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NEW METHODOLOGY FOR CONSTRUCTION OF
OXYGEN-CONTAINING HETEROCYCLES

presented by

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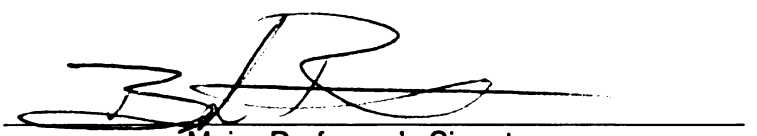
has been accepted towards fulfillment
of the requirements for the

M.S. degree in Chemistry



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NEW METHODOLOGY FOR CONSTRUCTION OF OXYGEN-CONTAINING HETEROCYCLES

By

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ABSTRACT

NEW METHODOLOGY FOR CONSTRUCTION OF
OXYGEN-CONTAINING HETEROCYCLES

By

Zhihua Shang

In this thesis we report a new methodology that utilizes ring-closing metathesis (RCM) to make oxygen-containing heterocycles. The motif is approached by a novel stereoselective nucleophilic attack on cyclic orthoesters to generate a bis-alkene intermediate. RCM of the bis-alkene would lead to a bicyclic ketal and selective reduction of the ketal would yield the oxygen-containing heterocycle. Heterocycles of various ring sizes could be constructed if this strategy is applicable. The stereocontrol in the methodology could be accessed via Sharpless asymmetric dihydroxylation and translated to the final product via substrate control.

My results to date have been promising in seteroselective nucleophilic attack on cyclic orthoesters. However, the diastereomer of the bis-alkene obtained from *anti* attack would only lead to the strained inside-out bicyclic ketals, which was either difficult to be constructed by RCM or too unstable to be isolated once formed. Approaches to achieve opposite diastereoselectivity have been tried without success. Mechanism of a previously reported transformation of cyclic orthoesters was also elucidated in this thesis.

To my parents

To those who fight minor depression

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Finally, I would like to quote a word from my genius friend Chen, who said 'if God makes me ordinary all my life, I will take it and thank him until death; yet if there is a tiny bit of uncertainty about it, I will fight for that uncertainty until death.'

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LIST OF ABBREVIATIONS

Ac	acetyl
SAD	Sharpless asymmetric dihydroxylation
Ar	Aryl
aq	aqueous
Bn	benzyl
CH_2Cl_2	dichloromethane
CSA	camphorsulfonic acid
DCM	dichloromethane
DIBAL	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DMF	N, N-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
d.r.	diastereomeric ratio
ee	enantiomeric excess
equiv	equivalent
GC	gas chromatography
h	hour
HWE	Horners-Wadsworth-Emmons reaction
L.A.	Lewis acid
min	minute
mL	milliliter

mmol	millimole
MS	mass spectrometry
NaHMDS	sodium bis(trimethylsilyl)amide
NMO	*n*-methylmorpholine-*n*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
PDC	pyridimium dichromate
PG	protecting group
Ph	phenyl
PMP	*p*-methoxyphenyl
PPTS	pyridinium *p*-toluenesulfonate
RT	room temperature
TBS	*t*-butyldimethylsilyl
TEA	triethylamine
Th	2-thiazolyl
THF	tetrahydrofuran
THP	tetrahydropyran
TMS	trimethylsilyl
TsOH	*p*-toluenesulfonic acid

Chapter 1

Background: A Brief Review of Oxygen-Containing Hetereocycle Synthesis

1.1. Introduction

Oxygen-containing heterocycles are an important class of organic compounds due to their immense biological and industrial importance. Many pharmaceuticals and biologically active agrochemicals contain oxygen heterocycles, as do countless additives and modifiers used in industries as varied as cosmetics, reprography, information storage, and plastics. One of the simplest oxygen-containing heterocycles, tetrahydrofuran (THF), is a five-membered cyclic ether. This motif represents the core structure in a variety of biologically important natural products such as polyether antibiotics and annonaceous acetogenins. For example, molvizarin, a member of the annonaceous acetogenin family, contains two THFs in the structure and has selectivity for targeting ovarian cancer cell replication over a million times greater than its activity towards other cell lines.[1a] The inostamycin family of polyether antibiotics, which contain two trisubstituted THF rings, elicit a wide range of pharmacological effects including significant anti-HIV and anticancer activities.[1b] Several members of the schlerophytin diterpene family also have a THF embedded in the polycyclic structure. These compounds show significant cytotoxic activity (**Figure 1-1**).[1c]

Organic chemistry has its origins in the study of natural products and this is reflected in the ongoing interest in natural product synthesis. Natural products are often isolated in only small quantities from natural sources which can make it difficult to obtain sufficient material for complete biological evaluation. Organic chemists can provide a solution to this problem by devising creative laboratory syntheses. Efficient construction

of the core structures in the natural products is often the key step in a proposed synthetic scheme. Thus, stereoselective, reliable and convenient syntheses of oxygen-containing heterocycles has always been an important goal for organic chemists. Because of the varying substituents present in these heterocycles, the synthesis of oxygen-containing heterocycles, especially stereoselective synthesis, has also been a challenge for organic chemists. Over the past century, organic chemists have invested much effort in the development of methodologies to construct oxygen-containing heterocycles. The goal of developing these methodologies is obviously to prepare these compounds in a milder, higher yielding, asymmetric or 'greener' way.

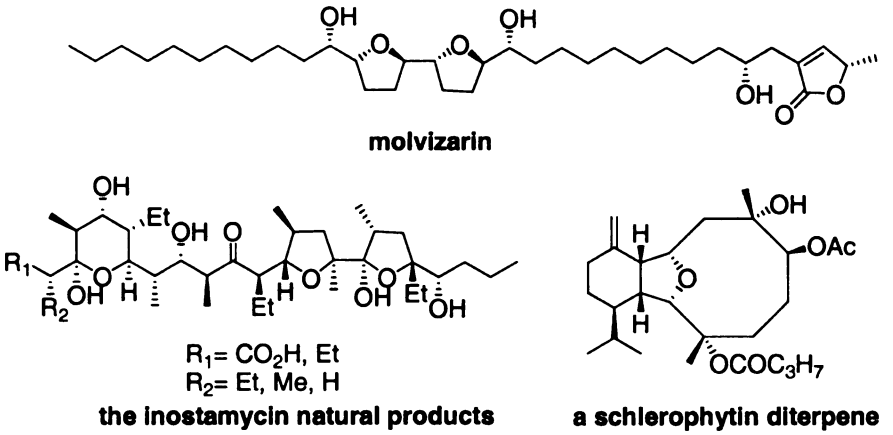


Figure I-1. Examples of natural products containing a THF ring

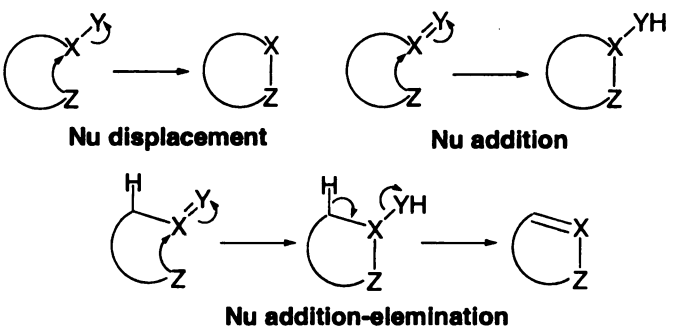
1.2. Strategies to Construct Oxygen-Containing Heterocycles

1.2.1. Intramolecular C-O Bond Formation

Construction of an oxygen-containing ring can be approached in two major ways. The ring can be formed by final construction of either a C-C or a C-O bond. The ring-forming reaction can be divided into two broad groups. Reactions in which a 'single' ring bond is formed in the ring-closure process are stepwise reactions termed cyclization

reactions, whereas those in which two ring bonds are formed with no elimination of small molecules are concerted reactions called cycloaddition reactions.[2] Cycloaddition reactions, especially 1,3-dipolar cycloadditions[3] and hetero-Diels-Alder reactions[4] provide useful synthetic routes to five- and six-membered oxygen-containing heterocycles. However, the work described herein falls into the former class of cyclization reactions.

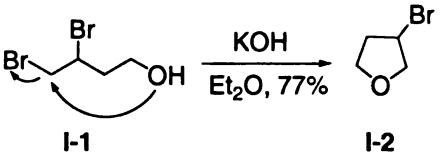
Cyclization reactions involve many intramolecular versions of common σ- or π-bond-forming processes. By far the most common are those in which a nucleophilic atom interacts with an electrophile. The predominant reaction types are nucleophilic displacement at a saturated carbon atom, nucleophilic addition to unsaturated carbon, and nucleophilic addition-elimination (**Scheme I-1**).



Scheme I-1. General scheme of nucleophile-electrophile cyclization

A cyclization process usually involves prior transformation to set the functionality and stereochemistry in an acyclic intermediate. The subsequent cyclization closes up the intermediate to form the ring in an intramolecular fashion. In the 'traditional' method of making an oxygen-containing heterocycle, the carbon skeleton is usually established in pre-cyclization steps, followed by the final C-O bond formation by intramolecular nucleophilic attack of the hydroxyl group on a carbon electrophile. Common carbon

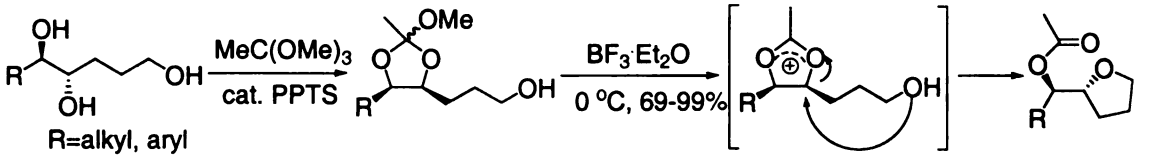
electrophiles that have been used include alkyl halides, epoxides and aldehydes, *etc.* The well-known Williamson ether synthesis was one of the earliest methods used to form cyclic ethers in this fashion (**Scheme I-2**).[5]



I-1 I-2

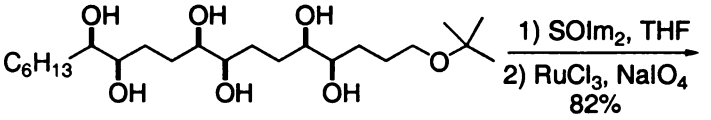
Scheme I-2. Intramolecular Williamson ether synthesis

Even today, intramolecular nucleophilic substitution and addition are popular tools to cyclize oxygen-containing rings. Organic chemists are continually searching for new and better carbon electrophiles that can be installed in an acyclic intermediate. For example, Borhan *et. al.*[6] have converted a series of 1,2,n-trisubstituted triols (**I-3**) into a substituted THF (**I-5**) by using cyclic orthoesters (**I-4**) as *in situ* electrophiles (**Scheme I-3**). Rychnovsky *et. al.*[7] have reported cascade cyclizations of cyclic sulfates (**I-7**) to generate polysubstituted THFs (**Scheme I-4**).

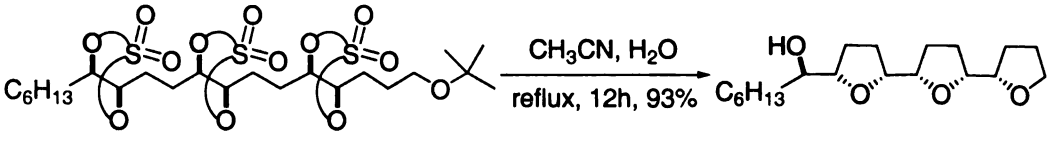


I-3 I-4 I-5

Scheme I-3. Borhan's synthesis of substituted THFs using cyclic orthoesters



I-6

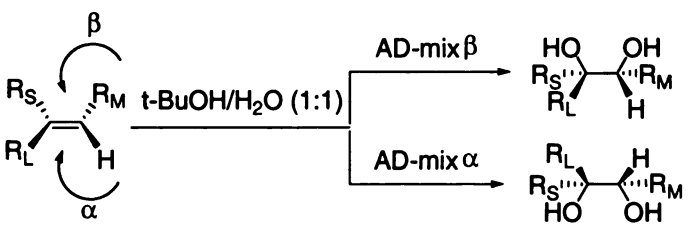


I-7 I-8

Scheme I-4. Rychnovsky's cascade cyclization of cyclic sulfates

In both Borhan's and Rychnovsky's work, the stereochemistry of the final products is translated from the starting vicinal diols. This chirality is initially set using Sharpless asymmetric dihydroxylation.

The Sharpless aymmetric dihydroxylation (SAD), developed by Sharpless *et. al.*[8] in early 1990s, converts an olefin to a vicinal diol with great stereoselectivity induced by the chelation of the osmium catalyst with an enantiomerically pure chiral ligand. All of the necessary ingredients in the SAD (catalyst system, oxidant, and ligand) are solids and preformulated and commercialized as two "cake mixes", one for each enantiomer. "AD-mix α" contains $K_2OsO_4 \cdot H_2O$ and $K_3Fe(CN)_6$ as the cooxidants, $(DHQ)_2PHAL$ (dihydroquinine phthalazine) as the chiral ligand and K_2CO_3 as a base additive while "AD-mix β" uses $(DHQD)_2PHAL$ (dihydroquinidine phthalazine) instead of $(DHQ)_2PHAL$. Depending on the substitution pattern of the double bond and the types of cake mixes used, one can easily predict, for a simple olefin, which enantiomer diol will be obtained using the mnemonic depicted in **Scheme I-5**.



Scheme I-5. Sharpless asymmetric dihydroxylation mnemonic for predicting absolute stereochemistry

Although there are a variety of well-established "reagent-control" methodologies, including the Sharpless asymmetric epoxidation[9] and the Jacobsen-Katsuki[10] and Shi epoxidations,[11] the structural requirements of the parent olefin can limit synthetic strategy. Compared to asymmetric epoxidations, the well-defined Sharpless asymmetric

dihydroxylation is less limited in substrate scope. Since its inception, substantial progress has been attained in the development of ligands for the SAD that generate high levels of enantioselectivity from unfunctionalized olefins of various substitution patterns.[8a] This flexibility has made the SAD a popular a tool for organic chemists to set the chirality of a vicinal diol from an easily obtained olefin and transfer this chirality into the synthesis of oxygen-containing heterocycles.

1.2.2. Intramolecular C-C bond Formation: Ring-Closing Metathesis (RCM)

Intramolecular C-C bond formation has not been used as a traditional method in the synthesis of heterocycles before mid-1990s because of the harsh conditions and intolerance of many functional groups to the radical[12] and carbene reactions[13] used to form the C-C bonds. The low efficiency and selectivity in forming a non-polar bond also presents difficulties to synthetic chemists. However, the development of ring-closing metathesis has radically changed the way chemists view C-C bond formation as an method for the syntheses of heterocycles.

Ring-closing metathesis, catalyzed by transition metal carbenes, converts acyclic dienes to cycloolefins via the loss of ethylene or its equivalent. The olefin metathesis reaction has been known since the 1960s, but it was not until the early 1990s that this transformation became an important tool in synthetic organic chemistry. In 1992, Grubbs and Fu published two seminal papers describing the application of ring-closing metathesis to the synthesis of simple five-, six-, and seven-membered monocyclic systems containing oxygen and nitrogen atoms using a molybdenum catalyst first prepared by Schrock.[14] After this exciting report, many organic chemists became interested in using RCM to form the functionalized rings present in natural products and

other biologically active compounds, and a number of elegant applications of RCM in total synthesis have been reported, many of which will be discussed in this chapter.

There are two main types of catalysts in use for RCM today. The first group consists of ruthenium-complexes such as **A** and **B**, whereas the second group is comprised of molybdenum complexes such as **C** (**Figure 1-2**). The catalysts **A** and **B** are most commonly used for the RCM reactions, namely first and second generation Grubbs catalyst. The functional group tolerance of the ruthenium and the molybdenum catalysts can vary somewhat, but the Mo-based complexes suffer the disadvantage of being very air and moisture sensitive. The high selectivity and reactivity of **A**, **B** and **C** for the formation of carbon-carbon π-bonds minimizes protecting group manipulations while enabling the use of RCM as an excellent alternative to other ring-forming reactions for the efficient construction of complex cyclic targets having a variety of ring sizes.

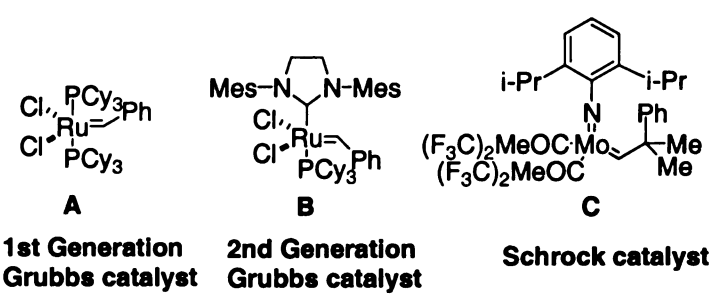
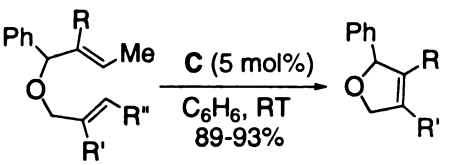


Figure 1-2. Grubbs and Schrock catalyst

The considerable potential of RCM as a useful reaction in synthesis of oxygen-containing heterocycles was clearly revealed in 1992 when Grubbs and co-workers reported that allylic ethers having a variety of substitution patterns (**I-9**) could be cyclized in the presence of Schrock's molybdenum catalyst **C** to give dihydrofurans (**I-10**) and dihydropyrans in excellent yields (**Schemes I-6**).[14] It was noteworthy that even tetra-

substituted double bonds could be formed in high yields, although it was necessary to run the reaction for longer periods.



R, R', R"= H or CH_3

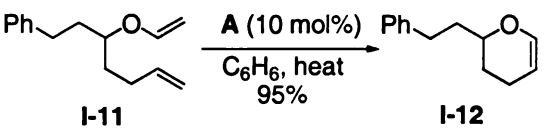
I-9 **I-10**

Scheme I-6. First synthesis of oxygen-containing heterocycles using RCM

The Schrock catalyst **C** is highly active, but its general suitability for RCM reactions is somewhat limited, since it is not compatible with a wide range of functionalities such as any protic functional groups like thiols, alcohols and carboxylic acids.[15] It is also very moisture and air sensitive, so special precautions must be employed. It was thus significant that Grubbs reported in 1993 that the ruthenium alkylidene **A** was an active metathesis catalyst that could be employed to form cyclic ethers in excellent yields.[14b] Although **A** could not be used to form tri- or tetrasubstituted double bonds, this new catalyst tolerated a wide range of functional groups, and it could be used in reagent grade solvents without an inert atmosphere. These seminal reports were the spark that ignited a wide range of studies that expanded the scope of RCM reactions in organic synthesis. There have subsequently been many reports of applications of RCM using **A** and the more reactive catalyst **B** to the syntheses of a diverse array of mono- and poly- heterocyclic compounds, some in enantiomerically pure form.[16]

Schrock's catalyst **C** was used to prepare the first 3,4-dihydropyrans by RCM.[17] Early reports suggested that enol ethers were poor substrates for Grubbs' catalyst **A**, because the carbene resulting from the initial metathesis of the vinyl ether and **A** seemed

to be inert to further reaction.[18] However, Sturino was able to use **A** to catalyze the cyclizations of a variety of vinyl ethers, including the highly efficient conversion of **I-11** to **I-12** (**Scheme I-7**).[19]



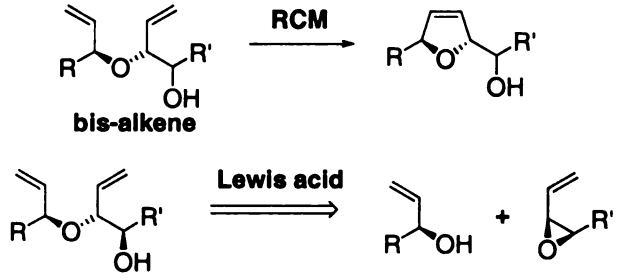
I-11 **I-12**

Scheme I-7. Cyclization of vinyl ethers using Grubbs catalyst **A**

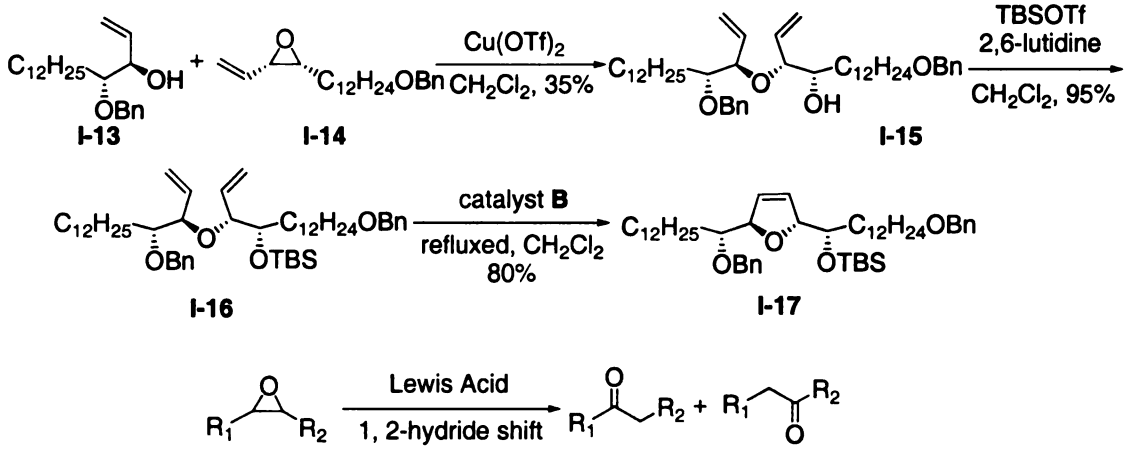
The great efficiency of RCM in carbon-carbon bond formation and compatibility with various functional groups have stimulated strategic reconsiderations of stereoselective synthetic approaches to oxgen-containing heterocycles. The focus has changed to the synthesis of the acyclic intermediate for RCM, an intermediate with two olefin moieties tethered by an oxygen atom, a bis-alkene (**Scheme I-8**). Efforts have been made to synthesize this type of intermediate and most of them involve an intermolecular nucleophilic attack on a carbon electrophile. The following discussion will survey strategies applied in the synthesis of natural products containing THF rings using RCM reactions. The key in these strategies is how to generate the bis-alkene intermediate in an efficient and stereocontrolled manner.

