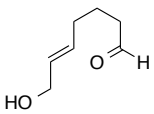
The general rearrangement cyclization procedure was followed with **S2** (28 mg, 0.22 mmol), Et_3SiH (51 mg, 0.44 mmol), Re_2O_7 (3.2 mg, 0.0057 mmol), and DCM (11 mL). The reaction was stirred at rt for 48 h, then was quenched with 5 drops of pyridine. After evaporation of the solvent under slightly reduced presssure, 5 μl of benzyldimethylsilane was added into the crude as an internal standard. The mixture was dissolved in $CDCl_3$ and ^1H NMR showed a yield of 90%. ^1H NMR data matched those from a previously prepared sample.[86]



S3

Reagents and conditions
a) PCC, Celite, CH_2Cl_2. b) Methyl acrylate, Grubbs-Hoveyda 2nd generation metathesis catalyst, CH_2Cl_2, reflux, 72% (two steps). c) $(MeO)_3CH$, PPTs, MeOH, 50 °C, 88%. d) DIBAL-H, CH_2Cl_2, –78 °C. e) HOAc, H_2O (1:1), rt, 91% (two steps).

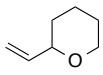
Scheme C2 Synthesis of substrate **S3**



(*E*)-7-Hydroxyhept-5-enal (S3)

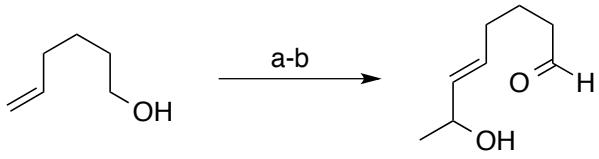
^1H NMR (300 MHz, $CDCl_3$) δ 9.71-9.76 (m, 1H), 5.50-5.72 (m, 2H), 3.90-4.20 (m, 2H), 2.43 (t, J = 7.2 Hz, 2H), 2.00-2.13 (m, 2H), 1.93 (br, 1H), 1.70 (p, J = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.6, 131.4, 130.3, 63.4, 43.1, 31.4, 21.4; IR (neat) 3399, 2996, 2935, 2862, 2726, 1721, 1676, 1456, 1438, 1364, 1208, 1169, 1112, 972, 840 cm^{-1}; LRMS calcd

for $C_7H_{10}O$ $[M\text{-}H_2O]^+$ 110, found 110. Note: HRMS was not possible for this compound due to its low molecular weight. GC evidence for purity is included in the spectra section.



2-Vinyltetrahydro-*2H*-pyran (4-7)

The general rearrangement cyclization procedure was followed with **S3** (23 mg, 0.18 mmol), Et_3SiH (42 mg, 0.36 mmol), Re_2O_7 (2.6 mg, 0.0054 mmol), and DCM (9.0 mL). The reaction was stirred at rt for 96 h, then was quenched with 5 drops of pyridine. After evaporation of the solvent under slightly reduced presssure, 5 μl of benzyldimethylsilane was added into the crude as an internal standard. The mixture was dissolved in $CDCl_3$ and ^1H NMR showed a yield of 70%. ^1H NMR data for this compound matched those from a from a prior study.[2]

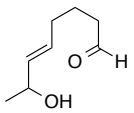


Reagents and conditions

a) PCC, Celite, CH_2Cl_2; b) (*Z*)-hex-3-ene-2,5-diol, Grubbs-Hoveyda 2nd generation metathesis catalyst, CH_2Cl_2, rt, 43% for two steps.

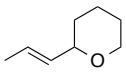
Scheme C3 Synthesis of substrate **4-34**

(*E*)-7-Hydroxyoct-5-enal (25)



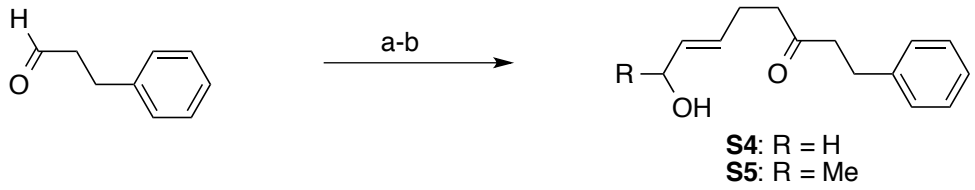
^1H NMR (400 MHz, $CDCl_3$) δ 9.72 (t, *J* = 1.6, 1H), 5.42-5.59 (m, 2H), 4.20 (t, *J* = 6.4 Hz, 1H), 2.41 (dt, *J* = 1.6, 7.2 Hz, 2H), 2.05 (br, 1H), 2.03 (q, *J* = 6.4 Hz, 2H), 1.69 (p, *J* = 7.2 Hz, 2H), 1.21 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.7, 135.5, 129.2, 68.6, 43.1, 31.3, 23.4, 21.4; IR (neat) 3408, 2971, 2930, 2870, 2722, 1722, 1670, 1454, 1392,

1368, 1142, 1105, 1060, 971, 864 cm^{-1}; HRMS (EI) calcd for $C_8H_{14}O_2$ $[M]^+$ 142.0994, found 141.1006.



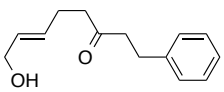
(*E*)-2-(Prop-1-en-1-yl)tetrahydro-*2H*-pyran (4-8)

The general reductive cyclization procedure was followed with **25** (21 mg, 0.15 mmol), Et_3SiH (34 mg, 0.29 mmol), Re_2O_7 (2.1 mg, 0.0044 mmol), and DCM (7.4 mL). The reaction was stirred at rt for 36 h, then was quenched with 5 drops of pyridine. After evaporation of the solvent under slightly reduced presssure, 5 μl of benzyldimethylsilane was added into the crude as an internal standard. The mixture was dissolved in $CDCl_3$ and ^1H NMR showed a yield of 87%. The 1H NMR was compared to the literature for the same compound. ^1H NMR data for this compound matched those from a prior study.[3]



Reagents and conditions
a) But-3-en-1-ylmagnesium bromide, Et_2O, 0 °C, 66%. b) PCC, Celite, CH_2Cl_2, 94%. c) (Z)-2-Butene-1,4-diol or (Z)-hex-3-ene-2,5-diol, Grubbs-Hoveyda 2nd generation metathesis catalyst, CH_2Cl_2, rt, 51% (R = H), 65% (R = Me).

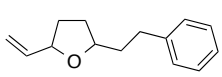
Scheme C4 Synthesis of substrates **S4** and **S5**



(*E*)-8-Hydroxy-1-phenyloct-6-en-3-one (S4)

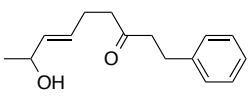
^1H NMR (400 MHz, $CDCl_3$) δ 7.27-7.34 (m, 2H), 7.17-7.25 (m, 3H), 5.61-5.72 (m, 2H), 4.09 (d, *J* = 3.6, 2H), 2.93 (t, *J* = 7.6, 2H), 2.76 (t, *J* = 7.6, 2H), 2.52 (t, *J* = 7.2, 2H), 2.35 (p, *J* = 6.8, 2H, 1.59 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.3, 141.0, 131.0,

130.0, 128.5, 128.3, 126.1, 63.5, 42.3, 42.2, 29.7, 26.2. IR (neat) 3406, 3061, 3027, 2924, 1710, 1603, 1495, 1453, 1407, 1371, 1091, 1003, 972, 750, 700 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{17}O$ $[M\text{-}OH]^+$ 201.1279, found 201.1286.



2-Phenethyl-5vinyltetrahydrofuran (4-9)

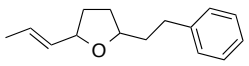
The general reductive cyclization procedure was followed with **S4** (26 mg, 0.12 mmol), Et_3SiH (28 mg, 0.24 mmol), Re_2O_7 (1.7 mg, 0.0036 mmol), and DCM (6 mL). The reaction was stirred at rt for 20 h, then was quenched with 5 drops of pyridine. After evaporation of the solvent, the crude material was purified by flash chromatography (1-5% ethyl acetate in hexanes) to give the product (21 mg, 86%, dr = 57:43). ^1H NMR (400 MHz, $CDCl_3$) δ 7.26-7.32 (m, 2H), 7.17-7.25 (m, 3H), 5.82-5.95 (m, 1H), 5.22-5.32 (m, 1H), 5.08-5.14 (m, 1H), 4.42-4.48 (m, 0.43H), 4.29-4.36 (m, 0.57H), 4.01-4.08 (m, 0.43H), 3.89-3.97 (m, 0.57H), 2.75-2.84 (m, 1H), 2.64-2.74 (m, 1H), 1.89-2.17 (m, 3H), 1.75-1.86 (m, 1H), 1.65-1.74 (m, 1H), 1.53-1.65 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 139.7, 139.6, 128.4, 128.3, 125.7, 115.2, 114.9, 80.1, 79.6, 79.1, 78.6, 37.81, 37.76, 32.58, 32.54, 32.0, 31.8, 31.1; IR (neat) 3083, 3062, 3026, 2932, 2862, 1603, 1495, 1454, 1426, 1107, 1051, 989, 921, 746, 699 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{19}O$ $[M+H]^+$ 203.1436, found 203.1420.



(*E*)-8-Hydroxy-1-phenylnon-6-en-3-one (S5)

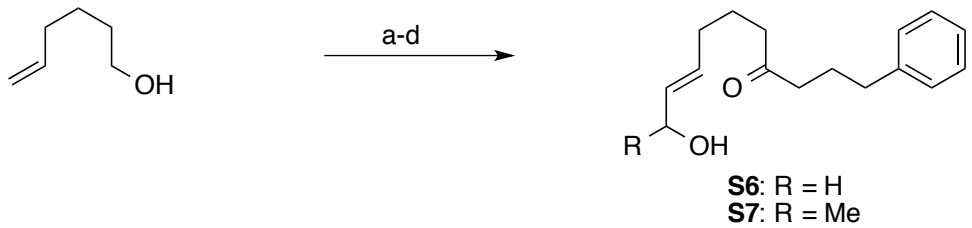
^1H NMR (400 MHz, $CDCl_3$) δ 7.28-7.33 (m, 2H), 7.18-7.24 (m, 3H), 5.50-5.66 (m, 2H), 4.26 (p, *J* = 6.4 Hz, 1H), 2.93 (t, *J* = 7.2 Hz, 2H), 2.76 (d, *J* = 7.2 Hz, 2H), 2.50 (d, *J* = 7.2 Hz, 2H), 2.31 (t, *J* = 7.2 Hz, 2H), 1.80 (br, 1H), 1.26 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.3, 141.0, 135.2, 128.8, 128.5, 128.3, 126.1, 68.6, 44.3, 42.3,

29.7, 26.1, 23.4; IR (neat) 3405, 3027, 2968, 2925, 1710, 1603, 1495, 1453, 1407, 1369, 1063, 970, 749, 700 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{21}O_2$ $[M+H]^+$ 233.1542, found 233.1527.



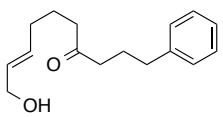
(*E*)-2-Phenethyl-5-(prop-1-en-1-yl)tetrahydrofuran (4-10)

The general reductive cyclization procedure was followed with **S5** (45 mg, 0.19 mmol), Et_3SiH (45 mg, 0.38 mmol), Re_2O_7 (2.8 mg, 0.0058 mmol), and DCM (9.6 mL). The reaction was stirred at 0 °C for 24 h, then was quenched with 5 drops of pyridine. After evaporation of the solvent, 5 μl of benzyldimethylsilane was added into the crude as an internal standard, then the mixture was dissolved in $CDCl_3$ and ^1H NMR showed a yield of 57% (dr = 1:1). ^1H NMR (400 MHz, $CDCl_3$) δ 7.26-7.32 (m, 2H), 7.16-7.25 (m, 3H), 5.65-5.77 (m, 1H), 5.46-5.55 (m, 1H), 4.37 (q, *J* = 7.2 Hz, 0.5H), 4.24 (q, *J* = 7.2 Hz, 0.5H), 4.03 (p, *J* = 6.8 Hz, 0.5H), 3.88 (p, *J* = 6.8 Hz, 0.5H), 2.74-2.83 (m, 1H), 2.62-2.72 (m, 1H), 2.04-2.11 (m, 1H), 1.87-2.03 (m, 2H), 1.74-1.85 (m, 1H), 1.71 (d, *J* = 6.4 Hz, 3H), 1.53-1.68 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.3, 142.27, 132.5, 132.4, 128.4, 128.3, 127.7, 127.4, 125.7, 80.2, 79.5, 78.8, 78.5, 37.9, 37.8, 32.9, 32.59, 32.56, 32.3, 32.0, 31.3, 17.75, 17.71; IR (neat) 3061, 3026, 2934, 2859, 1603, 1495, 1453, 1377, 1047, 1000, 964, 927, 746, 699 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{21}O$ $[M+H]^+$ 217.1592, found 217.1604.



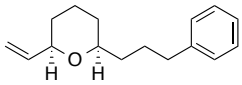
Reagents and conditions
a) PCC, Celite, CH_2Cl_2. b)(3-Phenylpropyl)magnesium bromide, Et_2O, 0 °C, 60% (two steps). c) PCC, Celite, CH_2Cl_2, 97%. c) (Z)-2-Butene-1,4-diol or (Z)-hex-3-ene-2,5-diol, Grubbs-Hoveyda 2nd generation metathesis catalyst, CH_2Cl_2, rt, 66% (R = H), 77% (R = Me).

Scheme C5 Synthesis of substrates **S6** and **S7**



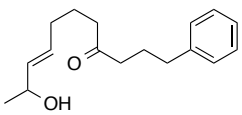
(*E*)-10-Hydroxy-1-phenyldec-8-en-4-one (S6)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.33 (m, 2H), 7.17-7.24 (m, 3H), 5.60-5.70 (m, 2H), 4.04-4.18 (m, 2H), 2.63 (t, *J* = 7.6 Hz, 2H), 2.42 (t, *J* = 7.6 Hz, 2H), 2.40 (t, *J* = 7.6 Hz, 2H), 2.12 (br, 1H), 2.02-2.09 (m, 2H), 1.92 (p, *J* = 7.2 Hz, 2H), 1.67 (p, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.0, 141.6, 131.8, 129.9, 128.5, 128.4, 126.0, 63.5, 42.00, 41.98, 35.1, 31.6, 25.2, 23.1; IR (neat) 3405, 3061, 3025, 2934, 2861, 1709, 1603, 1496, 1453, 1408, 1372, 1091, 999, 971, 748, 700 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{22}O_2$ $[M]^+$ 246.1620, found 246.1622.



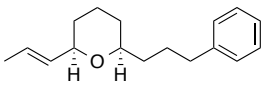
***Cis*-2-(3-phenylpropyl)-6-vinyltetrahydro-2H-pyran (4-11)**

The general reductive cyclization procedure was followed with **S6** (30 mg, 0.12 mmol), Et_3SiH (29 mg, 0.25 mmol), Re_2O_7 (1.8 mg, 0.0037 mmol), and DCM (6.2 mL). The reaction was stirred at rt for 15 h then was quenched with 5 drops of pyridine. After evaporation of the solvent, the crude residue was purified by flash chromatography (1-5% ethyl acetate in hexanes) to give the product (26 mg, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.31 (m, 2H), 7.16-7.22 (m, 3H), 5.88 (ddd, *J* = 4.2, 10.4, 17.2 Hz, 1H), 5.25 (dt, *J* = 1.6, 17.2 Hz, 1H), 5.09 (dt, *J* = 1.6, 10.4 Hz, 1H), 3.82 (ddddd, *J* = 0.8, 1.6, 2.4, 5.2, 10.8 Hz, 1H), 3.36 (dddd, *J* = 2.4, 5.2, 8.8, 9.2 Hz, 1H), 2.64 (t, *J* = 7.2 Hz, 2H), 1.76-1.91 (m, 2H), 1.45-1.75 (m, 6H), 1.15-1.36 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.7, 139.7, 128.5, 128.3, 114.4, 78.3, 77.7, 36.2, 36.0, 31.5, 31.3, 27.5, 23.6; IR (neat) 3083, 3062, 3025, 2934, 2857, 1603, 1495, 1453, 1439, 1409, 1367, 1310, 1201, 1130, 1091, 1048, 988, 917, 748, 698 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{23}O$ $[M+H]^+$ 231.1749, found 231.1748.



