CARBON-CARBON BOND CONSTRUCTION USING ELECTRON TRANSFER INITIATED CYCLIZATION REACTIONS. RUTHENIUM-CATALYZED HYDROESTERIFICATION AND ITS APPLICATION TOWARDS THE SYNTHESIS OF INTEGRAMYCIN

by

Lijun Wang

BS, Nanjing University, 1997

MS, University of Pittsburgh, 2003

Submitted to the Graduate Faculty of

Arts and Sciences in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh

2005

UNIVERSITY OF PITTSBURGH

FACULTY OF ARTS AND SCIENCES

This dissertation was presented

by

Lijun Wang

It was defended on

July 19th, 2005

and approved by

Kay Brummond

Dennis P. Curran

Billy Day

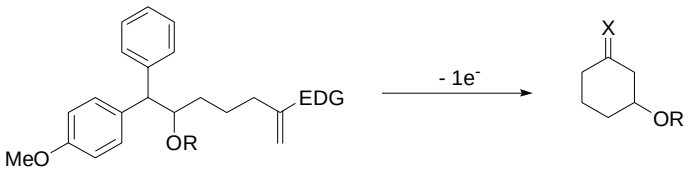
Paul E. Floreancig
Dissertation Director

CARBON-CARBON BOND CONSTRUCTION USING ELECTRON TRANSFER INITIATED CYCLIZATION REACTIONS. RUTHENIUM-CATALYZED HYDROESTERIFICATION AND ITS APPLICATION TOWARDS THE SYNTHESIS OF INTEGRAMYCIN

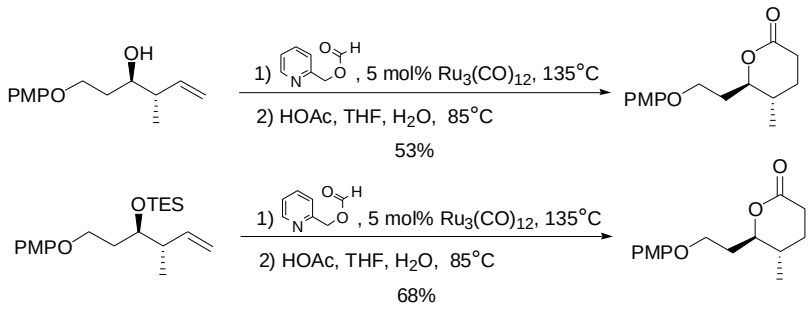
Lijun Wang, PhD

University of Pittsburgh, 2005

Electron transfer initiated cyclization reactions were successfully applied to the construction of carbon-carbon bonds after tuning the chemoselectivity and reactivity of the substrates. Olefins and allenes with several different electron-donating groups served as good nucleophiles in cyclization reactions to generate various carbocycles. Cascade cyclizations involving C-C bond formation also proved to be successful. In most cases, cyclizations gave good to excellent yields with short reaction times.



A general protocol has been developed for synthesizing lactones from allylic and homoallylic alcohols using ruthenium-catalyzed hydroesterifications. The lactone synthesis only requires 1-2 steps and can be conducted in one pot. The experimental procedure is simple and the efficiency is considerably improved compared to that of multi-step sequences. Mechanistic studies with deuterium labeling showed that the competition between hydrometalation, β-hydride elimination, and reductive elimination determines the efficiency and regioselectivity of the hydroesterification reactions.



Two major fragments of integramycin have been synthesized. The synthesis of the C16-C35 spiroketal unit of integramycin was accomplished in a convergent and stereoselective manner. The sequence includes the usage of a highly efficient ruthenium-mediated hydroesterification reaction. This sequence also demonstrates the efficiency of C,O-dianioic additions into lactones as a method for producing spiroketals in a single operation without recourse to extensive protecting group manipulations. The synthesis of the *cis*-decalin unit of integramycin was achieved using a cycloaddition and an allylic rearrangement as key steps. The dienyne substrate of the cycloaddition was synthesized enantioselectively in 36% yield over 9 steps. The conditions of the cycloaddition using [(naph)Rh(cod)]SbF_6 were optimized and the diastereoselectivity of the cycloaddition was found to be temperature and solvent dependant.

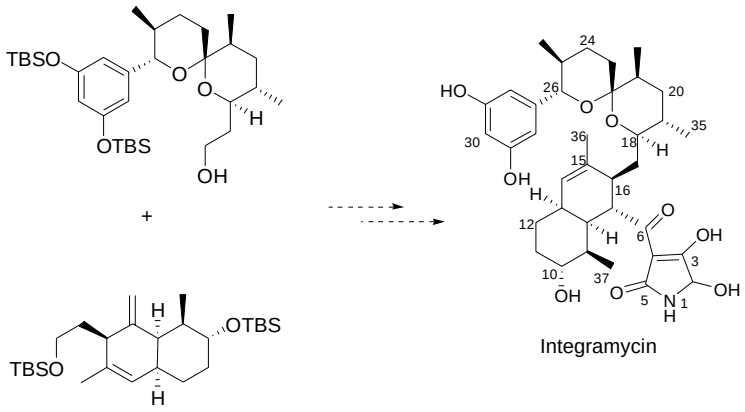


TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SCHEMES

LIST OF ABBREVIATIONS

AIBN	2,2′-Azobisisobutyronitrile
9-BBN	9-Borabicyclo[3.3.1]nonane
BHT	Butylated hydroxytoluene
Bn	Benzyl
CI	Chemical ionization
COD	1,5-Cyclooctadiene
DCE	1,2-Dichloroethane
DEAD	Diethyl azodicarboxylate
DIAD	Diisopropyl azodicarboxylate
DHP	2,3-Dihydropyran
DIBAH	Diisobutylaluminum hydride
DIPEA	Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMPI	Dess-Martin periodinane
DMSO	Dimethylsulfoxide
dr	Diastereomeric ratio
ee	Enantiomeric excess
EI	Electron impact ionization
ESI	Electron spray ionization
GC	Gas chromatography
HIV-1	Human immunodeficiency virus 1
HRMS	High-resolution mass spectrometry
Imi	Imidazole
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
LDBB	Lithium *p*,*p*′-di-*t*-butylbiphenylide
*m*CPBA	*meta*-Chloroperoxybenzoic acid

MOM	Methoxymethyl
NMO	4-Methylmorpholine *N*-oxide
$NMQPF_6$	*N*-methylquinolinium hexafluorophosphate
Ms	Methanesulfonyl
naph	Naphthalene
NBSH	*o*-Nitrobenzenesulfonylhydrazine
NOE	Nuclear Overhauser Effect
NOESY	A 2D NOE related experiment
P or PG	Protecting group
PMP	*para*-Methoxylphenyl
PPTS	Pyridinium *para*-toluene sulfonate
RCM	Ring closing metathesis
SET	Single electron transfer
TBAF	Tetrabutylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
TBSCl	*tert*-Butyldimethylsilyl chloride
TBSOTf	*tert*-Butyldimethylsilyl triflate
TES	Triethylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Ts	*p*-Toluenesulfonyl
TS	Transition state

ACKNOWLEDGEMENTS

This is probably the best opportunity for me to express my appreciation to many people who have helped me. First of all, I would like to thank my advisor Dr. Paul E. Floreancig. He has been a fantastic advisor to work for in the past five years. Thank him for the challenging and rewarding projects, for showing me the way to the chemistry world, and for his effort to make me a better chemist.

I would like to think Dr. Brummond, Dr. Curran, and Dr. Day for the guidance they gave me as my committee members, and thank Dr. Wipf for serving as my proposal mentor. Their help and advices are greatly appreciated. I would also like to thank many graduate students and post docs in the Chemistry Department that helped me in providing inspiring discussions and sharing reagents. All the faculty and students in the Department together have made a friendly and supportive environment to work in. The past five years have amounted to an incredible experience for me.

The road I have been through hasn't been always even, and I will certainly need to thank my parents, family, and many friends for their support. Especially thank my wife Jia for her support in all aspects and her understanding when I "devoted" the majority of my time to chemistry.

Many thanks to my lab mates as well. Their generous help was another reason that made me go this far. Danielle, Satish, and Chris, you guys really helped me a lot at the beginning when I just started and thereafter. Butch and Jay, we encouraged each other and shared a lot of happy and rough times in the lab as well as in basketball and football games. Alex, Mike, Conor, Shuangyi, Wangyang, Jen, and Hyung-Hoon, good luck and now it is up to you guys to make the group even stronger…

Chapter 1. Carbon-carbon bond construction using electron transfer initiated cyclization reactions

1.1 Introduction

Single electron transfer (SET) has attracted increasing attention in the past two decades in search for new synthetic methods as many important reactions have been found to proceed through SET mechanisms.[1] The extensive investigation has led to numerous publications and applications. Examples include Burch reduction,[2] Ullmann coupling,[3] preparation of alkyllithium from alkyliodides[4,5] or phenyl thioethers,[6] photosensitized isomerizations and rearrangements.[7]

Radical ions, generated from single electron reduction or oxidation of neutral molecules, are capable of undergoing a variety of reactions.[8,9] The reaction conditions are usually mild, non-acidic, and tolerant of many functional groups. For example, properly designed radical cations can undergo mesolytic cleavage of generally inert bonds, forming radical fragments and cationic fragments. The cationic fragments can serve as good electrophiles that otherwise require acidic conditions for their generation.

Not confined to chemistry, the electron transfer process also plays a key role in many other science and technology fields, such as in semiconductor photocatalysis, xerography, photography and others.[7] In biological systems, many transformations proceed in SET mechanisms, such as oxidative phosphorylation, DNA-photolyase reaction,[7] and the important photosynthesis that provides the major energy source to creatures on the earth.

1.1.1 Radical ions

In an SET process, one-electron reduction or oxidation of a neutral substrate generates a radical anion or radical cation. A simple illustration of the molecular orbital change is shown in Figure 1.1.[10]

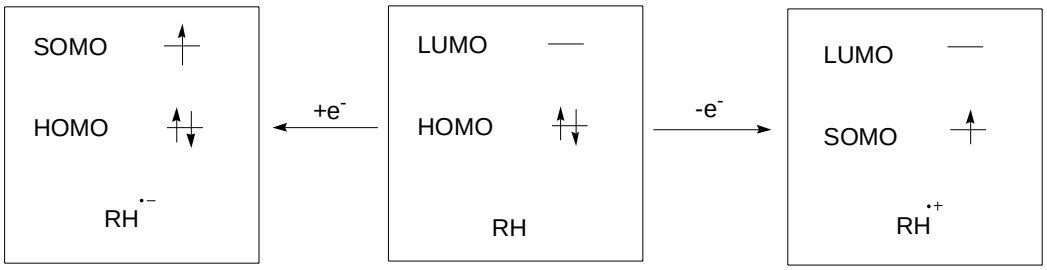


Figure 1.1. The formation of radical ions by SET processes.

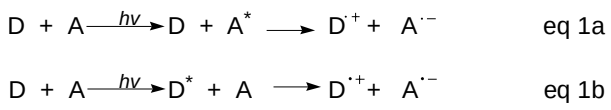
In the following a few paragraphs, the generation and some typical reactions of radical ions will be discussed.

1.1.2 Formation of radical ions

1.1.2.1 Photoinduced electron transfer

Photoinduced electron transfer can be considered as a process where light energy is absorbed and transformed into chemical energy.[7] In most cases, target molecules do not have the ability to absorb or transform photoenergy; therefore the presence of a photosensitizer is necessary to relay the energy from light. Upon photoexcitation, a photosensitizer induces a chemical change to its neighboring molecule by single electron transfer mechanism. In case 1a) of Scheme 1.1, a photosensitizer serves as an electronically excited acceptor (A) to oxidize the donor (D) into a

radical cation. In the case of 1b) a photosensitizer serves as an electron donor (D) to reduce A into a radical anion.[7,10]

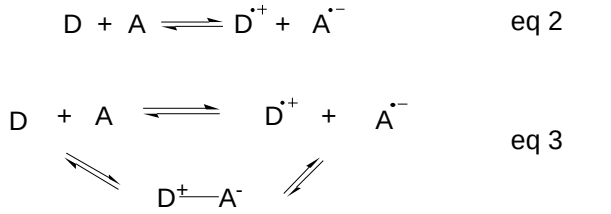


Scheme 1.1. Photoinduced electron transfer.

Because of the large amount of energy provided by photons (~360 KJ/mol for UV light), photoinduced electron transfer is a great way to generate radical ions that may be difficult to achieve by other routes. However, the selectivity of the reactions under photochemical conditions might be poor and photosensitive functional groups could be destroyed.

1.1.2.2 Chemical oxidation

Generating radical cations by ground state oxidation of neutral molecules is also commonly employed. It is operationally simpler than photooxidation and does not need special apparatus. However, this method might not oxidize substrates with high oxidation potentials. The scenario is described in equation 2 of Scheme 1.2:



Scheme 1.2. ET under ground state oxidation conditions.

Although equation 2 is a simple representation of ET, the process could be more complicated. The encounter between donors and acceptors can lead to outer-sphere electron transfer to form $A^{\bullet-}$ and $D^{\bullet+}$, or lead to a polar association with bond formation to generate $D^{+}—A^{-}$, which can then undergo inner-sphere dissociation to form $A^{\bullet-}$ and $D^{\bullet+}$. The recombination between $A^{\bullet-}$ and $D^{\bullet+}$ is also possible (equation 3 of Scheme 1.2).[9]

A list of commonly used chemical oxidants is discussed below.

Ce(IV)

Ceric ammonium nitrate (CAN) is one of the most commonly used chemical oxidants. It is stable and commercially available at a low price. It is soluble in water and polar organic solvents such as alcohols, acetone, and acetonitrile. In less polar solvents such as 1,2-dichloroethane (DCE) or dichloromethane it is insoluble, but when using $[Bu_4N][HSO_4]$ as a phase-transfer catalyst reactions can be carried out in $CHCl_3$.[11] Alternatively, ceric bis(tetra-*n*-butylammonium) nitrate (CTAN), another source of Ce(IV) which is soluble in less polar solvents such as CH_2Cl_2, can be easily made and applied in reactions.[12]

The oxidation potential of Ce(IV) varies depending on the counterions and solvents. For example, Ce(IV) has an oxidation potential $E^{o\prime}$ of 0.88 V (*vs.* Fc) in water, while in $HClO_4$, the value is 1.30 V (*vs.* Fc).[13] Ce(IV) can react through either inner sphere (coordination followed by electron transfer) or outer sphere (electron transfer without prior coordination) mechanisms.

Ag(I)

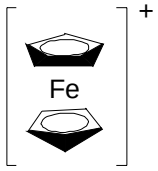
Silver(I) salts are also excellent one-electron oxidants and are widely used, although they are more expensive than cerium salts. Silver(I) salts are soluble in different types of organic solvents

such as CH_2Cl_2, acetone, THF, MeCN, alcohols and toluene. An advantage of silver(I) salts is that their oxidation strength is adjustable according to the solvents and counterions. For example, $AgPF_6$ in acetone has an $E^{o\prime}$ of 0.18 V (*vs.* Fc), while in CH_2Cl_2, the $E^{o\prime}$ value is *ca.* 0.65 V (*vs.* Fc).[13]

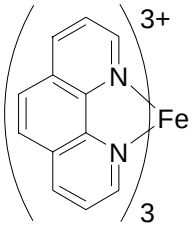
In addition to oxidation, the silver(I) ion may abstract halide or bind to the oxygen or sulfur in the presence of these atoms in a reaction.[13] Also, silver(I) salts are usually hygroscopic and photosensitive, therefore their handling might need extra caution. As a consequence, silver salts may not be applicable in reactions involving complex molecules.

Fe(III)

Mainly, two iron(III) complexes are widely used: ferrocenium ion, $[FeCp_2]^+$ and phenanthrolineiron(III), $[Fe(phen)_3]^{3+}$.



$[FeCp_2]^+$



$[Fe(phen)_3]^{3+}$

Adjusting the ring substitution pattern can alter the oxidation potential of the ferrocenium ion. The $E^{o\prime}$ values of ferrocenium ions vary from –0.63 V (for $[Fe(\eta\text{-}C_5H_4NMe_2)_2$, *vs.* Fc][14] to 0.64 V (for $[Fe(\eta\text{-}C_5H_4CF_3)_2]$, *vs.* Fc).[15] The oxidation potential of the parent ferrocene/ferrocenium ion (Fc) is found to be almost constant in various solvents, making it desirable as a standard electrode to replace standard calomel electrode (SCE).[16]

Phenanthrolineiron(III) is also a mild one-electron oxidant with oxidation potentials that are adjustable by tuning the ligand substituents. For example, depending on the substituent X, the trications $[Fe(phenX_2\text{-}4,7)_3]^{3+}$ give oxidation potentials from 0.6 V (*vs.* Fc, X = H) to –0.26 V [*vs.* Fc, X = $NH(CH_2)_3NH_2$].[13] Fe(III) oxidants are cheap and readily accessible, but they usually have high molecular weights because of the number of ligands they bear. Thus, the mass amount of Fe(III) salts to be used in reactions can be large.

There are many other one-electron oxidants such as 2,3-dichloro-5,6-dicyanoquinone (DDQ, $E^{o\prime}$ = 0.13 V *vs.* Fc in MeOH)[13], which is also commonly used.

1.1.2.3 Anodic oxidation

Generating radical cations through single electron transfer between an electrode and a substrate in solution is also well precedented.[17-19] The electrode potential can be controlled to the desired value according to the desired transformation, hence, this is a good method that provides chemo- and regioselectivities.[8] Also, the neutral reaction conditions allow a wide range of functional groups.[19] Moreover, anodic oxidation has been called an environmentally benign method since no chemical oxidants are used, as noted by Connelly who states: "Electrodes are among the most benign reagents in synthetic applications".[13] Polar solvents such as methanol, THF, CH_2Cl_2, and acetonitrile are often used under anodic conditions. The presence of electrolytes such as lithium perchlorate, tetraethylammonium tosylate, and tetrabutylammonium tetrafluoroborate is also necessary to increase the conductivity of the solution and to provide counterions of the intermediates around the electrodes.[19]

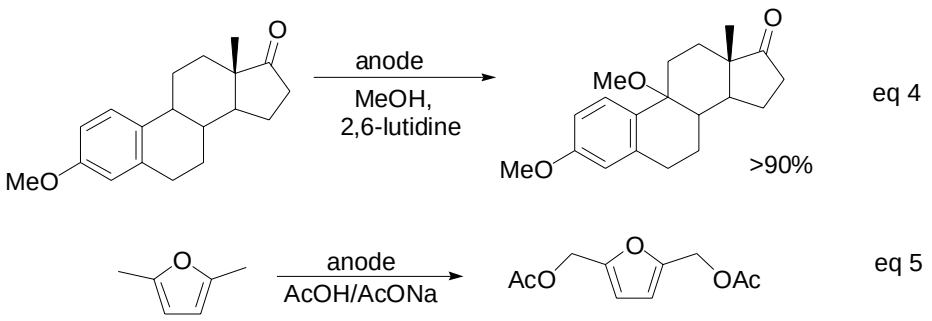
1.1.3 Reaction pathways of radical cations

Radical cations are highly reactive and can undergo several types of reactions depending on the property of the substrate and the reaction conditions. The main transformations are: C-C

bond dissociation, C-H bond dissociation (deprotonation), C-Si bond dissociation and others, as summarized by Schmittel.[8]

1.1.3.1 C-H bond dissociation

C-H dissociation is a major pathway that many radical cations undergo, and numerous reports have shown the applications of this pathway. In equation 4 of Scheme 1.3, the benzylic proton on the tertiary carbon was deprotonated preferentially, and the resulting tertiary carbon radical was further oxidized to a carbocation, which was attacked by methanol to give the product.[20]

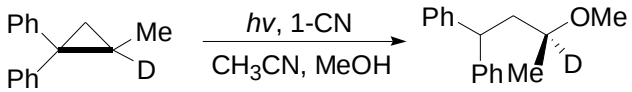


Scheme 1.3. C-H bond dissociations.

In equation 5, two allylic protons were deprotonated, followed by the same sequence in equation 4 to generate the diacetate product (no yield was given).[21]

1.1.3.2 C-C bond dissociation

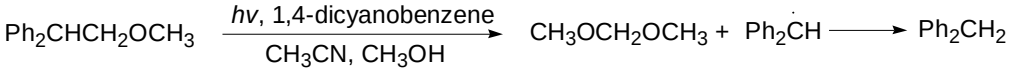
C-C bond dissociation often needs a special driving force to compete with C-H bond activation, which is why initial studies employed strained substrates to achieve C-C bond cleavage. Dinnocenzo and coworkers showed that the radical cation of optically active cyclopropane underwent a S_N2 type replacement by methanol from the back of the ring to give the ring-opened product with an inverted stereocenter at C2 (Scheme 1.4).[22]



1-CN = 1-cyanonaphthalene

Scheme 1.4. C-C bond dissociation of a cyclopropane.

Arnold and coworkers[23] demonstrated that by adjusting the substituent pattern, C-C bond activation is preferred over C-H activation (Scheme 1.5). The diphenylethyl ether substrate underwent C-C bond cleavage and generated an acetal and diphenylmethane that is consistent with the formation of the diarylmethyl radical. In this type of substrate, the two phenyl rings decrease the C-C bond dissociation energy of the single-electron species sufficiently to lead to of C-C bond cleavage in preference to C-H bond cleavage.



Scheme 1.5. C-C bond dissociation of a diphenylethyl ether.

An important rule regarding C-C or C-H bond cleavage is depicted in Figure 1.2.[8] In this type of radical cation, A-B bond cleavage is preferential to the A-arene bond cleavage. This is attributed to the overlap between the σ* orbital of the A-B bond and the π system of the phenyl which weakens the A-B bond. Also, the orbital alignment stabilizes the incipient radical generated from A-B bond cleavage. Indeed, the cleavage of the A-arene bond is seldom observed.

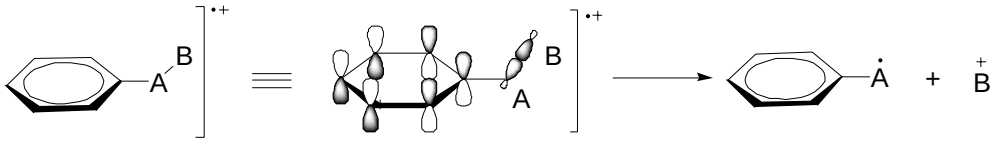


Figure 1.2. A-B bond cleavage is preferred over arene-A.

Baciocchi and coworkers[24] found that the deprotonation of *p*-neopentyltoluene happens predominately at the methyl group on the benzene ring, because in its most stable conformation (Figure 1.3), the C-H bonds in the neopentyl group do not align to the SOMO orbital of the radical cation, which is not suitable for the cleavage according to the rule stated above. These results indicate that both thermodynamics of bond cleavage and orbital alignment considerations influence the rates of bond cleavage reactions.

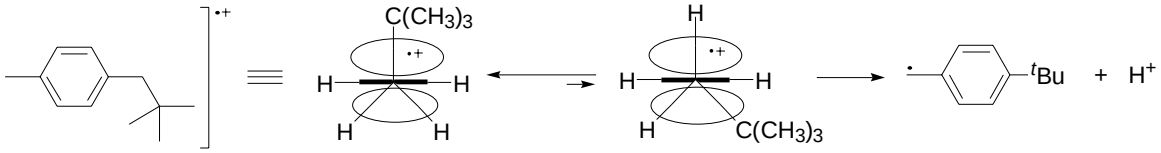
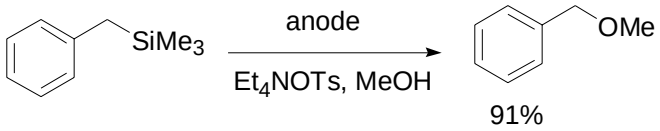


Figure 1.3. Relationship between the SOMO orbital and the bond to be cleaved.

1.1.3.3 C-Si bond dissociation

In the presence of heteroatoms (Si, S and others), C-X bond dissociation is another possible reaction pathway for radical cations.

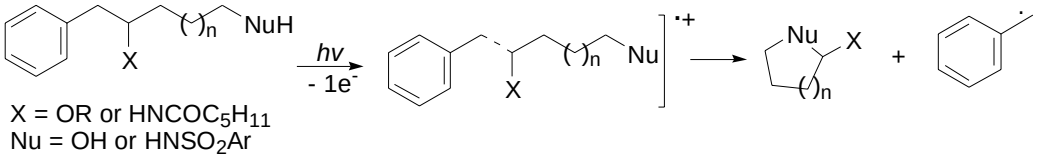
In Scheme 1.6, the trimethylsilyl group acted as a proton surrogate (C-$SiMe_3$ cleavage *vs.* C-H cleavage). The initially formed radical cation from the neutral molecule fragmented at C-Si bond to form the benzylic radical and the trimethylsilyl cation. The benzyl radical was further oxidized to a carbocation, which was attacked by methanol to give the product.[25]



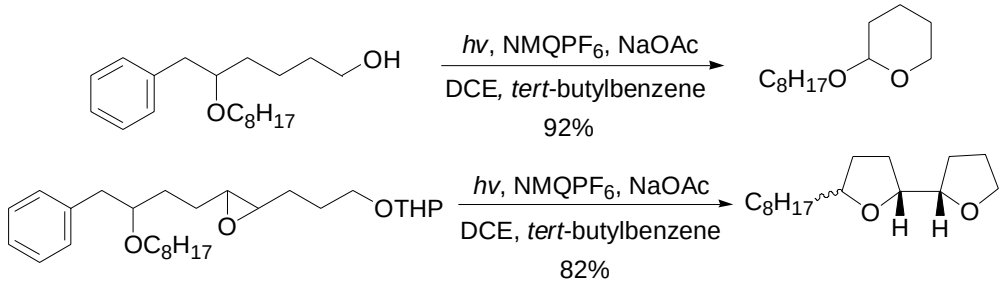
Scheme 1.6. C-Si bond cleavage.

1.1.3 ETIC reactions

Prompted by the advances in mechanistic understanding of ET reactions, our group has developed a new cyclization method — electron transfer initiated cyclizations (ETIC).[26] The general form of ETIC reactions is shown in Scheme 1.7. The substrate is initially oxidized to a radical cation with a weakened benzylic C-C bond, then the benzylic radical serves as a leaving group that is displaced intramolecularly by oxygen or nitrogen nucleophiles to give rise to the heterocycles. Many furanosides, pyranosides, and other heterocyclic ring systems have been prepared using this method.[27,28] Two examples are shown below in Scheme 1.8.



Scheme 1.7. Electron transfer initiated cyclization reactions.

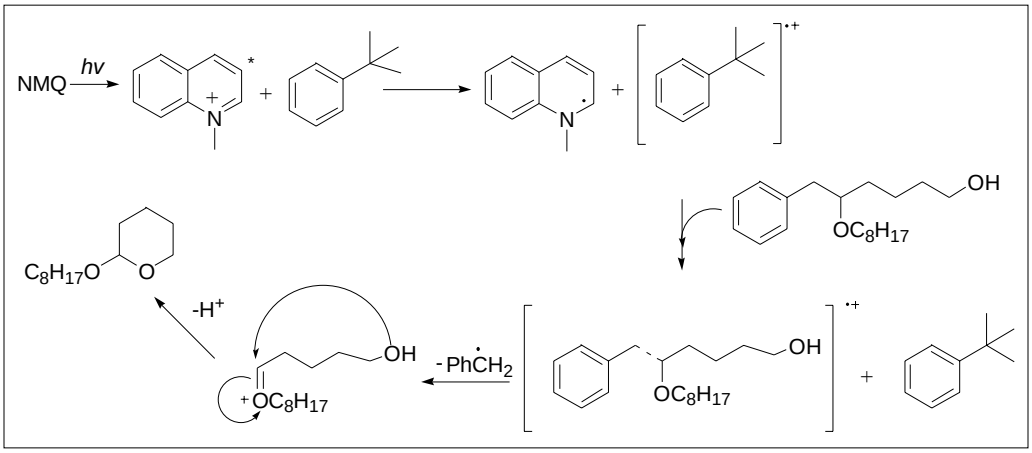


Scheme 1.8. Examples of ETIC reactions.

The unique strategy of ETIC reactions has great potential in designing novel synthetic pathways. This strategy allows the use of a benzyl radical as the leaving group, and it is feasible to incorporate the inert benzyl group into the substrate in the early stage of a synthesis. The relatively mild reaction conditions tolerate acid- or base-sensitive groups, and the

chemoselectivity of the oxidation and the reactivity of the system can be tuned by introducing substituents onto the arene and benzylic positions respectively. Finally, various types of nucleophiles are expected to be reactive with the highly electrophilic (radical) cations.

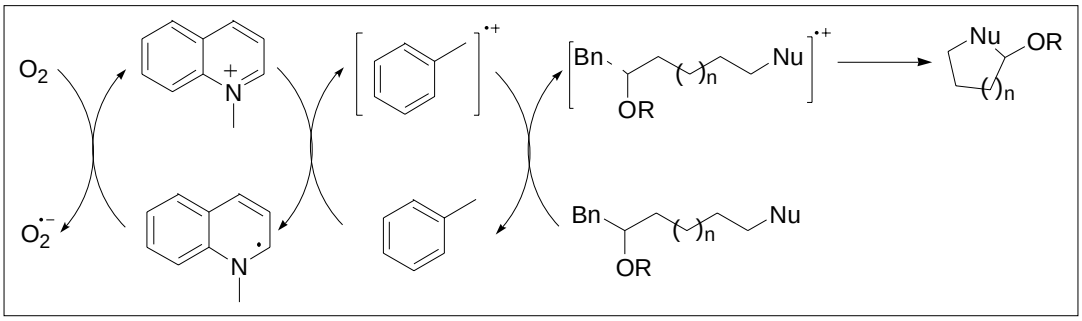
The mechanism of ETIC reactions is illustrated in Scheme 1.9.[29] In the reaction, *N*-methylquinolinium hexafluorophosphate ($NMQPF_6$) serves as the cationic photosensitizer to initiate the reaction, *tert*-butylbenzene is the cosensitizer, relaying the energy from excited $NMQPF_6$ to the cyclization substrate, 1,2-dichloroethane (DCE) is the solvent, and NaOAc is a base to neutralize any acid that is formed in the reaction.



Scheme 1.9. The mechanism of ETIC reactions.

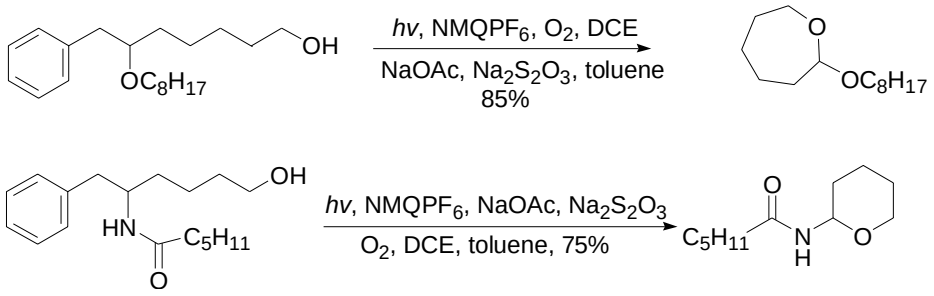
In the sequence shown above, it is necessary to use excess amount of $NMQPF_6$ (usually 2 equivalents), but large amounts of $NMQPF_6$ can make product isolation difficult. In order to improve the efficiency, we developed a catalytic protocol (Scheme 1.10).[29] $NMQPF_6$ is used in a catalytic quantity and O_2 is the terminal oxidant. As little as 2.5 mol % of $NMQPF_6$ was found to be sufficient to drive the cyclization reactions to completion. Solid $Na_2S_2O_3$ is applied in the reactions to reduce reactive oxygen species such as superoxide and benzylperoxy radicals that

arise in the reactions. The more volatile and less expensive cosensitizer toluene was used to replace *tert*-butylbenzene, further facilitating product isolation.



Scheme 1.10. Aerobic quinolinium catalyst regeneration.

Many cyclizations were performed under catalytic conditions and afforded yields comparable or superior to those when $NMQPF_6$ was used stoichiometrically (Scheme 1.11).[29] Catalytic conditions also allow ETIC reactions to be conducted on multi-gram scale.



Scheme 1.11. Aerobic ETIC reactions.

1.1.4 Adjusting chemoselectivity and reactivity

Tuning the reactivity and chemoselectivity of the cyclization substrates will allow a broader range of nucleophiles and reaction conditions. In order to understand the relationship between

radical cation reactivity and the substrate structure, equation 6 can be used, which is derived from a thermodynamic cycle:

$$A\text{—}B \rightarrow A^{\bullet} + B^{\bullet} \qquad \text{BDE(S)}$$

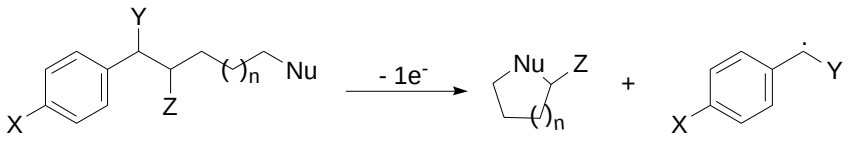
$$B^{\bullet} \rightarrow B^{+} + e^{-} \qquad E_{pa}(E)$$

$$\underline{A\text{—}B^{\bullet+} + e^{-} \rightarrow A\text{—}B} \qquad \underline{-E_{pa}(S)}$$

$$A\text{—}B^{\bullet+} \rightarrow A^{\bullet} + B^{+} \qquad \text{BDE(RC)}$$

$$\text{BDE(RC)} = \text{BDE(S)} - E_{pa}(S) + E_{pa}(E) \qquad \text{eq 6}$$

In the equation, BDE(RC) defines the mesolytic bond dissociation energy of the radical cation, BDE(S) is the homolytic bond dissociation energy of the same bond in the neutral substrate, $E_{pa}(S)$ defines the oxidation potential of the substrate, and $E_{pa}(E)$ is the oxidation potential of the radical corresponding to the fragment that ultimately becomes the electrophile.

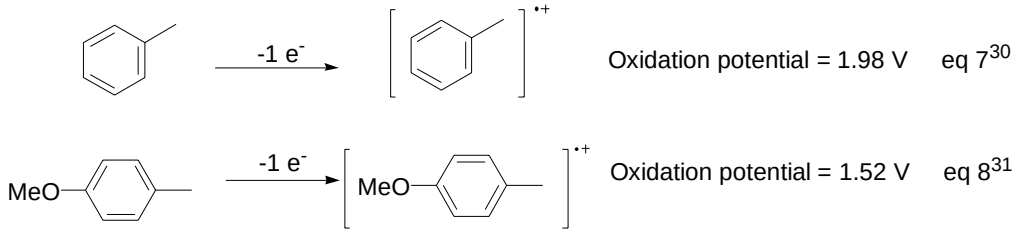


X = oxidation potential modulating group
Y = reactivity modulating group
Z = electron-donating group
Nu = nucleophilic group

Scheme 1.12. Tuning the reactivity and chemoselectivity of ETIC substrates.

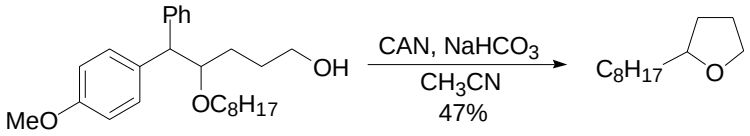
With regards to our cyclization substrates (Scheme 1.12), the placement of a methoxy group in the *para* position of the phenyl ring (X = OMe) is expected to lower the oxidation potential of the arene part by ~0.5 V (derived from Scheme 1.13),[30,31] which is anticipated to improve the chemoselectivity of the reaction and allow the incorporation of sensitive nucleophiles into the substrate. Although this change stabilizes the radical cation and increases the benzylic bond dissociation energy by approximately 11 kcal/mol, an additional phenyl group (Y = Ph in

Scheme 1.12) at the benzylic position can partially offset this stabilizing effect by activating the radical cation, and decreasing the bond dissociation energy by 4-8 kcal/mol while providing good reactivity.



Scheme 1.13. Adjusting the chemoselectivity.

The incorporation of a *para*-methoxy group lowers the oxidation potential of the substrate. Consequently, milder oxidation conditions with CAN can be used to initiate the reactions, in addition to photochemical conditions. The following cyclization used ceric ammonium nitrate (CAN) as the oxidant and gave a 47% yield (Scheme 1.14).[32] Changing the reaction conditions to ground state oxidation conditions using CAN simplifies both the reaction procedures and the reaction equipment.

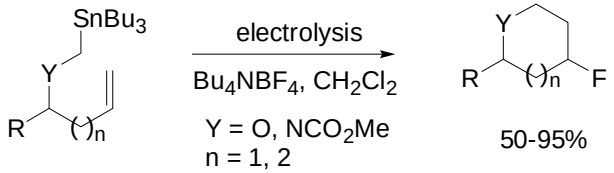


Scheme 1.14. ETIC reactions under oxidation conditions using CAN.

1.1.5 Construction of C-C bonds

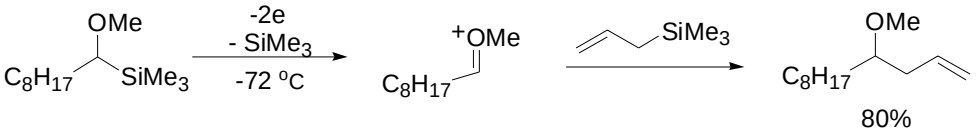
The construction of carbon-carbon bonds using electron transfer reactions has been reported. Yoshida and coworkers (Scheme 1.15)[33] used anodic oxidation of α-stannyl ethers to generate

oxygen-stabilized carbocations, which underwent nucleophilic attack by C-C π-bonds to form heterocycles. Fluoride ions served as external nucleophiles to quench the reactions.



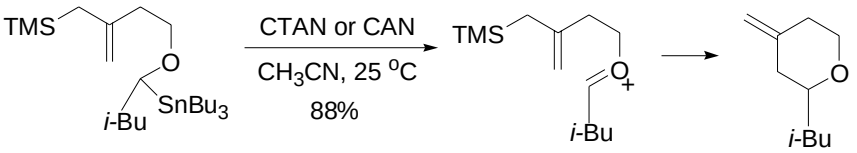
Scheme 1.15. Construction of C-C bond using α-stannyl ethers.

In their more recent work (Scheme 1.16)[17] they showed that under electrolysis conditions, α-silyl ethers underwent SET oxidation twice, losing 2 electrons and the trimethylsilyl group to generate alkoxycarbenium ions. Allyltrimethylsilane and other nucleophiles then attacked the alkoxycarbenium ions to form new C-C bonds. The non-nucleophilic solvent deuterated dichloromethane was used in the reaction and, to improve the conductivity of the solution, the electrolyte tetrabutylammonium tetrafluoroborate was used.



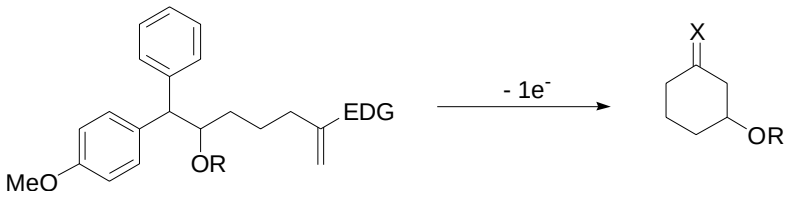
Scheme 1.16. Formation of C-C bond using α-silyl ethers.

Mariano and Chen[34] used chemical oxidation conditions with CAN or CTAN to construct C-C bonds (Scheme 1.17). The oxocarbenium ions formed after oxidative cleavage of C-Sn bonds were attacked by the olefin on the allylsilane group to form heterocycles. However, stannyl reagents are usually expensive and difficult to prepare and manipulate, which limits the applicability of this method.



Scheme 1.17. C-C bond construction using α-stannyl ethers.

Construction of carbon-carbon bonds is one of the most important aspects in organic synthesis. Although numerous methods have been established to reach this goal, novel approaches to the construction of C-C bonds are still valuable in the development of new synthetic strategies. Promoted by the extensive achievements of ET processes, and to expand the scope of our ETIC reactions, we decided to start a project, using olefin π-bonds as nucleophiles to construct C-C bonds. Reasonable design of the nucleophilicity of the olefin π-bonds and tailoring the reactivity and chemoselectivity of the cyclization substrates are expected to lead to the realization of this objective (Scheme 1.18).



Scheme 1.18. General structure designed to construct C-C bonds.

1.2 Results

After proving that ETIC reactions are successful in preparing heterocycles, we moved on to expand ETIC reactions to construct carbocycles. Our early work using substrates with unsubstituted arenes was unsuccessful,[35] presumably because of the high oxidation potential of the arene relative to the olefin nucleophile. Under photooxidative conditions, the olefin nucleophile was oxidized preferentially because of its low oxidation potential.

In consideration of the introduction of a *para*-methoxy group to the arene lowers its oxidation potential, we designed substrates (Figure 1.4) based on the structure shown in Scheme 1.18. The electron-donating group (EDG) on the olefin is expected to increase the nucleophilicity of the double bond and facilitate the cyclization.[36]

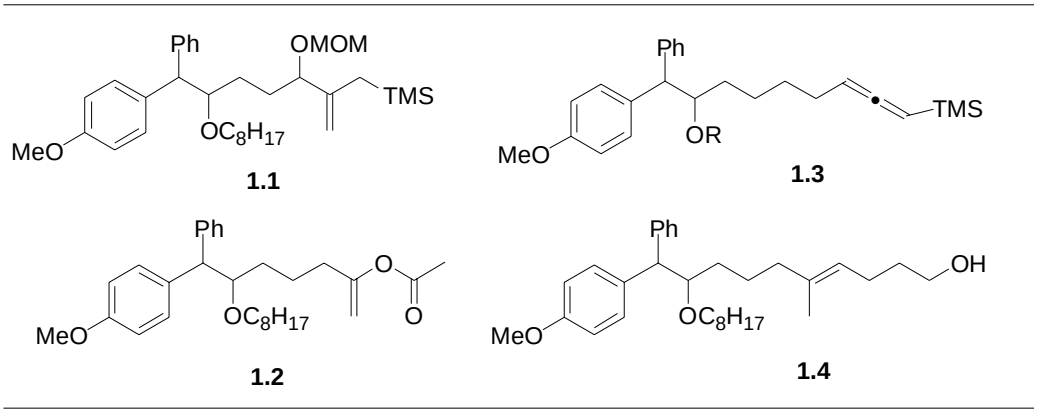
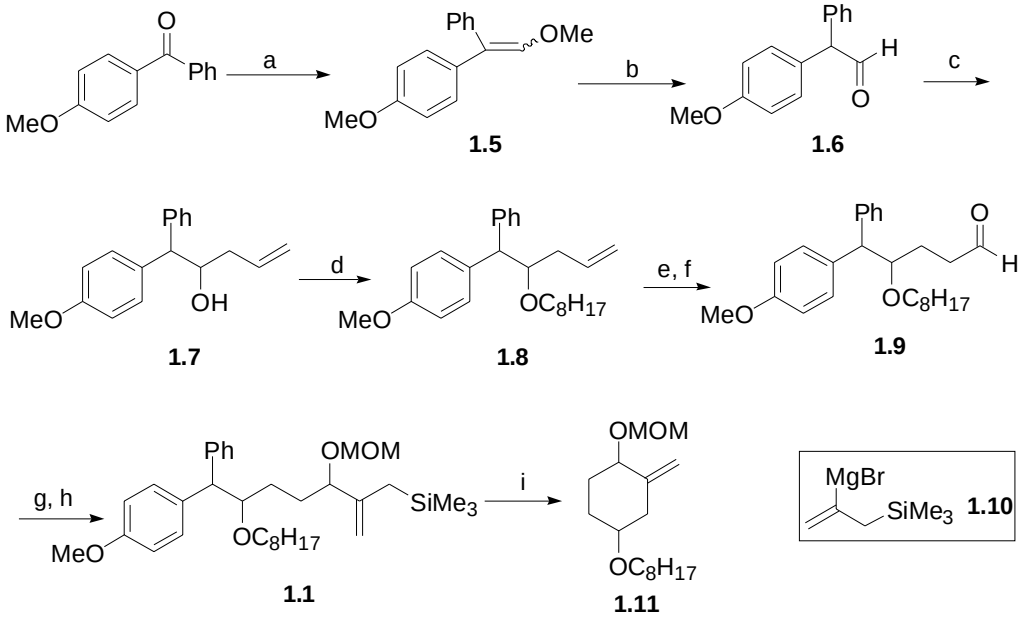


Figure 1.4. Substrates designed to construct C-C bonds.

1.2.1 C-C bond construction using an allylsilane as the nucleophile

The first substrate we prepared was allylsilane **1.1** through the synthetic sequence shown in Scheme 1.19. Commercially available *para*-methoxybenzophenone was treated with PPh_3=CH(OMe) to afford enol ether **1.5** in 66% yield. Enol ether **1.5** was then hydrolyzed to its

aldehyde **1.6** under acidic conditions at 50 ˚C in 90% yield. A nucleophilic addition to the aldehyde by allylmagnesium bromide gave alcohol **1.7** in 47% yield. Alkylation of the resulting alcohol under solvent free conditions[37] at 120 ˚C using NaH and 1-iodooctane afforded octyl ether **1.8** in 95% yield. These conditions proved to be superior to our typical method of using NaH in DMF at room temperature. A hydroboration (53%) of **1.9** followed by Dess-Martin oxidation (88%) generated aldehyde **1.9**. Addition of Grignard **1.10**[38] to aldehyde **1.9** followed by protection of the resultant secondary alcohol with a methoxymethyl group provided the cyclization substrate **1.1** (2 diastereomers with 1:1 ratio) in 40% yield over 2 steps.



Reagents: a) PPh_3=CH(OMe), THF, -78 ^oC to rt, 66%. b) NaI, 20% H_2SO_4, 1,4-dioxane, 50 ^oC, 90%. c) CH_2=$CHCH_2MgBr$, THF, 0 ^oC, 47%. d) NaH, $C_8H_{17}I$, 120 ^oC, 95%. e) BH_3, THF; NaOH, H_2O_2, 53%. f) Dess-Martin Periodinane, CH_2Cl_2, 88%. g) **1.10,** THF, -78 ^oC. h) CH_3OCH_2OCl, $^iPr_2EtN$, DMAP, CH_2Cl_2, 35^oC, 40% over 2 steps. h) DCE, $NaHCO_3$, 4 Å mol. sieves, 40 ^oC; CAN (in CH_3CN), 71%.

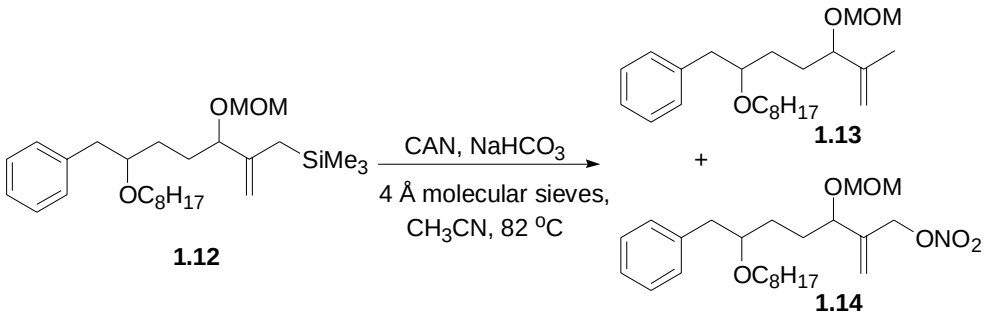
Scheme 1.19. The synthesis of allylsilane **1.1** and its cyclization.

Substrate **1.1** was subjected to ground state oxidation conditions using ceric ammonium nitrate (CAN) in acetonitrile as the oxidant, 1,2-dichloroethane (DCE) as the solvent, 4 Å molecular

sieves as the water scavenger, and $NaHCO_3$ as the base to neutralize any acid that is formed in the reaction. At 40 ˚C, the cyclization was complete within 10 minutes generating methylene cyclohexane product **1.11** (2 diastereomers with 1.7:1 ratio) in 71% yield. This was our first success in constructing C-C bonds using the ETIC protocol, and the results clearly indicated that the chemoselectivity and reactivity of the substrate were indeed what we expected with olefin π-bonds serving as good nucleophiles in the reaction. This success paved the way for more opportunities for further investigations of C-C bond construction using ETIC reactions.

Photochemical conditions (*hv*, DCE, toluene, $NMQPF_6$, O_2, NaOAc, $Na_2S_2O_3$, 4 Å molecular sieves) also effected the cyclization of **1.1** to **1.11** but the reaction was much slower, taking 5 hours and providing only a 50% yield.

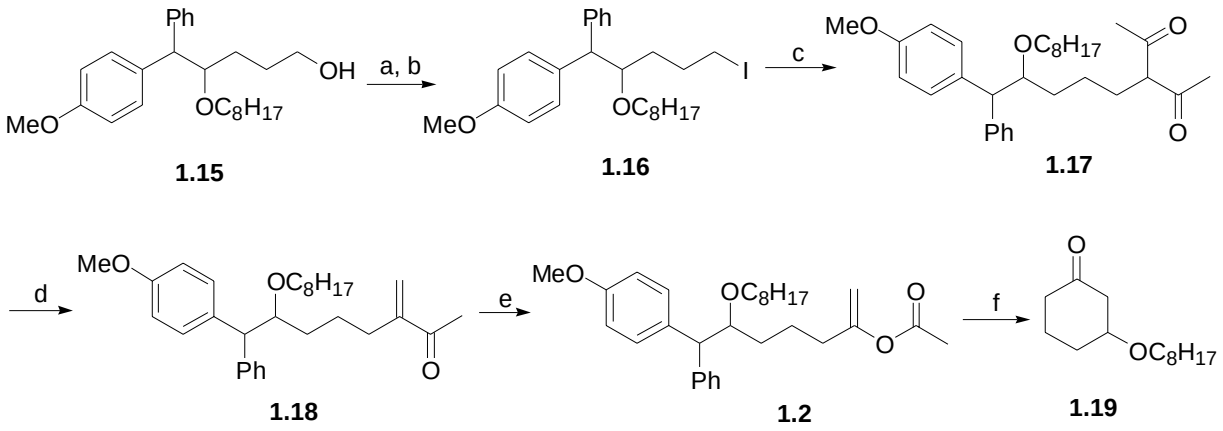
To further compare and confirm the importance of tuning the chemoselectivity and reactivity of the substrate, substrate **1.12** (Scheme 1.20) was prepared. **1.12** did not give any cyclization product under chemical oxidation conditions using CAN, even after elongated time (3.5 h) and at elevated temperature (82 ˚C). Under these harsher conditions, the substrate was consumed and the isolated products are consistent with structures **1.13** and **1.14**.



Scheme 1.20. Products derived from substrate **1.12**.

1.2.2 C-C bond construction using an enol acetate as the nucleophile

In order to broaden the scope of this cyclization, we prepared several substrates that contain various olefinic nucleophiles. The sequence to make enol acetate **1.2** is shown in Scheme 1.21. Alcohol **1.15** was converted to its mesylate, which was displaced by iodide to provide **1.16** in 92% yield over 2 steps. Iodide **1.16** was converted to diketone **1.17** using 2,4-pentanedione under basic conditions in refluxing acetone in 56% isolated yield at 60% conversion.[39] **1.17** underwent deacylative condensation with formaldehyde to form enone **1.18** in 58% yield.[40] Treatment of enone **1.18** with $SnCl_4$, 1,2-(diamino)cyclohexane, and a mild oxidant bis(trimethylsilyl) peroxide in the presence of 4 Å molecular sieves[41] afforded Baeyer-Villiger product **1.2** in 71% yield.



Reagents: a) Et_3N, MsCl, CH_2Cl_2, 0 ^oC. b) NaI, acetone, reflux, 92% over 2 steps. c) 2,4-pentanedione, K_2CO_3, acetone, reflux, 56%. d) K_2CO_3, HCOH, H_2O, 1,4-dioxane, 35 ^oC, 58%. e) 4 Å mol. sieves, *trans*-1,2-(diamino)cyclohexane, $SnCl_4$, CH_2Cl_2, 0 ^oC; TMSOOTMS, 71%. f) $NaHCO_3$, 4 Å mol. sieves, DCE; CAN (in CH_3CN), 50 ^oC, 94%.

Scheme 1.21. The synthesis of enol acetate substrate **1.2** and its cyclization.

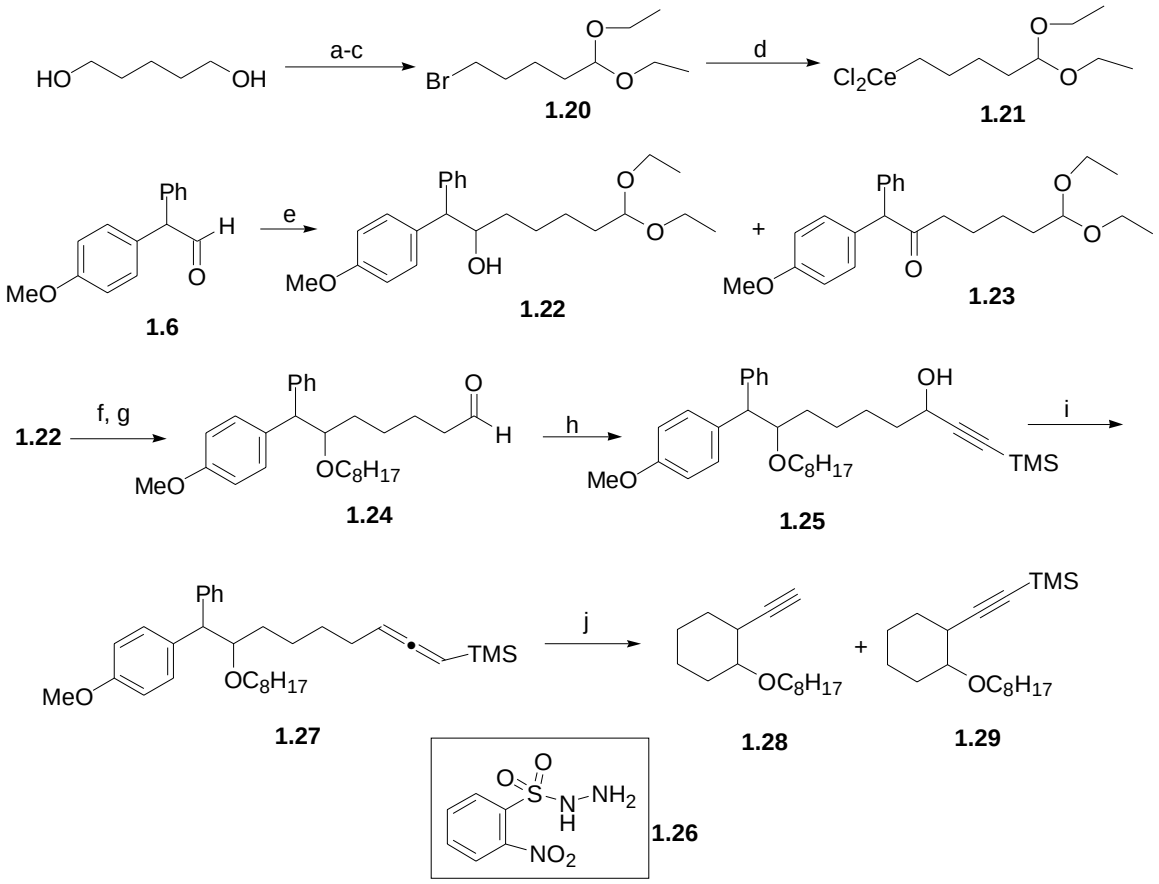
Under oxidation conditions using CAN at 50 ˚C, enol acetate **1.2** underwent facile cyclization giving the desired cyclohexanone product **1.19** in 94 % yield. The cyclization was complete immediately after CAN was added and the end of the reaction could be judged by the color of the

reaction changing from orange to yellow. Under photochemical conditions, the reaction time increased greatly to 2 h and only gave a 75% yield of the product.