One of the most popular methods to make a bis-alkene is the reaction of a complex alcohol (2° or 3°) with a vinyl epoxide under acidic conditions (**Scheme I-8**). However, the relatively poor nucleophilicity of secondary or tertiary alcohols and the high basicity of the corresponding alkali-metal alkoxides are often problematic. The importance of finding a proper Lewis acid to activate the epoxide cannot be overstated. Extensive work has been performed in optimizing conditions, especially screening Lewis acids, yet with limited success.[20] In Mioskowski's total synthesis of solamin[21], the

central THF core was obtained by means of a RCM reaction. The RCM substrate **I-15** was prepared from a vinyl-substituted epoxide **1-14** by reaction with a 2° allylic alcohol **1-13**, both synthesized from propargylic alcohol using Sharpless asymmetric epoxidation. Despite efforts to modulate the basicity of the alkoxide by forming a copper alkoxide, the yield was low. The major by-product arises from a 1,2-hydride shift that converts the epoxide into a ketone under the Lewis acidic conditions (**Scheme I-9**).



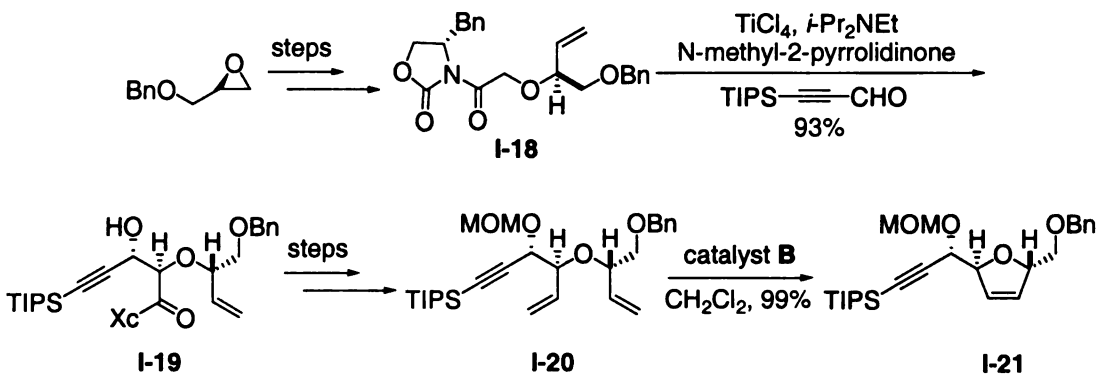
Scheme I-8. RCM approach to generate substituted THF rings



Scheme I-9. RCM application in Mioskowski's total synthesis of solamin

Asymmetric aldol reactions can also be used to generate bis-alkenes with good stereocontrol. In the synthesis of (+)-gigantecin, Crimmins *et. al.*[22] exploited a modified asymmetric aldol protocol using chlorotitanium enolates of oxazolidinone glycolates **I-18** to make the bis-alkene intermediate **1-20** (**Scheme I-10**). The limitation of this methodology is that asymmetric aldol reactions may only be applied to certain substrates

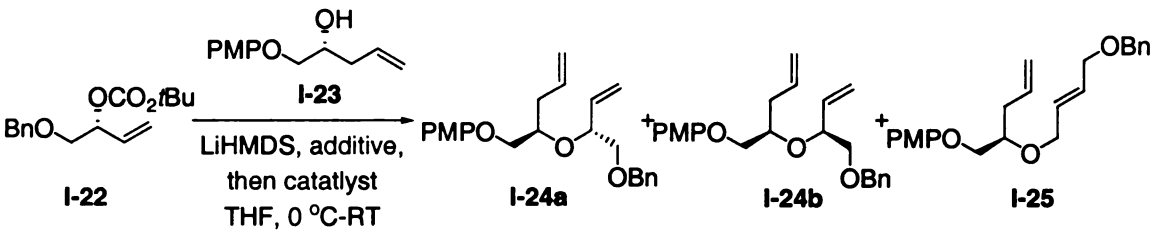
as the harsh conditions may be intolerant to many functional groups and stereoselectivity achieved with the help of a chiral auxiliary may not always be good depending on whether it is a matched or mismatched case.



Scheme I-10. Construction of THF ring using asymmetric aldol and RCM reaction in Crimmins's total synthesis of (+)-gigantecin

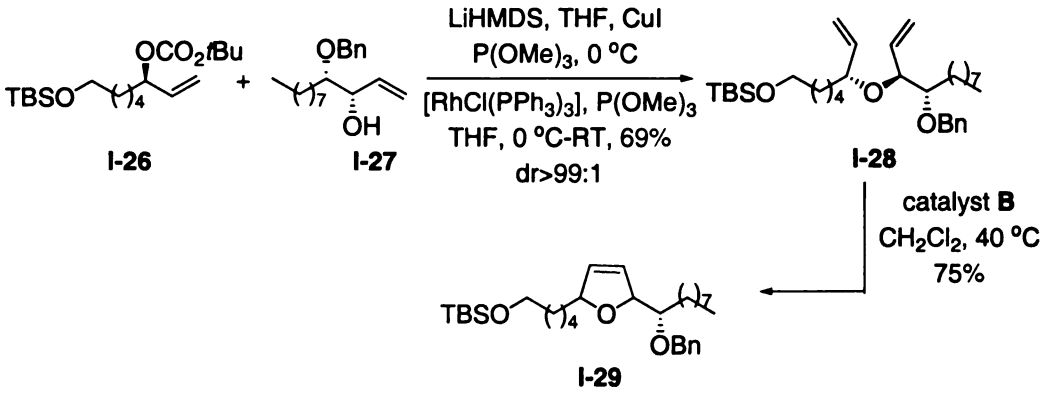
The transition-metal-catalyzed intermolecular allylic etherification is a fundamentally important cross-coupling strategy for the construction of enantiomerically enriched allylic ethers.[23] The problem in the application of this strategy is the poor nucleophicility of a complex alcohol and activation of the allylic carbon. In response to these underlying problems, Evans *et. al.* has done inspiring work by developing a regioselective and enantiospecific rhodium-catalyzed allylic etherification with copper(I) alkoxides as nucleophiles (**Scheme I-11**).[24] The transmetalation of an alkali-metal alkoxide served to diminish its basicity, thereby promoting the etherification of a soft metal - allyl electrophile.[25] The stereospecific etherification of the acyclic enantiomerically enriched allylic carbonate (**I-22**) with secondary alkenyl alcohols (**I-23**) followed by RCM affords the *cis*- and *trans*-disubstituted cyclic ethers. The method was successfully applied in the total synthesis of gaur acid. Treatment of the allylic carbonate **I-26** with the trimethylphosphite-modified Wilkinson catalyst and the copper(I) alkoxide

derived from the allylic alcohol **I-27**, afforded the diene **I-28** in 69% yield with excellent regioselectivity and enantiospecificity (**Scheme I-12**). The inherent advantage of this approach is the ability to vary both ring size and relative configuration as a direct function of the alkenyl alcohol nucleophile employed in the cross-coupling reaction. However, there are also limitations. The enantiomerically pure allylic carbonate is required for the reaction and it is prepared by an initial kinetic resolution of the allylic alcohol followed by acylation. The cost of the Rhodium catalyst should also be taken into consideration.



Catalyst $RhCl(PPh_3)_3/P(OMe)_3$ **Additive** $CuI/P(OMe)_3$ **24/25** 49:1 **d.r. 24a/24b** >99:1 **Yield** 72%

Scheme I-11. Rhodium-catalyzed allylic etherification with the copper(I) alkenyl alkoxide



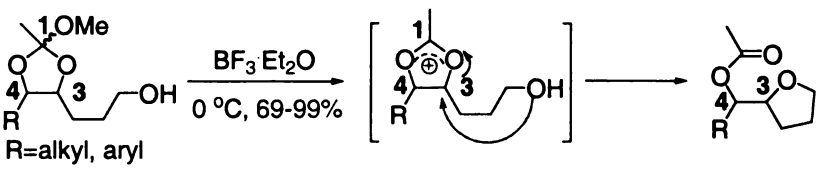
Scheme I-12. Construction of cyclic ethers using RCM in Evan's total synthesis of gaur acid

From the strategies discussed above, we see success as well as limitations in applying RCM to construct oxygen-containing heterocycles. So are there other ways to

generate the bis-alkene intermediate, milder, higher yielding and stereoselective ways? My research was initiated to search answers to this question.

1.3. Proposed Strategy to Construct Oxygen-Containing Heterocycles

Orthoesters represent a class of masked acid derivatives that greatly modify the reactivity pattern of the parent carboxylates and permit entry into a much broader range of nucleophilic and electrophilic transformations.[26] As electrophiles, orthoesters are more reactive than epoxides, allylic esters, *etc.* They can easily transform into oxocarbenium cations under acidic conditions without side reactions. Our group has been interested in developing new methodologies using orthoester chemistry. We have reported a general and practical cyclization to construct THF and THP structures from 1,2,*n*-triols based on the Lewis acid-mediated cyclization of cyclic orthoesters.[6] As depicted in **Scheme I-13,** ionization of the cyclic orthoester **I-30** with a Lewis acid leads to a reactive acetoxonium species **I-31**, which displacement at C-3 with the pendant hydroxyl yields the cyclized ether **I-32.**

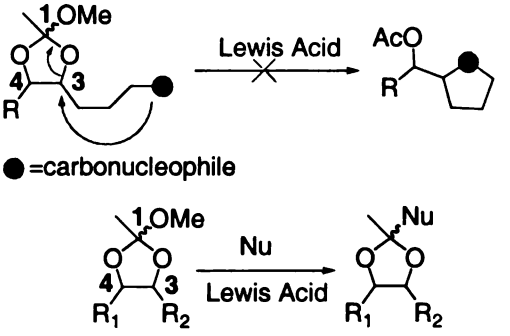


I-30 **I-31** **I-32**

Scheme I-13. Our group's previous research on orthoesters

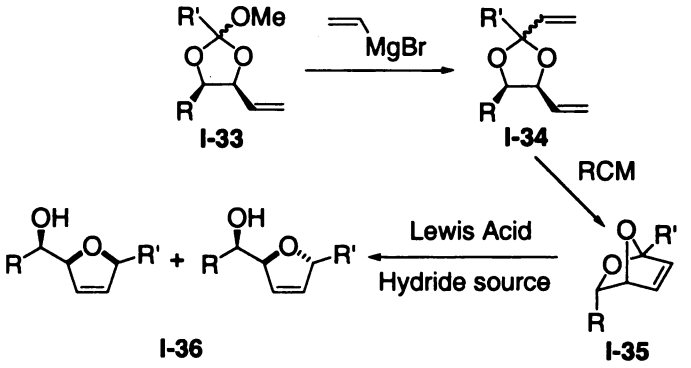
As a continuation of this work, intramolecular nucleophilic attack by carbon nucleophiles was tried on similar substrate to form carbocycles yet without any success. However, we found that, similar to nucleophilic attack on cyclic acetals,[27] nucleophiles such as Grignards and allyl trimethylsilane could introduce vinyl and allyl functional

groups intermolecularly to C-1, but the conditions were not optimized (**Scheme I-14**). Stereoselectivity of the nucleophilic attack at C-1 are expected with different stereochemistry established at C-3 and C-4, which will be further discussed in **Chapter 2.2.1**.



Scheme I-14. Origin of proposed strategy

If one of the olefin moieties is already established in the ortho ester substrate **I-33**, introduction of another alkene by intermolecular nucleophilic displacement would generate the bis-alkene **I-34**. Success of the ring closing metathesis and control of the correct C-O bond cleavage in reductive ring opening of **I-35**[28] would lead to the desired THF core **I-36** (**Scheme I-15**).

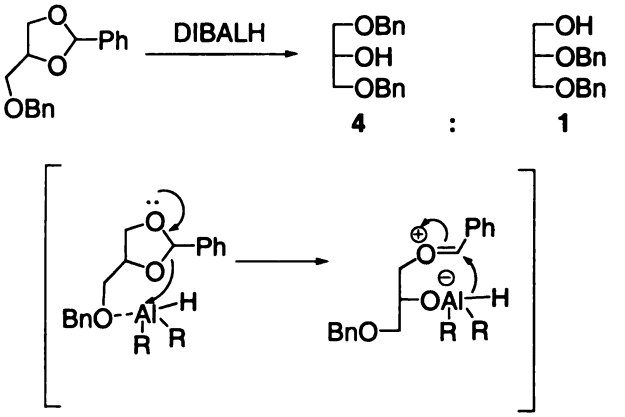


Scheme I-15. Proposed strategy to make substituted THF

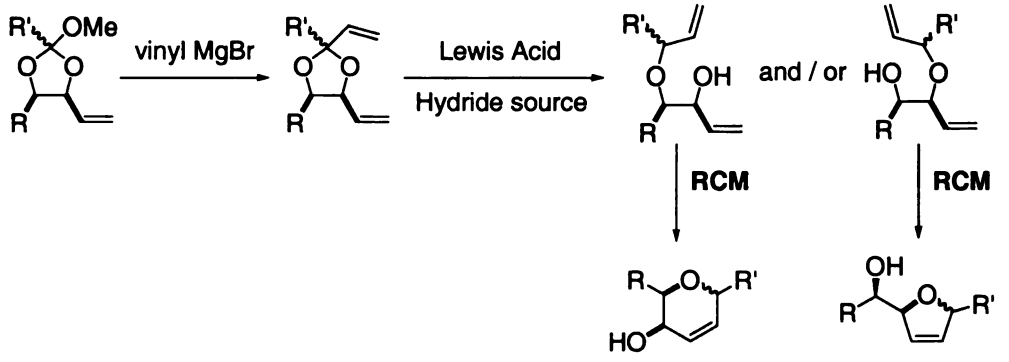
The major advantage of this strategy is that the stereochemistry in the bis-alkene could be accessed via Sharpless asymmetric dihydroxylation and translated to the final

product via substrate control. Also, the cleavage of the temporary oxy-bridge in the last step would be facile and selective due to the strain release and judicious choice of reducing agents.[28c]

Alternatively, if RCM proves to be unfeasible for generating the bicyclic system, we may have to control the reductive ring opening before RCM. Regioselective reduction of cyclic ketals can be achieved using proper Lewis acid and hydride source.[28a,b] In the example shown in **Scheme I-16**, the regioselective cleavage of C-O bond is presumed to occur via intramolecular delivery of hydride. This approach could also offer the possibility of preparing disubstituted tetrahydropyrans with stereocontrol **(Scheme I-17)**.

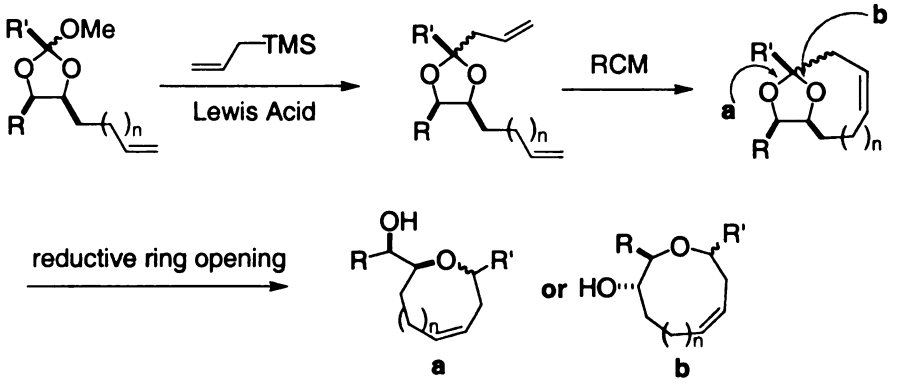


Scheme I-16. Regioselective reduction of cyclic acetals



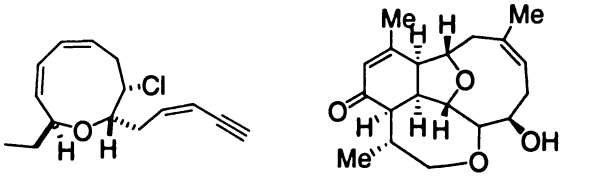
Scheme I-17. Alternative strategy for generation of THF and THP rings

Larger oxygen-containing heterocycles could also be made using this strategy if longer side chains are installed in the substrate. Depending on which carbon-oxygen bond is cleaved (a or b), different products could be obtained (**Scheme I-18**).



Scheme I-18. Extension of our strategy to make larger oxygen-containing heterocycles

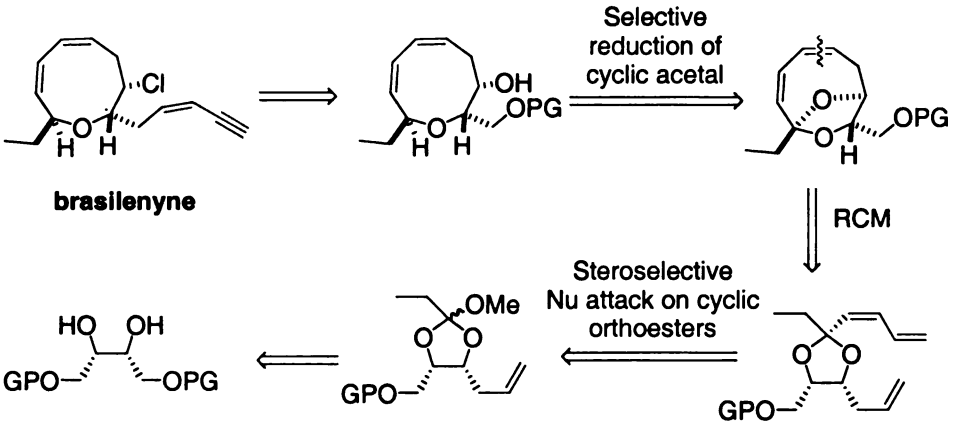
These structures are not new in the nature either. Listed in **Figure I-3** are a couple of examples of natural products with substructures containing larger oxygen-containing heterocycles.[29]



brasilenyne **pachyclavulariaenone D**

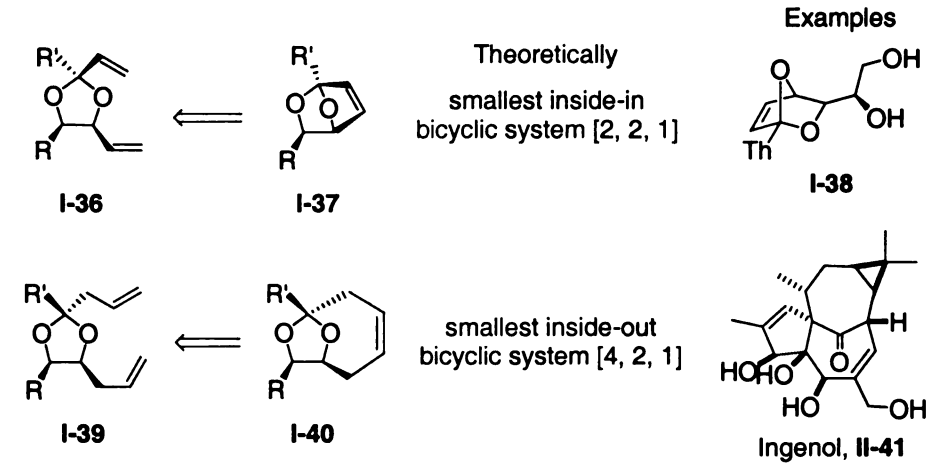
Figure I-3. Examples of natural products with larger oxygen-containing heterocycles

A brief retrosynthetic analysis of brasilenyne from a vicinal diol using proposed strategy is shown in **Scheme I-19**.



Scheme I-19. Retrosythetic analysis of brasilenyne using proposed strategy

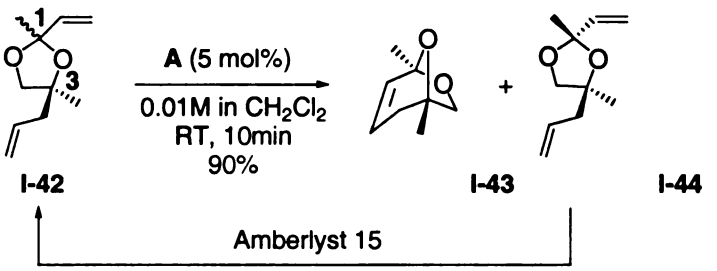
Presumably, different epimers at C-1 (**I-36, I-39**) obtained would lead to different bicyclic ketal systems (**I-37, I-40**). Theoretically, the smallest inside-in bicyclic system that can be formed is [2,2,1] (**I-37**) while the smallest inside-out system would be [4,2,1] (**I-40**). Examples of both systems (**I-38, I-41**) can be found in the literature (**Scheme I-20**).[30] However, no study has been reported on inside-out byciclic ketals. It is obvious from sterics that the inside-out system is more strained, which would be potentially difficult for the RCM yet an advantage for the reductive ring opening.