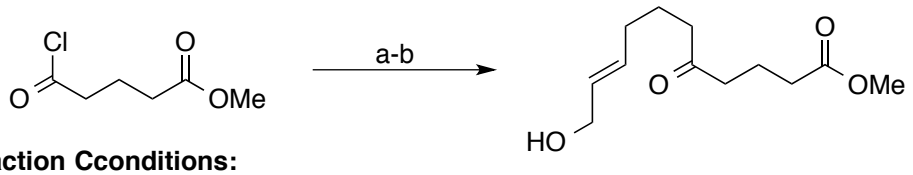
(*E*)-10-Hydroxy-1-phenylundec-8-en-4-one (S7)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.34 (m, 2H), 7.18-7.24 (m, 3H), 5.45-5.65 (m, 2H), 4.28 (p, *J* = 6.4 Hz, 1H), 2.64 (t, *J* = 7.2 Hz, 2H), 2.43 (t, *J* = 7.2 Hz, 2H), 2.40 (t, *J* = 7.2 Hz, 2H), 2.04 (q, *J* = 6.8 Hz, 2H), 1.93 (p, *J* = 7.6 Hz, 2H), 1.68 (p, *J* = 7.6 Hz, 2H), 1.63 (br, 1H), 1.27 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.8, 141.6, 135.1, 129.8, 128.5, 128.4, 126.0, 68.8, 42.01, 41.98, 35.1, 31.5, 25.2, 23.5, 23.1; IR (neat) 3405, 3026, 2930, 1709, 1603, 1496, 1453, 1408, 1370, 1063, 970, 937, 748, 700 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{23}O_2$ $[M-H]^+$ 259.1698, found 259.1697.



***Cis*-2-(3-Phenylpropyl)-6-((*E*)-prop-1-en-1-yl)tetrahydro-2H-pyran (4-12)**

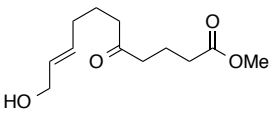
The general reductive cyclization procedure was followed with **S7** (45 mg, 0.17 mmol), Et_3SiH (40 mg, 0.34 mmol), Re_2O_7 (2.5 mg, 0.0052 mmol), and DCM (8.6 mL). The reaction was stirred at 0 °C for 30 h, then was quenched with 5 drops of pyridine. After evaporation of the solvent, 5 μl of benzyldimethylsilane was added into the crude mixture as an internal standard, then the mixture was dissolved in $CDCl_3$ and ^{1}H NMR was taken to determine a 62% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.30 (m, 2H), 7.15-7.21 (m, 3H), 5.68 (ddq, *J* = 1.2, 6.4, 15.2 Hz, 1H), 5.52 (ddq, *J* = 1.6, 6.0, 15.2 Hz, 1H), 3.75 (dd, *J* = 6.4, 10.8 Hz, 1H), 3.34 (dddd, *J* = 1.6, 5.2, 5.6, 12.4 Hz, 1H), 2.63 (t, *J* = 7.2 Hz, 2H), 1.73-1.88 (m, 2H), 1.70 (d, *J* = 6.4 Hz, 3H), 1.58-1.72 (m, 3H), 1.42-1.53 (m, 3H), 1.13-1.36 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.7, 132.8, 128.5, 128.2, 126.3, 125.6, 78.2, 77.7, 36.3, 36.1, 31.7, 31.2, 27.6, 23.6, 17.9; IR (neat) 3061, 3025, 2933, 2856, 1603, 1459, 1453, 1439, 1377, 1325, 1198, 1078, 1034, 964, 934, 747, 698 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{25}O$ $[M+H]^+$ 245.1905, found 245.1911.



Reaction Cconditions:

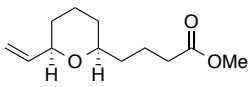
a) Pent-4-en-1-ylmagnesium bromide, Et_2O, 0 ºC, 74%; B) (*Z*)-2-Butene-1,4-diol, Grubbs-Hoveyda 2nd generation matathesis catalyst,CH_2Cl_2, 54%.

Scheme C6 Synthesis of substrate **4-13**



Methyl (*E*)-11-hydroxy-5-oxonudec-9-enoate (4-13)

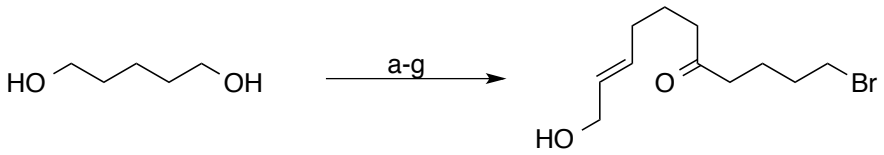
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.41-5.87 (m, 2H), 4.05-4.18 (m, 2H), 3.67 (s, 3H), 2.46 (t, *J* = 7.2 Hz, 2H), 2.41 (t, *J* = 7.2 Hz, 2H), 2.34 (t, *J* = 7.2 Hz, 2H), 1.98-2.12 (m, 2H), 1.89 (p, *J* = 7.2 Hz, 2H), 1.67 (p, *J* = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.1, 173.7, 132.0, 130.0, 63.6, 51.6, 41.9, 41.6, 33.0, 31.5, 23.0, 18.9; IR (neat) 3447, 2949, 2868, 1735, 1711, 1438, 1414, 1375, 1315, 1254, 1202, 1172, 1092, 1004, 972 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{21}O_4$ $[M+H]^+$ 229.1440, found 229.1446.



Methyl 4-(*Cis*-6-vinyltetrahydro-2H-pyran-2-yl) butanoate (4-14)

The general reductive cyclization procedure was followed with **4-13** (26 mg, 0.12 mmol), Et_3SiH (27 mg, 0.23 mmol), Re_2O_7 (1.7 mg, 0.0034 mmol), and DCM (5.7 mL). The reaction was stirred at rt for 30 h, then was quenched with 5 drops of pyridine. After evaporation of the solvent, 5 μl of benzyldimethylsilane was added into the crude mixture as an internal standard, then the mixture was dissolved in $CDCl_3$. ^{1}H NMR was taken to show a yield of 81%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (ddd, *J* = 5.2, 10.8, 17.2 Hz, 1H), 5.22 (dt, *J* = 1.6, 17.2 Hz, 1H), 5.07 (dt, *J* = 1.6, 10.8 Hz, 1H), 3.80 (ddddd, *J* = 1.2, 1.2, 2.4, 4.8, 10.4 Hz, 1H), 3.66 (s, 3H), 3.34 (dddd, *J* = 2.0, 5.2, 7.2, 11.2 Hz, 1H), 2.27-2.40 (m, 2H), 1.67-1.90 (m, 3H),

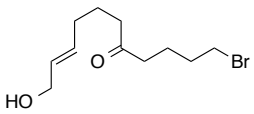
1.42-1.65 (m, 5H), 1.15-1.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 139.6, 114.3, 78.2, 77.3, 51.5, 35.8, 34.1, 31.4, 31.2, 23.5, 21.1; IR (neat) 2935, 2844, 1740, 1455, 1437, 1365, 1310, 1247, 1199, 1172, 1091, 1045, 1021, 989, 917 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{21}O_3$ $[M+H]^+$ 213.1491, found 213.1508.



Reaction Cconditions:

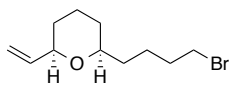
a) NaH, THF, then TBSCl, 0 ºC, 56%; b) Py•SO_3, DMSO, Et_3N, CH_2Cl_2, 88%; c) Pent-4-en-1-ylmagnesium bromide, Et_2O, 0 ºC, 70%; d) Py•SO_3, DMSO, Et_3N, CH_2Cl_2, 79%; e)Bu_4NF, THF, 100%; f) CBr_4, Ph_3P, CH_2Cl_2, 0 ºC, 80%; g) (*Z*)-2-Butene-1,4-diol, Grubbs-Hoveyda 2nd generation matathesis catalyst,CH_2Cl_2, 55%.

Scheme C7 Synthesis of substrate **4-15**



(*E*)-1-Bromo-11-hydroxyundec-9-en-5-one (4-15)

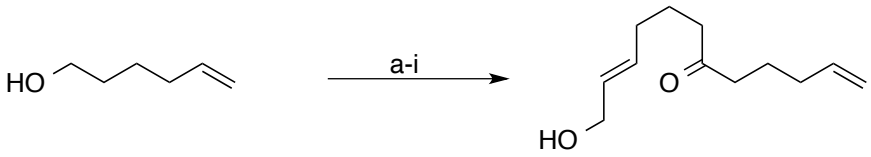
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.29-5.93 (m, 2H), 4.07-4.16 (m, 2H), 3.39 (t, *J* = 6.6 Hz, 2H), 2.41 (q, *J* = 6.6 Hz, 4H), 1.99-2.12 (m, 2H), 1.84 (p, *J* = 6.6, 2H), 1.60-1.76 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.3, 131.9, 129.9, 63.5, 41.9, 417, 33.3, 32.1, 31.5, 23.0, 22.3; IR (neat) 3405, 2936, 2867, 1710, 1438, 1409, 1373, 1254, 1237, 1089, 999, 971, 740, 645 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{18}BrO$ $[M-OH]^+$ 245.0541, found 245.0539.



***Cis*-2-(4-Bromobutyl)-6-vinyltetrahydro-2H-pyran (4-16)**

The general reductive cyclization procedure was followed with **4-15** (47 mg, 0.18 mmol), Et_3SiH (42 mg, 0.35 mmol), Re_2O_7 (2.6 mg, 0.0054 mmol), and DCM (8.9 mL). The reaction was stirred at rt for 24 h, then was quenched with 5 drops of pyridine. After

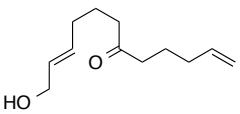
evaporation of the solvent, the crude mixture was purified by flash chromatography (1-5% ethyl acetate in hexanes) to give the product (41 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (ddd, *J* = 5.2, 10.4, 17.2 Hz, 1H), 5.23 (dt, *J* = 1.6, 17.2 Hz, 1H), 5.08 (dt, *J* = 1.6, 10.4 Hz, 1H), 3.80 (ddddd *J* = 1.0, 1.6, 2.6, 5.2, 10.8 Hz, 1H), 3.41 (t, *J* = 7.2 Hz, 2H), 3.33 (dddd, *J* = 1.6, 4.4, 4.8, 12.0 Hz, 1H), 1.82-1.91 (m, 3H), 1.40-1.67 (m, 7H), 1.14-1.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6, 114.3, 78.2, 77.5, 35.6, 33.9, 32.9, 31.4, 31.3, 24.3, 23.6. IR (neat) 3011, 2935, 2859, 1646, 1455, 1438, 1409, 1367, 1310, 1254, 1239, 1205, 1127, 1078, 1046, 988, 919, 737, 648 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{18}BrO$ $[M-H]^+$ 245.0541, found 245.0540.



Reaction Cconditions:

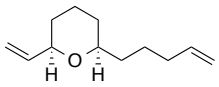
a) PCC, Celite, CH_2Cl_2; b) Methyl acrylate, Grubbs-Hoveyda 2nd generation metathesis catalyst, CH_2Cl_2, reflux, 72% for two steps; c) $(MeO)_3CH$, PPTS, MeOH, 50 ºC, 88%; d)DIBAL-H, CH_2Cl_2, -78 ºC; e) HOAC, H_2O (1:1), 91% for two steps; f) TBSCl, imidazole, CH_2Cl_2, 58%; g) Pent-4-en-1-ylmagnesium bromide, Et_2O, 0 ºC, 80%; h) Py•SO_3, DMSO, Et_3N, CH_2Cl_2, i) Bu_4NF, THF, 85% for two steps.

Scheme C8 Synthesis of substrate **4-17**



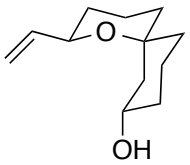
(*E*)-12-Hydroxydodeca-1,10-dien-6-one (4-17)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67-7.81 (m, 1H), 5.55-5.67 (m, 2H), 4.90-5.03 (m, 2H), 3.99-4.10 (m, 2H), 2.38 (t, *J* = 7.5 Hz, 4H), 2.02 (q, *J* = 6.6 Hz, 4H), 1.95 (br, 1H), 1.64 (p, *J* = 7.5 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.1, 138.0, 131.9, 129.9, 115.2, 63.5, 42.0, 41.9, 33.1, 31.6, 23.1, 22.8; IR (neat) 3405, 3076, 2934, 2865, 1710, 1640, 1439, 1411, 1372, 1089, 999, 971, 913 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{19}O$ $[M-OH]^+$ 179.1436, found 179.1427.



***Cis*-2-(pent-4-en-1-yl)-6-vinyltetrahydro-2H-pyran (4-18)**

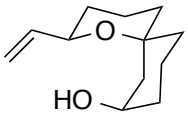
The gneral reductive cyclization procedure was followed with **4-17** (38 mg, 0.19 mmol), Et_3SiH (45 mg, 0.38 mmol), Re_2O_7 (2.8 mg, 0.0058 mmol), and DCM (9.6 mL). The reaction was stirred at rt for 20 h, then was quenched with 5 drops of pyridine. After evaporation of the solvent, 5 μl of benzyldimethylsilane was added into the crude residue as an internal standard. The mixture was dissolved in $CDCl_3$ and ^1H NMR showed a yield of 90 %. ^1H NMR (400 MHz, C_6D_6) δ 5.82 (ddd, J = 5.2, 10.4, 17.2 Hz, 1H), 5.80 (ddt, J = 6.8, 10.0, 17.2 Hz, 1H), 5.22 (d, J = 17.2 Hz, 1H), 5.07 (d, J = 10.4 Hz, 1H), 4.99 (dd, J = 1.2, 17.2 Hz, 1H), 4.93 (d, J = 10.0 Hz, 1H), 3.80 (dd, J = 4.0, 10.4 Hz, 1H), 3.32 (p, J = 5.2 Hz, 1H), 2.05 (p, J = 6.8 Hz, 2H), 1.80-1.89 (m, 1H), 1.37-1.65 (m, 7H), 1.13-1.34 (m, 2H); ^{13}C NMR (100 MHz, C_6D_6) δ 139.7, 139.0, 114.4, 114.3, 78.2, 77.7, 36.0, 33.9, 31.5, 31.3, 24.9, 23.6; IR (neat) 3077, 2934, 2858, 1641, 1456, 1439, 1410, 1367, 1310, 1199, 1079, 1048, 988, 910 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{19}O$ $[M-H]^+$ 179.1436, found 179.1445.



***rac*-(2*R*,6*R*,8*S*)-2-vinyl-1-oxaspiro(5,5)undecan-8-ol (4-19)**

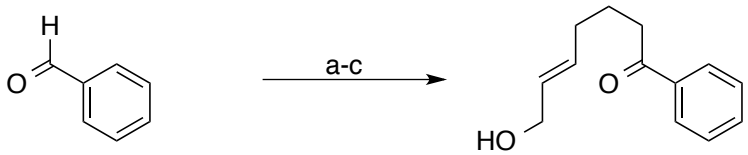
The gneral reductive cyclization procedure was followed with **4-17** (36.6 mg, 0.187 mmol), no Et_3SiH, Re_2O_7 (2. mg, 0.0056 mmol), and DCM (9.3 mL). The reaction was stirred at rt for 10 h, then was quenched with 5 drops of pyridine. After evaporation of the solvent, the crude residue was purified by flash chromatography (10-30% ethyl acetate in hexanes) to give **4-19** (slow eluting, 26.3 mg, 71.9%) and **4-20** (fast eluting, 7.9 mg, 21.6%). ^1H NMR (400 MHz, $CDCl_3$) δ 5.82 (ddd, J = 5.2, 10.8, 17.6 Hz, 1H), 5.21 (dt, J = 1.6, 17.6, 1H), 5.05 (dt, J = 1.6, 10.8, 1H), 4.05 (ddddd, J = 0.8, 1.2, 1.6, 4.8, 11.6, 1H), 3.76 (tt,

J = 4.0, 11.2, 1H), 2.69 (dddd, *J* = 2.0, 2.4, 4.4, 13.2, 1H), 1.94-2.02 (m, 1H), 1.69-1.86 (m, 3H), 1.61-1.69 (m, 2H), 1.54-1.61 (m, 2H), 1.24-1.46 (m, 2H), 1.13-1.31 (m, 3H), 0.89 (dd, *J* = 11.2, 13.2, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 140.2, 114.0, 74.1, 70.1, 67.0, 39.1, 38.4, 36.1, 36.0, 31.5, 19.5, 19.2; IR (neat) 3338, 2935, 2866, 1645, 1450, 1365, 1312, 1248, 1200, 1152, 1113, 1041, 1015, 990, 919, 855, 809 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{21}O_2$ $[M+H]^+$ 197.1542, found 197.1565.



***rac*-(2*R*,6*R*,8*R*)-2-vinyl-1-oxaspiro(5,5)undecan-8-ol (4-20)**

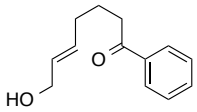
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (ddd, *J* = 4.6, 10.4, 17.2, 1H), 5.27 (dt, *J* = 1.6, 17.2, 1H), 5.09 (dt, *J* = 1.6, 10.4, 1H), 4.23 (dd, *J* = 5.6, 11.2, 1H), 3.92-3.40 (m, 1H), 3.54 (d, *J* = 10.0, 1H), 2.45-2.53 (m, 1H), 1.93-2.05 (m, 1H), 1.60-1.82 (m, 5H), 1.37-1.55 (m, 4H), 1.20-1.35 (m, 4H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 139.3, 115.0, 74.2, 71.6, 67.7, 39.9, 36.4, 34.1, 33.3, 31.5, 19.0, 15.9; IR (neat) 3430, 2936, 2864, 1724, 1645, 1554, 1450, 1408, 1361, 1294, 1205, 1120, 1102, 1066, 1023, 986, 920, 803 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{21}O_2$ $[M+H]^+$ 197.1542, found 197.1514.