1.2.3 C-C bond constructions with an allene as the nucleophile

Substrate **1.3** with the trimethylsilylallene moiety (Scheme 1.22) was also prepared and subjected to ETIC conditions. 1,5-Pentanediol was mono-brominated[42] with HBr in toluene at reflux and the resulting monobromo alcohol was oxidized to its aldehyde, which was then converted to its acetal **1.20**. Transformation of **1.20** to its Grignard reagent followed by transmetalation with $CeCl_3$ furnished organocerium species **1.21**.[43] **1.21** reacted with aldehyde **1.6** and afforded alcohol **1.22** in 66% yield. Ketone **1.23** was also isolated in 11% yield and was reduced to **1.22** with $NaBH_4$. Alkylation of **1.22** (57%) followed by deprotection of the acetal (~100%) gave aldehyde **1.24**. Addition of lithium trimethylsilylacetylide to aldehyde **1.24** generated propargylic alcohol **1.25** in 75% yield. **1.25** was treated with PPh_3, DEAD, and *o*-nitrobenzenesulfonylhydrazine **1.26**[44] in THF under Myers's conditions[45] to provide the cyclization substrate **1.27** in 84% yield.

Under ground state oxidation conditions using CAN at 40 ˚C, allene **1.3** provided 81% yield of the desired alkyne product **1.28** (two diastereomers, *trans* : *cis* = 1.2 : 1) in less than 3 min. Silylalkyne **1.29** was isolated in 10% yield and was converted to the desired product by treating it with TBAF. The overall yield of **1.28** was 91%. Under photochemical conditions, only 13% yield was obtained.



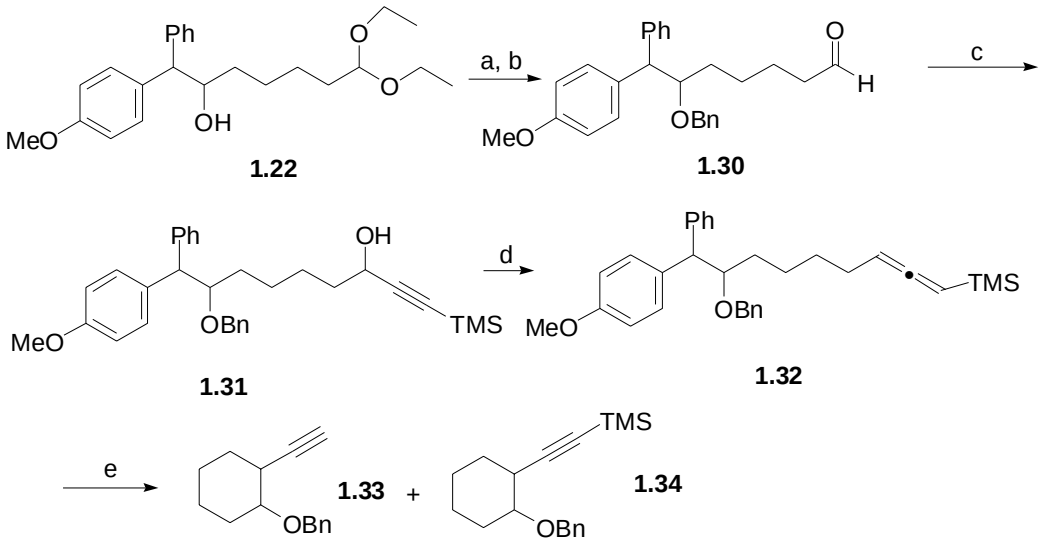
Reagents: a) 48% HBr, toluene, reflux. b) PCC, CH_2Cl_2. c) $HC(OEt)_3$, EtOH, PTSA, 51% over 3 steps. d) Mg, I_2, THF; $CeCl_3$, THF. e) **1.21**, THF, 0 ^oC, 77%. f) NaH, $C_8H_{17}I$, 120 ^oC, 57%. g) TFAA, $CHCl_3$, H_2O, 0 ^oC, ~100%. h) Li-≡-TMS, THF, 0 ^oC, 75%. i) PPh_3, THF; DEAD; **1.25**; **1.26**, -10 ^oC, 84%. j) DCE, $NaHCO_3$, 4 Å mol. sieves,40 ^oC; CAN (in CH_3CN), 91%.

Scheme 1.22. The preparation of allene substrate **1.27** and its cyclization.

1.2.4. Cleavable ethers as electron-donating groups

Ethers that can be more readily cleaved than the octyl group broaden the scope of the method by allowing further manipulation of the cyclization products. To test this possibility, benzyl ether substrate **1.32** was prepared in a similar way to **1.27** (Scheme 1.23). Alkylation of alcohol **1.22** with NaH and benzyl bromide (57%) followed by hydrolysis of the resulting acetal (84%) provided aldehyde **1.30**. Addition of lithium trimethylsilylacetylide (84%) to aldehyde **1.30**

followed by allene formation of the resulting propargylic alcohol **1.31** (64%) under Myers's conditions[45] generated cyclization substrate **1.32**.



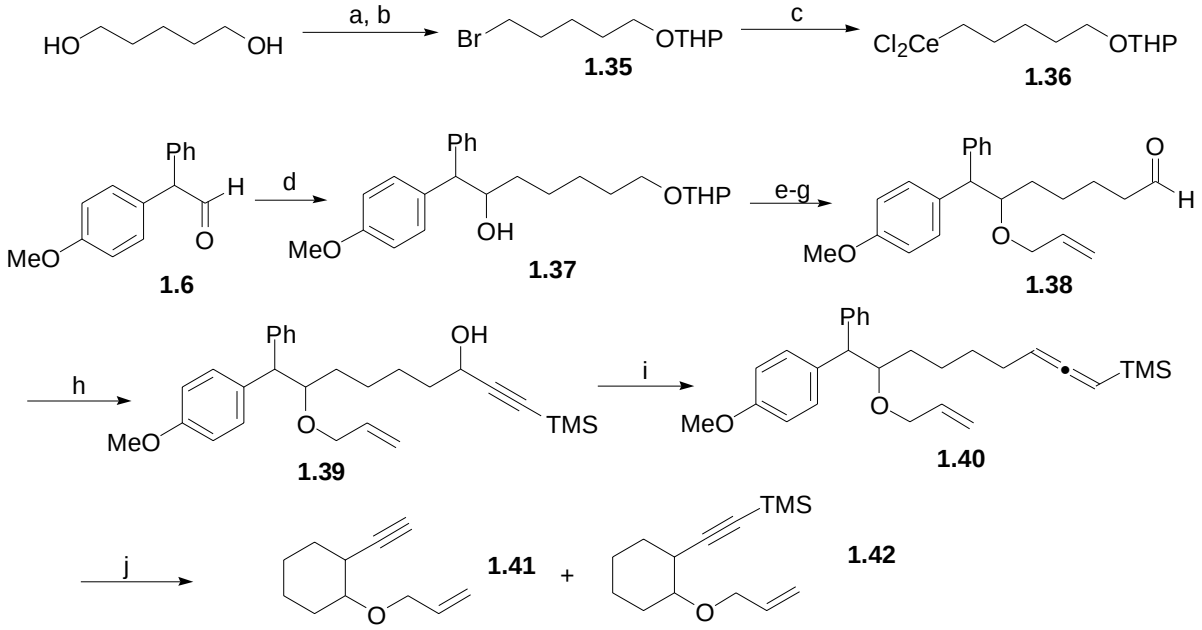
Reagents: a) NaH, BnBr, DMF, 57%. b) TFAA, $CHCl_3$, H_2O, 0 ^oC, 84%. c) Li-≡-TMS, THF, 0 ^oC, 84%. e) PPh_3, THF; DEAD; **1.26**, -10 ^oC, 64%. f) $NaHCO_3$, 4 Å mol. sieves, DCE, 40 ^oC; CAN (in CH_3CN), 66%.

Scheme 1.23. The synthesis of substrate **1.32** and its cyclization.

Substrate **1.32** underwent cyclization under chemical oxidation conditions using CAN, but afforded lower yield than **1.27**. It generated 52% yield of the desired product **1.33** as two diastereomers (*trans* : *cis* = 1.3 : 1) and 3.5% yield of silylalkyne **1.34**. 16% of the starting material was recovered. Silylalkyne **1.34** was converted to the desired product **1.33** by treating it with TBAF. The overall yield based upon unrecovered starting material was 66%.

Allyl ether **1.40** was also prepared as shown in Scheme 1.24. 1,5-Pentanediol was mono-brominated[42] with HBr in toluene at reflux and the resulting monobromo alcohol was protected as its THP ether **1.35**. **1.35** was converted to its Grignard reagent, which was then transmetalated to the organocerium species **1.36**. Addition of **1.36** to aldehyde **1.6** generated alcohol **1.37** in

66% yield. Alkylation of **1.37** with allyl bromide followed by deprotection of THP ether (84% over 2 steps) and Dess-Martin oxidation (77%) provided aldehyde **1.38**. Similar carbonyl addition onto **1.38** with lithium trimethylsilylacetylide (77%) generated propargylic alcohol **1.39**, which was subjected to Meyers's allene formation conditions[45] to provide the cyclization substrate **1.40** in 77% yield.



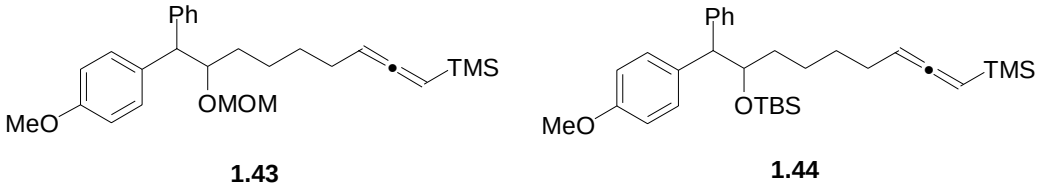
Reagents: a) 48% HBr, toluene, reflux. b) 3,4-dihydropyran, PPTS, CH_2Cl_2, 40% over 2 steps. c) Mg, I_2, THF; $CeCl_3$, THF, 0 ^oC. d) **1.36**, 0^oC, THF, 66%. e) NaH, allyl bromide, DMF. f) MeOH, PTSA, rt, 84% over 2 steps. g) Dess-Martin periodinane, CH_2Cl_2, 77%. h) Li-≡-TMS, THF, 0 ^oC, 77%. i) PPh_3, THF; DEAD; **1.26**; -10 ^oC, 77%. j) $NaHCO_3$, 4 Å mol sieves, DCE; CAN (in CH_3CN), rt, 72%.

Scheme 1.24. The preparation of substrate **1.40** and its cyclization.

Under ground state oxidation conditions using CAN the cyclization reaction of **1.40** was finished within 10 min at room temperature. Because the cyclization products are somewhat volatile, the yields of the reaction were measured with GC using 1-iodooctane as the internal standard. The cyclization generated 65% of the desired product **1.41** as two diastereomers (*trans*

: *cis* = 1.3 : 1) and 7% of silylalkyne **1.42** as two diastereomers in 1 : 1 ratio. The overall yield was 72% of the desired product.

Two other ether groups were also incorporated into the cyclization substrates to replace octyl ethers. Methoxymethyl ether substrate **1.43** and silyl ether **1.44** (Scheme 1.25) were prepared using the same strategy employed to make allyl ether **1.40**. Unfortunately, neither of them gave good cyclization yields. Silyl ether **1.44** gave ~9% yield of the product under ground state oxidation conditions using CAN and ~30% yield under photochemical conditions. As for MOM ether **1.43**, practically no cyclization product was generated under either conditions.



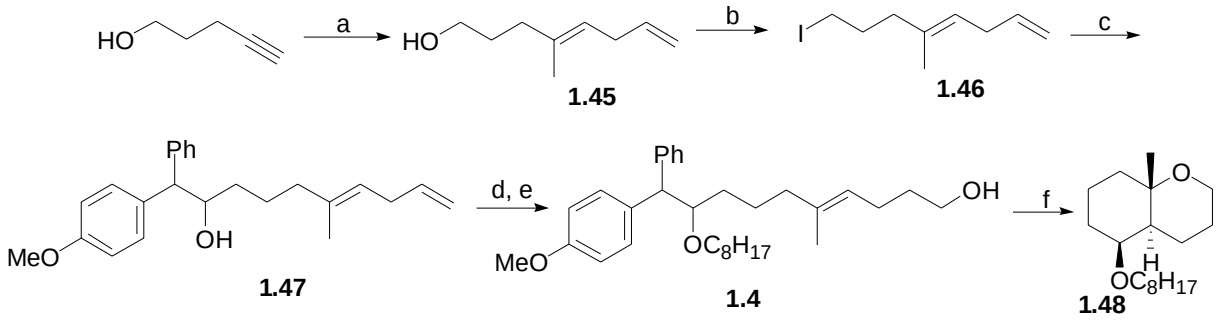
1.43 **1.44**

Scheme 1.25. Substrates **1.43** and **1.44**.

1.2.5. Cascade cyclization involving C-C bond formation

Using a trisubstituted olefin as the nucleophile creates possibilities for initiating oxidative cascade cyclizations. To test this idea, we prepared substrate **1.4** (Scheme 1.26), which contains two nucleophiles: a hydroxyl group and an olefin. The trisubstituted olefin was synthesized using the protocol developed by Negeshi.[46] A carboalumination of pent-4-yn-1-ol with Me_3Al and Cp_2ZrCl_2 in the presence of H_2O[47] followed by a palladium catalyzed coupling reaction with allyl bromide generated alcohol **1.45** in 75% yield. Alcohol **1.45** was then transformed into iodide **1.46** with I_2 in the presence of PPh_3 and imidazole giving 87% yield. The iodide was treated with *tert*-butyl lithium,[48] and the resulting alkyllithium species was transmetalated with

$CeCl_3$. The resultant organocerium reagent added onto aldehyde **1.6** to afford **1.47** in 65% yield. Alkylation of **1.47** (90%) followed by hydroboration (46%) using disiamylborane[49] provided cyclization substrate **1.4**.



Reagent: a) Cp_2ZrCl_2, $AlMe_3$, H_2O, CH_2Cl_2; $Pd(PPh_3)_4$, CH_2=$CHCH_2Br$, 75%. b) PPh_3, imid, I_2, CH_2Cl_2, 87%. c) *t*-BuLi, Et_2O, pentane, -78 ^oC to rt; $CeCl_3$, THF, -78 ^oC; aldehyde **1.6**, 65%. d) NaH, $C_8H_{17}I$, 120 ^oC, 90%. e) Disiamylborane, THF; NaOH, H_2O_2, 46%. f) *h*ν, $NMQPF_6$, O_2, DCE, NaOAc, $Na_2S_2O_3$, 4 Å mol. sieves, toluene, rt, 49%.

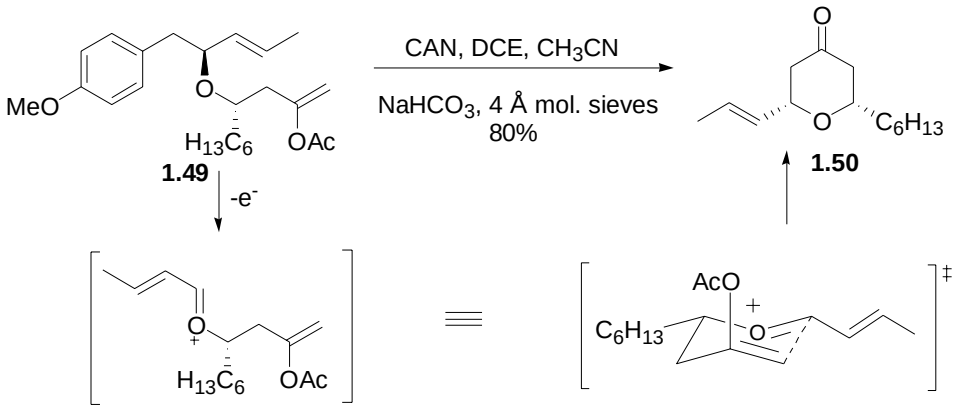
Scheme 1.26. Cascade cyclization including C-C bond formation.

Under chemical oxidation conditions using CAN, the cyclization of substrate **1.4** took less than 5 minutes at room temperature and gave the desired product **1.48** in 32% yield. Under photochemical conditions, the reaction yield was improved to 49%. Under both conditions, product **1.48** was the only isomer that was isolated.

1.2.6 Stereocontrol by ETIC reactions

ETIC reactions also provide opportunities to generate stereocontrol in C-C bond formations. As shown in Scheme 1.27, superior stereocontrol is expected for the 6-*endo*-pathway due to its strong preference for chair transition states and an (*E*)-configuration of the oxocarbenium ion. John Seiders in our lab has demonstrated that subjecting **1.49** to standard ETIC conditions (DCE,

$NaHCO_3$, CAN, and CH_3CN) at room temperature resulted in oxidative cleavage and cyclization to form tetrahydropyrone **1.50** with complete stereocontrol in 80% yield.[50]



Scheme 1.27. Stereocontrol of ETIC reactions.

In consideration of the extensive presence of 2,4,6-trisubstituted tetrahydropyrans in biologically active natural products, many substrates have been synthesized by Seiders and subjected to oxidative cyclization conditions to test the generality of this method. As demonstrated by examples shown in Table 1.1, excellent yields and diastereoselectivity were obtained, proving the efficiency and generality of this method. A project aimed at the total synthesis of Leucascandrolide A[51] with an ETIC reaction as the key step is currently under way.

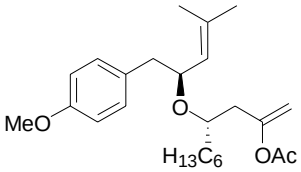
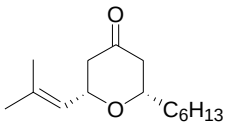
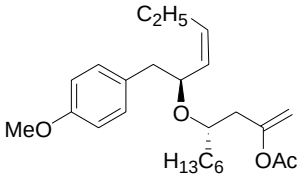
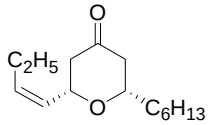
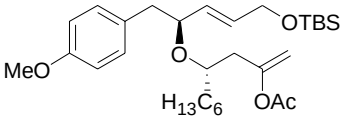
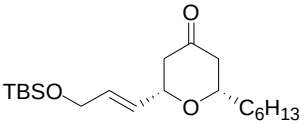
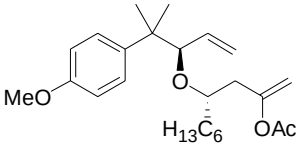
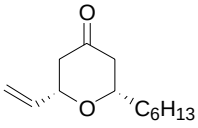
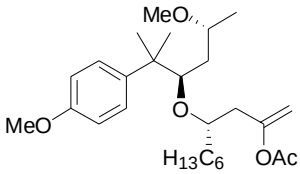
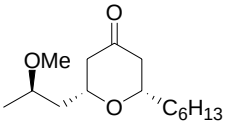
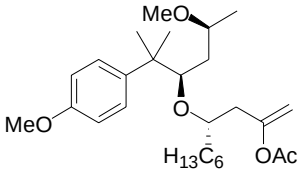
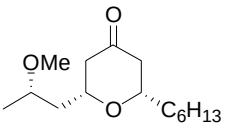
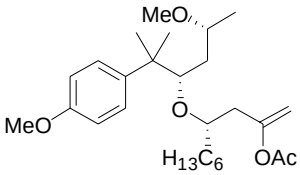
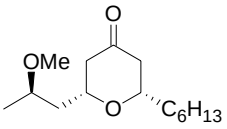
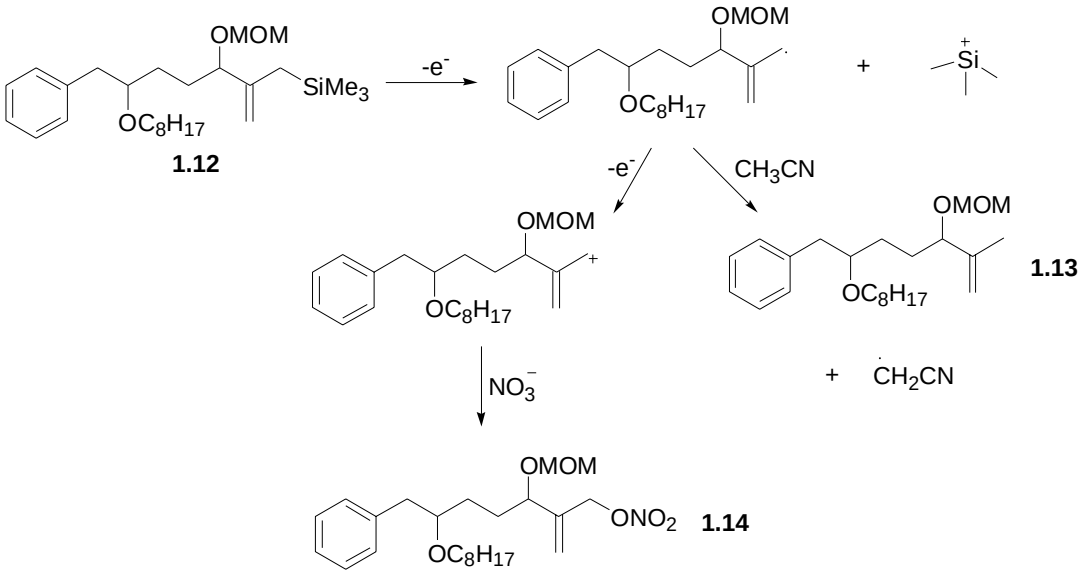
Entry	Substrate	Product	yield (%)
1			80
2			70
3			79
4			70
5			100
6			97
7			96

Table 1.1. Using ETIC reactions to generate stereocontrol.

1.3 Discussion

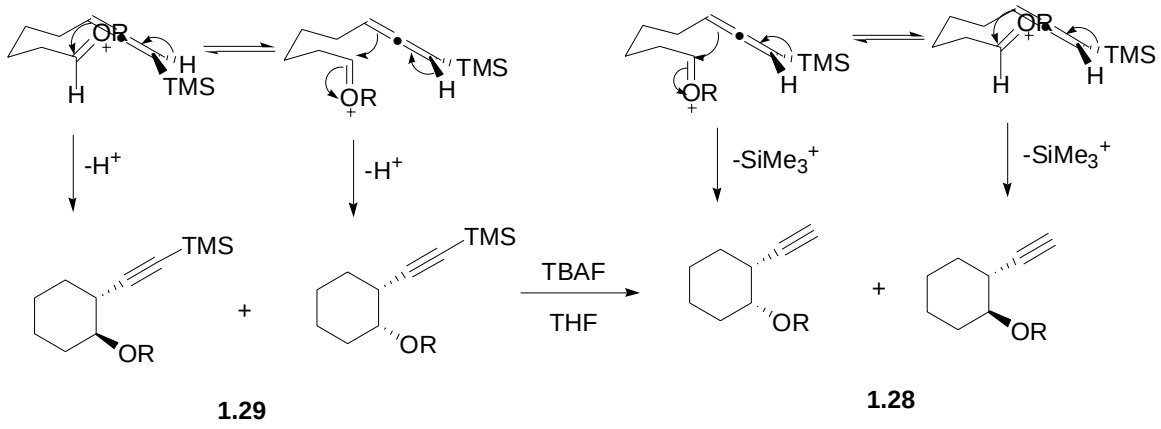
Monobenzene substrate **1.12** (Scheme 1.28) did not give any cyclization product under chemical oxidation conditions using CAN. The isolated products are consistent with structures **1.13** and **1.14**, which were derived from C-Si bond cleavage. After single-electron oxidation, the resulting radical cation cleaves the C-Si bond, forming an allylic radical and a trimethylsilyl cation. The allylic radical can either abstract H· from solvent to form product **1.13** or be further oxidized to a carbocation. The carbocation then undergoes nucleophilic attack by a nitrate to form **1.14**. The results showed that the cyclization does not proceed without proper tuning of the chemoselectivity and reactivity of the substrates.



Scheme 1.28. Decomposition of monobenzene substrate **1.12**.

Under oxidation conditions using CAN, allene substrate **1.27** provided 81% yield of the alkyne product **1.28**. And interestingly, silylalkyne **1.29** (Scheme 1.29) was isolated in 10%

yield. Product **1.29** is generated from proton loss of the cationic intermediate (Scheme 1.29). Silylalkyne **1.29** was converted to the desired product by treating it with TBAF. This cyclization showed that allenes, which can be readily made under Meyers's conditions, with their continuous π-bonds can also serve as good nucleophiles in ETIC reactions to generate alkyne products. The cyclization did not provide good diastereoselectivity (1.2:1). In the transition state, the oxonium ion can reside either in an equatorial or axial position and the energy difference between these two conformations is small.

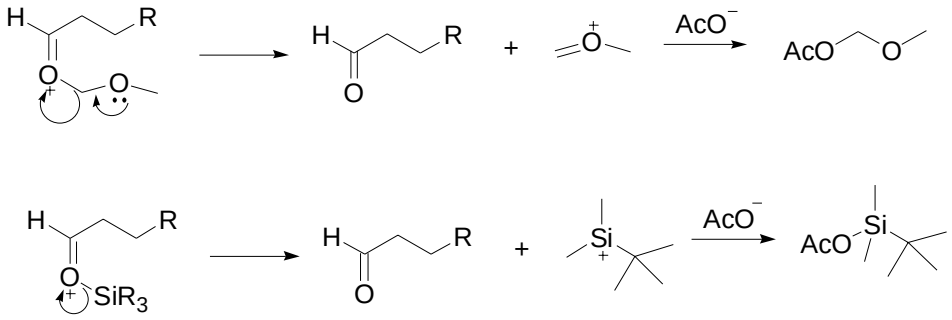


Scheme 1.29. Formation of **1.29** and the cleavage of the TMS group.

Benzyl ether substrate **1.32** and allyl ether **1.40** underwent cyclizations under oxidation conditions using CAN, showing that cleavable ethers can also serve as electron donating groups in these reactions, which allows further manipulation of the cyclization products.

Methoxymethyl ether substrate **1.43** and silyl ether **1.44** were also subjected to cyclization conditions. It is an especially interesting point to test the silyl ether substrate, since it is a commonly used protecting group and easily accessible. Also, utilizing silyl ethers, if successful, could expand the reactivity adjusting group to silyl ethers. Unfortunately, neither substrate gave

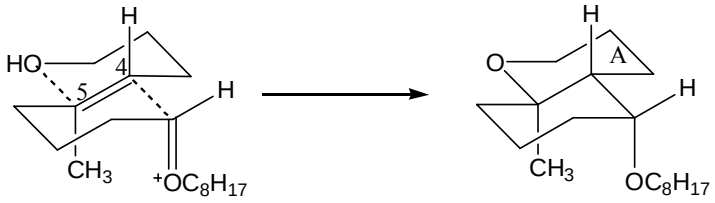
good cyclization yields. The proposed decomposition mechanism of these two substrates is shown in Scheme 1.30. In the case of **1.43**, the oxocarbenium ion intermediate generated from benzylic cleavage of the radical cation could decompose to an aldehyde and a new oxonium ion. The resulting oxonium ion could be attacked by external base such as acetate, to form the ester product. In a similar manner, the oxonium ion generated from **1.44** underwent cleavage at the weakened O-Si bond position to form a molecule of aldehyde and a stabilized silicon cation. The silicon cation could be captured by external base to form an ester product. In the crude NMR of the cyclization products of both substrates, evident aldehyde peaks were found. No extensive effort was put on the product separation, since the aldehyde was not the desired product. However, similar reactions were proven to be useful in traceless release of ketones and aldehydes from polymer supports as demonstrated recently by our group.[52]



Scheme 1.30. Possible decomposition pathways for substrates **1.43** and **1.44**.

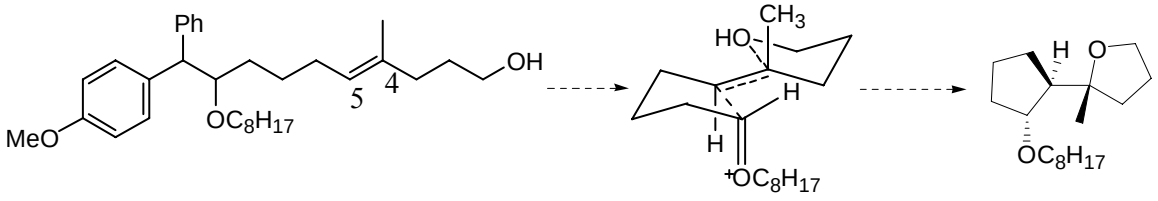
The cyclization of **1.4** suggests that a cascade reaction involving π-bond nucleophile is feasible. Interestingly, the reaction generated the expected cyclization product as a single diastereomer with both methyl and octyloxy groups residing in axial positions. The reaction

appears to prefer taking a synclinal transition state to anti-periplanar TS. The result is consistent with literature precedents such as Johnson's cyclization.[53]



Scheme 1.31. The cascade reaction.

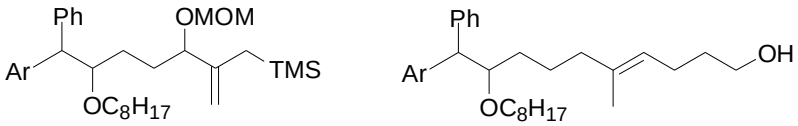
In the cascade cyclization (Scheme 1.31), ring closure of A ring was 6-endo type and no 5-exo ring closure was observed, although either one is favored according to Baldwin's rules. The reason may be that C5 supports a partial positive charge better than C4, since a methyl group resides on C5. This also suggests that combined with variant substituent patterns or stereocontrol factors, many interesting products can be designed. For example, the substrate shown in Scheme 1.32, with the methyl group residing on C4, is expected to undergo cyclization and yield a product that contains two continuous 5-membered rings.



Scheme 1.32. Substrate designed to yield continuous 5-membered rings.

Because CAN is not soluble in DCE, it is necessary to use acetonitrile as co-solvent in the cyclizations. But in some cases, acetonitrile might also function as a nucleophile and lower the

cyclization yield. To avoid this problem and to increase the yield of the cascade cyclization, ceric bis(tetra-*n*-butylammonium) nitrate (CTAN), which is soluble in CH_2Cl_2, was made and used in the reactions. Substrates **1.1** and **1.4** (Scheme 1.33) were treated with CTAN under the same conditions as when CAN was used, but no cyclization occurred. After elongated time (5 h for **1.1**) and at elevated temperature (reflux in CH_2Cl_2 for **1.4**), only a very small amount of desired products formed, and the majority of starting material was recovered. The reason for the different reactivities of CAN and CTAN could be that CAN has bare Ce(IV) cations that can coordinate onto the arene and facilitate the single electron oxidation. While for CTAN, cerium cations are surrounded by butyl groups and the coordination with arenes cannot occur.



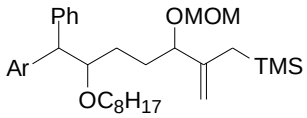
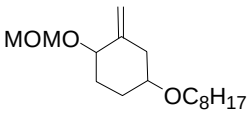
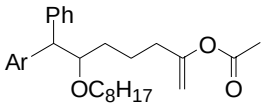
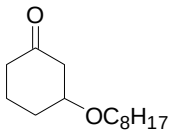
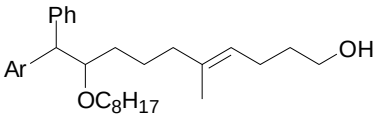
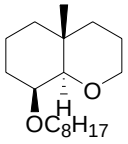
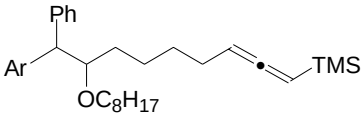
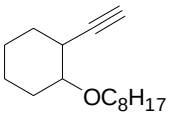
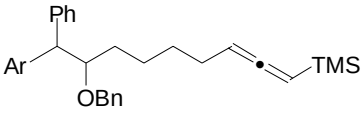
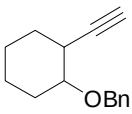
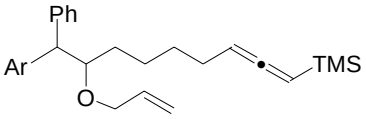
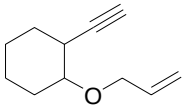
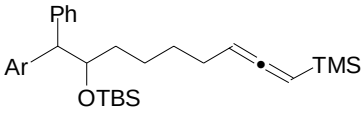
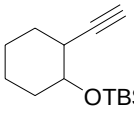
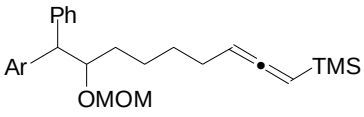
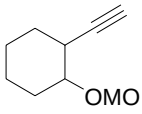
1.1 **1.4**

Scheme 1.33. Substrates that were treated with CTAN.

1.4. Summary

ETIC reactions have been successfully expanded to the construction of carbon-carbon bonds after tuning the chemoselectivity and reactivity of the substrates. Table 1.2 summarizes the conditions and yields of the cyclizations that lead to C-C bond formation. In most cases, cyclizations gave good to excellent yields with short reaction times. The results clearly indicated that ETIC reactions are highly effective in constructing C-C bonds. Olefins and allenes with several different electron-donating groups served as good nucleophiles in the cyclization reactions to generate various carbocycles. Cascade cyclizations involving C-C bond formation were also proven to be successful, providing the desired chromene product as a single diastereomer. Several ether groups were incorporated into the cyclization substrates to replace octyl ethers, allowing for further manipulations of the cyclization products.

The results also showed that in most cases, ground state oxidation conditions using CAN are preferable for C-C bond formation relative to photochemical conditions, which are relatively simple and do not require special equipment.

substrate[a]	product	yield (%) ground state oxidation conditions[b]	yield (%) photochemical conditions[c]
		71	50
		94	75
		32	49
		91	13
		66	
		72	
		~9	~30
		0	~8

[a] Ar = *p*-MeOPh. [b] ground state oxidation conditions: DCE, $NaHCO_3$, 4 Å molecular sieves, CAN in CH_3CN. [c] Photochemical conditions: *hv*, O_2, DCE, toluene, $NMQPF_6$, $Na_2S_2O_3$, 4 Å molecular sieves, NaOAc.

Table 1.2. C-C bond construction using ETIC reactions.

1.5 References

(1) Gaillard, E. R.; Whitten, D. G. "*Acc. Chem. Res.* **1996**, *29*, 292-297.

(2) Schultz, A. G. *Chem. Commun.* **1999**, 1263-1271.

(3) Ma, D.; Xia, C. *Org. Lett*. **2001**, *3,* 2583-2586.

(4) Lin, J.; Bent, B. E. *J. Am. Chem. Soc.* **1993**, *115*, 6943-6950.

(5) Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.* **1990**, *55,* 5404-5406.

(6) Cohen, T.; Bhupathy, M. *Acc. Chem. Res.* **1989**, *22*, 152-161.

(7) Kavarnos, G. J. "Fundamentals of Photoinduced Electron Transfer" VCH, **1993**.

(8) Schmittel, M.; Burghart, A. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2550-2589.

(9) Eberson, L. "Electron Transfer Reactions in Organic Chemistry", Springer, Berlin. **1987**.

(10) Balzani, V. (Ed.) "*Organic Molecules*" Vol. 2, "*Electron Transfer in Chemistry*", Schmittel, M.; Ghorai, M. K.; Wiley-VCH Weinheim, **2001**.

(11) Adam, W.; Miranda, M. A.; Mojarrad, F.; Sheikh, H. *Chem. Ber.* **1994**, *127*, 875-879.

(12) Dehmlow, E. V.; Makrandi, J. K. *J. Chem. Res., Synop.* **1986**, 32-33.

(13) Connelly, N. G.; Geiger, W. E. *Chem. Rev.* **1996**, *96*, 877-910.

(14) Stahl, K. P.; Boche, G.; Massa, W. *J. Organomet. Chem.* **1984**, *277*, 113-125.

(15) Gassman, P. G.; Winter, C. H. *J. Am. Chem. Soc.* **1986**, *108*, 4228-29.

(16) Gritzner, G.; Kuta, J. *Pure Appl. Chem.* **1984**, *56*, 461-466.

(17) Suga, S.; Suzuki, S.; Yamamoto, A.; Yoshida, J. *J. Am. Chem. Soc.* **2000**, *122*, 10244-10245.

(18) Duan, S.; Moeller, K. D. *Org. Lett.* **2001**, *3*, 2685-2688.

(19) Moeller, K. D. *Tetrahedron* **2000**, *56*, 9527-9554.

(20) Ponsold, K.; Kasch, H. *Tetrahedron Lett.* **1979,** *20*, 4463-4464.

(21) Baggaley, A. J.; Brettle, R. *J. Chem. Soc. Chem. Commun.* **1966**, 108.

(22) Dinnocenzo, J. P.; Todd, W. P.; Simpson, T. R.; Gould, I. R. *J. Am. Chem. Soc.* **1990**, *112*, 2462-2464.

(23) Arnold, D. R.; Maroulis, A. J *J. Am. Chem. Soc.* **1976**, *98*, 5931-5937.

(24) Baciocchi, E.; Bietti, M; Lanzalunga, O. *Acc. Chem. Res.* **2000**, *33*, 243-251.

(25) Yoshida, J.; Murata, T.; Isoe, S. *Tetrahedron Lett.* **1986**, *27*, 3373-3376.

(26) Kumar, V. S.; Floreancig, P. E. *J. Am. Chem. Soc.* **2001**, *123*, 3842-3843.

(27) Kumar, V. S.; Aubele, D. L.; Floreancig, P. E. *Org. Lett.* **2002**, *4*, 2489-2492.

(28) Aubele, D. L.; Floreancig, P. E. *Org. Lett.* **2002**, *4*, 3443-3446.

(29) Kumar, V. S.; Aubele, D. L.; Floreancig, P. E. *Org. Lett.* **2001**, *3*, 4123-4125.

(30) Freccero, M.; Pratt, A.; Albini, A.; Long, C. *J. Am. Chem. Soc.* **1998**, *120*, 284-297.

(31) *Encyclopedia of Electrochemistry of the Elements* Bard, A. J. (Ed) Marcel Dekker, Inc. New York, **1984**, vol 15, p 48.

(32) Seiders, J. R., II; Wang, L.; Floreancig, P. E. *J. Am. Chem. Soc.* **2003**, *125,* 2406-2407.

(33) Yoshida, J.; Ishichi, Y.; Isoe, S. *J. Am. Chem. Soc.* **1992**, *114*, 7594-7595.

(34) Chen, C.; Mariano, P. S. *J. Org. Chem.* **2000**, *65*, 3252-3254.

(35) Aubele, D. L.; Floreancig, P. E. "Unpublished Results".

(36) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66-77.

(37) Chapman, J. J.; Reid, J. R. *J. Org. Chem.* **1989**, *54*, 3757-3759.

(38) Trost, B. M.; Grese, T. A.; Chan, D. M. T. *J. Am. Chem. Soc.* **1991**, *113*, 7350-7362.

(39) Shono, T.; Kashimura, S.; Sawamura, M.; Soejima, T. *J. Org. Chem.* **1988**, *53*, 907-910.

(40) Ayed, T. B.; Amri, H. *Syn. Commun.* **1995**, *25*, 3813-1819.

(41) Göttlich, R.; Yamakoshi, K.; Sasai, H.; Shibasaki, M. *Synlett* **1997**, 971-973.

(42) Chong, J. M.; Heuft, M. A.; Rabbat, P. *J. Org. Chem.* **2000**, *65*, 5837-5838.

(43) Takeda, N.; Imamoto, T. *Org. Synth.* **1999**, *76*, 228-238.

(44) Myers, A. G.; Zheng, B. *J. Org. Chem.* **1997**, *62*, 7507.

(45) Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492-4493.

(46) Negishi, E.; Liou, S.-Y.; Xu, C.; Huo, S. *Polyhedron*, **2000**, *19*, 591-592.

(47) Wipf, P. and Lim, S.; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1068-1071.

(48) Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.* **1990**, *55*, 5404-5406.

(49) Zweifel, G.; Nagase, K.; Brown, H. C. *J. Am. Chem. Soc.* **1962**, *84*, 190-195.

(50) Wang, L.; Seiders, J. R., II; Floreancig, P. E. *J. Am. Chem. Soc.* **2004**, *126*, 12596-12603.

(51) D'Ambrosio, M.; Guerriero, A.; Debitus, C.; Pietra, F. *Helv. Chim. Acta.* **1996**, *79*, 51-60.

(52) Liu, H.; Wan, S.; Floreancig, P. E. *J. Org. Chem.* **2005**, *70*, 3814-3818.

(53) Johnson, W. S.; Elliott, J. D.; Hanson, G. J. *J. Am. Chem. Soc*. **1984**, *106*, 1138-1139.

1.6 Experimental

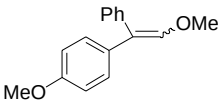
General Experimental:

Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on Bruker Avance 300 spectrometers at 300 MHz and 75 MHz, respectively. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. The solvent peak or the internal standard tetramethylsilane were used as reference values. For ^{1}H NMR: $CDCl_3$ = 7.27 ppm, TMS = 0.00 ppm. For ^{13}C NMR: $CDCl_3$ = 77.23, TMS = 0.00. For proton data: s = singlet; d = doublet; t = triplet; q = quartet; p = pentet; dd = doublet of doublets; dt = doublet of triplets; ddt = doublet of doublet of triplets; ddq = doublet of doublet of quartets; br = broad; m = multiplet; app t = apparent triplet; app q = apparent quartet; app p = apparent pentet.

High resolution and low resolution mass spectra were recorded on a VG 7070 spectrometer. Infrared (IR) spectra were collected on a Mattson Gygnus 100 spectrometer.

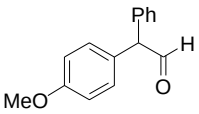
Analytical thin layer chromatography (TLC) was performed on E. Merck pre-coated (25 nm) silica gel 60F-254 plates. Visualization was done under UV (254 nm). Flash column chromatography was performed using ICN SiliTech 32-63 60Å silica gel. Reagent grade ethyl acetate and hexanes (commercial mixture) were purchased from EM Science and used as is for chromatography. Reagent grade methylene chloride (CH_2Cl_2), dicholoroethane ($C_2H_4Cl_2$), acetonitrile (CH_3CN) and toluene were distilled from CaH_2. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl prior to use. Anhydrous (*N*,*N*)-dimthylformamide (DMF), methanol (MeOH), dimethyl sulfoxide (DMSO), acetone were purchased from Aldrich and used as is.

1-Methoxy-4-(2-methoxy-1-phenylvinyl)benzene (1.5)



To a suspension of (methoxymethyl)triphenylphosphonium chloride (11.64 g, 34.0 mmol) in THF (100 mL) at –78 °C was added LDA (34.0 mmol, 0.4 M in THF) dropwise. The color of the reaction changed to deep orange. After 0.5 h, a solution of 4-methoxybenzophenone (5.15 g, 24.3 mmol) in THF (50 mL) was added and the resulting mixture was allowed to warm to rt. The reaction mixture was stirred for 2 h and was quenched with saturated NH_4Cl (5 mL). The organic layer was separated, washed with water (10 mL) and brine (10 mL), then was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was dissolved in EtOAc (30 mL) and the solution was added to stirring hexanes (200 mL) dropwise. A precipitate formed and the suspension was filtered through a short pad of Celite. The filtrate was concentrated under reduced pressure and the resulting residue was purified by flash chromatography (4% EtOAc in hexanes) to give the desired product as a clear oil (3.83 g, 66%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22-7.40 (m, 6H), 7.14 (d, J = 8.2 Hz, 1H), 6.83 (m, 2H), 6.41 (s, 50% of 1H), 6.39 (s, 50% of 1H), 3.82 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 158.3, 145.8, 140.8, 138.1, 133.0, 131.1, 130.2, 129.9, 129.5, 128.3, 128.0, 126.6, 126.5, 120.2, 120.1, 113.8, 113.5, 60.5, 55.3, 55.2; IR (neat) 3030, 2999, 2931, 2834, 1631, 1606, 1510, 1493, 1441, 1286, 1229, 1172, 1104, 1035, 832, 765, 698 cm^{-1}; HRMS-EI (m/z) calcd for $C_{16}H_{16}O_2$ [M^+] 240.1150, found 240.1154.

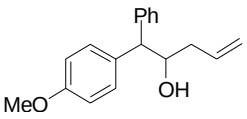
(4-Methoxyphenyl)phenylacetaldehyde (1.6)



To enol ether **1.5** (1.6 g, 6.7 mmol) in 1,4-dioxane (50 mL) were added NaI (7.6 g, 50.9 mmol) and H_2SO_4 (2 M solution, 6 mL). The resulting mixture was heated at 50 °C overnight. The reaction mixture was concentrated on a rotary evaporator to

remove most of the dioxane, and the resulting mixture was extracted with EtOAc (3 × 30 mL). The organic layers were combined and washed with water (10 mL), aqueous $NaHCO_3$ (10 mL), and brine (10 mL), then were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (10% EtOAc in hexanes) to afford the desired product (1.29 g, 90%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.93 (s, 1H), 7.14-7.39 (m, 7H), 6.91 (d, *J* = 8.7 Hz, 2H), 4.85 (d, *J* = 2.2 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.6, 159.0, 136.7, 130.2, 129.0, 128.9, 128.2, 127.4, 114.4, 63.2, 55.1; IR (neat) 2933, 2835, 1720, 1608, 1509, 1421, 1251, 1179, 1033, 828, 699 cm^{-1}; HRMS-EI (m/z) calcd for $C_{15}H_{14}O_2$ [M^+] 226.0993, found 226.1001.

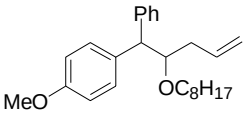
1-(4-Methoxyphenyl)-1-phenylpent-4-en-2-ol (1.7)



To a stirring solution of aldehyde **1.6** (1.0 g, 4.42 mmol) in THF (20 mL) at 0 °C was added allylmagnesium bromide (1 M in THF, 14 mL, 14 mmol) dropwise. The reaction mixture was stirred at 0 °C for 0.5 h then was quenched with saturated NH_4Cl solution (10 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The organic layers were combined, washed with water (15 mL) and brine (15 mL), then were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (15-30% EtOAc in hexanes) to furnish the desired product (0.565 g, 47%, 2 diastereomers) as a clear oil. Faster eluting diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.43 (m, 7H), 6.88 (d, J = 6.8 Hz, 2H), 5.93 (ddt, J = 9.6, 17.0, 7.4 Hz, 1H), 5.17 (dd, J = 9.1, 0.9 hz, 1H), 5.11 (dd, J = 17.0, 1.5 Hz, 1H), 4.41 (dt, *J* = 3.5, 8.3 Hz, 1H), 3.93 (d, *J* = 8.3 Hz, 1H), 3.80 (s, 3H), 2.35-2.43 (m, 1H), 2.15-2.25 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2, 141.8, 135.0, 134.5, 129.3, 128.8, 126.7,

117.9, 114.1, 73.1, 57.2, 55.3, 39.6; IR (neat) 3453, 2906, 2822, 1510, 1248, 1178, 1034, 700 cm^{-1}; HRMS-EI (m/z) calcd for $C_{18}H_{20}O_2$ (M^+) 268.1463, found 268.1463. Slower eluting diastereomer: ^1H NMR (300 MHz, $CDCl_3$) δ 7.19-7.37 (m, 7H), 6.89 (d, J = 8.7 Hz, 2H), 5.94 (ddt, J = 9.5, 17.1, 7.3 Hz, 1H), 5.14 (d, J = 9.5 Hz, 1H), 5.08 (dd, J = 17.1, 1.4 Hz, 1H), 4.41 (dt, J = 3.5, 8.3 Hz, 1H), 3.91 (d, J = 8.3 Hz, 1H), 3.80 (s, 3H), 2.33-2.36 (m, 1H), 2.17-2.20 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 142.8, 135.1, 135.0, 133.4, 129.9, 128.8, 128.6, 128.3, 126.7, 117.9, 114.3, 73.1, 57.2, 55.3, 39.7.

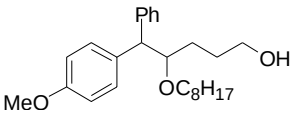
1-Methoxy-4-(2-octyloxy-1-phenyl-pent-4-enyl)benzene (1.8)



To neat alcohol **1.7** (0.56 g, 2.10 mmol) at rt were added NaH (60% in mineral oil, 0.36 g, 9.0 mmol) and 1-iodooctane (3.20 g, 13.3 mmol). The resulting mixture was heated to 120 °C and was stirred overnight at that temperature. The reaction mixture was cooled to 0 °C, diluted with 5 mL of hexanes, and quenched with an ice chunk. The resulting mixture was extracted with 50% EtOAc in hexanes (3 × 10 mL). The organic layers were combined, washed with H_2O (10 mL) and brine (10 mL), then were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (0-4% EtOAc in hexanes) to afford the desired product (0.75 g, 95%) as a mixture of 2 diastereomers: ^1H NMR (300 MHz, $CDCl_3$) δ 7.13 -7.38 (m, 7H), 6.79-6.83 (m, 2H), 5.84-5.93 (m, 1H), 4.95-5.07 (m, 2H), 3.91-3.99 (m, 2H), 3.74 (s, 50% of 3H), 3.73 (s, 50% of 3H), 3.43 (app dt, *J* = 8.4, 6.3 Hz, 1H), 3.05 (app dt, *J* = 8.4, 6.3 Hz, 1H), 2.20-2.35 (m, 2H), 1.10-1.40 (m, 12H), 0.92 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2, 143.4, 142.8, 135.2, 135.1, 134.4, 130.2, 129.6, 129.1, 128.6, 128.5, 128.2, 126.3, 126.2, 117.2, 113.9, 113.6, 82.3, 82.2, 70.6, 55.2, 37.2, 37.0, 32.0, 30.2, 29.5, 29.4, 26.3, 22.8, 14.3; IR (neat)

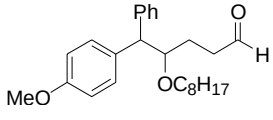
3027, 2998, 2927, 2855, 1610, 1510, 1463, 1248, 1178, 1099, 699 cm^{-1}; HRMS-EI (m/z) calcd for $C_{23}H_{31}O_2$ $[M - C_3H_5]^+$ 339.2324, found 339.2312.

5-(4-Methoxyphenyl)-4-octyloxy-5-phenylpentan-1-ol (1.15)



To a stirring solution of olefin **1.8** (0.80 g, 2.10 mmol) in THF (8 mL) at 0 °C was added BH_3·THF (1 M in THF, 6.5 mL, 6.5 mmol) dropwise. The reaction mixture was stirred at 0 °C for 10 min and was quenched with NaOH (20% aqueous solution, 1.5 mL) and H_2O_2 (30%, 1.5 mL). The resulting mixture was stirred for 0.5 h and saturated Na_2SO_3 (10 mL) was added slowly. After additional 0.5 h, the organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The organic layers were combined, washed with H_2O (10 mL) and brine (10 mL), then were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (15-20% EtOAc in hexanes) to provide the desired product (0.44 g, 53%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14-7.37 (m, 7H), 6.81-6.85 (d, *J* = 8.7 Hz, 2H), 3.99-4.05 (m, 2H), 3.76 (s, 3H), 3.54-3.66 (m, 2H), 3.40 (dt, *J* = 8.7, 6.5 Hz, 1H), 3.04 (dt, *J* = 8.7, 6.5 Hz, 1H), 1.60-1.72 (m, 2H), 1.13-1.37 (m, 14H), 0.91 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 157.9, 143.0, 142.8, 134.6, 134.4, 129.8, 129.6, 129.3, 128.7, 128.3, 128.0, 126.1, 126.0, 113.8, 113.1, 82.3, 82.2, 70.4, 62.6, 54.9, 54.6, 31.8, 29.9, 29.3, 29.2, 29.1, 28.3, 28.2, 25.9, 22.6, 14.1; IR (neat): 3382, 2928, 1610, 1513, 1248, 1178, 1035, 910, 699 cm^{-1}; HRMS-EI (m/z) calcd for $C_{26}H_{36}O_2$ $[M - H_2O]^+$ 380.2715, found 380.2714.

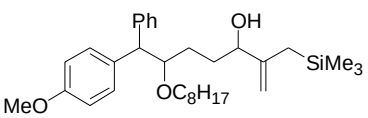
5-(4-Methoxyphenyl)-4-octyloxy-5-phenylpentanal (1.9)



To a stirring mixture of alcohol **1.15** (445 mg, 1.12 mmol) and $NaHCO_3$ (235 mg, 2.8 mmol) in CH_2Cl_2 (10 mL) at 0 ˚C was added Dess-Martin

periodinane (458 mg, 1.35 mmol). The ice bath was removed and the reaction mixture was stirred at rt for 1 h. Saturated $NaHCO_3$ (3 mL) and saturated $Na_2S_2O_3$ (3 mL) were added to the reaction mixture. The resulting cloudy mixture was stirred at rt for 0.5 h. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined, washed with H_2O and brine, then were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (10% EtOAc in hexanes) to provide the desired product (380 mg, 88%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.70 (s, 1H), 7.18-7.43 (m, 7H), 6.85-6.92 (m, 2H), 3.99 (br s, 2H), 3.76 (2 singlets, 3H), 3.29 (dt, *J* = 8.3, 6.4 Hz, 1H), 2.99 (dt, *J* = 8.3, 6.4 Hz, 1H), 2.38-2.42 (m, 2H), 1.93-2.00 (m, 1H), 1.69-1.77 (m, 1H), 1.17-1.38 (m, 12H), 0.93 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.0, 158.2, 158.2, 142.6, 134.3, 134.2, 129.8, 129.3, 128.7, 128.5, 128.3, 128.1, 126.3, 126.2, 113.0, 113.5, 81.5, 81.4, 70.7, 70.6, 55.8, 54.9, 39.8, 39.7, 31.8, 29.9, 29.3, 29.2, 25.9, 25.7, 25.6, 22.6, 14.1; IR (neat) 3061, 3028, 2999, 2926, 2855, 1723, 1610, 1510, 1455, 1301, 1248, 1178, 1035, 700 cm^{-1}; LRMS-CI (m/z) calcd for $C_{26}H_{36}O_3$ 397.27 $[M + H]^+$, found 397.