Scheme I-20. Inside-in and inside-out bicyclic ketal systems

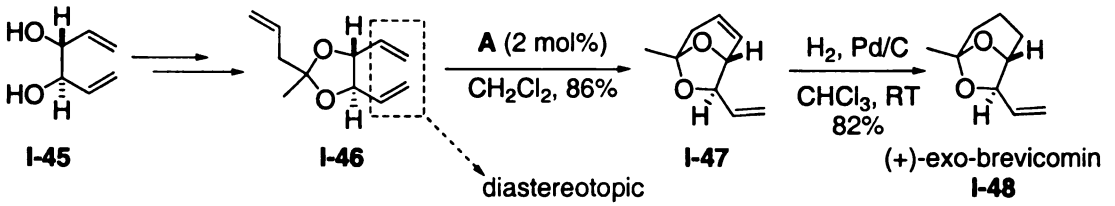
Applications of RCM to the syntheses of bridged bicyclic oxygen heterocycles are relatively rare, despite the fact that such structures are commonly found in natural

products[31] and are useful templates in organic synthesis.[32] Grubbs first reported a synthesis of the bicyclic ether (-)-frontalin, employing an approach that featured a RCM reaction.[33] The metathesis substrate was prepared as a mixture of C-1 epimers **I-42**, in which the absolute stereochemistry at C-3 was set by an asymmetric Mukaiyama allylation. When this mixture was treated with first generation Grubbs catalyst, the cyclized product **I-43** was obtained. The uncyclized '*trans*' epimer **I-44** was equilibrated under acidic conditions to provide a mixture of both epimers that was resubjected to the RCM conditions (**Scheme I-21**).



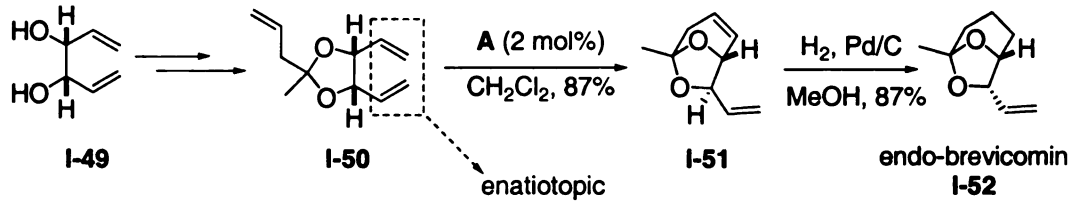
Scheme I-21. Grubbs' synthesis of (-)-frontalin using RCM

Burke *et. al.* have also developed a concise strategy for the stereoselective synthesis of bridged bicyclic ethers that has been applied to the preparation of a number of targets.[34] For example, an enantiomerically pure diol **I-45** was transformed in two steps into the ketal **I-46** wherein the two vinyl groups are diastereotopic (**Scheme I-22**).[34a] The RCM reaction of **I-46** in the presence of first generation Grubbs catalyst furnished the bridged bicyclic ketal **I-47** with complete diastereoselectivity. Catalytic hydrogenation of **I-47** then gave the natural product (+)-*exo*-brevicomin **II-48**.



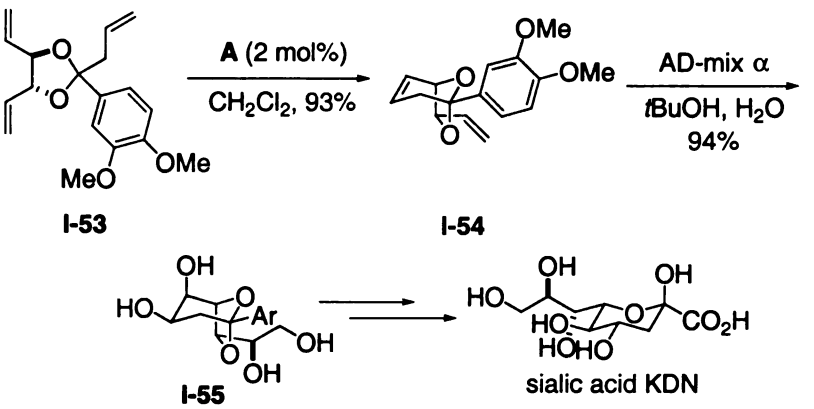
Scheme I-22. Burke's methodology to synthesize bridged bicyclic ethers using RCM

When the corresponding achiral (*meso*-) diol **I-49** was used as the starting material, the derived ketal **I-50**, in which the two vinyl groups are enantiotopic, underwent RCM to give the bicyclic ketal **I-51**, reduction of which then provided *endo*-brevicomin **I-52** (**Scheme I-23**).



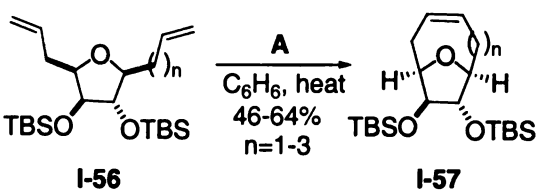
Scheme I-23. Burke's methodology to synthesize bridged bicyclic ethers using RCM

Hydrogenation of the carbon-carbon double bond formed by the RCM reaction of a diene might be regarded as an undesirable waste of functionality. It is thus noteworthy that Burke has exemplified a more expedient use of such a double bond in developing a synthesis of sialic acids, a family of biologically important compounds related to neuraminic acid.[34b] Bis-hydroxylation of the double bond in **I-54** under Sharpless conditions after RCM gave the tetraol **I-55** which was converted into the acetate and then transformed into the sialic acid KDN (**Scheme I-24**).[34c]



Scheme I-24. Burke's synthesis of sialic acid KDN

A RCM approach toward medium-sized oxabicyclic systems in enantiomerically pure form is depicted in **Scheme I-25**. The dienes (**I-56**) were easily synthesized in a stereospecific fashion from inexpensive, commercially available carbohydrates using straightforward procedures. Upon treatment with first generation Grubbs catalyst in refluxing benzene, they underwent metathesis to afford the bicyclic products (**I-57**) in good yields.[35]

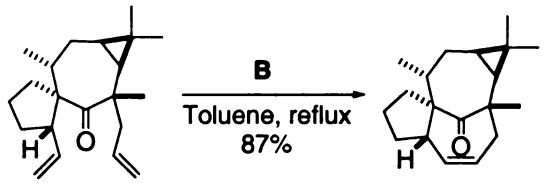


Scheme I-25. Using RCM to make medium-sized oxabicyclic systems

Both Grubbs and Burke prepared the cyclic ketal intermediate in a traditional way: ketalization of a vicinal diol with a ketone, which will lead to a mixture of C-1 epimers. In Grubbs' synthesis of (-)-frontalin, he re-equilibrated unreacted epimer back to the mixture of both epimers in order to make full use of the starting ketal while Burke took advantage of the C_2 symmetry of the starting diol, which made RCM with either of the diastereotopic vinyl groups lead to the same product. The proposed strategy herein

would yield one major C-1 epimer of the cyclic ketal, which would offer more synthetic flexibility, if successful.

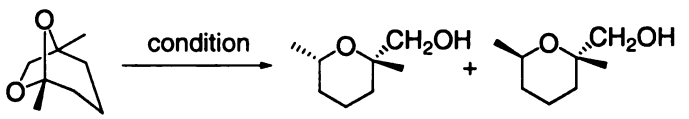
The work of Grubbs and Burke does not describe the construction of inside-out bicyclic systems. In fact, formation of the strained inside-out bicyclic system via RCM has also been proved possible in the successful synthesis of Ingenol (**Scheme I-26**).[36] Second generation Grubbs catalyst was used to transform the *trans*-diene substrate **I-58** into an inside-out [4, 4,1] bicyclic system **I-59** in fairly good yield.



I-58 **I-59**

Scheme I-26. Synthesis of Ingenol via RCM

A detailed discussion on the reductive ring opening of bicyclic acetals is not presented here since my research work has not proceeded that far. However, considering the strain present in the bicyclic system, the reduction process would be expected to be facile and selective. The following example illustrates this type of reduction can be performed in a regio- and stereoselective fashion by internal or external delivering of the hydride (**Scheme I-27**).[37]



condition	Yield	*cis*	*trans*
DIBALH	82	3	97
Et_3SiH, $TiCl_4$	82	99	1

Scheme I-27. Reductive ring opening of bicyclic ketals

Chapter 2

Results and Discussion

2.1. Study of RCM on Model Substrates

My study started by investigating the feasibility to construct larger bicyclic ketals and the possibility to make inside-out bicyclic systems using RCM reactions. By repeating the work of Grubbs' and Burke's, the reaction of a vicinal diol with a ketone was used to generate the ketals as a mixture of C-1 epimers and then each of the epimers was subjected to RCM conditions. The basic structure of model substrates is shown in **Figure II-1**. The side chain of the substrate was installed with enough carbons (for example, m=1, n=1) so that the inside-out system could possibly form.

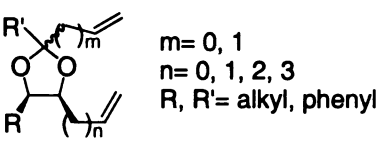
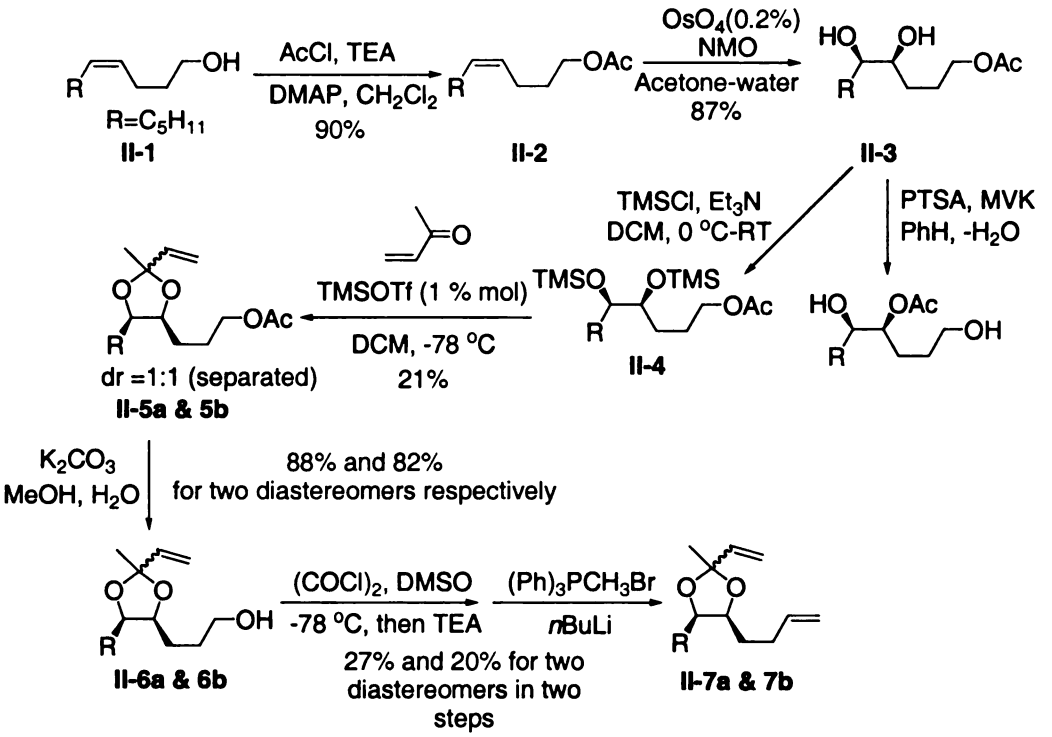


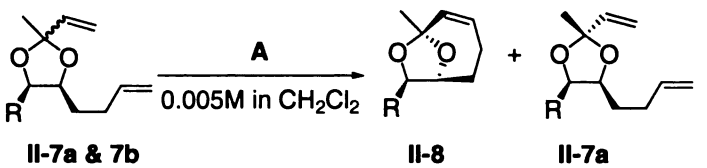
Figure II-1. Model substrates

Commercially available *cis*-4-decen-1-ol (**II-1**) was chosen as the starting substrate, which was protected as acetate (**II-2**) or silyl ether. The Upjohn procedure[38] gave the *cis* diol **II-3** in good yield. In a first attempt, vinyl ketal was made by refluxing diol with methylvinylketone and catalytic TsOH in benzene under Dean-Stark conditions. However, the product was mostly transesterified diol-ester instead of the ketal. The problem was solved utilizing TMSOTf as catalyst for ketalization.[39] Two diastereomers **II-5a** and **II-5b** (d.r. 1:1) were obtained and separated. The following deprotection, oxidation, and Wittig olefination led to the model substrate **II-7a** and **II-7b** (**Scheme II-1**).



Scheme II-1. Synthesis of model substrates using traditional ketalization

Similar to Grubbs' result,[33] RCM worked well for one of the C-1 epimers **II-7b** to form the [4,2,1] bicyclic system using first generation Grubbs catalyst **A**. The cyclized product **II-8** was obtained in about 30% yield yet could not be purified. However, evidence from NMR and GC-MS suggested the existence of **II-8**. There was no reaction for the corresponding *trans* isomer **II-7a** even when second generation Grubbs catalyst **B** was used and refluxed overnight. Concentration of the substrate can be crucial for success of the reaction. 0.01M solution of **II-7a** in dichloromethane yield only polymerized products upon cross metathesis reactions (**Scheme II-2**).



Scheme II-2. Early study of RCM on model substrates

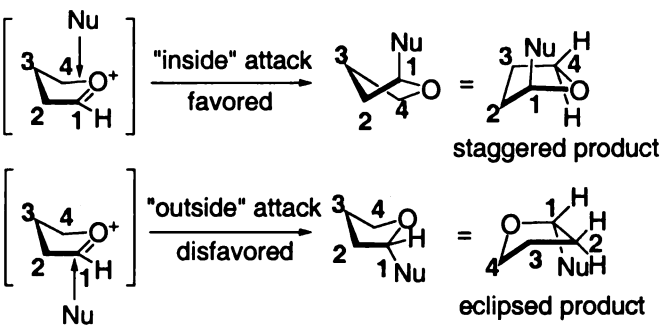
The results confirmed the feasibility of the proposed strategy to construct larger bicyclic acetals though it failed to yield inside-out systems. The low yields and poor stereoselctivity using traditional methods to make cyclic ketals could be overcome by applying stereoselective nucleophilic attack on cyclic orthoesters. Research on generation of inside-out bicyclic systems would be continued by screening various conditions.

2.2. Stereoselective Nucleophilic Attack at C-1

2.2.1. Optimization of Conditions

As discussed in **Chapter 1**, the stereoselective nucleophilic attack at the orthoester carbon C-1 is unique compared to ketalization to form a mixture of diastereomeric acetals. Therefore, it is essential to study and discuss the stereoselective nucleophilic attack in advance.

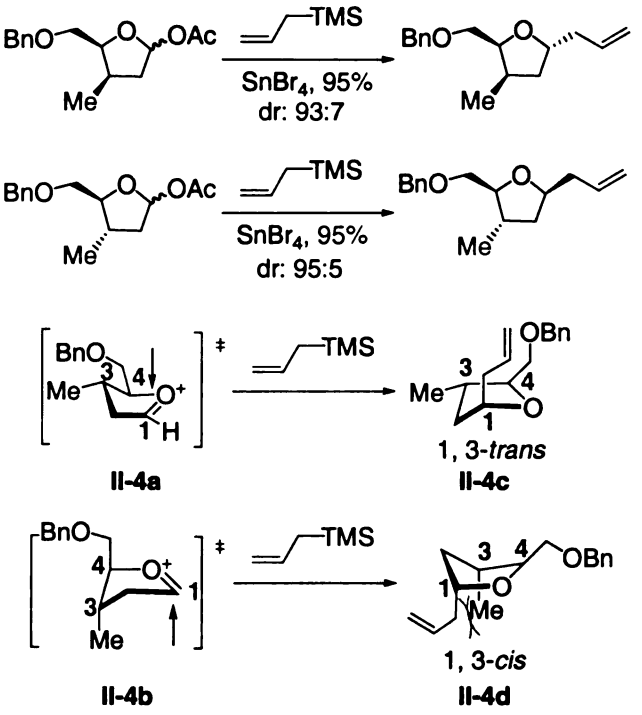
Woerpel *et. al.*[40] have extensively studied on the stereoselective addition of carbon nucleophiles to five-membered oxo-carbenium ions, which is structurally similar to the intermediate derived from our orthoester substrates. The diastereoselectivity was suggested to arise from the nucleophile attacking five-membered ring oxocarbenium ion in the envelope conformation, attacking preferentially from the inside face of the envelope. Attack from the outside face is disfavored, because of eclipsing interactions between the substituents at C-1 and C-2 in the product (**Scheme II-3**).



Scheme II-3. Woerpel's model of stereoselective nucleophilic attack of five-membered oxo-carbenium cations

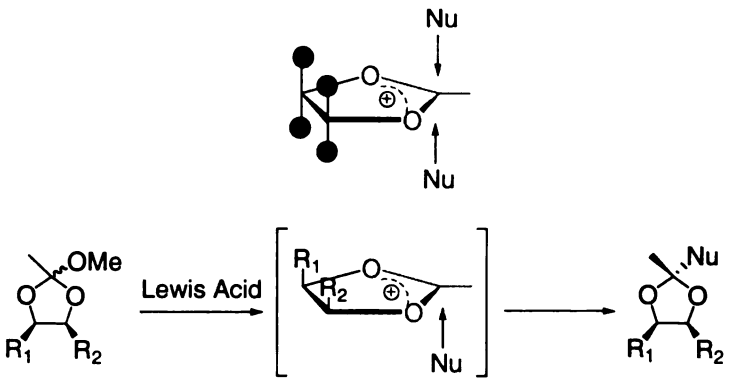
In addition, his study indicated that the impetus to minimize eclipsing interactions is not the only factor that governs selectivity, but that the overall three-dimensional structure of the ring must be favorable as well. In other words, substituents on the ring also play an important role on the stereoselectivity.

The "inside-attack" model provides an explanation for the stereoselectivity of nucleophilic substitution of five-membered cyclic acetals (**Scheme II-4**).[40a] For example, the cation derived from 3-methyl-substituted acetal could exist as two conformers **II-4a** and **II-4b**. Attack from "inside" the cation **II-4a** would lead to the 1,3-*trans* product **II-4c** as first-formed conformer. Alternatively, "inside attack" on the diaxial conformer **II-4b** would be disfavored because of developing, destabilizing 1,3-diaxial interactions between the nucleophile and the alkyl group in the product **II-4d**. Therefore, the 1,3-*trans* product **II-4c** would be expected to predominate.



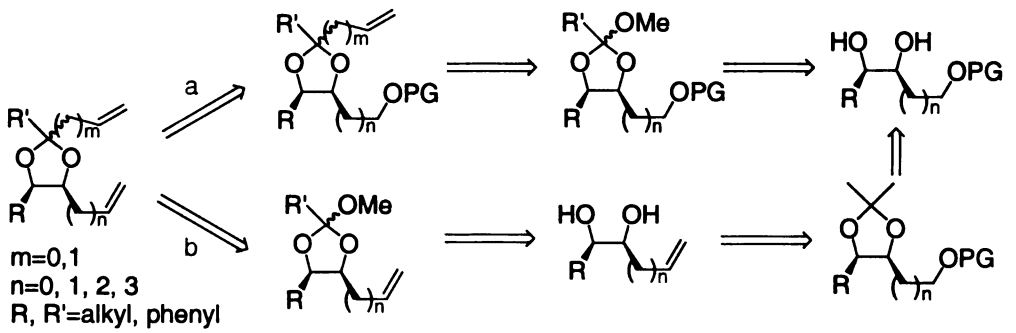
Scheme II-4. Stereoselectivity of nucleophilic attack of 3-substituted five-membered cyclic acetals

Analogy could be made from Woerpel's model to our substrate. However, because of the involvement of two oxygen atoms in the formation of the oxocarbenium cation, the hybridization of both oxygens and C-1 become sp^2. Therefore, the five-membered-ring oxocarbenium cation has become planar rather than envelope-like and the stereoselectivity of nucelophilic attack would totally depend on the relative stereochemistry of substituents on C-3 and C-4 (R_1 and R_2, respectively). If R_1 and R_2 are *syn* to each other, *anti*-attack would be expected in order to avoid steric hindrance. If R_1 and R_2 are *anti* to each other, the situation would become more complicated and may depend heavily on the identity of the substituents at C-3 and C-4. That is why *cis*-1,2-diols are chosen as initial target substrates, which can be easily obtained by using the Upjohn method [38] on a Z-alkene (**Scheme II-5**).