Reaction Cconditions:

a) Pent-4-en-1-ylmagnesium bromide, Et_2O, 0 ºC, 89%; b) PCC, Celite, CH_2Cl_2, rt, 98%; c) (*Z*)-2-Butene-1,4-diol,Grubbs-Hoveyda 2nd generation metathesis catalyst, CH_2Cl_2, 67%.

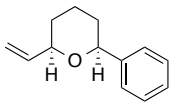
Scheme C9 Synthesis of substrate **4-21**



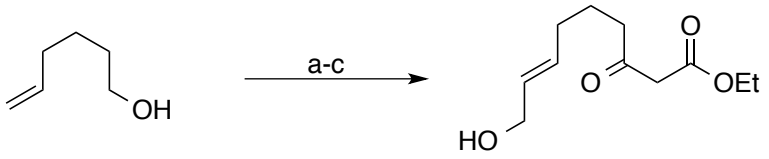
(*E*)-7-Hydroxy-1-phenylhept-5-en-1-one (4-21)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92-7.97 (m, 2H), 7.51-7.58 (m, 1H), 7.42-7.48 (m, 2H), 4.07-4.18 (m, 2H), 2.97 (t, *J* = 6.8 Hz, 2H), 2.11-2.20 (m, 2H), 1.84 (p, *J* = 6.8 Hz, 2H), 1.78 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.3, 137.0, 133.0, 132.0, 130.0, 128.6, 128.0, 63.6, 37.8, 31.7, 23.6; IR (neat) 3399, 3060, 2934, 2865, 1681, 1597, 1580, 1448, 1408, 1368, 1227, 1200, 1181, 1158, 1087, 972, 740, 691 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{17}O_2$ $[M+H]^+$ 205.1224, found 205.1218.

***Cis*-2-phenyl-6-vinyltetrahydro-2H-pyran (4-22)**



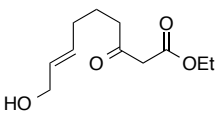
The general reductive cyclization procedure was followed with **4-21** (38 mg, 0.18 mmol), Et_3SiH (43 mg, 0.37 mmol), Re_2O_7 (2.7 mg, 0.0055 mmol), and DCM (9.2 mL). The reaction was stirred at rt for 24 h, then was quenched with 5 drops of pyridine. After evaporation of the solvent, the crude residue was purified by flash chromatography (1-5% ethyl acetate in hexanes) to give the product (32 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.44 (m, 2H), 7.31-7.38 (m, 2H), 7.24-7.30 (m, 1H), 5.98 (ddd, *J* = 1.6, 10.8, 17.6 Hz, 1H), 5.33 (dt, *J* = 1.6, 17.6 Hz, 1H), 5.13 (dt, *J* = 1.6, 10.8 Hz, 1H), 4.46 (dd, *J* = 2.4, 11.2 Hz, 1H), 4.06 (ddddd *J* = 0.8, 1.6, 2.4, 5.2, 11.2 Hz, 1H), 1.96-2.04 (m, 1H), 1.83-1.90 (m, 1H), 1.69-1.82 (m, 2H), 1.39-1.60 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 139.5, 128.2, 127.2, 125.9, 114.4, 79.8, 78.7, 33.7, 31.3, 24.0; IR (neat) 3064, 3029, 2936, 2855, 1645, 1604, 1495, 1452, 1438, 1410, 1374, 1352, 1300, 1256, 1210, 1131, 1078, 1048, 988, 917, 951, 698 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{15}O$ $[M-H]^+$ 187.1123, found 187.1126.



Reaction Cconditions:

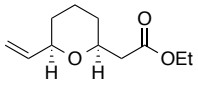
a) PCC, Celite, CH_2Cl_2, rt; b) Ethyl diazoacetate, $SnCl_2$, CH_2Cl_2, 79% for two steps; c) (*Z*)-2-Butene-1,4-diol,Grubbs-Hoveyda 2nd generation metathesis catalyst, CH_2Cl_2, 31%.

Scheme C10 Synthesis of substrate **4-23**



Ethyl (*E*)-9-hydroxy-3-oxonon-7-enoate (4-23)

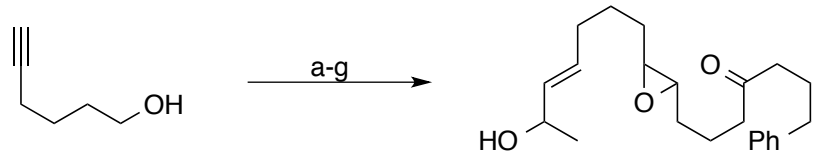
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.40-5.80 (m, 2H), 4.17 (q, *J* = 7.2, Hz 2H), 4.06 (d, *J* = 3.6 Hz, 2H), 3.41 (s, 2H), 2.53 (t, *J* = 7.2 Hz, 2H), 2.00-2.12 (m, 2H), 1.85 (br, 1H), 1.69 (p, *J* = 7.2 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.6, 167.3, 131.6, 130.2, 63.4, 61.4, 49.4, 42.1, 31.4, 22.7, 14.1; IR (neat) 3421, 2983, 2936, 1741, 1714, 1646, 1445, 1411, 1368, 1315, 1258, 1180, 1091, 1028, 972 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{17}O_3$ $[M\text{-}OH]^+$ 197.1178, found 197.1182.



Ethyl 2-(*Cis*-6-vinyltetrahydro-2H-pyran-2-yl) acetate (4-24)

The general reductive cyclization procedure was followed with **4-23** (34 mg, 0.16 mmol), Et_3SiH (37 mg, 0.31 mmol), Re_2O_7 (2.3 mg, 0.0047 mmol), and DCE (7.9 mL). The reaction was stirred at 55 °C for 20 h, then was quenched with 5 drops of pyridine. After evaporation of the solvent, 5 μl of benzyldimethylsilane was added to the crude residue as an internal standard. The mixture was dissolved in $CDCl_3$ and ^{1}H NMR was used to determine a yield of 85%. ^{1}H NMR (400 MHz, C_6D_6) δ 5.82 (ddd, *J* = 5.2, 10.8, 17.2 Hz, 1H), 5.25 (dt, *J* = 1.6, 17.2 Hz, 1H), 4.98 (dt, *J* = 1.6, 10.8 Hz, 1H), 3.96 (q, *J* = 6.8 Hz, 2H), 3.83 (dddd, *J* = 2.0, 5.6, 7.6, 10.8 Hz, 1H), 3.68 (ddddd, *J* = 1.2, 1.6, 2.8, 5.2, 10.8 Hz, 1H), 2.59 (dd, *J* = 7.2, 14.8

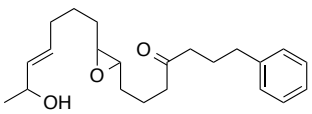
Hz, 1H), 2.26 (dd, *J* = 5.6, 14.8 Hz, 1H), 1.47-1.54 (m, 1H), 1.34-1.41 (m, 1H), 1.28-1.34 (m, 1H), 1.18-1.28 (m, 1H), 1.10-1.18 (m, 1H), 0.99-1.09 (m, 1H), 0.95 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 170.4, 139.6, 113.3, 77.8, 74.1, 59.8, 41.7, 31.2, 30.8, 23.2, 13.9; IR (neat) 2982, 2936, 2860, 1738, 1647, 1440, 1411, 1370, 1336, 1295, 1248, 1191, 1150, 1134, 1075, 1042, 989, 921, 875 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{18}O_3$ $[M]^+$ 198.1256, found 198.1251.



Reaction Cconditions:

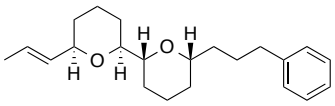
a) DIBAL-H, hexanes, rt, then I_2, THF, -78 ºC; b) Pent-e-en-1-ylmagnesium bromide, $(dppf)_2PdCl_2$, Et_2O, 52% for two steps; c) PCC, Celite, CH_2Cl_2, 84%; d) (3-Phenylpropyl)magnesium bromide, Et_2O, 0 ºC; e) PCC, Celite, Ch_2Cl_2, 98%; f) MCPBA, $NaHCO_3$, Ch_2Cl_2, 0 ºC, 73%; g) (*Z*)-2-Butene-1,4-diol,Grubbs-Hoveyda 2nd generation metathesis catalyst, CH_2Cl_2, 61%.

Scheme C11 Synthesis of substrate **4-25**



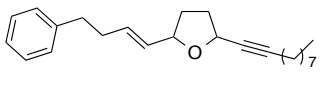
(*E*)-1-(3-(6-Hydroxyhept-4-en-1-yl)oxiran-2-yl)-7-phenylheptan-4-one (4-25)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.32 (m, 2H), 7.15-7.22 (m, 3H), 5.50-5.66 (m, 2H), 4.26 (p, *J* = 6.4 Hz, 1H), 2.60-2.68 (m, 4H), 2.39-2.48 (m, 4H), 2.03-2.12 (m, 2H), 1.92 (p, *J* = 7.2 Hz, 2H), 1.87 (br, 1H), 1.71 (p, *J* = 7.2, 2H), 1.40-1.64 (m, 6H), 1.26 (d, *J* = 6.4, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.4, 141.6, 134.9, 130.0, 128.5, 128.4, 126.0, 68.7, 58.4, 58.3, 42.2, 41.9, 35.1, 31.8, 31.43, 31.41, 25.5, 25.2, 23.5, 20.3; IR (neat) 3446, 3025, 2930, 2859, 1710, 1602, 1496, 1453, 1409, 1370, , 1145, 1064, 892, 747, 700 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{32}O_3Na$ $[M+Na]^+$ 367.2249, found 367.2239.



***rac*-(2*R*, 2′*S*, 6*R*, 6′*R*)-6-(3-Phenylpropyl)- 6′-((*E*)-prop-1-en-1-yl)octahydro-2H, 2′H-2, 2′-bipyran (4-26)**

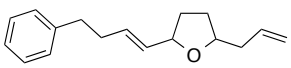
The general reductive cyclization procedure was followed with **4-25** (61 mg, 0.18 mmol), Et_3SiH (41 mg, 0.35 mmol), Re_2O_7 (2.6 mg, 0.0053 mmol), and DCM (8.8 mL). The reaction was stirred at rt for 36 h, then was quenched with 5 drops of pyridine. After evaporation of the solvent, the crude residue was purified by preparative TLC (5% ethyl acetate in hexanes) to give the product (39 mg, 68%). ^{1}H NMR (400 MHz, C_6D_6) δ 7.15-7.21 (m, 2H), 7.05-7.15 (m, 3H), 5.54-5.70 (m, 2H), 3.72 (dd, *J* = 4.8, 10.0 Hz, 1H), 3.23-3.36 (m, 2H), 3.13 (dddd, *J* = 2.4, 4.4, 8.0, 10.8 Hz, 1H), 2.52 (t, *J* = 7.6 Hz, 2H), 1.98-2.10 (m, 2H), 1.77-1.88 (m, 1H), 1.48-1.72 (m, 4H), 1.56 (d, *J* = 6.4 Hz, 3H), 1.23-1.46 (m, 7H), 1.05-1.15 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 142.7, 133.4, 128.4, 128.3, 125.6, 124.6, 80.9, 80.6, 77.9, 77.5, 36.2, 36.0, 32.3, 31.9, 28.5, 28.3, 27.7, 23.4, 23.3, 17.5; IR (neat) 3061, 3025, 2932, 2854, 1603, 1459, 1453, 1439, 1463, 1303, 1249, 1197, 1093, 1043, 964, 940, 747, 698 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{32}O_2$ $[M]^+$ 328.2402, found 328.2407.



(*E*)-2-(Dec-1-yn-1-yl)-5-(4-phenylbut-1-en-1-yl) tetrahydro-furan (4-29)

The general cyclization procedure was followed with **4-27** (same as **2-10**, 27 mg, 0.12 mmol), potassium dec-1-yn-1-yltrifluoroborate (59 mg, 0.24 mmol), Re_2O_7 (1.8 mg, 0.0036 mmol), and DCM (6 mL). The reaction was stirred at rt for 12 h and another portion of Re_2O_7 (1.8 mg, 0.0036 mmol) added. The reaction was stirred at rt for another 12 h, then was quenched with 5 drops of pyridine. After evaporation of the solvent, the crude residue was purified by flash

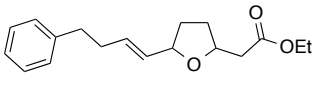
chromatography (1-5% ethyl acetate in hexanes) to give the product (33 mg, 81%, dr = 46:54). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.31 (m, 2H), 7.16-7.22 (m, 3H), 5.75 (dt, *J* = 6.4, 15.2 Hz, 1H), 5.59 (ddt, *J* = 1.2, 7.2, 15.2 Hz, 0.46H), 5.48 (ddt, *J* = 1.2, 7.2, 15.2 Hz, 0.54H), 4.69 (tt, *J* = 2.0, 6.4 Hz, 0.54H), 4.56 (tt, *J* = 2.0, 6.4 Hz, 0.46H), 4.49 (q, *J* = 7.6 Hz, 0.54H), 4.27 (q, *J* = 7.6 Hz, 0.46H), 2.63-2.76 (m, 2H), 2.30-2.40 (m, 2H), 2.18-2.24 (m, 2H), 2.09-2.18 (1H), 1.90-2.08 (m, 1.54H), 1.74-1.82 (0.46), 1.57-1.65 (m, 1H), 1.45-1.56 (m, 2H), 1.35-1.43 (m, 2H), 1.31-1.34 (m, 8H), 0.86-0.92 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9, 141.8, 132.2, 132.0, 131.5, 130.8, 128.5, 128.4, 128.3, 125.8, 85.34, 85.31, 80.7, 80.2, 79.4, 68.6, 68.4, 35.55, 35.53, 34.09, 34.08, 33.9, 33.8, 32.06, 32.02, 31.9, 29.2, 29.1,2, 29.10, 28.90, 28.88, 28.66, 22.7, 18.4, 18.81, 14.1; IR (neat) 3061, 3026, 2927, 2855, 1603, 1495, 1454, 1335, 1190, 1157, 1034, 967, 746, 698 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{35}O$ $[M+H]^+$ 339.2688, found 339.2702.



(*E*)-2-Allyl-5-(4-phenylbut-1-en-1-yl)tetrahydrofuran (4-31)

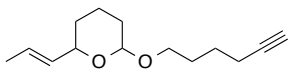
The general cyclization procedure was followed with **4-27** (27 mg, 0.12 mmol), allyltrimethylsilane (57 mg, 0.50 mmol), Re_2O_7 (1.8 mg, 0.0037 mmol), and DCM (6.2 mL). The reaction was initiated at 0 °C, then warmed up slowly to rt and stirred at rt for a total of 16 h, after which the reaction was quenched with 5 drops of pyridine. After evaporation of the solvent, the crude residue was purified by flash chromatography (1-5% ethyl acetate in hexanes) to give the product (26 mg, 86%, dr = 53:47). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.34 (m, 2H), 7.19-7.24 (m, 3H), 5.80-5.92 (m, 1H), 5.70-5.80 (m, 1H), 5.48-5.57 (m, 1H), 5.06-5.16 (m, 2H), 4.40 (q, *J* = 6.8 Hz, 0.47H), 4.27 (q, *J* = 6.8 Hz, 0.53H), 4.09 (p, *J* = 6.4 Hz, 0.47H), 3.96 (p, *J* = 6.4 Hz, 0.53H), 2.65-2.80 (m, 2H), 2.33-2.48 (m, 3H), 2.22-2.32 (m, 1H), 1.94-2.12 (m, 2H), 1.56-1.70 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9, 135.04, 134.99, 131.71, 131.66, 131.4,

128.46, 128.44, 128.3, 125.8, 116.85, 116.81, 80.2, 79.7, 78.8, 78.4, 40.45, 40.42, 35.6, 34.1, 32.8, 32.0, 31.6, 30.6; IR (neat) 3063, 3026, 2929, 2855, 1641, 1603, 1495, 1453, 1362, 1052, 994, 966, 913, 746, 698 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{22}O$ $[M]^+$ 242.1671, found 242.1704.