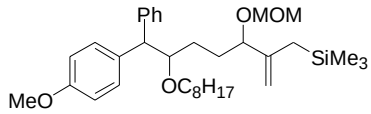
7-(4-Methoxyphenyl)-6-octyloxy-7-phenyl-2-trimethylsilylmethyl-hept-1-en-3-ol



To a stirring solution of 2-bromo-3-(trimethylsilyl)propene (88 mg, 0.45 mmol) in THF (1 mL) at -78 ˚C was added *tert*-butyllithium (1.35 M in pentane, 0.71 mL, 0.96 mmol) dropwise. The reaction mixture was stirred for 45 min at -78˚C and at -20˚C for 30 min. A solution of $MgBr_2$ (0.45 mmol in 1 mL of Et_2O) was added and the resulting cloudy mixture was allowed to warm to rt over 2 h. The resulting clear solution was added to a solution of aldehyde **9** (100 mg, 0.25 mmol) in THF (1 mL) at –78 ˚C. The

reaction mixture was stirred for 15 min then was poured into a mixture of ether (20 mL) and saturated NH_4Cl (10 mL). The organic layer was separated, and the aqueous layer was extracted with ether (3 × 10 mL). The combined organic layers were washed with H_2O and brine, then were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was used directly in the next step. A small amount of the unstable product was purified for characterization: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14-7.38 (m, 7H), 6.80-6.83 (d, *J* = 8.5 Hz, 2H), 4.87 (s, 1H), 4.64 (s, 1H), 3.98 (br s, 2H), 3.89 (br s, 1H), 3.77 (s, 3H), 3.34 (dt, *J* = 8.5, 6.5 Hz, 1H), 3.02 (dt, *J* = 8.5, 6.5 Hz, 1H), 2.01 (br s, 1H), 1.74 (br s, 1H), 1.53-1.73 (m, 4H), 1.12-1.37 (m, 12H), 0.87 (t, *J* = 6.8 Hz, 3H), 0.03 (s, 9H); LRMS-CI (m/z) calcd for $C_{32}H_{50}O_3Si$ 511.35 [M + H]$^+$, found 511.

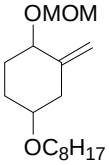
[3-Methoxymethoxy-7-(4-methoxyphenyl)-2-methylene-6-octyloxy-7-phenylheptyl]-trimethylsilane (1.1)



To the crude 7-(4-methoxyphenyl)-6-octyloxy-7-phenyl-2-trimethylsilylmethylhept-1-en-3-ol in DIPEA (1.5 mL) at 0 ˚C was added MOMCl (0.1 mL, 1.3 mmol), followed by a small crystal of DMAP. The resulting mixture was warmed to 35 ˚C and was stirred at that temperature for 5 h. Saturated NH_4Cl (1 mL) was added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 × 5 mL). The organic layers were combined, washed with H_2O (5 mL) and brine (5 mL), then were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (EtOAc/CH_2Cl_2/hexanes = 3/10/87) to afford the desired product (55 mg, 40% over 2 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18-7.38 (m, 7H), 6.80-6.84 (m, 2H), 4.84 (s, 1H), 4.71 (s, 1H), 4.56-4.59 (m, 1H), 4.41-4.46 (m, 1H), 3.92-3.98 (m, 2H),

3.76-3.78 (m, 4H), 3.36-3.40 (m, 1H), 3.28 (d, J = 2.2 Hz, 50% of 3H), 3.20 (d, J = 7.0 Hz, 50% of 3H), 3.04-3.07 (m, 1H), 1.47-1.62 (m, 4H), 1.15-1.40 (m, 14H), 0.89, (t, J = 6.7 Hz, 3H), 0.01 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 146.1, 146.0, 143.4, 143.1, 142.9, 135.2, 134.9, 134.6, 130.3, 130.1, 129.6, 129.2, 128.9, 128.7, 128.6, 128.2, 126.3, 126.2, 113.9, 113.6, 110.4, 93.9, 82.7, 80.3, 80.1, 70.7, 70.4, 56.1, 55.6, 55.3, 32.0, 30.3, 29.6, 29.5, 29.0, 26.3, 22.9, 21.2, 14.3, -0.8; IR (neat) 2928, 2855, 1511, 1464, 1248, 1098, 1035, 841, 698 cm^{-1}; HRMS-EI (m/z) calcd for $C_{32}H_{49}O_2Si$ $[M - OCH_2OCH_3]^+$ 493.3502, found 493.3523.

1-Methoxymethoxy-2-methylene-4-octyloxycyclohexane (1.11)



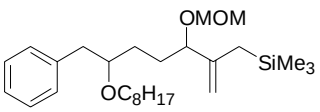
To allylsilane **1.1** (41 mg, 0.074 mmol) in DCE (3.0 mL) were added $NaHCO_3$ (82 mg, 0.98 mmol) and 4 Å molecular sieves (82 mg). The resulting mixture was warmed to 40 °C, then a solution of CAN (101 mg, 0.185 mmol) in acetonitrile (0.9 mL) was added dropwise. After 10 min, the reaction mixture was filtered through a short plug of silica gel. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by flash chromatography (3% EtOAc in hexanes) to afford the desired product (16.6 mg, 71%) as 2 diastereomers (~1.7:1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.98 (s, 1H, 63% of 1H), 4.94 (m, 37% of 1H), 4.92 (m, 37% of 1H), 4.86 (m, 63% of 1H), 4.68 (d, J = 6.6 Hz, 63% of 1H, OCH_2O), 4.63 (d, J = 6.6 Hz, 63% of 1H, OCH_2O), 4.65 (d, J = 6.6 Hz, 37% of 1H, OCH_2O), 4.54 (d, J = 6.6 Hz, 37% of 1H, OCH_2O), 4.03-4.05 (m, 63% of 1H), 3.21-3.50 (m, 3H), 3.24-3.36 (m, 37% of 1H), 3.38 (s, 63% of 3H, OCH_3), 3.40 (s, 37% of 3H, OCH_3), 2.57 (dd, J = 3.7, 13.1 Hz, 63% of 1H), 2.41 (dd, J = 4.5, 11.3 Hz, 37% of 1H), 2.22-2.30 (m, 37% of 1H), 2.10-2.14 (m, 63% of 1H), 1.94-2.07 (m, 2H), 1.69-1.83 (m, 1H), 1.46-1.59 (m, 4H), 1.26 (m, 10H), 0.86 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.9, 144.8, 112.8, 109.9, 94.7, 93.7, 77.4, 76.2, 74.3,

68.6, 68.4, 55.6, 55.5, 38.6, 37.7, 32.1, 30.4, 30.3, 30.1, 30.0, 29.9, 29.7, 29.5, 28.6, 27.2, 26.4, 22.9, 14.3; IR (neat) 2927, 2855, 1449, 1156, 1106, 1038 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{32}O_3$ [M^+] 284.2351, found 284.2346.

Cyclization of 1.1 under photochemical conditions:

To allylsilane **1.1** (50 mg, 0.09 mmol) in DCE (5.0 mL) were added $NMQPF_6$ (1.3 mg, 0.0045 mmol), NaOAc (100 mg, 1.22 mmol), $Na_2S_2O_3$ (100mg, 0.63 mmol), 4 Å molecular sieves (100 mg) and toluene (1 mL). The resulting mixture was stirred at rt while bubbling air gently and irradiating with a medium pressure mercury lamp at a distance of 4 cm. After 3 h, additional 3 mg (0.01 mmol) of $NMQPF_6$ was added and the reaction mixture was allowed to proceed for another 1 h. The reaction mixture was filtered through a short plug of silica gel, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by flash chromatography (3% EtOAc in hexanes) to provide the desired product (12.9 mg, 50%) as 2 diastereomers in ~1.7:1 ratio.

(3-Methoxymethoxy-2-methylene-6-octyloxy-7-phenylheptyl)trimethylsilane (1.12)



This substrate was prepared following the same sequence used to make allylsilane **1.1**.

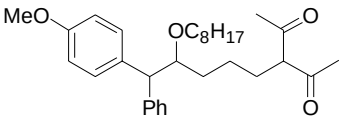
^1H NMR (300 MHz, $CDCl_3$) δ 7.16-7.29 (m, 5H), 4.85-4.87 (m, 50% of 2H), 4.72-4.73 (m, 50% of 2H), 4.59 (dd, *J* = 1.5, 6.7Hz, 50% of 2H), 4.44 (dd, *J* = 2.0, 6.7Hz, 50% of 2H), 3.81-3.88 (m, 1H), 3.35-3.54 (m, 3H), 3.31 (s, 50% of 3H), 3.28 (s, 50% of 3H), 2.81 (ddd, *J* = 4.6, 6.2, 13.5 Hz, 1H), 2.65 (ddd, *J* = 3.1, 6.2, 13.5 Hz, 1H), 1.25-1.90 (m, 18H), 0.86 (t, *J* = 6.8 Hz, 3H), 0.02 (s, 9H); IR (neat) 2924, 2852, 1250, 1091, 1029, 845 cm^{-1}; HRMS (EI) calcd for $C_{27}H_{48}O_3Si$ [M^+] 448.3372, found 448.3380.

CAN oxidation of 1.12:

To a stirring mixture of **1.12** (40 mg, 0.89 mmol), $NaHCO_3$ (83 mg, 1.0 mmol), and acetonitrile (3 mL) at rt was added CAN (97 mg, 0.177 mmol). The resulting mixture was stirred at rt for 1.5 h, then was heated under reflux for 1 h. The reaction mixture was cooled to rt and additional CAN (64 mg) was added. The resulting mixture was heated at reflux for another 1 h. The reaction mixture was cooled to rt and was filtered through a short plug of silica gel. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by flash chromatography (4-7% of EtOAc in hexanes). No cyclization product was detected. The two products obtained are consistent to alkane **13** and nitrate **1.14**. **1.13**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20-7.27 (m, 5H), 4.87-4.89 (2 singlets, 2H), 4.59 (d, *J* = 6.6 Hz, 1H), 4.45-4.47 (d, *J* = 6.6 Hz, 1H), 3.91-3.96 (m, 1H), 3.36-3.45 (m, 3H), 3.32 (s, 50% of 3H), 3.26 (s, 50% of 3H), 2.82 (ddd, *J* = 6.4, 9.6, 13.2 Hz, 1H), 2.66 (ddd, *J* = 6.0, 9.8, 13.2 Hz, 1H), 1.51-1.76 (m, 6H), 1.64 (s, 3H), 1.20-1.30 (m, 10H), 0.86 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2, 144.1, 139.5, 139.4, 129.8, 129.7, 129.6, 128.4, 126.2, 120.6, 114.1, 114.0, 93.8, 81.0, 80.6, 80.4, 80.0, 69.9, 69.8, 55.6, 41.2, 41.1, 32.0, 30.7, 30.3, 29.9, 29.7, 29.6, 29.4, 29.3, 26.4, 22.8, 22.5, 17.0, 16.9, 14.3; IR (neat) 2927, 2855, 1449, 1097, 1033, 898, 699 cm^{-1}; LRMS (EI) calcd for $C_{22}H_{35}O$ $[M - OCH_2OCH_3]^+$ 315, found 315. **1.14**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19-7.27 (m, 5H), 5.31-5.32 (2 singlets, 1H), 5.25-5.28 (2 singlets, 1H), 4.92 (d, *J* = 13.6 Hz, 1H), 4.85 (d, *J* = 13.6 Hz, 1H), 4.57 (dd, *J* = 1.3, 6.8 Hz, 1H), 4.46 (d, *J* = 6.8 Hz, 1H), 4.04-4.09 (m, 1H), 3.37-3.45 (m, 3H), 3.31 (s, 50% of 3H), 3.29 (s, 50% of 3H), 2.83 (dt, *J* = 7.2, 13.6 Hz, 1H), 2.63 (dt, *J* = 7.2, 13.6 Hz, 1H), 1.50-1.65 (m, 6H), 1.20-1.30 (m, 10H), 0.86 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.5, 140.4, 139.1, 129.6, 128.4, 126.2, 118.6, 94.3, 94.2, 80.7, 80.4, 77.9, 78.2, 71.6, 71.5, 70.0, 69.9, 55.8, 41.1, 41.0, 32.0, 30.6, 30.3, 30.2, 30.1, 29.9, 29.6, 29.4, 26.4,

22.8, 22.5, 14.3; IR (neat) 2926, 2851, 1636, 1277, 1092, 1027, 843 cm^{-1}; LRMS (EI) calcd for $C_{22}H_{34}NO_4$ $[M - OCH_2OCH_3]^+$ 376, found 376.

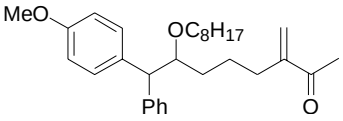
3-[5-(4-Methoxyphenyl)-4-octyloxy-5-phenylpentyl]-pentane-2,4-dione (1.17)



To a stirring mixture of alcohol **1.15** (1.53 g, 3.83 mmol) and triethylamine (1.55 g, 15.31 mmol) in CH_2Cl_2 (20 mL) at 0 ˚C was added MsCl (0.66g, 5.74 mmol) dropwise. After 0.5 h, water was added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, washed with water, saturated $NaHCO_3$ and brine, then were dried over Na_2SO_4, filtered and concentrated under reduce pressure. The resulting residue was dissolved in 20 mL of acetone and NaI (2.87 g, 19.14 mmol) was added. The resulting mixture was heated at reflux for 1.5 h. The reaction mixture was cooled to rt and was concentrated under reduced pressure. The resulting residue was dissolved in water and ethyl acetate, the organic layer was separated and the aqueous layer was extracted with ether. The organic layers were combined, washed with water and brine, then were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (8% EtOAc in hexanes) to provide iodide **1.16** (1.79 g, 92%). To a stirring mixture of iodide **1.16** (969 mg, 1.91 mmol), 2,4-pentanedione (385 mg, 2.86 mmol), and anhydrous acetone (1 mL) was added potassium carbonate (403 mg, 2.02 mmol). The resulting mixture was heated at reflux for 22 h. The reaction mixture was cooled to rt and was filtered through Celite. The filtrate was concentrated under reduced pressure. The resulting residue was purified by flash chromatography (7-10% EtOAc in hexanes) to provide the desired product (514 mg, 56%) and unreacted starting material (389 mg, 40%). **1.17** exists as a ~1:1 mixture of dione and enol: ^1H

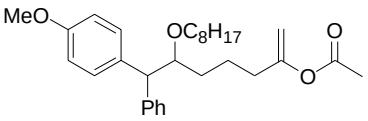
NMR (300 MHz, $CDCl_3$) δ 7.17-7.37 (m, 7H), 6.80-6.84 (m, 2H), 3.87-3.95 (m, 2H), 3.77 (s, 3H), 3.54 (t, *J* = 7.7 Hz, 50% of 1H, enone α-H), 3.30 (dt, *J* = 8.7, 6.7 Hz, 1H), 3.01 (dt, *J* = 8.7, 6.7 Hz, 1H), 2.06 (s, 3H), 2.05 (s, 3H), 1.17-1.76 (m, 18H), 0.86 (t, *J* = 6.7 Hz, 3H); IR (neat) 3466, 2924, 2851, 1698, 1608, 1509, 1458, 1359, 1247, 1174, 1359, 1032, 722, 688 cm^{-1}; LRMS (EI) calcd for $C_{23}H_{27}O_3$ $[M - OC_8H_{17}]^+$ 351.2, found 351.

8-(4-Methoxyphenyl)-3-methylene-7-octyloxy-8-phenyloctan-2-one (1.18)



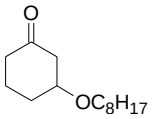
To a stirring mixture of dione **1.17** (637 mg, 1.32 mmol) and formaldehyde (37% aqueous solution, 0.33 mL, 4.1 mmol) in 1,4-dioxane (1 mL) was added K_2CO_3 (500 mg, 3.6 mmol) in water (0.33 mL). The resulting mixture was stirred for 12 h at 35˚C. More water was added and the resulting mixture was extracted with ethyl acetate. The combined organic layers were washed with water and brine, then were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (7-30% ethyl acetate in hexanes) to give the desired product (348 mg, 58%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17-7.39 (m, 7H), 6.80-6.84 (m, 2H), 5.96 (s, 1H), 5.70 (s, 1H), 3.91-3.97 (m, 2H), 3.77 (s, 3H), 3.35 (dt, *J* = 8.7, 6.7 Hz, 1H), 3.01 (dt, *J* = 8.7, 6.7 Hz, 1H), 2.30 (s, 3H), 2.16-2.30 (m, 2H), 1.47-1.57 (m, 4H), 1.13-1.44 (m, 12H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 199.8, 158.1, 149.2, 143.0, 135.2, 129.5, 129.0, 128.6, 128.5, 128.2, 126.1, 124.8, 113.9, 82.4, 70.6, 32.5, 31.9, 30.6, 30.2, 29.8, 29.5, 29.3, 26.2, 26.0, 24.0, 22.8, 14.2; IR (neat) 2927, 2855, 1678, 1610, 1454, 1248, 1100, 1035, 699 cm^{-1}; LRMS (ESI) calcd for $C_{30}H_{42}O_3Na$ $[M + Na]^+$ 473.3, found 473.3.

Acetic acid 6-(4-methoxyphenyl)-1-methylene-5-octyloxy-6-phenylhexyl ester (1.2)



To a stirring mixture of 4 Å molecular sieves (100 mg, flame dried under vacuum) and CH_2Cl_2 (4 mL) were added racemic *trans*-1,2-(diamino)cyclohexane (0.572 M in CH_2Cl_2, 0.50 mL, 0.29 mmol) and $SnCl_4$ (1 M in CH_2Cl_2, 0.29 mL, 0.29 mmol). After the reaction mixture was cooled to 0 ˚C, bis(trimethylsilyl)peroxide (211 mg, 1.0 mmol) was added, followed by a solution of enone **1.18** (117 mg, 0.26 mmol) in CH_2Cl_2 (4 mL) after 7 min. The reaction mixture was stirred at rt for 40 h. Solid $Na_2S_2O_3$ (~100 mg) was added and the resulting mixture was stirred for another 3 h. The reaction mixture was filtered through a short pad of Celite, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by flash chromatography (5-10% EtOAc in hexanes) to provide the desired product (87 mg, 71%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24-7.34 (m, 7H), 6.87-6.91 (m, 2H), 4.75-4.77 (m, 2H), 3.98-4.04 (m, 2H), 3.84 (s, 3H), 3.41 (dt, *J* = 8.7, 6.4 Hz, 1H), 3.09 (dt, *J* = 8.7, 6.6 Hz, 1H), 2.21-2.29 (m, 2H), 2.18 (s, 3H), 1.59-1.66 (m, 4H), 1.26-1.50 (m, 12H), 0.94 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 158.1, 156.4, 143.0, 135.1, 129.5, 129.0, 128.2, 126.2, 114.0, 101.4, 82.3, 70.6, 55.7, 55.3, 33.5, 32.2, 32.0, 30.2, 29.5, 29.4, 26.2, 22.8, 22.2, 21.2, 14.3; IR (neat) 2927, 2854, 1756, 1511, 1248, 1199, 1178, 1101, 698 cm^{-1}; LRMS (ESI) calcd for $C_{30}H_{42}O_4Na$ $[M + Na]^+$ 489.3, found 489.3.

3-Octyloxycyclohexanone (1.19)



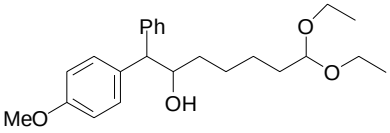
To enol acetate **1.2** (100 mg, 0.22 mmol) in DCE (8.0 mL) were added $NaHCO_3$ (200 mg, 2.38 mmol) and 4 Å molecular sieves (200 mg). The resulting mixture was heated to 50 ˚C. A solution of CAN (294 mg, 0.54 mmol) in acetonitrile (2.6 mL) was added to the resulting mixture dropwise. After 5 min, the reaction mixture was cooled to rt and was filtered through a short plug of silica gel. The filtrate was concentrated under reduced pressure,

and the residue was purified by flash chromatography (4% EtOAc in hexanes) to afford the desired product (46 mg, 94%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.65-3.75 (m, 1H), 3.38 (app t, J = 6.6 Hz, 2H), 2.57 (dd, J = 14.0, 3.8 Hz, 1H), 2.41 (dd, J = 14.0, 7.3 Hz, 1H), 2.28 (app t, J = 6.4 Hz, 2H), 1.93-2.05 (m, 2H), 1.78-1.82 (m, 1H), 1.65-1.69 (m, 1H), 1.48-1.55 (m, 2H), 1.26 (br s, 10H), 0.85 (t, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 210.1, 68.7, 47.9, 41.3, 32.0, 30.3, 30.1, 29.6, 29.5, 26.4, 22.9, 20.9, 14.3; IR (neat) 2925, 2849, 1715, 1453, 1099 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{26}O_2$ [M^+] 226.1932, found 226.1923.

Cyclization of 1.2 under photochemical conditions:

To **1.2** (29.6 mg, 0.064 mmol) in DCE (5.0 mL) in a borosilicate flask were added $NMQPF_6$ (0.9 mg, 0.0032 mmol), NaOAc (60 mg, 0.73 mmol), $Na_2S_2O_3$ (60 mg, 0.38 mmol), 4 Å Molecular sieves (60 mg) and toluene (1 mL). The resulting mixture was stirred at rt while bubbling air gently and irradiating with a medium pressure mercury lamp at a distance of 4 cm for 2 h. The reaction mixture was filtered through a short plug of silica gel, and the filtrate was concentrated under vacuum. The resulting residue was purified by flash chromatography (4% EtOAc in hexanes) to afford the desired product (11 mg, 75%).

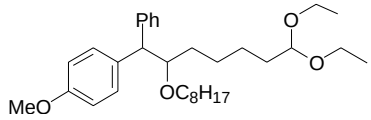
7,7-Diethoxy-1-(4-methoxyphenyl)-1-phenylheptan-2-ol (1.22)



THF (4.6 mL) was added dropwise to dry $CeCl_3$ solid (0.68 g, 2.76 mmol) at 0 °C with stirring. The resulting suspension was subjected to sonication for 1 h. A Grignard solution [made from bromide **1.20** (0.76 g, 3.17 mmol) and magnesium ribbon (76 mg, 3.17 mmol) in 5 mL of THF] was added to the $CeCl_3$ suspension dropwise at 0 °C. The reaction mixture turned yellow. After 1.5 h, a solution of aldehyde **1.6** (0.5 g, 2.4 mmol) in THF (2 mL) was added to the reaction mixture dropwise at 0 °C. The resulting mixture was stirred for 50 min and was quenched with 10% acetic acid (10

mL). The organic layer was separated and the aqueous layer was extracted with EtOAc. The organic layers were combined, washed with H_2O, saturated $NaHCO_3$, and brine, then were dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the resulting residue by flash chromatography (20-25% EtOAc in hexanes) provided the desired product (612 mg, 66%) as 2 diastereomers. Ketone product **1.23** (100 mg, 11%) was also isolated, which was reduced to the desired alcohol with $NaBH_4$, giving a 77% overall yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19-7.38 (m, 7H), 6.81 (d, *J* = 6.6 Hz, 50% of 2H), 6.82 (d, *J* = 6.6 Hz, 50% of 2H), 4.43 (t, *J* = 5.7 Hz, 1H), 4.28-4.32 (m, 1H), 3.81 (d, *J* = 8.3 Hz, 1H), 3.77 (s, 3H), 3.57-3.65 (m, 2H), 3.42-3.52 (m, 2H), 1.40-1.61 (m, 4H), 1.30-1.40 (m, 4H), 1.17 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.4, 142.0, 134.8, 129.36, 129.0, 128.9, 128.4, 128.0, 126.6, 114.0, 103.1, 74.0, 61.1, 61.0, 58.1, 55.4, 35.1, 33.8, 25.9, 24.9, 15.6; IR (neat) 3462, 2973, 2934, 1610, 1511, 1248, 1177, 1036, 700 cm^{-1}; LRMS (EI) calcd for $C_{22}H_{29}O_3$ $[M - OC_2H_5]^+$ 341.2, found 341. Also, HRMS (EI) calcd for $C_{22}H_{28}O_3$ $[M - OC_2H_5 - H]^+$ 340.2038, found 340.2021. Ketone product **1.23**: δ 7.22-7.35 (m, 7H), 6.84 (d, *J* = 6.6 Hz, 50% of 2H), 6.85 (d, *J* = 6.6 Hz, 50% of 2H), 4.43 (t, *J* = 5.5 Hz, 1H), 3.82 (s, 1H), 3.79 (s, 3H), 3.58-3.64 (m, 2H), 3.41-3.51 (m, 2H), 2.52 (t, *J* = 7.1 Hz, 2H), 1.55-1.64 (m, 2H), 1.25-1.36 (m, 4H), 1.18 (t, *J* = 7.0 Hz, 6H).

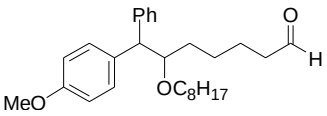
1-(7,7-Diethoxy-2-octyloxy-1-phenylheptyl)-4-methoxybenzene



To neat alcohol **1.22** (0.3 g, 0.78 mmol) at rt were added NaH (60% in mineral oil, 123 mg, 3.11 mmol) and 1-iodooctane (1.43 g, 6.21 mmol). The resulting mixture was heated to 120 °C and was stirred overnight at that temperature. The reaction mixture was cooled to 0 °C and was diluted with hexanes (5 mL). Water (2 mL) was added slowly to the resulting mixture. The organic layer was separated and

the aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, then were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (5% EtOAc in hexanes) to provide the desired product (220 mg, 57%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17-7.40 (m, 7H), 6.81 (d, *J* = 8.6 Hz, 50% of 2H), 6.82 (d, *J* = 8.6 Hz, 50% of 2H), 4.41 (t, *J* = 5.6 Hz, 1H), 3.95 (d, *J* = 7.9 Hz, 1H), 3.90-3.94 (m, 1H), 3.76 (2 singlets, 3H), 3.61-3.67 (m, 2H), 3.45-3.51 (m, 2H), 3.32-3.40 (m, 1H), 3.00-3.06 (m, 1H), 1.17-1.60 (m, 20H), 1.21 (t, *J* = 6.7 Hz, 6H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 143.5, 143.0, 135.2, 134.6, 130.1, 129.4, 128.9, 128.5, 128.4, 128.1, 126.2, 126.1, 113.8, 113.5, 102.9, 82.6, 82.5, 70.5, 60.9, 55.7, 55.1, 33.6, 32.9, 32.8, 31.9, 30.2, 29.4, 29.3, 26.2, 25.30, 25.1, 24.9, 22.7, 15.4, 14.2; IR (neat) 2924, 2847, 1705, 1506, 1239 cm^{-1}.

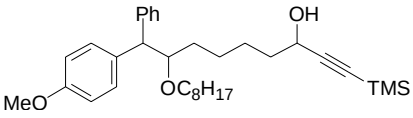
7-(4-Methoxyphenyl)-6-octyloxy-7-phenyl-heptanal (1.24)



To 1-(7,7-diethoxy-2-octyloxy-1-phenylheptyl)-4-methoxybenzene (0.22 g, 0.44 mmol) in $CHCl_3$ (8 mL) at 0 °C was added 50% aqueous trifluoroacetic acid (4 mL). After 1.5 h, saturated $NaHCO_3$ was added to the reaction mixture until no gas evolution was seen. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, then were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue (0.19 g, ~100%) was sufficiently pure to be used in the next step. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.69 (s, 1H), 7.17-7.40 (m, 7H), 6.81 (d, *J* = 7.9 Hz, 2H), 3.95 (d, *J* = 7.9 Hz, 1H), 3.92 (br s, 1H), 3.75 (s, 3H), 3.33 (dt, *J* = 8.1, 6.5 Hz, 1H), 3.03 (dt, *J* = 8.1, 6.5 Hz, 1H), 2.32 (t, *J* = 6.2, 2H), 1.16-1.55 (m, 18H), 0.89 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.5, 158.0,

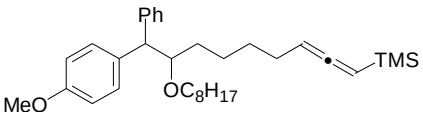
143.2, 142.8, 135.0, 134.4, 131.1, 130.0, 129.4, 128.9, 128.4, 128.1, 126.2, 126.0, 113.8, 113.5, 82.3, 82.2, 70.6, 70.5, 55.6, 55.1, 43.7, 32.7, 32.5, 31.8, 30.1, 29.4, 29.3, 26.1, 24.9, 24.8, 22.7, 22.1, 14.1; IR (neat) 2924, 2852, 1700, 1511, 1454, 1239 cm^{-1}.

9-(4-Methoxyphenyl)-8-octyloxy-9-phenyl-1-trimethylsilylnon-1-yn-3-ol (1.25)



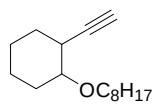
To a stirring solution of trimethylsilylacetylene (0.22 g, 2.25 mmol) in THF (5 mL) at 0 °C was added *n*-BuLi (1.6 M in hexanes, 1.26 mL, 2.0 mmol) dropwise. The reaction mixture was stirred at 0 °C for 45 min. The resulting solution was added to a solution of aldehyde **1.24** (190 mg, 0.44 mmol) in THF (3 mL) at 0 °C. After stirred at 0 °C for 1 h, the reaction mixture was quenched with saturated NH_4Cl. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, then were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (10% EtOAc in hexanes) to afford the desired product (172 mg, 75%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18-7.40 (m, 7H), 6.81 (d, *J* = 8.6 Hz, 2H), 4.32 (t, *J* = 6.2 Hz, 1H), 3.97 (d, *J* = 8.1 Hz, 1H), 3.90 (br s, 1H), 3.77 (s, 3H), 3.35 (dt, *J* = 8.6, 6.7 Hz, 1H), 3.01 (dt, *J* = 8.6, 6.7 Hz, 1H), 1.89 (br s, 1H, OH), 1.60-1.68 (m, 2H), 1.14-1.5 (m, 18H), 0.90 (t, *J* = 6.7 Hz, 3H), 0.18 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 143.5, 143.0, 135.3, 134.7, 130.1, 129.5, 129.0, 128.6, 128.5, 128.2, 126.2, 113.9, 113.6, 107.0, 89.4, 82.5, 70.7, 62.9, 62.9, 55.9, 55.3, 37.8, 32.9, 32.0, 30.2, 29.5, 29.4, 26.2, 25.4, 25.3, 25.1, 22.8, 14.3, 0.1; IR (neat) 3429, 2926, 2855, 2170, 1512, 1033, 1243, 835 cm^{-1}; HRMS (EI) calcd for $C_{32}H_{47}O_3$ $[M - CH_3]^+$ 507.3294, found 507.3302.

[9-(4-Methoxyphenyl)-8-octyloxy-9-phenylnona-1,2-dienyl] trimethylsilane (1.27)



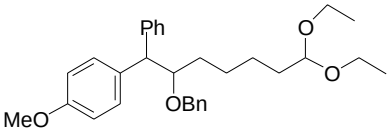
To a stirring solution of PPh_3 (0.13 g, 0.49 mmol) in THF (2.5 mL) at -10 °C was added DEAD (86 mg, 0.49 mmol). The reaction mixture turned yellow. The reaction mixture was stirred at –10 °C for 10 min, and a solution of alcohol **1.25** (172 mg, 0.33 mmol) in THF was added. After another 10 min, a solution of NBSH **1.26** (208 mg, 0.82 mmol) in THF (2 mL) was added. The reaction temperature was allowed to increase to rt slowly. After 2.5 h, the reaction mixture was concentrated under reduced pressure. The resulting residue was dissolved in EtOAc (2 mL), and the resulting solution was added to stirring hexanes (50 mL) dropwise. A precipitate formed and the resulting suspension was filtered through a thin silica gel plug eluting with 5% EtOAc in hexanes. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by flash chromatography (5% EtOAc in hexanes) to afford the desired product (140 mg, 84%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18-7.37 (m, 7H), 6.7 (d, J = 8.5Hz, 2H), 4.84 (dt, J = 6.8, 3.5 Hz, 1H), 4.69 (ddd, J = ~0.8, 6.8, 13.6 Hz, 1H), 3.93 (d, J = 7.8 Hz, 1H), 3.86 (br s, 1H), 3.77 (2 singlets, 3H), 3.31 (dt, J = 8.7, 6.6 Hz, 1H), 2.97 (dt, J = 8.7, 6.6 Hz, 1H), 1.90 (br s, 1H), 1.12-1.55 (m, 18H), 0.86 (t, J = 6.9 Hz, 3H), 0.08 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.1, 158.0, 143.6, 135.4, 134.7, 130.2, 129.5, 129.1, 128.6, 128.4, 128.1, 126.2, 113.9, 113.5, 83.4, 82.6, 70.6, 55.7, 55.3, 33.0, 31.9, 31.7, 30.2, 30.0, 29.5, 29.4, 28.0, 26.2, 25.1, 22.8, 14.2, -0.7; IR (neat) 2922, 2851, 1936, 1611, 1508, 1449, 1251, 1097, 1104, 851 cm^{-1}; HRMS (EI) calcd for $C_{33}H_{50}O_2$ [M^+] 506.3580, found 506.3590.

1-Ethynyl-2-octyloxycyclohexane (1.28)



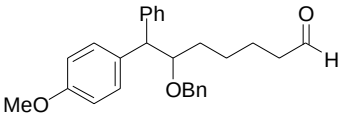
To allene **1.27** (73 mg, 0.145 mmol) in DCE (4.0 mL) were added $NaHCO_3$ (140 mg, 1.67 mmol) and 4 Å molecular sieves (140 mg). The stirring mixture was heated to 40 ˚C, then a solution of CAN (198 mg, 0.362 mmol) in acetonitrile (1.2 mL) was added dropwise. After 10 min, the reaction mixture was filtered through a short plug of silica gel. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by flash chromatography (20% toluene in hexanes) to afford the desired alkyne (28 mg, 81%, as 2 diastereomers in 1.2:1 ratio) and silylalkyne **1.29** (4.4 mg, 10%). The latter was converted to the titled product by treating it with TBAF, which gave a 91% overall yield. ***cis*-Isomer** of **1.28** (faster eluting diastereomer)[1]: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.50 (dt, *J* = 9.2, 6.7 Hz, 1H), 3.37 (dt, *J* = 9.2, 6.7 Hz, 1H), 3.22 (app dt, *J* = 8.5, 4.1 Hz, 1H), 2.97 (br s, 1H), 2.07 (d, *J* = 2.4 Hz, 1H), 1.70-1.75 (m, 1H), 1.26-1.70 (m, 19H), 0.86 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 85.0, 78.0, 70.6, 68.7, 32.8, 32.1, 30.2, 29.6, 29.5, 28.7, 26.4, 23.9, 22.9, 22.1, 14.3; IR (neat) 3310, 2930, 2847, 2114, 1457, 1366, 1100 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{28}O$ [M^+] 236.2140, found 236.2141. ***trans*-Isomer** of **1.28** (slower eluting diastereomer)[1]: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.49-3.57 (m, 2H), 3.19 (app dt, *J* = 3.9, 8.0 Hz, 1H), 2.38-2.45 (m, 1H), 2.06 (d, *J* = 2.4 Hz, 1H), 1.96-1.99 (m, 2H), 1.47-1.69 (m, 6H), 1.27 (br, 12H), 0.86 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 87.0, 79.7, 69.6, 69.1, 35.0, 32.0, 30.5, 30.2, 29.8, 29.6, 29.4, 26.3, 24.1, 23.4, 22.8, 14.2; IR (neat) 3306, 2926, 2855, 2166, 2114, 1449, 1362, 1104, 839 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{28}O$ [M^+] 236.2140, found 236.2149. **Silylalkyne 1.29:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.51 (dt, *J* = 9.1, 6.7 Hz, 1H), 3.37 (dt, *J* = 9.1, 6.5 Hz, 1H), 3.27 (app dt, *J* = 8.7, 3.8 Hz, 1H), 2.90 (m, 1H), 1.26-1.76 (m, 20H), 0.86 (t, *J* = 6.7 Hz, 3H), 0.15 (s, 9H); HRMS (EI) calcd for $C_{19}H_{36}OSi$ [M^+] 308.2535, found 308.2533.

1-(2-Benzyloxy-7,7-diethoxy-1-phenylheptyl)-4-methoxybenzene



To alcohol **1.22** (0.1 g, 0.26 mmol) in DMF (3 mL) at rt was added NaH (60% in mineral oil, 36 mg, 0.91 mmol). The reaction mixture was stirred for 10 min, then benzyl bromide (0.27 g, 1.55 mmol) was added dropwise. After 1.5 h, an ice chunk was added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 × 5 mL). The combined organic layers were washed with water and brine, then were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (8% EtOAc in hexanes) to provide the desired product (91 mg, 57%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22-7.49 (m, 10H), 7.00-7.10 (m, 2H), 6.87 (d, *J* = 8.7 Hz, 50% of 2H), 6.83 (d, *J* = 8.7 Hz, 50% of 2H), 4.40 (dt, *J* = 1.1, 5.7 Hz, 1H), 4.31 (d, *J* = 10.9 Hz, 1H), 4.12 (d, *J* = 10.9 Hz, 1H), 4.04-4.10 (m, 2H), 3.79 (2 singlets, 3H), 3.55 (dq, *J* = 9.3, 7.1 Hz, 2H), 3.41 (dq, *J* = 9.3, 7.1 Hz, 2H), 1.25-1.58 (br, 8H), 1.17 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 143.2, 142.9, 138.6, 138.5, 134.9, 134.4, 130.1, 129.4, 129.0, 128.5, 128.2, 127.9, 127.4, 126.2, 126.2, 113.9, 113.6, 102.9, 82.4, 82.3, 72.4, 61.0, 60.9, 55.7, 55.6, 55.1, 33.6, 32.7, 32.6, 25.1, 15.0, 24.9, 15.4, 14.2; IR (neat) 3060, 3028, 2972, 2937, 1610, 1510, 1452, 1249, 1062, 698 cm^{-1}; LRMS (EI) calcd for $C_{27}H_{28}O_2$ $[M - CH_2Ph - H]^+$ 384.2, found 384.

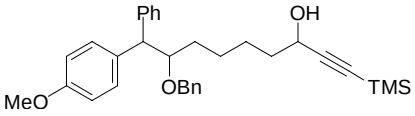
6-Benzyloxy-7-(4-methoxyphenyl)-7-phenylheptanal (1.30)



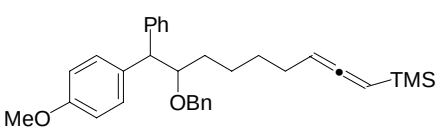
To 1-(2-benzyloxy-7,7-diethoxy-1-phenylheptyl)-4-methoxybenzene (275 mg, 0.58 mmol) in $CHCl_3$ (8 mL) at 0 °C was added 50% aqueous trifluoroacetic acid (4 mL). The reaction mixture was stirred at 0 °C for 1.5 h, then saturated $NaHCO_3$ was added until no gas evolution was seen. The organic layer was separated

and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, then were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (15% EtOAc in hexanes) to provide the desired product (197 mg, 84%) as a mixture of 2 diastereomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.71 (2 singlets, 1H), 7.19-7.37 (m, 10H), 7.00-7.10 (m, 2H), 6.81 (d, *J* = 8.8 Hz, 50% of 2H), 6.82 (d, *J* = 8.8 Hz, 50% of 2H), 4.30 (d, *J* = 10.9 Hz, 1H), 4.13 (d, *J* = 10.9 Hz, 1H), 4.00-4.10 (m, 2H), 3.79 (2 singlets, 3H), 2.28-2.35 (m, 2H), 1.39-1.55 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.6, 158.2, 143.1, 142.8, 138.5, 134.8, 134.3, 130.1, 129.4, 129.0, 128.5, 128.5, 128.2, 128.0, 127.5, 126.4, 126.3, 114.0, 113.7, 82.1, 82.0, 72.6, 55.7, 55.2, 43.8, 32.6, 32.5, 24.8, 24.7, 22.1; IR (neat) 3027, 2932, 1716, 1509, 1250, 1173, 1029, 698 cm^{-1}; LRMS (CI) calcd for $C_{20}H_{23}O_3$ $[M - CH_2Ph]^+$ 311.16, found 311.

8-Benzyloxy-9-(4-methoxyphenyl)-9-phenyl-1-trimethylsilyl-non-1-yn-3-ol (1.31)



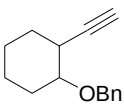
Prepared following the procedure for **1.25**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19-7.36 (m, 10H), 7.00-7.09 (m, 2H), 6.81-6.89 (m, 2H), 4.37 (d, *J* = 10.9 Hz, 1H), 4.16 (d, *J* = 10.9 Hz, 1H), 4.28-4.32 (m, 1H), 4.00-4.10 (m, 2H), 3.79 (2 singlets, 3H), 2.00 (br s, 1H), 1.44-1.67 (m, 8H), 0.21 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 143.2, 142.9, 138.6, 138.6, 135.0, 134.5, 130.2, 129.5, 129.1, 128.6, 128.3, 128.3, 128.1, 127.5, 126.4, 126.3, 114.0, 113.7, 107.0, 89.4, 82.4, 82.3, 72.6, 62.8, 62.7, 55.9, 55.8, 55.3, 37.7, 32.9, 32.8, 25.4, 25.3, 25.0, 24.9, 0.1; IR (neat) 3431, 2929, 2858, 2166, 1511, 1449, 1244, 1034, 845 cm^{-1}; HRMS (EI) calcd for $C_{32}H_{40}O_3Si$ $[M^+]$ 500.2746, found 500.2766.



[8-Benzyloxy-9-(4-methoxyphenyl)-9-phenylnona-1,2-dienyl]trimethylsilane (1.32)

Prepared following the procedure for **1.27**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20-7.40 (m, 10H), 7.00-7.10 (m, 2H), 6.82 (d, *J* = 8.5 Hz, 50% of 2H), 6.81 (d, *J* = 8.5 Hz, 50% of 2H), 4.85-4.90 (m, 1H), 4.69 (app dq, *J* = 1.4, 6.8 Hz, 1H), 4.43 (d, *J* = 10.9 Hz, 1H), 4.20 (d, *J* = 10.9 Hz, 1H), 4.01-4.06 (m, 2H), 3.78 (2 singlets, 3H), 1.89-1.93 (m, 2H), 1.27-1.58 (br, 6H), 0.09 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.1, 158.2, 143.4, 143.0, 138.7, 135.1, 134.5, 130.3, 129.5, 129.1, 128.6, 128.3, 128.0, 127.5, 126.3, 114.0, 113.7, 83.4, 82.6, 72.6, 55.8, 55.7, 55.3, 32.8, 32.6, 29.9, 27.9, 25.0, 24.9, -0.6; IR (neat) 2929, 1936, 1510, 1247, 839, 697 cm^{-1}; HRMS (EI) calcd for $C_{32}H_{40}O_2Si$ [M^+] 484.2797, found 484.2806.

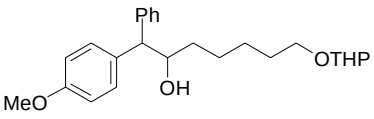
(2-Ethynyl-cyclohexyloxymethyl)benzene (1.33)



To a stirring mixture of allene **1.32** (71 mg, 0.148 mmol) in DCE (5.0 mL) were added $NaHCO_3$ (140 mg, 1.67 mmol) and 4 Å molecular sieves (140 mg). The resulting mixture was warmed to 40 °C, and a solution of CAN (203 mg, 0.37 mmol) in acetonitrile (1.5 mL) was added dropwise. After 10 min, the reaction mixture was filtered through a short plug of silica gel. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by flash chromatography (0.5-2% EtOAc in hexanes) to provide the desired alkyne (16.5 mg, 52%) as 2 diastereomers in 1.3:1 ratio. Silylalkyne **1.34** (1.5 mg, 3.5%) and unreacted starting material (11 mg, 15.5%) were also isolated. The overall yield was 66% based upon unrecovered starting material. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14-7.34 (m, 5H), 4.62-4.49 (d, *J* = 12.3 Hz, ~50% of 1H), 4.59 (s, ~50% of 2H), 4.58 (d, *J* = 12.3 Hz, ~50% of 1H), 3.30-3.37 (m, 1H), 2.92 (br s, 43% of 1H), 2.41-2.48 (m, 57% of 1H), 1.94 (m, 1H, alkyne proton), 1.11-1.9 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.1, 128.5, 127.9, 127.8, 127.6, 87.0, 85.0, 79.4, 77.0, 71.4, 70.8, 70.2, 69.5, 35.2, 32.9, 30.6, 30.3, 29.9, 29.6, 28.6, 24.1,

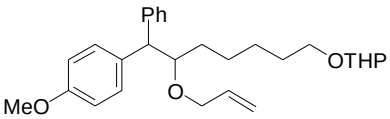
23.7, 22.1; IR (neat) 3305, 2934, 2858, 2114, 1443, 1097, 735, 697 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{17}O$ $[M - H]^+$ 213.1279, found 213.1275.

1-(4-Methoxyphenyl)-1-phenyl-7-(tetrahydropyran-2-yloxy)heptan-2-ol (1.37)



Prepared following the procedure for **1.22**. ^1H NMR (300 MHz, $CDCl_3$) δ 7.15-7.47 (m, 7H), 6.77 (d, *J* = 6.6 Hz, 50% of 2H), 6.78 (d, *J* = 6.7 Hz, 50% of 2H), 4.50 (t, J = 3.5 Hz, 1H), 4.22-4.30 (m, 1H), 3.63-3.88 (m, 3H), 3.72 (s, 3H), 3.40-3.46 (m, 1H), 3.27-3.35 (m, 1H), 1.13-1.70 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2, 142.0, 129.3, 128.9, 126.8, 114.1, 99.0, 73.9, 67.6, 62.5, 58.0, 55.3, 35.1, 30.9, 29.8, 26.4, 25.8, 25.8, 25.6, 19.8; IR (neat) 3452, 2939, 2858, 1603, 1506, 1454, 1250, 1173, 1116, 1075, 1029 cm^{-1}.

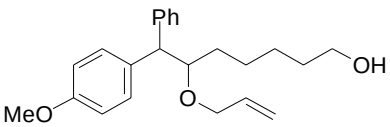
2-[6-Allyloxy-7-(4-methoxyphenyl)-7-phenyl-heptyloxy]tetrahydropyran



To alcohol **1.37** (1.5 g, 3.77 mmol) in DMF (25 mL) at 0 °C was added NaH (60% in mineral oil, 452 mg, 11.31 mmol,). The reaction mixture was stirred for 10 min, then allyl bromide (2.28 g, 18.84 mmol) was added dropwise. The ice bath was removed and the reaction mixture was stirred at rt for 2.5 h. An ice chunk was added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic layers were washed with water and brine, then were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (15% EtOAc in hexanes) to afford the desired product: ^1H NMR (300 MHz, $CDCl_3$) δ 7.18-7.40 (m, 7H), 6.81 (d, *J* = 8.7 Hz, 50% of 2H), 6.82 (d, *J* = 8.7 Hz, 50% of 2H), 5.64-5.69 (m, 1H), 5.01-5.10 (m, 2H), 4.55 (distorted t, 1H), 3.97-3.99 (m, 2H),

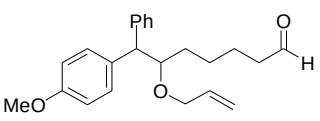
3.78 (2 singlets, 3H), 3.64-3.99 (m, 4H), 3.50-3.54 (m, 1H), 3.34-3.38 (m, 1H), 1.28-1.71 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 143.2, 142.6, 135.2, 135.1, 134.9, 134.3, 130.0, 129.3, 129.1, 128.9, 128.4, 128.2, 127.6, 126.0, 125.9, 115.9, 113.7, 113.4, 98.6, 82.3, 82.2, 71.4, 71.3, 67.2, 61.9, 55.5, 55.4, 54.8, 32.9, 32.8, 30.6, 29.5, 26.2, 25.4, 25.1, 24.9, 19.5; IR (neat) 2939, 2862, 1610, 1511, 1453, 1249, 1178, 1137, 1129, 1077, 1034, 990, 700 cm^{-1}; LRMS (ESI) calcd for $C_{28}H_{38}O_4Na$ $[M + Na]^+$ 461.27, found 461.2.

6-Allyloxy-7-(4-methoxyphenyl)-7-phenylheptan-1-ol



To 2-[6-allyloxy-7-(4-methoxyphenyl)-7-phenylheptyloxy]-tetrahydropyran obtained above in methanol (20 mL) at rt was added *para*-toluenesulfonic acid (50 mg). The resulting mixture was stirred at rt for 5 h, then was concentrated under reduced pressure. The resulting residue was purified by flash chromatography (30-45% EtOAc in hexanes) to afford the desired product (1.12 g, 84% over 2 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19-7.43 (m, 7H), 6.83 (d, J = 8.6 Hz, 50% of 2H), 6.84 (d, J = 8.6 Hz, 50% of 2H), 5.64-5.79 (m, 1H), 5.04-5.14 (m, 2H), 4.01 (br s, 2H), 3.81 (dd, J = 5.5, 12.3 Hz, 1H), 3.75 (2 singlets, 3H), 3.61 (dd, J = 5.5, 12.3 Hz, 1H), 3.50 (t, J = 6.4 Hz, 2H), 2.36 (br s, 1H), 1.38-1.51 (m, 6H), 1.14-1.20 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 143.2, 142.7, 135.1, 135.0, 134.3, 130.1, 129.4, 129.0, 128.4, 128.4, 128.1, 126.2, 126.1, 116.3, 113.8, 113.5, 82.3, 71.6, 71.6, 62.5, 55.6, 55.6, 55.1, 33.0, 32.9, 32.6, 25.8, 25.1, 25.0; IR (neat) 3385, 2935, 2859, 1610, 1511, 1248, 1178, 1035, 700 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{24}O_2$ $[M - OC_3H_5 - H]^+$ 296.1776, found 296.1774.

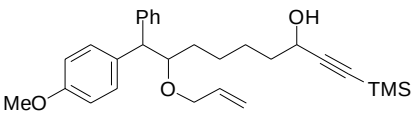
6-Allyloxy-7-(4-methoxyphenyl)-7-phenylheptanal (1.38)



To a stirring mixture of 6-allyloxy-7-(4-methoxyphenyl)-7-

phenylheptan-1-ol (1.12 g, 3.16 mmol), $NaHCO_3$ (796 mg, 9.48 mmol) and CH_2Cl_2 (20 mL) at 0 °C was added Dess-Martin periodinane. After 1 h, saturated $NaHCO_3$ and $Na_2S_2O_3$ solutions were added to the reaction mixture. The resulting mixture was stirred at rt for another 0.5 h. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, then were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (15% EtOAc in hexanes) to afford the desired product (858 mg, 77%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.70 (m, 1H), 7.18-7.41 (m, 7H), 6.82 (m, *J* = 8.6 Hz, 2H), 5.62-5.77 (m, 1H), 5.02-5.17 (m, 2H), 4.03 (br s, 2H), 3.79 (ddd, *J* = 1.2, 5.7, 12.3 Hz, 1H), 3.76 (s, 3H), 3.61 (app dd, *J* = 5.7, 12.3 Hz, 1H), 2.33-2.38 (m, 2H), 1.27-1.60 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.4, 158.1, 143.1, 142.6, 135.2, 135.1, 134.9, 134.2, 130.1, 129.5, 129.0, 128.5, 128.5, 128.2, 126.3, 126.2, 116.4, 113.9, 113.6, 82.2, 82.2, 71.7, 71.7, 55.7, 55.6, 55.2, 43.7, 32.9, 32.7, 24.9, 24.8, 22.1; IR (neat) 2936, 1722, 1510, 1248, 1033, 700cm^{-1}; LRMS (EI) calcd for $C_{20}H_{22}O_3$ $[M - OC_3H_5 - H]^+$ 310, found 310.

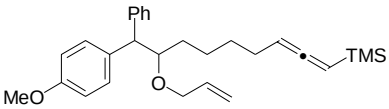
8-Allyloxy-9-(4-methoxyphenyl)-9-phenyl-1-trimethylsilyl-non-1-yn-3-ol (1.39)



Prepared following the procedure for **1.25**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18-7.42 (m, 7H), 6.82 (d, *J* = 8.8Hz, 50% of 2H), 6.83 (d, *J* = 8.8 Hz, 50% of 2H), 5.63-5.76 (m, 1H), 4.95-5.07 (m, 2H), 4.30 (dd, *J* = 5.6, 10.8 Hz, 1H), 3.99 (br s, 2H), 3.80 (ddd, *J* = 1.3, 5.7, 12.3 Hz, 1H), 3.75 (2 singlets, 3H), 3.61 (ddd, *J* = 1.3, 5.7, 12.3 Hz, 1H), 2.46 (m, 1H), 1.60-1.68 (m, 2H), 1.30-1.50 (m, 6H), 0.20 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.02, 143.20, 142.70, 135.15, 135.01, 134.36, 130.12, 129.46, 129.02, 128.49, 128.16, 126.25, 126.17, 116.49, 113.90, 113.59, 107.24, 89.04, 82.29,

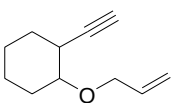
71.74, 62.59, 55.73, 55.16, 37.60, 33.04, 32.93, 25,17, 25.03, 24.94, 0.01; IR (neat) 3416, 2941, 2861, 1610, 1511, 1249, 1178, 1074, 1035, 843, 700 cm^{-1}; HRMS (EI) calcd for $C_{27}H_{36}O_3Si$ [M – CH_3 + H]$^+$ 436.2433, found 436.2419.

[8-Allyloxy-9-(4-methoxyphenyl)-9-phenylnona-1,2-dienyl]trimethylsilane (1.40)



Prepared following the procedure for **1.27**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24-7.48 (m, 7H), 6.88 (d, *J* = 8.8 Hz, 50% of 2H), 6.89 (d, *J* = 8.8 Hz, 50% of 2H), 5.70-5.84 (m, 1H), 5.08-5.24 (m, 2H), 4.95 (app dt, *J* = 6.8, 3.5 Hz, 1H), 4.79 (app dq, *J* = 0.8, 6.8 Hz, 1H), 3.94-4.04 (m, 2H), 3.88 (ddd, *J* = 1.3, 5.7, 12.3 Hz, 1H), 3.82 (2 singlets, 3H), 3.69 (ddd, *J* = 1.3, 5.7, 12.3 Hz, 1H), 1.99-2.02 (m, 2H), 1.52-1.58 (m, 4H), 1.41-1.46 (m, 2H), 0.19 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.1, 158.1, 143.4, 142.8, 135.3, 135.2, 134.4, 130.2, 129.5, 129.1, 128.6, 128.4, 128.2, 126.2, 126.2, 116.4, 113.9, 113.6, 83.4, 82.6, 71.7, 55.7, 55.2, 33.0, 32.9, 29.9, 27.9, 25.1, 25.0, -0.7; IR (neat) 2934, 2852, 1936, 1506, 1244, 835 cm^{-1}; HRMS (EI) calcd for $C_{28}H_{38}O_2Si$ [M^+] 434.2641, found 434.2661.