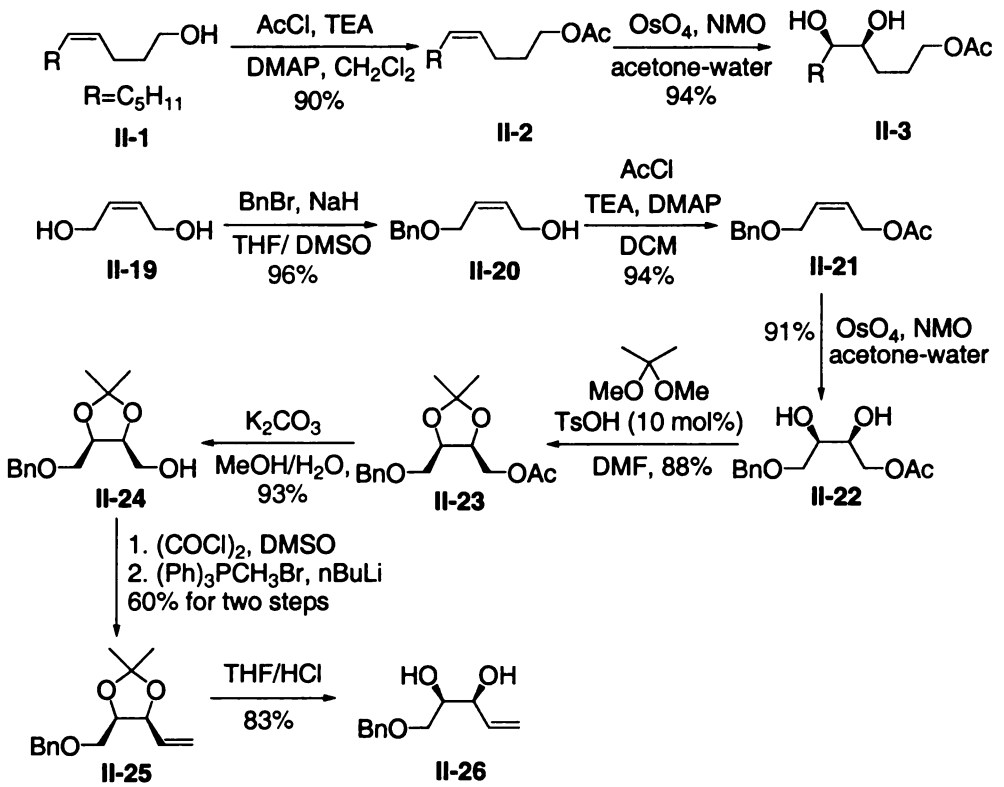


Scheme II-5. Model for stereoselective nucleophilic attack of cyclic orthoesters

There are two possible routes to make the desired substrates using the orthoester chemistry, based on which double bond is formed first (**Scheme II-6**). Both approaches have been studied and typical transformations to make the diol precursors are listed in **Scheme II-7**.



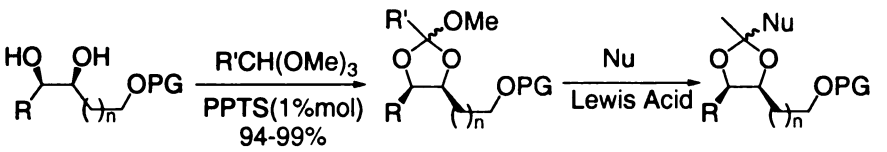
Scheme II-6. Two routes to approach the model substrate

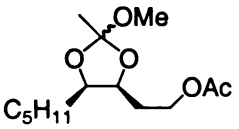
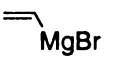
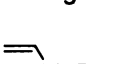
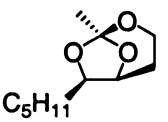
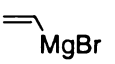
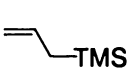
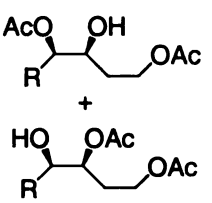
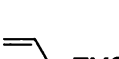
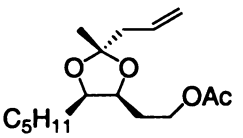


Scheme II-7. Typical procedures to make diol precursors of model substrates

Once the desired precursors were prepared, different nucleophiles, Lewis acids and reaction conditions were tried for the nucleophilic attack of the orthoesters. Some of the results are listed in **Table II-1**. As expected, nucleophiles attack opposite R_1 and R_2. All the products obtained were single diastereomers.

Table II-1. Optimization of conditions for stereoselective nucleophilic attack of cyclic orthoesters

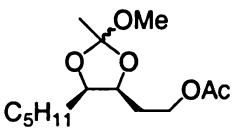
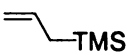
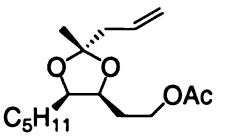
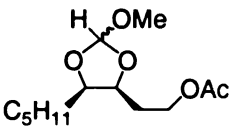
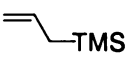
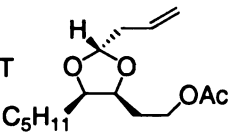
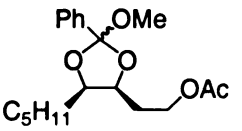
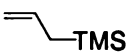
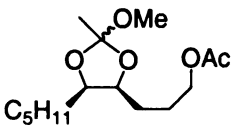
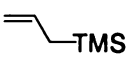
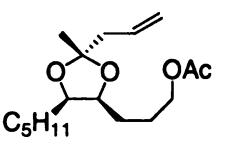
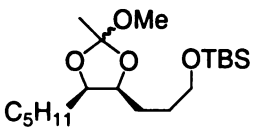
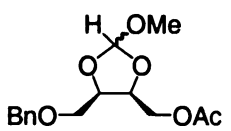
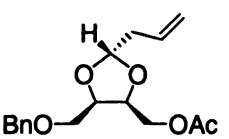


Substrate	Nu[a]	L.A.	Condition	Product	Yield[b]
		N/A	Et_2O, RT	mixture	N/A
		N/A	THF, RT		57%
		N/A	toluene, reflux	mixture	N/A
		$BF_3{\cdot}Et_2O$ (10 mol%)	THF, RT		quantitative
		$SnBr_4$ (1equiv)	CH_2Cl_2, -78 °C- RT		30%[c]

a. 3 equiv vinylmagnesiumbromide and 2 equiv allyltrimethylsilane were used. b. All are isolated yields for single diastereomers unless specified. c. Yield of two steps (intermediate orthoester not isolated).

It was found that allylation works with stoichiometric $SnBr_4$ Lewis acid in dichloromethane. Catalytic conditions for allylation were optimized using 4 equivalents of allyltrimethylsilane and 25 mol% of $SnBr_4$. Different substrates derived from different diols and orthoesters were examined and most of them led to good yields under these condition (**Table II-2**). The relative stereochemistry for the product was confirmed by nOe experiments.

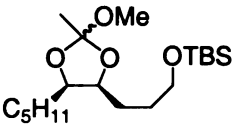
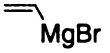
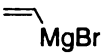
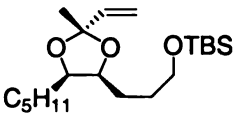
Table II-2. Allylation of different substrates under optimized conditions

Substrate	Nu	L.A.	Condition	Product	Yield
 **II-27**		$SnBr_4$ (25 mol%)	CH_2Cl_2, -78 °C - RT	 **II-33**	91%
 **II-28**		$SnBr_4$ (25 mol%)	CH_2Cl_2, -78 °C - RT	 **II-34**	91%
 **II-29**		$SnBr_4$ (25 mol%)	CH_2Cl_2, -78 °C - RT	mixture[d]	N/A
 **II-30**		$SnBr_4$ (25 mol%)	CH_2Cl_2, -78 °C - RT	 **II-35**	80%
 **II-31**		$SnBr_4$ (25 mol%)	CH_2Cl_2, -78 °C - RT	mixture[e]	N/A
 **II-32**		$SnBr_4$ (25 mol%)	CH_2Cl_2, -78°C - RT	 **II-36**	71%

d. The orthobenzoate is unstable and the major product isolated is methyl benzoate.
e. TBS group fell off.

Vinylization was also achieved when TBS was chosen as protecting group for the hydroxyl group and excessive vinylmagnesiumbromide was used in toluene and refluxed. A single diastereomer was obtained in moderate yield (**Table II-3**).

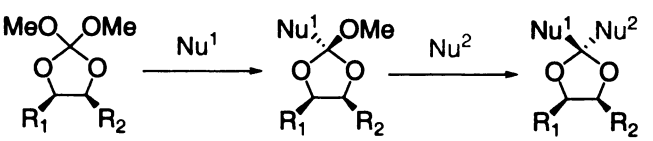
Table II-3. Conditions for vinylization

Substrate	Nu	L.A.	Condition	Product	Yield
		—	THF, RT	mixture	N/A
		—	toluene, reflux	 **II-37**	45%

2.2.2. Attempts to Make the Other C-1 Epimer

Since the product ketal derived from anti-attack on the intermediate orthoester can only lead to the strained inside-out system after RCM (**Scheme I-20**), methods to achieve the opposite diastereoselectivity are highly desired. Based on the orthoester chemistry and the oxocarbenium cation intermediate discussed above, orthocarbonates was tried to substitute for orthoesters to obtain the *cis* diastereomer.

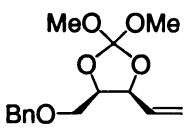
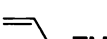
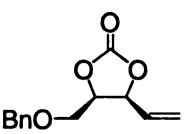
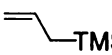
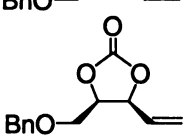
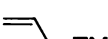
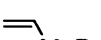
Assuming that the methoxy group in a cyclic orthocarbonate is similar, in terms of sterics, to the methyl group at C-1 in a cyclic orthoacetate, similar nucleophilic attack would be expected at C-1 of orthocarbonates. After introduction of first nucleophile (Nu^1) to C-1, the orthocarbonate would become an orthoester, which is then subjected to second nucleophilic attack (Nu^2) under similar conditions. Twice *anti*-attack would eventually direct Nu^1 to the position relative *syn* to R_1 and R_2 (**Scheme II-8**). Thus, the *cis* diastereomer would be obtained when Nu^1 contains alkene functionality.



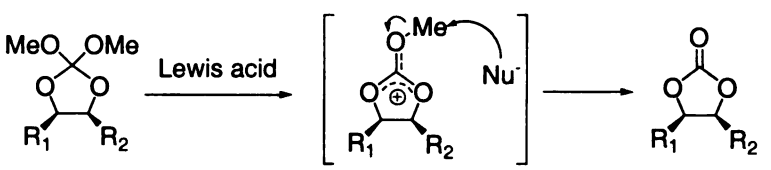
Scheme II-8. Proposed strategy to achieve opposite stereoselectivity

Different orthocarbonates, nucleophiles, Lewis acids and conditions were examined but none met with success. The major problem occurs when the first nucleophile is being introduced under acidic conditions. The orthocarbonate (**II-38**) readily transforms into the cyclic carbonate (**II-39**), which prevents the second nucleophilic attack (**Table II-4**).

Table II-4. Attempts to make *cis* diastereomers using orthocarbonates

Substrate	Nu	L.A.	Condition	Product	Yield
 **II-38**		$SnBr_4$ (25 mol%)	CH_2Cl_2, -78 °C - RT		60%
		TMSOTf (10 mol%)	CH_2Cl_2, -78 °C - RT	 **II-39**	52%
		$BF_3{\cdot}Et_2O$ (10 mol%)	CH_2Cl_2, -78 °C - RT	mixture	N/A
		N/A	toluene, reflux	mixture	N/A

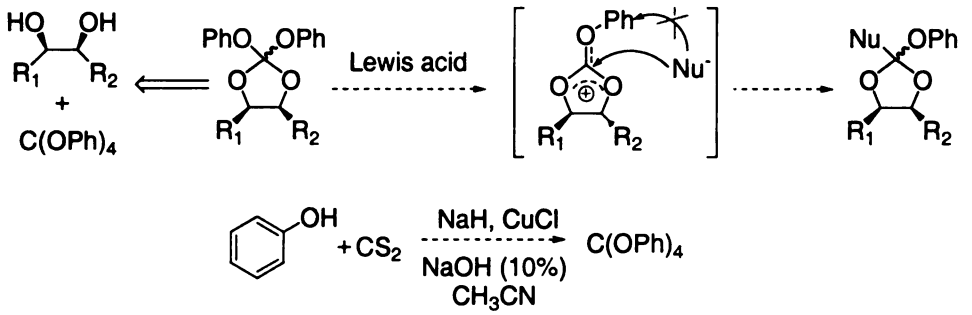
A possible reason for this transformation is that when the oxo-carbenium cation intermediate is formed, the nucleophile is more likely to attack the remaining methoxy carbon rather than C-1 (**Scheme II-9**).



Scheme II-9. Possible mechanism for formation of cyclic carbonates

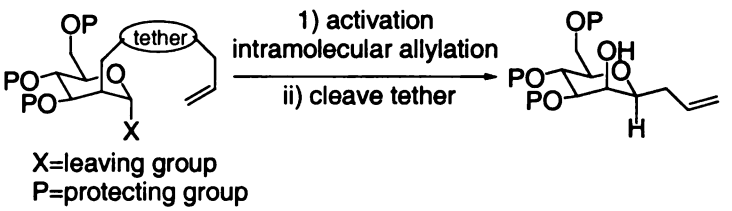
A potential solution to this problem is to make the intermediate oxocarbonium less susceptible to nucleophilic attack, for example, to replace methoxy with a phenoxy

group. However, several attempts to make tetraphenyl orthocarbonate failed following Samuelson's procedure (**Scheme II-10**).[41]



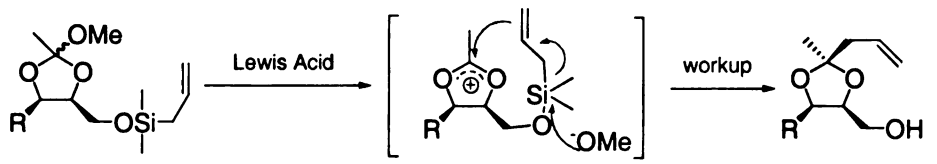
Scheme II-10. Alternative strategy to use orthocarbonates

An intramolecular delivery strategy was also tried to achieve the opposite diastereoselectivity. The strategy was first introduced by Stork [42] and Hindsgaul,[43] both of whom exploited an axial alcohol in a sugar derivative to temporarily attach the acceptor to a suitable donor. Activation of the donor then results in intramolecular transfer of the acceptor to the anomeric center (**Scheme II-11**).



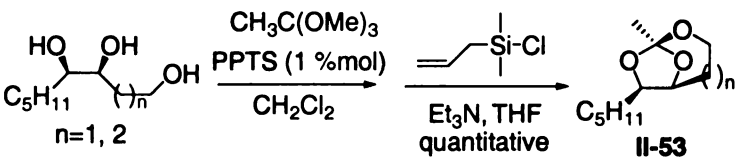
Scheme II-11. Use of an intramolecular delivery strategy

I was interested in investigating the possibility of using a similar strategy to achieve *syn* nucleophilic attack by delivering an allyl nucleophile that has been tethered through a silyl ether linkage to the substrate (**Scheme II-12**). The intramolecular delivery, if applicable, would lead to a *syn* attack to avoid steric hindrance.



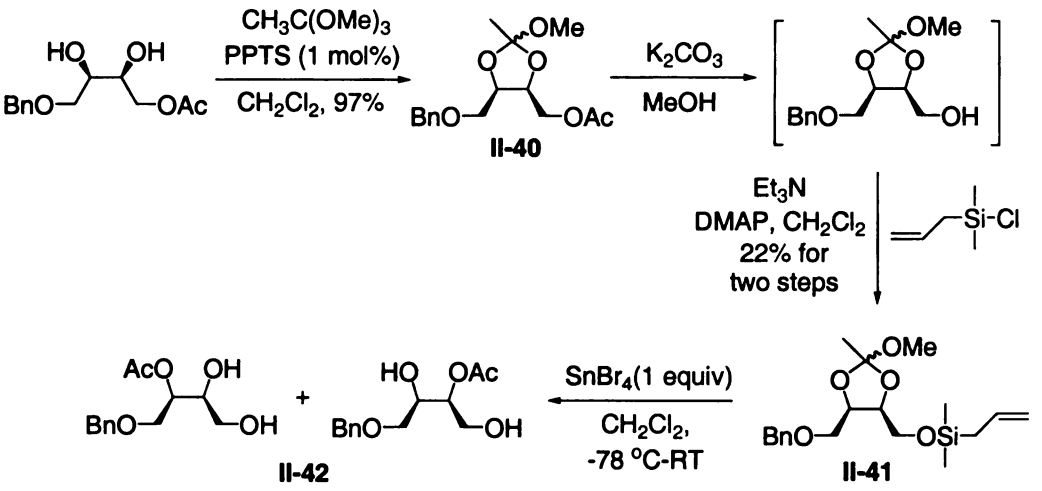
Scheme II-12. Proposed intramolecular delivery strategy using a silyl ether linkage

Initial attempts focused on generating the allyldimethylsilyl ether *in situ* after formation of the orthoester from the triol. However, only the bicyclic orthoester **II-53** was isolated after workup (**Scheme II-13**). The mechanism of this transformation will be discussed in **Chapter 2.4**.



Scheme II-13. One-pot approach to make the silyl ether linkage

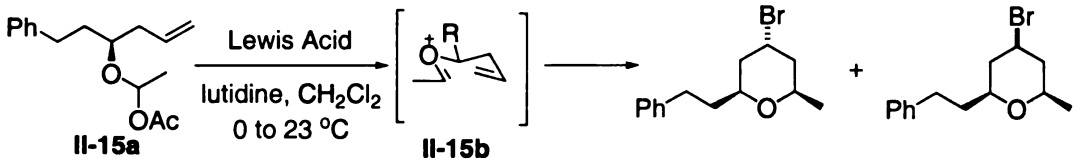
Stepwise attempt was also investigated. The primary alcohol was first protected as an acetate and de-protected after the cyclic orthoester **II-40** was made. The intermediate was then treated with allylchlorodimethylsilane. The silyl ether **II-41** was finally obtained, although in poor yield, and subjected to $SnBr_4$ in dichloromethane. However, no desired products were obtained and the products were identified as a mixture of hydrolyzed derivatives of orthoesters **II-42** (**Scheme II-14**).



Scheme II-14. Stepwise approach to make the silyl ether linkage

2.3. Attempts of Intramolecular Prins-Type Cyclization on Cyclic Orthoesters

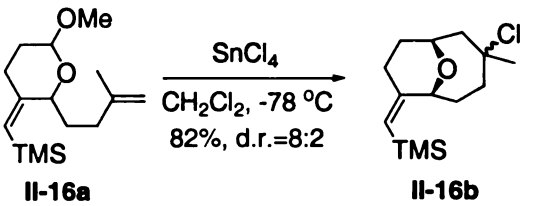
The electrophilic cyclization of homoallylic ethers with aldehydes under strongly acidic conditions was initially explored by Hanschke [44] and later by Stapp,[45] and came to be known as the Prins cyclization. A typical Prins cyclization is a concerted process which usually involves the attack of an olefinic electron pair onto an electrophilic carbon followed by trapping of the carbon cation by another nucleophile. The reaction leads to formation of tetrahydropyrans (THP) with stereocontrol achieved presumably through a six-member transition state.[46] For example, Rychnovsky *et. al.*[47] reported a stereoselective synthesis of 2,4,6-trisubstituted THP rings using Prins cyclization of α-acetoxy homoallylic ethers **II-15a**. The electrophilic intermediate is an oxocarbenium cation **II-15b** formed under acidic conditions and different stereoselectivity can be achieved when different Lewis acids are used (**Scheme II-15**).



Lewis Acid / Yield	II-15c	II-15d
$SnBr_4$	9%	79%
TMSBr	98%	0

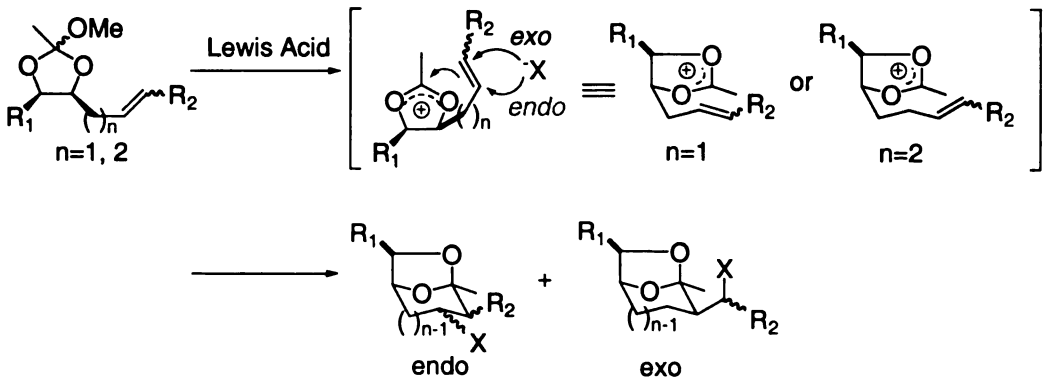
Scheme II-15. Prins cyclizations of α-acetoxy homoallylic ethers

The Prins cyclization has also been used to construct oxygen-bridged medium-sized carbocycles (**Scheme II-16**).[48]



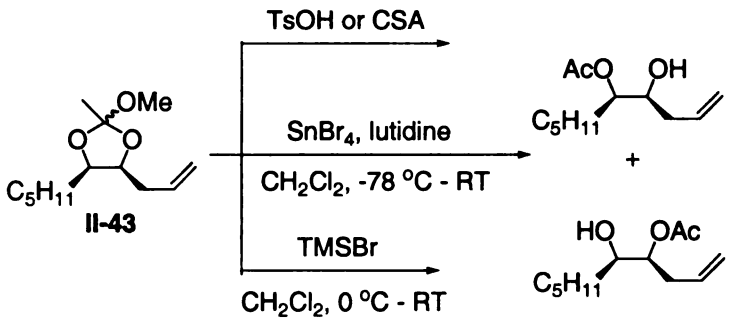
Scheme II-16. Prins cyclizations to make oxygen-bridged carbocycles

Since an orthoester is easily transformed into an oxocarbenium cation under acidic conditions and a double bond can be installed in our substrate, theoretically Prins reaction could be applied to our system to construct a bicyclic acetal system. Depending on the size of the ring to be formed and the stability of the carbocation intermediate, both *endo*- and *exo*-attacks are expected (**Scheme II-17**).