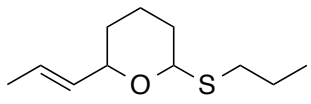
Ethyl-(*E*)-2-(5-(4-phenylbut-1-en-1yl)tetrahydrofuran-2-yl) acetate (4-33)

The general cyclization procedure was followed with **4-27** (29 mg, 0.13 mmol), *tert*-butyl-((1-ethoxyvinyl)oxy)dimethylsilane (131 mg, 0.655 mmol), Re_2O_7 (1.8 mg, 0.0036 mmol), and DCM (6 mL). The reaction was initiated at 0 °C, then was warmed up slowly to rt and stirred for a total of 24 h, after which the reaction was quenched with 5 drops of pyridine. After evaporation of the solvent, the crude residue was purified by flash chromatography (2-10% ethyl acetate in hexanes) to give the product (17 mg, 46%, dr = 3:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.32 (m, 2H), 7.15-7.22 (m, 3H), 5.67-5.78 (m, 1H), 5.45-5.54 (m, 1H), 5.25-5.46 (m, 2H), 4.16 (q, *J* = 7.2 Hz, 2H), 2.62-2.78 (m, 3H), 2.43-2.51 (m, 1H), 2.30-2.42 (m, 2H), 1.98-2.20 (m, 2H), 1.58-1.70 (m, 2H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 141.9, 131.8, 131.5, 131.3, 128.4, 128.3, 125.8, 80.3, 79.7, 75.5, 75.2, 60.4, 41.1, 41.0, 35.5, 34.1, 32.7, 32.0, 31.9, 31.1, 14.2; IR (neat) 3085, 3061, 3026, 2977, 2934, 1734, 1672, 1603, 1496, 1453, 1369, 1338, 1299, 1253, 1187, 1095, 1052, 968, 747, 700 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{23}O_3$ $[M-H]^+$ 287.1647, found 287.1655.



(*E*)-2-(Hex-5-yn-1-yloxy)-6-(prop-1-en-1-yl)tetrahydro-2H-pyran (4-36)

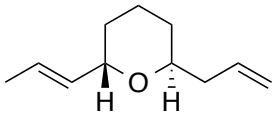
The general cyclization procedure was followed with **4-34**[1] (19 mg, 0.13 mmol), 5-hexyn-1-ol (26 mg, 0.27 mmol), Re_2O_7 (1.9 mg, 0.0040 mmol), and DCM (6.7 mL). The reaction was stirred at rt for 30 min, then was quenched with 5 drops of pyridine. After evaporation of the solvent, the crude residue was purified by flash chromatography (1-5% ethyl acetate in hexanes) to give the product (26 mg, 87%, dr = 65:35). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.69 (ddq, *J* = 0.8, 6.4, 17.2 Hz, 1H), 5.53 (ddq, *J* = 1.6, 6.8, 17.2 Hz, 0.35H), 5.47 (ddq, *J* = 1.6, 6.8, 17.2 Hz, 0.65H), 4.81-4.85 (m, 0.65H), 4.41 (dd, *J* = 2.4, 9.6 Hz, 0.35H), 4.13 (dd, *J* = 7.2, 10.4 Hz, 0.65H), 3.92 (dt, *J* = 6.8, 9.6 Hz, 0.35H), 3.84 (dd, *J* = 6.0, 10.4 Hz, 0.35H), 3.69 (dt, *J* = 6.4, 9.6 Hz, 0.65H), 3.46 (dt, *J* = 6.4, 9.6 Hz, 0.35H), 3.41 (dt, *J* = 6.4, 9.6 Hz, 0.65H), 1.19-2.26 (m, 2H), 1.95 (t, *J* = 2.4 Hz, 0.65H), 1.93 (t, *J* = 2.4 Hz, 0.35H), 1.80-1.92 (m, 1H), 1.50-1.78 (m, 11H), 1.22-1.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.4, 131.8, 127.1, 126.3, 102.1, 97.3, 84.4, 76.4, 69.5, 68.36, 68.32, 68.0, 66.3, 31.4, 31.1, 31.0, 29.6, 28.8, 25.5, 25.2, 22.1, 18.3, 18.2, 18.0, 17.81, 17.78; IR (neat) 3306, 2939, 2866, 1455, 1438, 1373, 1329, 1262, 1144, 1121, 1069, 1044, 1022, 988. 966, 929, 888, 629 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{23}O_2$ $[M+H]^+$ 223.1698, found 223.1687.



(*E*)-2-(prop-1-en-1-yl)-6-(propylthio)tetrahydro-2*H*-pyran (4-38)

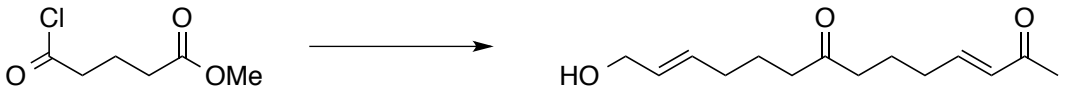
The general cyclization procedure was followed with **4-34** (20.2 mg, 0.142 mmol), propanethiol (21.6 mg, 0.284 mmol), 3*Re_2O_7 (2.1 mg, 0.0042 mmol), and DCM (7.1 mL). The reaction was stirred at rt for 2h (2.1 mg, 0.0042 mmol R_2O_7 was added three times at time 0, 40 min, 80min), then was quenched with 5 drops of pyridine. After evaporation of the

solvent, the crude residue was purified by flash chromatography (1-5% ethyl acetate in hexanes) to give the product (20.0 mg, 70%, dr = 53:47). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.63-5.75 (m, 1H), 5.45-5.56 (m, 1H), 5.34 (d, *J* = 4.8, 0.53H), 4.48-4.56 (m, 1H), 3.81(dd, *J* = 6.0, 10.4, 0.43H), 2.46-2.75 (m, 2H), 1.50-2.00 (m, 11H), 1.28-1.53 (m, 1H), 0.99 (t, *J* = 7.2, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.14, 132.06, 127.3, 126.6, 82.5, 81.8, 79.1, 69.1, 32.6, 32.4, 31.54, 31.48, 31.0, 30.3, 24.2, 23.4, 23.2, 19.4, 17.9, 17.8, 13.6; IR (neat) 2936, 2857, 1453, 1438, 1376, 1338, 1293, 1261, 1236, 1191, 1071, 1020, 964, 933, 909 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{21}OS$ $[M+H]^+$ 201.1313, found 201.1329.



trans-2-allyl-6((_E_)-prop-1-en-1-yl)tetrahydro-2H-pyran (4-40)

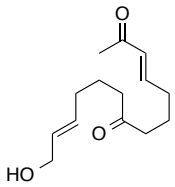
The general cyclization procedure was followed with **4-34** (28.4 mg, 0.20 mmol), Et_3SiH (92 mg, 0.80 mmol), HCat 2-1 ($[3,5\text{-}(CF_3)_2C_6H_3NH]_2SO_2$, 10.4 mg, 0.02 mmol), Re_2O_7 (2.9 mg, 0.006 mmol), and DCM (10 mL). The reaction was stirred at 0 °C for 20 h, then was quenched with 5 drops of pyridine. After evaporation of the solvent under slightly reduced presssure, 5 μl of benzyldimethylsilane was added into the crude as an internal standard. The mixture was dissolved in $CDCl_3$ and ^{1}H NMR showed a yield of 83%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (ddt, *J* = 6.8, 10.0, 17.2, 1H), 5.56-5.71 (m, 2H), 5.02-5.11 (m, 2H), 4.28 (m, 1H), 3.79 (dq, *J* = 2.8, 7.2, 1H), 2.39 (tp, *J* = 1.2, 7.2, 1H), 2.01 (tp, *J* = 1.2, 7.2, 1H), 1.61-1.75 (m, 7H), 1.49-1.57 (m, 1H), 1.30-1.40 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.4, 131.5, 127.3, 116.4, 72.1, 70.7, 38.9, 29.8, 29.7, 18.6, 17.9; IR (neat) 2935, 2856, 1688, 1641, 1441, 1375, 1278, 1200, 1178, 1139, 1035, 965, 912, 861, 838 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{19}O$ $[M+H]^+$ 167.1436, found 167.1455.



Reagents and Cconditions:

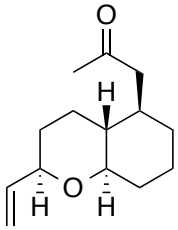
a) Pent-4-en-1-ylmagnesium bromide, Et_2O, 0 ºC, 74%; B) DIBAL-H, CH_2Cl_2, -78 ºC, 88%; c) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2; d) Diethyl (2-oxopropyl)phosphonate, NaH, THF, 79% for two steps; e) (*Z*)-2-Butene-1,4-diol, Grubbs-Hoveyda 2nd generation matathesis catalyst, CH_2Cl_2, 68%.

Scheme C12 Synthesis of substrate **4-44**



(3*E*, 12*E*)-14-Hydroxytetradeca-3, 12-diene-2, 8-dione (4-44)

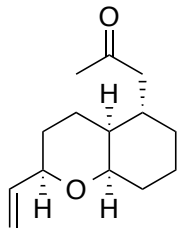
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (dt, *J* = 6.8, 16.0 Hz, 1H), 6.06 (dt, *J* = 1.6, 16.0 Hz, 1H), 5.44-5.68 (m, 2H), 4.04-4.17 (m, 2H), 2.36-2.45 (m, 4H), 2.18-2.26 (m, 2H), 2.23 (s, 3H), 1.99-2.09 (m, 2H), 1.75 (p, *J* = 7.6 Hz, 2H), 1.66 (p, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.1, 198.7, 147.3, 131.8, 130.0, 63.5, 42.1, 41.7, 31.8, 31.5, 26.9, 23.0, 21.9; IR (neat) 3445, 3000, 2935, 1709, 1672, 1626, 1413, 1363, 1256, 1186, 1090, 974 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{22}O_3$ $[M]^+$ 238.1569, found 238.1595.



***rac*-1-((2*R*, 4a*R*, 5*R*, 8a*R*)-2-Vinyloctahydro-2H-chromen-5-yl)propan-2-one (4-45)** The general reductive cyclization procedure was followed with **4-44** (20 mg, 0.086 mmol), Et_3SiH (20 mg, 0.17 mmol), Re_2O_7 (1.2 mg, 0.0026 mmol), and DCM (4.3 mL). The reaction was stirred at rt for 20 h, then was quenched with 5 drops of pyridine. After evaporation of the solvent, the crude residue was purified by flash chromatography (2% -8% ethyl acetate in hexanes) to give the products (17 mg, 92%, **4-45**:**4-46** = 2:1).

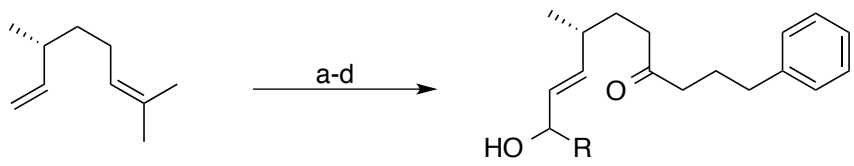
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (ddd, *J* = 6.0, 10.8, 17.2 Hz, 1H), 5.24 (dt, *J* = 1.6, 17.2 Hz, 1H), 5.10 (dt, *J* = 1.6, 10.4 Hz, 1H), 3.83 (ddddd *J* = 1.2, 1.2, 2.4, 5.6, 11.2 Hz, 1H), 3.09 (ddd, *J*

= 4.0, 9.6, 10.8 Hz, 1H), 2.59 (dd, *J* = 4.0, 16.4 Hz, 1H), 2.16 (dd, *J* = 8.4 Hz, 16.4, 1H), 2.15 (s, 3H), 1.90-1.96 (m, 1H), 1.85 (dq, *J* = 3.6, 12.8 Hz, 1H), 1.71-1.80 (m, 2H), 1.61-1.70 (m, 2H), 1.31-1.45 (m, 3H), 1.15 (dq, *J* = 4.0, 12.4 Hz, 1H), 0.90-1.13 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.8, 139.3, 115.0, 81.1, 78.1, 47.4, 45.6, 36.8, 32.6, 32.5, 32.1, 30.7, 27.7, 23.8; IR (neat) 3079, 2925, 2858, 1716, 1645, 1447, 1357, 1301, 1262, 1229, 1207, 1158, 1061, 989, 921, 882, 866, 840 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{22}O_2$ $[M]^+$ 222.1620, found 222.1623.



rac-1-((2*R*, 4a*S*, 5*S*, 8a*R*)-2-vinyloctahydro-2H-chromen-5-yl)propan-2-one (4-46)

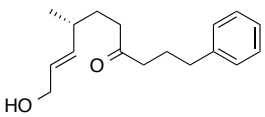
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91 (ddd, *J* = 6.0, 10.4, 17.2 Hz, 1H), 5.25 (dt, *J* = 1.6, 17.2 Hz, 1H), 5.09 (dt, *J* = 1.6, 10.4 Hz, 1H), 3.88 (ddddd *J* = 0.8, 1.2, 2.0, 4.8, 9.6 Hz, 1H), 3.64 (q, *J* = 2.8 Hz, 1H), 2.57 (dd, *J* = 4.0, 15.6 Hz, 1H), 2.30-2.40 (m, 1H), 2.15 (s, 3H), 2.12 (dd, *J* = 8.8, 15.6 Hz, 1H), 1.85-1.94 (m, 2H), 1.88-1.76 (m, 2H), 1.44-1.66 (m, 2H), 1.36-1.43 (m, 3H), 1.18-1.24 (m, 1H), 0.92-1.03 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.2, 139.7, 114.6, 79.1, 75.7, 48.8, 39.7, 32.8, 32.3, 30.6, 29.7, 26.6, 25.9, 20.6; IR (neat) 3079, 2932, 2861, 1715, 1645, 1443, 1410, 1358, 1308, 1269, 1231, 1198, 1160, 1153, 1110, 1065, 1050, 1031, 988, 919, 899, 838 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{23}O_2$ $[M]^+$ 223.1698, found 223.1706.



Reaction Cconditions:

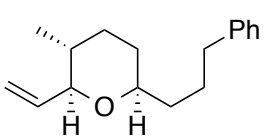
a) O_3, CH_2Cl_2, -78 ºC, then Me_2S, rt, 56%; b) (3-Phenylpropyl)magnesium bromide, Et_2O, 0 ºC, 73%; c) PCC, Celite, CH_2Cl_2, 98%; d) (*Z*)-2-Butene-1,4-diol or (*Z*)-hex-3-ene-2,5-diol, Grubbs-Hoveyda 2nd metathesis catalyst, CH_2Cl_2, 41% (R = H), or 67% (R = CH_3).

Scheme C13 Synthesis of substrates **4-58** (R = H) and **4-61** (R = CH_3)



(*R*, *E*)-10-Hydroxy-7-methyl-1-phenyldec-8-en-4-one (4-58)

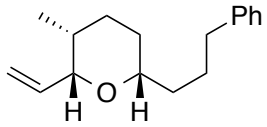
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.33 (m, 2H), 7.16-7.24 (m, 3H), 5.60 (dt, *J* = 5.6, 15.2 Hz, 1H), 5.50 (dd, *J* = 7.6, 15.2 Hz, 1H), 4.09 (d, *J* = 6.0 Hz, 2H), 2.63 (t, *J* = 7.6 Hz, 2H), 2.42 (t, *J* = 7.6 Hz, 2H), 2.37 (t, *J* = 7.6 Hz, 2H), 2.12 (heptet, *J* = 7.2 Hz, 1H), 2.09 (br, 1H), 1.92 (p, *J* = 7.2 Hz, 2H), 1.48-1.67 (m, 2H), 1.02 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.2, 141.6, 137.5, 128.5, 128.4, 128.3, 126.0, 63.5, 42.0, 40.6, 36.1, 35.1, 30.4, 25.2, 20.5; IR (neat) 3411, 3061, 3026, 2928, 2867, 1710, 1603, 1496, 1454, 1409, 1374, 1263, 1214, 1094, 1007, 973, 748, 700 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{24}O_2$ $[M]^+$ 260.1776, found 260.1772.



(2*S*, 3*R*, 6*R*)-3-Methyl-6-(3-phenylpropyl)-2-vinyltetrahydro-2H-pyran (4-59)

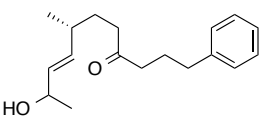
The general reductive cyclization procedure was followed with **4-58** (44 mg, 0.17 mmol), Ph_3SiH (88 mg, 0.34 mmol), Re_2O_7 (2.5 mg, 0.0048 mmol), and DCM (8.4 mL). The reaction was stirred at rt for 15 h, then was quenched with 5 drops of pyridine. After evaporation of the solvent, the crude residue was purified by flash chromatography (1-5% ethyl acetate in hexanes)

to give the product (34 mg, 82%, **4-59**:**4-60** = 9:1). ^{1}H NMR (400 MHz, C_6D_6) δ 7.13-7.19 (m, 2H), 7.04-7.10 (m, 2H), 5.89 (ddd, *J* = 6.8, 10.4, 17.2 Hz, 1H), 5.28 (ddd, *J* = 1.2, 2.0, 17.2 Hz, 1H), 5.08 (ddd, *J* = 1.2, 2.0, 10.4 Hz, 1H), 3.27 (dd, 6.8, 9.6 Hz, 1H), 3.13 (dddd, *J* = 2.4, 4.8, 7.2, 10.8 Hz, 1H), 2.51 (t, *J* = 7.6 Hz, 2H), 1.78-1.90 (m, 1H), 1.54-1.70 (m, 3H), 1.13-1.44 (m, 4H), 0.97 (dq, *J* = 4.0, 12.0 Hz, 1H), 0.71 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 142.6, 138.5, 128.4, 128.2, 125.6, 115.5, 84.9, 76.9, 36.1, 35.3, 32.7, 32.0, 27.7, 17.5; IR (neat) 3082, 3062, 3025, 2927, 2847, 1645, 1603, 1495, 1455, 1408, 1376, 1303, 1227, 1152, 1097, 1075, 1017, 989, 922, 748, 698 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{25}O$ $[M+H]^+$ 245.1905, found 245.1906.