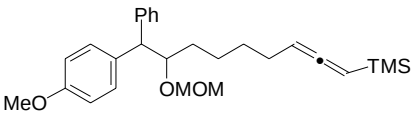
1-Allyloxy-2-ethynylcyclohexane (1.41)



To allene **1.40** (52 mg, 0.12 mmol) in DCE (3.0 mL) were added $NaHCO_3$ (100 mg, 1.19 mmol) and 4 Å molecular sieves (100 mg). To this stirring mixture at rt was added a solution of CAN (185 mg, 0.34 mmol) in acetonitrile (0.9 mL) dropwise. After 10 min, the reaction mixture was filtered through a short plug of silica gel eluting with CH_2Cl_2. The reaction yields were measured with GC using 1-iodooctane as the internal standard. The yield of **1.41** (*trans*/*cis* = 1.3/1) was 65%. ***cis*-Diastereomer** of **1.41** (faster eluting diastereomer)[1]: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.58-6.06 (m, 1H), 5.31 (app dq, *J* = 17.2, 1.6 Hz, 1H), 5.08-5.19 (m, 1H), 4.03-4.16 (m, 2H), 3.33-3.39 (app dt, *J* = 8.2, 4.1 Hz, 1H), 2.96 (br s, 1H), 2.09 (d, *J* = 2.5

Hz, 1H), 1.25-1.93 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.7, 116.8, 84.9, 70.7, 69.6, 33.1, 29.6, 28.6, 23.7, 22.1; IR (neat) 3308, 2936, 2859, 2591, 2115, 1444, 1084, 922 cm^{-1}. ***trans*-Diastereomer** of **1.41** (slower eluting diastereomer)[1]: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.84-6.01 (m, 1H), 5.27 (app dq, *J* = 17.2, 1.6 Hz, 1H), 5.07 (app dq, *J* = 10.3, 1.6 Hz, 1H), 4.09 (app d, *J* = 5.5 Hz, 2H), 3.28 (app dt, *J* = 3.7, 8.1 Hz, 1H), 2.40-2.48 (m, 1H), 2.08 (d, *J* = 2.3 Hz, 1H), 1.94-1.99 (m, 2H), 1.62-1.71 (m, 2H), 1.23-1.48 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.7, 116.6, 86.9, 79.2, 70.5, 69.4, 35.1, 30.5, 30.4, 24.1, 23.4; IR (neat) 3308, 2934, 2859, 2602, 2100, 1659, 1449, 1097, 1079, 922 cm^{-1}; HRMS (EI) calcd for $C_8H_{11}O$ [M – allyl group]$^+$ 123.0809, found 123.0808. **Silylalkyne 1.42** (7%, 2 diastereomers in 1:1 ratio): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88-5.99 (m, 1H), 5.28 (app dd, *J* = 1.6, 17.2 Hz, 1H), 5.13 (app dd, *J* = 1.4, 10.4 Hz, 1H), 4.05-4.15 (m, 2H), 3.36 (dt, *J* = 8.6, 3.7 Hz, ~50% of 1H), 3.26 (dt, *J* = 3.7, 8.1 Hz, ~50% of 1H), 2.87 (app dt, *J* = 5.6, 2.8 Hz, ~50% of 1H), 2.41 (app dt, *J* = 4.1, 8.2 Hz, ~50% of 1H), 1.92-1.99 (m, 2H), 1.60-1.71 (m, 4H), 1.32-1.44 (m, 2H), 1.23-1.41 (m, 4H), 0.15 (s, 9H); IR (neat) 2935, 2858, 2166, 1244, 1075, 857, 841 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{19}OSi$ [M – allyl group]$^+$ 195.1205, found 195.1201.

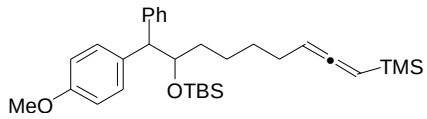
[8-Methoxymethoxy-9-(4-methoxyphenyl)-9-phenylnona-1,2-dienyl]trimethylsilane (1.43)



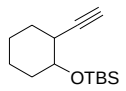
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.48 (m, 7H), 6.88 (d, J = 8.7 Hz, 2H), 4.94-4.97 (m, 1H), 4.79 (q, J = 6.8 Hz, 1H), 4.53 (d, J = 6.9 Hz, 1H), 4.31-4.45 (m, 2H), 4.07 (d, J = 8.5 Hz, 1H), 3.82 (2 singlets, 3H), 3.10 (2 singlets, 3H), 1.97-2.02 (m, 2H), 1.50-1.80 (m, 4H), 1.35-1.45 (m, 2H), 0.18 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.1, 158.1, 143.0, 142.7, 134.8, 134.3, 130.2, 129.5, 129.1, 128.6, 128.3,

126.4, 126.3, 113.9, 113.7, 96.1, 96.0, 83.3, 82.6, 80.5, 80.4, 55.6, 55.4 55.3, 32.8, 32.6, 30.0, 29.97, 29.90, 27.9, 24.4, 24.2, -0.81; IR (neat) 2935, 1936, 1511, 1248, 1148, 1036, 840 cm^{-1}.

1-[2-(*tert*-Butyldimethylsilyloxy)-1-phenyl-9-trimethylsilylnona-7,8-dienyl]-4-methoxybenzene (1.44)



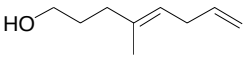
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.42 (m, 7H), 6.85 (d, J = 8.4 Hz, 2H), 4.90-4.95 (m, 1H), 4.73 (q, J = 6.8 Hz, 1H), 4.31-4.34 (m, 1H), 3.98-4.02 (m, 1H), 3.78 (2 singlets, 3H), 1.93-1.97 (m, 2H), 1.33-1.54 (m, 6H), 0.83 (2 singlets, 9H), 0.15 (s, 9H), -0.01 (2 singlets, 3H), -0.45 (2 singlets, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.2, 158.2, 142.7, 142.8, 135.5, 134.1, 130.9, 129.8, 129.7, 128.9, 128.3, 128.2, 126.1, 113.8, 113.7, 83.4, 82.7, 76.3, 75.9, 55.9, 55.6, 55.3, 35.7, 35.5, 30.0, 28.0, 26.0, 24.3, 24.2, 23.9, 18.1, -0.6, -4.2, -5.3; IR (neat) 2929, 2852, 1936, 1511, 1248, 1096, 836, 698 cm^{-1}.



***tert*-Butyl-(2-ethynylcyclohexyloxy)dimethylsilane**

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.76-3.80 (m, 50% of 1H), 3.61-3.65 (m, 50% of 1H), 2.56-2.60 (m, 50% of 1H), 2.29-2.35 (m, 50% of 1H), 2.04 (d, *J* = 2.4 Hz, 50% of 1H), 2.01 (d, *J* = 2.4 Hz, 50% of 1H), 1.80-1.90 (m, 2H), 1.64-1.75 (m, 2H), 1.45-1.53 (m, 2H), 1.26-1.34 (m, 2H), 0.90 (2 singlets, 9H), 0.09 (s, 6H); IR (neat) 2924, 2853, 2166, 1731, 1465, 1244, 835 cm^{-1}.

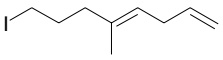
(*E*)-4-Methylocta-4,7-dien-1-ol (1.45)



To a stirring solution of Cp_2ZrCl_2 (0.69 g, 2.37 mmol) in CH_2Cl_2 (20 mL) at –23 °C was added $AlMe_3$ (2 M in hexanes, 8.91 mL, 17.8 mmol) dropwise, followed by water (107 mg, 5.94 mmol). After 10 min, a mixture of 4-pentyn-1-ol (0.5 g, 5.94 mmol) and $AlMe_3$ (0.98 mL, 2 mmol) in 5 mL of CH_2Cl_2 (made by adding $AlMe_3$ solution slowly into the pentynol

solution at 0 °C, the resulting mixture was then stirred at rt for 20 min.) was added to the reaction mixture slowly at –23 °C. The cold bath was removed and the reaction mixture was allowed to warm to rt slowly. After 5 h, a mixture of $Pd(PPh_3)_4$ (0.2 g, 0.178 mmol) and allyl bromide (0.72 g, 5.94 mmol) in THF (10 mL) was added to the reaction mixture at rt. After 12 h, saturated K_2CO_3 (5 mL) was added to the reaction mixture at 0 °C cautiously. Some Na_2SO_4 solid was then added. The resulting thick mixture was stirred for 5 min and was filtered through a Celite pad. The filtrate was concentrated under reduced pressure. The resulting residue was purified by flash chromatography (15% EtOAc in hexanes) to afford the desired product (625 mg, 75%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.72-5.86 (m, 1H), 5.18-5.23 (m, 1H), 4.92-5.04 (m, 2H), 3.53 (dt, *J* = 1.5, 6.6 Hz, 2H), 2.73 (t, *J* = 6.7 Hz, 2H), 2.06 (t, *J* = 7.5 Hz, 2H), 1.63-1.73 (m, 2H), 1.62 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.3, 136.1, 121.76, 114.2, 62.5, 35.9, 32.3, 30.8, 15.9; IR (neat) 3331, 2937, 1635, 1437, 1061, 908 cm^{-1}; HRMS (EI) calcd for $C_9H_{16}O$ [M^+] 140.1201, found 140.1203.

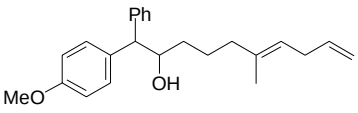
(*E*)-8-Iodo-5-methylocta-1,4-diene (1.46)



To a stirring mixture of alcohol **1.45** (2.12 g, 15.16 mmol), PPh_3 (5.57 g, 21.22 mmol), imidazole (1.44 g, 21.22 mmol) and CH_2Cl_2 (50 mL) at 0 °C was added iodine (5.39 g, 21.22 mmol). After 30 min, saturated Na_2SO_3 was added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, washed with H_2O and brine, then were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (straight hexanes) to provide the desired product (3.29 g, 87%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.71-5.85 (m, 1H), 5.20 (dt, *J* = 0.9, 7.2 Hz, 1H), 4.93-5.08 (m, 2H), 3.11 (t, *J* =

6.9 Hz, 2H), 2.72-2.77 (m, 2H), 2.08 (t, *J* = 6.8 Hz, 2H), 1.88-1.95 (m, 2H), 1.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.01, 134.27, 122.89, 114.38, 40.08, 32.29, 31.60, 15.92, 6.59; IR (neat) 2975, 2932, 2842, 1637, 1429, 1217, 1166, 992, 909 cm^{-1}; HRMS (EI) calcd for $C_9H_{15}I$ [M^+] 250.0218, found 250.0219.

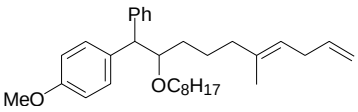
(*E*)-1-(4-Methoxyphenyl)-6-methyl-1-phenyldeca-6,9-dien-2-ol (1.47)



To iodide **1.46** (3.29 g, 13.16 mmol) in 200 mL of mixed solvents of *n*-pentane/ether (3:2 by volume) at –78 °C was added *t*-BuLi (1.18 M in hexanes, 14.4 mL, 17.0 mmol) dropwise. The reaction mixture turned cloudy. After 5 min, the reaction mixture was allowed to warm to 0 °C and stirred at 0 °C for 1.5 h, then at rt for another 1.5 h. The resulting solution was cannulated into a suspension of anhydrous $CeCl_3$ (3.244 g, 13.16 mmol) in THF (43 mL) at –78 °C. The reaction mixture was warmed to 0 °C and was stirred at 0 °C for 40 min. A solution of aldehyde **1.6** (1.98 g, 8.77 mmol) in THF (10 mL) was added dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 10 min, warmed at rt for 30 min, then was quenched with 10% Acetic acid (30 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc. The organic layers were combined, washed with H_2O, saturated $NaHCO_3$ and brine, then were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (13% EtOAc in hexanes) to provide the desired product (1.99 g, 65%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18-7.32 (m, 7H), 6.86 (d, *J* = 6.6 Hz, 50% of 2H), 6.85 (d, *J* = 6.6 Hz, 50% of 2H), 5.69-5.82 (m, 1H), 5.07-5.13 (m, 1H), 4.90-5.01 (m, 2H), 4.28-4.33 (m, 1H), 3.81 (d, *J* = 8.2 Hz, 1H), 3.77 (s, 3H), 2.68 (t, *J* = 6.4 Hz, 2H), 1.94 (t, *J* = 5.7 Hz, 2H), 1.55 (s, 3H), 1.41-1.67 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 143.0, 137.6, 136.6, 133.6, 130.0, 128.8, 128.3, 126.6, 121.6,

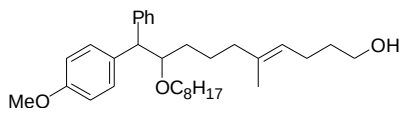
114.4, 114.3, 73.9, 58.1, 55.4, 39.6, 34.8, 32.4, 29.5, 24.2,16.0; IR (neat) 3559, 3446, 2933, 1610, 1510, 1452, 1249, 1178, 1034, 700 cm^{-1}; HRMS (EI) calcd for $C_{24}H_{30}O_2$ $[M^+]$ 350.2245, found 350.2236.

(*E*)-1-Methoxy-4-(6-methyl-2-octyloxy-1-phenyldeca-6,9-dienyl)benzene



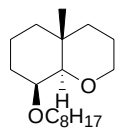
To alcohol **1.47** (1.98 g, 5.68 mmol) at rt was added NaH (60% in mineral oil, 0.8 g, 21 mmol). After 5 min, 1-iodooctane (6.82 g, 28.4 mmol) was added. The reaction mixture was heated to 120 °C and was stirred overnight at that temperature. The reaction mixture was cooled down to rt, diluted with hexanes, and was quenched with an ice chunk. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic layers were washed with water and brine, then were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (5% EtOAc in hexanes) to provide the desired product (2.35 g, 90%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16-7.40 (m, 7H), 6.80 (d, *J* = 7.5 Hz, 2H), 5.70-5.83 (m, 1H), 5.07-5.12 (m, 1H), 4.92-5.02 (m, 2H), 3.93 (d, *J* = 7.9, 1H), 3.86-3.90 (m, 1H), 3.77 (2 singlets, 3H), 3.31 (dt, *J* = 8.6, 6.5 Hz, 1H), 2.99 (dt, *J* = 8.5, 6.5 Hz, 1H), 2.69 (t, *J* = 6.7 Hz, 2H), 1.90 (t, *J* = 6.9 Hz, 2H), 1.54 (s, 3H), 1.13-1.54 (m, 16H), 0.85 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 143.5, 143.1, 137.6, 136.5, 135.3, 134.8, 130.1, 129.5, 129.0, 128.6, 128.4, 128.1, 126.2, 126.1, 121.48, 114.2, 113.8, 113.5, 82.5, 82.4, 70.6, 70.5, 55.7, 55.6, 55.2, 39.7, 32.5, 32.3, 31.9, 30.2, 29.8, 29.5, 26.3, 26.2, 23.6, 22.8, 15.9, 14.2; IR (neat) 2928, 2855, 1510, 1510, 1463, 1248, 1178, 1101, 1038, 699 cm^{-1}; HRMS (EI) calcd for $C_{32}H_{46}O_2$ $[M^+]$ 462.3497, found 462.3491.

(*E*)-10-(4-Methoxyphenyl)-5-methyl-9-octyloxy-10-phenyldec-4-en-1-ol (1.4)



To a stirring solution of 2-methylbutene (1.28 mL, 12.12 mmol) in THF (12 mL) at –5 °C was added BH_3·THF (1 M in THF, 6.1 mL, 6.1 mmol) dropwise. The reaction mixture was stirred for 45 min at –5 °C. The resulting solution was added to a solution of (*E*)-1-methoxy-4-(6-methyl-2-octyloxy-1-phenyldeca-6,9-dienyl)benzene (1.4 g, 3.03 mmol) in THF (12 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h. Water (1 mL), NaOH (3 mL, 10%) and H_2O_2 (3 mL, 30%) were added to the reaction mixture successively. After 2 h, the organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, then were dried over Na_2SO_4, filtered and concentration under reduced pressure. The resulting residue was purified by flash chromatography (15% EtOAc in hexanes) to afford the desired product (0.67 g, 46%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18-7.29 (m, 7H), 6.81 (d, *J* = 8.6 Hz, 2H), 5.05 (t, *J* = 7.1 Hz, 1H), 3.95 (d, *J* = 9.5 Hz, 1H), 3.89-3.92 (m, 1H), 3.78 (2 singlets, 3H), 3.59 (t, *J* = 6.3 Hz, 2H), 3.36 (dt, *J* = 8.3, 6.5 Hz, 1H), 3.03 (dt, *J* = 8.6, 6.5 Hz, 1H), 2.01 (q, *J* = 7.2 Hz, 2H), 1.90 (t, *J* = 6.8 Hz, 2H), 1.55 (s, 3H), 1.15-1.70 (br, 18H), 0.85 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 143.2, 135.9, 135.5, 129.6, 129.1, 128.3, 126.2, 123.9, 144.0, 113.6, 82.5, 70.6, 62.9, 55.8, 55.4, 39.8, 32.9, 32.3, 32.0, 30.3, 29.6, 29.4, 26.3, 24.3, 23.4, 22.9, 16.0, 14.3; IR (neat) 3368 (br), 2928, 2855, 1510, 1457, 1248, 1177, 1100, 1036, 698 cm^{-1}; LRMS (CI) calcd for $C_{32}H_{49}O_3$ $[M + H]^+$ 481, found 481. Also, LRMS (ESI) calcd for $C_{32}H_{48}O_3Na$ $[M + Na]^+$ 503.4, found 503.5.

(4R,8S,9R)-4-Methyl-8-ocyloxy-9-octahydrochromene (1.48)



To alcohol **1.4** (100 mg, 0.21 mmol) in DCE (6.0 mL) were added $NMQPF_6$ (3.0 mg, 0.01 mmol), NaOAc (200 mg, 2.44 mmol), $Na_2S_2O_3$ (200 mg, 1.26 mmol), 4 Å Molecular sieves (200 mg), and toluene (1 mL). The resulting mixture was stirred at rt while bubbling air gently and irradiating with a medium pressure mercury lamp at a distance of 4 cm. After 80 min, additional $NMQPF_6$ (1 mg, 0.0035 mmol) was added to the reaction mixture and the reaction was allowed to proceed for another 20 min. The reaction mixture was filtered through a plug of silica gel, and the filtrate was concentrated under vacuum. The resulting residue was purified by flash chromatography (3% EtOAc in hexanes) to afford the desired product (28.9 mg, 49%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.77 (dt, *J* = 3.5, 11.9 Hz, 1H), 3.62 (app ddt, *J* = 5.2, 11.8, 1.4 Hz, 1H), 3.40 (dt, *J* = 9.0, 6.3 Hz, 1H), 3.30 (app dt, *J* = 2.5, 5.2 Hz, 1H), 3.10 (dt, *J* = 9.0, 6.3Hz, 1H), 1.83-1.91 (m, 2H), 1.59-1.71 (m, 4H), 1.45-1.56 (m, 4H), 1.20-1.39 (m, 13H), 1.35 (s, 3H), 0.87 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 79.2, 74.9, 69.6, 61.3, 49.1, 40.7, 32.1, 30.4, 29.6, 29.5, 29.3, 27.8, 26.6, 23.4, 22.9, 19.5, 18.3, 14.3; IR (neat) 2928, 2858, 1454, 1082 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{34}O_2$ [M^+] 282.2558, found 282.2563.

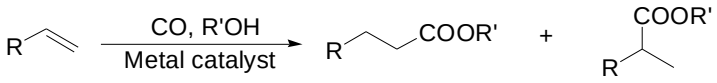
References in experimental of Chapter 1:

(1) Stereochemistry was assigned based on literature analogy. See: Wille, U.; Lietzau, L. *Tetrahedron* **1999**, *55*, 10119-10134.

Chapter 2. Ruthenium-catalyzed olefin hydroesterification: synthesis of lactones from allylic and homoallylic alcohols

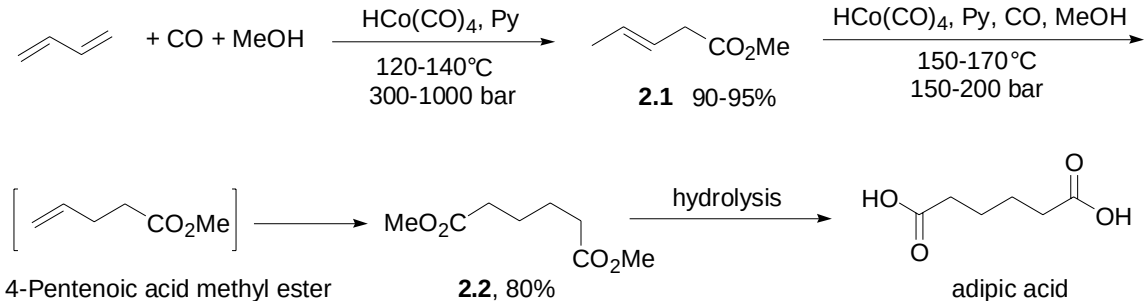
2.1 Introduction

Hydroesterification is an important reaction that converts olefins or alkynes into esters with carbon monoxide and alcohols catalyzed by transition metal catalysts (eq 1).[1] It is one of the easiest ways to form new carbon-carbon bonds, to homologate olefins by one carbon, and to generate new functional groups. It also can be a very atom economic process since all the atoms in the starting material are incorporated into the product.



eq 1

Hydroesterification is the basis of many industrial processes and lab scale syntheses. Some important industrial products such as propionic acid and its esters, diethylketones, linear fatty acid esters, and 2-aryl propionic acids are synthesized using hydroesterification reactions.[1-3] BASF used a three-stage process with hydroesterification reactions as key steps in the synthesis of adipic acid (Scheme 2.1).[4] In the first step, butadiene was treated under hydroesterification conditions to yield 3-pentenoic acid ester (**2.1**). In the second step, ester **2.1** was subjected to other hydroesterification conditions to undergo tandem isomerization (to give 4-pentenoic acid methyl ester) and hydroesterification to furnish dimethyl adipate (**2.2**), which was hydrolyzed to yield adipic acid.



Scheme 2.1. BASF's adipic acid synthesis.

Hydroesterification is most commonly carried out using CO and an alcohol under high temperature and high pressure in the presence of transition metal catalysts. In the past several decades, a variety of catalysts have been developed and applied in diverse systems. At the same time, many hydroesterification reagents other than toxic CO gas have been developed, which are particularly convenient for laboratory scale syntheses. Various olefins and alkynes were also tested under hydroesterification conditions to explore the substrate scope of hydroesterification reactions.

2.1.1 Catalysts

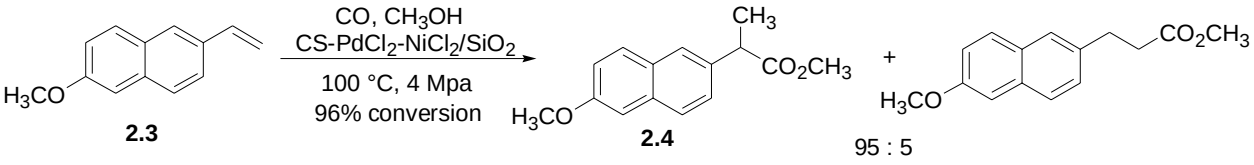
There are an abundance of catalysts available for hydroesterification reactions. Commonly used are Pd, Rh, Ru, Pt, and Co catalysts. Among these catalysts palladium and rhodium are the most attractive because of their tolerance of many functional groups, mild reaction conditions (70-140 °C), and providing relatively high yields. Some representative Pd and Rh catalysts are $PdCl_2(PPh_3)_2$, $Rh_6(CO)_{16}$, RhCl(dppb), $RhCl(CO)(PPh_3)_2$, $RhCl_3$, and $RhCl(PPh_3)_3$.[4]

Ruthenium and cobalt catalysts (e.g. $Co_2(CO)_8$, $HCo(CO)_4$, $Ru_3(CO)_{12}$, Ru(cod)(cot), and $RuCl_2(PPh_3)_3$) have seen increasingly frequent usage because of their relatively low cost. Ruthenium catalysts, such as $Ru_3(CO)_{12}$, are especially good at activating the C-H bond of formate.[5] The disadvantage of these catalysts is the fairly harsh reaction conditions required.

High temperature >140 °C and high pressure >100 atm are often necessary to activate the reactions.[6]

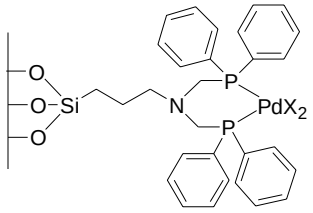
Other transition metal catalysts such as iron (e.g. $H_2Fe_2(CO)_8$ and $Fe_2(CO)_9$), and nickel (e.g. $Ni(CO)_4$) catalysts are also often seen to be used in hydroesterifications.[7] Bimetallic or polymetallic catalysts that contain more than one metal species have been reported and many have shown enhanced reactivity and selectivity. Examples are platinum (e.g. $H_2PtCl_6/SnCl_2$ and $PtCl_2(DIOP)/SnCl_2$)[8] and palladium ($PdCl_2$-$CuCl_2$)[4] catalysts.

Homogeneous catalysts can provide fast reaction rates but they are difficult to be recovered. Catalysts attached to solid or polymers have the advantage of being recyclable and have attracted increasing attention. Xia and co-workers reported the chitosan-SiO_2 (CS) supported bimetallic catalyst system CS-$PdCl_2$-$NiCl_2/SiO_2$, which showed good reactivity and regioselectivity in hydroesterification reactions.[9] As shown in Scheme 2.2, hydroesterification of vinylnaphthalene (**2.3**) provided a branched ester (**2.4**) as the major product with an efficient conversion rate.



Scheme 2.2. Hydroesterification using polymer-supported catalyst.

Alper reported polyamidoamine-SiO_2 supported $Pd(PPh_3)_2$ catalyst, which has high reactivity and can be recycled and reused multiple times for hydroesterifications (Scheme 2.3).[10]



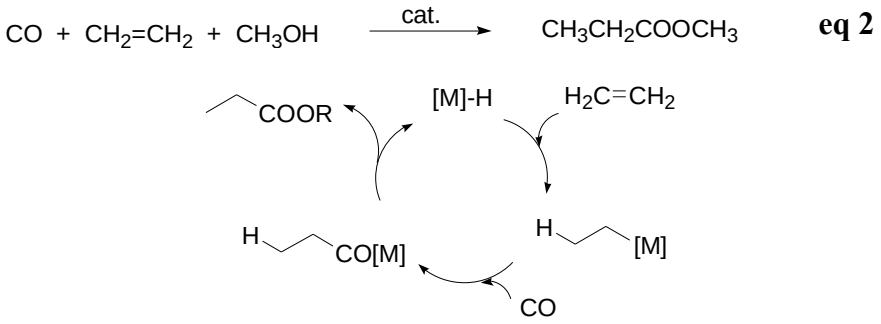
Scheme 2.3. Polyamidoamin-SiO_2 supported palladium catalyst.

2.1.2 Hydroesterification reagents

The most commonly employed hydroesterification reagent is CO gas in combination with alcohols. However, in consideration of the toxicity of CO gas, the use of nontoxic carbonyl sources such as formic acid, formate esters, and formamides would be desirable,[11] especially on lab scale syntheses. Initial attempts employing these reagents still often require the presence of CO gas, although under lower pressures, to obtain satisfactory yields. After extensive research in the past two decades, many conditions have appeared with improved efficiency even in the absence of CO gas.

2.1.2.1 Hydroesterification using CO and its mechanism

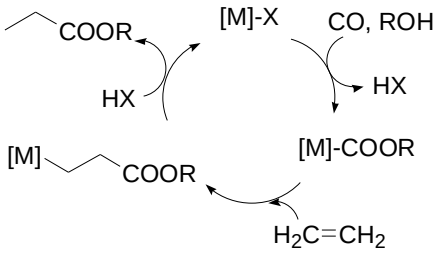
Using CO in combination with alcohols has the advantage of easy access of the inexpensive starting materials for industrial mass production, which has become the basis of many industrial processes. MeOH and EtOH are the alcohols that are usually used (eq 2). Two generally accepted mechanisms for this process have been proposed.[8] As shown in Scheme 2.4, the catalytic cycle can start with the insertion of an olefin into M-H bond of a hydridometal species, followed by CO insertion and solvolysis. This mechanism is believed to be a true catalytic cycle and is supported by ab initio MO calculations.[12]



Scheme 2.4. Catalytic cycle involves hydridometal species.

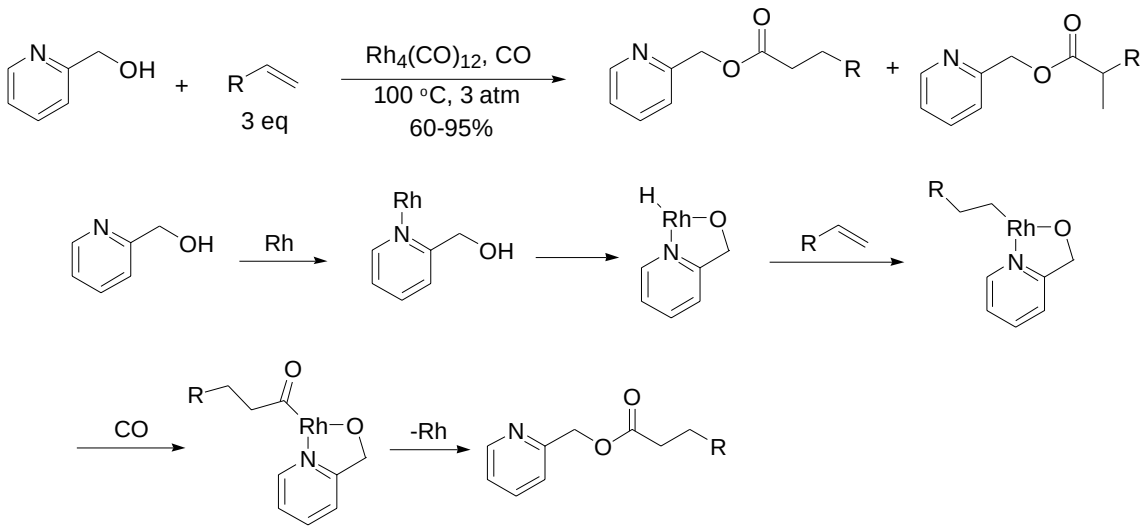
The hydridometal species can form in several ways. For example, in a palladium catalyzed system, hydrogen can be the hydride source by undergoing: $Pd^{2+} + H_2 \rightleftharpoons [Pd\text{-}H]^+ + H^+$. When an alcohol is used, a process involves $Pd^{2+} + CH_3OH \rightleftharpoons [Pd\text{-}OCH_3]^+ + H^+$ and $[Pd\text{-}OCH_3]^+ \rightarrow [Pd\text{-}H]^+ + HCHO$ provides the hydride source. Water can also be used to serve this role.[3]

Alternatively, the reaction may start from an alkoxycarbonylmetal species, which is generated from the insertion of an alcohol into an M-CO species (Scheme 2.5). Insertion of an olefin into the metal-carbonyl bond of the alkoxycarbonylmetal, followed by acid cleavage of the metal-alkyl bond results in the ester formation.[3,12]



Scheme 2.5. Catalytic cycle involves alkoxycarbonylmetal species.

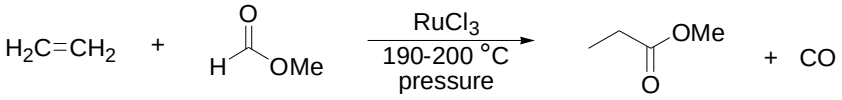
Chatani and co-workers discovered that 2-pyridylmethanol provides faster hydroesterifications than methanol (Scheme 2.6).[6] The accelerated reaction rate is explained by the coordination between the pyridyl nitrogen atom with rhodium catalyst to facilitate the reaction (Figure 2.6).[6]



Scheme 2.6. Hydroesterification using 2-pyridylmethanol and its mechanism.

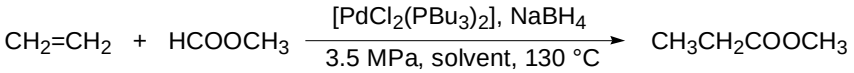
2.1.2.2 Formate esters

Using formate esters in hydroesterification reactions was first reported by Sneeden *et al*. in 1983. They described hydroesterification reactions of ethylene using methyl or ethyl formate and $RuCl_2(PPh_3)_3$ under high pressure. Propionates were obtained in low yields (Scheme 2.7).[13]



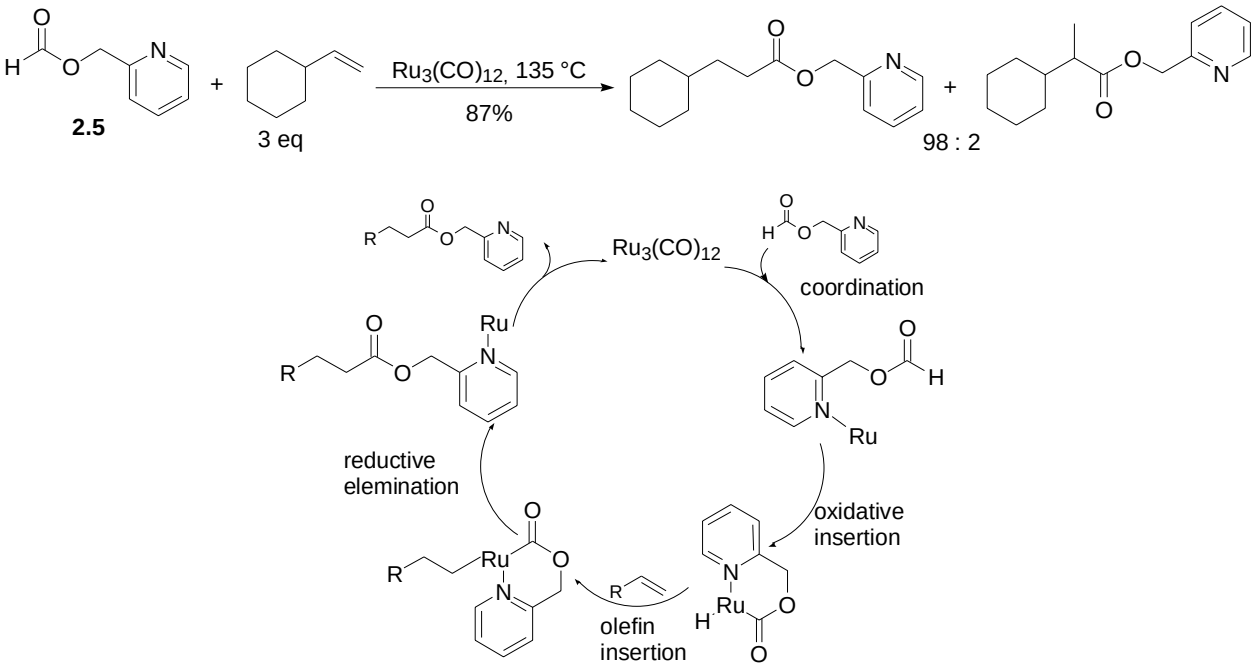
Scheme 2.7. Formate esters as hydroesterification reagents.

Grévin and Kalck reported the first palladium-catalyzed hydroesterification with formate esters (Scheme 2.8).[14] The reaction was conducted at 130 °C in the presence of $PdCl_2(PBu_3)_2$ and $NaBH_4$. Complex $[PdHCl(PBu)_3)_2]$ generated in situ by reacting $PdCl_2(PBu_3)_2$ with $NaBH_4$ is proposed to be the actual catalyst. Up to 90% yield was reported.



Scheme 2.8. Hydroesterifications with formate ester and Pd catalyst.

Chang and co-workers found 2-pyridylmethyl formate (**2.5**) to be a superior hydroesterification reagent (Scheme 2.9).[15] No carbon monoxide was needed and the reaction could be conducted under normal pressure. Good to excellent yields were obtained when olefins were used in excess. Exclusive linear ester formation was observed for substrates that have allylic branching. The reactions are believed to be facilitated by the nitrogen chelation with ruthenium, which minimizes destructive decarbonylation of activated acyl hydride intermediates. A chelation complex of 2-pyridylmethanol with ruthenium has been crystallized and the structure was confirmed by x-ray diffraction analysis.[16]

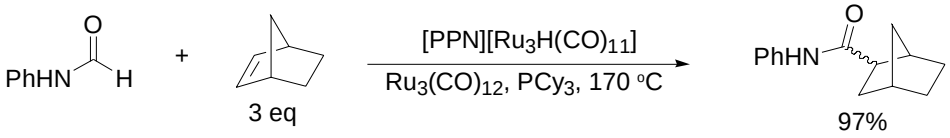


Scheme 2.9. Chang's hydroesterification and its proposed mechanism.

2.1.2.3 Formic acid and formamides

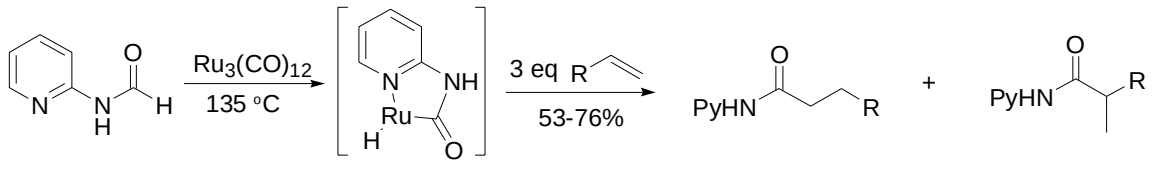
Hydrocarboxylation and hydroamidation are two types of reactions closely related to hydroesterification. The mechanisms and conditions of these reactions are very similar and products can be interconverted. When using formic acid as the carbonyl source, the process is called hydrocarboxylation. It has been widely used in industry in the preparation of highly branched C5 and C10 acids from alkenes.[1]

Using a formamide as the carbonyl source, a process called hydroamidation, generates an amide ultimately. Kondo *et al*. demonstrated that reactions of olefins with formanilide afforded amides in high yields when catalyst [PPN][$Ru_3H(CO)_{11}$] was used in the presence of PCy_3 (Scheme 2.10).[5]



Scheme 2.10. Hydroamidations with formanilides.

Chang and co-workers described the hydroamidation of olefins with *N*-(2-pyridyl)formamide catalyzed by $Ru_3(CO)_{12}$. The reactions gave moderate to good yields ranging from 53-70% (Scheme 2.11).[17]

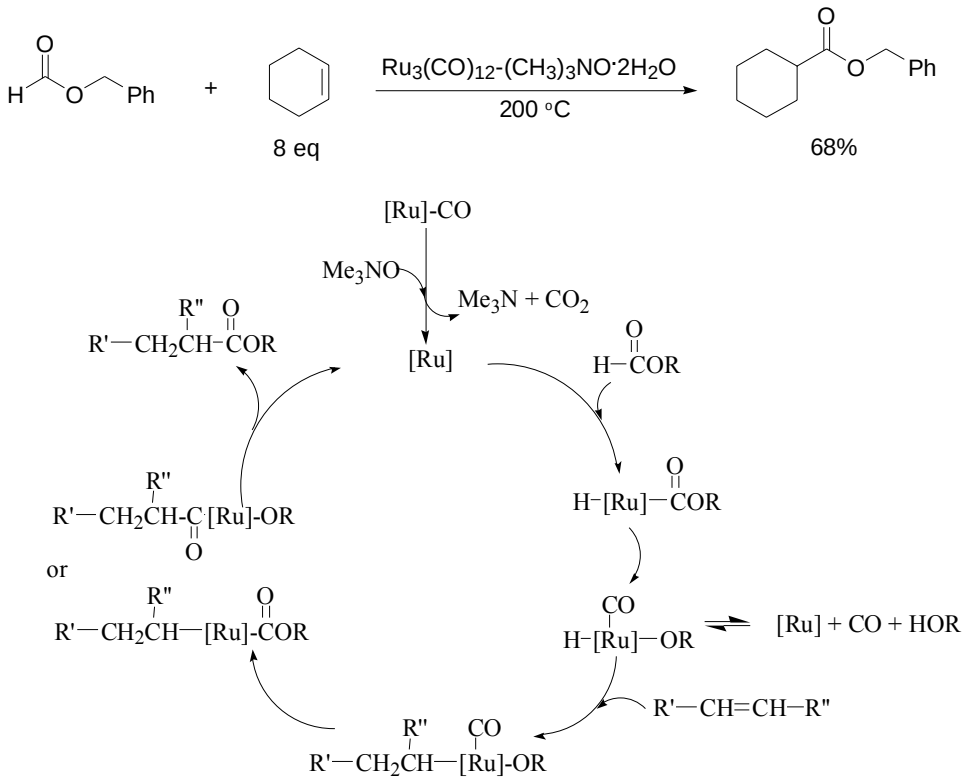


Scheme 2.11. Hydroamidations with *N*-(2-pyridyl)formamide.

2.1.3 Co-catalyst

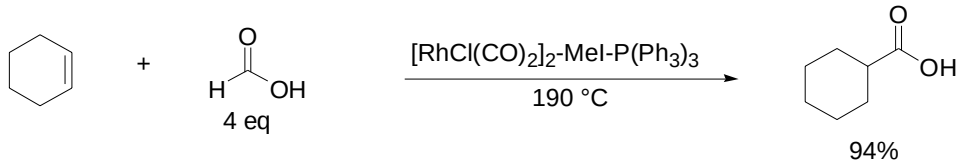
Many researchers reported a rate accelerating effect when co-catalysts are present in hydroesterification reactions. The co-catalysts reported to date include amine oxides, amines, and iodides.

Watanabe and co-workers reported the enhanced reactivity and efficiency of $Ru_3(CO)_{12}$ in the presence of $Me_3NO{\cdot}2H_2O$ in comparison to when $Ru_3(CO)_{12}$ was used alone (Scheme 2.12).[18] The reaction of benzyl formate with 8 eq of cyclohexene gave 68% yield of the desired product when a co-catalyst was used, while the yield was only 31% without the co-catalyst. The mechanism of the rate acceleration was proposed. The carbonyl ligand on the metal can be oxidized to CO_2 by Me_3NO, therefore leaving free coordinating sites for the formate and olefin (Scheme 2.12). Similar effects have been observed for other ruthenium[19] and osmium[20] catalysts.



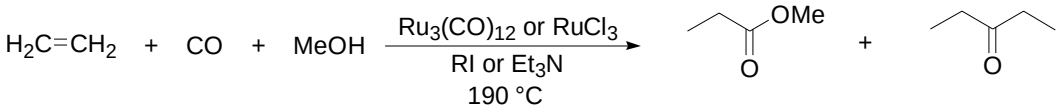
Scheme 2.12. Rate acceleration by Me_3NO and its mechanism.

Iodide was also observed to accelerate the hydroesterification reactions (Scheme 2.13).[21] In the following reaction, MeI was found to be the best co-catalyst, which allowed as few as 1 mol% of Rh catalyst to be used. No CO gas was necessary in the reaction.



Scheme 2.13. Rate acceleration by iodide.

In Hidai's synthesis of ketones and esters from olefins using hydroesterifications (Scheme 2.14),[22] iodides such as MeI, PhI, and I_2 increased the reaction rate by 50-fold when used together with $Ru_3(CO)_{12}$. When using a 10:1 ratio of NaI/$Ru_3(CO)_{12}$, the reaction rate was found to increase by 1200 times. It was proposed that iodide salts reacted with $Ru_3(CO)_{12}$ under the reaction conditions yielding $[HRu_3(CO)_{11}]^-$ and $[Ru(CO)_3I_3]^-$, which are more reactive species and are responsible for the higher reactivity.



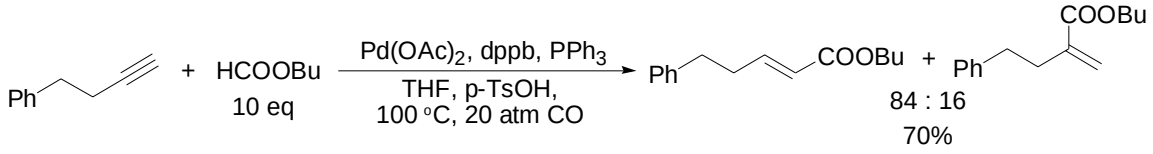
Scheme 2.14. Rate acceleration by iodide or amine.

Rate accelerating effects by amines were also reported by Hidai.[22] For example, in their hydroesterification reactions, using $RuCl_3$ alone is 270 times faster then using $Ru_3(CO)_{12}$ alone, while a combination of $RuCl_3$ and Et_3N was 520 times faster than using $Ru_3(CO)_{12}$ alone

(Scheme 2.14). Similar effects were observed when Et_3N[23] or pyridine[24] were used in hydroformylation reactions.

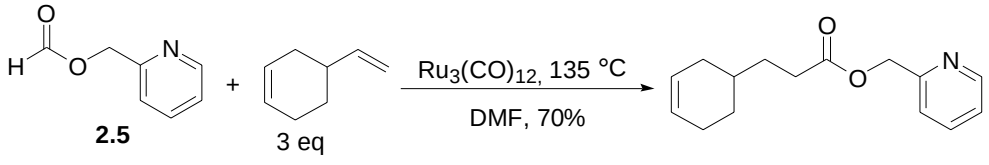
2.1.4 Hydroesterification substrates

Alkynes can undergo hydroesterifications to yield *α,β*-unsaturated esters.[25,26] Alper found that treating alkynes with palladium catalyst in the presence of butyl formate, PPh_3, PTSA, and 20 atm CO afforded the desired esters in good yields (Scheme 2.15).[25] Internal alkynes also undergo the same type of reactions. The regioselectivity is dependent on steric effects with the formate approaching from the less hindered end. When the steric difference is small, the regioselectivity is poor.



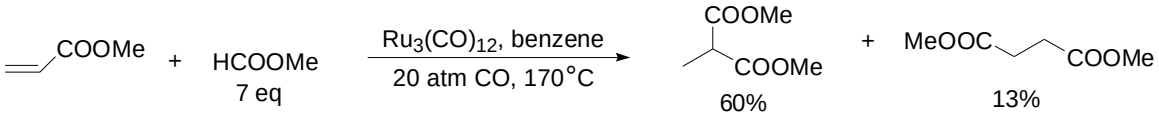
Scheme 2.15. Hydroesterifications of alkynes.

Dienes are also suitable hydroesterification substrates. Chang and co-workers reported a selective hydroesterification of terminal double bonds in the presence of internal double bonds. The following reaction gave an excellent 70% yield with the formate **2.5** being the limiting reagent (Scheme 2.16).[26]



Scheme 2.16. Selective hydroesterification of dienes.

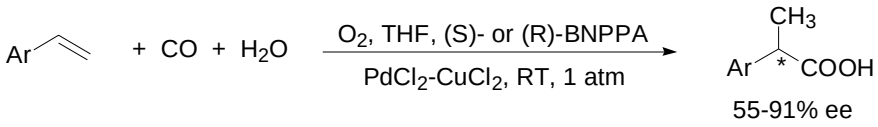
α,β-Unsaturated esters were also reported to undergo hydroesterifications. Hidai and co-workers described that *α,β*-unsaturated esters with various substitutents underwent facile hydroesterification and yielded a mixture of regioisomers. For example, methyl acrylate afforded a 60% yield of the dimethyl methylmalonate, together with 13% of dimethyl succinate (Scheme 2.17).[27]



Scheme 2.17. Hydroesterifications of *α,β*-unsaturated esters.

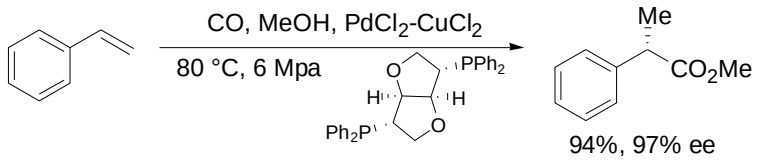
2.1.5 Enantioselective hydroesterification

Introducing enantioselectivity will certainly make hydroesterifications even more powerful, especially in the context of the synthesis of natural products, pharmaceuticals, and other fine chemicals. However, because of the harsh reaction conditions and complex reaction pathways, it is often difficult to achieve enantioselectivity and only a few examples have been reported. Alper and Hamel reported the enantioselective hydrocarboxylation of aromatic olefins in the presence of (*S*)- or (*R*)-1,1'-binaphthyl-2-2'-diyl hydrogen phosphate (BNPPA). Optical yields of 55-91% were achieved (Scheme 2.18).[28]



Scheme 2.18. Enantioselective hydroesterifications.

Zhou *et al*. reported asymmetric hydroesterification using mixed catalyst $PdCl_2$-$CuCl_2$ and a biphosphine ligand. The hydroesterification of styrene yielded methyl 2-phenylpropionate in 94% yield and 97% ee (Scheme 2.19).[29]



Scheme 2.19. Asymmetric hydroesterifications.

As demonstrated from above examples, hydroesterifications are a powerful class of reactions but with limitations. The harsh reaction conditions have restricted its application to mostly simple substrates with few functional groups. Under the reaction conditions, extensive olefin isomerization often occurs and an olefin has to be used in excess amount, with the carbonyl reagent (e.g. formate) as the limiting reagent. However, many times the olefin may be less accessible than the carbonyl reagent. Finding milder hydroesterification conditions to minimize olefin isomerization will be one major task for the researchers in this area. Its fulfillment will help to expand the scope of this reaction to more complex olefins and to maximally execute its potential.

2.1.7 Converting homoallylic alcohols into lactones

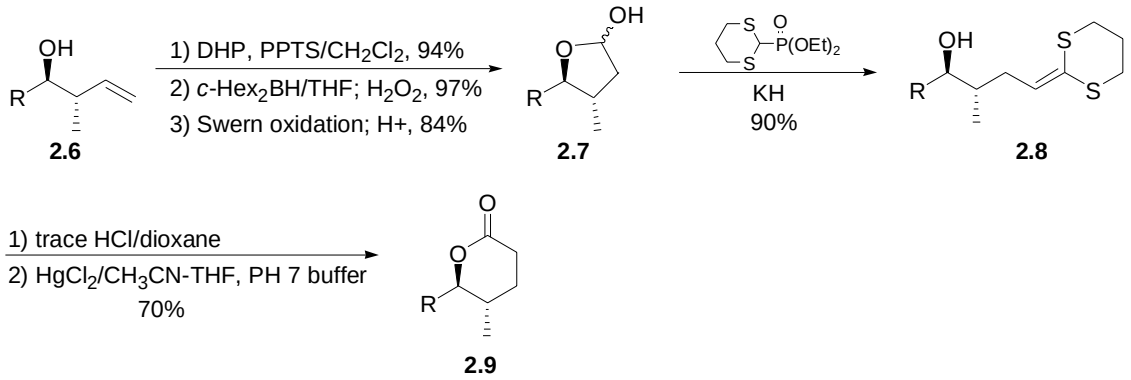
Homoallylic alcohols represent a class of valuable starting materials. They can be easily synthesized from the allylation of aldehydes. Moreover, asymmetric allylation is a thoroughly studied reaction, which provides easy access to enantiomerically pure homoallylic alcohols. The

alcohol and olefin functional groups on homoallylic alcohols allow various transformations, which make them desirable substrates for the synthesis of more advanced products.

Lactones, on the other hand, are common components of natural products and many pharmaceuticals. Converting homoallylic alcohols into lactones is a practical way of accessing these more advanced intermediates.

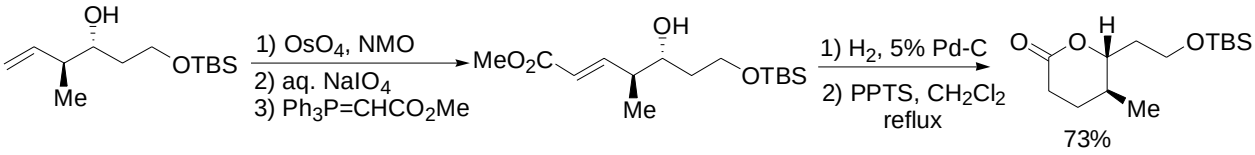
While many syntheses of lactones from homoallylic alcohols have been reported, most of them require multi-step sequences. One-carbon homologation of olefins in the synthesis of δ-lactones is often the most difficult step to accomplish and many solutions have been developed, such as a Wittig reaction.

In Suzuki's synthesis of protomycinolide IV, the authors used a five-step sequence to convert a homoallylic alcohol into a lactone.[30] As shown in Scheme 2.20, alcohol **2.6** was first protected with a THP group. Hydroboration of the resulting olefin followed by oxidation afforded a lactol (**2.7**), which underwent a Horner-Emmons reaction with Mikolaiczyk reagent to give the ketene dithioacetal (**2.8**). Cyclization under mild acidic conditions followed by hydrolysis of the dithoacetal afforded the lactone **2.9**.



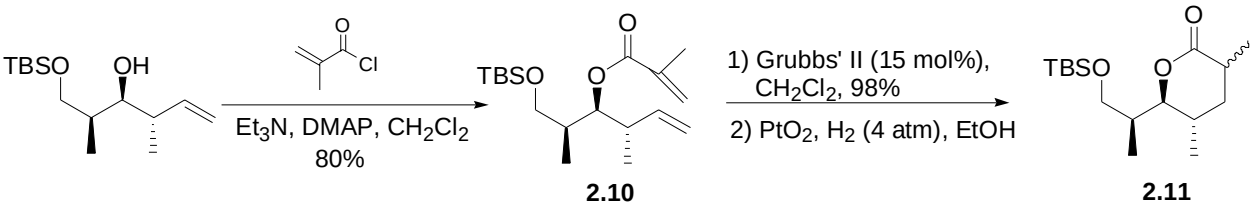
Scheme 2.20. Suzuki's lactone synthesis.

The most commonly used sequence is shown in Scheme 21.[31,32] Homoallylic alcohols are subjected to a 5-step sequence, including dihydroxylation, oxidation, Wittig reaction, hydrogenation, and lactonization to afford the desired lactone.



Scheme 2.21. Typical Lactone Synthesis Sequence in the Literature.

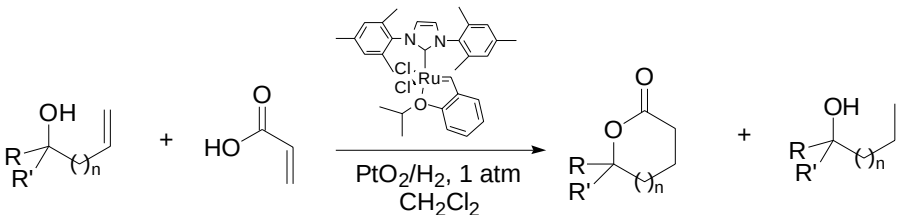
A powerful reaction, ring closing metathesis, was also applied in the transformation of homoallylic alcohols into lactones. In Cossy's synthesis of (+)-methynolide, a homoallylic alcohol was first converted into an ester (**2.10**) with methacryloyl chloride. The resulting diene then underwent ring closing metathesis in the presence of Grubbs' II catalyst to afford an enelactone, which was reduced under hydrogenation conditions to yield the desired lactone (**2.11**) as a 1:1 mixture of diastereomers (Scheme 2.22).[33]



Scheme 2.22. Lactone synthesis using ring closing metathesis.