Scheme II-17. Proposed Prins cyclization of cyclic orthoesters

Many substrates and conditions were investigated for the Prins cyclization. Unfortunately none of them worked. The major products after workup were the hydrolyzed derivatives of orthoesters (**Scheme II-18**). Substrates with electron rich double bonds (**II-49, II-50, II-51**), which can form more stable carbon cation intermediates, were also tried yet without success (**Figure II-2**).



Scheme II-18. Attempts for Prins cyclization of cyclic orthoesters

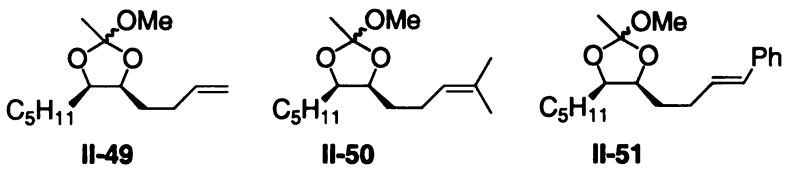
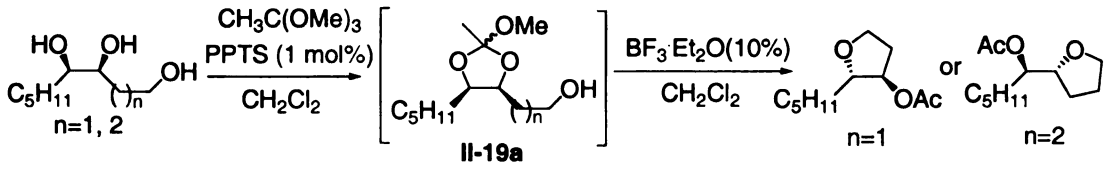


Figure II-2. Other substrates tried for Prins cyclization

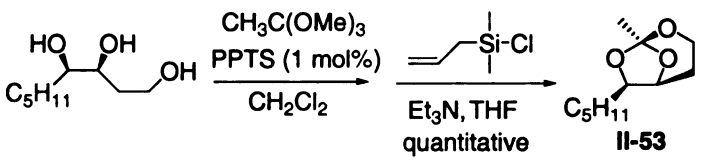
2.4. Correction of Mechanism of Lewis Acid-Mediated Cyclization of Cyclic Orthoesters Derived from 1,2,n-triols

Our group's previous research has revealed a one-pot method to access cyclic ethers directly from 1,2,*n*-triols via the intermediacy of a cyclic orthoester.[6] We have proposed a mechanism that ionization of the intermediate orthoester with a Lewis acid leads to a reactive acetoxonium species, which upon intramolecular displacement with the pendant hydroxyl yields the cyclized ether (**Scheme II-19**). However, as it is a one-pot method, the intermediate orthoester with a free hydroxyl group **II-19a** was not isolated.



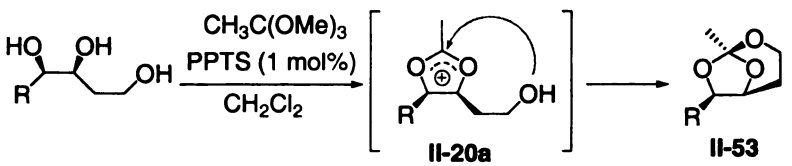
Scheme II-19. Our groups' previous study on cyclic orthoesters

In my study of orthoesters, I have isolated, more than once, bicyclic orthoesters **II-53**. Further studies have revealed that this type of compounds are the real intermediates for the transformations discussed in **Scheme II-19**. When the assumed intermediate was obtained under reported acidic condition and then treated with allylchlorodimethylsilane, no silyl ether was formed; only the bicylic orthesters **II-53** was isolated quantatively (**Scheme II-13**).



Scheme II-13. Unexpected discovery of bicyclic ortho esters

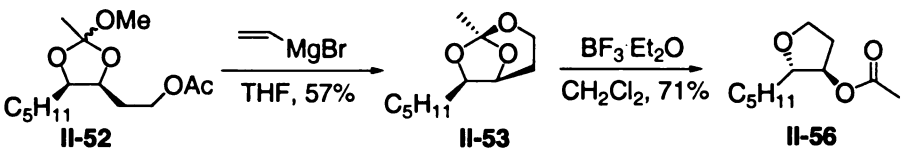
The only reasonable explanation for this would be that the **II-53** was already formed after treating the triol with trimethyl orthoacetate under slightly acidic conditions (PPTS). A more detailed mechanism involves the free hydroxyl attacking C-1 of the oxocarbenium cation **II-20a** formed under acidic conditions (**Scheme II-20**).



Scheme II-20. Correction of mechanism

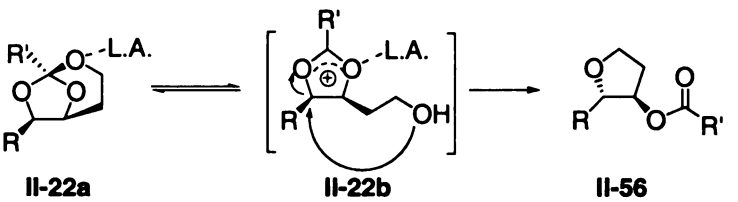
The proposed mechanism was further confirmed when bicyclic orthoester **II-53**, obtained from orthoester **II-52** treated with vinylmagnesiumbromide, transformed rapidly

into substituted tetrahydrofuran **II-56** with addition of $BF_3 \cdot Et_2O$, as reported (**Scheme II-21**).[48]



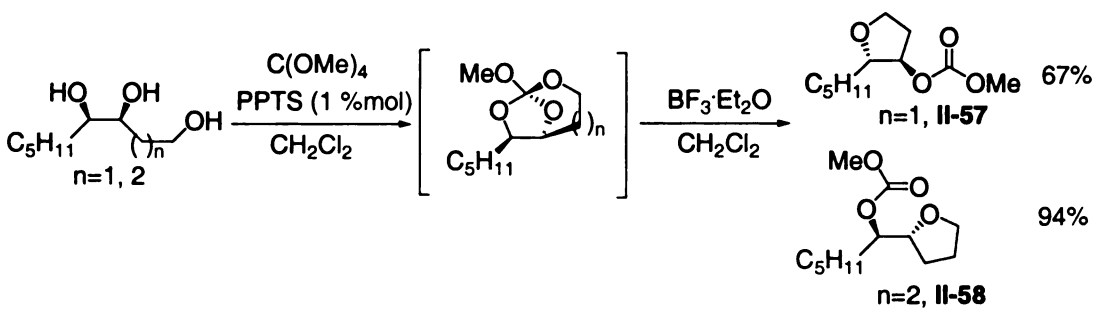
Scheme II-21. Further confirmation of corrected mechanism

The transformation from **II-53** to **II-56** can be explained by the equilibrium between the bicyclic orthoester **II-22a**, which is coordinated to Lewis acid, and a five-membered dioxonium cation **II-22b** under Lewis acidic conditions. The formation of the stable THF ring **II-56** is the thermodynamic trap, which drives the transformation forward (**Scheme II-22**).[49]



Scheme II-22. Mechanism for transformation of byciclic orthoester to substituted THF

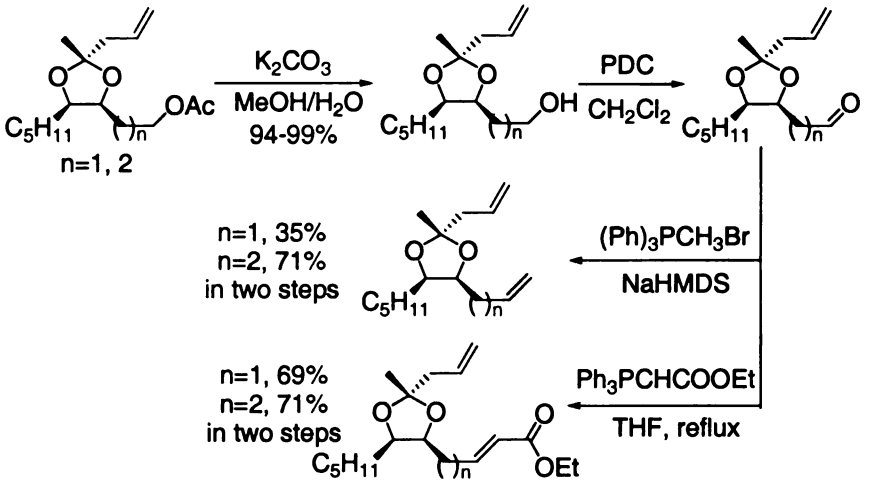
The study was also extended to cyclic orthocarbonates and similar results were obtained (**Scheme II-23**).



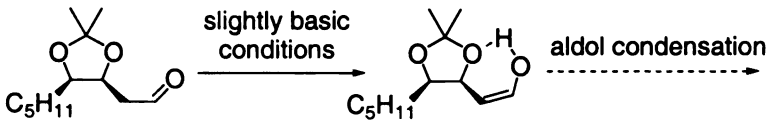
Scheme II-23. Extended chemistry to orthocarbonates

2.5. Study of Ring-Closing Metathesis of Model Substrates

The model substrates were made following the routes discussed in **Chapter 2.2** (**Scheme II-6**). Some of the transformations are listed below (**Scheme II-24**). It took some time to screen the conditions for oxidation of the primary alcohol to the aldehyde. Pyridimium dichromate (PDC) was found to be the best. However, it still does not work very well for one of the substrates derived from *cis*-3-nonen-1-ol due to potential aldol condensation induced by enolate formation (**Scheme II-25**). Both the electron rich and poor olefins have been made because both of them have been reported to be used in olefin metathesis.[50]



Scheme II-24. Final steps to make model substrates for RCM

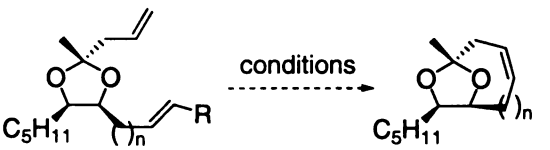


Scheme II-25. Substrate that has trouble for the oxidation to aldehyde

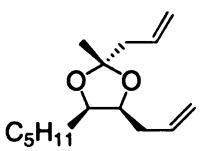
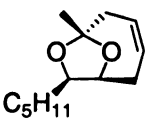
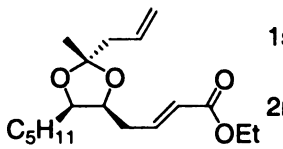
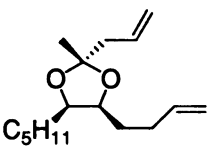
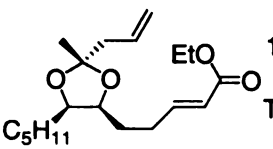
Various conditions were utilized in the RCM to construct the inside-out bicyclic acetal (**Table II-5**). Unfortunately, either inseparable mixtures were obtained or starting material was recovered except when 20% of second generation Grubbs catalyst were used in toluene and refluxed. Evidence from both ^{13}C NMR and GC-MS suggested the

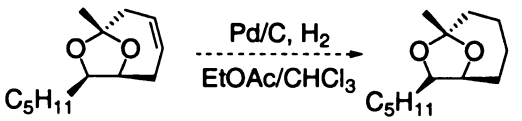
existence of cyclized product **II-65**. Compared to starting diene **II-61,** new peaks in ^{13}C NMR between 130-125 ppm suggested the formation of new double bond. In GC-MS, the parent peak *m/z* 210 matched the molecular weight of **II-65**. However, probably due to strain of the system, it was too unstable to be isolated even after reduction of the double bond by catalytic hydrogenation (**Scheme II-26**).

Table II-5. RCM of model substrates



R=H, COOEt; n=1, 2

Substrate	Conditions	Products	Idenification
 **II-61**	1st generation Grubbs catalyst (80 mol%) 2nd generation Grubbs catalyst (20 mol%) Toluene (0.004M), Reflux	Inseparable mixture  **II-65**, Unstable	N / A ^{1}H, ^{13}C NMR(not pure) GC-MS
 **II-63**	1st generation Grubbs catalyst(80 mol%) 2nd generation Grubbs catalyst(20 mol%) Toluene (0.004M), Reflux	Recovered S.M. Inseparable mixture	^{1}H, ^{13}C NMR N / A
 **II-62**	1st generation Grubbs catalyst (80 mol%) Toluene (0.004M), Reflux	Inseparable mixture	N / A
 **II-64**	1st generation Grubbs catalyst(80 mol%) Toluene (0.004M), Reflux	Recovered S.M.	^{1}H, ^{13}C NMR



II-65, Mixtures **II-66**

Scheme II-26. Hydrogenation of the double bond after RCM

2.6. Conclusions

In conclusion, my results to date have been promising in seteroselective nucleophilic attack on cyclic orthoesters. However, the C-1 epimer obtained from *anti* attack would only lead to the strained inside-out bicyclic ketals after RCM. It was proved that the inside-out system was not only difficult to be constructed by RCM but too unstable to be isolated once formed. Possible solutions to these problems are: using more active Schrock catalyst for RCM; trapping the inside-out intermediate by *in situ* hydrolysis or reduction of the ketal. The opposite diastereoselectivity was not obtained by using either orthocarbonate chemistry or intramolecular delivery strategy. However, the strategy of twice nucleophilic attack on cyclic orthocarbonates could still be applied if better ways could be found to make the tetraphenyl orthocarbonate derivatives. The Prins cyclization reaction was found not applicable on the five-membered oxocarbenium intermediate.

The unexpected discovery of the bicyclic orthoester intermediates helped elucidate the mechanism of previously reported reactions.

Further improvement needs to be done to make the methodology applicable.

Chapter 3

Experimental

3.1. General Information

All commercially available starting materials were used without further purification. Commercially available starting materials were obtained from Aldrich, Acros Strem Chemicals and Alfa Aesar. Some compounds were prepared as previously reported. All of the spectral data for known compounds either matched those reported by Aldrich or by comparison to literature reports. ^{1}H, ^{13}C NMR and nOe spectra were recorded on either a 300 MHz NMR spectrometer (VARIAN INOVA) or on a 500 MHz NMR spectrometer (VARIAN VXR). Column chromatography was performed using Silicycle (40-60 μm) silica gel. Analytical TLC was done using pre-coated silica gel 60 F_{254} plates. GC-MS analyses were carried out with HP5890 GC and HP4286 MS.

3.1.1. Orgins of Starting Materials

Materials obtained from Aldrich: allyltrimethylsilane, benzyltriphenylphosphonium chloride, $BF_3{\cdot}Et_2O$, *cis*-4-decen-1-ol, methylvinylketone, methyltriphenylphosphonium bromide, *cis*-3-nonen-1-ol, NaHMDS (1.0 M in THF), PDC, *iso*propyltriphenylphosphonium iodide, tetramethylorthocarbonate, tin(IV) tetrabromide, trimethylorthoacetate, trimethylorthobenzoate, trimehtylorthoformate, vinylmagnesiumbromide (1.0 M in THF).

Materials obtained from Acros: allylchlorodimethylsilane.

Materials obtained from Strem Chemicals: first and second generation Grubbs catalyst.

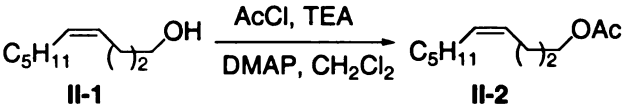
Materials obtained from Alfa Aesar: *cis*-2-buten-1,4-diol.

The triphenylphosphine ylide for HWE reaction was made previously by other group members.

3.1.2. List of Compounds that were Compared to Literature Reports

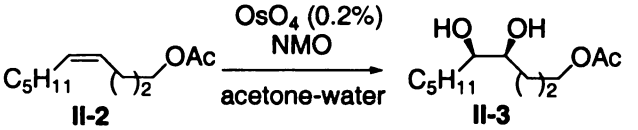
II-21,[51] **II-53**,[49] **II-56, 57, 58**.[6]

3.2. Data for Chapter 2.1



II-1 II-2

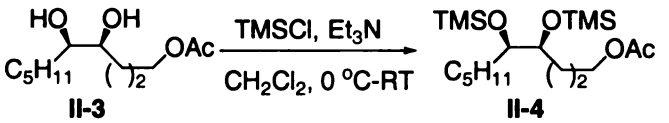
Preparation of compound II-1: *cis*-4-Decen-1-ol **II-1** (3.125 g, 20 mmol) was dissolved in dichloromethane (100 mL) and TEA (2.5 mL, 33 mmol), and DMAP (0.12 g, 5 mol%) were added. AcCl (0.22 mL, 30 mmol) was added afterwards. The reaction was stirred at ambient temperature for 30 min. The resulting solution was washed with water (2 x), brine (2 x) and then dried with Na_2SO_4. Purification by Flash Chromatography (5% AcOEt/hexane) afforded 3.567 g acetal ester **II-2** (90%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.35 (2H, m), 4.03 (2H, t, J = 6.6 Hz), 2.06 (4H, m), 2.02 (3H, s), 1.65 (2H, p, J = 7.5 Hz), 1.27 (6H, m), 0.87 (3H, t, J = 7.2 Hz).



II-2 II-3

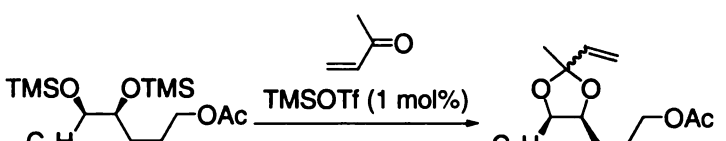
Preparation of compound II-3: To a mixture of N-methylmorphline-N-oxide (NMO, 2.29 g, 18 mmol), acetone/H_2O (18 mL/2 mL) and OsO_4 (0.1 mL, 0.02M, 0.2 mol%) was added **II-2** (2.400 g, 12.1 mmol). The reaction was stirred overnight at ambient temperature. $Na_2S_2O_4$ (0.115 g) and water (10 mL) were added to the resulting solution, which was saturated with NaCl subsequently and extracted with EtOAc (3 x).

The combined organic layers were dried with Na_2SO_4 and evaporated. Flash chromatography (75% EtOAc / hexane, 1% MeOH) afforded 2.450 g diol **II-3** (87%). ^1H NMR ($CDCl_3$, 300 MHz) δ 4.07 (2H, t, J = 6.3 Hz), 3.58 (2H, br), 2.02 (3H, s), 1.85 (2H, m), 1.66 (2H, m), 1.44 (4H, m), 1.27 (4H, br), 0.86 (3H, t, J = 6.3 Hz).



II-3 **II-4**

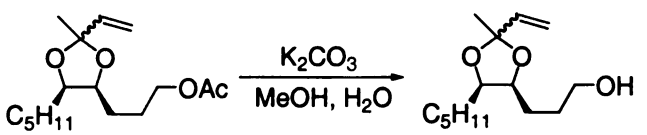
Preparation of compound II-4: To a solution of diol **II-3** (0.800 g, 3.44 mmol) in dichloromethane (25 mL) was added TEA (2.5 mL) and cooled to 0 °C. TMSCl (2.2 mL, 17.2 mmol) was added subsequently and the solution was warmed up to ambient temperature after addition. The reaction was complete in 2 h. The solution was washed with saturate $NaHCO_3$ very quickly, dried with Na_2SO_4, concentrated and subjected to the next step without purification.