(2*R*, 3*R*, 6*S*)-3-methyl-6-(3-phenylpropyl)-2-vinyltetrahydro-2H-pyran (4-60)

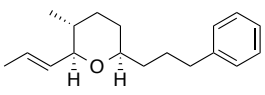
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.31 (m, 2H), 7.15-7.22 (m, 3H), 5.80 (ddd, *J* = 4.8, 10.8, 17.2 Hz, 1H), 5.23 (dt, *J* = 1.6, 17.2 Hz, 1H), 5.11 (dt, *J* = 1.6, 10.8 Hz, 1H), 3.95-3.40 (m, 1H), 3.31-3.39 (m, 1H), 2.64 (t, *J* = 7.2 Hz, 2H), 1.59-1.87 (m, 6H), 1.32-1.55 (m, 3H), 0.92 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.7, 138.8, 128.5, 128.2, 125.6, 114.1, 80.5, 78.2, 36.13, 36.05, 31.8, 30.8, 27.5, 26.1, 11.9; IR (neat) 3084, 3062, 3025, 2931, 2854, 1645, 1603, 1495, 1453, 1409, 1379, 1326, 1206, 1107, 1077, 1037, 990, 919, 747, 698 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{24}O$ $[M]^+$ 244.1827, found 244.1822.



(7*R*, *E*)-10-Hydroxy-7-methyl-1-phenylundec-8en-4-one (4-61)

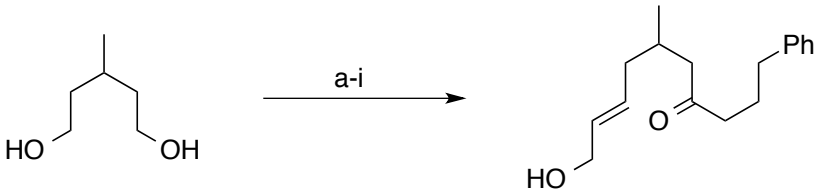
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.33 (m, 2H), 7.17-7.24 (m, 3H), 5.41-5.53 (m, 2H), 4.27 (p, *J* = 6.4 Hz, 1H), 2.64 (t, *J* = 7.6 Hz, 2H), 2.422 (t, *J* = 7.2 Hz,

1H), 2.418 (t, *J* = 7.2 Hz, 1H), 2.37 (t, *J* = 7.6 Hz, 1H), 2.36 (t, *J* = 7.6 Hz, 1H), 2.05-2.14 (m, 1H), 1.92 (p, *J* = 7.2 Hz, 2H), 1.79 (br, 1H), 1.58-1.67 (m, 1H), 1.48-1.58 (m, 1H), 1.27 (d, *J* = 6.4 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 1.5H), 1.00 (d, *J* = 6.8 Hz, 1.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.0, 210.9, 141.6, 135.5, 135.4, 133.5, 128.5, 128.4, 126.0, 68.69, 68.67, 42.0, 40.63, 40.60, 36.01, 35.98, 35.1, 30.4, 25.2, 23.61, 23.57, 20.56, 20.54; IR (neat) 3411, 3061, 3026, 2963, 2927, 2868, 1710, 1603, 1496, 1453, 1408, 1371, 1293, 1062, 972, 945, 748, 700 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{25}O$ $[M\text{-}OH]^+$ 257.1905, found 257.1883.



(2*R*, 3*R*, 6*R*)-3-Methyl-6-(2-phenylpropyl)-2((*E*)-prop-1-en-1-yl)tetrahydro-2H-pyran (4-62)

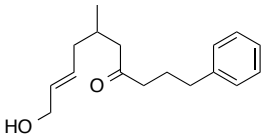
The general reductive cyclization procedure was followed with **4-61** (41 mg, 0.15 mmol), Et_3SiH (35 mg, 0.30 mmol), Re_2O_7 (2.2 mg, 0.0045 mmol), and DCM (7.5 mL). The reaction was stirred at 0 °C for 22 h, then was warmed to rt and stirred for another 2 h. The reaction was quenched with 5 drops of pyridine. After evaporation of the solvent, 5 μl of benzyldimethylsilane was added into the crude as an internal standard. The mixture was dissolved in C_6D_6 and ^{1}H NMR showed a yield of 77% (dr = 11:1). ^{1}H NMR (400 MHz, C_6D_6) δ 7.13-7.19 (m, 2H), 7.04-7.10 (m, 3H), 5.67 (ddq, *J* = 0.4, 6.4, 15.2 Hz, 1H), 5.57 (ddq, *J* = 1.2, 6.8, 15.2 Hz, 1H), 3.30 (dd, *J* = 7.2, 9.6 Hz, 1H), 3.17 (dddd, *J* = 2.4, 4.8, 7.2, 10.8 Hz, 1H), 2.53 (t, *J* = 7.2 Hz, 2H), 1.80-1.93 (m, 1H), 1.59-1.72 (m, 3H), 1.57 (d, *J* = 6.4 Hz, 3H), 1.17-1.42 (m, 4H), 1.02 (dq, *J* = 4.4, 12.8 Hz, 1H), 0.75 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 142.6, 132.1, 128.5, 128.2, 127.0, 125.6, 85.8, 77.0, 36.2, 36.1, 35.5, 32.8, 32.1, 27.7, 17.8, 17.5; IR (neat) 3061, 3026, 2927, 2847, 1603, 1496, 1453, 1376, 1325, 1151, 1079, 1031, 1014, 964, 747, 698 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{27}O$ $[M+H]^+$ 259.2062, found 259.2069.



Reaction Cconditions:

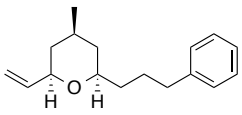
a) NaH, THF, then TBSCl, 0 ºC, 51%; b) Py•SO_3, Et_3N, CH_2Cl_2, 84%; c) Triethyl phosphonateacetate, NaH, THF, 0 ºC, 98%; d) DIBAL-H, CH_2Cl_2, - 78 ºC, 98%; e) TBDPSCl, imidazole, CH_2Cl_2; f) HCl (1.0M), THF, H_2O (1:1); 85% for two steps; g) Py•SO_3, DMSO, Et_3N, CH_2Cl_2, 60%; j) Bu_4NF, THF, 94%.

Scheme C14 Synthesis of substrate **4-63**



(*E*)-10-hydroxy-6-methyl-1-phenyldec-8-en-4-one (4-63)

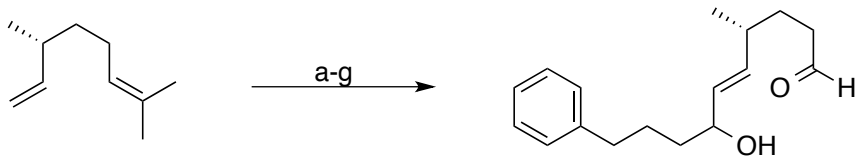
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.30 (m, 2H), 7.13-7.21 (m, 3H), 5.55-5.66 (m, 2H), 4.06 (d, *J* = 3.2 Hz, 2H), 2.60 (t, *J* = 7.6 Hz, 2H), 2.33-2.40 (m, 3H), 2.13-2.20 (m, 1H), 2.08 (h, *J* = 6.8 Hz, 1H), 1.93-2.03 (m, 2H), 1.88 (p, *J* = 7.2 Hz, 2H), 1.76 (br, 1H), 0.88 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.71, 141.6, 131.1, 130.5, 128.5, 128.4, 126.0, 63.5, 49.4, 42.6, 39.5, 35.1, 29.1, 25.2, 19.9; IR (neat) 3403, 3061, 3025, 2927, 2870, 1708, 1602, 1495, 1454, 1407, 1372, 1212, 1085, 1005, 972, 748, 700 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{23}O$ $[M\text{-}OH]^+$ 243.1749, found 243.1748.



rac-(2*R*, 4*S*, 6*R*)-4-Methyl-2-(3-phenylpropyl)-6-vinyltetrahydro-2H-pyran (4-64)

The general rearrangement cyclization procedure was followed with **4-63** (40 mg, 0.15 mmol), Et_3SiH (36 mg, 0.31 mmol), Re_2O_7 (2.2 mg, 0.0046 mmol), and DCM (7.6 mL). The reaction was stirred at rt for 20 h, then was quenched with 5 drops of pyridine. After evaporation of the solvent, the crude mixture was purified by flash chromatography (1-5% ethyl acetate in hexanes)

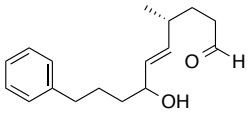
to give the product (35 mg, 88%, dr > 30:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.31 (m, 2H), 7.15-7.21 (m, 3H), 5.88 (m, ddd, *J* = 5.6, 10.4, 17.2 Hz, 1H), 5.25 (dt, *J* = 1.6, 17.2 Hz, 1H), 5.09 (dt, *J* = 1.6, 10.4 Hz, 1H), 3.81 (ddddd, *J* = 1.2, 2.0, 3.2, 5.2, 11.2 Hz, 1H), 3.56 (dddd, *J* = 1.6, 5.2, 8.8, 9.2 Hz, 1H), 2.64 (t, J = 7.6 Hz, 2H), 1.75-1.87 (m, 1H), 1.58-1.75 (m, 5H), 1.44-1.55 (m, 1H), 0.95 (d, *J* = 6.4 Hz, 3H), 0.82-1.00 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.7, 139.6, 128.5, 128.3, 125.6, 114.4, 77.9, 77.2, 40.06, 40.0, 36.03, 36.02, 30.23, 27.6, 22.3; IR (neat) 3083, 3062, 3025, 2947, 2924, 2862, 2836, 1647, 1603, 1495, 1454, 1409, 1370, 1310, 1181, 1133, 1092, 1081, 1029, 988, 919, 748, 698 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{25}O$ $[M+H]^+$ 245.1905, found 245.1928.



Reaction Cconditions:

a) O_3, CH_2Cl_2, -78 ºC, then Me_2S, rt, 56%; b) $(MeO)_3CH$, TsOH, MeOH, 50 ºC, 58%; c) Methyl acrylate, Grubbs-Hoveyda 2nd generation metathesis catalyst, CH_2Cl_2, reflux, 72%; d) DIBAL-H, CH_2Cl_2, -78 ºC, 94%; e) Py•SO_3, DMSO, Et_3N, CH_2Cl_2, 89%; f) (3-Phenylpropyl)magnesium bromide, Et_2O, 0 ºC, 92%; g) HOAc, H_2O (1:1), 92%.

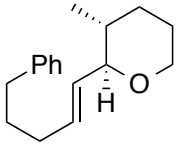
Scheme C15 Synthesis of substrate **4-65**



(4*R*, *E*)-7-Hydroxy-4-methyl-10-phenyldec-5-enal (4-65)

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.62-9.68 (m, 1H), 7.15-7.23 (m, 2H), 7.05-7.14 (m, 3H), 5.30-5.42 (m, 2H), 3.98 (p, *J* = 5.1 Hz, 1H), 2.56 (t, *J* = 7.2 Hz, 2H), 2.32 (q, *J* = 6.6 Hz, 2H), 1.98-2.14 (m, 1H), 1.40-1.70 (m, 7H), 0.94 (d, *J* = 6.6 Hz, 1.5H), 0.93 (d, *J* = 6.6 Hz, 1.5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.7, 202.5, 142.3, 136.3, 136.2, 132.6, 128.4, 128.3, 125.8, 72.7, 41.9, 36.9, 36.1, 35.8, 28.7, 27.3, 20.54, 20.49; IR (neat) 3412, 3025,

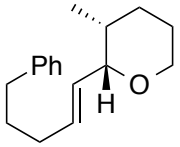
2928, 2861, 1721, 1603, 1495, 1453, 1374, 1081, 1017, 973, 749. 699 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{24}O_2Na$ $[M+Na]^+$ 283.1674, found 283.1681.



(2*R*, 3*R*)-3-Methyl-2-((*E*)-5-phenylpent-1-en-1-yl)tetrahydro-2H-pyran (4-66)

The general reductive cyclization procedure was followed with **4-65** (42 mg, 0.16 mmol), Et_3SiH (37 mg, 0.32 mmol), Re_2O_7 (2.3 mg, 0.0048 mmol), and DCM (8.0 mL). The reaction was stirred at rt for 24 h, then was quenched with 5 drops of pyridine. After evaporation of the solvent, the crude residue was purified by flash chromatography (1-5% ethyl acetate in hexanes) to give the product (32 mg, 83%, dr = 3:1).

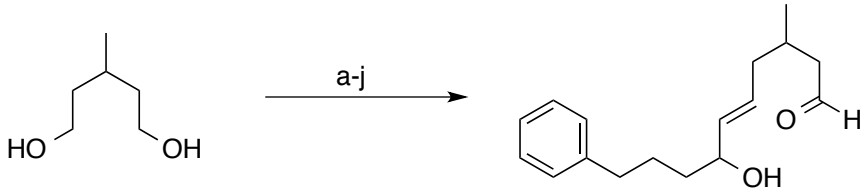
4-66: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.32 (m, 2H), 7.16-7.22 (m, 3H), 5.73 (dt, *J* = 6.8, 15.2 Hz, 1H), 5.45 (ddt, *J* = 1.2, 8.0, 15.2 Hz, 1H), 4.01 (ddt, *J* = 1.6, 4.4, 11.2 Hz, 1H), 3.43 (ddd, *J* = 2.4, 11.2, 12.4 Hz, 1H), 3.31 (dd, *J* = 8.0, 9.2 Hz, 1H), 2.64 (t, *J* = 8.0 Hz, 2H), 2.05-2.16 (m, 2H), 1.80-1.88 (m, 1H), 1.63-1.79 (m, 3H), 1.51-1.59 (m, 1H), 1.35-1.47 (m, 1H), 1.19 (dq, *J* = 4.0, 12.8 Hz, 1H), 0.80 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 133.8, 130.4, 128.5, 128.3, 125.7, 85.2, 68.1, 35.7, 35.4, 32.4, 31.9, 30.9, 26.6, 18.2; IR (neat) 3025, 2927, 2846, 1603, 1495, 1455, 1373, 1222, 1152, 1095, 1071, 1034, 986, 967, 745, 698 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{23}O$ $[M-H]^+$ 243.1749, found 243.1743.



(2*S*, 3*R*)-3-methyl-2-((*E*)-5-phenylpent-1-en-1-yl)tetrahydro-2H-pyran (minor)

Minor product: ^{1}H NMR (400 MHz, C_6D_6) δ 7.13-7.20 (m, 2H), 7.03-7.10 (m, 2H), 5.77 (ddt, *J* = 1.6, 6.8, 15.2 Hz, 1H), 5.49 (ddt, *J* = 1.6, 5.2, 15.2 Hz, 1H), 3.87-3.94 (m, 2H), 3.31 (dt, *J* = 2.8,

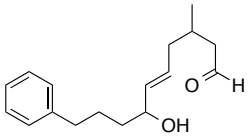
11.2 Hz, 1H), 2.49 (t, J = 8.0 Hz, 2H), 1.99 (q, J = 7.2 Hz, 2H), 1.55-1.71 (m, 4H), 1.39-1.54 (m, 2H), 0.97-1.05 (m, 1H), 0.99 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 142.4, 130.5, 130.2, 128.4, 128.3, 125.7, 79.9, 67.6, 35.3, 32.7, 32.0, 31.2, 30.3, 21.4, 12.6; IR (neat) 3061, 3026, 2932, 2855, 1603, 1495, 1453, 1378, 1354, 1269, 1215, 1202, 1143, 1118, 1092, 1074, 1054, 1030, 1011, 965, 745, 698 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{23}O$ [M-H]$^+$ 243.1749, found 243.1755.



Reaction Cconditions:

a) NaH, THF, then TBSCl, 0 ºC, 51%; b) Py•SO_3, Et_3N, CH_2Cl_2, 84%; c) Triethyl phosphonateacetate, NaH, THF, 0 ºC, 98%; d) HF•Pyridine, THF, 99%; e) PCC, Celite, CH_2Cl_2; f) *p*-TsOH, BnOH, Na_2SO_4, THF, 50% for two steps; g) DIBAL-H, CH_2Cl_2, -78 ºC, 97%; h) Py•SO_3, DMSO, Et_3N, Ch_2C_2, 64%; i) (3-Phenylpropyl)magnesium bromide, Et_2O, 0 ºC, 87%; j) CF_3CO_2H, THF, H_2O, 82%.