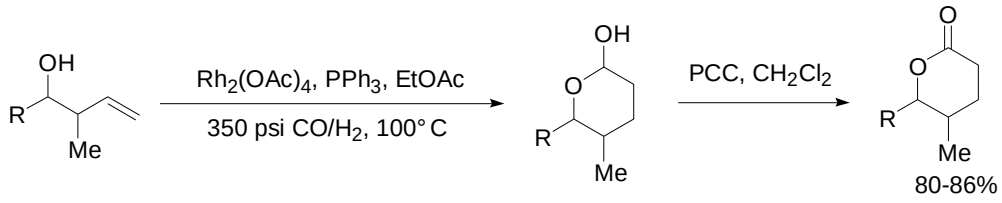
Later, Cossy and co-workers developed a general protocol using a tandem cross-metathesis/hydrogenation/cyclization reaction to synthesize lactones from homoallylic alcohols. In the same reaction vessel, both the cross metathesis catalyst and the hydrogenation catalyst

were present. Cross metathesis between the homoallylic/allylic alcohol and acrylic acid occurred first, followed by hydrogenation and cyclization to afford the lactones in 35-70% yields (Scheme 2.23).[34] The method has the drawbacks of using expensive catalysts and providing low yields. Also, undesired hydrogenation often occurs before cross metathesis and shuts down the desired reaction pathway.



Scheme 2.23. Cossy's one-pot lactone synthesis.

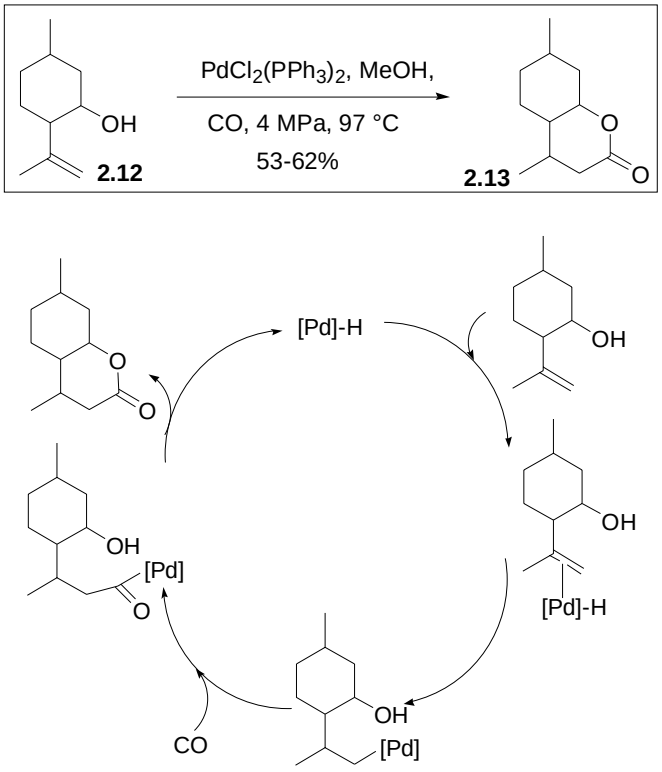
Wuts and co-workers developed a protocol using a hydroformylation followed by an oxidation (Scheme 2.24).[35] A homoallylic alcohol was treated with CO and H_2 gas under high pressure (350 psi) and high temperature (100 °C) in the presence of Rh catalyst and PPh_3 to generate a lactol, which was then oxidized to a lactone in excellent overall yield. This method, however, needs special equipment, large amounts of CO gas, and expensive catalysts.



Scheme 2.24. Lactone formation under high pressure.

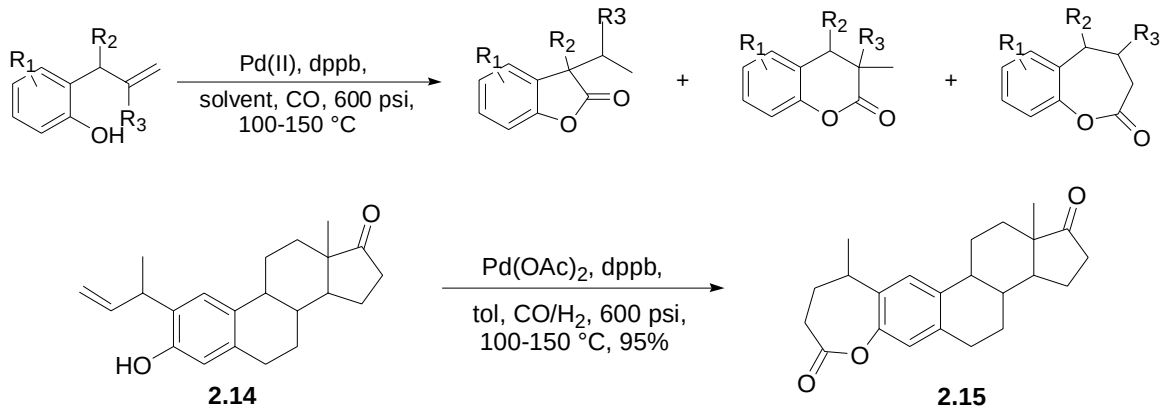
Kalck and co-workers used a palladium catalyzed hydroesterification to convert isopulegol (**2.12**) into its lactone. In the presence of CO gas at 97 °C, lactone **2.13** was obtained in 53-62%

yield (Scheme 2.25).[36] Because a palladium catalyst was used, the reaction could be conducted at fairly mild 97 °C. However, this method has the drawback of using CO gas under high pressure. Also, the scope of this reaction was not studied since this is the only example in this report. The mechanism of the reaction was also proposed (Scheme 2.25).[36]



Scheme 2.25. Palladium-catalyzed lactonization of isopulegol.

Alper and co-workers found that when 2-allylphenols were treated with CO under 600 psi in the presence of palladium catalyst, a mixture of 5-, 6- and 7-membered lactones was formed (Scheme 2.26).[37] Changing the reaction conditions, substitution patterns on the aromatic ring, and reagents lead to various ratios among the products. Allylphenol **2.14** gave an excellent 95% yield to 7-membered lactone **2.15** (Scheme 2.26). However, too often the yields are poor and the selectivity is low. The substrate scope is limited to allylphenols.



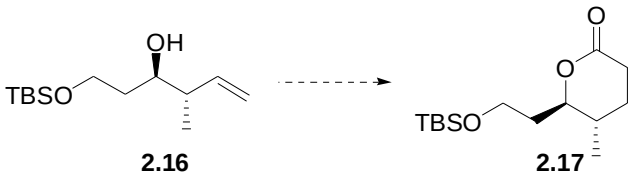
Scheme 2.26. Lactone formations from allylphenols.

As summarized above, the transformation of homoallylic alcohols into lactones often needs multiple steps when not using hydroesterification conditions. The operation is lengthy and the cost of reagents is high. Using hydroesterification can shorten the sequence greatly; however, the reactions need to be performed under high pressure and high temperature involving the use of CO gas. Therefore, expensive equipment is needed.

Our goal, in consideration of but not limited to lab scale synthesis, is to find a system that can fulfill the transformation of homoallylic alcohols into lactones with low cost and without resorting to special equipment. Developing mild conditions is another goal, which will broaden the tolerance of functional groups and the scope of this transformation. Applying hydroesterification reactions with new carbonyl-bearing reagents will be one way to achieve these goals.

2.2 Results

In our study of total synthesis of integramycin, we sought a transformation that enables the conversion of homoallylic alcohol **2.16** into lactone **2.17** (Scheme 2.27). Hydroesterification is an excellent way to realize this goal but the existing reaction conditions are often too harsh because high pressure CO gas at high temperature is needed. We conceived that the hydroesterification conditions recently developed by Chang[15] would provide the opportunity of achieving this goal under milder conditions.

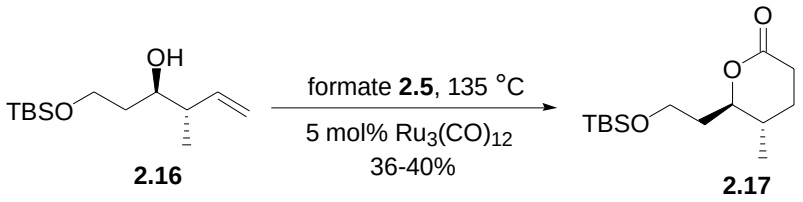


2.16 **2.17**

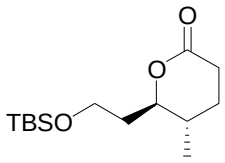
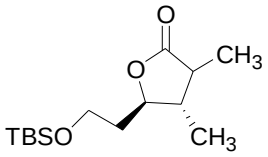
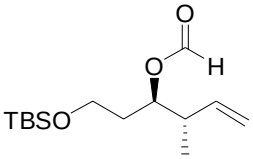
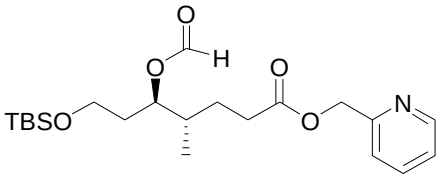
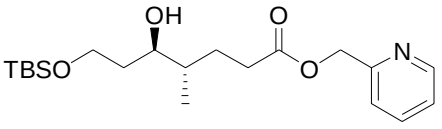
Scheme 2.27. Converting homoallylic alcohols to lactones.

2.2.1 Initial results

Treatment of alcohol **2.16** with 2-pyridylmethyl formate **2.5** (3 eq) and a catalytic amount of $Ru_3(CO)_{12}$ (5 mol%) at 135 ºC for 4 h, as a validation of our hypothesis, furnished the desired lactone **2.17** in 36% yield (Scheme 2.28).[38] When using 5 equivalents of **2.5** and elongated reaction time (4 h at 135 ºC and 11 h at 125 ºC), the yield was slightly improved to 40%. A careful separation of the reaction mixture and NMR spectroscopy analysis revealed the identities of the side products of the reaction (Table 2.1). γ-Lactone **2.18** was isolated in a significant 18% yield with a 1:2.3 ratio to the desired lactone. Starting material **2.16** and its formate ester **2.19** were isolated in a combined ~10% yield. Ester byproducts **2.20** and **2.21** were isolated in 13% and 1% yields, respectively.



Scheme 2.28. Lactonization of **2.16**.

product		yield (%)[a]
starting material	**2.16**	4
	**2.17**	40
	**2.18**	18
	**2.19**	5
	**2.20**	13
	**2.21**	1

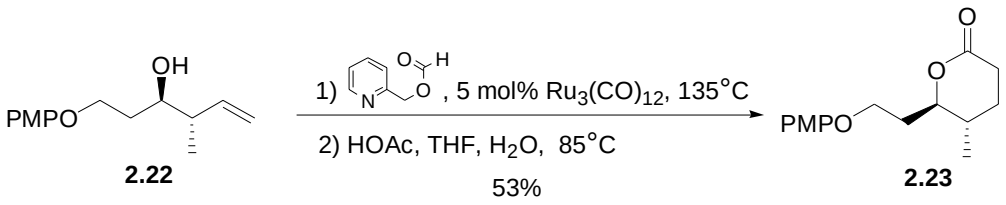
[a] All yields were isolated yields. Reaction conditions: a mixture of **2.16**, 5 eq of 2-pyridylmethyl formate, and 5 mol% of $Ru_3(CO)_{12}$ was stirred at 135 ºC for 4 h, and at 125 ºC 11 h.

Table 2.1. Product distribution of the hydroesterification/lactonization reaction.

Even though the reaction yield is modest, the reaction indeed shows advantages over literature precedents. The reaction conditions are much simpler and the ruthenium catalyst is relatively inexpensive. Moreover, the two ester byproducts promise a better yield since they can be hydrolyzed to the desired lactone under acidic conditions.

2.2.2 Improved conditions

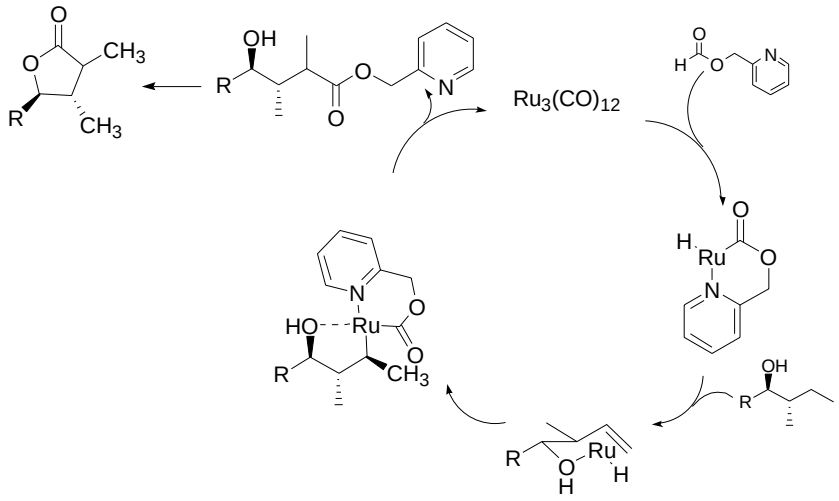
The ester byproducts **2.20** and **2.21** can be converted to the desired lactone under acidic conditions. However, the TBS protecting group would not survive acidic conditions and needed to be changed. We then synthesized homoallylic alcohol **2.22** with a *para*-methoxylphenyl (PMP) protecting group on the primary alcohol, which is robust and allows acidic hydrolysis. After hydroesterification at 135 ºC for 4 h, the reaction mixture was subjected to various acidic conditions to cyclize the ester byproducts. Heating the reaction mixture in HOAc/THF/H_2O (3:1:1) at 85 °C was found to be the best hydrolysis conditions. Indeed, this one-pot hydroesterification followed by acidic hydrolysis protocol converted homoallylic alcohol **2.22** into lactone **2.23** in an improved 53% yield (Scheme 2.29).[38]



Scheme 2.29. One-pot protocol of hydroesterification followed by hydrolysis.

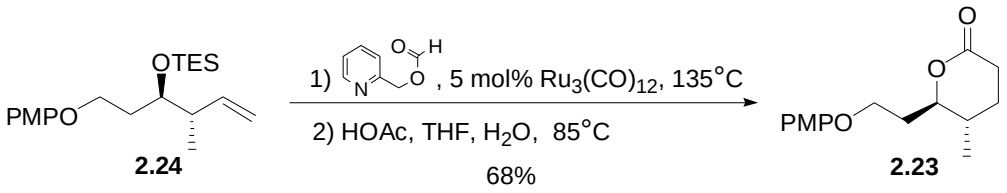
In the hydroesterification/lactonization reaction of **2.16** (Scheme 2.28), the γ-lactone **2.18** formed in 18% yield, which is higher than expected according to Chang's observation of

exclusive linear product formation in the presence of a branching group at the allylic position. We rationalized this by invoking a coordinating effect of the free hydroxyl group with the ruthenium catalyst to generate a kinetically favored 5-membered intermediate, which lowers the barrier of the formation of the branched alkylmetal complex (Scheme 2.30). A compelling precedent for a coordinating group causing a regiochemical reversal in hydrometalation reactions has been provided through the Evans group's studies on metal-catalyzed hydroborations.[39]



Scheme 2.30. Coordination facilitated γ-lactone formation.

To suppress coordination, the hydroxyl group was protected as a silyl ether. Silyl ether **2.24** (Scheme 2.31) was treated under hydroesterification conditions followed by acidic hydrolysis, and afforded the desired lactone in an improved 68% yield. While requiring one additional step relative to the one-pot lactone synthesis, the increase in efficiency should prove to be useful for homoallylic alcohols that are difficult to access.

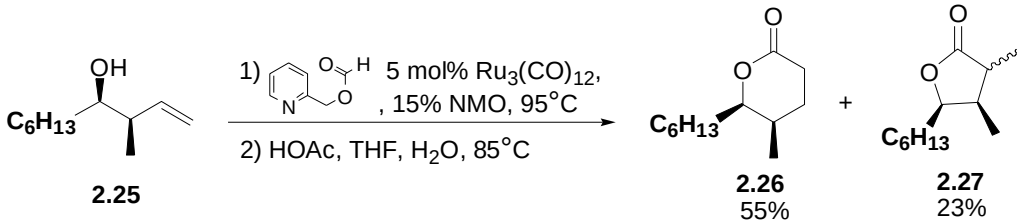


Scheme 2.31. Improved efficiency of silyl ethers.

2.2.3 Rate acceleration by addition of co-catalyst

It is known that amine oxide such as Me_3NO can facilitate metal-catalyzed hydroesterifications.[18] *N*-methyl morpholine *N*-oxide (NMO) was also observed to promote cobalt-catalyzed Pauson-Khand reactions in Schreiber's study.[40]

We investigated the effect of addition of NMO in our hydroesterification reactions. To our delight, a significant rate accelerating effect was observed when NMO was applied in the reactions.[41] For example, in the presence of NMO, the hydroesterification of **2.22** went to >98% conversion at 135 ^{o}C in less then 1.5 h. While in the absence of NMO, it took 12 h for the reaction to reach this conversion. The addition of NMO also enables reduction of the reaction temperature to as low as 90-95 ^{o}C without affecting the reaction yield (Scheme 2.32.), which extends the substrate scope of this method to compounds that do not tolerate extreme heat. The new conditions also enhance the reaction rate for sterically hindered substrates at 135 ^{o}C and facilitate large scale reactions. Using these conditions, 100 mmol scale reactions have been conducted in our lab without significant loss of yield.[42]



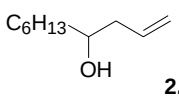
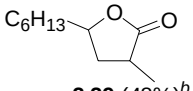
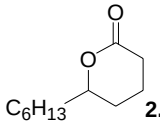
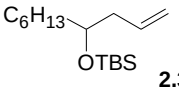
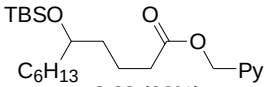
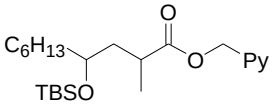
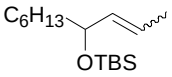
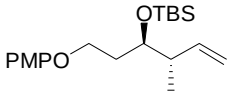
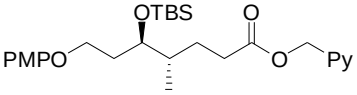
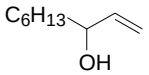
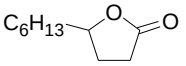
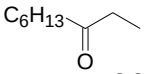
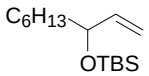
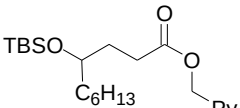
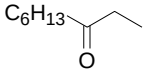
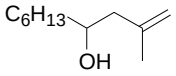
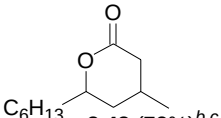
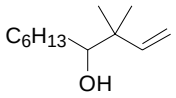
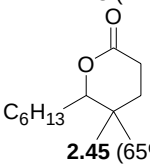
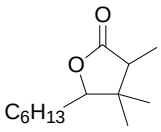
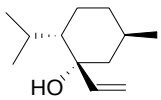
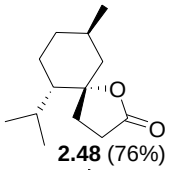
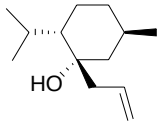
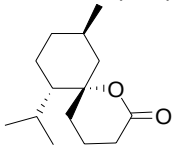
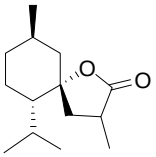
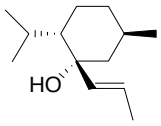
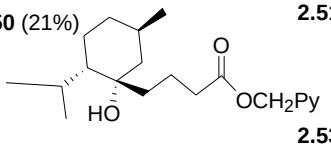
Scheme 2.32. Enhanced reaction rate by addition of NMO.

2.2.4 Scope

To gauge the scope of this reaction with functionalized olefins as limiting reagents and to assess the potential of hydroxyl coordination to alter the regiochemical outcome of the hydroesterification reaction, we prepared several substrates and exposed them to hydroesterification conditions (Table 2.2).[41] Homoallylic alcohol **2.28** (entry 1), in which the absence of branching at the allylic carbon was expected to be less detrimental to the formation of the branched product relative to substrate **2.22**, indeed provided γ-lactone **2.29** (48%) as a diastereomeric mixture and δ-lactone **2.30** (25%). This result, while not immediately useful in a synthetic sense, demonstrates that coordination has the capacity to reverse the regiochemical outcome of hydroesterification reactions. As expected, hydroesterification of silyl ether **2.31** (entry 2) provided a mixture of linear ester **2.32** and branched ester **2.33** in an approximately 3:1 ratio. The major product in this reaction was olefin isomer **2.34**. In the presence of an allylic group, however, the olefin isomerization was suppressed and a linear ester (**2.36**) was obtained in an excellent 80% yield (entry 3).

Allylic alcohol **2.37** (entry 4) only provided a moderate yield of the γ-lactone **2.38** (45%), with ketone **2.39** generated from starting material isomerization as the major byproduct. The destructive isomerization can be suppressed by protecting the allylic alcohol with a silyl group (entry 5). Ether **2.40** underwent facile hydroesterification and gave the ester product **2.41** in 78% yield, ultimately providing an excellent method for γ-lactone formation from allylic alcohols.

1,1-Disubstituted alkene **2.42** (entry 6) reacted efficiently, albeit slowly, to form lactone **2.43** as a 1:1 mixture of diastereomers in 72% yield. Hindered neopentyl and tertiary alcohols proved to be very suitable substrates. Disubstitution at the allylic position (entry 7) actually resulted in quantitative hydroesterification, though the linear to branched ratio was only approximately 2:1.

entry	substrate[a]	products (yield)		
1	 **2.28**	 **2.29** (48%)[b]	 **2.30** (25%)	
2	 **2.31**	 **2.32** (28%)	 **2.33** (9%)	 **2.34** (33%)
3	 **2.35**	 **2.36** (80%)		
4	 **2.37**	 **2.38** (45%)	 **2.39** (28%)	
5	 **2.40**	 **2.41** (78%)	 **2.39** (5%)	
6	 **2.42**	 **2.43** (72%)[b,c]		
7	 **2.44**	 **2.45** (65%)	 **2.46** (35%)	
8	 **2.47**	 **2.48** (76%)		
9	 **2.49**	 **2.50** (21%)	 **2.51** (19%)	 **2.52** (20%)
		 **2.53** (37%)		

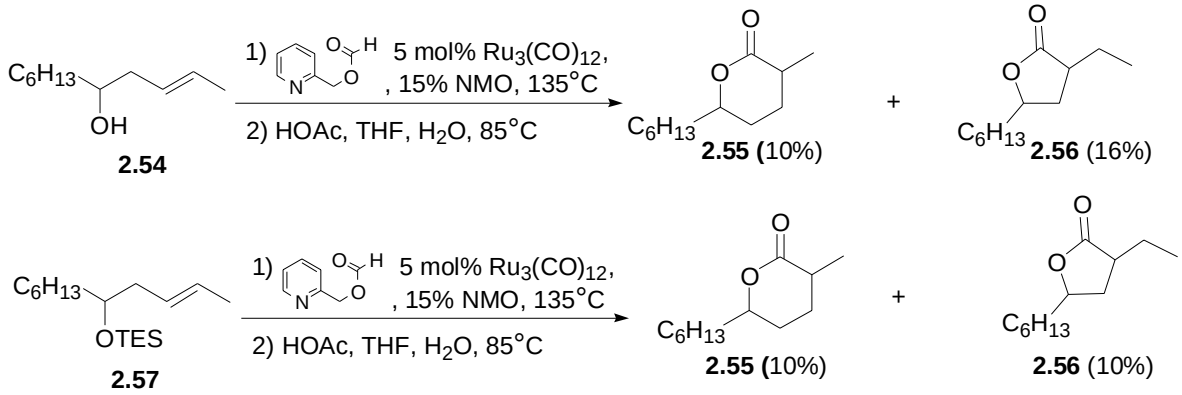
[a]General conditions: substrate, $Ru_3(CO)_{12}$ (5 mol%), and NMO (5-15 mol%) were stirred at 100-135 °C in 2-pyridylmethyl formate for 1.5-12 h. HOAc/THF/H_2O was added to complete lactonization when necessary. [b]Isolated as 1:1 mixture of diastereomers. [c]Yield at 89% conversion.

Table 2.2. Scope of tandem hydroesterification/lactonization reactions.

Hindered substrates reacted most efficiently in sealed tubes, most likely because the substrates are somewhat volatile and can be lost upon prolonged heating.

Spirolactones, common components of some natural products,[43] can also be synthesized under our conditions. Notably, menthone derivatives **2.47** and **2.49**, which were poor substrates for Cossy's[34] metathesis-based lactonization strategy, were converted to spirolactones **2.48** and **2.50** in satisfactory yields. Allylic alcohol **2.47** (entry 8) afforded lactone **2.48** in a good 76% yield, while **2.49** (entry 9) gave a mixture of products including lactone **2.50** (21%) and ester **2.53** (37%). Although ester **2.53** cyclized only reluctantly under thermal conditions, it can be converted to lactone **3.50** in quantitative yield by treatment with NaH in THF.

Internal olefins were also tested under the reaction conditions. After 12 h heating, olefin **2.54** only produced small amounts of the lactone products **2.55** and **2.56**. When the alcohol was protected with a silyl group, the reactivity was not improved. The reaction also only provided low yields to the lactones (Scheme 2.33). These results showed that internal homoallylic alcohols are much less reactive than terminal homoallylic alcohols under our conditions.



Scheme 2.33. Low reactivity of internal olefins.

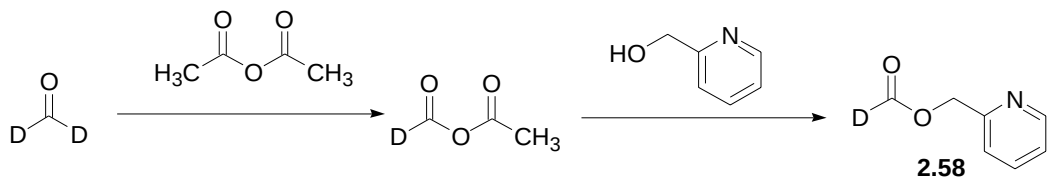
2.2.5 Mechanistic study

The hydroxyl group and allylic methyl group appeared to play important roles in determining the reaction efficiency and regioselectivity. For example, compound **2.31** (Table 2.2, entry 2),

which does not have an allylic Me group or free OH, gave the linear ester **2.32** in a 28% yield and the branched ester **2.33** in a 13% yield, with starting material isomer **2.34** as the major product (33%). This is in sharp contrast to **2.35** (Table 2.2, entry 3), which gave 80% yield of the linear product; it is also in contrast to **2.28** (Table 2.2, entry 1), which give a 73% overall hydroesterification yield.

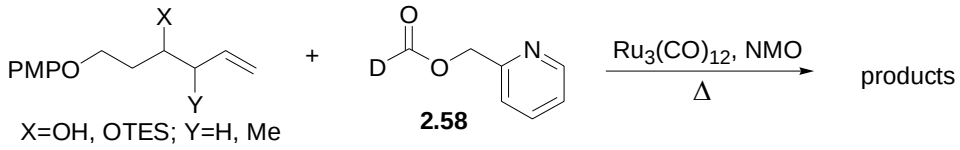
The formation of varying amounts of olefin isomers of the starting materials (Table 2.2, entries 2&9) and ketone **2.39** (Table 2.2, entry 4) suggests that *β*-hydride elimination can be competitive with reductive elimination, thereby challenging our original hypothesis of product selectivity being set in the hydrometalation step (Scheme 2.30).

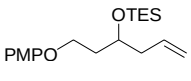
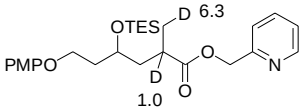
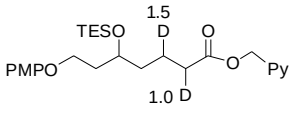
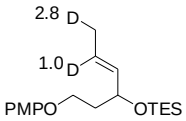
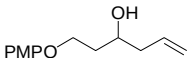
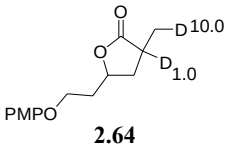
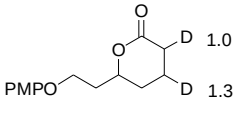
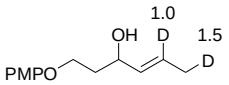
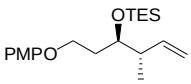
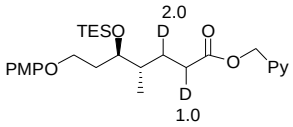
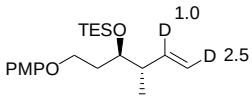
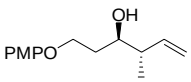
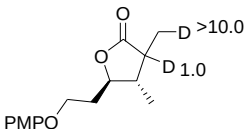
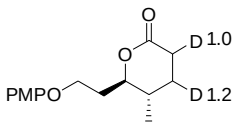
To obtain a clearer image of the reaction pathways and the roles of hydroxyl and methyl groups, mechanistic study applying deuterium labeling was conducted. Deuterium labeled 2-pyridylmethyl formate **2.58**, prepared by a reaction from commercially available DCO_2D as shown in Scheme 2.34 was used as the mechanistic probe in the hydroesterification reactions. After the reactions were completed, the products were separated and analyzed with deuterium NMR. In these experiments we define α-deuteration as deuterium incorporation on the carbon bearing the ester group and *β*-deuteration as deuterium incorporation on the adjacent carbon. Exclusive *β*-deuteration would be expected if product regiochemistry were solely dictated by the initial hydrometalation step, whereas a mixture of α- and *β*-deuteration would be expected if hydrometalation were reversible.



Scheme 2.34. Deuterated 2-pyridylmethyl formate.

Compounds **2.22**, **2.24**, **2.59** and **2.60** were subjected to the reaction conditions and the results are listed in Table 2.3. A striking observation from this work is that little or no selectivity is observed in the site of deuterium incorporation in most of the reaction products. Also noteworthy is that stopping the hydroesterification of **2.24** prior to complete conversion resulted in the isolation of starting material in which deuterium was incorporated at both vinylic positions. These results strongly indicate that hydrometalation is reversible and that regiochemical preferences in this step cannot be the sole determinant in the partitioning between linear and branched products for this series of compounds.

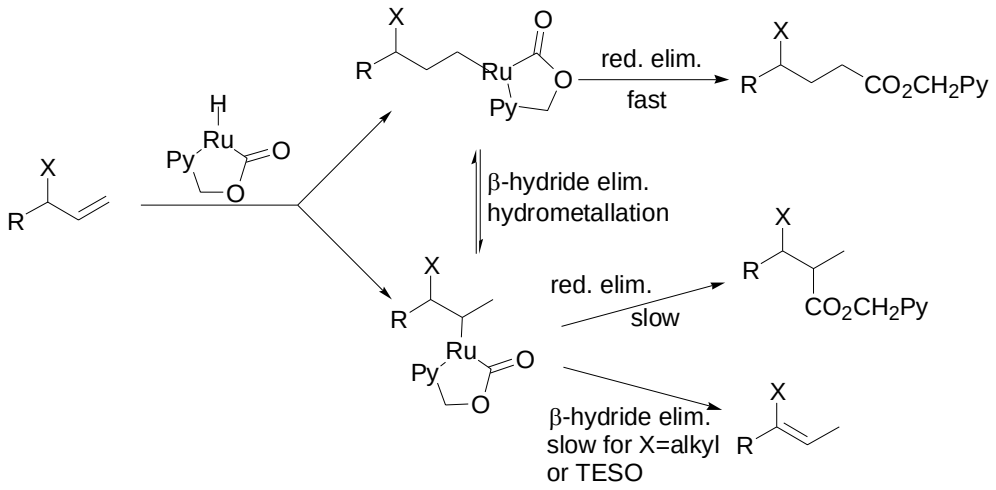


Entry	Substrate [a]	Products and deuterium distribution: Branched product	Linear porduct	Starting material or its isomer
1	 **2.59**	 **2.61**	 **2.62**	 **3.63**
2 [b]	 **2.60**	 **2.64**	 **2.65**	 **2.66**
3	 **2.24**	Not isolated	 **2.67**	 **2.68**
4	 **2.22**	 **2.69**	 **2.70**	Not isolated

[a] General procedure: substrate, $Ru_3(CO)_{12}$ (5 mol %), and NMO (5-15 mol %) were stirred at 135 °C in deuterated 2-pyridylmethyl formate for 1.5-12 h. [b] Reaction conducted at 100 °C.

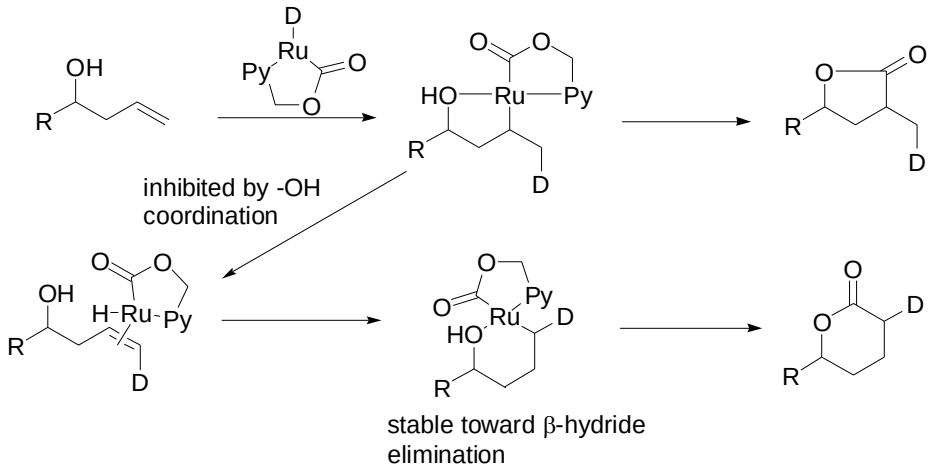
Table 2.3. Deuterium distribution of deuterioesterification products.

Scheme 2.35 shows a revised mechanism that is consistent with the deuteration patterns shown in Table 2.3. Hydrometalation proceeds with no selectivity, even with substrates that are branched at the allylic position. *β*-Hydride elimination is, in most cases, rapid relative to reductive elimination. Internal olefin formation by *β*-hydride elimination accounts for starting material isomerization. As discussed above, these products undergo hydroesterification reactions only very slowly under our conditions. Allylic branching suppresses starting material isomerization, leading to enhanced efficiency for ester formation for all substrates except allylic alcohols. The selectivity for linear products thus arises from reductive elimination being more efficient for primary alkylruthenium species than for secondary species, either through having an inherently lower energy of activation or through *β*-hydride elimination being significantly faster for secondary alkylruthenium compounds. Branching provides a further drive for linear product formation. This can be attributed to steric hindrance disfavoring the branched isomer as the alkylruthenium intermediates equilibrate prior to *β*-hydride elimination.



Scheme 2.35. Mechanistic pathways for hydroesterification.

The conspicuous diminution of α-deuteration in the branched products of entries 2 and 4 provides compelling evidence for the role of heteroatom coordination (Scheme 2.36). These data indicate that the primary alkylruthenium species undergoes reductive elimination in nearly exclusive preference to *β*-hydride elimination. This result is most economically ascribed to the hydroxyl group occupying the coordination site that is required for *β*-hydride elimination. By analogy, coordination must slow *β*-hydride elimination to a sufficient extent in branched intermediates for reductive elimination to become a competitive pathway. Although this analysis explains improved efficiency for branched product formation, it does not explain its preference from **2.28**. In this reaction we postulate that branched hydrometalation is favored over linear hydrometalation, possibly resulting from hydroxyl coordination, thereby increasing the concentration of the secondary alkylruthenium species and promoting branched product formation.

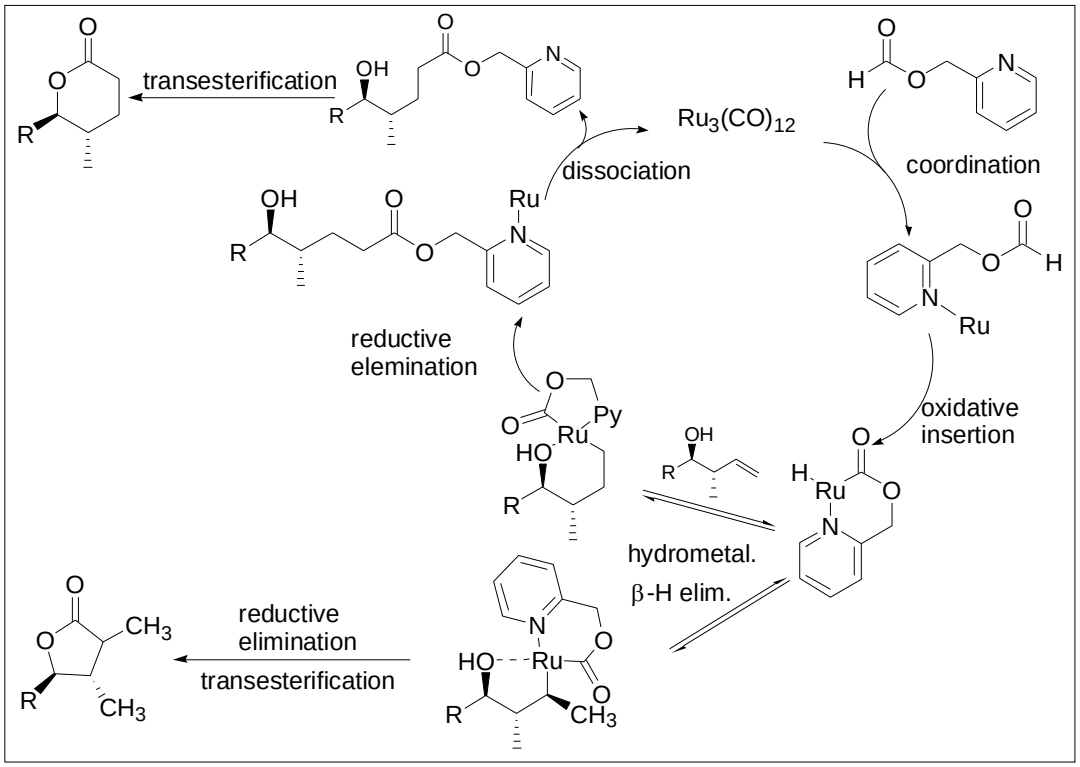


Scheme 2.36. Role of coordination in hydroesterification.

Finally, a complete image of the reaction mechanism is described in Scheme 2.37. Ruthenium initially coordinates to the nitrogen atom of 2-pyridylmethyl formate **2.5**, then undergoes

oxidative insertion into the C-H bond, generating a 6-membered chelate. Olefin insertion into the Ru-H bond results in a linear alkyl-Ru complex and a branched alkyl-Ru complex. Both complexes can undergo β-hydride elimination to afford either starting material or its isomer. The two complexes can also undergo reductive elimination to give the corresponding esters, which then undergoes transesterification to provide the δ- and γ-lactones.

The competition between hydrometalation, *β*-hydride elimination, and reductive elimination determines the efficiency and regioselectivity of the reaction. The allylic methyl group and free OH dictate the winner of the competition. Realizing the factors influencing the reaction pathways will help to design conditions and formate reagents to improve the reaction efficiency. It will also help in the design of substrates suitable for hydroesterifications.



Scheme 2.37. Mechanism of the tandem hydroesterification/lactonization.

2.3 Summary

We have developed a general protocol for synthesizing lactones from allylic and homoallylic alcohols. The lactone synthesis only requires one step (for allylic alcohols) or two steps (for homoallylic alcohols) that can be conducted in one pot. The experimental procedure is simple and the efficiency is considerably improved compared to that of multi-step sequences.

We have demonstrated that hydroesterification reactions of functionalized olefins can proceed efficiently even when the olefin is used as the limiting reagent. These processes proceed most effectively when branching is present at the allylic position to suppress olefin isomerization. Homoallylic hydroxyl groups promote the formation of branched esters to a modest extent. Mechanistic studies with deuterated pyridylmethyl formate show that, whereas the hydroxyl group might very well influence the regiochemistry of the hydrometalation step, the partitioning of products between linear and branched isomers is dependent upon the relative rates of reductive elimination between primary and secondary alkylruthenium species. The hydroxyl group serves to slow β-hydride elimination of the secondary alkylruthenium species to an extent that allows reductive elimination to be a viable process.

Application of hydrometalation/reductive elimination processes to complex molecule synthesis will ultimately require an understanding of the effects of remote functional group on regiochemistry and efficiency. Elucidating the consequences of heteroatom coordination through mechanistic studies of the type described herein will prove to be beneficial in the design of procedural variants that expand the scope of this useful reaction class.

2.4 References

(1) Kiss, G. *Chem. Rev.* **2001**, *101*, 3435-3456.

(2) Alper, H.; Hamel, N. *J. Am. Chem. Soc.* **1990**, *112*, 2803-2804.

(3) Vavasori, A.; Cavinato, G.; Toniolo, L. *J. Mol. Catal. A: Chem.* **2001**, *176*, 11-18.

(4) Beller M.; Cornils, B.; Frohning, C. D.; Kohlpainter, C. W. *J. Mol. Catal. A: Chem.* **1995**, *104*, 17-85.

(5) Kondo, T.; Okada, T.; Mitsudo, T. *Organometallics* **1999**, *18*, 4123-4127.

(6) Yokota, K.; Tatamidani, H.; Fukumoto, Y.; Chatani, N. *Org. Lett.* **2003**, *5*, 4329-4331.

(7) Bird, C. W. *Chem. Rev.* **1962**, *62*, 283-302.

(8) Ojima, I. *Chem. Rev.* **1988**, *88*, 1011-1030.

(9) Zhang, J.; Xia, C.-G. *J. Mol. Catal. A: Chem.,* **2003**, *206*, 59-65.

(10) Reynhardt, J. P. K.; Alper, H. *J. Org. Chem.* **2003**, *68*, 8353-8360.

(11) Wiedemann, S. H.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2004**, *6*, 1685-1687.

(12) Kawana, M.; Nakamura, S.; Watanabe, E.; Urata, H. *J. Organomet.Chem*. **1997**, *542*, 185-189.

(13) Isnard, P.; Denise, B.; Sneeden, R. P. A.; Cognion, J. M.; Durual, P. *J. Organomet. Chem.* **1983**, *256*, 135-139.

(14) Grevin, J.; Kalck, P. *J. Organomet. Chem.* **1994**, *476*, C23-C24.

(15) Ko, S.; Na, Y.; Chang, S. *J. Am. Chem. Soc*. **2002**, *124*, 750-751.

(16) Ko, S.; Lee, C.; Choi, M.-G.; Na, Y.; Chang, S. *J. Org. Chem.* **2003**, *68*, 1607-1610.

(17) Ko, S.; Han, H.; Chang, S. *Org. lett.* **2003**, *5*, 2687-2690.

(18) Kondo, T.; Yoshii, S.; Tsuji, Y.; Watanabe, Y.; *J. Mol. Catal.* **1989**, *50*, 31-38.

(19) Johnson, B. F. G.; Lewis, J.; Pippard, D. *J. Organomet. Chem.* **1978**, *145*, C4-C6.

(20) Rankin, J.; Benyei, A. C.; Poole, A. D.; Cole-Hamilton, D. J. *J. Chem. Soc., Dalton Trans.,* **1999**, 3771-3782.

(21) Simonato, J.-P. *J. Mol. Catal. A: Chem.* **2003**, *197*, 61-64.

(22) Hidai, M.; Koyasu, Y.; Chikanari, K.; Uchida, Y. *J. Mol. Catal.* **1987**, *40*, 243-254.

(23) Isnard, P.; Denise, B.; Sneeden, R. P. A. *J. Organomet. Chem.* **1982**, *240*, 169-177.

(24) Mirbach, M. F.; Mirbach, M. J. *J. Mol. Catal.* **1985**, *32*, 59-75.

(25) Ali, B. E.; Alper, H. *J. Mol. Catal. A: Chem.* **1995**, *96*, 197-201.

(26) Na, Y. Ko, S.; Hwang, L. K.; Chang, S. *Tetrahedron Lett.* **2003**, *44*, 4475-4478.

(27) Suzuki, Y.; Katoh, H.; Ishii, Y.; Hidai, M. *J. Mol. Catal. A: Chem.* **1995**, *95*, 129-133.

(28) Alper, H.; Hamel, N. *J. Am. Chem. Soc.* **1990**, *112*, 2803-2804.

(29) Zhou, H.; Hou, J.; Cheng, J.; Lu, s.; Fu, H.; Wang, H. *J. Organomet. Chem.* 1997, 543, 227-228.

(30) Suzuki, K.; Tomooka, K.; Katayama, E.; Matsumoto, T.; Tsuchihashi, G. *J. Am. Chem. Soc.* **1986**, *108*, 5221-5229.

(31) Cuzzupe, A. N.; Hutton, C. A.; Lilly, M. J.; Mann, R. K.; Mcrae, K. J.; McRae, K. J.; Zammit, S. C.; Rizzacasa, M. A. *J. Org. Chem.* **2001***, 66*, 2382-2393.

(32) Wipf, P.; Reeves, J. T. *J. Chem. Soc., Chem. Commun.* **2002**, 2066-2067.

(33) (a) Cossy, J.; Bauer, D.; Bellosta, V. *Synlett* **2002**, *5*, 715-718. (b) Cossy, J.; Bauer, D.; Bellosta, V. *Tetrahedron* **2002**, *58*, 5909-5922.

(34) Cossy, J.; Bargiggia, F.; BouzBouz, S. *Org. Lett.* **2003**, *5*, 459-462.

(35) Wuts, P. G. M.; Obrzut, M. L.; Thompson, P. A. *Tetrahedron Lett*. **1984**, *25*, 4051-4054.

(36) Chenal, T.; Cipres, I.; Jenck, J.; Kalck, P. *J. Mol. Catal.* **1993**, *78*, 351-366.

(37) El Ali, B.; Okuro, K.; Vasapollo, G.; Alper, H. *J. Am. Chem. Soc.* **1996**, *118*, 4264-4270.

(38) Wang, L.; Floreancig, P. E. *Org. Lett.* **2004**, *6*, 569.

(39) (a) Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1992**, *114*, 6671-6679. (b) Evans, D. A.; Fu, G. C.; Anderson, B. A. *J. Am. Chem. Soc.* **1992**, *114*, 6679-6685.

(40) Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Tetrahedron Lett.***1990**, *31*, 5289.

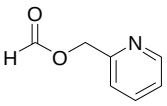
(41) Wang, L. Floreancig, P. E. *Org. Lett*. **2004**, *6*, 4207.

(42) Seiders, J. R., II; Floreancig, P. E. unpublished results.

(43) (a) Caloprisco, E.; Fourneron, J.-D.; Faure, R.; Demarne, F.-E. *J. Agric. Food Chem.* **2002**, *50*, 78-80. (b) Johnson, W. S.; Dumas, D. J.; Berner, D. *J. Am. Chem. Soc.* **1982**, *104*, 3510-3511. (c) Anjaneyulu, A. S. R.; Venugopal, M. J. R. V.; Sarada, P.; Clardy, J.; Lobkovsky, E. *Tetrahedron Lett.* **1998**, *39*, 139-142. (d) Yamaki, M.; Bai, L.; Kato, T.; Inoue, K.; Takagi, S.; Yamagata, Y.; Tomita, K. *Phytochem*. **1993**, *6*, 1497-1498.

2.5 Experimental

2-pyridylmethyl formate (2.5)[1]



To stirring acetic anhydride (6.5 mL, 69 mmol) at 0 °C was added formic acid (2.6 mL, 99%, 69 mmol) dropwise. The reaction mixture was stirred at room temperature for 2 h. The resulting formic acetic anhydride was cannulated to a stirring mixture of 2-pyridylmethanol (5 g, 46 mmol), $NaHCO_3$ (5.7 g, 69 mmol), and THF (23 mL). After stirring at rt for 1 h, saturated aq $NaHCO_3$ was added to the reaction mixture until gas evolution stopped. The resulting mixture was extracted with EtOAc (3x). The organic layers were combined and washed with H_2O, saturated aq $NaHCO_3$, and brine, then were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (40% EtOAc in hexanes) to give the desired product (6.1 g, ~100%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (d, *J* = 5.6 Hz, 1H), 8.20 (s, 1H), 7.76 (dt, *J* = 1.8, 7.7 Hz, 1H), 7.41 (d, *J* = 7.7 Hz, 1H), 7.30 (dd, *J* = 5.2, 7.7 Hz, 1H), 5.20 (s, 2H).

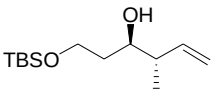
General information for olefin hydroesterification:

For small scale reactions, sample vials with screw cap can be used. In cases when the starting material is volatile, sealed pressure tubes are suitable. For large scale reactions, flasks equipped with condensers can be used. *CAUTION: While the authors never met any situation where the pressure was sufficiently high to cause an explosion, placing the reaction vessels behind blast shield is recommended.*

Representative hydroesterification procedure: To the substrate (1.0 mmol) in a pressure tube were added $Ru_3(CO)_{12}$ (32 mg, 0.05 mmol), NMO (17 mg, 0.15 mmol), and 2-pyridylmethyl formate **2.5** (408 mg, 3 mmol). The tube was flushed with argon, sealed, then placed behind a blast shield. The reaction mixture was heated to 135 °C with stirring over 20-30 min. After stirring at 135 °C for 2-18 h, the reaction mixture was cooled to 0 °C. The cap was removed with caution. The reaction mixture was purified by flash chromatography.

Representative hydrolysis procedure: Upon completion of the hydroesterification, the reaction mixture was dissolved in THF (2 mL), HOAc (6 mL), and H_2O (2 mL). The resulting mixture was heated at 85 °C for 12 h then concentrated under reduced pressure. The resulting residue was purified by flash chromatography.

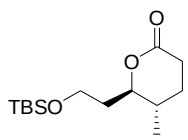
(3*R*, 4*S*)-1-*tert*-Butyldimethylsilyloxy-4-methylhex-5-en-3-ol (2.16)[2]



To a stirring mixture of potassium *tert*-butoxide (4.68 g, 41.7 mmol, dried under vacuum overnight at 80 °C) in THF (50 mL) at –78 °C was added *trans*-2-butene (7.5 mL, 83.3 mmol) *via* cannula. *n*-BuLi (1.56 M in hexanes, 26.7 mL, 42.7 mmol) was added dropwise over 40 min. The reaction mixture turned orange. The resulting mixture was stirred at –48 °C for 15 min then cooled to –78 °C again. A solution of (-)-*B*-methoxydiisopinocampheylborane (1 M in THF, 50 mL, 50 mmol) was added at a speed of ~1 mL/min. The reaction mixture was stirred for 0.5 h and $BF_3{\cdot}Et_2O$ (6.67 mL, 55.8 mmol) was added dropwise. After 5 min, a solution of aldehyde 3-(*tert*-butyldimethylsilyloxy)-propanal[3] (7.1 g, 37.6 mmol) in THF (20 mL) was added slowly. The resulting viscous mixture was stirred for 2 h at –78 °C. NaOH (3 N, 50 mL) and H_2O_2 (30%, 30 mL) were added to the reaction

mixture. Cold bath was removed and the reaction mixture was stirred at rt for 30 min. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic layers were washed with water and brine, then were dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by flash chromatography (2% acetone in hexanes) to give the desired product (6.14 g, 67%) as a colorless oil: $[\alpha]^{23}_D$ –6.7º (*c* = 1.80, $CHCl_3$); $[\alpha]^{23}_D$ –3.4º (*c* = 1.30, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.77 (m, 1H), 5.02-5.08 (m, 2H), 3.74-3.94 (m, 2H), 3.65-3.69 (m, 1H), 3.23 (s, 1H, OH), 2.17 (m, 1H), 1.60 (m, 2H), 1.02 (d, *J* = 5.2 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.9, 115.3, 75.2, 62.9, 44.2, 35.8, 26.1, 18.4, 15.9, -5.3; IR (neat) 3452, 2956, 2929, 2858, 1471, 1463, 1255, 1087, 836, 776 cm^{-1}; HRMS (EI) calcd for $C_9H_{21}O_2Si$ $[M - CH_3CHCH_2{=}CH_2]^+$ 189.1311, found 189.1316.

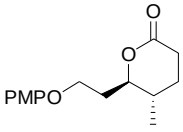
(5*S*,6*R*)-6-[2-(*tert*-Butyldimethylsilyloxy)ethyl]-5-methyltetrahydropyran-2-one (2.17)



To a mixture of olefin **2.16** (0.5 g, 2.05 mmol) and 2-pyridylmethyl formate **2.5** (1.39 g, 12.23 mmol) in a sample vial was added $Ru_3(CO)_{12}$ (65 mg, 0.102 mmol). Nitrogen gas was flushed into the vial to remove air and then the sample vial was capped. The reaction mixture was heated to 135 °C with stirring over 30 min. The reaction mixture was stirred at 135 °C for 4 h then at 125 °C for 12 h. The reaction mixture was cooled to 0 °C. The cap of the sample vial was removed. The reaction mixture was purified by flash chromatography (20-35% EtOAc in hexanes) to afford the desired product (222 mg, 40%): $[\alpha]^{23}_D$ +48.0º (*c* = 2.04, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.07 (dt, *J* = 2.3, 9.5 Hz, 1H), 3.75-3.87 (m, 2H), 2.57-2.67 (m, 1H), 2.41-2.53 (m, 1H), 1.87-2.05 (m, 2H), 1.70-1.77 (m, 2H), 1.49-1.62 (1H), 1.01 (d, *J* = 6.5 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6,

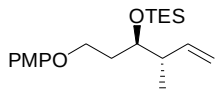
82.6, 58.6, 36.7, 32.5, 29.5, 27.8, 25.92, 18.2, 17.5, -5.4; IR (neat) 2956, 2929, 2856, 1738, 1252, 1208, 1090, 836, 776 cm^{-1}; HRMS (EI) calcd for $C_{10}H_{19}O_3Si$ $[M - C(CH_3)_3]^+$ 215.1108, found 215.1109.

(5*S*,6*R*)-6-[2-(4-Methoxyphenoxy)ethyl]-5-methyltetrahydropyran-2-one (2.23)



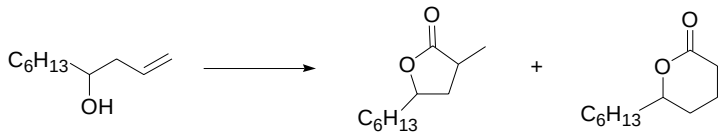
Hydroesterification was conducted using **3.22** (120 mg, 0.51 mmol), $Ru_3(CO)_{12}$ (13 mg, 0.02 mmol) and 2-pyridylmethyl formate **2.5** (207 mg, 1.52 mmol) at 135 °C for 3 h. Hydrolysis was followed. Purification by flash chromatography (35-40% EtOAc in hexanes) gave the desired product (72 mg, 53%): $[\alpha]^{23}_D$ +63.6º (*c* = 1.23, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 6.80 (s, 4H), 4.00-4.20 (m, 3H), 3.72 (s, 3H), 2.54 (ddd, *J* = 4.7, 6.9, 17.8 Hz, 1H), 2.39 (ddd, *J* = 6.9, 9.6, 16.7 Hz, 1H), 2.13-2.26 (m, 1H), 1.84-1.97 (m, 1H), 1.67-1.79 (m, 1H), 1.49-1.58 (m, 1H), 1.01 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 153.8, 152.8, 115.4, 114.6, 82.6, 63.9, 55.6, 33.4, 32.6, 29.5, 27.8, 17.2; IR (neat) 1732, 1508, 1232, 1037 cm^{-1}; HRMS-EI (m/z) calcd for $C_{15}H_{20}O_4$ $[M^+]$ 264.1362, found 264.1362.