II-4 **II-5a & b**

Preparation of compound II-5a & 5b: A stirred solution of **II-4** (1.505 g, 5.3 mmol) and TMSOTf (0.05 mL, 1 mol%) in dichloromethane (20 mL) was cooled to –78 °C and added methylvinylketone (2.2 mL, 26 mmol) subsequently. The reaction was stirred at –78 °C under N_2 overnight. The reaction was complete in 20 h (monitored by TLC) and quenched by addition of dry pyridine (0.05 mL) at the same temperature, poured into a saturate $NaHCO_3$ solution (10 mL) and extracted with ether (3 x). The combined extracts were dried over a 1:1 mixture of Na_2CO_3 and Na_2SO_4, and the solvent was removed under reduced pressure. Flash chromatography (10% EtOAc/hexane)

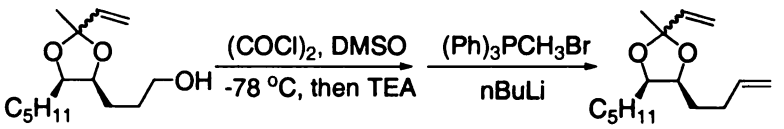
afforded two mixtures of diastereomers (**II-5a & 5b**), 0.134 g and 0.140 g respectively (21% in total) and each with a d. r. 5/1. Parallel reactions were run for both of the diastereomers in the following transformations. ^{1}H NMR **II-5a** ($CDCl_3$, 300 MHz) δ 5.76 (1H, q, *J* = 10.5 Hz), 5.30 (1H, dd, *J* = 17.1, 1.8 Hz), 5.06 (1H, dd, *J* = 10.5, 1.5 Hz), 4.06 (2H, m), 3.94 (2H, m), 2.02 (3H, s), 1.82 (2H, m), 1.66 (2H, m), 1.46 (4H, m), 1.42 (3H, s), 1.27 (4H, br), 0.86 (3H, t, *J* = 6.6 Hz); ^{13}C NMR **II-5a** ($CDCl_3$, 75 MHz) δ 171.2, 139.3, 114.1, 106.1, 77.8, 77.1, 64.3, 31.5, 29.2, 26.3, 26.1, 25.7, 25.1, 22.2, 20.6, 13.7. ^{1}H NMR **II-5b** ($CDCl_3$, 300 MHz) δ 5.81 (1H, q, *J* = 10.5 Hz), 5.38 (1H, dd, *J* = 17.1, 1.8 Hz), 5.06 (1H, dd, *J* = 10.5, 1.5 Hz), 4.06 (4H, m), 2.02 (3H, s), 1. 82 (2H, m), 1.66 (2H, m), 1.46 (4H, m), 1.37 (3H, s), 1.27 (4H, br), 0.86 (3H, t, *J* = 6.6 Hz); ^{13}C NMR **II-5b** ($CDCl_3$, 75 MHz) δ 171.1, 140.9, 114.1, 106.5, 78.4, 78.0, 64.3, 31.8, 29.2, 25.9, 25.5, 25.4, 24.7, 22.5, 20.9, 14.1.



II-5a & b **II-6a & b**

Preparation of compound II-6a & 6b: Each of the two diastereomers in **II-5a & b** (0.134 g, 0.47 mmol) was dissolved in MeOH/H_2O (10 mL/2 mL) and K_2CO_3 (0.154 g, 0.94 mmol) was added. The reaction was stirred at ambient temperature overnight. Water (5 mL) was added and the organic layer was separated from the aqueous layer, which was extracted by ether (3 x) and dried over Na_2SO_4. Flash chromatography (67% EtOAc/hexane, 1% MeOH) afforded 0.101 g product **II-6a** (82%) and its C-1 epimer **II-6b** 0.126 g (88%). ^{1}H NMR **II-6a** ($CDCl_3$, 300 MHz) δ 5.91 (1H, q, *J* = 10.5 Hz), 5.43 (1H, dd, *J* = 17.4, 1.5 Hz), 5.07 (1H, dd, *J* = 10.5, 1.5 Hz), 4.07 (2H, m), 3.64 (2H, t, *J* = 6.0 Hz), 1.80 (1H, br), 1. 82 (2H, m), 1.68 (2H, m), 1.46 (4H, m), 1.38 (3H, s), 1.34 (4H,

br), 0.85 (3H, t, J = 6.6 Hz); ^{13}CNMR **II-6a** ($CDCl_3$, 75 MHz) δ 140.8, 114.2, 106.5, 78.7, 78.5, 62.7, 31.8, 29.8, 29.3, 26.2, 25.9, 24.6, 22.5, 14.0.^{1}H NMR **II-6b** ($CDCl_3$, 300 MHz) δ 5.76 (1H, q, J = 10.5 Hz), 5.30 (1H, dd , J = 17.4, 1.5 Hz), 5.07 (1H, dd, J = 10.5, 1.5 Hz), 3.94 (2H, m), 3.65 (2H, t, J = 6.0 Hz), 2.01 (1H, br), 1.82 (2H, m), 1.68 (2H, m), 1.46 (4H, m), 1.43 (3H, s), 1.34 (4H, br), 0.86 (3H, t, J = 6.5 Hz); ^{13}CNMR **II-6b** ($CDCl_3$, 75 MHz) δ 139.3, 114.2, 106.1, 78.0, 77.9, 62.7, 31.8, 29.8, 29.7, 26.8, 26.6, 26.0, 22.5, 14.0.

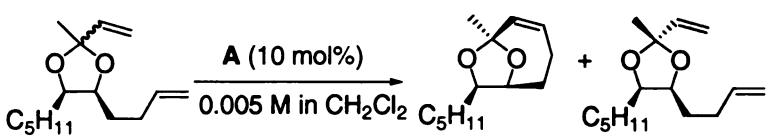


II-6a & b **II-7a & b**

Preparation of compound II-7a & 7b: To a solution of oxalyl chloride (0.12 mL, 1.35 mmol) in dichloromethane (5 mL) was slowly added DMSO (0.22 mL, 3.12 mmol) in dichloromethane (1 mL) at –78 °C, and successively alcohol **II-6a** (0.126 g, 0.52 mmol) or **II-6b** (0.101 g, 0.50 mmol) in dichloromethane (2 mL) was added dropwise. After the mixture was stirred at –78 °C for 15 min, TEA (0.56 mL, 4.05 mmol) was added to the reaction mixture and allowed to warm up to 0 °C. After addition of saturate NH_4Cl (10 mL) and extraction with dichloromethane, the organic phase was washed with brine and dried over $MgSO_4$. Evaporation of solvent afforded crude aldehyde, which was subjected to the following Wittig reaction without separation.

THF (5 mL) was added to methyltriphenylphosphonium bromide (203 mg, 0.57 mmol) at 0 °C, and then a hexane solution of 2.5 M n-butyllithum (0.22 mL, 0.55 mmol) was added at 0 °C for 30 min and the temperature was raised to ambient for 1 h. After addition of saturate NH_4Cl (10 ml), the reaction was extracted with ether (3 x). The organic layer was washed with brine (1 x) and dried over $MgSO_4$. Flash chromatography

(5% EtOAc/hex) afforded desired product **II-7a** 0.033 g (27%) and its diastereomer **II-7b** 0.017 g (20%). ^{1}H NMR **II-7a** ($CDCl_3$, 300 MHz) δ 5.92 (1H, q, J = 10.8 Hz), 5.77 (1H, m), 5.43 (1H, dd, J = 17.1, 1.5 Hz), 5.06 (1H, dd, J = 10.5, 1.5 Hz), 4.96 (1H, m), 4.07 (2H, m), 2.24 (1H, m), 2.07 (1H, m) 1.80 (1H, br), 1.57 (2H, m), 1.46 (2H, m), 1.38 (3H, s), 1.27 (6H, br), 0.86 (3H, m); ^{13}C NMR **II-7a** ($CDCl_3$, 75 MHz) δ 141.3, 138.1, 114.9, 114.1, 106.2, 78.5, 77.8, 31.6, 30.3, 29.3, 28.7, 25.9, 24.7, 22.6, 14.1. ^{1}H NMR **II-7b** ($CDCl_3$, 300 MHz) δ 5.80 (1H, m), 5.77 (1H, q, J = 10.8 Hz), 5.34 (1H, dq, J = 17.1, 1.5 Hz), 5.06 (1H, dq, J = 10.5, 1.5 Hz), 4.95 (1H, m), 3.94 (2H, m), 2.24 (1H, m), 2.07(1H, m), 1.57 (2H, m), 1.46 (2H, m), 1.43 (3H, s), 1.27 (6H, br), 0.86 (3H, m); ^{13}C NMR **II-7b** ($CDCl_3$, 75 MHz) δ 139.4, 138.2, 114.8, 114.0, 106.0, 77.8, 77.3, 31.9, 30.4, 29.7, 29.2, 26.7, 26.0, 22.6, 14.0.



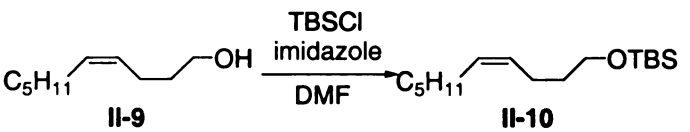
II-7a & b **II-8** **II-7a**

Preparation of compound II-8: II-7a (0.033 g, 0.1 mmol) was dissolved in dichloromethane (21 mL) and 1st generation Grubbs catalyst (**A**, 1.2 mg, 10 mol%) in dichloromethane (7 mL) was added dropwise at ambient temperature. The reaction was stirred at ambient temperature overnight. **II-7a** was not consumed at all (monitored by TLC). More catalyst (**A**, 1 mg) was added and the reaction refluxed overnight. **II-7a** was still not consumed. Second generation Grubbs catalyst (**B**, 1 mg) was added and the solution was refluxed for another 12h. **II-7a** was recovered.

Run parallel reaction for **II-7b** (0.017 g) in dichloromethane (10 mL). First generation Grubbs catalyst (**A**, 1 mg, 10 mol%) in dichloromethane (5 mL) was added dropwise at ambient temperature. After the reaction was stirred for 12 h, a major product

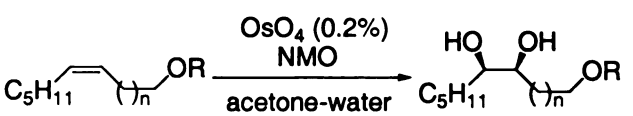
was formed (monitored by TLC). Pipet chromatography afforded 5 mg **II-8** (not pure, < 30%). Yet no good ^{13}CNMR could be obtained. Characteristic ^{1}H NMR **II-8** ($CDCl_3$, 500 MHz) δ 5.85-5.75 (2H, m), 4.05 (2H, m), 1.48 (3H, s); GC-MS *m/z* 210 M^+, 139 [M-C_5H_{11}]$^+$.

3.3. Data for Chapter 2.2.1

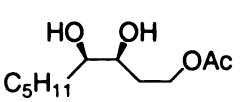


II-9 **II-10**

Preparation of compound II-10: *tert*-butyldimethyl-silyl chloride (5.426 g, 36.00 mmol) was added to a solution of *cis*-3-decen-1-ol **II-9** (4.688 g, 30.0 mmol) and imidazole (5.100 g, 75.0 mmol,) in N, N-dimethylformamide (DMF, 2 ml/g of alkenol, 10 mL) at ambient temperature and stirred for 10 h. Water was added and ethylacetate (1 x) was used to extract the solution. The extract was then concentrated and flash chromatography (5% EtOAc/hexane, 1% TEA) afforded silyl ether **II-10** 1.826 g (99%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.37 (2H, m), 3.57 (2H, t, J = 7.2 Hz), 2.28 (2H, q, J = 6.9 Hz), 2.01 (2H, q, J = 6.9 Hz), 1.26 (8H, m), 0.87 (9H, s), 0.85 (3H, m), 0.03(6H, s).

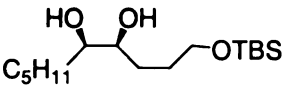


Preparation of compound II-11 & II-12: For general procedure of dihydroxylation, please refer to **II-3.**



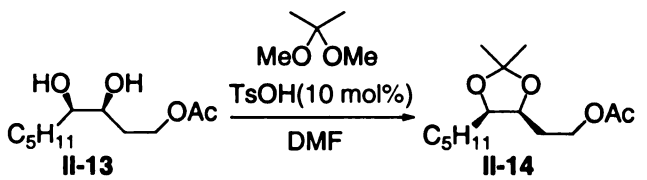
II-11

II-11 was prepared in 85% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.07 (2H, t, J = 6.3 Hz), 3.58 (2H, br), 2.02 (3H, s), 1.85 (2H, m), 1.66 (2H, m), 1.44 (4H, m), 1.27 (4H, br), 0.86 (3H, t, J = 6.3 Hz).



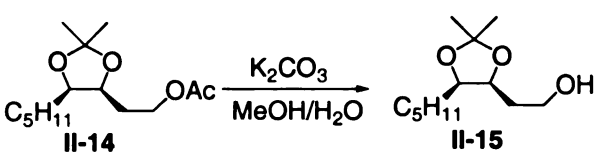
II-12

II-12 was prepared in 95% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.59 (4H, m), 1.65 (2H, m), 1.40 (2H, m), 1.37 (2H, m), 1.26 (6H, m, br), 0.86 (9H, s), 0.84 (3H, m), 0.02 (6H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 74.4, 74.3, 63.6, 31.9, 31.6, 29.4, 28.5, 25.8, 22.6, 22.5, 18.3, 14.1, -5.5.



II-13 **II-14**

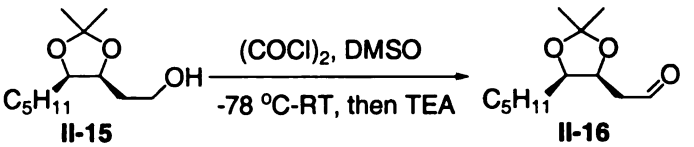
Preparation of compound II-14: 2,2-dimethoxypropane (0.74 mL, 6.0 mmol) was added to a mixture of diol **II-13** (0.872 g, 4.0 mmol) and TsOH (26 mg, 10% mol) in N, N-dimethylformide (20 mL). The mixture was stirred for 2 h and TLC showed that the reaction was complete. Water (40 mL) was added and ethylacetate was used to extract the solution. The extract was then concentrated and flash chromatography (10% EtOAc/hexane) afforded product **II-14** 1.021 g (99%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.23 (2H, m), 4.07 (2H, m), 2.01(3H, s), 1.70 (2H, m), 1.48 (2H, m), 1.39 (3H, s), 1.29 (3H, s), 1.27 (6H, m, br), 0.85 (3H, t, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.0, 107.7, 77.8, 74.5, 61.7, 31.8, 29.4, 29.1, 28.5, 26.0, 22.5, 21.0,14.0.



II-14 **II-15**

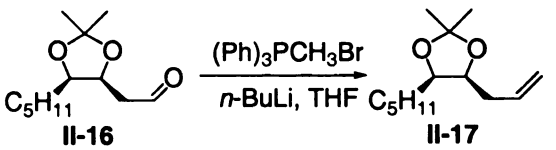
Preparation of compound II-15: For general procedure of hydrolysis of acetates, please refer to **II-6.**

II-15 was prepared in quantitive yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.20 (1H, m), 4.05 (1H, m), 3.79 (2H, m), 2.47 (1H, q, J = 3.9 Hz), 1.71 (2H, m), 1.55 (2H, m), 1.42 (3H, s), 1.30 (3H, s), 1.27 (6H, m, br), 0.85 (3H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 107.5, 79.2, 78.0, 62.0, 28.3, 25.9, 25.6, 22.1, 18.2. 11.1.



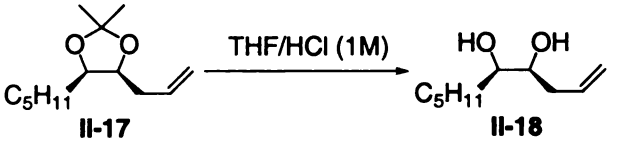
II-15 **II-16**

Preparation of compound II-16: To a solution of oxalyl chloride (0.21 mL, 2.4 mmol) in dichloromethane (24 mL) was slowly added anhydrous DMSO (0.34 mL, 4.8 mmol, 2.4eq) at –78 °C, and successively alcohol **II-15** (0.433 g, 2.0 mmol) in dichloromethane (20 mL) was dropwise added. After the mixture was stirred at -78°C for 15 min, triethylamine (1.5 mL) was added to the reaction mixture and allowed to warm up to 0 °C. After addition of saturate NH_4Cl and extraction with dicholoromethane, the organic phase was washed with brine and dried over $MgSO_4$. The crude mixture was concentrated under reduced pressure and purification by flash chromatography (20% EtOAc/hexane) afforded 0.213 g product **II-16** (49%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.78 (1H, t, J = 3.6 Hz), 4.54 (1H, m), 4.13 (1H, m), 2.48 (2H, m), 1.45 (2H, m), 1.40 (3H, s), 1.31 (3H, s), 1.26 (6H, m, br), 0.85 (3H, t, J = 6.6 Hz).



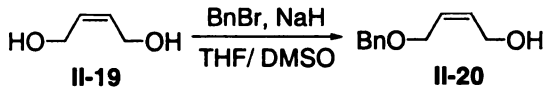
II-16 **II-17**

Preparation of compound II-17: THF (17 mL) was added to methyltriphenylphosphonium bromide (0.68 g, 1.9 mmol) at 0 °C, and then a hexane solution of 1.6 M n-butyllithum (1.2 mL, 1.9 mmol) was added at 0 °C. After 30min, aldehyde **II-16** (0.263 g, 1.24 mmol) in THF (6 mL) was dropwise added to the reaction mixture and stirring was continued for 30min and then at ambient temperature for 1 h. After addition of saturate NH_4Cl, the reaction was extracted with ether. The combined organic layer was washed with brine and dried over $MgSO_4$. The crude mixture was concentrated under reduced pressure and purification by flash chromatography (5% EtOAc/hexane) afforded 0.113 g alkene **II-17** (43%). ^1H NMR ($CDCl_3$, 300 MHz) δ 5.82 (1H, m), 5.07 (2H, m), 4.05 (2H, m), 2.23 (2H, m), 1.48 (2H, m), 1.28 (6H, m, br), 1.42 (3H, s), 1.31 (3H, s), 0.85 (3H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 134.9, 117.0, 107.5, 78.0, 77.4, 34.6, 31.9, 29.5, 28.5, 25.94, 25.92, 22.5, 14.0.



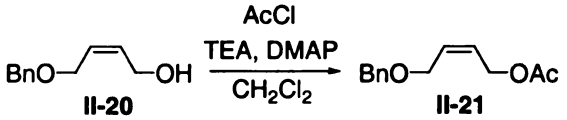
II-17 **II-18**

Preparation of compound II-18: Acetonide **II-17** (0.237g, 1.1 mmol) was dissolved in THF/HCl (1N) and the reaction was stirred overnight. The mixture was extracted with ether (3 x) and the combined organic phase was washed with brine (1 x) and dried with Na_2SO_4. The crude mixture was concentrated under reduced pressure and purification by flash chromatography (75% EtOAc/hexane) afforded 0.132g diol **II-18** in 69% yield. ^1H NMR ($CDCl_3$, 300 MHz) δ 5.80 (1H, m), 5.10 (2H, dt, J = 9.3, 1.2 Hz), 3.59 (2H, m), 2.64 (2H, s, br), 2.20 (2H, m), 1.40 (2H, m), 1.25 (6H, m, br), 0.84 (3H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.0, 117.9, 74.0, 73.4, 35.8, 31.8, 31.5, 25.6, 22.5, 13.9.



II-19 **II-20**

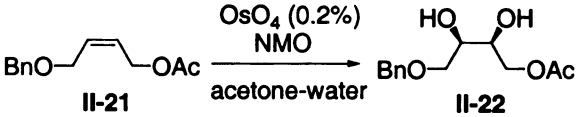
Preparation of Compound II-20: A solution of *cis*-2-buten-1,4-diol (**II-19**, 2.20 g, 25.0 mmol) in THF (63 mL) was added dropwise to a suspension of NaH (1.1 g of a 60% dispersion in mineral oil, 27.5 mmol) in a 4:1 mixture of dry THF/DMSO (125 mL). The mixture was stirred at ambient temperature for 30 min, then a solution of benzyl bromide (4.70 g, 27.5 mmol) in THF (63 mL) was added dropwise. The mixture was heated to 60 °C overnight. After cooling, an equal volume of water was added and the mixture extracted with diethyl ether(3 x). The combined organics were washed with brine, dried over sodium sulfate, and the solvent was removed under reduced pressure. The residue was column chromatographed (33% EtOAc/hexane) to give 2.58 g **II-20** in 58% yield. Dibenzyl ether (1.00 g) was obtained as by product. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35 (5H, m), 5.8 (2H, m), 4.5 (2H, s), 4.15 (2H, br), 4.1 (2H, d, J = 6.3 Hz).



II-20 **II-21**

Preparation of compound II-21: For general procedure of acylation, please refer to **II-2.**

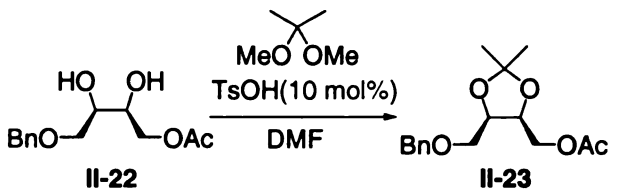
II-21 was made in 94% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35 (5H, m), 5.75 (2H, m), 4.60 (2H, d, J = 6.3 Hz), 4.50 (2H, s), 4.10 (2H. d, J = 6.6 Hz), 2.02 (3H, s).



II-21 **II-22**

Preparation of compound II-22: for general procedure of dihydroxylation, please refer to **II-3.**

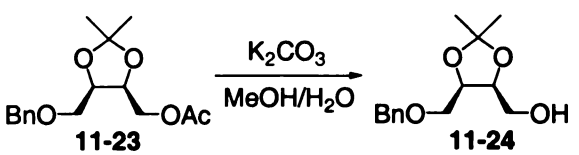
II-22 was made in 91% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31 (5H, m), 4.53 (2H, s), 4.23 (2H, q, *J* = 6.0 Hz), 3.84 (1H, m), 3.73(1H, m), 2.80 (2H, t, *J* = 5.4 Hz), 2.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.6, 137.4, 128.5, 127.9, 127.8, 73.6, 71.2, 71.1, 70.1, 65.8, 20.8.