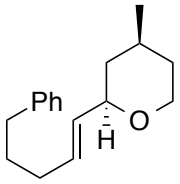
Scheme C16 Synthesis of substrate **4-67**



(*E*)-7-hydroxy-3-methyl-10-phenyldec-5-enal (4-67)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73-9.77 (m, 1H), 7.25-7.31 (m, 2H), 7.15-7.21 (m, 3H), 5.54-5.63 (m, 1H), 5.45-5.53 (m, 1H), 4.09 (q, J = 6.0 Hz, 1H), 2.65 (t, J = 7.2 Hz, 3H), 2.39-2.46 (m, 1H), 2.11-2.28 (m, 2H), 1.97-2.10 (m, 2H), 1.48-1.78 (m, 5H), 0.98 (d, J = 6.4 Hz, 1.5H), 0.97 (d, J = 6.4 Hz, 1.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.7, 202.6, 142.3, 135.6, 129.1, 129.0, 128.4, 128.3, 125.872.8, 72.7, 50.4, 50.3, 39.5, 39.4, 36.9, 35.8, 28.18, 28.17, 27.3, 19.96, 19.93; IR (neat) 3420, 3084, 3061, 3025, 2929, 2860, 2720, 1722,

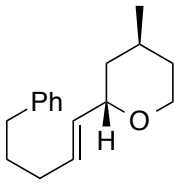
1602, 1496, 1454, 1379, 1251, 1097, 1081, 1013, 972, 749, 699 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{23}O_2$ $[M+Na]^+$ 259.1698, found 259.1692.



rac-(2*R*, 4*S*)-4-Methyl-2-((*E*)-5-phenylpent-1-en-1-yl)tetrahydro-2H-pyran (4-68)

The general reductive cyclization procedure was followed with **4-67** (42 mg, 0.16 mmol), Et_3SiH (38 mg, 0.32 mmol), Re_2O_7 (2.3 mg, 0.0048 mmol), and DCM (8.1 mL). The reaction was stirred at rt for 36 h, then was quenched with 5 drops of pyridine. After evaporation of the solvent, the crude residue was purified by flash chromatography (1-5% ethyl acetate in hexanes) to give the product (34 mg, 87%, dr = 4.6:1).

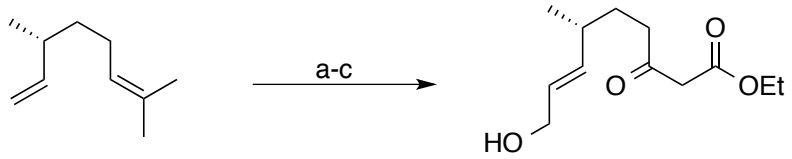
4-68: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.33 (m, 2H), 7.17-7.23 (m, 3H), 5.72 (dt, *J* = 6.4, 15.6 Hz, 1H), 5.45 (dd, *J* = 6.4, 15.6 Hz, 1H), 4.05 (dd, *J* = 3.6, 11.2 Hz, 1H), 3.77 (dd, *J* = 6.4, 10.8 Hz, 1H), 3.49 (dt, *J* = 1.6, 12.0 Hz, 1H), 2.65 (t, *J* = 7.6 Hz, 2H), 2.10, (q, *J* = 7.2 Hz, 2H), 1.75 (p, *J* = 7.6 Hz, 2H), 1.60-1.65 (m, 2H), 1.50-1.60 (m, 1H), 1.24 (dq, *J* = 4.0, 12.0 Hz, 1H), 1.05 (q, *J* = 12.4 Hz, 1H), 0.97 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 131.7, 131.2, 128.5, 128.3, 125.7, 78.0, 68.0, 40.9, 35.4, 34.5, 31.9, 30.8, 30.3, 22.3; IR (neat) 3084, 3061, 3026, 2922, 2839, 2728, 2641, 1673, 1603, 1495, 1454, 1368, 1305, 1255, 1171, 1091, 1028, 990, 967, 911, 877, 839, 745, 698 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{23}O$ $[M-H]^+$ 243.1749, found 243.1745.



rac-(2*S*, 4*S*)-4-methyl-2-((*E*)-5-phenylpent-1-en-1-yl)tetrahydro-2H-pyran (minor product)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.31 (m, 2H), 7.15-7.21 (m, 3H), 5.68 (ddt, *J*

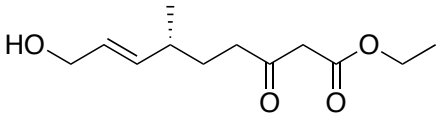
= 0.8, 6.4, 15.6 Hz, 1H), 5.54 (dd, *J* = 5.6, 15.6 Hz, 1H), 3.68-3.80 (m, 2H), 2.63 (t, *J* = 7.6 Hz, 2H), 2.09 (q, *J* = 7.2 Hz, 2H), 2.00 (hexet, *J* = 6.0 Hz, 1H), 1.69-1.79 (m, 3H), 1.62-1.69 (m, 1H), 1.39-1.46 (m, 1H), 1.23-1.38 (m, 1H), 1.05 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 131.8, 131.2, 128.5, 128.3, 125.7, 72.6, 62.3, 37.9, 35.4, 32.7, 32.0, 30.8, 24.9, 19.4; IR (neat) 3061, 3026, 2953, 2925, 2853, 1603, 1495, 1454, 1379, 1346, 1334, 1271, 1245, 1188, 1079, 1052, 968, 745, 698 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{23}O$ $[M-H]^+$ 243.1749, found 243.1753.



Reaction Cconditions:

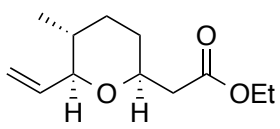
a) O_3, CH_2Cl_2, -78 ºC, then Me_2S, rt, 56%; b) Ethyl diazoacetate, $SnCl_2$, rt, 80%; c) (*Z*)-2-Butene-1,4-diol, Grubbs-Hoveyda 2nd metathesis catalyst, CH_2Cl_2, rt, 45%.

Scheme C17 Synthesis of substrate **4-69**



Ethyl-(*R*, *E*)-9-hydroxy-6-methyl-oxonon-7-enoate (4-69)

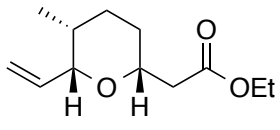
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.58 (dt, *J* = 5.4, 15.3 Hz, 1H), 5.44 (dd, *J* = 7.8, 15.3 Hz, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 4.05 (d, *J* = 5.4 Hz, 2H), 3.40 (s, 2H), 2.49 (t, *J* = 7.2 Hz, 2H), 2.12 (heptet, *J* = 6.9 Hz, 1H), 2.02 (br, 1H), 1.48-1.70 (m, 2H), 1.25 (t, *J* = 7.2 Hz, 3H), 0.98 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.9, 167.4, 137.3, 128.6, 63.4, 61.4, 49.4, 40.8, 36.2, 30.0, 20.5, 14.1; IR (neat) 3413, 2960, 2930, 2871, 1741, 1714, 1645, 1455, 1411, 1369, 1314, 1256, 1158, 1094, 1029, 974 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{20}O_4$ $[M]^+$ 228.1362, found 228.1364.



ethyl 2-((2*S*, 5*R*, 6*S*)-5-methyl-6-vinyltetrahydro-2H-Pyran-2-yl) acetate (4-70)

The general rearrangement cyclization procedure was followed with **4-69** (41 mg, 0.179 mmol), Et_3SiH (42 mg, 0.357 mmol), Re_2O_7 (2.6 mg, 0.0054 mmol), DCM (8.9 mL), the reaction was stirred at RT for 72 hrs, after which the reaction was quenched with 5 drops of pyridine. After evaporation of the solvent, 5 μl of benzyldimethylsilane was added into the crude as an internal standard, then the mixture was dissolved in CDCl3 and 1H NMR was taken to give a yield of 92% (dr = 4.8:1). When the same reaction was performed in DCE at 50 °C for 24 hrs, a yield of 88% (dr = 4.4 :1) was obtained.

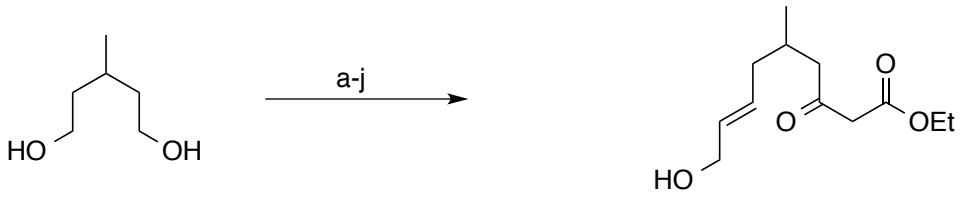
4-70: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (ddd, *J* = 7.2, 10.4, 17.6 Hz, 1H), 5.24 (ddd, *J* = 1.2, 2.0, 17.6 Hz, 1H), 5.16 (ddd, *J* = 1.2, 2.0, 10.4 Hz, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.79 (ddd, *J* = 2.0, 6.4, 8.4, 9.2 Hz, 1H), 3.41 (dd, *J* = 7.2, 9.6 Hz, 1H), 2.61 (dd, *J* = 7.2, 15.2 Hz, 1H), 2.41 (dd, *J* = 6.4, 15.2 Hz, 1H), 1.84 (dq, *J* = 3.2, 12.0 Hz, 1H), 1.67-1.74 (m, 1H), 1.30-1.42 (m, 2H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.19-1.30 (m, 1H), 0.81 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 137.6, 117.0, 85.3, 74.0, 60.4, 41.6, 34.8, 32.3, 31.6, 17.6, 14.2. IR (neat) 2978, 2929, 2873, 2852, 1738, 1644, 1458, 1376, 1339, 1299, 1271, 1251, 1229, 1185, 1151, 1101, 1071, 1033, 991, 958, 924, 854 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{20}O_3$ $[M]^+$ 212.1412, found 212.1408.



ethyl 2-((2*R*, 5*R*, 6*R*)-5-methyl-6-vinyltetrahydro-2H-Pyran-2-yl) acetate (Minor)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (ddd, *J* = 4.8, 10.8, 17.6 Hz, 1H), 5.20 (dt, *J* = 2.0, 17.6 Hz, 1H), 5.09 (dt, *J* = 2.0, 10.8 Hz, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 4.01-4.04 (m, 1H), 3.83 (dddd, *J* =

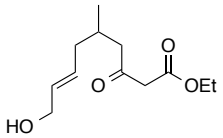
3.2, 6.0, 8.4, 9.2 Hz, 1H), 2.61 (dd, *J* = 7.2, 14.8 Hz, 1H), 2.43 (dd, *J* = 6.0, 14.8 Hz, 1H), 1.78-1.88 (m, 1H), 1.72-1.78 (m, 1H), 1.65-1.72 (m, 1H), 1.41-1.57 (m, 2H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.92 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 138.2, 114.2, 80.5, 74.8, 60.3, 41.7, 31.3, 30.5, 25.7, 14.3, 11.8; IR (neat) 2974, 2933, 2857, 1740, 1645, 1453, 1411, 1379, 1337, 1284, 1255, 1214, 1174, 1145, 1106, 1069, 1035, 992, 921, 856 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{20}O_3$ $[M]^+$ 212.1412, found 212.1416.



Reaction Cconditions:

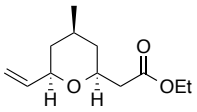
a) NaH, THF, then TBSCl, 0 ºC, 51%; b) Py•SO_3, Et_3N, CH_2Cl_2, 84%; c) Triethyl phosphonateacetate, NaH, THF, 0 ºC, 98%; d) DIBAL-H, CH_2Cl_2, -78 ºC, 98%; e) TBDPSCl, imidazole, CH_2Cl_2; f) HCl (1.0M), THF/H_2O (1:1), 85% for two steps; g) Py•SO_3, DMSO, Et_3N, CH_2Cl_2, 91%; i) Bu_4NF, THF, 86%.

Scheme C18 Synthesis of substrate **4-71**



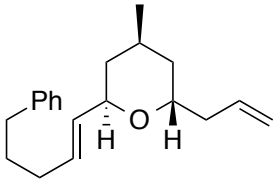
Ethyl (*E*)-9-hydroxy-5-methyl-3-oxonon-7-enoate (4-71)

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.52-5.68 (m, 2H), 4.17 (q, *J* = 7.2 Hz, 2H), 4.06 (d, *J* = 3.9 Hz, 3H), 3.40 (s, 2H), 2.52 (dd, *J* = 6.0, 16.8 Hz, 1H), 2.31 (dd, *J* = 6.9, 16.8 Hz, 1H), 2.14 (octet, *J* = 6.6 Hz, 1H), 1.90-2.08 (m, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.5, 167.4, 131.4, 130.3, 63.4, 61.4, 49.8, 49.5, 39.5, 28.9, 20.0, 14.1; IR (neat) 3416, 2959, 2929, 2873, 1741, 1713, 1644, 1461, 1410, 1369, 1318, 1237, 1154, 1086, 1027, 973 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{19}O_3$ $[M\text{-}OH]^+$ 211.1334, found 211.1332.



rac-Ethyl-2-((2*S*, 4*S*, 6*S*)-4-methyl-6-vinyltetrahydro-2H-pyran-2yl) acetate (4-72)

The general reductive cyclization procedure was followed with **4-71** (40 mg, 0.17 mmol), Et_3SiH (40 mg, 0.35 mmol), Re_2O_7 (2.5 mg, 0.0052 mmol), and DCE (8.6 mL). The reaction was stirred at 55 °C for 36 h, then was quenched with 5 drops of pyridine. After evaporation of the solvent, 5 μl of benzyldimethylsilane was added into the crude residue as an internal standard. The mixture was dissolved in $CDCl_3$ and ^1H NMR showed a yield of 82% (single isomer). ^1H NMR (400 MHz, C_6D_6) δ 5.84 (ddd, *J* = 4.8, 10.4, 17.2 Hz, 1H), 5.26 (dt, *J* = 1.6, 17.2 Hz, 1H), 5.00 (dt, *J* = 1.6, 10.4 Hz, 1H), 3.97 (q, *J* = 7.2 Hz, 2H), 3.83 (dddd, *J* = 2.0, 6.0, 7.6, 11.2 Hz, 1H), 3.68 (ddq, *J* = 1.6, 5.2, 11.2 Hz, 1H), 2.61 (dd, *J* = 7.2, 15.2 Hz, 1H), 2.28 (dd, *J* = 5.6, 15.2 Hz, 1H), 1.35-1.41 (m, 1H), 1.23-1.35 (m, 2H), 0.96 (t, *J* = 7.2 Hz, 3H), 0.64-0.89 (m, 2H), 0.71 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 170.5, 139.5, 113.3, 77.5, 73.7, 59.8, 41.5, 39.7, 39.4, 29.8, 21.8, 13.9; IR (neat) 2981, 2952, 2926, 2905, 2870, 2838, 1738, 1647, 1457, 1443, 1411, 1371, 1319, 1256, 1196, 1171, 1134, 1087, 1031, 1006, 990, 922, 861 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{21}O_3$ $[M+H]^+$ 213.1491, found 213.1509.

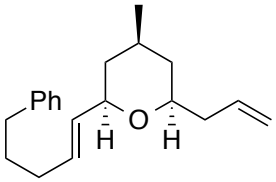


rac-(2*S*, 4*S*, 6*R*)-2allyl-4-methyl-6((*E*)-5-phenylpent-1-en-1-yl)tetra-hydro -2*H*-pyran (4-73)

The general rearrangement cyclization procedure was followed with **4-67** (53 mg, 0.204 mmol), allyltrimethylsilane (93 mg, 0.814 mmol), Re_2O_7 (3.0 mg, 0.0061 mmol), Hcat-1 $(3,5\text{-}(CF_3)_2C_6H_3NH]_2SO_2$, 10.6 mg, 0.0204 mmol), DCM (10.2 mL), the reaction was was initiated at 0 °C and warm up slowly to rt. After a total stirring for 20 h, the reaction was

quenched with 5 drops of pyridine. After evaporation of the solvent, flash chromatography (1-3% ethylacetate in hexanes) give mixture of four isomers in 41.1 mg yield. (71%, dr = 24:3:2:1), of which two major was isolated and characterized.

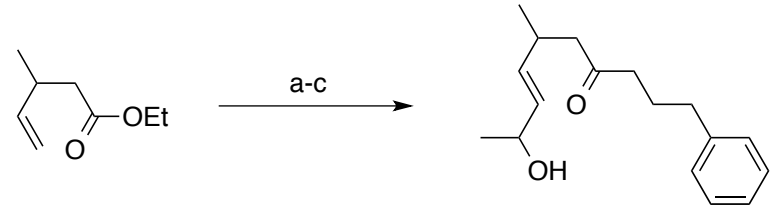
Major 1 (slow eluting): ^{1}H NMR (400 MHz, C_6D_6) δ 7.12-7.20 (m, 2H), 7.02-7.10 (m, 3H), 5.81 (dddd, *J* = 6.4, 7.6, 14.0, 16.8, 1H), 5.70 (ddt, *J* = 0.8, 6.4, 15.6, 1H), 5.56 (ddt, *J* = 1.2, 5.2, 15.6, 1H), 5.01-5.09(m, 2H), 4.04 (q, *J* = 6.8, 1H), 3.95 (dd, *J* = 4.4, 10.4, 1H), 2.45-2.52 (m, 1H), 2.48 (t, *J* = 7.6, 2H), 2.02-2.12 (m, 1H), 1.98 (q, *J* = 7.2, 2H), 1.61 (p, *J* = 7.6, 2H), 1.49-1.58 (m, 1H), 1.42-1.59 (m, 1H), 1.29-1.36 (m, 1H), 1.16-1.25 (m, 1H), 0.95 (q, *J* = 11.6, 1H), 0.78 (d, *J* = 6.4, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 142.3, 136.0, 132.8, 129.5, 128.4, 128.2, 125.7, 115.8, 72.4, 69.5, 41.0, 36.1, 35.3, 35.3, 31.8, 31.0, 24.6, 22.4; IR (neat) 3063, 3026, 2924, 2855, 1641, 1603, 1495, 1454, 1369, 1265, 1191, 1095, 1055, 1015, 995, 967, 911, 746, 698 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{28}O$ $[M]^+$ 284.2140, found 284.2166.