Triethyl{(1*R*,2*S*)-1-[2-(4-methoxyphenoxy)ethyl]-2-methylbut-3-enyloxy}silane (2.24)



To a stirring solution of alcohol **2.22** (162 mg, 0.68 mmol) and imidazole (102 mg, 1.5 mmol) in CH_2Cl_2 (7 mL) at room temperature was added chlorotriethylsilane (0.21 mL, 1.23 mmol) dropwise. The resulting mixture was stirred for 1 h and saturated NH_4Cl solution (2 mL) was added. The organic layer was separated and the aqueous layer was extracted with ether (2x). The organic layers were combined and washed with brine, then were dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by flash chromatography (1-3% EtOAc in hexanes) to afford the desired product (224 mg, 94%):

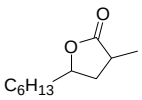
$[\alpha]^{23}_{D}$ +12.8º (*c* = 0.98, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (s, 4H), 5.83-5.92 (m, 1H), 5.06-5.13 (m, 2H), 3.96-4.03 (m, 3H), 3.79 (s, 3H), 2.36-2.47 (m, 1H), 1.79-1.97 (m, 2H), 1.09 (d, *J* = 7.0 Hz, 3H), 0.98 (t, *J* = 7.8 Hz, 9H), 0.60 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.8, 153.3, 140.7, 115.3, 114.9, 114.7, 72.4, 65.4, 55.7, 43.8, 33.0, 14.6, 7.1, 5.3; IR (neat) 2950, 2873, 1508, 1231, 1045 cm^{-1}; HRMS-EI (m/z) calcd for $C_{20}H_{34}O_3Si$ [M^+] 350.2277, found 350.2274.



2.28 **2.29** **2.30**

Hydroesterification was conducted using **2.28** (100 mg, 0.64 mmol), $Ru_3(CO)_{12}$ (20 mg, 0.03 mmol), NMO (3.8 mg, 0.03 mmol), and 2-pyridylmethyl formate (261 mg, 1.9 mmol) at 135 °C for 2 h. Hydrolysis was followed. The reaction mixture was analyzed by GC using *n*-$C_8H_{17}I$ as the internal standard to get the yields (**2.29:** 48%; **2.30:** 25%). The reaction mixture was concentrated and the resulting residue was also purified by flash chromatography (20-25% EtOAc in hexanes) to give the desired products.

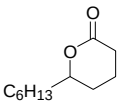
5-Hexyl-3-methyldihydrofuran-2-one (2.29)



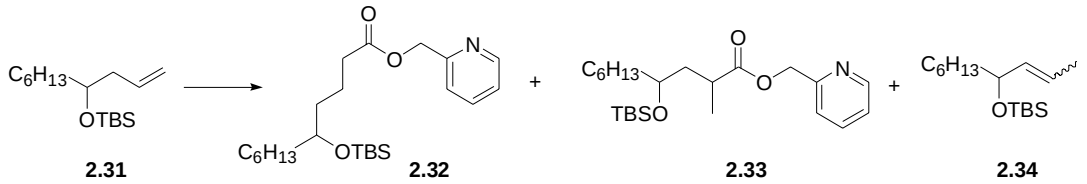
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.41-4.47 (app tt, *J* = 5.2, 7.4 Hz, 50% of 1H), 4.24 (ddt, *J* = 5.2, 7.3, 10.3 Hz, 50% of 1H), 2.56-2.63 (m, 1H), 2.40 (ddd, *J* = 5.4, 8.5, 13.4 Hz, 50% of 1H), 2.05 (ddd, *J* = 4.9, 8.9, 12.8 Hz, 50% of 1H), 1.96 (td, *J* = 7.5, 12.8 Hz, 50% of 1H), 1.18-1.50 (m, 13.5H), 0.80 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.1, 179.6, 78.7, 78.5, 37.4, 35.9, 35.6, 35.5, 34.1, 31.7, 29.05, 29.02, 25.4, 25.3,

22.5, 15.9, 15.1, 14.1; IR (neat) 1772, 1460, 1188 cm^{-1}; HRMS-EI (m/z) calcd for $C_{11}H_{21}O_2$ [M + H]$^+$ 185.1541, found 185.1548.

6-Hexyltetrahydropyran-2-one (2.30)[4]

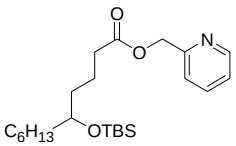


^{1}H NMR (300 MHz, $CDCl_3$) δ 4.19-4.27 (m, 1H), 2.49-2.57 (m, 1H), 2.36-2.45 (m, 1H), 1.43-1.99 (m, 4H), 1.15-1.35 (m, 10H), 0.81 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 80.7, 35.9, 31.7, 29.5, 29.1, 27.8, 24.9, 22.6, 18.5, 14.1; IR (neat) 1736, 1506, 1224 cm^{-1}.



Hydroesterification was conducted using **2.31** (172 mg, 0.64 mmol), $Ru_3(CO)_{12}$ (20 mg, 0.03 mmol), NMO (11 mg, 0.1 mmol), and 2-pyridylmethyl formate (261 mg, 1.9 mmol) at 135 °C for 2.5 h. The reaction was continued for another 2 h after additional $Ru_3(CO)_{12}$ (20 mg, 0.03 mmol), NMO (11 mg, 0.1 mmol), and 2-pyridylmethyl formate (261 mg, 1.9 mmol) were added. Purification by flash chromatography (4→20→25% EtOAc in hexanes) afforded **2.32** (73 mg, 28%), **2.33** (23 mg, 9%), and **2.34** (57 mg, 33%).

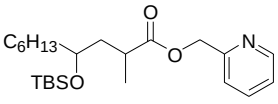
5-(*tert*-Butyldimethylsiloxy)undecanoic acid pyridin-2-ylmethyl ester (2.32)



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (d, *J* = 4.1 Hz, 1H), 7.67 (t, *J* = 7.7 Hz, 1H), 7.22 (d, *J* = 7.7 Hz, 1H), 7.20 (dd, *J* = 5.8, 6.6 Hz, 1H), 5.23 (s, 2H), 3.61 (app p, *J* = 5.6 Hz, 1H), 2.37 (t, *J* = 7.4 Hz, 2H), 1.66-1.82 (m, 2H), 1.41-1.52

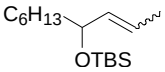
(m, 4H), 1.26 (br, 8H), 0.88 (br, 12 H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 156.2, 149.6, 136.9, 123.0, 121.9, 72.1, 66.8, 37.3, 36.6, 34.6, 32.0, 29.7, 26.1, 25.4, 22.8, 21.0, 18.3, 14.3, -4.2; IR (neat) 2927, 2852, 1741, 1255, 1152 cm^{-1}; HRMS-EI (m/z) calcd for $C_{19}H_{32}NO_3Si$ $[M - t\text{-Bu}]^+$ 350.2151, found 350.2138.

4-(*tert*-Butyldimethylsiloxy)-2-methyldecanoic acid pyridin-2-ylmethyl ester (2.33)

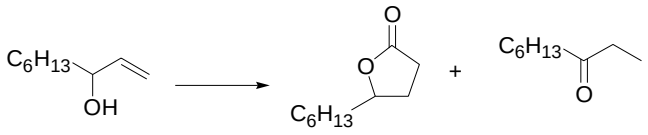


^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, *J* = 3.6 Hz, 1H), 7.65 (t, *J* = 7.7 Hz, 1H), 7.34 (d, *J* = 7.7 Hz, 1H), 7.16 (dd, *J* = 5.7, 6.5 Hz, 1H), 5.24 (s, 2H), 3.65-3.73 (m, 1H), 2.70-2.77 (m, 1H), 1.90-1.96 (m, 1H), 1.73 (br, 1H), 1.42-1.55 (m, 4H), 1.22-1.30 (m, 9H), 0.88 (br, 12H), 0.04 (br, 6H); IR (neat) 1741, 1465 cm^{-1}.

***tert*-Butyldimethyl-(1-propenylheptyloxy)silane (2.34)**



^{1}H NMR (300 MHz, $CDCl_3$) δ 5.32-5.56 (m, 2H), 4.36 (dd, *J* = 7.5, 12.6 Hz, 20% of 1H), 3.98 (dd, *J* = 6.0, 12.4 Hz, 80% of 1H), 1.66 (d, *J* = 5.2 Hz, 80% of 3H), 1.62 (d, *J* = 5.4 Hz, 20% of 3H), 1.27-1.57 (m, 10 H), 0.86-0.90 (m, 12H), 0.02-0.05 (4 singlets, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.3, 124.9, 122.9, 73.9, 68.6, 38.7, 32.1, 29.5, 26.2, 26.1, 25.6, 22.8, 18.5, 17.8, 14.3, 13.5, -4.0, -4.5; IR (neat) 1460, 1250, 1081, 835 cm^{-1}; HRMS-EI (m/z) calcd for $C_{13}H_{29}OSi$ $[M - C_3H_5]^+$ 229.1987, found 229.1989.

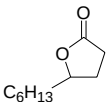


2.37 **2.38** **2.39**

Hydroesterification was conducted using **2.37** (142 mg, 1.0 mmol), $Ru_3(CO)_{12}$ (32 mg, 0.05 mmol), NMO (17 mg, 0.15 mmol), and 2-pyridylmethyl formate (408 mg, 3 mmol) at 135 °C for

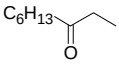
2 h. Purification by flash chromatography (10→30→60% ether in pentane) afforded **2.28** (68 mg, 40%) and **2.29** (40 mg, 28%).

5-Hexyldihydrofuran-2-one (2.28)[5]

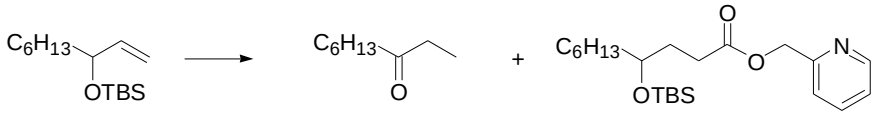


^{1}H NMR (300 MHz, $CDCl_3$) δ 4.43 (p, *J* = 7.0 Hz, 1H), 2.49 (dd, *J* = 7.1, 9.3 Hz, 2H), 2.26 (hextet, *J* = 6.6 Hz, 1H), 1.50-1.88 (m, 3H), 1.20-1.40 (m, 8H), 0.85 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.6, 81.3, 35.7, 31.8, 29.2, 29.0, 28.2, 25.3, 22.7, 14.2.

Nonan-3-one (2.29)[6]



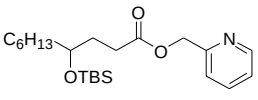
^{1}H NMR (300 MHz, $CDCl_3$) δ 2.37 (q, *J* = 7.3 Hz, 2H), 2.34 (t, *J* = 7.4 Hz, 2H), 1.52-1.64 (m, 2H), 1.22-1.37 (m, 6H), 1.03 (t, *J* = 7.5 Hz, 3H), 0.84 (t, *J* = 6.8 Hz, 3H).



2.40 **2.39** **2.41**

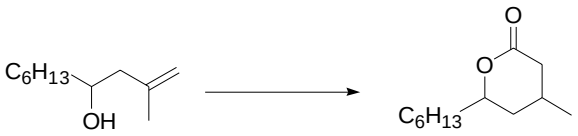
Hydroesterification was conducted using **2.40** (150 mg, 0.58 mmol), $Ru_3(CO)_{12}$ (18.7 mg, 0.03 mmol), NMO (10 mg, 0.089 mmol), xylenes (0.15 mL), and 2-pyridylmethyl formate (238 mg, 1.7 mmol) at 135 °C for 12 h. Purification by flash chromatography (0.5→10→30% EtOAc in hexanes) afforded **2.39** (4 mg, 5%) and **2.41** (181 mg, 78%).

4-(*tert*-Butyldimethylsiloxy)decanoic acid pyridin-2-ylmethyl ester (2.41)



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (d, *J* = 4.7 Hz, 1H), 7.62 (dt, *J* = 1.6, 7.7 Hz, 1H), 7.29 (d, *J* = 7.7 Hz, 1H), 7.15 (dd, *J* = 4.9, 6.9 Hz, 1H), 5.29 (s, 2H), 3.58 (app q, *J* = 5.5 Hz, 1H), 2.42 (t, *J* = 7.4 Hz, 2H), 1.61-1.88 (m, 2H), 1.22-1.39 (m,

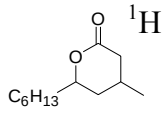
10H), 0.84 (br, 12H), 0.00 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 156.2, 149.5, 136.7, 122.8, 121.8, 71.2, 66.8, 37.1, 31.9, 31.8, 30.0, 29.5, 26.0, 25.2, 22.7, 18.2, 14.2, -4.3, -4.5; IR (neat) 1742, 1255, 1160 cm^{-1}; HRMS-EI (m/z) calcd for $C_{22}H_{38}NO_3Si$ $[M - H]^+$ 392.2621, found 392.2632.



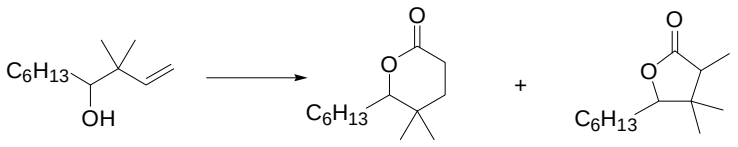
2.42 **2.43**

Hydroesterification was conducted using **2.42** (170 mg, 1.0 mmol), $Ru_3(CO)_{12}$ (32 mg, 0.05 mmol), NMO (17 mg, 0.15 mmol), and 2-pyridylmethyl formate (408 mg, 3 mmol) at 135 °C for 12 h. The reaction was continued for another 6 h after additional $Ru_3(CO)_{12}$ (32 mg, 0.05 mmol), NMO (17 mg, 0.15 mmol), and 2-pyridylmethyl formate (200 mg, 1.5 mmol) were added. Hydrolysis was followed. Purification by flash chromatography (10-15-20% EtOAc in hexanes) gave unreacted **2.42** (19 mg, 11%) and **2.43** (127 mg, 72% at 89% conversion).

6- Hexyl-4-methyltetrahydropyran-2-one (2.43)



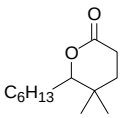
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.29-4.38 (m, 50% of 1H), 4.19-4.27 (m, 50% of 1H), 2.48-2.68 (m, 1H), 1.85-2.18 (m, 3H), 1.40-1.80 (m, 4H), 1.20-1.37 (m, 7H), 1.04 (d, J = 6.0 Hz, 50% of 3H), 0.98 (d, J = 5.5 Hz, 50 % of 3H), 0.82 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 171.7, 30.7, 77.4, 38.1, 37.5, 37.0, 36.1, 35.6, 35.1, 31.7, 29.1, 26.8, 25.2, 24.8, 23.9, 22.6, 21.7, 21.5, 14.1; IR (neat) 1731, 1239 cm^{-1}; HRMS-EI (m/z) calcd for $C_{12}H_{23}O_2$ $[M + H]^+$ 199.1698, found 199.1696.



2.44 **2.45** **2.46**

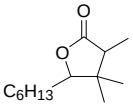
Hydroesterification was conducted using **2.44** (184 mg, 1.0 mmol), $Ru_3(CO)_{12}$ (32 mg, 0.05 mmol), NMO (17 mg, 0.15 mmol), and 2-pyridylmethyl formate (408 mg, 3 mmol) at 135 °C for 18 h. Hydrolysis was followed. The reaction mixture was analyzed by GC using $^{n}C_8H_{17}I$ as internal standard to get the yields (**2.45:** 65%; **2.46:** 35%). The reaction mixture was also concentrated and the resulting residue was purified by flash chromatography (10-25% EtOAc in hexanes) to give the products.

6-Hexyl-5,5-dimethyltetrahydropyran-2-one (2.45)



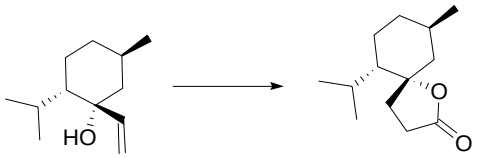
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.88 (dd, *J* = 3.6, 9.2 Hz, 1H), 2.46-2.53 (m, 2H), 1.43-1.73 (m, 6H), 1.20-1.35 (m, 6H), 0.96 (s, 3H), 0.90 (s, 3H), 0.82 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 87.9, 34.5, 32.0, 31.8, 30.1, 29.2, 27.5, 26.6, 26.2, 22.6, 19.6, 14.1; IR (neat) 1735, 1467, 1215, 1041 cm^{-1}; HRMS-CI (m/z) calcd for $C_{13}H_{25}O_2$ [M + H]$^+$ 213.1854, found 213.1855.

5-Hexyl-3,4,4-trimethyldihydrofuran-2-one (2.46)



^{1}H NMR (300 MHz, $CDCl_3$) δ 4.03 (dd, *J* = 5.9, 7.3 Hz, 50% of 1H), 3.87 (dd, *J* = 4.2, 8.6 Hz, 50% of 1H), 2.31 (q, *J* = 7.1 Hz, 50% of 1H), 2.30 (q, *J* = 7.4 Hz, 50% of 1H), 1.26-1.52 (m, 10H), 1.09 (t, *J* = 7.4 Hz, 50% of 3H), 1.05 (t, *J* = 7.1 Hz, 50% of 3H), 1.06 (s, 50% of 3H), 1.02 (s, 50% of 3H), 0.98 (s, 50% of 3H), 0.85 (2 triplets, both *J* = 6.0 Hz, 3H), 0.77 (s, 50% of 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.6, 179.0, 88.1, 87.9, 47.5, 44.9, 42.7, 41.1, 31.8,

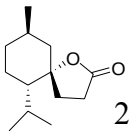
30.0, 29.3, 28.7, 27.0, 26.6, 23.5, 22.7, 22.4, 15.7, 14.2, 9.5, 8.1; IR (neat) 1774, 1465 cm^{-1}; HRMS-EI (m/z) calcd for $C_{13}H_{25}O_2$ $[M + H]^+$ 213.1854, found 213.1855.



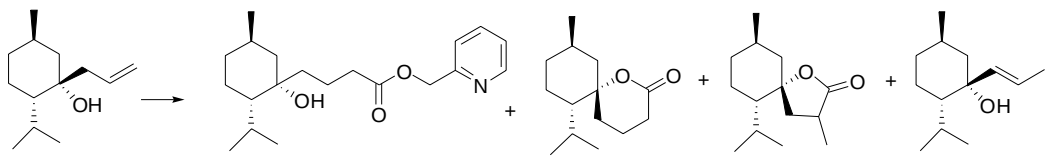
2.47 **2.48**

Hydroesterification was conducted using **2.47** (182 mg, 1.0 mmol), $Ru_3(CO)_{12}$ (32 mg, 0.05 mmol), NMO (17 mg, 0.15 mmol), and 2-pyridylmethyl formate (408 mg, 3 mmol) at 135 °C for 18 h. Purification by flash chromatography (10-20% EtOAc in hexanes) provided **2.48** (161 mg, 76%).

(5*S*,6*S*,9*R*)-6-Isopropyl-9-methyl-1-oxaspiro[4.5]decan-2-one (2.48)[7]



$[\alpha]^{23}_D$ -7.8° (*c* = 1.84, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 2.45-2.65 (m, 2H), 2.26 (ddd, *J* = 8.2, 9.9, 13.2 Hz, 1H), 1.90-2.01 (m, 1H), 1.73-1.85 (m, 4H), 1.48-1.60 (m, 2H), 1.07-1.26 (m, 2H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.84 (d, *J* = 6.0 Hz, 3H), 0.80 (d, *J* = 7.1 Hz, 3H), 0.80-1.00 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3, 89.6, 49.9, 49.5, 34.7, 31.4, 29.2, 28.7, 26.5, 24.0, 22.1, 21.8, 18.0; IR (neat) 1773, 1216, 1139 cm^{-1}; HRMS-EI (m/z) calcd for $C_{13}H_{22}O_2$ $[M^+]$ 210.1619, found 210.1613.

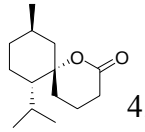


2.49 **2.53** **2.50** **2.51** **2.52**

Hydroesterification was conducted using **2.49** (196 mg, 1.0 mmol), $Ru_3(CO)_{12}$ (32 mg, 0.05 mmol), NMO (17 mg, 0.15 mmol), and 2-pyridylmethyl formate (408 mg, 3 mmol) at 135 °C for

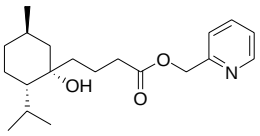
12 h. Purification by flash chromatography (5→10→15→20→40% EtOAc in hexanes) gave **2.53** (123 mg, 37%), **2.50** (46 mg, 21%), **2.51** (42 mg, 19%), and **2.52** (39 mg, 20%).

(6*S*,7*S*,10*R*)-7-Isopropyl-10-methyl-1-oxaspiro[5.5]undecan-2-one (2.50)



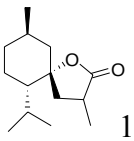
$[\alpha]^{23}_{D}$ +14.6º (*c* = 1.04, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.48 (ddd, *J* = 4.4, 4.9, 18.1 Hz, 1H), 2.38 (ddd, *J* = 7.7, 9.9, 18.1 Hz, 1H), 2.07 (dt, *J* = 4.9, 12.6 Hz, 2H), 1.93-2.02 (m, 2H), 1.76-1.85 (m, 3H), 1.63 (dt, *J* = 2.7, 13.2 Hz, 1H), 1.41-1.54 (m, 2H), 1.12-1.17 (m, 2H), 0.90-1.02 (m, 1H), 0.91 (d, *J* = 7.1 Hz, 3H), 0.83 (d, *J* = 7.1 Hz, 3H), 0.81 (d, *J* = 8.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 85.7, 50.4, 47.5, 34.9, 30.6, 30.0, 27.4, 26.1, 23.9, 22.4, 20.4, 17.7, 16.7; IR (neat) 1731, 1249 cm^{-1}; $C_{14}H_{24}O_2$ [M^+] 224.1776, found 224.2768.

4-[(1*S*,2*S*,5*R*)-1-Hydroxy-2-isopropyl-5-methylcyclohexyl]-butyric acid pyridin-2-ylmethyl ester (2.53)



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (d, *J* = 3.8 Hz, 1H), 7.79 (t, *J* = 7.4 Hz, 1H), 7.42 (d, *J* = 7.7 Hz, 1H), 7.32 (d, *J* = 6.9 Hz, 1H), 5.32 (s, 2H), 2.51 (t, *J* = 6.9 Hz, 2H), 2.10-2.19 (m, 1H), 1.46-1.86 (m, 10H), 1.10-1.24 (m, 2H), 0.96 (d, *J* = 7.1 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.3 Hz, 3H).

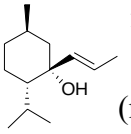
6-Isopropyl-3,9-dimethyl-1-oxaspiro[4.5]decan-2-one (2.51)



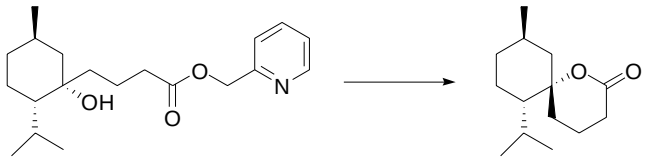
^{1}H NMR (300 MHz, $CDCl_3$) δ 2.7-2.83 (m, 1H), 2.47 (t, *J* = 12.0 Hz, 50% of 1H), 1.65-2.13 (m, 6.5 H), 1.49-1.65 (m, 3H), 1.26 (d, *J* = 7.1 Hz, 50% of 3H), 1.25 (d, *J* = 6.0 Hz, 50% of 3H), 1.00-1.20 (m, 2H), 0.93 (d, *J* = 7.1 Hz, 3H), 0.84 (d, *J* = 8.2 Hz, 3H), 0.79

(d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.2, 179.7, 87.3, 86.8, 51.3, 51.0, 48.1, 41.6, 38.6, 36.0, 34.8, 34.5, 29.1, 28.4, 26.9, 26.2, 24.0, 23.9, 22.2, 22.1, 21.4, 18.0, 17.7, 15.8; IR (neat) 1768, 1212 cm^{-1}; HRMS-EI (m/z) calcd for $C_{14}H_{24}O_2$ [M^+] 224.1776, found 224.2785.

(1*S*,2*S*,5*R*)-2-Isopropyl-5-methyl-1-propenylcyclohexanol (2.52)

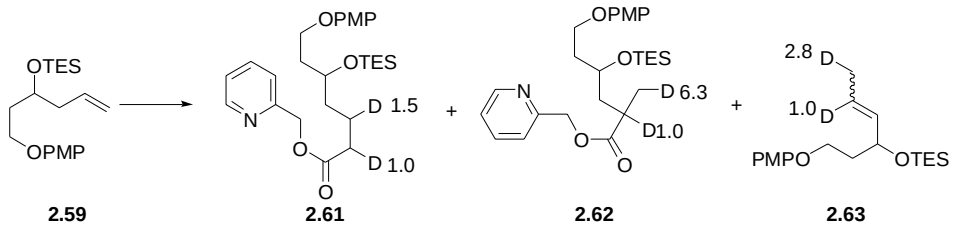


^{1}H NMR (300 MHz, $CDCl_3$) δ 5.61-5.70 (m, 1H), 5.43 (d, J = 15.4 Hz, 1H), 1.95-2.00 (m, 1H), 1.65-1.80 (m, 5H), 1.40-1.52 (m, 4H), 1.04-1.28 (m, 2H), 0.86 (d, J = 6.6 Hz, 3H), 0.85 (d, J = 6.0 Hz, 3H), 0.84 (d, J = 6.6 Hz, 3H).



2.53 **2.50**

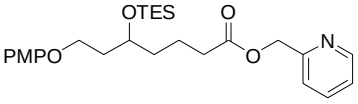
To ester **2.53** (40 mg, 0.12 mmol) in THF (2 mL) at 0 ^{o}C was added NaH (10 mg, 60% in mineral oil, 0.24 mmol). The ice bath was removed and the reaction mixture was stirred at rt for 20 min. Saturated aq NH_4Cl (1 mL) was added. The resulting mixture was extracted with ether (2x). The organic layers were combined and washed with brine, then were dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by flash chromatography (15% EtOAc in hexanes) to afford **2.50** (26 mg, ~100%).



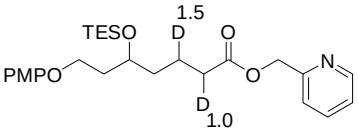
2.59 **2.61** **2.62** **2.63**

Hydroesterification was conducted using **2.59** (150 mg, 0.45 mmol), $Ru_3(CO)_{12}$ (14 mg, 0.022 mmol), NMO (7.8 mg, 0.07 mmol), and 2-pyridylmethyl formate-*d* (183 mg, 1.34 mmol) at 135 ^oC for 3 h. Purification by flash chromatography (4→25→30% EtOAc in hexanes) gave the linear product **2.61** (61 mg, 29%), the branched product **2.62** (17 mg, 8%), and **2.63** (22 mg, 15%).

7-(4-Methoxyphenoxy)-5-triethylsiloxyheptanoic acid pyridin-2-ylmethyl ester (2.61)

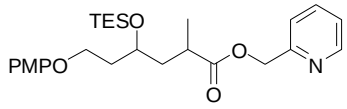


^1H NMR (300 MHz, $CDCl_3$) δ 8.58 (d, *J* = 4.1 Hz, 1H), 7.61 (dt, *J* = 1.6, 7.7 Hz, 1H), 7.32 (d, *J* = 7.9 Hz, 1H), 7.19 (dd, *J* = 4.9, 6.9 Hz, 1H), 6.82 (s, 4H), 5.24 (s, 2H), 3.94-4.01 (m, 3H), 3.76 (s, 3H), 2.42 (t, *J* = 7.4 Hz, 2H), 1.86-1.94 (m, 2H), 1.72-1.78 (m, 2H), 1.53-1.60 (m, 2H), 0.90 (t, *J* = 7.9 Hz, 9H), 0.57 (q, *J* = 7.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 156.1, 153.8, 153.3, 149.6, 136.9, 123.0, 121.9, 115.4, 114.8, 69.0, 66.9, 65.1, 55.9, 37.2, 36.7, 34.5, 20.9, 7.1, 5.2; HRMS-ESI (m/z) calcd for $C_{26}H_{39}NO_5SiNa$ $[M + Na]^+$ 496.2495, found 496.2490.



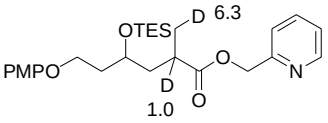
^2H NMR (300 MHz, $CHCl_3$) δ 2.52 (area: 1.0), 1.83 (area: 1.5).

6-(4-Methoxyphenoxy)-2-methyl-4-triethylsiloxyhexanoic acid pyridin-2-ylmethyl ester (2.62)



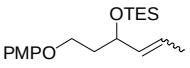
^1H NMR (300 MHz, $CDCl_3$) δ 8.58 (d, *J* = 4.4 Hz, 1H), 7.68 (t, *J* = 7.7 Hz, 1H), 7.36 (dd, *J* = 3.3, 7.7 Hz, 1H), 7.23 (dd, *J* = 5.5, 7.1 Hz, 1H), 6.82 (s, 4H), 5.23 (s, 2H), 3.97-4.04 (m, 3H), 3.77 (s, 3H), 2.66-2.75 (m, 1H), 1.89-2.11 (m, 3H), 1.54-1.65 (m, 1H),

1.24 (d, *J* = 8.2 Hz, 3H), 0.90 (2 triplets, *J* = 7.7 Hz, 9H), 0.53 (2 quartets, *J* = 7.9 Hz, 6H); HRMS-ESI (m/z) calcd for $C_{26}H_{39}NO_5SiNa$ $[M + Na]^+$ 496.2495, found 496.2502.

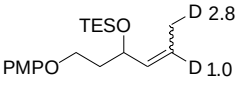


^{2}H NMR (300 MHz, $CHCl_3$) δ 2.66 (area: 1.0), 1.20 (area: 6.3).

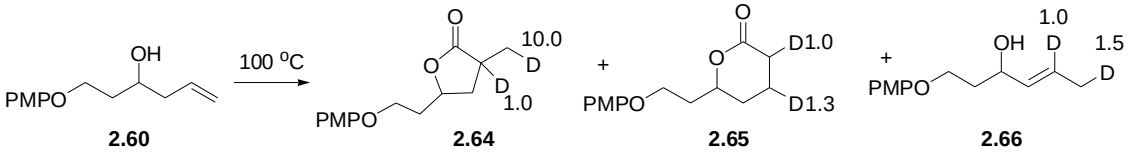
Triethyl-{1-[2-(4-methoxyphenoxy)ethyl]but-2-enyloxy}silane (2.63)



^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82 (s, 4H), 5.44-5.67 (m, 2H), 4.74 (app q, *J* = 7.0 Hz, 25% of 1H), 4.30 (app q, *J* = 6.4 Hz, 75% of 1H), 3.89-4.03 (m, 2H), 3.78 (s, 3H), 1.88-1.95 (m, 2H), 1.68 (d, *J* = 6.0 Hz, 75% of 3H), 1.63 (d, *J* = 5.2 Hz, 25% of 3H), 0.92 (q, *J* = 7.7 Hz, 9H), 0.58 (t, *J* = 7.9 Hz, 6H).



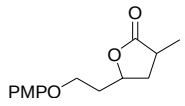
^{2}H NMR (300 MHz, $CHCl_3$) δ 5.59 (area: 1.0), 1.62 (area: 2.8).



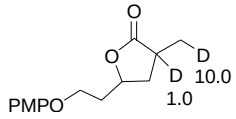
2.60 **2.64** **2.65** **2.66**

Hydroesterification was conducted using **2.60** (115 mg, 0.52 mmol), $Ru_3(CO)_{12}$ (16 mg, 0.026 mmol), NMO (9 mg, 0.077 mmol), and 2-pyridylmethyl formate-*d* (212 mg, 1.55 mmol) at 100 °C for 3 h. Purification by flash chromatography (15→25→35→50% EtOAc in hexanes) provided **2.64** (22 mg, 17%), **2.65** (20 mg, 16%), and **2.66** (18 mg, 15%).

5-[2-(4-Methoxyphenoxy)ethyl]-3-methyldihydrofuran-2-one (2.64)

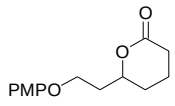


^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (s, 4H), 4.76 (tt, *J* = 5.5, 7.1 Hz, 50% of 1H), 4.58 (tt, *J* = 6.3, 12.1 Hz, 50% of 1H), 4.00-4.14 (m, 2H), 3.78 (s, 3H), 2.66-2.77 (m, 50% of 1H), 2.54-2.63 (m, 50% of 1H), 2.20 (ddd, *J* = 5.2, 8.8, 12.9 Hz, 1H), 2.01-2.14 (m, 3H), 1.28 (d, *J* = 6.8 Hz, 50% of 3H), 1.30 (d, *J* = 7.4 Hz, 50% of 3H); HRMS-EI (m/z) calcd for $C_{14}H_{18}O_4$ [M^+] 250.1205, found 250.1202.

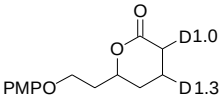


^{2}H NMR (300 MHz, $CHCl_3$) δ 2.66 (area: 1), 1.28 (area: 10).

6-[2-(4-Methoxyphenoxy)ethyl]tetrahydropyran-2-one (2.65)

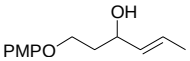


^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (s, 4H), 4.55 (dddd, *J* = 2.7, 5.5, 7.7, 10.4 Hz, 1H), 4.01-4.19 (m, 2H), 3.78 (s, 3H), 2.57 (td, *J* = 6.3, 17.6 Hz, 1H), 2.42 (ddd, *J* = 7.1, 8.2, 17.6 Hz, 1H), 1.86-2.16 (m, 5H), 1.56-1.69 (m, 1H); HRMS-EI (m/z) calcd for $C_{14}H_{18}O_4$ [M^+] 250.1205, found 250.1208.

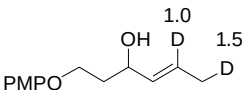


^{2}H NMR (300 MHz, $CHCl_3$) δ 2.40-2.50 (area: 1.0), 1.89 (area: 1.3).

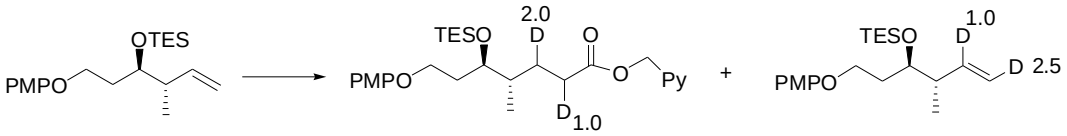
1-(4-Methoxyphenoxy)hex-4-en-3-ol (2.66)



^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (s, 4H), 5.70 (qd, *J* = 6.3, 15.4 Hz, 1H), 5.58 (ddd, *J* = 1.6, 6.9, 15.4 Hz, 1H), 4.37 (dd, *J* = 6.6, 12.9 Hz, 1H), 4.08 (td, *J* = 6.0, 9.6 Hz, 1H), 4.04 (td, *J* = 6.0, 9.6 Hz, 1H), 3.78 (s, 3H), 1.97 (app q, *J* = 6.0 Hz, 2H), 1.71 (d, *J* = 5.8 Hz, 3H).



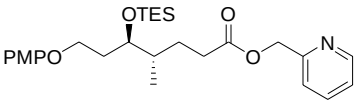
^{2}H NMR (300 MHz, $CHCl_3$) 5.70 (area: 1.0), 1.70 (area: 1.5).



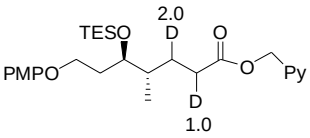
2.24 **2.67** **2.68**

Hydroesterification was conducted using **2.24** (124 mg, 0.35 mmol), $Ru_3(CO)_{12}$ (11 mg, 0.018 mmol), NMO (6 mg, 0.05 mmol), and 2-pyridylmethyl formate-*d* (145 mg, 1.1 mmol) at 135 ^oC for 2 h. Purification by flash chromatography (10→25% EtOAc in hexanes) provided **2.67** (67 mg, 37%) and **2.68** (44 mg, 35%).

7-(4-Methoxyphenoxy)-4-methyl-5-triethylsiloxyheptanoic acid pyridin-2-ylmethyl ester (2.67)

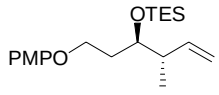


^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (d, *J* = 4.9 Hz, 1H), 7.69 (t, *J* = 7.9 Hz, 1H), 7.33 (d, *J* = 7.9 Hz, 1H), 7.22 (dd, *J* = 4.9, 6.6 Hz, 1H), 6.82 (s, 4H), 5.24 (s, 2H), 3.95 (t, *J* = 6.0 Hz, 2H), 3.88 (app p, *J* = 4.0 Hz, 1H), 3.76 (s, 3H), 2.36-2.58 (m, 2H), 1.74-1.88 (m, 3H), 1.59-1.70 (m, 1H), 1.42-1.55 (m, 1H), 0.89-0.95 (m, 12H), 0.55 (q, *J* = 7.9 Hz, 6H).

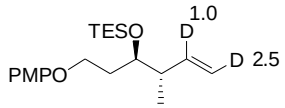


^{2}H NMR (300 MHz, $CHCl_3$) δ 2.44 (area:1.0), 1.73 (area: 1.0), 1.42 (area: 1.0).

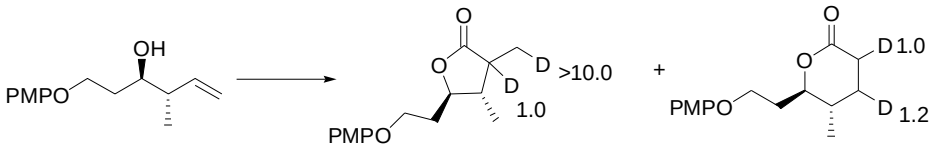
Triethyl-{1-[2-(4-methoxyphenoxy)ethyl]-2-methylbut-3-enyloxy}silane (2.68)



^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (s, 4H), 5.83-5.92 (m, 1H), 5.06-5.13 (m, 2H), 3.96-4.03 (m, 3H), 3.79 (s, 3H), 2.36-2.47 (m, 1H), 1.79-1.97 (m, 2H), 1.09 (d, *J* = 7.0 Hz, 3H), 0.98 (t, *J* = 7.8 Hz, 9H), 0.60 (q, *J* = 7.8 Hz, 6H).

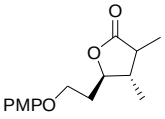


^{2}H NMR (300 MHz, $CHCl_3$) δ 5.79 (area: 1.0), 5.03 (area: 2.5).



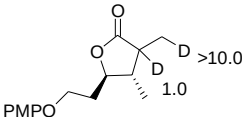
2.22 **2.69** **2.70**

Hydroesterification was conducted using **2.22** (100 mg, 0.42 mmol), $Ru_3(CO)_{12}$ (13 mg, 0.021 mmol), NMO (7 mg, 0.06 mmol), and 2-pyridylmethyl formate-*d* (174 mg, 1.3 mmol) at 135 ^oC for 2 h. Purification by flash chromatography (20→30→40% EtOAc in hexanes) provided the **2.69** (44 mg, 40%) and **2.70** (18 mg, 16%).



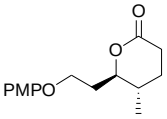
5-[2-(4-Methoxyphenoxy)ethyl]-3,4-dimethyldihydrofuran-2-one (2.69)

^1H NMR (300 MHz, $CDCl_3$) δ 6.84 (s, 4H), 4.31 (ddd, *J* = 3.7, 6.0, 9.3 Hz, 1H), 4.05-4.09 (m, 2H), 3.77 (s, 3H), 2.72 (app p, *J* = 7.7 Hz, 1H), 2.37 (app hextet, *J* = 7.0 Hz, 1H), 2.13 (dddd, *J* = 3.7, 7.4, 11.0, 14.4 Hz, 1H), 1.95 (app tt, *J* = 4.9, 9.3 Hz, 1H), 1.17 (d, *J* = 7.6 Hz, 3H), 1.05 (d, *J* = 7.1 Hz, 3H).

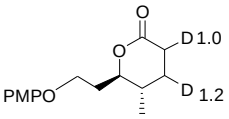


^2H NMR (300 MHz, $CHCl_3$) δ 2.67 (area: 1.0), 1.15 (area: >10).

6-[2-(4-Methoxyphenoxy)ethyl]-5-methyltetrahydropyran-2-one (2.70)



^1H NMR (300 MHz, $CDCl_3$) δ 6.80 (s, 4H), 4.00-4.20 (m, 3H), 3.72 (s, 3H), 2.54 (ddd, *J* = 4.7, 6.9, 17.8 Hz, 1H), 2.39 (ddd, *J* = 6.9, 9.6, 16.7 Hz, 1H), 2.13-2.26 (m, 1H), 1.84-1.97 (m, 2H), 1.67-1.79 (m, 1H), 1.49-1.58 (m, 1H), 1.01 (d, *J* = 6.6 Hz, 3H).



^2H NMR (300 MHz, $CHCl_3$) δ 2.47-2.61 (area: 1.2), 1.57-1.91 (area: 1.0).

References in experimental of Chapter 2

1) Ko, S.; Na, Y.; Chang, S. *J . Am. Chem.* Soc. **2002**, *124,* 750.

2) Andrus, M. B.; Argade, A. B. *Tetrahedron Lett.* **1996**, *37*, 5049-5052.

3) Pirrung, M. C.; Webster, N. J. G. *J. Org. Chem.* **1987**, *52*, 3603-3613.

4) Cossy, J.; Bargiggia, F.; Bouzbouz, S. *Org. Lett*. **2003**, *5*, 459.

5) Mino, T.; Masuda, S.; Nishio, M.; Yamashita, M. *J. Org. Chem.* **1997**, *62*, 2633.

6) Gottschalk, P. and Neckers, D. C. *J. Org. Chem.* **1985**, *50*, 3498.

7) Bachki, A.; Falvello, L. R.; Foubelo, F.; Yus, M. *Tetrahedron: Asymm.* **1997,** *8,* 2633.

Chapter 3. The synthesis of the C16-C35 fragment of integramycin

3.1 Introduction

Since the first diagnosed AIDS case reported in 1981, AIDS has brought devastating impact to numerous individuals and families. In the past two decades, more than 20 million people have died of AIDS and there are estimated 38 million people living with HIV in the whole world. In the United States, about 1 million people are living with HIV, and in the year of 2003 alone, about 14,000 Americans died of AIDS.[1]

The fight against AIDS in the past two decades has yielded important successes that can prolong life and reduce the physical effects of HIV infection. In the year 2004, there were 17 anti-HIV drugs approved by the FDA and available on the market, 16 of which targeted viral replication (reverse transcriptase and protease) and 1 of which targeted cell fusion.[2] Combination therapies using two types of drugs also emerged and showed their strength.[3] However, these therapies are often limited by the issues of regimen compliance, adverse side effects, and the emergence of mutated viral strains that are drug resistant.[4] The plasticity of HIV viruses often makes the existing therapies become less effective in the long term.[2] A cure of AIDS is still elusive. Identifying new therapeutic targets at different stages of the viral life cycle and developing new inhibitory agents will be one of the essential solutions.[5]

3.1.1 HIV-1 integrase

HIV-1 integrase is an enzyme responsible for the integration of the HIV genome into the host genome. Integration is an essential sequence in the replication cycle of HIV and other

retroviruses. It contains three steps: 3'-end processing, strand transfer, and DNA repair (Figure 3.1).[4,6,7]

HIV-1 integrase first recognizes the four nucleotide CAGT sequence at the termini of the viral DNA. It then removes the terminal 3' GT dinucleotide at both ends of the viral DNA, leaving a recessed CA with a free 3' hydroxyl group and an overhanging 5'-AC on the strand. This step is called 3'-end processing (3'-P).

In the second step, integrase cleaves the target DNA, and binds the 3' hydroxyl groups at both ends of the viral DNA onto the phosphate backbone of the target DNA. This step is termed strand transfer (ST). After this step is completed, the viral DNA is bound onto the host DNA covalently.

Finally, catalyzed by host repair enzymes, the irreversible incorporation of the HIV-1 genome into the host genome is completed by DNA gap filling and repair, which involves a series of DNA polymerization, dinucleotide excision, and ligation reactions to yield new viral progeny and the infection cycle is completed.

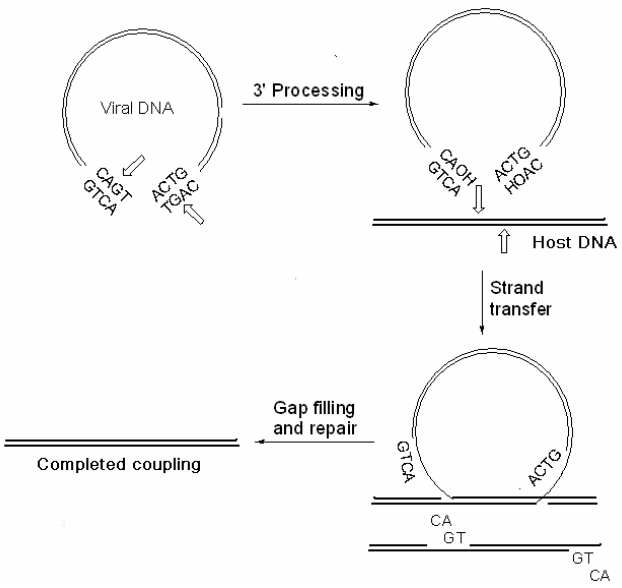
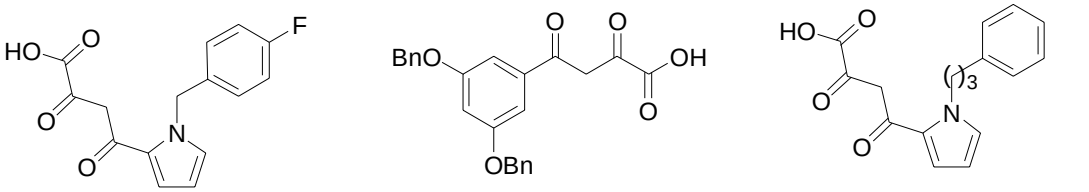


Figure 3.1. HIV-1 integration.

The development of chemotherapeutic agents for the treatment of HIV-1 infection has been focused on inhibitors of reverse transcriptase (catalyzes the conversion of viral RNA into DNA) and protease (hydrolyzes viral polyproteins into functional proteins). However, the unique nature of the integration process provides potential chemotherapeutic intervention safely targeting on integrase, which appears to be absent from the host. Furthermore, there is no known human homologue to integrase, which means that the inhibition of integrase may be very selective and present minimal toxicity to the human beings.[7] More than a decade of research in this area resulted in two drug candidates in clinical trials currently, and there are no drugs that act on HIV-1 integrase available on the market yet, indicating that we are just at the beginning of a discovering process and there is much more to be explored.[2]

3.1.2 Synthetic HIV-1 integrase inhibitors

Numerous compounds have been found to have biological activity against integrase.[2,8] Among them, diketo acids constitute a class of compounds that show good activity and selectivity. Merck scientists randomly screened more than 250,000 compounds and found that most of the potent compounds have a diketo acid functional group. Some examples are listed below; they demonstrate good to excellent potency against the integrase strand transfer reaction (Figure 3.2).[9]



L-731,988 IC_{50} = 0.05 μM L-708,906 IC_{50} = 0.10 μM L-731,927 IC_{50} = 0.50 μM

Figure 3.2. Diketo acids as HIV-1 integrase inhibitors.

5CITEP is an analog of diketo acid. It shows slightly superior potency to its diketo acid equivalent DKA1 (Figure 3.3).[10] The tetrazole group of 5CITEP is considered as an isosteric acid replacement. A complex of HIV-1 integrase with 5CITEP has been crystallized and the crytal structure demonstrated that 5CITEP bound to the core domain of HIV-1 integrase.[11]

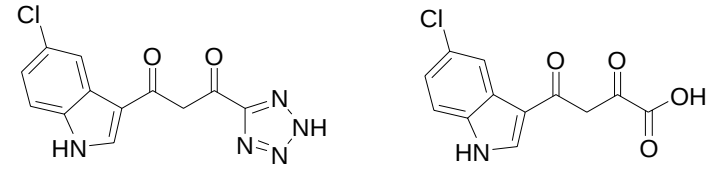


Figure 3.3. Diketo acid inhibitors of HIV-1 integrase.

S-1360 is a diketo acid derivative developed by Shionogi & Co. Ltd based on above findings. It demonstrates excellent potency with an IC_{50} value of 0.02 μM. This compound has proceeded to phase I/II clinical trial phase. Merck's L-870,810, which is called napthyridine carboxamide, has an IC_{50} value of 0.01 μM and has entered phase I clinical trial (Figure 3.4).[2]

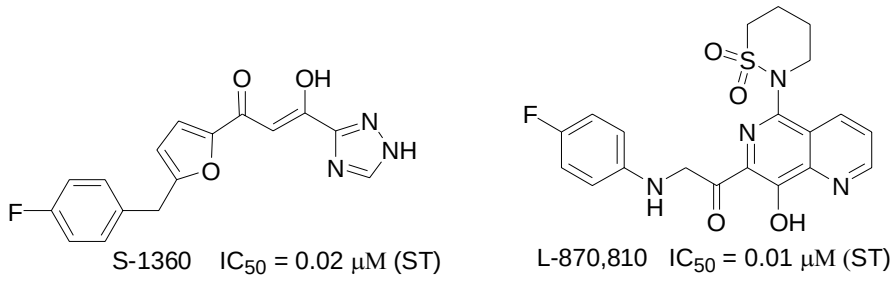


Figure 3.4. Compounds in clinical trials against HIV-1 integrase.

A second group of HIV-1 integrase inhibitors can be classified as polyhydroxylated compounds. Caffeic acid phenylethyl ester (CAPE) (Figure 3.5), a nontoxic apiary product, demonstrated moderate inhibitory activities with IC_{50} values of 19 and 220 μM against 3'-end

processing and strand transfer reactions.[12] Many analogs of CAPE have been prepared and tested against HIV-1 integrase. Digalloyl derivative **3.1** shows increased activity with an IC_{50} value of 4.7 μM against 3'-P,[13] dicaffeoyl-D,L-isoserine **3.2** has an improved IC_{50} of 0.37 μM,[14] and biscatechol acid **3.3** has an IC_{50} value of 0.23 μM, which also shows decreased cellular toxicity.[14] It is of particular interest to observe increased inhibitory activity in cell culture for these compounds, which would be very valuable in clinical trials.[2]

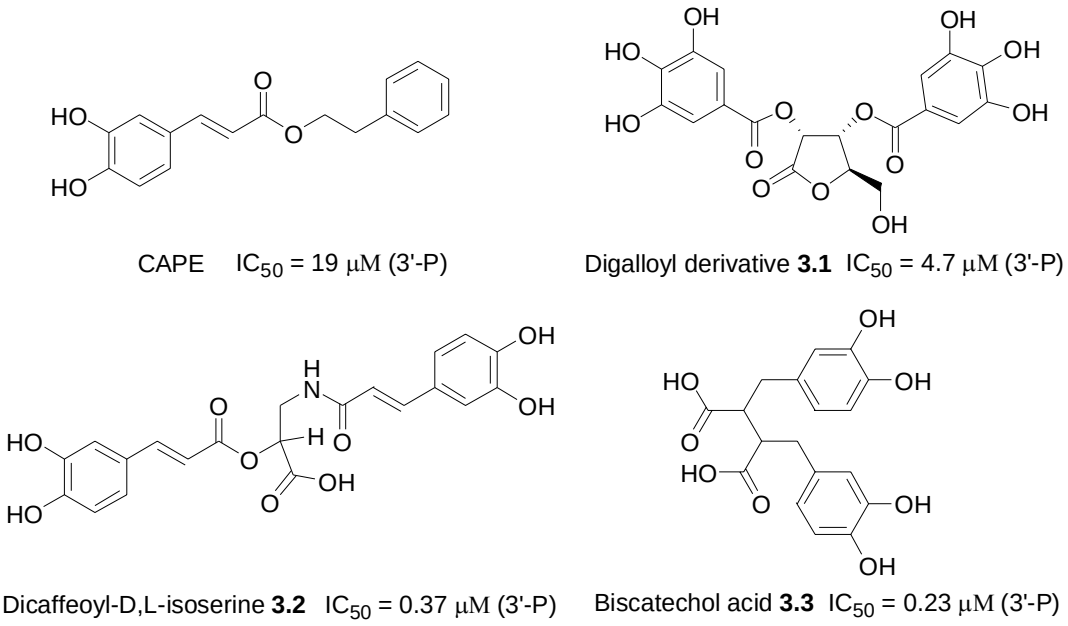


Figure 3.5. Polyhydroxylated compounds as HIV-1 integrase inhibitors.

A large number of other types of compounds, such as mononucleotides,[15] oligonucleotides,[5] peptides,[5] and sulfates[16] were also found to demonstrate inhibitory properties against HIV-1 integrase. For example, Maurer and co-workers synthesized a new class of sulfate compounds that inhibit both integrase and reverse transcriptase. This character will be very desirable considering that two therapies can be combined by using a single drug. The parent system

carbonyl J has an IC_{50} value of 4 μM (Figure 3.6).[16] After modification, compound **3.4** showed good activities against 3'-P and ST reactions with IC_{50} values of 0.2 and 0.33 μM.

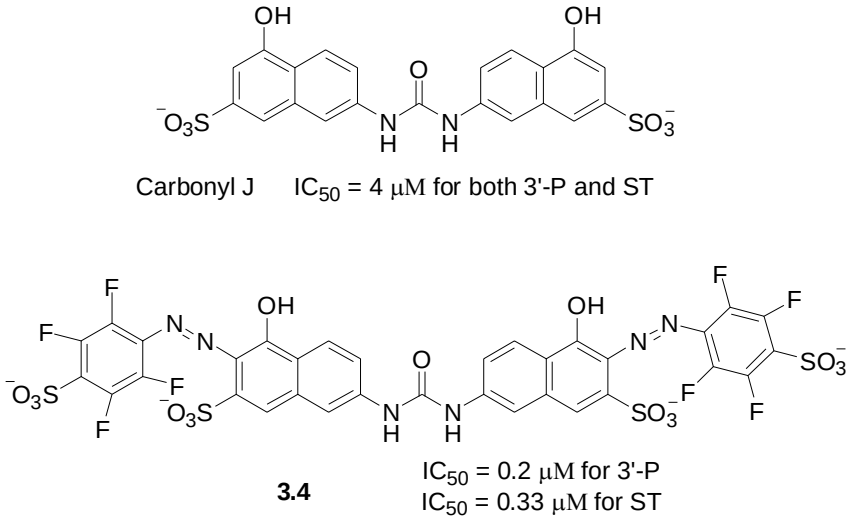


Figure 3.6. Carbonyl J and its derivative as HIV-1 integrase inhibitors.