II-22 **II-23**

Preparation of compound II-23: for procedure of making acetonide: please refer to **II-14.**

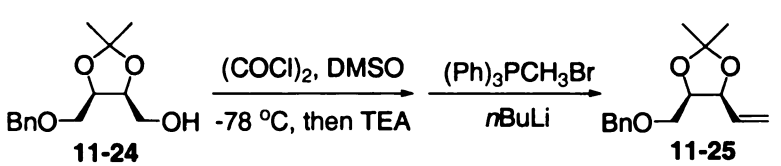
II-23 was made in 88% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31 (5H, m), 4.52 (2H, q, *J* = 12.0 Hz), 4.35 (3H, m), 4.05 (1H, m), 3.50 (2H, d, *J* = 9.6 Hz), 2.03 (3H, s), 1.44 (3H, s), 1.34 (3H, s).



11-23 **11-24**

Preparation of Compound II-24: For general procedure of hydrolysis of acetates, please refer to **II-6.**

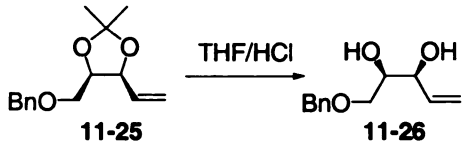
II-24 was made in 93% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35 (5H, m), 4.54 (2H, q, *J* = 12.0 Hz), 4.30 (2H, m), 3.60 (4H, d, *J* = 9.6 Hz), 2.60 (1H, t), 1.44 (s, 3H), 1.38 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.1, 128.5, 128.1, 127.9, 108.5, 75.3, 77.1, 73.8, 68.2, 60.8, 27.7, 25.1.



11-24 **11-25**

Preparation of Compound II-25: For procedure of oxidation and olefination: please refer to **II-7.**

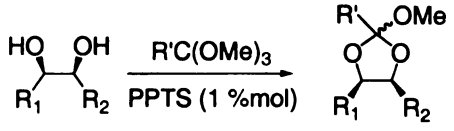
II-25 was made in 77% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31 (5H, m), 5.78 (1H, m), 5.34 (2H, m), 4.59 (2H, s), 4.20 (1H, t, J = 7.8 Hz), 3.90 (1H, m), 3.57 (2H, m), 1.43 (6H, s). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.9, 135.2, 128.3, 127.7, 127.6, 118.6, 109.4, 79.9, 79.4, 73.5, 69.3, 26.9.



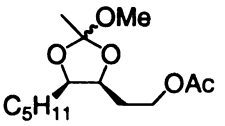
11-25 **11-26**

Preparation of Compound II-26: For procedure, please refer to **II-18.**

II-26 was made in 83% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35 (5H, m), 5.80 (1H, m), 5.31 (2H, dd, J = 16.5, 1.5 Hz), 4.56 (2H, m), 4.10 (1H, m), 3.62 (1H, m), 3.54 (2H, m), 2.90 (2H, br). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.9, 136.9, 136.4, 128.4, 127.8, 117.1, 74.1, 73.5, 72.8, 71.4.

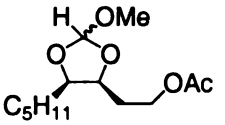


General procedure to make cyclic orthoesters II-27 to II-32, II-42: Orthoester (1.2 equiv) was added to a mixture of diol and PPTS (1 mol%) in dichloromethane (0.1M). The mixture was stirred for 15 min. The crude mixture was concentrated under reduced pressure and purified by flash chromatography (10% EtOAc/hexane, 5% TEA). All the cyclic orthoesters were obtained as a mixture of C-1 epimers. The ^{1}H and ^{13}C NMR data shown are for the major isomer peaks.



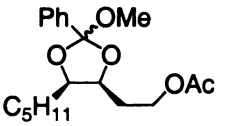
II-27

II-27 was made in 99% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.12 (2H, m), 4.24 (2H, m), 3.22 (3H, s), 2.01 (3H, s), 1.71 (2H, m), 1.51 (3H, s), 1.48 (2H, m), 1.27 (6H, m, br), 0.85 (3H, t, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.0, 120.2, 78.1, 75.0, 61.6, 50.3, 31.7, 29.4, 29.0, 25.9, 22.5, 22.4, 20.9, 14.0.



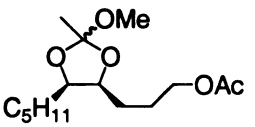
II-28

II-28 was made in 99% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.65 (1H, s), 4.14(2H, m), 4.26 (2H, m), 3.28 (3H, s), 2.02 (3H, s), 1.70 (2H, q, J = 6.6 Hz), 1.47 (2H, m), 1.28 (6H, m, br), 0.85 (3H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.0, 114.7, 77.2, 74.4, 61.4, 51.9, 31.7, 29.0, 28.6, 25.9, 22.5, 20.9, 13.9.



II-29

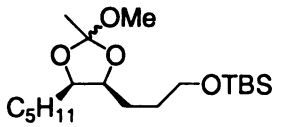
II-29 was obtained as a mixture of cyclic orthobenzoate and a majority of methyl benzoate.



II-30

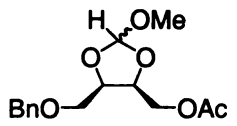
II-30 was made in 88% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.20 (2H, m), 4.07 (2H, m), 3.24 (3H, s), 2.01 (3H, s), 1.84 (1H, m), 1.64 (1H, m), 1.52 (3H, s), 1.48 (4H, m),

1.27 (6H, m, br), 0.85 (3H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.1, 120.2, 78.0, 75.0, 61.6, 50.3, 31.7, 29.4, 29.0, 25.9, 22.5, 22.4, 21.3, 20.9, 14.0.



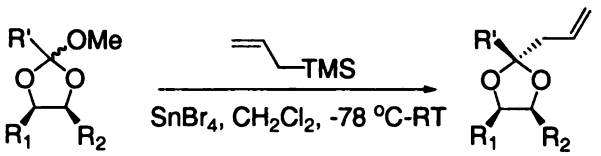
II-31

II-31 was made in 93% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.21 (2H, m), 3.64 (2H, m), 3.25 (3H, s), 1.52 (3H, s), 1.50 (4H, m), 1.29 (6H, m, br), 0.80 (9H, s), 0.02 (6H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 120.0, 78.6, 78.5, 62.7, 50.2, 31.8, 31.6, 29.4, 25.9, 22.8, 22.5, 18.4, 14.0, -5.3.



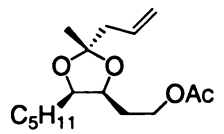
II-32

II-32 was made in 90% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31 (5H, m), 5.78 (1H, s), 4.52 (2H, s), 4.50 (2H, m), 4.38 (1H, m), 4.12 (1H, m), 3.54 (1H, d, J = 5.1 Hz), 3.31(3H, s), 2.03 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.6, 137.3, 128.4, 127.8, 115.5, 74.9, 74.6, 73.6, 71.2, 67.5, 62.4, 51.9, 20.8.



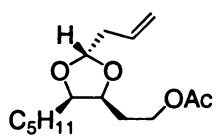
General procedure for allylation of cyclic orthoesters: $SnBr_4$ (0.25 equiv) in CH_2Cl_2 (0.1 M) was added dropwise to a solution of cyclic orthoester and allyltrimethylsilane (2.0 equiv) in dichloromethane (0.1 M) at -78^{o}C and the mixture was stirred at -78^{o}C for 30min and another 2.0 equiv allyltrimethylsilane was added and the mixture was warmed up to room temperature and stirred overnight. The reaction was

quenched with saturate $NaHCO_3$, extracted with ether and dried with Na_2SO_4. The crude mixture was concentrated under reduced pressure and purification by flash chromatography (5% EtOAc/hexane, 1% TEA) afforded allylation product as a single diastereomer.



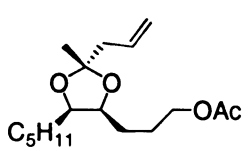
II-33

II-33 was made in 91% yield. ^1H NMR ($CDCl_3$, 300 MHz) δ 5.75 (1H, m), 5.02 (2H, dd, J = 13.8, 3.3 Hz), 4.23 (2H, m), 4.06 (2H, m), 2.32 (2H, d, J = 6.6 Hz), 2.01 (3H, s), 1.68 (2H, m), 1.46 (2H, m), 1.31 (3H, s), 1.25 (6H, m, br), 0.84 (3H, t, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.9, 133.7, 117.8, 108.6, 78.0, 74.7, 61.7, 44.0, 31.8, 29.5, 29.2, 26.3, 25.9, 22.5, 20.9, 13.9. GC-MS *m/z* 243 $[M-C_3H_5]^+$. NOE1D data proved the relative *anti* stereochemistry between the allyl group and substituents at C-3 and C-4.



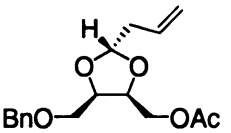
II-34

II-34 was made in 91% yield. ^1H NMR ($CDCl_3$, 300 MHz) δ 5.76 (1H, m), 5.07 (3H, m), 4.09 (4H, m), 2.30 (2H, t, J = 5.7 Hz), 1.99 (3H, s), 1.69 (2H, m), 1.46 (2H, m), 1.25 (6H, m, br), 0.84 (3H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.9, 132.4, 118.0, 101.8, 78.1, 75.0, 61.6, 39.8, 31.7, 28.5, 27.6, 25.9, 22.5, 20.9, 13.9. NOE1D data proved the relative *anti* stereochemistry between the allyl group and substituents at C-3 and C-4.



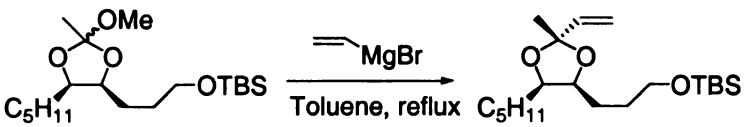
II-35

II-35 was made in 80% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.80 (1H, m), 5.04 (2H, dd, J = 13.8, 3.9 Hz), 4.04 (4H, m), 2.32 (2H, d, J = 7.2 Hz), 2.01 (3H, s), 1.84 (1H, m), 1.62 (1H, m), 1.46 (4H, m), 1.32 (3H, s), 1.27 (6H, m, br), 0.84 (3H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.9, 133.9, 117.8, 108.4, 78.2, 77.7, 64.3, 44.1, 31.8, 29.6, 26.4, 26.3, 25.9, 25.4, 22.5, 20.9, 13.9.



II-36

II-36 was made in 71% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30 (5H, m), 5.80 (1H, s), 5.26 (1H, t, J = 4.5 Hz), 5.16 (2H, m), 4.52 (2H, d, J = 2.1 Hz), 4.37 (2H, m), 4.20 (2H, m), 3.54 (2H, m), 2.37 (2H, t, J = 5.7 Hz), 2.04 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.7, 137.4, 131.9, 128.4, 127.9, 127.8, 118.4, 103.7, 75.7, 75.4, 73.6, 67.7, 62.3, 39.4, 20.8.

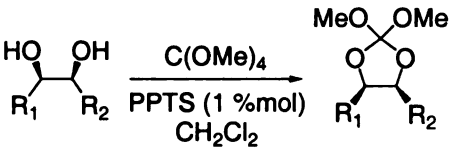


II-31 **II-37**

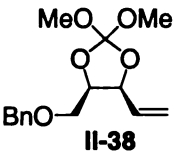
Preparation of compound II-37: Vinylmagnesium bromide (1.0 M in THF, 1.5 mL) was added to a solution of **II-31** (0.180 g, 0.5 mmol) in dry toluene (5 mL). After being refluxed overnight, the mixture was poured into aqueous NH_4Cl and extracted with ether. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography (10% EtOAc/hexane, 1% TEA) afforded 0.080 g product (not pure, <45%). Characteristic ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.76 (1H, q, J = 10.5 Hz), 5.30 (1H, dd, J = 15.6, 1.8 Hz), 5.06 (1H, dd, J = 8.7, 1.8 Hz), 3.95 (2H, m),

3.60 (2H, m), 4.06 (4H, m), 1.42 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.5, 113.9, 106.0, 78.0, 77.8, 62.9, 31.9, 29.7, 29.5, 26.7, 26.2, 25.9, 22.6, 18.3, 14.0, -5.3.

3.4. Data for Chapter 2.2.2

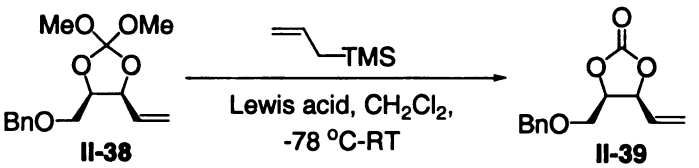


General procedure to make cyclic ortho carbonates: Tetramethyl orthocarbonate (1.2 equiv) was added to a mixture of vicinal diol and PPTS (1 mol%) in dichloromethane (0.1 M). The crude mixture was concentrated under reduced pressure and purification by flash chromatography.



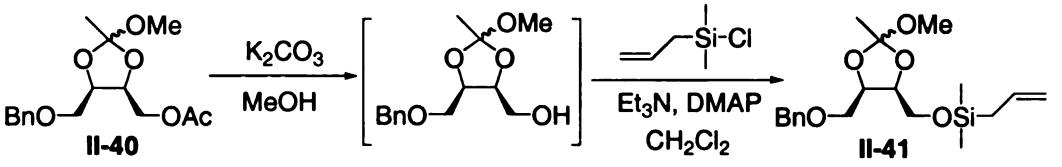
II-38

II-38 was made in 63% yield. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.35 (5H, m), 5.85 (1H, m), 5.30 (2H, m), 4.58 (2H, s), 4.50 (1H, m), 4.10 (1H, m), 3.62 (2H, d, J = 9.6), 3.41 (6H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.8, 134.3, 131.8, 128.4, 127.7, 127.6, 119.2, 80.2, 79.6, 73.4, 69.0, 51.5.

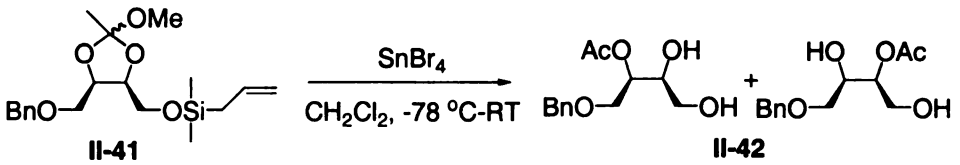


Attempts of nucleophilic attack on cyclic orthocarbonates: Lewis acid ($SnBr_4$, 25 mol% or TMSOTf 10 mol%) in CH_2Cl_2 was added dropwise to a solution of cyclic orthocarbonate **II-38** and allyltrimethylsilane (1.0 equiv) in CH_2Cl_2 (0.1M) at –78 °C and the mixture was stirred at –78 °C for 30 min and warmed up to ambient temperature

overnight. The reaction was quenched with saturate $NaHCO_3$, extracted with ether and dried with Na_2SO_4. The crude mixture was concentrated under reduced pressure and purification by flash chromatography (10% EtOAc/hexane, 5% TEA) afforded cyclic carbonate **II-39** (60% for $SnBr_4$, 52% for TMSOTf). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.30 (5H, m), 5.86 (1H, m), 5.39 (2H, t, J = 15.0 Hz), 4.95 (1H, t, J = 6.6 Hz), 4.58 (2H, q, J = 9.0 Hz), 4.40 (1H, p, J = 3.6 Hz), 3.66 (2H, dq, J = 11.4, 3.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 186.3, 137.0, 132.3, 128.6, 128.1, 127.7, 120.8, 80.1, 78.8, 73.7, 67.8.



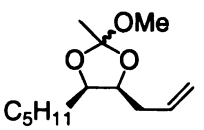
Preparation of compound II-41: Cyclic orthoester **II-40** (0.303 g, 0.98 mmol) was was dissolved in methanol (10 mL) and K_2CO_3 (0.204 g, 1.46 mmol) was added. The reaction was stirred at ambient temperature for 2 h. The suspension was filtered and the solvent was removed under reduced pressure. The oil-like intermediate was dissolved in dichloromethane (10 mL) and TEA (0.34 mL, 2.44 mmol) and DMAP (1 mg, 5 mol%) were added. Allylchlorodimethylsilane (0.15 mL, 0.98 mmol) was added afterwards. The reaction was stirred at ambient temperature for 1 h. The resulting solution was washed with water (2 x), brine (2 x) and then dried with Na_2SO_4. Removal of the solvent afforded crude product **II-41** 0.077 g in 22% yield. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.31 (5H, m), 5.72 (1H, m), 4.83 (2H, m), 4.54 (2H, q, J = 12.0 Hz), 4.49 (1H, m), 4.35 (1H, m), 4.67 (4H, m), 3.27 (3H, s), 1.56 (3H, s), 1.54 (2H, d, J = 19.2 Hz), 0.07 (6H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.0, 133.7, 128.4, 127.7, 113.8, 77.9, 77.2, 73.4, 68.3, 61.3, 50.4, 24.2, 21.7, -2.6.



II-41 **II-42**

Attempts for intramolecular nucleophilic delivery of II-41: $SnBr_4$ (0.093 g, 0.22 mmol) in dichloromethane (0.5 mL) was added dropwise to a solution of **II-41** (0.524 g, 2.0 mmol) in dichloromethane (60 mL) at –78 °C and the mixture was stirred at –78 °C for 30 min and the mixture was warmed up to room temperature overnight. The reaction was quenched with saturated $NaHCO_3$, extracted with ether and dried with Na_2SO_4. The crude mixture was concentrated under reduced pressure and purification by flash chromatography afforded a mixture of hydrolyzed derivatives of the cyclic orthoesters **II-42** in quantitive yield. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.32 (5H, m), 5.35 (2H, m), 4.53 (2H, q, J = 12.0 Hz), 3.56 (4H, m), 2.10 (3H, ds); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.0, 169.9, 137.4, 128.4, 127.9, 127.8, 77.2, 73.4, 71.2, 70.8, 29.9, 20.8, 20.7.

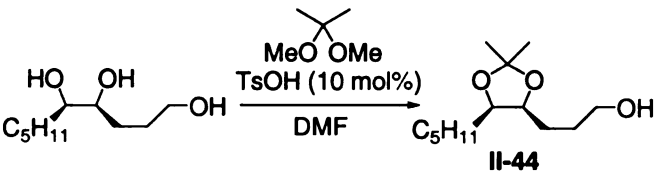
3.5. Data for Chapter 2.3



II-43

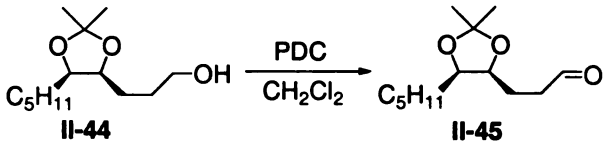
Preparation of Compound II-43: for procedure, please refer to **II-27.**

II-43 was made in quantitive yield. ^1H NMR ($CDCl_3$, 300 MHz) δ 5.81 (1H, m), 5.09 (2H, m), 4.25 (2H, m), 3.25 (3H, s), 2.24 (2H, m), 1.53 (3H, s), 1.48 (2H, m), 1.25 (6H, m, br), 0.84 (3H, m).

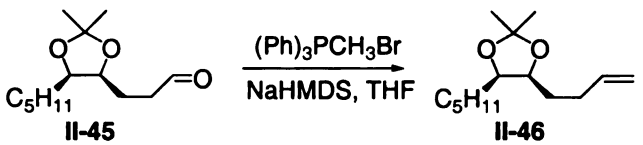


Preparation of Compound II-44: for procedure, please refer to **II-14.**

II-44 was made in 88% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.01 (2H, m), 3.63 (2H, t, J = 6.0 Hz), 2.22 (1H, br), 1.65 (2H, m), 1.55 (2H, m), 1.47 (2H, m), 1.40 (3H, s), 1.30 (3H, s), 1.26 (6H, m, br), 0.85 (3H, m).

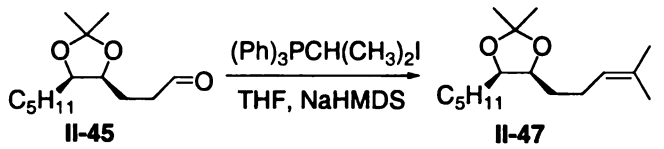


Oxidation of alcohol using PDC: Alcohol **II-44** (3.455 g, 15 mmol) was dissolved in dichloromethane (40 mL) and PDC (8.46 g, 1.5 equiv.) was added. The reaction was stirred at ambient temperature for 24 h. The resulting suspension was filtered and evaporated and purification by column chromatography (20% EtOAc/hexane) afforded aldehyde **II-45** 2.21g (65%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.78 (1H, t, J = 1.8 Hz), 4.03 (2H, m), 2.56 (2H, m), 1.49 (4H, m), 1.38 (3H, s), 1.28 (3H, s), 1.27 (6H, m, br), 0.85 (3H, m).