***rac*-(2*R*, 4*S*, 6*R*)-2allyl-4-methyl-6((*E*)-5-phenylpent-1-en-1-yl)tetra-hydro -2*H*-pyran**

Major 2 (fast eluting): ^{1}H NMR (400 MHz, C_6D_6) δ 7.14-7.20 (m, 2H), 7.02-7.20 (m, 3H), 5.99 (dddd, *J* = 6.4, 7.6, 14.4, 17.2, 1H), 5.71 (ddt, *J* = 1.0, 6.4, 15.2, 1H), 5.57 (ddt, *J* = 1.2, 5.6, 15.2, 1H), 5.03-5.12 (m, 2H), 4.04 (dd, *J* = 5.6, 11.6, 1H), 3.58 (dddd, *J* = 2.0, 5.6, 6.4, 12.0, 1H), 2.47 (t, *J* = 7.6, 2H), 2.35-2.44 (m, 1H), 2.13-2.22 (m, 1H), 1.97 (q, *J* = 7.2, 2H), 1.87-1.96 (m, 1H), 1.53-1.66 (m, 3H), 1.42 (ddd, *J* = 5.2, 12.0, 16.8, 1H), 1.28 (dq, *J* = 2.0, 13.2, 1H), 1.18 (dq, *J* = 2.0, 13.2, 1H), 0.94 (d, *J* = 7.2, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 142.3, 135.5, 132.7, 129.7, 128.4, 128.2, 125.7, 116.1, 72.1, 71.1, 41.3, 37.7, 36.6, 35.3, 31.9, 30.9, 25.7, 17.8; IR (neat) 3064, 3026, 2929, 2852, 1641, 1603, 1495, 1455, 1379, 1336, 1317,

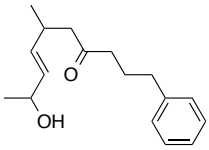
1247, 1189, 1058, 993, 967, 911, 746, 698 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{28}O$ $[M]^+$ 284.2140, found 284.2122.



Reaction Cconditions:

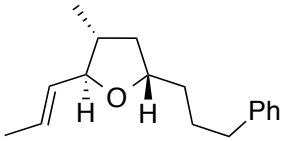
a) (MeO)NHMe•HCl, Me_3Al, CH_2Cl_2, -78 ºC to rt, 71%; b) (3-Phenylpropyl)magnesium bromide, Et_2O, 0 ºC, 51%; c) (*Z*)-Hex-3-ene-2,5-diol, Grubbs-Hoveyda 2nd generation metathesis catalyst, CH_2Cl_2, 50%.

Scheme C19 Synthesis of substrate **4-74**

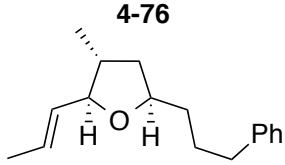


(*E*)-9-hydroxy-6-methyl-1-phenyldec-7en-4-one (4-74)

^1H NMR (300 MHz, $CDCl_3$) δ 7.16-7.24 (m, 2H), 7.05-7.14 (m, 3H), 5.35-5.51 (m, 2H), 4.14 (p, *J* = 6.3 Hz, 1H), 2.61 (heptet, *J* = 6.6 Hz, 1H), 2.53 (t, *J* = 7.5 Hz, 2H), 2.19-2.36 (m, 4H), 1.81 (p, *J* = 7.5 Hz, 2H), 1.73 (br, 1H), 1.14 (d, *J* = 6.3 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.8, 141.6, 134.6, 133.0, 128.5, 128.4, 126.0, 68.61, 68.57, 49.7, 42.6, 35.1, 31.94, 31.91, 25.1, 23.49, 23.45, 20.1; IR (neat) 3411, 3061, 3026, 2964, 2928, 2871, 1709, 1603, 1496, 1454, 1407, 1369, 1278, 1148, 1063, 1030, 971, 937, 748, 700 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{23}O$ $[M\text{-}OH]^+$ 243.1749, found 243.1742.



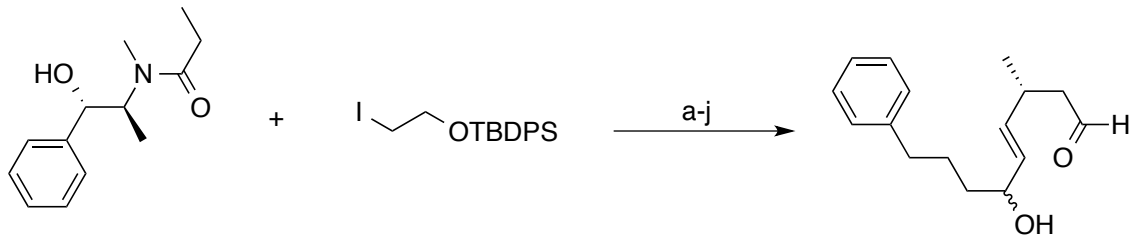
4-76



***rac*-(2*R*, 3*R*, 5*S*)-3-Methyl-5-(3-phenylpropyl)-2-((*E*)-prop-1-en-1-yl)tetrahydrofuran and rac-(2*R*, 3*R*, 5*R*)-3-methyl-5-(3-phenylpropyl)-2-((*E*)-prop-1-en-1-yl) tetrahydrofuran (4-75)**

The general reductive cyclization procedure was followed with **4-74** (39

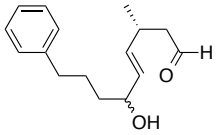
mg, 0.15 mmol), Et_3SiH (35 mg, 0.30 mmol), Re_2O_7 (2.2 mg, 0.0045 mmol), and DCM (7.5 mL). The reaction was stirred at 0 °C for 10 h, then was quenched with 5 drops of pyridine. After evaporation of the solvent, 5 μl of benzyldimethylsilane was added into the crude mixture as an internal standard. Then the mixture was dissolved in $CDCl_3$ and ^1H NMR showed a yield of 75% (dr = 5:3:1, two major are shown). Preparative TLC with 5% ethyl acetate in hexanes gave the two major products as an inseparable mixture (dr = 65:35). ^1H NMR (400 MHz, $CDCl_3$) δ 7.25-7.31 (m, 2H), 7.15-7.21 (m, 3H), 5.64-5.76 (m, 1H), 5.39-5.48 (m, 1H), 3.99-4.06 (m, 0.65H), 3.92-3.99 (m, 0.35), 3.73 (t, *J* = 8.4 Hz, 0.65H), 3.65 (t, *J* = 8.0 Hz, 0.35H), 2.64 (t, *J* = 6.8 Hz, 2H), 2.17 (p, *J* = 6.0 Hz, 0.65H), 1.82-1.97 (m, 1H), 1.74-1.81 (m, 1H), 1.70-1.74 (m, 3H), 1.58-1.70 (m, 2.70H), 1.45-1.55 (m, 1H), 1.23 (dt, *J* = 9.6, 11.6 Hz, 0.65H), 0.95-1.00 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 131.3, 128.7, 128.5, 128.2, 125.7, 87.5, 86.5, 78.5, 77.8, 41.5, 40.8, 39.7, 39.0, 36.2, 36.03, 35.96, 27.9, 27.8, 17.83, 17.80, 16.6, 15.7; IR (neat) 3061, 3026, 2954, 2929, 2858, 1603, 1496, 1453, 1376, 1329, 1125, 1107, 1084, 1029, 1007, 964, 930, 748, 698 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{25}O$ $[M+H]^+$ 245.1905, found 245.1891.



Reaction Cconditions:

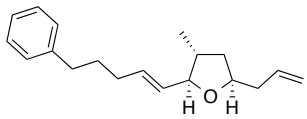
a) LDA, THF, -78 ºC to rt, 92%; b) LiH_2NBH_3, THF, 0 ºC, 90%; c) Py•SO_3, DMSO, Et_3N, CH_2Cl_2, 81% d) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0 ºC; e)HF•Py, THF, 80% for two steps; f) PCC, Celite, CH_2Cl_2, rt; g) $(MeO)_3CH$, PPTS, MeOH, 50 ºC, 83% for two steps; h) DIBAL-H, CH_2Cl_2, -78 ºC, 97%; i) Py•SO_3, DMSO, Et_3N, CH_2CL_2; j) (3-Phenylpropyl)magnesium bromide, Et_2O, 0 ºC, 48 % for two steps.

Scheme C20 Synthesis of substrate **4-76**



(3*R*, *E*)-6-Hydroxy-3-methyl-9-phenylnon-4-enal (4-76)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (t, *J* = 2.0 Hz, 1H), 7.27-7.34 (m, 2H), 7.18-7.24 (m, 3H), 5.62 (dd, *J* = 6.8, 15.2 Hz, 1H), 5.50 (ddd, *J* = 0.8, 6.4, 15.2 Hz, 1H), 4.09 (q, *J* = 6.4 Hz, 1H), 2.80 (heptet, *J* = 6.8 Hz, 1H), 2.66 (t, *J* = 6.8 Hz, 2H), 2.36-2.50 (m, 2H), 1.85 (br, 1H), 1.50-1.78 (m, 5H), 1.11 (d, *J* = 6.8 Hz, 2H), 1.10 (d, *J* = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.21, 202.15, 142.3, 135.10, 135.07, 132.3, 128.4, 128.3, 125.8, 72.61, 72.58, 50.25, 50.21, 38.86, 36.83, 35.8, 31.0, 27.3, 20.37, 20.31; IR (neat) 3416, 3061, 3025, 2929, 2861, 2723, 1722, 1602, 1495, 1453, 1406, 1374, 1261, 1081, 1010, 973, 739, 699 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{21}O$ $[M\text{-}OH]^+$ 229.1592, found 229.1586.



(2*R*, 3*R*, 5*R*)-5-Allyl-3-methyl-2-((*E*)-5-phenylpent-1-en-1-yl)tetrahydrofuran (4-77)

The general cyclization procedure was followed with **4-76** (43 mg, 0.17 mmol), allyltrimethylsilane (79 mg, 0.69 mmol), Re_2O_7 (2.5 mg, 0.0052 mmol), and DCM (8.7 mL). The reaction was initiated at 0 °C and then warmed up slowly to rt, then was stirred at rt for a total of 20 h. The reaction was quenched with 5 drops of pyridine. After evaporation of the solvent, the crude material was purified by flash chromatography (1-5% ethyl acetate in hexanes) to give the product (45 mg, 95%, dr = 5.0:1.7:1). The mixture of products was then redissolved in 8.5 ml DCM and Re_2O_7 (4.2 mg, 0.0087 mmol) was added. The reaction was refluxed for 36 hrs and then quenched with 5 drops of pyridine. After evaporation of the solvent, the crude material was purified by flash chromatography (1-5% ethyl acetate in hexanes) to give the product (43 mg, 91%, dr = 8.7:1:1.3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.31 (m, 2H), 7.16-7.21 (m, 3H), 5.83 (ddt, *J* = 7.2, 10.0, 17.2 Hz, 1H), 5.71 (dt, *J* = 6.8, 15.2 Hz, 1H), 5.45 (ddt, *J* = 1.2, 8.0, 15.2 Hz,

1H), 5.03-5.12 (m, 2H), 4.00-4.07 (m, 1H), 3.68 (t, J = 7.6 Hz, 1H), 2.63 (t, J = 7.6 Hz, 2H), 2.32-2.40 (m, 1H), 2.19-2.27 (m, 1H), 2.06-2.14 (m, 2H), 1.82-1.91 (m, 2H), 1.68-1.78 (m, 2H), 1.60-1.68 (m, 1H), 0.98 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 135.0, 133.4, 130.4, 128.5, 128.3, 125.7, 116.8, 87.7, 77.3, 41.0, 39.0, 38.9, 35.4, 31.8, 30.9, 16.4; IR (neat) 3062, 3025, 2927, 2855, 1639, 1602, 1495, 1453, 1375, 1362, 1321, 1103, 1025, 995, 966, 913, 745, 698 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{25}O$ $[M-H]^+$ 269.1905, found 269.1894.

BIBLIOGRAPHY

1. Chabardes, P.; Grard, C.; Schneider, C. *DE1965377A*, **1970**.
2. (a) Katsuki, T. *Comprehensive Asymmetric Catallysis*; (b) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. Eds. *Springer: Berlin* **1999***, 2*, 621.
3. Charette, A. B.; Marcoux, J. –F. *Synlett* **1995***, 12*, 1197.
4. Uma, R.; Crevisy, C.; Gree, R. *Chem. Rev.* **2003***, 103*, 27.
5. (a) Leavell, K. H.; Lewis, E. S. *Tetrahedron* **1972***, 28*, 1167; (b) Lewis, E. S.; Hill, J. T. *J. Am. Chem. Soc.* **1969***, 91*, 7458; (c) Lewis, E. S.; Hill, J. T.; Newmann, E. R. *J. Am. Chem. Soc.* **1968***, 90*, 662.
6. (a) Babler, J. H.; Olsen, D. O.; Arnold, W. H. *J. Org. Chem.* **1974***, 39*, 1656; (b) Babler, J. H.; Olsen, D. O. *Tetrahedron Lett*. **1974***, 15*, 351; (c) Kogami, J.; Kumanotani, J. *Bull. Chem. Soc. Jpn.* **1974***, 47*, 226.
7. (a) Overman, L. E.; Campbell, C. B.; Knoll, F. M. *J. Am. Chem. Soc.* **1978***, 100*, 4482; (b) Overman, L. E.; Campbell, C. B. *J. Org. Chem.* **1976***, 41*, 3338.
8. (a) Overman, L. E.; Knoll, F. M. *Tetrahedron Lett*. **1979***, 26*, 321; (b) Henry, P. M. *J. Am. Chem. Soc*. **1972***, 94*, 5200; (c) Sabel, A.; Smidt, J.; Jira, R.; Prigge, H. *Chem. Ber.* **1969***, 102*, 2939.
9. (a) Takatsuto, S.; Ishiguro, M.; Ikekawa, N. *J. Chem. Soc., Chem. Commun*. **1982**, 258; (b) Kirihata, M.; Kawahara, S.; Ichimoto, I.; Udea, H. *Agrc. Biol. Chem*. **1990***, 54*, 753;

(c) Kurokawa, N.; Ohfune, Y. *Tetrahedron Lett*. **1985***, 26*, 83. (d) Nakazawa, M.; Sakamoto, Y.; Takahashi, T.; Tomooka, K.; Ishikawa, K.; Nakai, T. *Tetrahedron Lett*. **1993***, 34*, 5923; (e) Mahrwald, R.; Schick, H.; Piunitsky, K. K.; Schwartz, S. *J. Prakt. Chem*. **1990***, 332*, 403; (f) Grieco, P. A.; Tuthill, P. A.; Sham, H. L. *J. Org. Chem*. **1981***, 46*, 5005; (g) Grieco, P. A.; Takigawa, T.; Bongers, S. L.;Tanaka, H. *J. Am. Chem. Soc*. **1980***, 102*, 7587; (h) Trost, B. M.; Timko, J. M.; Stanton, J. L. *J. Chem. Soc. Chem. Commun*. **1978**, 436.

10. Chabardes, P.; Kuntz, E.; Varagnat, J. *Tetrahedron* **1977***, 33*, 1775.
11. Ninagawa, Y.; Nishida, T.; Itoi, K. *DE2307468A1*, **1973**.
12. Kane, B. J. *US4254291A*, **1981**.
13. Matsubara, S.; Takai, K.; Nozaki, H. *Tetrahedron Lett.* **1983***, 24*, 3741.
14. Matsubara, S.; Okazoe, T.; Oshima, K.; Takai, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1985***, 58*, 844.
15. Hosogai, T.; Fujita, Y.; NInagawa, Y.; Nishida, T. *Chem. Lett*. **1982**, 357.
16. Belgacem, J.; Kress, J.; Osborn, J. A. *J. Am. Chem. Soc.* **1992***, 114*, 1501.
17. Belgacem, J.; Kress, J.; Osborn, J. A. *J. Mol. Catal.* **1994***, 86*, 267.
18. Fronczek, F. R.; Luck, R. L.; Wang, G. *Inorg. Chem. Commun.* **2002***, 5*, 384.
19. Narasaka, K.; Kusama, H.; Hayashi, Y. *Chem. Lett*. **1991**, 1413.
20. Narasaka, K.; Kusama, H.; Hayashi, Y. *Tetrahedron* **1992***, 48*, 2059.
21. Thome, A.; Roeper, M.; Kneuper, H. J. *DE4228887A1*, **1994**.
22. Jacob, J.; Espenson, J. H.; Jensen, J. H.; Gordon, M. S. *Organometallics,* **1998***, 17*, 1835.
23. Wang, G.; Jimtaisong, A.; Luck, R. L. *Organometallics,* **2004***, 23*, 4522.
24. Bellemin-Laponnaz, S.; Gisie, H.; Le Ny, J. P.; Osborn, J. A. *Angew. Chem. Int. Ed.* **1997***, 36*, 976.
25. Bellemin-Laponnaz, S.; Le Ny, J. P.; Osborn, J. A. *Tetrahedron Lett.* **2000***, 41*, 1549.