3.1.3 Natural product as HIV-1 integrase inhibitors

Nature provides an enormous collection of natural products with complex structures and new properties. For thousands of years, natural products have been the main source of medicines. In modern drug discovery, natural products still play a crucial role by providing new motifs in search of new drugs. From 1981 to 2002, 49% of the small-molecule New Chemical Entities (NCEs) introduced were natural products, semi-synthetic natural product analogues, or synthetic compounds based on natural products.[17] Novel structures of natural products may lead to the discovery of inhibitors of HIV-1 integrase that suppress quick drug resistance developed by HIV viruses. The investigation of natural products and their analogs will greatly expand the scope of HIV-1 integrase inhibitor candidate pool and provide new insights in the design of drugs with novel properties.

Many natural products have been isolated and tested against HIV-1 integrase. Several examples are shown in Figure 3.7.[18] These compounds show moderate to good anti-HIV1 integrase activities. Among these compounds, integramycin is of particular interest to us.

Integramycin was isolated from *Actinoplanes* sp by Singh *et al.* in 2002.[18d] It contains a novel hexacyclic structure and inhibits the recombinant HIV-1 integrase strand transfer reaction with an IC_{50} value of 4 μM. The structure itself presents an intriguing target for synthetic organic chemist. There is no reported total synthesis of integramycin yet. Moreover, it has a diketo acid moiety (F ring) and a polyhydroxylated aromatic ring (A ring), two motifs often seen in integrase inhibitors but not often in the same molecule. The combination of these two motifs may be responsible for its biological activity.

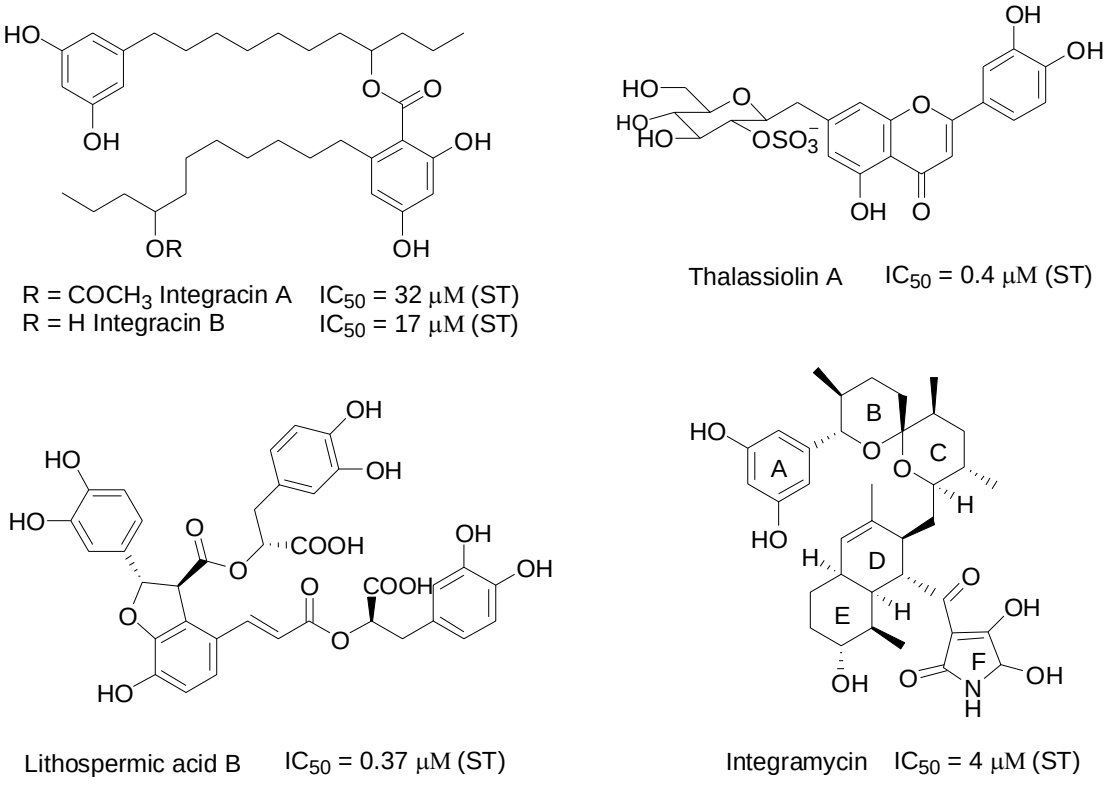
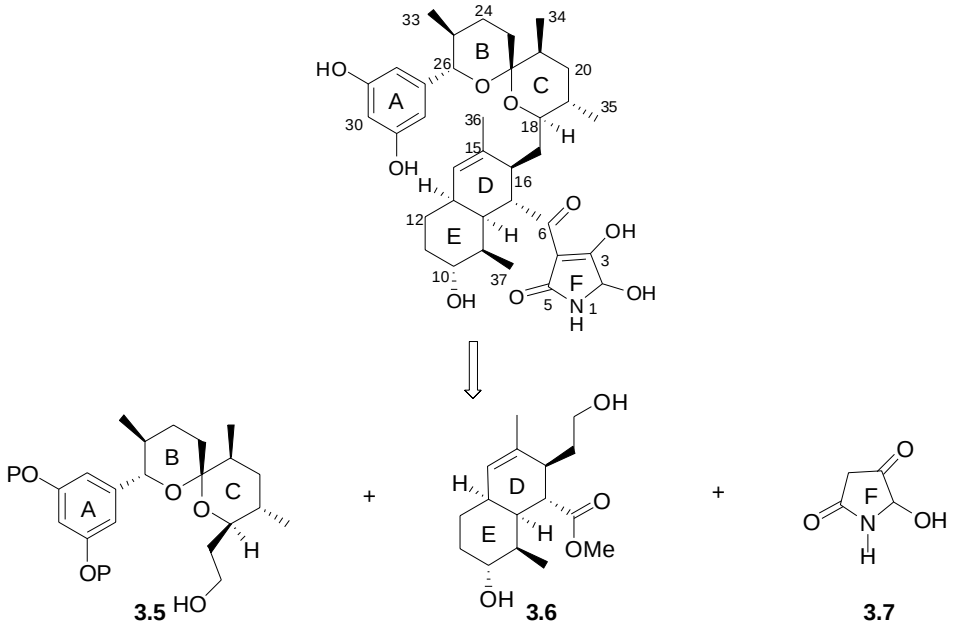


Figure 3.7. Natural product inhibitors of HIV-1 integrase.

Integramycin may serve as a lead structure in the search for new anti-HIV drugs. The synthesis of integramycin and its analogs may lead to drug candidates with stronger potency. The study of its structure-activity relationship will help to understand the mechanism of its inhibition of HIV-1 integrase, which will further facilitate the design of new drugs in the future. A potent derivative of integramycin, if discovered, could be used in new therapeutic methods in the treatment of AIDS, which can be applied alone or in combination with other existing methods.[18d]

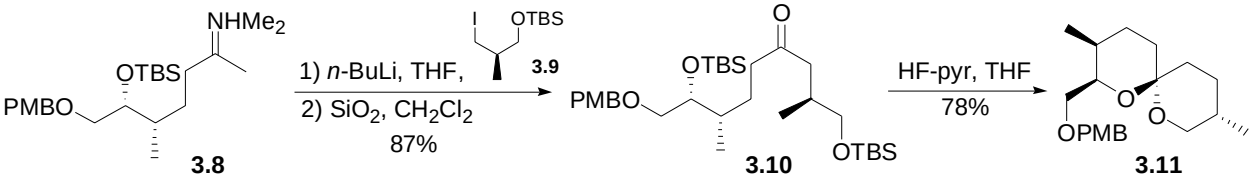
3.1.4 Retrosynthetic analysis of integramycin

Integramycin was reduced into three subtarget molecules: the C16-C35 fragment with the spiroketal unit **3.5**, the C6-C17 fragment with the *cis*-decalin unit **3.6**, and the side chain pyrrolidinedione **3.7** (Scheme 3.1). Each subtarget has a functional group on its terminus which will allow connection between them. This strategy allows the reduction of this complex molecule into three easier individual syntheses. Eventual connection of the three molecules will allow the completion of the total synthesis convergently.



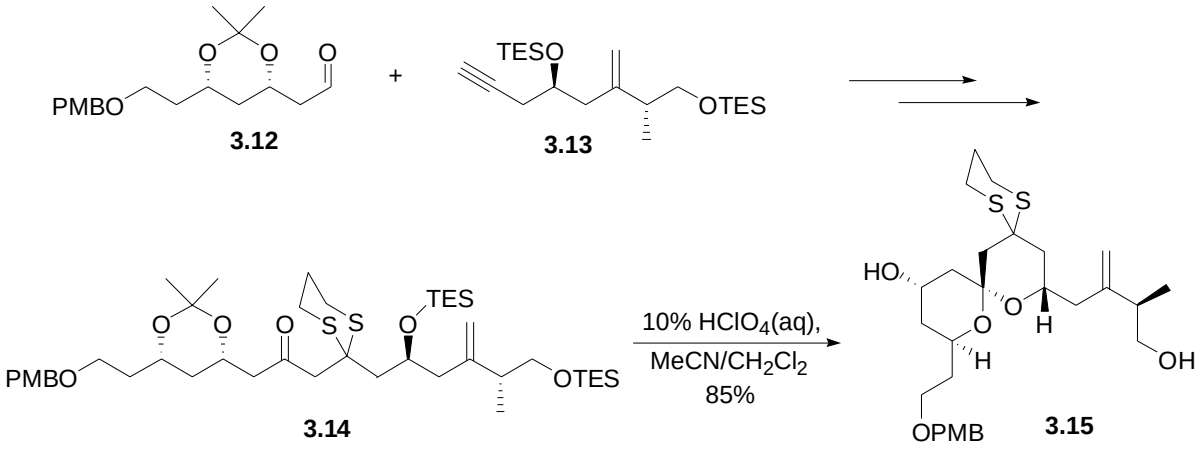
Scheme 3.1. Synthetic strategy.

Numerous ways have been developed to synthesize spiroketals, the key feature of the C16-C35 fragment of integramycin. For example, in the synthesis of spirofungins A and B by Dias, a coupling reaction of a hydrazone **3.8** and an alkyl iodide **3.9** followed by a hydrolysis provided a ketone product **3.10**. Removal of the TBS group on **3.10** promoted spontaneous spiroketal formation furnishing **3.11** in 78% yield (Scheme 3.2).[19a]



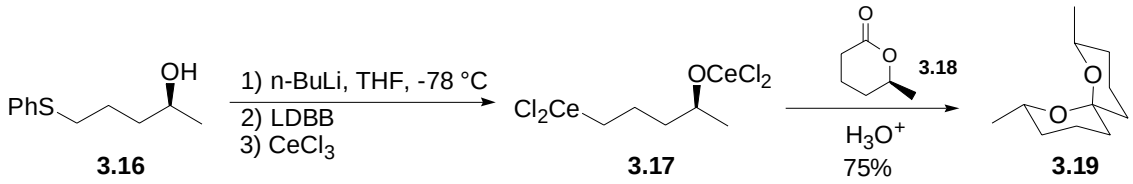
Scheme 3.2. Spiroketal synthesis by Dias.

Similarly, in Ley's synthesis of spongistatin 1, deprotection of the TES and acetal groups on ketone **3.14** was followed by a simultaneous cyclization to afford spiroketal **3.15** in 85% yield. The ketone was prepared from an aldehyde (**3.12**) and an alkyne (**3.13**) in several steps (Scheme 3.3).



Scheme 3.3. Spiroketal synthesis by Ley.

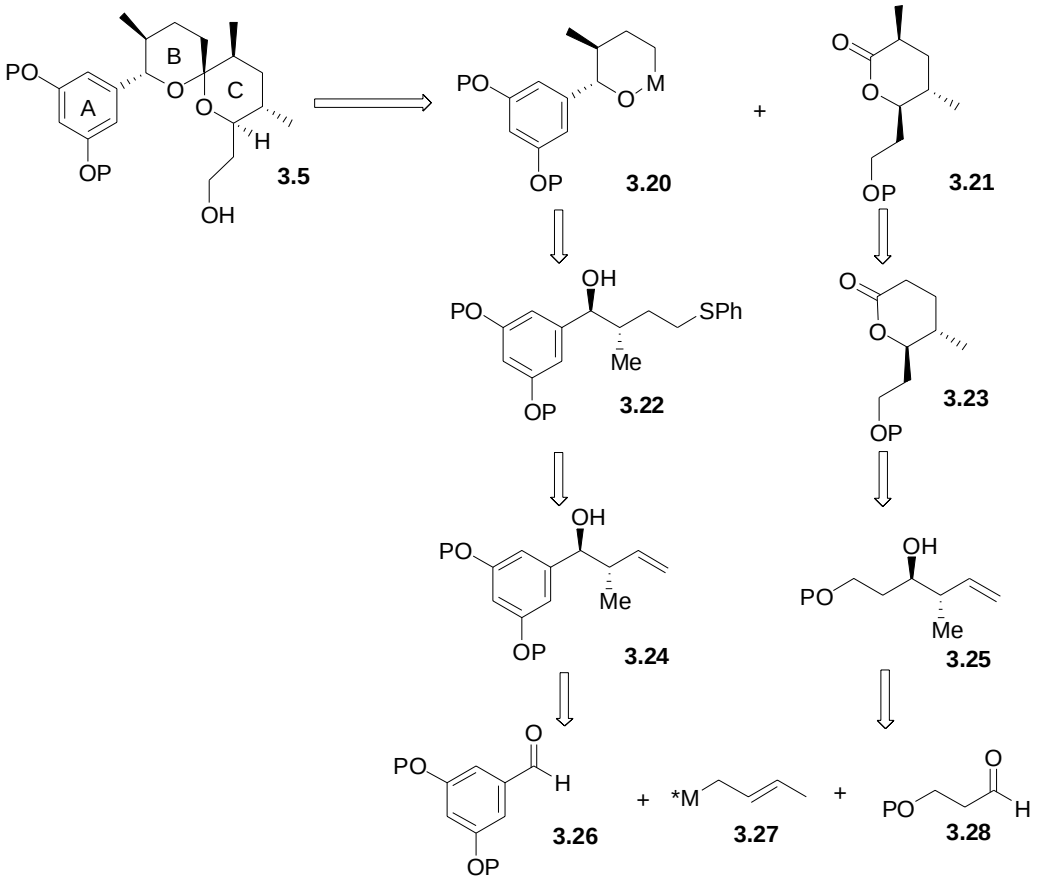
In Cohen's two-pot enantioselective synthesis of spiroketal pheromone, a dicerium species (**3.17**), generated from a phenylthio ether (**3.16**) underwent a carbonyl addition onto lactone (**3.18**). The resulting product, upon acidic aqueous workup, furnished spiroketal (**3.19**) in 75% yield (Scheme 3.4). Although this method was employed to a fairly simple system, it provides one of the most efficient approaches to spiroketals.[19c]



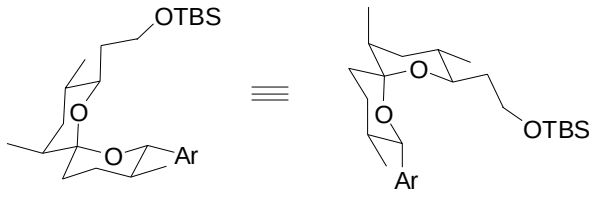
3.16 **3.17** **3.19**

Scheme 3.4. Cohen's spiroketal construction.

To minimize protecting group manipulations, we envisioned that the C16-C35 fragment of integramycin **3.5** can be accessed by a coupling reaction of two fragments: a dianion species **3.20** carrying the aromatic ring and a lactone **3.21** bearing a protected hydroxyl group (Scheme 3.5). The spiroketal formation is expected to be spontaneous upon acidic treatment of the coupling product of **3.20** and **3.21** as demonstrated in Cohen's example.[19c] The spiroketal, once formed, should take the desired configuration because of the double anomeric effect (Scheme 3.6).[19c] If not, acid-catalyzed conditions should drive the spiroketal to the thermodynamically favored configuration taking the alkoxy groups in axial positions on both rings.[20]



Scheme 3.5. Retro synthesis of the C16-C35 fragment of integramycin.



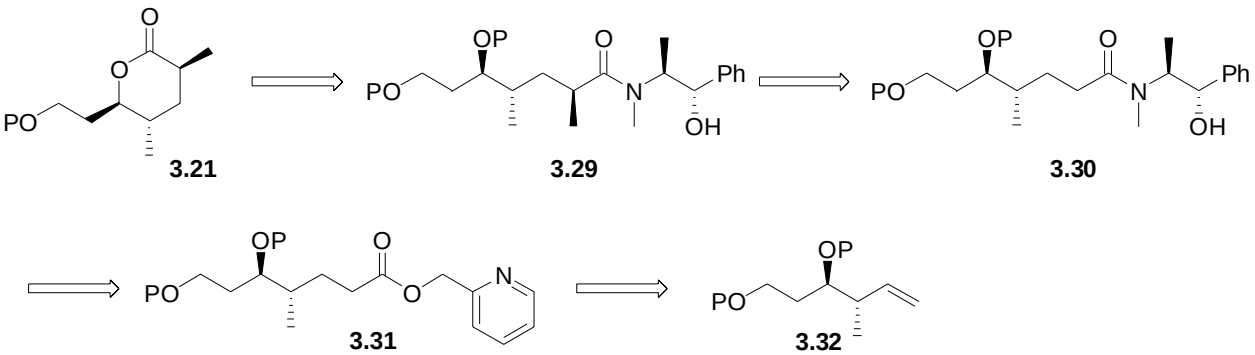
Scheme 3.6. The desired configuration of the spiroketal.

The dianion species **3.20** can be generated from an alcohol **3.22** bearing a phenylthio group *via* a reduction reaction.[19c] Alcohol **3.22** can be synthesized from homoallylic alcohol **3.24** through a radical reaction with PhSH.[19c] Lactone **3.21** is accessible by methylation of lactone

3.23, which can be obtained from homoallylic alcohol **3.25** using the strategy developed in Chapter 2.

Homoallylic alcohols **3.24** and **3.25** can be prepared from asymmetric crotylation reactions of aldehydes **3.26** and **3.28** employing the same (*E*)-crotylmetallic reagent **3.27**. Various asymmetric crotylating reagents are available, such as Brown's crotyldiisopinocampheyl-boranes,[21] Roush's crotylboronates,[22] Denmark's crotyltrichlorosilane catalyzed with bisphosphoramide,[23] and Hafner's crotyltitanium taddolate reagent.[24]

As an alternative approach to lactone **3.21**, Myers' pseudoephedrine[25] chiral auxiliary can be used (Scheme 3.7). In the forward sense, pseudoephedrine amide **3.30** can be methylated under Myers conditions to set up the α-stereocenter with excellent stereoselectivity to yield **3.29**. The protecting group on the secondary alcohol of product **3.29** can be selectively removed and the resulting product should cyclize under acidic conditions to furnish lactone **3.21**. Amide **3.30** can be obtained from homoallylic alcohol **3.32** using a hydroesterification reaction followed by a amide alcoholysis.



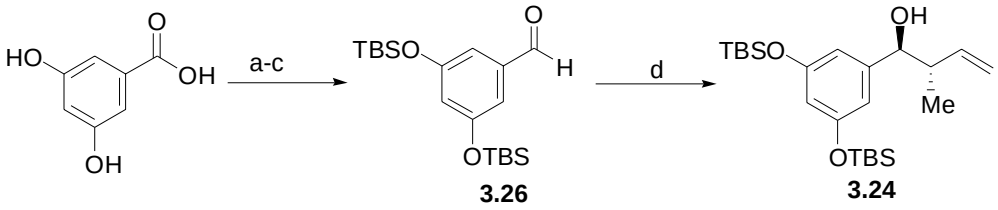
Scheme 3.7. Approach to lactone **3.21** using Myers chiral auxiliary.

3.2. Results

3.2.1. The Synthesis of the precursor of dianion species 3.20

The synthesis of the precursor of **3.8** started from the preparation of 3,5-di-(*tert*-butyldimethylsilyloxy)benzaldehyde **3.26**, which was synthesized using a combination of several known procedures (Scheme 3.8). Commercially available 3,5-dihydroxybenzoic acid was reduced to an alcohol using BH_3·THF. Oxidation of the resulting alcohol to its aldehyde with Jones' reagent followed by a protection of the hydroxyl groups on the benzene ring as *tert*-butyldimethylsilyl ethers gave the desired aldehyde **3.26** in a 34% yield over 3 steps.

The asymmetric crotylation of aldehyde **3.26**, however, proved to be more difficult than expected. Crotylation using Brown's *E*-(–)-$(Ipc)_2$crotylborane (derived from (+)-α-pinene)[21] gave a 91% yield of homoallylic alcohol **3.24** with poor diastereoselectivity (anti:syn = 2.3:1, determined by ^{1}H NMR). The two diastereomers are inseparable (Scheme 3.8).

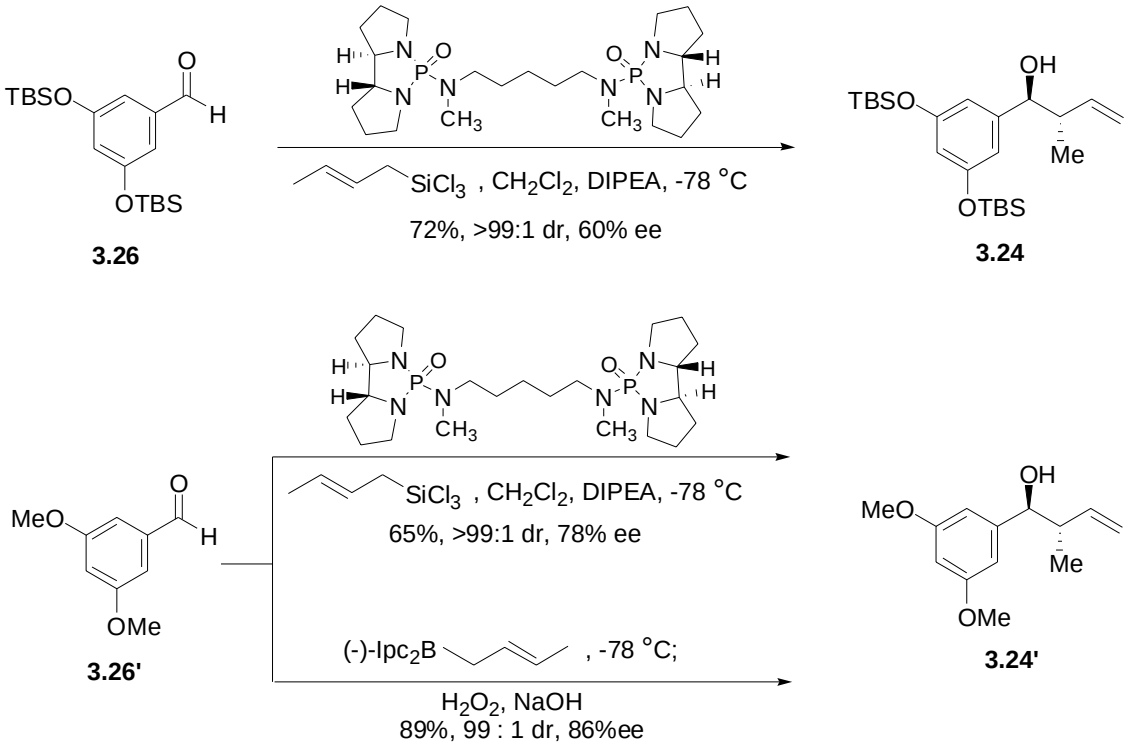


Reagents: a) 1M BH_3 in THF. b) CrO_3, H_2O, acetone. c) TBDMSCl, ^{i}Pr$_2$EtN, DMF; 34% over 3 steps. d) *E*-(-)-$(Ipc)_2$crotylborane, THF, -78 ^{o}C; H_2O_2, NaOH; 91%, 2.3:1 dr.

Scheme 3.8. The synthesis of homoallylic alcohol **3.24**.

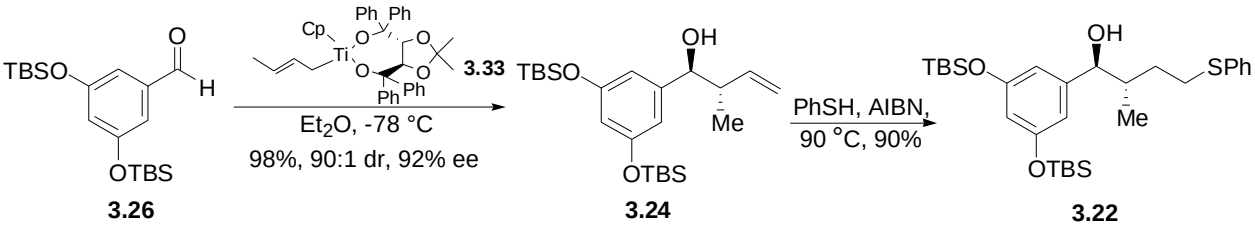
Crotylation using crotyltrichlorosilane in the presence of Denmark's bisphosphoramide catalyst[23] was also investigated (Scheme 3.9). Under Denmark's conditions, crotylation of aldehyde **3.26** yielded homoallylic alcohol **3.24** with an excellent diastereoselectivity (99:1), but

moderate enantioselectivity (60% ee, determined by Mosher's ester analysis) and yield (72%). To prove whether the bulky TBS protecting groups on **3.26** has adverse influence on the desired transition states of the crotylation reactions, the TBS protecting groups were changed to methyl groups. Substrate **3.26'** improved the crotylation ee to 78% when using Denmark's method, which is in accord with literature precedents (Scheme 3.9).[23] However, this reaction was not adopted because the deprotection of methyl groups in the final stage of the synthesis can be difficult. Also, Denmark's bisphosphoramide catalyst is difficult to prepare. Crotylation of aldehyde **3.26'** using Brown's reagent also afforded improved dr (99:1) and ee (86%) (Scheme 3.9).



Scheme 3.9. Crotylations of **3.26** and **3.26'**.

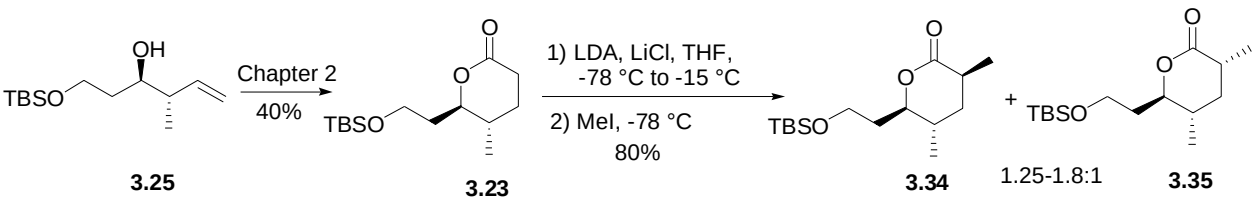
Hafner's crotyltitanium taddolate[24] has been claimed to tolerate a broad range of substrates, even mismatched cases. This reagent was prepared and tested for our crotylation. To our delight, the crotylation of aldehyde **3.26** using Hafner's reagent (**3.33**) proceeded efficiently and furnished **3.24** in 92% ee with essentially complete diastereocontrol (90:1 dr) and quantitative yield (98%) (Scheme 3.10). The resulting homoallylic alcohol **3.24** was then heated with AIBN in PhSH to provide thiophenyl ether **3.22** in a 90% yield.[19c] Thioether **3.22** is the progenitor of the dianion species **3.20**.



Scheme 3.10. Hafner's crotylation.

3.2.2. The synthesis of lactone 3.21

Several sequences were examined to convert homoallylic alcohol **3.25** into lactone **3.21**. In the first sequence, known homoallylic alcohol **3.25**[19b] was converted to lactone **3.23** in a 40% yield using the strategy developed in Chapter 2. Lactone **3.23** was treated with LDA followed by MeI in the presence of LiCl[25] and afforded a 1.25-1.8:1 mixture of methylation products **3.34** and **3.35** in a 80% yield, slightly favoring the desired lactone **3.34** (Scheme 3.11). Lithium chloride was found to be a crucial additive in the reaction to accelerate the alkylation rate. In the presence of LiCl, methylation was complete within 5 min at –78 ºC, sharply in contrast to when in the absence of LiCl, methylation only proceeded to ~80% completion after 45 min at –78 ºC.



Scheme 3.11. Methylation of lactone **3.23**.

The methylation of lactone **3.23** proceeded with poor diastereoselectivity, which is consistent with one literature precedent.[26] The reason may be that the two substituents on the half chair transition state of the lactone enolate reside in equatorial positions and do not provide diastereofacial bias, and the energy difference between the chair and boatlike methylation products is minimal (Figure 3.8).[26]

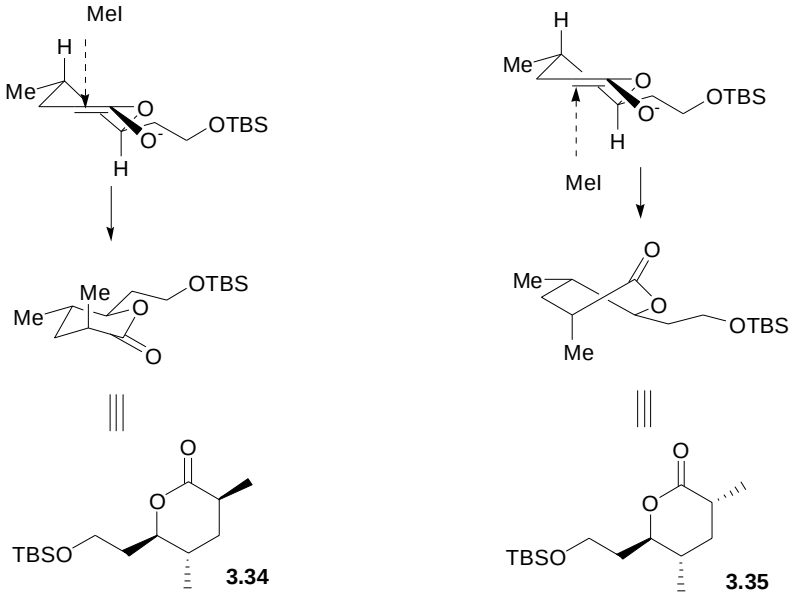
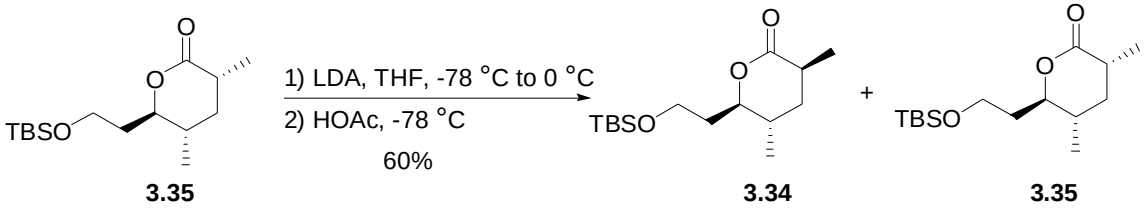


Figure 3.8. Transition states of methylation of lactone **3.23**.

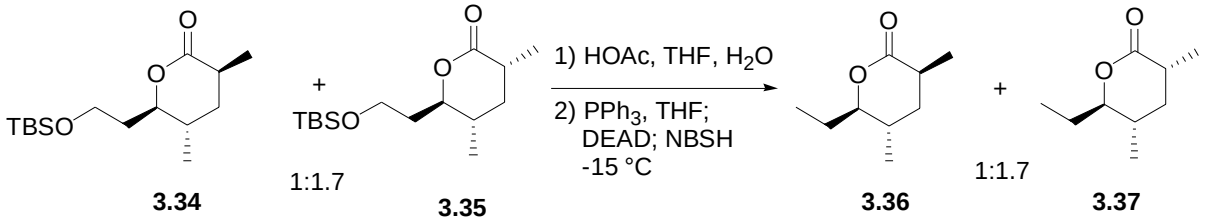
Undesired lactone **3.35** can be epimerized to improve the yield of **3.34**. Deprotonation of **3.35** with LDA followed by protonation of the resulting lactone enolate with HOAc provided a 0.8:1 mixture of **3.34** and **3.35** in 60% yield (Scheme 3.12). The overall yield for the transformation of **3.23**→ **3.34** was 60% over 2 steps.



3.35 **3.34** **3.35**

Scheme 3.12. The isomerization of lactone **3.35**.

The configurations of the methylation product **3.34** and its epimer **3.35** were assigned after comparing them with literature analogs. The α-H of the undesired diastereomer **3.35** has a lower chemical shift than that of the desired one **3.34**. The α-H of **3.35** also has a coupling pattern of ddq and coupling constants of 13.2, 6.2, and 7.0 Hz, which are consistent with literature data.[27] Further confirmation of the assignment was obtained after converting **3.34** and **3.35** to compounds **3.36** and **3.37**, which were previously prepared by Bartlett[28] (Scheme 3.13). A 1:1.7 mixture of **3.34** and **3.35** was desilylated using acetic acid and then deoxygenated under Myers' conditions[29] to afford a 1:1.7 mixture of **3.36** and **3.37**, which showed identical spectra to Bartlett's compounds.[28]

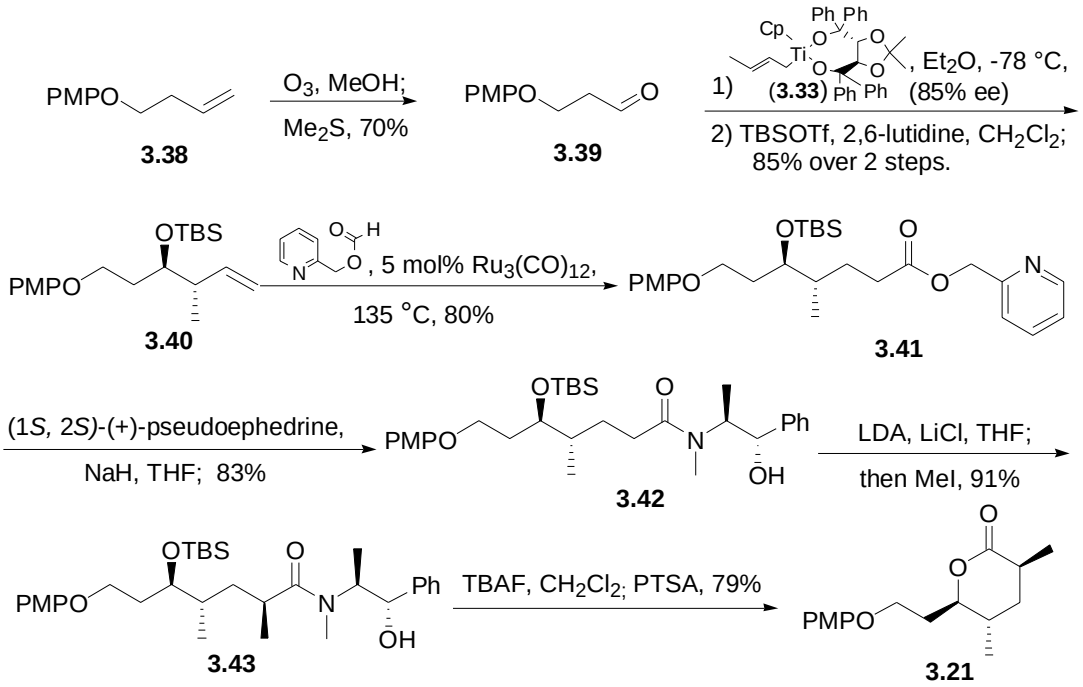


3.34 **3.35** **3.36** **3.37**

Scheme 3.13. Converting **3.34** and **3.35** to Bartlett's Compounds.

The above sequence has the advantage of being very concise (Scheme 3.11). It only needs two steps to prepare lactone **3.34** from homoallylic alcohol **3.25**. However, the overall yield and diastereoselectivity are not satisfactory. Based on the observation that silyl ether protected homoallylic alcohols undergo hydroesterification and give high yield of the corresponding linear esters, we designed a sequence to combine the usage of a hydroesterification reaction and a methylation using pseudoephedrine chiral auxiliary.

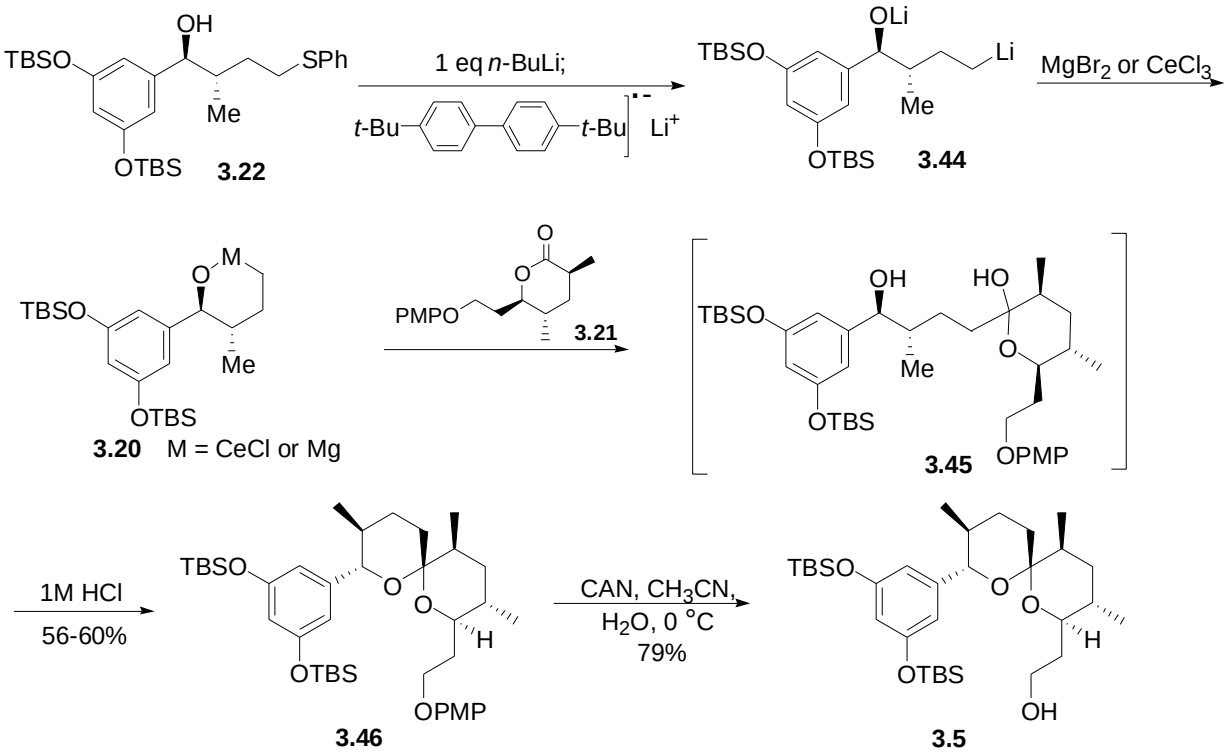
The sequence started with known PMP-protected butenol[30] **3.38** (Scheme 3.14). Ozonolysis of **3.38** afforded aldehyde **3.39** in a 70% yield. Crotylation of aldehyde **3.39** using Hafner's crotyltitanium taddolate[24] (**3.33**) and subsequent protection using TBSOTf yielded silyl ether **3.40** (85% over 2 steps). Ether **3.40** was subjected to our previous hydroesterification conditions, affording 2-pyridylmethyl ester **3.41** in a 80% yield. Transformation of **3.41** into pseudoephedrine amide **3.42** (83%), through a variant of Myers' aminolysis conditions, followed by methylation[25] provided amide **3.43** (91%). One-pot removal of the silyl group of **3.43** followed by acid-mediated lactonization gave lactone **3.21** in a 79% yield. This sequence provided lactone **3.21** in an efficient 48% yield from ether **3.40** over 4 steps.



Scheme 3.14. Lactone synthesis using pseudoephedrine chiral auxiliary.

3.2.3. Coupling of dianion species 3.20 and lactone 3.21

Coupling of **3.20** and **3.21** (Scheme 3.15) was achieved with Cohen's method.[19] Deprotonation of the hydroxyl group of thioether **3.22** with one equivalent of *n*-BuLi followed by reduction of the sulfide with lithium di-*tert*-butylbiphenylide (LDBB) generated a dilithium intermediate **3.44** which underwent transmetalation with anhydrous $CeCl_3$ to afford **3.20**. Addition of lactone **3.21** to the resulting alkylcerium species **3.20** afforded, following an acidic aqueous work-up, the desired spiroketal **3.46** in a 60% yield through intermediate **3.45**. This reaction, however, proved to be somewhat capricious due to technical difficulties associated with preparing the alkylcerium reagent. An exploration of alternate reagents for effecting the transmetalation reaction showed that $MgBr_2$, prepared in situ from 1,2-dibromoethane and Mg metal, promoted spiroketal formation in 56% yield and with greater reproducibility than the alkylcerium addition.



Scheme 3.15. Spiroketal formation.

The PMP protecting group of **3.46** was easily removed using cerium ammonium nitrate (CAN) in wet CH_3CN to give **3.5** in 79% yield. Alcohol **3.5** is well-suited for subsequent elaboration of the C1-C15 portion of integramycin. Significant overlap in the ^1H NMR spectra of the spiroketals precluded their rigorous structural assignment through NOESY analysis. Therefore, we removed the silyl groups from **3.46** to form **3.47** as a solid that crystallized as its monohydrate. This allowed our stereochemical assignments to be validated by single-crystal X-ray diffraction analysis of the monohydrate of **3.47** (Figure 3.9).

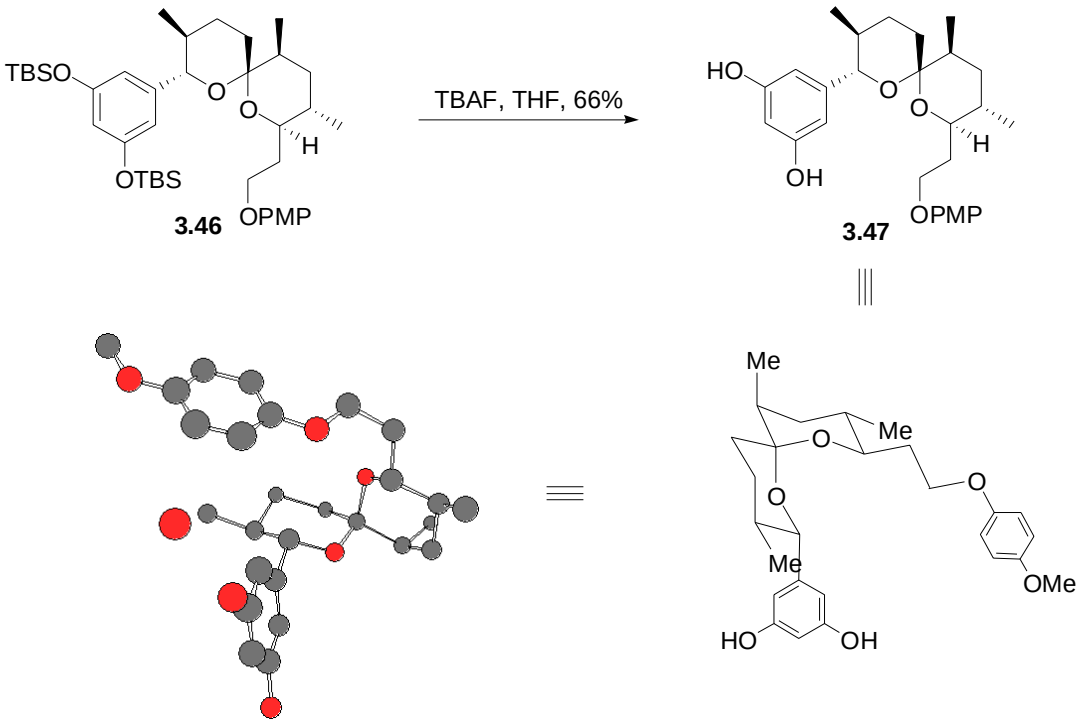
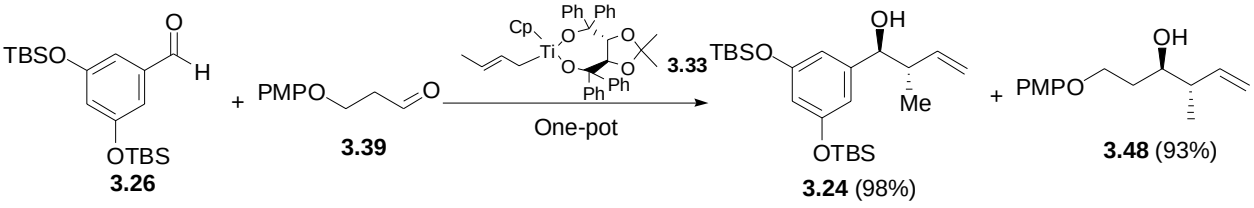


Figure 3.9. Crystal structure of **3.47**.

3.3. Discussion

Given that the separation of homoallylic alcohols **3.24** and **3.48** was expected to be facile on the basis of their significantly different polarities, we subjected a mixture of aldehydes **3.26** and **3.39** to simultaneous crotylation with Hafner's reagent **3.33** (Scheme 3.16). This experiment showed that the additions proceed independently without interfering each other, providing the homoallylic alcohols **3.24** and **3.48** with yields and stereoselectivities that are comparable to each individual reaction while eliminating one experimental setup, workup, and chromatographic separation. This experiment may be expanded to parallel synthesis of multiple homoallylic alcohols in one pot with asymmetric crotylations.



Scheme 3.16. One-pot crotylation of two aldehydes.

3.4 Summary

The synthesis of the C16-C35 fragment of integramycin was accomplished in a convergent and stereoselective manner. The synthesis took 10 steps from commercially available materials (longest linear sequence, 14 steps overall). The sequence includes the usage of a highly efficient ruthenium-mediated hydroesterification reaction. This sequence also demonstrates the efficiency of C,O-dianionic additions into lactones as a method for producing spiroketals in a single operation without recourse to extensive protecting group manipulations. Also, Hafner's crotylation was found to be superior to Brown's or Denmark's crotylations in the synthesis of homoallylic alcohol **3.24**.

3.5 References

(1) *2004 report on the global HIV/AIDS epidemic: 4th global report*, UNAIDS, WHO Library Cataloguing-in-Publication Data.

(2) Johnson, A. A.; Marchand, C.; Pommier, Y. *Cur. Top. Med. Chem.* **2004**, *4*, 1059-1077.

(3) Lythgo, P. A. *BioTeach J.* **2004**, *2*, 81-87.

(4) Anthony, N. J. *Cur. Top. Med. Chem.* **2004**, *4*, 979-990.

(5) Tarrago-Litvak, L.; Andreola, M. L.; Fournier, M.; Nevinsky, G. A.; Parissi, V.; de Soultrait, V. R.; Litvak, S. *Cur. Pharm. Des*. **2002***, 8*, 595-614.

(6) Chiu, T. K.; Davies, D. R. *Cur. Top. Med. Chem.* **2004**, *4*, 965-977.

(7) Craigie, R. *J. Biol. Chem.* **2001**, *276*, 23213-23216.

(8) Pommier, Y.; Marchand, C.; Neamati, N. *Antiviral Res.* **2000**, *47*, 139-148.

(9) (a) Hazuda, D. J.; Felock, P.; Witmer, M.; Wolfe, A.; Stillmock, K.; Grobler, J. A.; Espeseth, A.; Gabryelski, L.; Schleif, W.; Blau, C.; Miller, M. D. *Science*, **2000**, *287*, 646-650. (b) Wai, J. S.; Egbertson, M. S.; Payne, L. S.; Fisher, T. E.; Embrey, M. W.; Tran, L. O.; Melamed, J. Y.; Langford, H. M.; Guare, J. P., Jr.; Zhuang, L.; Grey, V. E.; Vacca, J. P.; Holloway, M. K.; Naylor-Olsen, A. M.; Hazuda, D. J.; Felock, P. J.; Wolfe, A. L.; Stillmock, K. A.; Schleif, W. A.; Gabryelski, L. J.; Young, S. D. *J. Med. Chem.* **2000**, *43*, 4923-4926.

(10) Marchand, C.; Zhang, X.; Pais, G. C. G.; Cowansage, K.; Neamati, N.; Burke, T. R. Jr.; Pommier, Y. *J. Bio. Chem.* **2002**, *277*, 12596-12603.

(11) Goldgur, Y.; Craigie, R.; Cohen, G. H.; Fujiwara, T.; Yoshinaga, T.; Fujishita, T.; Sugimoto, H.; Endo, T.; Murai, H.; Davies, D. R. *Natl. Acad. Sci. USA*, **1999**, *96*, 13040-13043.

(12) Fesen, M. R.; Kohn, K. W.; Leteurtre, F.; Pommier, Y. Proc. *Natl. Acad. Sci. USA*, **1993**, *90*, 2399-2403.

(13) Hwang, D. J.; Kim, S. N.; Choi, J. H.: Lee, Y. S. *Bioorg. Med. Chem.* **2001**, *9*, 1429-1437.

(14) Reinke, R. A.; King, P. J.; Victoria, J. G.; McDougall, B. R.; Ma, G.; Mao, Y.; Reinecke, M. G.; Robinson, W. E., Jr. *J. Med. Chem.* **2002**, *45*, 3669-3683.

(15) Nair, V. *Rev. Med. Virol.* **2002**, *12*, 179-193.

(16) Maurer, K.; Tang, A. H.; Kenyon, G. L.; Leavitt, A. D. *Bioorg. Chem.* **2000**, *28*, 140-155.

(17) Koehn, F. E.; Carter, G. T. *Drug Dis.* **2005**, *4*, 206-220.

(18) For integracins, see: (a) Singh, S. B.; Zink, D. L.; Bills, G. F.; Pelaez, F.; Teran, A.; Collado, J.; Silverman, K. C.; Lingham, R. B.; Felock, P.; Hazuda, D. J. *Tetrahedron Lett.* **2002**, *43*, 1617-1620. For thalassiolin A, see: (b) Rowley, D. C.; Hansen, M. S.; Rhodes, D.; Sotriffer, C. A.; Ni, H.; McCammon, J. A.; Bushman, F. D.; Fenical, W. *Bioorg. Med. Chem.* **2002**, *10*, 3619-3625. For lithospermic acid B, see: Abd-Elazem, I. S.; Chen, H. S.; Bates, R. B.; Huang, R. C. C. *Antiviral Res.* **2002**, *55*, 91-106. For integramycin, see: Singh, S. B.; Zink, D. L.; Heimbach, B.; Genilloud, O.; Teran, A.; Silverman, K. C.; Lingham, R. B.; Felock, P.; Hazuda, D. J. *Org. Lett.* **2002**, *4*, 1123-1126.

(19) (a) Dias, L. C.; de Oliveira, L. G. *Org. Lett.* **2004**, *6*, 2587-2590. (b) Gaunt, M. J.; Jessiman, A. S.; Orsini, P.; Tanner, H. R.; Hook, D. F.; Ley, S. V. *Org. Lett*. **2003**, *5*, 4819-4822. (c) Cohen, T.; Tong, S. *Tetrahedron* **1997**, *53*, 9487-9496.

(20) Grieco, P. A.; Williams, E.; Tanaka, H.; Gilman, S. *J. Org. Chem.* **1980**, *45*, 3537-3539.

(21) (a) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293-294. (b) Andrus, M. B.; Argade, A. B. *Tetrahedron Lett.* **1996**, *37*, 5049-5052.

(22) Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339-6348.

(23) Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2001**, *123*, 9488-9489.

(24) Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, G.; Rothe-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc*. **1992**, *114*, 2321-2336.

(25) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496-6511.

(26) Evans, D. A. *Asymmetric Synthesis* (Edited by Morrison, J. D.), Vol. 3, Chapter 1, pp. 50-56. Academic Press, New York, **1984**.

(27) (a) Pilli, R. A.; de Andrade, C. K. Z.; Souto, C. R. O.; de Meijere, A. *J. Org. Chem.* **1998**, *63*, 7811-7819. (b) Horita, K.; Inoue, T.; Tanaka, K.; Yonemitsu, O. *Tetrahedron* **1996**, *52*, 531-550. (c) Kocieński, P. J.; Brown, R. C. D.; Pommier, A.; Procter, M.; Schmidt, B. *J. Chem. Soc., Perkin Trans. 1,* **1998**, 9-39.

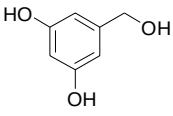
(28) Bartlett, P. A.; Richardson, D. P.; Myerson, J. *Tetrahedron* **1984**, *40*, 2317-2327.

(29) Myers, A. G.; Movassaghi, M.; Zheng, B. *J. Am. Chem. Soc.* **1997**, *119*, 8572-8573.

(30) Corey, E. J.; Guzman-Perez, A.; Noe, M. C. *J. Am. Chem. Soc.* **1995**, *117*, 10805-10816.