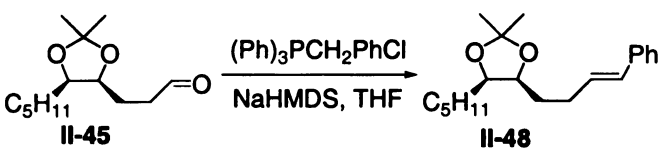
Preparation of Compound II-46: please refer to **II-17.**

II-46 was made in 65% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.81 (1H, m), 4.98 (2H, m), 4.01 (2H, m), 2.22 (1H, m), 2.05 (1H, m), 1.48 (4H, m), 1.40 (3H, s), 1.30 (3H, s), 1.28 (6H, m, br), 0.85 (3H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.2, 114.8, 107.3, 78.0, 77.3, 31.9, 30.3, 29.6, 29.0, 28.6, 26.0, 25.9, 22.5, 14.0.



II-45 **II-47**

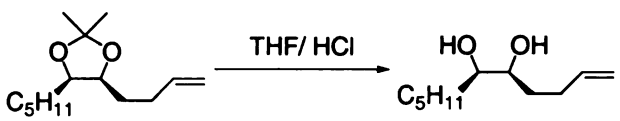
Preparation of Compound II-47: THF (15 mL) was added to *iso*propyltriphenylphosphonium iodide (1.82 g, 3.5 mmol) at 0 °C, and then a THF solution of 1.0 M NaHMDS (4.3 mL, 4.3 mmol) was added at 0 °C. After 30min, aldehyde **II-45** (0.800 g, 3.5 mmol) in THF (15mL) was dropwise added to the reaction mixture and stirring was continued at 0 °C for 30min and then at ambient temperature for 1 h. After addition of saturate NH_4Cl (10 mL), the reaction was extracted with ether (3 x) and washed with brine (1 x) and dried over Na_2SO_4. Flash Chromatography (10% EtOAc/hexane) afforded desired product **II-47** 0.446 g (51%). ^1H NMR ($CDCl_3$, 300 MHz) δ 5.09 (1H, m), 3.98 (2H, m), 2.00 (1H, m), 2.12 (1H, m), 1.65 (3H, s), 1.58 (3H, s), 1.47 (4H, m), 1.39 (3H, s), 1.28 (3H, s), 1.27 (6H, m), 0.85 (3H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 132.0, 123.9, 107.2, 78.1, 77.5, 31.9, 29.9, 29.6, 28.6, 26.0, 25.7, 24.6, 22.5, 17.6, 14.0.



II-45 **II-48**

Preparation of Compound II-48: THF (30 mL) was added to benzyltriphenylphosphonium chloride (1.64 g, 3.5 mmol) at 0 °C, and then a THF solution of 1.0 M NaHMDS (4.3 mL, 4.3 mmol) was added at 0 °C. After 30 min, aldehyde **II-45** (0.800 g, 3.5 mmol) in THF (15 mL) was dropwise added to the reaction mixture and stirring was continued at 0 °C for 30min and then at ambient temperature for 1h. After quenched with saturate NH_4Cl (10 mL), the reaction was extracted with ether

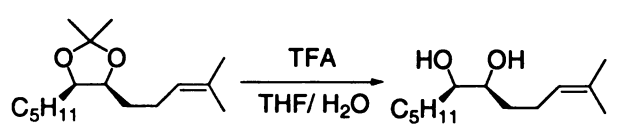
(3 x) and washed with brine (1 x) and dried over Na_2SO_4. Flash chromatography (10% EtOAc/hexane) afforded desired product **II-48** 1.06 g (68%). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.29 (5H, m), 6.24 (1H, m), 5.66 (1H, m), 4.03 (2H, m), 2.38 (1H, m), 2.24 (1H, m), 1.65 (2H, m), 1.49 (2H, m), 1.43 (3H, s), 1.32 (3H, s), 1.28 (6H, m, br), 0.86 (3H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 130.3, 130.0, 128.4, 128.1, 126.9, 125.9, 107.4, 78.0, 77.3, 31.9, 30.2, 29.6, 29.6, 28.6, 26.0, 25.9, 22.5, 14.0.



II-46 **II-49**

Preparation of Compound II-49: For procedure, please refer to **II-18.**

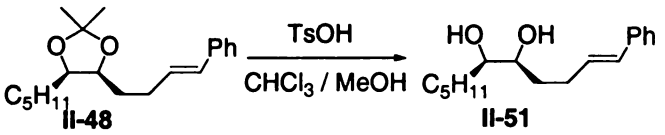
II-49 was made in 71 % yield. ^1H NMR ($CDCl_3$, 300 MHz) δ 5.80 (1H, m), 5.10 (2H, dt, J = 10.8, 1.5 Hz), 3.59 (2H, m), 2.50 (2H, s, br), 2.20 (2H, m), 1.48 (4H, m), 1.25 (6H, m, br), 0.84 (3H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.0, 117.9, 74.0, 73.4, 34.9, 31.8, 31.5, 25.6, 24.1, 22.5, 13.9.



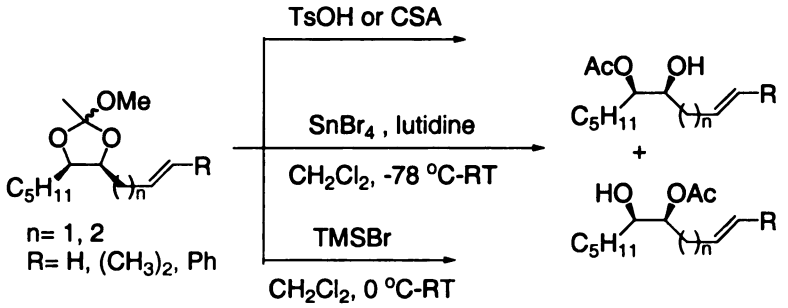
II-47 **II-50**

Preparation of Compound II-50: II-47 (0.446 g, 1.1 mmol) was dissolved in 4:1 THF/H_2O (10 mL) and trifloroacetic acid (0.34 mL) was added. The reaction was stirred overnight. The mixture was extracted with ether (3 x) and the combined organic phase was washed with brine (1 x) and dried with $MgSO_4$. The crude mixture was concentrated under reduced pressure and purification by flash chromatography (75% EtOAc/hexane, 1% MeOH) afforded 0.131 g product **II-50** (35%) and recovered starting material **II-47** 0.240 g. ^1H NMR ($CDCl_3$, 300 MHz) δ 5.11 (1H, m), 3.57 (2H, m), 2.10 (2H, m), 1.67

(3H, s), 1.61 (3H, s), 1.44 (4H, m), 1.28 (6H, m), 0.86 (3H, m). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 134.0, 125.8, 74.1, 73.5, 31.9, 31.6, 28.6, 26.0, 25.3, 24.6, 22.5, 19.3, 14.0.



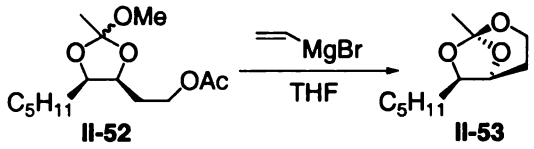
Preparation of Compound II-51: II-48 (0.338 g, 1.2mmol) and TsOH (10 mol%) was dissolved in 1:1 CH_3Cl/MeOH (10 mL) and one drop of water was added. The reaction was stirred overnight. The mixture was concentrated under reduced pressure, dissolved in ether, washed with brine (1 x) and dried with Na_2SO_4. The crude mixture was concentrated under reduced pressure and purification by flash chromatography (75% EtOAc/hexane, 1% MeOH) afforded 0.229 g product **II-51** (78%). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.29 (5H, m), 6.24 (1H, m), 5.66 (1H, m), 3.60 (2H, m), 2.40 (1H, m), 2.28 (1H, m), 1.49 (4H, m), 1.28 (6H, m, br), 0.86 (3H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 130.5, 130.1, 128.5, 126.9, 125.9, 74.7, 74.0, 31.8, 31.3, 30.7, 29.5, 25.6, 22.6, 14.0.



General procedure for Prins cyclization of cyclic orthoesters: Cyclic orthoester prepared from diol (**II-49, II-50** and **II-51)** was dissolved in dichloromethane (0.005 M) under certain temperatures and protic acid (10 mol%) or Lewis acid (1.0 equiv)

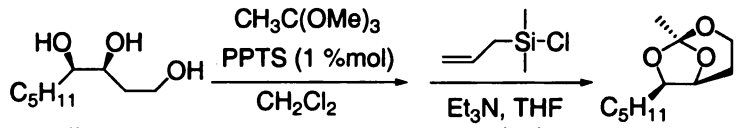
was added. The reaction was stirred overnight. The major products obtained are mixtures of hydrolyzed derivatives of orthoesters.

3.6. Data for Chapter 2.4



II-52 II-53

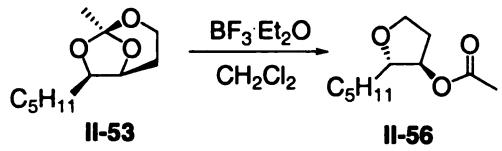
Preparation of Compound II-53: Vinylmagnesium bromide (1.0 M in THF, 2.2 mL) was added to a solution of cyclic orthoester **II-52** (0.274 g, 1.0 mmol) in dry THF (20 mL). After being stirred overnight, the mixture was poured into aqueous NH_4Cl and extracted twice with ether. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography (10% EtOAc/hexane) afforded 0.113 g bicyclic orthoester **II-53** in 57% yield. ^1H NMR ($CDCl_3$, 300 MHz) δ 4.22 (1H, br), 4.04 (2H, m), 3.71 (1H, dd, J = 7.5 Hz), 2.15 (1H, m), 1.78 (1H, m), 1.50 (3H, s), 1.48 (2H, m), 1.26 (6H, m), 0.85 (3H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 118.6, 79.8,. 74.8, 58.7, 31.8, 31.5, 27.7, 26.2, 23.6, 22.6, 13.9.



II-54 II-55

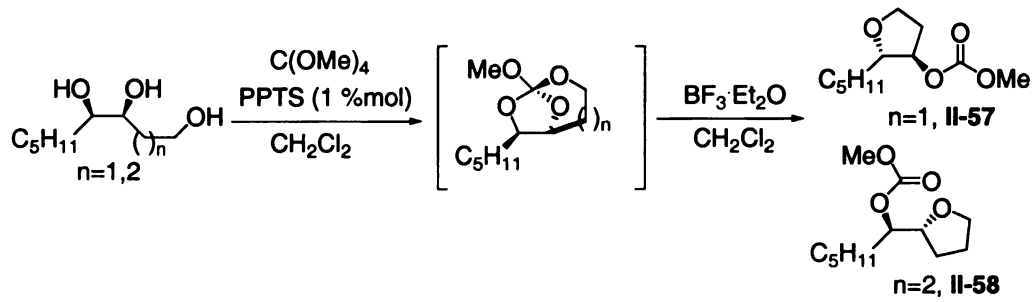
Preparation of Compound II-55: Triol **II-54** (0.095 g, 0.5 mmol), obtained from dihydroxylation of *cis*-4-decen-1-ol, was dissolved in dichloromethane (5 mL) and PPTS (1 mg, 1 mol%) and trimethyl orthoacetate (0.09 mL, 0.75 mmol) was added. The reaction was stirred for 10 min and the solution was concentrated under reduced pressure. The crude intermediate was dissolved in THF (5 mL). Triethylamine (0.11 mL, 0.8

mmol) and allylchlorodimethylsilane (0.101 g, 0.75 mmol) were added consequently. The reaction was stirred at ambient temperature for 1 h and quenched with water. The organic layer was washed with brine (2 x) and then dried with Na_2SO_4. Removal of the solvent afforded 0.100 g crude product bicyclic orthoester **II-55** (100%).



II-53 **II-56**

Preparation of Compound II-56: Bicyclic orthoester **II-53** (0.037 g, 0.18 mmol) was dissolved in dichloromethane (2 mL) and $BF_3 \cdot Et_2O$ (2.4 μL, 0.01 mmol) was added at 0 °C. The crude mixture was concentrated under reduced pressure and purification by flash chromatography (15% EtOAc/hexane) afforded 0.037 g product **II-56** in 100% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.22 (1H, m), 3.98 (1H, q, J = 7.8 Hz), 3.71 (2H, m), 2.25 (1H, m), 2.04 (3H, s), 1.97 (1H, m), 1.51 (2H, m), 1.30 (6H, m, br), 0.85 (3H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.6, 81.7, 74.6, 65.7, 33.4, 31.9, 28.8, 26.0, 22.5, 21.0, 14.0.



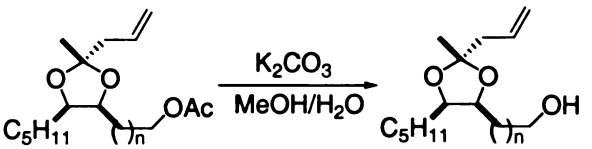
Preparation of Compound II-57 & II-58: For procedure, please refer to **II-38** & **II-56.**

II-57 was made in 94% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.12 (1H, m), 3.98 (1H, q, J = 7.8 Hz), 3.74 (3H, s), 3.72 (2H, m), 2.27 (1H, m), 2.00 (1H, m), 1.57 (2H, m),

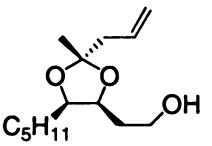
1.26 (6H, m, br), 0.85 (3H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.5, 81.6, 78.5, 65.6, 54.7, 33.4, 31.8, 28.6, 26.1, 22.5, 13.9.

II-58 was made in 67% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.63 (1H, m), 3.88 (1H, m), 3.74 (3H, s), 3.73 (2H, m), 1.87 (2H, m), 1.71 (2H, m), 1.56 (2H, m), 1.26 (6H, m, br), 0.85 (3H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.2, 79.9, 79.5, 68.2, 54.6, 31.6, 30.8, 27.8, 25.9, 24.8, 22.4, 13.9.

3.7. Data for Chapter 2.5

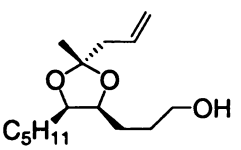


Preparation of compound II-59 & II-60: For procedure, please refer to **II-6.**



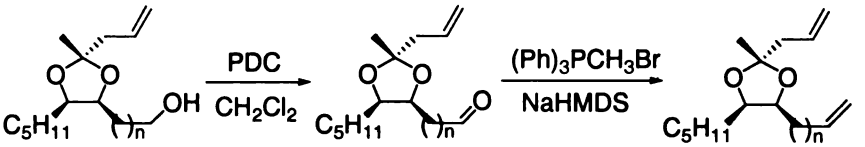
II-59

II-59 was made in 94% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.78 (1H, m), 5.04 (2H, dd, J = 12.6, 4.2 Hz), 4.22 (1H, m), 4.07 (1H, m), 3.78 (2H, m), 2.38 (1H, br), 2.32 (2H, d, J = 6.9 Hz), 1.73 (2H, m), 1.50 (2H, m), 1.35 (3H, s), 1.26 (6H, m, br), 0.84 (3H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 133.6, 118.0, 108.7, 78.2, 77.5, 61.2, 43.9, 32.0, 31.8, 31.6, 29.6, 26.2, 25.9, 22.6, 14.0.

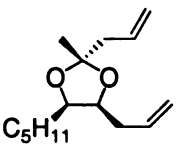


II-60

II-60 was made in 99% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.77 (1H, m), 5.04 (2H, dd, *J* = 11.4, 4.2 Hz), 4.04 (2H, m), 3.64 (2H, q, *J* = 6.0 Hz), 2.32 (2H, d, *J* = 7.2 Hz), 2.15 (1H, br), 1.68 (2H, m), 1.50 (4H, m), 1.34 (3H, s), 1.27 (6H, m, br), 0.85 (3H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 133.9, 117.9, 108.4, 78.4, 78.3, 62.7, 44.0, 31.8, 29.9, 29.8, 26.8, 26.4, 25.9, 22.5, 14.0.

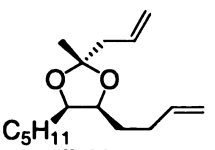


Preparation of compound II-61 & II-62: For procedure of oxidation of alcohol using PDC and Wittig olefination, please refer to **II-44** and **II-17.**



II-61

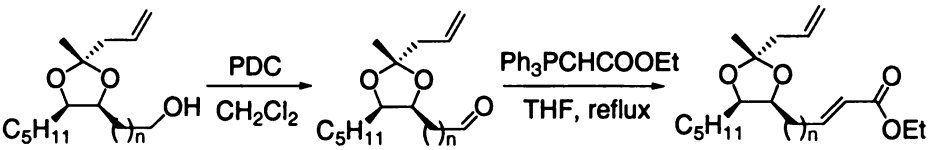
II-61 was made in 35% yield for two steps. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.83 (2H, m), 5.06 (4H, m), 4.22 (1H, m), 4.08 (1H, m), 2.33 (2H, d, *J* = 7.2 Hz), 2.19 (2H, m), 1.48 (2H, m), 1.35 (3H, s), 1.26 (6H, m, br), 0.84 (3H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 134.8, 133.8, 117.8, 116.9, 108.4, 78.2, 77.6, 44.0, 34.6, 31.8, 29.6, 26.4, 25.9, 22.5, 14.0.



II-62

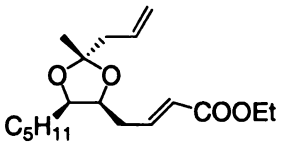
II-62 was made in 71% yield for two steps. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.77 (2H, m), 5.00 (4H, dd, m), 4.02 (2H, m), 2.32 (2H, d, *J* = 7.2 Hz), 2.22 (1H, m), 2.05 (1H, m), 1.47 (4H, m), 1.34 (3H, s), 1.28 (6H, m, br), 0.84 (3H, m); ^{13}C NMR ($CDCl_3$, 75

MHz) δ 138.2, 134.0, 117.7, 114.8, 108.3, 78.3, 77.6, 44.1, 31.9, 30.3, 29.8, 29.2, 26.4, 25.9, 22.5, 14.0.



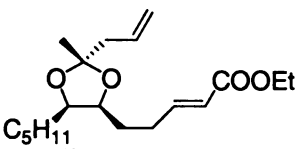
Preparation of compound II-63 & II-64: For procedure of oxidation of alcohol using PDC, please refer to **II-44.**

General procedure of HWE reaction: The crude aldehyde was dissolved in THF (0.1 M) and triphenylphosphine ylide (1.5 equiv) was added. The suspension was then heated to reflux for 3 h. After quenched with saturate NH_4Cl (10 ml), the reaction was extracted with ether (3 x) and washed with brine (1 x) and dried over Na_2SO_4. Flash chromatography (5% EtOAc/hex, 5% TEA) afforded desired product.



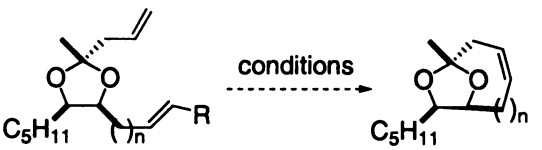
II-63

II-63 was made in 65% yield for two steps. ^1H NMR ($CDCl_3$, 300 MHz) δ 6.95 (1H, dt, J = 15.6, 6.9 Hz), 5.87 (1H, d, J = 15.6 Hz), 5.77 (1H, m), 5.05 (2H, dd, J = 13.8, 1.5 Hz), 4.16 (2H, q, J = 7.2 Hz), 4.11 (2H, m), 2.33 (2H, d, J = 7.5 Hz), 2.30 (2H, m), 1.49 (2H, m), 1.35(3H, s), 1.30 (6H, m, br), 1.26 (3H, t, J = 7.2 Hz), 0.87 (3H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.3, 145.1, 133.7, 123.4, 118.0, 108.8, 78.2, 74.6, 60.2, 43.9, 33.4, 31.8, 29.6, 26.3, 26.0, 22.5, 14.2, 14.0.

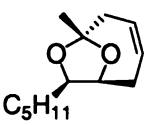


II-64

II-64 was made in 71% yield for two steps. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.95 (1H, p, *J* = 7.8 Hz), 5.81 (1H, d, *J* = 15.6 Hz), 5.76 (1H, m), 5.05 (2H, dd, *J* = 13.2, 4.8 Hz), 4.15 (2H, q, *J* = 7.2 Hz), 4.01 (2H, m), 2.33 (2H, d, *J* = 6.9 Hz), 2.30 (1H, m), 1.61 (1H, m), 1.46 (4H, m), 1.32 (3H, s), 1.27 (9H, m, br), 0.87 (3H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.5, 148.3, 133.8, 121.7, 117.8, 108.4, 78.2, 77.3, 60.1, 44.0, 31.8, 29.6, 28.8, 28.5, 26.4, 26.0, 22.5, 14.2, 14.0.



General procedure for RCM on model substrates: Bis-alkene (**II-61, II-62, II-63 & II-64**) was dissolved in toluene (0.004 M) and four portions of **A** (80 mol% in total) or **B** (20 mol% in total) was added every 45 min and the mixture was refluxed. The reaction was monitored by TLC. The reaction mixture was filtered through a thin silica pad and the solvent was evaporated to afford crude product.



II-65

II-65 was obtained as a mixture of more than two compounds which can not be purified even after hydrogenation of the double bond. Both ^{13}C NMR and GC-MS suggested the existence of cyclized product. Characteristic ^{13}C NMR ($CDCl_3$, 125 MHz) δ 128.7, 128.4, 126.5, 126.1, 110.1, 81.3, 79.6; GC-MS *m/z* 210 M^+, 139 $[M\text{-}C_5H_{11}]^+$.

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