26. Schelecht, M. F. in *Comprehensive organic synthesis*, ed. Trost, B. M.; Fleming, I. *Pergamon, Oxford* **1991***, 7*, 815

27. Luzzio, F. A., in *Organic Reactions*, ed. Paquette, L. A.; *Wiley, New York* **1999***, 53*, 1.

28. Wietzerbin, K.; Bernadou, J.; Meunier, B.; *Eur. J. Inorg. Chem*. **2000**, 1391.

29. Luzzio, F. A. *Tetrahedron,* **2012***, 68*, 5323.

30. Schoop, T.; Roesky, H. W.; Noltemeyr, M.; Schmidt, H. G. *Organometallics,* **1993***, 12*, 571.

31. Morrill, C.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005***, 127*, 2842.

32. Morrill, C.; Beutner, G. L.; Grubbs, R. H. *J. Org. Chem.* **2006***, 71*, 7813.

33. (a) Schoop, T.; Roesky, H.W.; Noltemeyer, M.; Schimidt, H. G. *Organometallics* **1993**, *12*, 571; (b) Toreki, R.; Schrock, R.R.; Davis, W. M. *J. Am. Chem. Soc*. **1992***, 114*, 3367; (c) Danopolous, A. A.; Longley, C. J.; Wilkinson, G.; Hussain, B.; Hursthouse, M. B. *Polyhedron* **1989***, 8*, 2657; (d) Nugent, W. A. *Inorg, Chem*. **1983***, 22*, 965.

34. Zheng, H.; Lejkowski, M.; Hall, D. G. *Chem. Sci.* **2011***, 2*, 1305.

35. Bellemin-Laponnaz, S.; Le Ny, J. P.; Dedieu, A. *Chem. A. Eur. J.,* **1999***, 5*, 57.

36. (a) Guo, H.; Dong, C. G.; Kim, D. S.; Urabe, D.; Wang, J.; Kim, J. T.; Liu, X.; Sasaki, T.; Kishi, Y. *J. Am. Chem. Soc.* **2009***, 131*, 15387; (b) Wipf, P.; Ribe, S. *J. Org. Chem.* **1998***, 63*, 6454; (c) Oppolzer, W.; Radinov, R. N. *Helv. Chim. Acta* **1992***, 75*, 170; (d) F. Langer, Schwink, L.; Devasagayaraj, A.; Chavant, Y. P.; Knochel, P. *J. Org. Chem.* **1996***, 61*, 8229; e) Soai, K.; Ookawa, A.; Kaba, T.; Ogawa, K. *J. Am. Chem. Soc.* **1987***, 109*, 7111.

37. (a) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987***, 109*, 5765; (b) Ebner, D. C.; Bagdanoff, J. T.; Ferreira, E. M.; McFadden, R. M.; Caspi, D. D.; Trend, R. M.; Stoltz, B. M. *Chem. Eur. J.* **2009***, 15*, 12978; (c) Schultz, M. J.; Hamilton, S. S.; Jensen, D. R.; Sigman, M. S. *J. Org.Chem*.

2005*, 70*, 3343; (d) Ruble, J. C.; Latham, H. A.; Gu, G. C. *J. Am. Chem. Soc*. **1997***, 119*, 1492; (e) Birman, V. B.; Li, X. *Org. Lett.* **2006***, 8*, 1351.

38. Corey, E. J.; Helal, C. J. *Angew. Chem. Int. Ed.* **1998***, 37*, 1987.

39. (a) Trost, B. M.; (b) Toste, F. D. *J. Am. Chem. Soc.* **2000***, 122*, 11262; (b) Trost, B. M.; Tang, W.; Toste, F. D. *J. Am. Chem. Soc.* **2005***, 127*, 14785.

40. Mandal, A. K.; Schneekloth, J. S.; Kuramochi, K.; Crews. C. M. *Org. Lett.* **2006***, 8*, 427.

41. Hutchison, J. M.; Lindsay, H. A.; Dormi, S. S.; Jones, G. D.; Vicic, D. A.; McIntosh, M. C. *Org. Lett.* **2006***, 8*, 3663.

42. Seiders, J. R.; Jung, H. H.; Floreancig, P. E. *Angew. Chem. Int. Ed.* **2007***, 46*, 8464.

43. Munday, R. H.; Denton, R. M.; Anderson, J. C. *J. Org. Chem.* **2008***, 73*, 8033.

44. Numajiri, Y.; Takahashi, T.; Doi, T. *Chem. Asian J.* **2009***, 4*, 111.

45. Yun, S. Y.; Hansen, E. C.; Volchkov, I.; Cho, E. J.; Lo, W. Y.; Lee, D. *Angew. Chem. Int. Ed.* **2010***, 49*, 4261.

46. Trost, B. M.; Amans, D.; Seganish, W. M.; Chung, C. K. *Chem. Eur. J.* **2012***, 18*, 2961.

47. Volchkov, I.; Lee, D. *J. Am. Chem. Soc.* **2013***, 135*, 5324.

48. Hansen, E. C.; Lee, D. *J. Am. Chem. Soc.* **2006***, 128*, 8142.

49. Volchkov, I.; Park, S.; Lee, D. *Org. Lett.* **2011***, 13*, 3530.

50. Zakarian, A.; Tom J.; Stivala, C. E.; Saito, T.; Herrmann, A. T. *J Am. Chem. Soc.* **2010***, 132*, 5962.

51. Akai, S.; Tanimoto, K.; Kanao, Y.; Egi, M.; Yamamoto, T.; Kita, Y. *Angew. Chem. Int. Ed*. **2006***, 45*, 2592.

52. Akai, S.; Hanada, R.; Fujiwara, N.; Kita, Y.; Egi, M. *Org. Lett*. **2010***, 12*, 4900.

53. Xie, Y.; Floreancig, P. E. *Chem. Sci.* **2011***, 2*. 2423.

54. Tadpetch, K.; Rychnovsky, S. D. *Org. Lett.* **2008***, 10*, 4839.

55. Nising, C. F.; Brase, S. *Chem. Soc. Rev.* **2008***, 37*, 1218.

56. a) Gonzalez, N.; Rodriguez, J.; Jimenez, C. *J. Org. Chem*. **1999***, 64*, 5705; (b) Mitchell, S. S.; Rhodes, D.; Bushman, F. D.; Faulkner, D. *J. Org. Lett*. **2000***, 2*, 1605.

57. a) Uenura, D.; Chou, T.; Haino, T.; Nagatsu, A.; Fukuzawa, S.; Zheng, S. H.; Chen, H. S. *J. Am. Chem. Soc.* **1995***, 117*, 1155; b) Chou, T.; Haino, T.; Kuramoto, M.; Uemura, D. *Tetrahedron Lett*. **1996***, 37*, 4027.

58. Spartan (Wavefunction, Irvine, CA) calculations were performed by conducting a conformational search followed by semi-empirical energy calculations using the AM1 basis set.

59. a) Raju, B. R.; Saikia, A. K. *Molecules*, **2008***, 13*, 1942; b) Brimble, M. A.; Furkert, D. P. *Curr. Org. Chem*. 2003, 7, 1461; c) Mead, K. T.; Brewer, B. N. *Curr. Org. Chem*. **2003***, 2*, 227.

60. Ito, Y.; Konoike, T.; Saegusa, T. *J. Am. Chem. Soc*. **1975***, 97*, 2912.

61. Angyal, S. J. *Carbohydr. Chem. Biochem*. **1984***, 42*, 15.

62. Satake, M.; Ofuji, K.; Naoki, H.; James, K. J.; Furey, A.; Mcmahon, T.; Silke, J.; Yasumoto, T. *J. Am. Chem. Soc*. **1998***, 120*, 9967.

63. a) Sugimoto, T.; Ishihara, J.; Murai, A. *Tetrahedron Lett.* **1997***, 38*, 7379; b) McCauley, J. A.; Nagasawa, K.; Lander, P. A.; Mischke, S. G.; Simones, M. A.; Kishi, Y. *J. Am. Chem. Soc*. **1998***, 120*, 7647; c) Ishihara J.; Sugimoto, T.; Murai, A. *Synlett*, **1998**, 603; d) Nakamura, S.; Inagaki, J.; Sugimoto, T.; Kudo, M.; Nakajima, M.; and Hashimoto, S.*Org. Lett.* **2001***, 3*, 4075; e) Sakamoto, S.; Sakazaki, H.; Hagiwara, K.; Kamada, Kl; Ishii, K.; Noda, T.; Inoue, M.; Hirama, M. *Angew. Chem. Int. Ed*. **2004***, 43*, 6505; f) Lu, C. D.; Zakarian, *Org. Lett*. **2007***, 9*, 3161; g) Stivala, C. E.; Zakarian, A. *J. Am. Chem.*

Soc. **2008***, 130*, 3774; h) Aroaz, R.; Servent, D.; Molgo, J.; Iorga, B. I.; Fruchart-Gaillard, C.; Benoit, E.; Gu. Z.; Stivala, C.; Zakarian, A. *J. Am. Chem. Soc*. **2011***, 133*, 10499.

64. a) Casey, B. M.; Flowers, R. A.; *J. Am. Chem. Soc*. **2011***, 133*, 11492; b) Avetta, C. T.; Konkol, L. C.; Taylor, C. N.; Dugan, K. C.; Stern, C. L.; Thomson, R. J. *Org. Lett*. **2008***, 10*, 5621; c) Demertino, M. P.; Chen, K.; Baran, P. S. *J. Am. Chem. Soc*. **2008***, 130*, 11546.

65. a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980***, 102*, 5974; b) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y.; *J. Am. Chem. Soc.* **1997***, 119*, 11224; c) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunga, M.; Hansen, K. B.; Gould, A. E.; M. E. Furrow, Jacobsen, E. N. *J. Am. Chem. Soc.* **2002***, 124*, 1307; d) Kakei, H.; Tsuji, R.; Ohshima, T.; Shibasaki, M.; *J. Am. Chem. Soc.* **2005***, 127*, 8962; e) Wang, X.; List, B.; *Angew. Chem.* **2008***, 120*, 1135; *Angew. Chem. Int. Ed.* **2008***, 47*, 1119; f) Li, Z.; Yamamoto, H. *J. Am. Chem. Soc.* **2010***, 132*, 7878.

66. a) Simpson, G. L.; Heffron, T. P.; Merino, E.; Jamison, T. F. J. Am. Chem. Soc. 2006, 8, 4375; b) Marshall, J. A.; Mikowski, A. M.; *Org. Lett.* **2007***, 8*, 4375; c) Morimoto, Y.; Okita, T.; Takaishi, M.; Tanaka, T. *Angew. Chem.* **2007***, 119*, 1150; *Angew. Chem. Int. Ed.* **2007***, 46*, 1132; d) Vilotijevic, I.; Jamison, T. F. *Science,* **2007***, 317*, 1189; e) Morimoto, Y.; Yata, H.; Nishikawa, Y.; *Angew Chem.* **2007***, 119*, 6601; *Angew. Chem. Int. Ed.* **2007***, 46*, 6481; f) Marshall, J. A.; Hann, R. K.; *J. Org. Chem.* **2008***, 73*, 6753; g) Xiong, Z.; Busch, R.; Corey, E. J.; Corey, E. J. *Org. Lett.* **2010***, 12*, 1512; h) Morten, C. J.; Byers, J. A.; Jamison, T. F. *J. Am. Chem. Soc.* **2011***, 133*, 1902.

67. Hayashi, N.; Kujiwara, K.; Murai, A. *Tetrahedron* **1997***, 53*, 12425; b) Zakarian, A.; Batch, A.; Holton, A. *J. Am. Chem. Soc.* **2003***, 125*, 7822; c) Valentine, J. C.; Mcdonald,

F. E.; Neiwert, W. A.; Hardcastle, K. I. *J. Am. Chem. Soc.* **2005***, 127*, 4586; d) Tong, R.; Walentine, J. C.; McDonald, F. E.; Cao, R.; Fang, X.; Hardcastle, K. I. *J. Am. Chem. Soc.* **2007***, 129*, 1050; e) Wan, S.; Gunaydin, H. Houk, K. N.; Floreancig, P. E. *J. Am. Chem. Soc.* **2007***, 129*, 7915; f) Tanuwidjala, J.; Ng, S.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2009***, 131*, 12084; g) Clausen, D. J.; Wan, S.; Floreancig, P. E. *Angew. Chem. Int. Ed.* **2011***, 50*, 5178.

68. Vilotijevic, I.; Jamison, T. F. *Angew. Chem.* **2009***, 121*, 5352; Angew. *Chem. Int. Ed. 2009,* **48**, 5250; b) Vilotjevic, I.; Jamison, T. F. *Marine Drugs* **2010***, 8*, 763.

69. Xie, Y.; Floreancig, P. E. *Angew. Chem.* **2013***, 125*, 653; *Angew. Chem. Int. Ed.* **2013***, 52*, 625.

70. Please see the supporting information for crystal structures and Ref. 69.

71. a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969***, 34*, 2543; b) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991***, 113*, 4092.

72. Herrmann, A. T.; Saito, T.; Stivala, C. E.; Tom, J.; Zakarian, A. *J. Am. Chem. Soc.* **2010***, 132*, 5962.

73. Tadpetch, K.; Rychonovsky, S. D. *Org. Lett.* **2008***, 10*, 4839.

74. Trost, B. M. Angew. Chem. 1995, 107, 285; *Angew. Chem. Int. Ed.* **1995***, 34*, 259.

75. Xie, Y.; Floreancig, P. E. *Angew. Chem. Int. Ed.* **2014***, 53*, 4926-4929.

76. a) Evans, P. A.; Cui, J.; Gharpure, R. J.; Hinkle, R. J. *J. Am. Chem. Soc.* **2003***, 125*, 11456; b) Evans, P. A.; Cui, J.; Gharpure, R. J. *Org. Lett.* **2003***, 5*, 3883; c) Hinkle, R. J.; Lian, Y.; Litvinas, N. D.; Jenkins, A. T.; Burnette, D. C. *Tetrahedron* **2005***, 61*, 11679.

77. Sittiwong, W.; Richardson, M. W.; Schiaffo, C. E.; Fisher, T. J.; Dussault, P. H. *Beilstein J. Org. Chem.* **2013***, 9*, 1526.

78. a) Kruse, C. G.; Poels, E. K.; Jonkers, F. L.; Vandergen, A. *J. Org. Chem.* **1978***, 43*, 3548; b) Green, M. E.; Rech, J. C.; Floreancig, P. E. *Angew. Chem.* **2008***, 120*, 7427; *Angew. Chem. Int. Ed.* **2008***, 47*, 7317.

79. a) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982***, 104*, 4976; b) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999***, 121*, 12208; c) Larsen, C. H.; Ridgway, B. H.;, Shaw, J. T.; Smith, D. M.; Woerpel, K. A. *J. Am. Chem. Soc.* **2005***, 127*, 10879.

80. Darses, S.; Genet, J. P. *Chem. Rev.* **2008***, 108*, 288.

81. a) Rodriguez, A. A.; Yoo, H.; Ziller, J. W.; Shea, K. J. *Tetrahedron Lett.* **2009***, 50*, 6830; b) Cranwell, P. B.; Hiscock, J. R.; Haynes, C. J. E.; Light, M. E.; Wells, N. J.; Gale, P. A. *Chem. Commun.* **2013***, 52*, 13424.

82. Xu, H.; Zuend, Z.; Wall, M. G.; Tao, Y.; Jacobsen, E. N. *Science,* **2010***, 327*, 986; b) Borovika, A.; Tang, P. I.; Klapman, S.; Nagorny, P. *Angew. Chem.* **2013***, 125*, 13666; *Angew. Chem. Int. Ed.* **2013***, 52*, 13424.

83. Horn, M.; Schapple, L. H.; Lang-Wittkowski, G.; Mayr, H.; Ofial, A. R. *Chem. Eur. J.* **2013***, 19*, 249.

84. Smith, D. M.; Tran, M. B.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003***, 125*, 14149.

85. Masato, K.; Tomoaki, S,; Shinji, T. *Angew. Chem. Int. Ed.* **2009***, 48*, 8948.

86. Hiroshi, I.; Kosuk, N.; Mugio, N.; Daiki, O.; Ikuo, S.; Shiya, S.; Hirofumi, Y.; Kosuke, N. *Chem. Lett.* **2010***, 39*, 830.