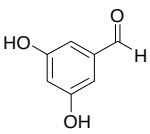
3.6 Experimental

3,5-Dihydroxybenzyl alcohol[1]



To a stirring solution of 3,5-dihydroxybenzoic acid (2.0 g, 13.0 mmol) in THF (10 mL) at 0 °C was added a solution of BH_3·THF (1 M in THF, 42 mL, 42 mmol) dropwise. The resulting mixture was heated under reflux for 2 h. The reaction mixture was cooled to 0 °C and deionized water was added dropwise. The resulting solution was stirred for 1 h and brine (~15 mL) was added. The organic layer was separated and the aqueous layer was extracted with diethyl ether. The organic layers were combined, washed with brine, then were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was dissolved in acetone (with minimal amount) and the resulting solution was added dropwise to stirring hexanes (200 mL). A precipitate formed and the resulting mixture was filter. The solid obtained was dried under vacuum and was used in the next step without further purification. ^{1}H NMR (300 MHz, acetone-d_6) δ 6.33-6.35 (d, J = 2.2 Hz, 2H), 6.19-6.22 (dd, J = 2.2, 2.2 Hz, 1H), 4.45 (s, 2H).[1]

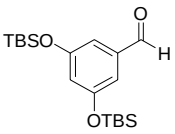
3,5-Dihydroxybenzaldehyde[2]



To sodium dichromate dihydrate ($Na_2Cr_2O_7 \cdot 2H_2O$, 4 g, 13.36 mmol) in deionized water (7 mL) was added concentrated sulfuric acid (4 mL) with shaking. Additional deionized water (6 mL) was added slowly, and the resulting solution was cooled to 0 °C. This freshly made Jones' reagent was added dropwise to a solution of 3,5-dihydroxybenzyl alcohol (~1.8 g, ~13 mmol) in acetone (90 mL) at 0 °C. The reaction mixture changed to dark green. Jones' reagent was kept adding until the color of the reaction turned to orange black. The

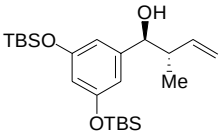
reaction mixture was stirred at 0 °C for 7 min then was poured into diethyl ether (500 mL). The organic layer was separated, washed with saturated $NaHCO_3$ solution (6 × 30 mL) and brine (5 × 30 mL), then was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was used in the next step without further purification. ^{1}H NMR (300 MHz, acetone-d_6) δ 9.84 (s, 1H), 8.74 (s, 2H), 6.87 (d, J = 2.3 Hz, 2H), 6.63 (dd, J = 2.3, 2.3 Hz, 1H).[2]

3,5-Bis-(*tert*-butyldimethylsilyloxy)benzaldehyde (3.26)[3]



To a stirring solution of 3,5-dihydroxybenzaldehyde (~0.9 g, 6.5 mmol) in DMF (13 mL) at 0 °C was added DIPEA (3.5 mL) followed by TBSCl (2.27 g, 15.07 mmol). The reaction mixture was stirred at rt for 1.5 h and was quenched with ice. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3×15 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution, water, and brine, then were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (2-3% EtOAc in hexanes) to provide the desired product (1.61 g, 34% over 3 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.86 (s, 1H), 6.95 (d, J = 2.3 Hz, 2H), 6.58 (dd, J = 2.3, 2.3 Hz, 1H), 0.99 (s, 18H), 0.22 (s, 12H).[3]

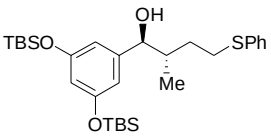
1-[3,5-Bis-(*tert*-butyldimethylsilyloxy) phenyl]-2-methylbut-3-en-1-ol (3.24)



To a solution/suspension of (4*R*, *trans*)-2,2-dimethyl-α,α,α',α'-tetraphenyl-1,3-dioxolane-4,5-dimethanol (1.91 g, 4.1 mmol) in distilled cyclohexane (100 mL) was added freshly sublimed $CpTiCl_3$ (0.9 g, 4.1 mmol). The reaction flask was fitted with a Soxhlet extractor containing MgO (4.0 g, flamed dried under vacuum). The reaction mixture was heated under reflux for 12 h. The solvent was removed. Absolute Et_2O (41 mL) was added and

the resulting solution was stirred for 15 min then was concentrated. This ether washing sequence was repeated two additional times. The resulting residue was dissolved in Et_2O (60 mL) and cooled to -78 ^oC. Crotylmagnesium chloride (0.5 M in THF, 8.2 ml, 4.1 mmol) was added. The resulting mixture was stirred at -78 ^oC for 0.5 h, warmed to 0 ^oC for 3 h, and recooled to -78 ^oC. Aldehyde **3.26** (1.165 g, 3.17 mmol) in ether (5 mL) was added. The reaction mixture was stirred at -78 ^oC for 2 h then was quenched with saturated NH_4Cl (10 mL). The resulting mixture was stirred at rt for 12 h then was filtered through Celite. The organic layer was separated and the aqueous layer was extracted with ether (3x). The organic layers were combined and washed with brine, then were dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by flash chromatography (2-10% EtOAc in hexanes) to afford the desired product (1.32 g, 98%): $[\alpha]^{23}_D$ -32.0º (*c* = 1.10, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 6.45 (d, *J* = 2.2 Hz, 2H), 6.26 (t, *J* = 2.6 Hz, 1H), 5.74 (ddd, *J* = 8.1, 10.3, 17.5 Hz, 1H), 5.15-5.20 (m, 2H), 4.23 (dd, *J* = 1.9, 7.6 Hz, 1H), 2.40 (app sextet, *J* = 7.2 Hz, 1H), 2.07 (d, *J* = 2.4 Hz, 1H, OH), 0.98 (s, 18H), 0.87 (d, *J* = 6.8 Hz, 3H), 0.19 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.6, 144.9, 140.8, 116.8, 112.2, 111.6, 77.9, 46.4, 25.9, 18.4, 16.7, -4.2; IR (neat) 3450, 2957, 2930, 2859, 1592, 1450, 1329, 1254, 1163, 1025, 1004, 833, 780 cm^{-1}; HRMS (EI) calcd for $C_{23}H_{42}O_3Si_2$ [M^+] 422.2672, found 422.2682.

(1*S*,2*S*)-1-[3,5-Bis-(*tert*-butyldimethylsilyloxy)phenyl]-2-methyl-4-thiophenylbutan-1-ol

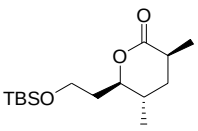


(3.22)

To a stirring solution of olefin **3.24** (220 mg, 0.52 mmol) in thiophenol (2 mL) was added AIBN (10 mg, 0.06 mmol). The resulting mixture was heated to 90 °C. An additional portion of AIBN (10 mg) was added every 2 h. The reaction mixture was stirred for 10

h, then was cooled to room temperature and diluted with diethyl ether. The resulting solution was washed successively with 5% of NaOH (5 × 3 mL) and brine (5 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (long silica gel plug, 3% of EtOAc in hexanes) to give the unreacted starting material (13 mg, 6%) and the desired product (234 mg, 90% at 94% conversion): $[\alpha]^{23}_D$ -23.3º (*c* = 1.04, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24-7.34 (m, 4H), 7.13-7.19 (m, 1H), 6.42 (d, *J* = 2.1 Hz, 2H), 6.26 (dd, *J* = 2.1, 2.1 Hz, 1H), 4.31 (d, *J* = 6.6 Hz, 1H), 2.99-3.09 (m, 1H), 2.85-2.95 (m, 1H), 1.90-2.05 (m, 2H), 1.86 (br s, 1H, OH), 1.50-1.60 (m, 1H), 0.99 (s, 18 H), 0.81 (d, *J* = 6.7 Hz, 3H), 0.20 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.7, 145.7, 137.1, 129.1, 129.0, 125.9, 111.9, 111.5, 78.7, 39.7, 32.1, 31.8, 25.9, 18.4, 16.1, -4.2; IR (neat) 2956, 2929, 2858, 1589, 1450, 1162, 831, 780 cm^{-1}; HRMS (EI) calcd for $C_{29}H_{48}O_3Si_2S$ [M^+] 532.2862, found 532.2873.

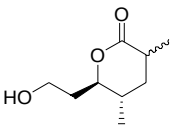
(3*S*,5*S*,6*R*)-6-[2-(*tert*-Butyldimethylsilyloxy)ethyl]-3,5-dimethyltetrahydropyran-2-one (3.34)



To a stirring solution of LDA (0.6 M in THF, 3.2 mL, 1.9 mmol) and LiCl (80 mg, 1.9 mmol, flame dried under vacuum) at –78 °C was added a solution of **3.23** (128 mg, 0.48 mmol) in THF (2 mL) dropwise. The reaction mixture was stirred at –78 °C for 30 min, warmed to –15 °C for 1 h, and was recooled to –78 °C. MeI (0.18 mL, 2.9 mmol) was added. After 10 min, saturated NH_4Cl solution (1 mL) was added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with ether. The organic layers were combined, washed with water and brine, then were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (15% diethyl ether

in hexanes) to give the desired product **3.34** (59 mg, 43%) and the unwanted isomer **3.35** (38 mg, 28%). Also, 14 mg of the starting material was isolated (11%). **3.24** (faster eluting diastereomer): $[\alpha]^{23}_{D}$ +84.7º (*c* = 0.64, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.06 (app dt, *J* = 2.2, 9.6 Hz, 1H), 3.68-3.86 (m, 2H), 2.55-2.68 (m, 1H), 1.84-1.99 (m, 2H), 1.65-1.74 (m, 2H), 1.19 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.7 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5, 80.3, 58.9, 38.7, 36.7, 35.6, 32.6, 31.7, 26.1, 18.4, 18.2, 16.5, -5.1; IR (neat) 2956, 2930, 2881, 2857, 1736, 1462, 1255, 1189, 1165, 836, 776 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{27}O_3Si$ [M-CH_3]$^+$ 271.1729, found 271.1730. **3.35** (slower eluting diastereomer): $[\alpha]^{23}_{D}$ +45.1º (*c* = 0.68, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.06 (app dt, *J* = 2.3, 9.5 Hz, 1H), 3.68-3.85 (m, 2H), 2.43-2.57 (ddq, *J* = 13.2, 6.2, 7.0 Hz, 1H), 1.88-1.98 (m, 2H), 1.68-1.75 (m, 2H), 1.27 (d, *J* = 7.1 Hz, 3H), 0.99 (d, *J* = 6.4 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 84.2, 58.8, 37.9, 37.1, 36.4, 33.9, 26.1, 18.4, 17.6, 17.4, -5.2; IR (neat) 2956, 2929, 2881, 2852, 2735, 1091, 836, 776 cm^{-1}.

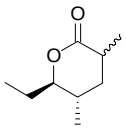
6-(2-Hydroxy-ethyl)-3,5-dimethyltetrahydropyran-2-one



To a 1:1.7 mixture of **3.34** and **3.35** (50 mg, 0.18 mmol) in THF (1 mL) was added glacial acetic acid (3 mL) and deionized water (1 mL). The reaction mixture was stirred at 35 °C overnight. The reaction mixture was concentrated under reduced pressure and the resulting residue was purified by flash chromatography (60% EtOAc in hexanes) to afford a 1:1.7 mixture of the desired products (24 mg, 0.14 mmol, 80%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.09 (m, 1H), 3.78-3.90 (m, 2H), 2.61-2.71 (m, 37% of 1H), 2.47-2.58 (m, 63% of 1H), 2.40 (br s, 1H), 1.69-2.07 (m, 5H), 1.26 (d, *J* = 7.0 Hz, 63% of 3H), 1.19 (d, *J* = 6.8

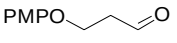
Hz, 37% of 3H), 1.01 (d, J = 6.6 Hz, 37% of 3H), 0.99 (d, J = 5.7 Hz, 63% of 3H); IR (neat) 3416, 1960, 2929, 2873, 1716, 1454, 1378, 1203, 1050 cm^{-1}.

6-Ethyl-3,5-dimethyltetrahydropyran-2-one (3.36 and 3.37)



To a stirring solution of PPh_3 (73 mg, 0.28 mmol) in THF (1 mL) at –30 °C was added DEAD (48 mg, 0.28 mmol). After 10 min, a 1:1.7 mixture of 6-(2-hydroxy-ethyl)-3,5-dimethyltetrahydropyran-2-one (24 mg, 0.14 mmol) in THF (1 mL) was added. After additional 10 min, a solution of NBSH (105 mg, 0.42 mmol) in THF (1 mL) was added to the reaction mixture. The reaction mixture was stirred at rt for 2 h, then was concentrated under reduced pressure. The resulting residue was dissolved in EtOAc (1 mL) and the resultant solution was added to hexanes (40 mL) dropwise. A precipitate formed and the resulting mixture was filtered through a Celite pad flushing with 5% EtOAc in hexanes. The filtrate was concentrated under reduced pressure and the resulting residue was purified by flash chromatography (30% EtOAc in hexanes) to afford a 1:1.7 mixture of **3.36** and **3.37**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.85-3.94 (m, 1H), 2.60-2.70 (m, 37% of 1H), 2.43-2.54 (m, 63% of 1H), 1.49-1.94 (m, 7H), 1.27 (d, J = 7.0 Hz, 63% of 3H), 1.21 (d, J = 6.8 Hz, 37% of 3H), 0.97-1.05 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.0, 88.2, 84.8, 37.8, 36.5, 35.4, 32.9, 32.7, 30.9, 26.4, 26.1, 18.1, 17.5, 16.6, 9.4, 8.9; IR (neat) 2955, 2922, 2851, 1731, 1460, 1372, 1101 cm^{-1}; HRMS (EI) calcd for $C_9H_{16}O_2$ [M^+] 156.1150, found 156.1143.

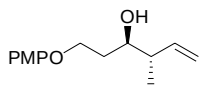
3-(4-Methoxyphenoxy)propionaldehyde (3.39)



To 1-but-3-enyloxy-4-methoxybenzene (2.0 g, 11.2 mmol) in MeOH (150 mL) at -42 ^{o}C was exposed to a stream of ozone for 30 min. Dimethyl sulfide (3 mL) was added and the

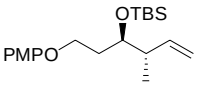
resulting mixture was allowed to warm to rt over 3 h. The reaction mixture was concentrated under reduced pressure. The resulting residue was dissolved in ether, washed with water and brine, then was dried over Na_2SO_4, filtered and concentrated. The resulting residue was then purified by flash chromatography (25% EtOAc in hexanes) to afford the desired product (1.4 g, 70%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.78 (t, *J* = 1.6 Hz, 1H), 6.81 (s, 4H), 4.18 (t, *J* = 6.0 Hz, 2H), 3.70 (s, 3H), 2.78 (dt, *J* = 1.6, 6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.5, 154.0, 152.5, 115.5, 114.6, 62.2, 55.5, 43.2; IR (neat) 2945, 2837, 1723, 1508, 1230, 1035 cm^{-1}; HRMS-EI (m/z) calcd for $C_{10}H_{12}O_3$ [M$^+$] 180.0786, found 180.0789.

(3*R*,4*S*)-1-(4-Methoxyphenoxy)-4-methylhex-5-en-3-ol (3.48)



Prepare following the procedure for **3.24**. $[\alpha]^{23}_D$ +6.9º (*c* = 1.27, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (s, 4H), 5.75-5.87 (m, 1H), 5.09-5.16 (m, 2H), 4.07-4.16 (m, 2H), 3.77 (s, 3H), 3.69-3.77 (m, 1H), 2.23 (app sextet of triplet, *J* = 6.8, 0.9 Hz, 1H), 2.19 (br, 1H, OH), 1.93 (dddd, *J* = 2.7, 5.5, 6.9, 14.3 Hz, 1H), 1.78 (dddd, *J* = 5.8, 6.3, 9.6, 15.1 Hz, 1H), 1.08 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.0, 153.0, 140.3, 116.5, 115.6, 114.8, 72.9, 66.7, 55.9, 44.4, 33.8, 16.2; IR (neat) 3452, 1509, 1231, 1029 cm^{-1}; HRMS-EI (m/z) calcd for $C_{14}H_{20}O_3$ [M$^+$] 236.1412, found 236.1414.

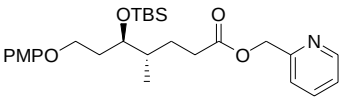
***tert*-Butyl{(1*R*,2*S*)-1-[2-(4-methoxyphenoxy)ethyl]-2-methylbut-3-enyloxy}dimethylsilane (3.40)**



To a solution of alcohol **3.48** (1.04 g, 4.4 mmol) in CH_2Cl_2 (40 mL) at 0 ^{o}C were added 2,6-lutidine (2.05 mL, 17.6 mmol) and TBSOTf (1.6 mL, 7.04 mmol). The reaction mixture was stirred at 0 ^{o}C for 2 h, then was quenched by adding 10% citric acid (10 mL). The

organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined and washed with brine, then were dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by flash chromatography (1-3% EtOAc in hexanes) to afford the desired product (1.33 g, 86%): $[\alpha]^{23}_D$ +7.5º (*c* = 0.98, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.88 (s, 4H), 5.83-5.95 (m, 1H), 5.09-5.15 (m, 2H), 3.95-4.03 (m, 3H), 3.79 (s, 3H), 2.40-2.51 (m, 1H), 1.81-1.99 (m, 2H), 1.11 (d, *J* = 6.9 Hz, 3H), 0.98 (s, 9H), 0.15 (s, 3H). 0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.9, 153.4, 140.8, 115.5, 114.9, 114.8, 72.5, 65.6, 55.9, 43.7, 32.9, 26.1, 18.3, 14.6, -4.2, -4.3; IR (neat) 1508, 1231, 1045, 830 cm^{-1}; HRMS-EI (m/z) calcd for $C_{20}H_{34}O_3Si$ [M^+] 350.2277, found 350.2273.

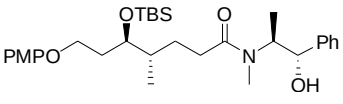
(4*S*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-7-(4-methoxyphenoxy)-4-methylheptanoic acid pyridin-2-ylmethyl ester (3.41)



To olefin **3.40** (350 mg, 1.0 mmol) in a sample vial were added $Ru_3(CO)_{12}$ (32 mg, 0.05 mmol) and 2-pyridylmethyl formate (408 mg, 3.0 mmol). The sample vial was flushed with Argon then was capped. The reaction mixture was heated to 135 ^{o}C with stirring over 30 min. After stirring at 135 ^{o}C for 12 h, the reaction mixture was cooled to rt. Additional $Ru_3(CO)_{12}$ (32 mg, 0.05 mmol) and 2-pyridylmethyl formate (408 mg, 3.0 mmol) were added. The resulting mixture was heated at 135 ^{o}C for 3 h. The reaction mixture was cooled to 0 ^{o}C, and the cap of the sample vial was removed. The reaction mixture was purified by flash chromatography (20-25% EtOAc in hexanes) to afford the desired product (388 mg, 80%): $[\alpha]^{23}_D$ +11.1º (*c* = 0.98, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (d, *J* = 4.7 Hz, 1H), 7.67 (ddd, *J* = 1.5, 7.7, 7.7 Hz, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.20 (dd, *J* = 4.9, 7.4 Hz, 1H), 6.85 (s, 4H), 5.27 (s, 2H), 3.97 (t, *J* = 6.3 Hz, 2H), 3.90-3.94 (m, 1H), 3.76 (s, 3H), 2.46-2.59 (m, 2H), 1.73-1.89

(m, 4H), 1.52-1.57 (m, 1H), 0.96 (d, J = 6.6 Hz, 3H), 0.92 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 155.8, 153.5, 153.0, 149.4, 136.6, 122.7, 121.6, 115.1, 114.5, 71.8, 66.6, 64.9, 55.5, 38.2, 32.2, 31.4, 27.7, 25.8, 18.0, 13.8, -4.5, -4.7; IR (neat) 1736, 1508, 1229, 1034cm^{-1}; HRMS-EI (m/z) calcd for $C_{27}H_{41}O_5NSi$ [M^+] 487.2754, found 487.2753.

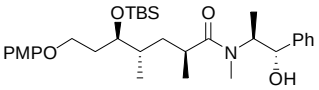
(4*R*,5*S*)-5-(*tert*-Butyldimethylsilyloxy)-7-(4-methoxyphenoxy)-4-methylheptanoic acid [(1*S*,2*S*)-(2-hydroxy-1-methyl-2-phenylethyl)]methylamide (3.42)



To a solution of (1*S*,2*S*)-pseudoephedrine (139 mg, 0.84 mmol, azeotropic removal water with toluene in vacuo before use) in THF (3 mL) at 0 °C was added NaH (60% in mineral oil, 32 mg, 0.79 mmol). The reaction mixture was stirred at 0 °C for 45 min and a solution of ester **3.42** (137 mg, 0.276 mmol) in THF (2 mL) was added. The resulting mixture was stirred at 0 °C for 40 min then was quenched with water. The organic layer was separated and the aqueous layer was extracted with ether (3x). The organic layers were combined and washed with brine, then were dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by flash chromatography (35-45% EtOAc in hexanes) to afford the desired product (125 mg, 83%, 2 rotamers in ~2.5 : 1 ratio): $[\alpha]^{23}_D$ +62.4º (c = 1.55, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24-7.36 (m, 5H), 6.83 (s, 70% of 4H), 6.80 (s, 30% of 4H), 4.60 (d, J = 7.8 Hz, 70% of 1H), 4.56 (d, J = 8.9 Hz, 30% of 1H), 4.38-4.43 (m, 1H), 3.95-4.00 (m, 2H), 3.85-3.91 (m, 1H), 3.77 (s, 70% of 3H), 3.76 (s, 30% of 3H), 2.93 (s, 30% of 3H), 2.81 (70% of 3H), 2.34-2.48 (m, 1H), 2.22-2.29 (m, 1H), 1.81-1.89 (m, 2H), 1.63-1.77 (m, 2H), 1.39-1.49 (m, 1H), 1.13 (d, J = 7.0 Hz, 70% of 3H), 0.99 (d, J = 7.0 Hz, 30% of 3H), 0.94 (d, J = 6.5 Hz, 30% of 3H), 0.92 (d, J = 6.5 Hz, 70% of 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, peaks shown in parentheses belong to the minor

rotamor) δ 175.7 (174.4), 153.8, 153.4, 142.7 (141.4), 128.6 (129.0), 127.8, 126.5 (127.1), 115.4, 114.8, 75.8, 72.3, 65.4, 59.3, 55.9 (58.6), 38.7, 32.7 (33.4), 31.6 (32.0), 28.1 (28.4), 27.0, 26.1, 18.3, 14.7 (15.6), 14.1; -4.2, -4.4; IR (neat) 2955, 2930, 1621, 1508, 1231, 1039 cm^{-1}; HRMS-EI (m/z) calcd for $C_{31}H_{49}NO_5Si$ [M^+] 543.3380, found 543.3361.

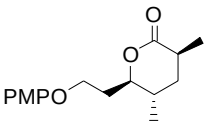
(2*S*,4*R*,5*S*)-5-(*tert*-Butyldimethylsilyloxy)-7-(4-methoxyphenoxy)-2,4-dimethylheptanoic acid [(1*S*,2*S*)-2-hydroxy-1-methyl-2-phenylethyl)]methylamide (3.43)



To a mixture of LiCl (120 mg, 2.8 mmol, flame dried under vacuum) and LDA (0.5 M in THF, 3.8 mL, 1.9 mmol) at -78 °C was added an ice-cooled solution of amide **3.42** (256 mg, 0.47 mmol) in THF (2 mL). The reaction mixture was stirred at -78 °C for 1 h, warmed to 0 °C for 10 min, then was cooled to -78 °C. MeI (0.18 mL, 2.8 mmol) was added dropwise. The resulting mixture was stirred at -78 °C for 10 min, 0 °C for 10 min then was quenched with saturated NH_4Cl solution (2 mL). The organic layer was separated and the aqueous layer was extracted with ether (3x). The organic layers were combined and washed with brine, then were dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by flash chromatography (35-50% EtOAc in hexanes) to afford the desired product (238 mg, 91%, 2 rotamers in ~2.5 : 1 ratio): $[\alpha]^{23}_D$ +63.4º (*c* = 1.03, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23-7.40 (m, 5H), 6.82 (br, 70% of 4H), 6.72 (m, 30% of 4H), 4.66 (d, *J* = 7.1 Hz, 70% of 1H), 4.58 (d, *J* = 8.8 Hz, 30% of 1H), 4.22 (app pentet, *J* = 6.9 Hz, 70% of 1H), 4.04 (app pentet, *J* = 7.9 Hz, 30% of 1H), 3.90-3.98 (m, 2H), 3.79 (ddd, *J* = 3.8, 3.8, 7.7 Hz, 1H), 3.77 (s, 70% of 3H), 3.76 (s, 30% of 3H), 2.94 (s, 30% of 3H), 2.81 (s, 70% of 3H), 2.57 (app sextet, *J* = 6.8 Hz, 1H), 1.69-1.90 (m, 3H), 1.37-1.49 (m, 2H), 1.22 (d, *J* = 7.1 Hz, 70% of 3H), 1.16 (d, *J* = 6.6 Hz, 30% of 3H), 1.01 (d, *J* = 6.6 Hz, 30% of 3H), 0.98 (d, *J* = 6.6 Hz, 70% of

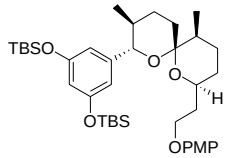
3H), 0.91 (d, J = 8.0 Hz, 30% of 3H), 0.88 (d, J = 8.0 Hz, 70% of 3H), 0.88 (s, 70% of 9H), 0.85 (s, 30% of 9H), 0.04 (s, 70% of 3H), 0.01 (s, 30% of 3H), -0.01 (s, 70% of 3H), -0.04 (s, 30% of 3H); ^{13}C NMR (75 MHz, $CDCl_3$, peaks shown in parentheses belong to the minor rotamer) δ 179.2 (178.0), 153.9, 153.4, 142.9 (141.4), 129.0, 128.7, 128.5, 127.7, 127.1, 126.4, 115.5, 114.9, 77.4 (75.8), 72.8, 65.5 (60.7), 56.0 (58.2), 36.8 (37.2), 36.6 (36.2), 34.6 (33.6), 31.7 (31.9), 26.1, 18.3, 17.1, 14.7, 14.1 (14.2), -4.1, -4.4; IR (neat) 2955, 2931, 1621, 1508, 1471, 1231, 1043 cm^{-1}; HRMS-EI (m/z) calcd for $C_{32}H_{51}NO_5Si$ [M^+] 557.3536, found 557.3555.

(3*S*,5*S*,6*R*)-6-[2-(4-Methoxyphenoxy)ethyl]-3,5-dimethyltetrahydropyran-2-one (3.21)



To a solution of amide **3.43** (185 mg, 0.33 mmol) in CH_2Cl_2 (5 mL) was added TBAF (226 mg, 0.86 mmol). The reaction mixture was stirred at rt for 24 h and *para*-toluenesulfonic acid (PTSA) was added until the PH of the reaction mixture was ~1. The resulting mixture was stirred at rt for additional 24 h then was concentrated under reduced pressure. The resulting residue was purified by flash chromatography (20% EtOAc in hexanes) to afford the desired product (73 mg, 79%): $[\alpha]^{23}_D$ +104.7º (c = 0.75, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81 (s, 4H), 4.03-4.21 (m, 3H), 3.75 (s, 3H), 2.60-2.68 (m, 1H), 2.16-2.24 (m, 1H), 1,88-1.95 (m, 2H), 1.64-1.74 (m, 2H), 1.19 (d, J = 6.8 Hz, 3H), 1.03 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.2, 153.9, 152.9, 115.5, 114.6, 80.0, 64.1, 55.7, 35.2, 33.2, 32.5, 31.7, 17.9, 16.2; IR (neat) 2934, 1743, 1508, 1232 cm^{-1}; HRMS-EI (m/z) calcd for $C_{16}H_{22}O_4$ [M^+] 278.1518, found 278.1520.

(2*R*,3*S*,5*S*,6*R*,8*S*,9*S*)-8-[3,5-Bis(*tert*-butyldimethylsilyloxy)phenyl]-2-[2-(4-methoxyphenoxy)ethyl]-3,5,9-trimethyl-1,7-dioxaspiro[5.5]undecane (3.46)



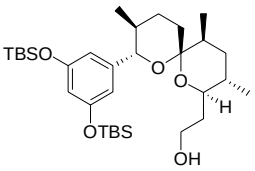
Procedure to make LDBB:

To a solution of 4,4'-di-*tert*-butylbiphenyl (DBB) (585 mg, 2.19 mmol) in THF (6 mL) under argon atmosphere was added lithium (15 mg, 2.19 mmol, cut into 3 pieces with surface oxide removed with a razor blade). The reaction mixture was sonicated at rt for 5 min, and then stirred at 5 °C for 12 h.

To sulfide **3.22** (450 mg, 0.84 mmol) in THF (5 mL) at -78 °C was added *n*-BuLi (1.6 M in hexanes, 0.53 mL, 0.85 mmol) dropwise. After 10 min, the reaction mixture was cannulated into a stirring solution of LDBB at -78 °C. The color of the solution changed from dark green to light brown. Additional LDBB was slowly cannulated into the reaction mixture until the color of the reaction just changed to light green, indicating the full reduction of sulfide **3.22**. The resulting mixture was stirred for 45 min at -78 °C then a solution of $MgBr_2$ [1.26 mmol, made by stirring Mg (35 mg, 1.46 mmol) and 1,2-dibromoethane (238 mg, 1.26 mmol) in 3 mL of ether at room temperature for 2 h] was added *via* cannula. The reaction turned to yellowish brown. The reaction mixture was stirred at -78 °C for 20 min, warmed to -42 °C for 10 min, and recooled to -78 °C. To this stirring solution was cannulated lactone **3.21** (125 mg, 0.449 mmol) in THF (1 mL). The resulting mixture was stirred at -78 °C for 15 min and allowed to warm to 0 °C over 15 min. After additiona 5 min, to the reaction mixture were added saturated NH_4Cl solution (1 mL) and HCl (3 M, 4 mL). The resulting mixture was stirred at room temperature for 1 h. The organic layer was separated and the aqueous layer was extracted with ether (3x). The organic layers were combined and washed with brine, then were dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by flash chromatography (1-3% EtOAc in hexanes) to afford the

desired product as a liquid (171 mg, 56%): $[\alpha]^{23}_D$ -25.0º (*c* = 1.70, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 6.82-6.96 (m, 4H), 6.42 (d, *J* = 2.2 Hz, 2H), 6..25 (t, *J* = 2.2 Hz, 1H), 4.29 (ddd, *J* = 4.9, 9.0, 9.0 Hz, 1H), 4.00 (ddd, *J* = 3.8, 5.8, 9.6 Hz, 1H), 3.91 (d, *J* = 9.3 Hz, 1H), 3.78 (s, 3H), 3.45 (ddd, *J* = 2.2, 10.4, 10.4 Hz, 1H), 2.18-2.24 (m, 1H), 1.70-1.85 (m, 4H), 1.44-1.60 (m, 4H), 1.19-1.24 (m, 2H), 1.00 (d, *J* = 7.1 Hz, 3H), 0.97 (s, 18H), 0.79 (d, *J* = 6.6 Hz, 3H), 0.43 (d, *J* = 5.8 Hz, 3H), 0.18 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2, 153.9, 153.6, 144.1, 115.6, 115.0, 113.4, 111.3, 98.2, 78.5, 71.2, 65.0, 55.9, 36.5, 35.9, 35.6, 33.3, 29.8, 28.7, 26.0, 18.5, 17.8, 15.4, -4.1; IR (neat) 2955, 2928, 2858, 1590, 1508, 1451, 1231, 1157, 1027, 832 cm^{-1}; HRMS-EI (m/z) calcd for $C_{39}H_{64}O_6Si_2$ [M^+] 684.4241, found 684.4251.

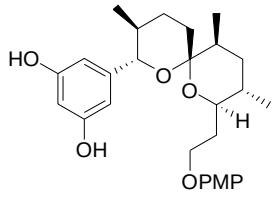
2-{(2*R*,3*S*,5*S*,6*R*,8*S*,9*S*)-8-[3,5-Bis(*tert*-butyldimethylsilyloxy)phenyl]-3,5,9-trimethyl-1,7-dioxaspiro[5.5]undec-2-yl}ethanol (3.5)



To spiroketal **3.46** (35 mg, 0.051 mmol) in CH_3CN (5 mL) at 0 °C was added a solution of CAN (140 mg, 0.255 mmol) in H_2O (1 mL) dropwise. After 7 min, the reaction mixture was diluted with CH_2Cl_2. The resulting solution was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (8% EtOAc in hexanes) to give the desired product (23.4 mg, 79%): $[\alpha]^{23}_D$ +14.5º (*c* = 0.51, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 6.45 (d, *J* = 2.2 Hz, 2H), 6.28 (t, *J* = 2.2 Hz, 1H), 3.96 (d, *J* = 9.3 Hz, 1H), 3.89 (br, 2H), 3.42 (ddd, *J* = 2.7, 9.5, 9.5 Hz, 1H), 3.20 (br, 1H, OH), 1.44-1.95 (m, 9H), 1.18-1.26 (m, 2H), 1.01 (d, *J* = 7.1 Hz, 3H), 0.98 (s, 18H), 0.71 (d, *J* = 6.6 Hz, 3H), 0.67 (d, *J* = 6.0 Hz, 3H), 0.19 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.24, 143.6, 113.2, 111.6, 98.7, 78.8, 77.0, 62.4, 36.5, 36.0, 35.0, 24.8, 32.9, 29.1, 28.8, 25.9, 18.5, 17.9, 17.8, 15.2, -4.2; IR (neat) 2960, 2929,

2858, 1588, 1449, 1152, 1024, 830 cm^{-1}; HRMS-EI (m/z) calcd for $C_{32}H_{58}O_5Si_2$ [M^+] 578.3823, found 578.3803.

5-{(2S,3S,6R,8R,9S,11S)-8-[2-(4-Methoxyphenoxy)ethyl]-3,9,11-trimethyl-1,7-dioxaspiro[5.5]undec-2-yl}benzene-1,3-diol (3.47)



To spiroketal **3.46** (30 mg, 0.044 mmol) in THF (3 mL) at room temperature was added TBAF (46 mg, 0.176 mmol). The reaction mixture was stirred for 1 h and then concentrated under reduced pressure. The resulting residue was purified by flash chromatography (35% EtOAc in hexanes) to afford the desired product as a solid (13.2 mg, 66%): $[\alpha]^{23}_D$ -28.2º (*c* = 0.73, acetone); ^{1}H NMR (500 MHz, acetone) δ 8.04 (br, 2H, OH), 6.95-6.97 (m, 2H), 6.85-6.88 (m, 2H), 6.32 (d, *J* = 2.3 Hz, 2H), 6.26 (t, *J* = 2.3 Hz, 1H), 4.32 (app dt, *J* = 4.6, 9.2 Hz, 1H), 4.03 (ddd, *J* = 3.7, 6.0, 9.2 Hz, 1H), 3.94 (d, *J* = 9.6 Hz, 1H), 3.71 (s, 3H), 3.47 (app dt, *J* = 2.3, 10.1 Hz, 1H), 2.18-2.22 (m, 1H), 1.74-1.82 (m, 2H), 1.63-1.70 (m, 2H), 1.49-1.57 (m, 4H), 1.38-1.44 (m, 1H), 1.21 (ddd, *J* = 2.3, 3.7, 12.8 Hz, 1H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.74 (d, *J* = 6.4 Hz, 3H), 0.41 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (125 MHz, acetone) δ 158.8, 154.6, 154.1, 145.1, 116.0, 115.4, 107.3, 102.5, 98.5, 79.0, 71.4, 64.9, 55.8, 37.0, 36.3, 36.1, 33.8, 33.7, 29.0, 18.0, 15.4; IR (neat) 3457, 3293, 2919, 1598, 1510, 1229, 1152 cm^{-1}; HRMS-EI (m/z) calcd for $C_{27}H_{36}O_6$ [M^+] 456.2512, found 456.2513.

References in experimental of Chapter 3

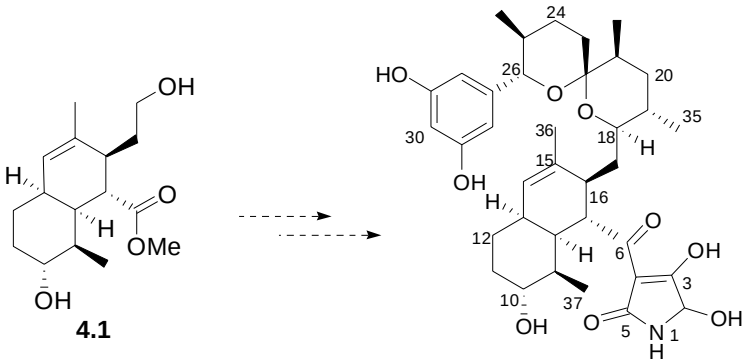
(1) Stewart, G. M.; Fox, M. A. *J. Am. Chem. Soc.* **1996**, *118*, 4354-4360.

(2) Lupton, J. M.; Hemingway, L. R.; Samuel, I. D. W.; Burn, P. L. *J. Mater. Chem.* **2000**, *10*, 867-871.

(3) Orsini, F.; Pelizzoni, F.; Bellini, B.; Miglierini, G. *Carbohydr. Res.* **1997**, *301*, 95-109.

Chapter 4. Study towards the synthesis of the *cis*-decalin unit of integramycin

4.1 Introduction

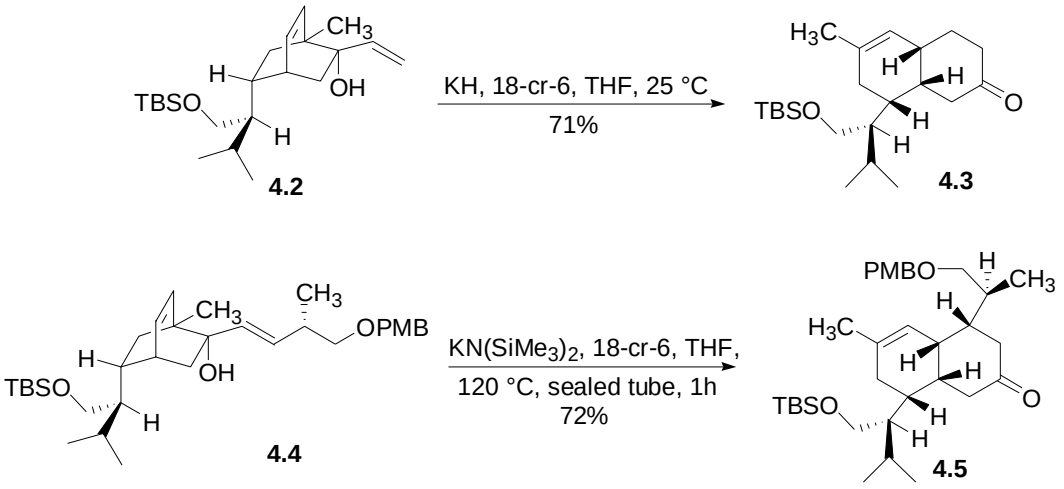


As discussed in Chapter 3, the synthesis of integramycin was reduced into three subtarget molecules, one of which is the *cis*-decalin unit of integramycin (**4.1**). Molecule **4.1** has two hydroxyl groups, one double bond, and one ester in a *cis*-decalin. The primary hydroxyl and the ester groups of **4.1** will allow the connection with other fragments of integramycin. The major challenge of this synthesis lies in the establishment of the *cis*-decalin structure. Because of their slightly higher conformational energy than *trans*-decalins, *cis*-decalins are more difficult to access. There are two common ways to synthesize *cis*-decalins in literature, using either an oxy-Cope rearrangement or a Diels-Alder reaction:

4.1.1 Oxy-Cope rearrangements in the synthesis of cis-decalins

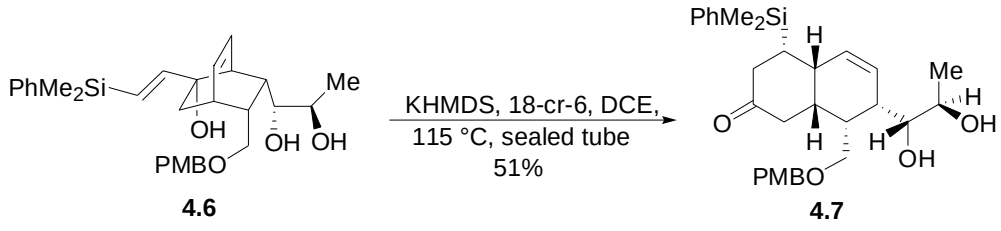
The oxy-Cope rearrangement, particularly its anionic variant, is one of the most widely used protocols to synthesize *cis*-decalins. Anionic oxy-Cope rearrangements were found to be significantly faster than neutral oxy-Cope rearrangements (up to 10^{10}-10^{17} times).[1] In Paquette's

study towards the total synthesis of vinigrol, 1,5-diene **4.2** underwent facile anionic oxy-Cope rearrangement at 25 °C, providing *cis*-decalin **4.3** in a 71% yield. However, analog **4.4** did not react until being heated to 120 °C in a sealed tube, affording *cis*-decalin **4.5** in a 72% yield (Scheme 4.1).[2]



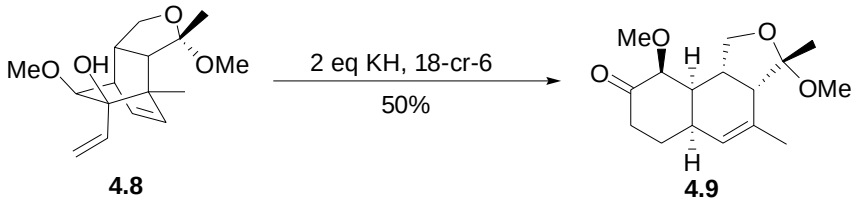
Scheme 4.1. Anionic oxy-Cope rearrangement in Paquette's synthesis towards vinigrol.

In Jin and co-workers' asymmetric synthesis of the core of superstolides, compound **4.6** was treated with KHMDS at 115 °C in a sealed tube in the presence of 18-crown-6, providing a *cis*-decalin (**4.7**) in 51% yield (Scheme 4.2).[3]



Scheme 4.2. Jin's preparation of *cis*-decalin **4.7** using an oxy-Cope rearrangement.

An oxy-Cope rearrangement was employed by Banwell and co-workers in their synthesis of the core of phomopsidin. Compound **4.8**, synthesized from *cis*-1,2-dihydrocatechol, was subjected to KH to initiate an anionic oxy-Cope rearrangement. The reaction provided the desired *cis*-decalin **4.9** in a 50% yield (Scheme 4.3).[4]



4.8 **4.9**

Scheme 4.3. Anionic oxy-Cope rearrangement used in the synthesis of phomopsidin.

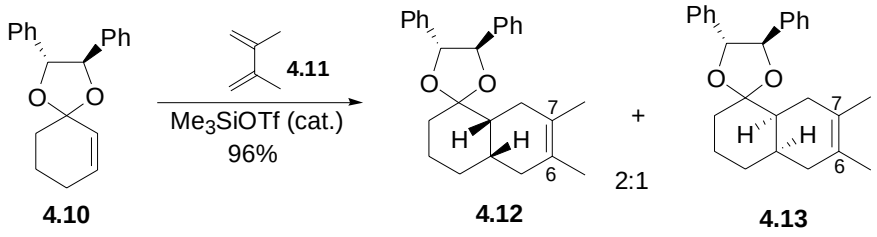
Anionic oxy-Cope rearrangements have many advantages. The stereochemical outcome is predictable based on the structure of the starting material, especially for cyclic starting materials.[5] The stereoselectivity is often adjustable and dependent on solvent, temperate, and the counterion metals.[2] Anionic oxy-Cope rearrangements also have drawbacks. Sometimes harsh conditions such as high temperature are needed to initiate the reactions, which means less functional group tolerance. The yields of the rearrangements can be low and are often in the range of 50-70%. Also, the stereoselectivity of the vinylation or allylation step in preparing the starting materials may be low.

4.1.2 Diels-Alder reactions in the synthesis of cis-decalins

The Diels-Alder reaction is one of the most powerful reactions in syntheses. It has the capability of establishing multiple new stereocenters and bonds in one manipulation. The transition state of a Diels-Alder reaction is often predicable which facilitates the design and

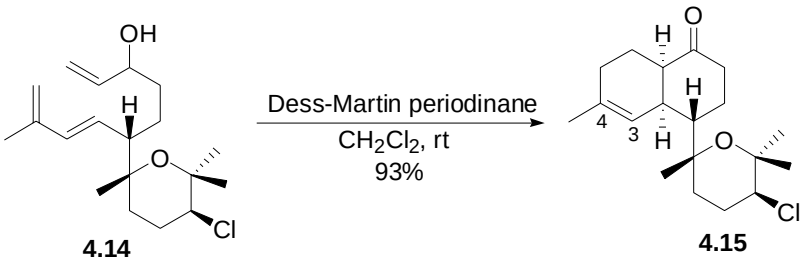
obtaining the desired product and stereochemistry. Numerous elegant total syntheses have been reported using Diels-Alder reactions as the key steps.[6] Furthermore, many asymmetric catalysts have been developed to provide enantioselective Diels-Alder reactions from achiral starting materials.[6]

Diels-Alder reactions are also used in the synthesis of *cis*-decalins. For example, compound **4.10**, which was synthesized from cyclohexenone and (1*R*,2*R*)-1,2-diphenylethane-1,2-diol, underwent an ionic Diels-Alder reaction with 2,3-dimethyl-1,3-butadiene (**4.11**) and afforded a mixture of *cis*-decalins in 2:1 ratio (Scheme 4.4).[7] Using this strategy by Anderson *et al.*, diastereoselectivity of up to 83% has been obtained.



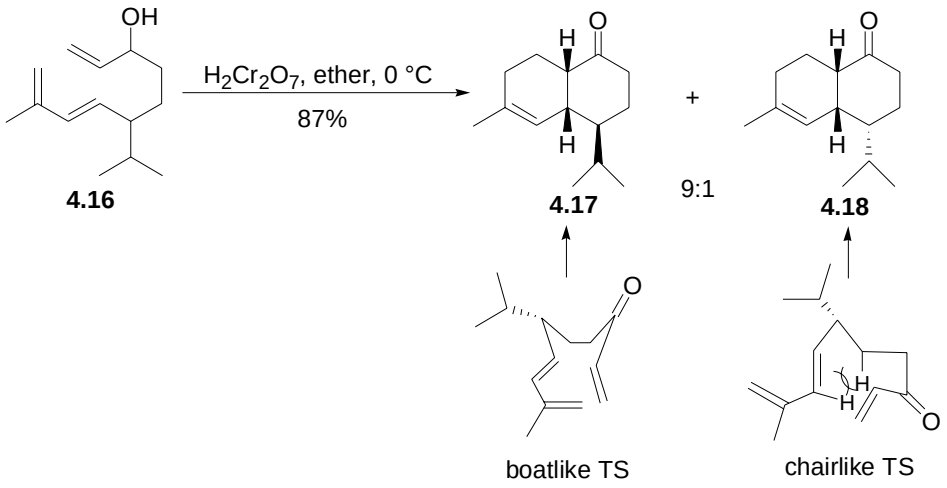
Scheme 4.4. Intermolecular Diels-Alder reactions in the synthesis of *cis*-decalins.

Intramolecular Diels-Alder reactions are arguably the most widely employed protocols to prepare *cis*-decalins. While an intermolecular Diels-Alder reaction furnishes *cis*-decalins with double bonds at the 6,7-position (Scheme 4.4), an intramolecular Diels-Alder reaction (IMDA) commonly leaves double bonds at the 3,4-position (Scheme 4.5). In Yamada's total synthesis of kalihinene X, triene alcohol **4.14** was oxidized with Dess-Martin periodinane in CH_2Cl_2 at room temperature, and the resulting trienone underwent spontaneous intramolecular Diels-Alder reaction to give *cis*-decalin **4.15** as a single diastereomer in 93% yield (Scheme 4.5).[8]



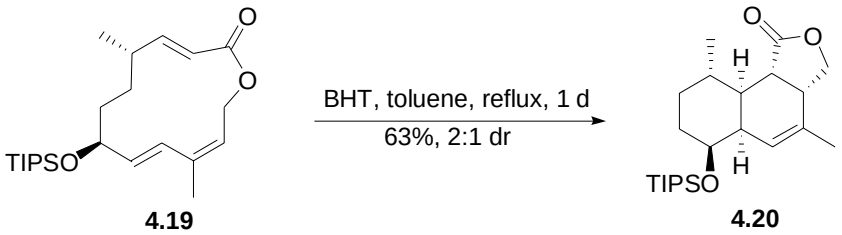
Scheme 4.5. Yamada's synthesis of kalihinene X using an IMDA.

A similar reaction had been reported by Taber and Gunn in their synthesis of (±)-torreyol. Triene alcohol **4.16**, upon treatment with $H_2Cr_2O_7$ in ether at 0 °C, underwent oxidation followed by spontaneous IMDA to afford *cis*-decalins **4.17** and **4.18** in a 9:1 ratio (Scheme 4.6).[9] The reaction was explained to take a boatlike *endo* transition state with the large isopropyl group *syn* to the angular hydrogens. The chairlike transition state was proposed to have higher energy because of a severe nonbonding interaction (Scheme 4.6).



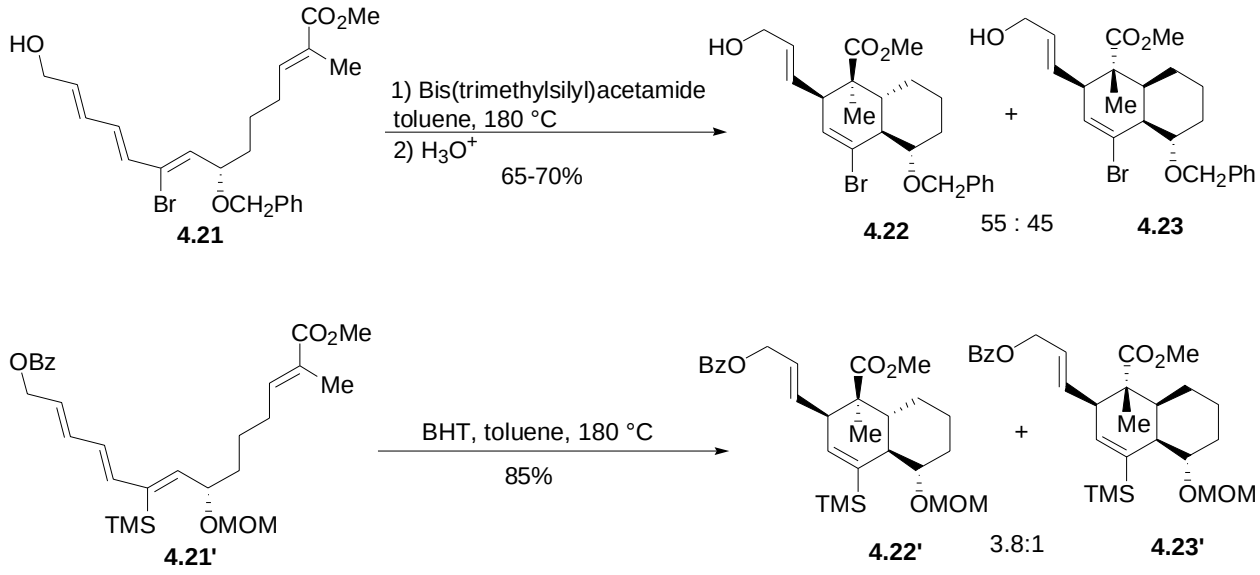
Scheme 4.6. Taber's synthesis of torreyol using an IMDA.

In Nakada's total synthesis of phomopsidin, a cyclic triene **4.19** was heated in refluxing toluene for one day and furnished a 2:1 mixture of diastereomers with the *cis*-decalin **4.20** as the major product (Scheme 4.7).[10]



Scheme 4.7. An IMDA of a cyclic triene **4.19**.

Depending on the substituents on the triene, IMDA's more often give a mixture of *trans*- and *cis*-decalins in complex systems. In Roush's synthesis of chlorothricolide, triene **4.21** was treated with bis(trimethylsilyl)acetamide (BSA) and the resulting TMS ether underwent an IMDA followed by silyl ether removal under acidic conditions. A mixture of *trans*-decalin **4.22** and *cis*-decalin **4.23** was generated in about 1:1 ratio (Scheme 4.8).[11] After modifying the substituents on the substrate, triene **4.21'** was found to furnish the *trans*-decalin **4.22'** as the major product.

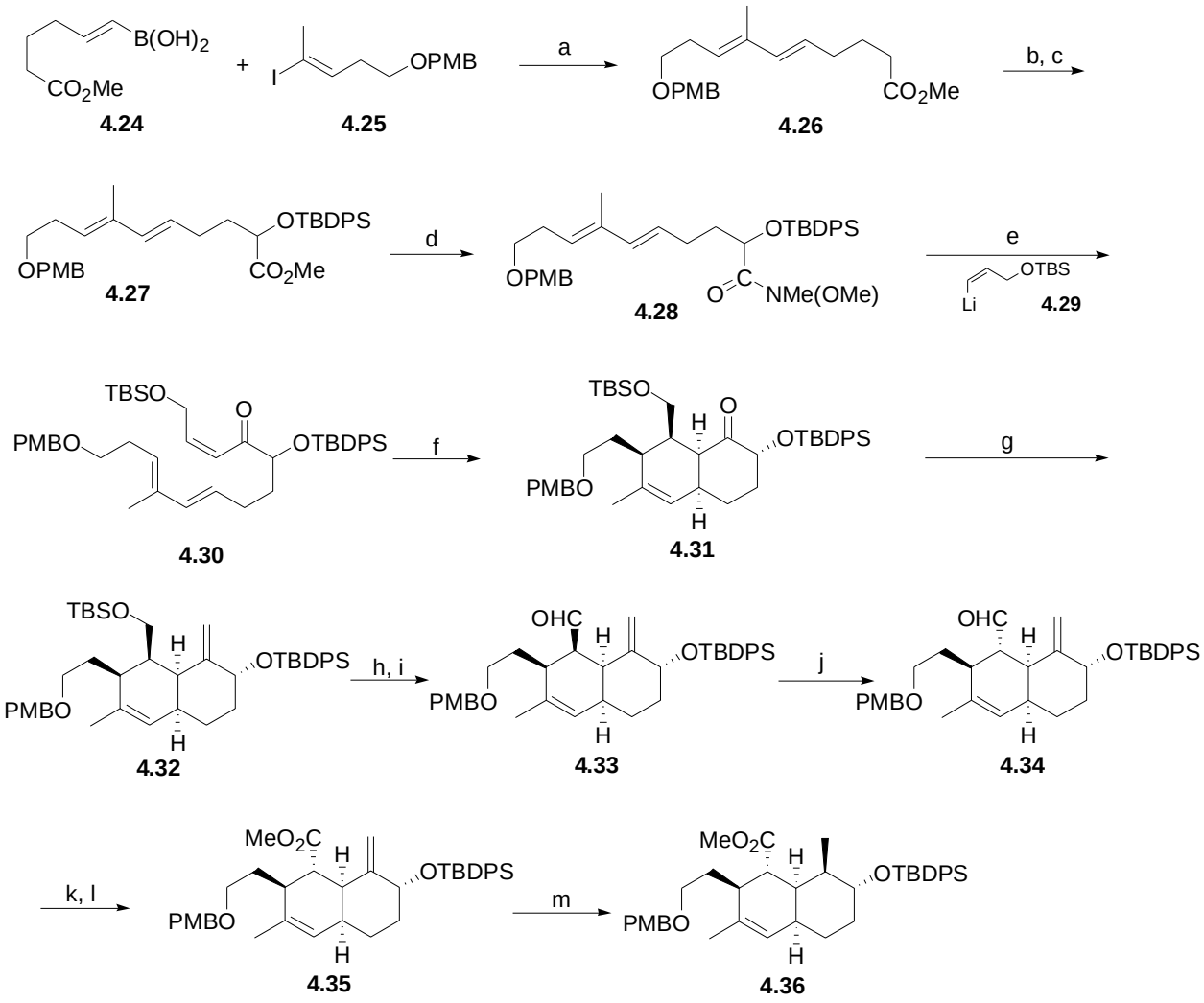


Scheme 4.8. IMDA's providing a mixture of *trans*- and *cis*-decalins.

Diels-Alder reactions have the advantage of providing quick access to multiple new stereocenters. However, they also have the disadvantage of often providing a mixture of diastereomers for complex systems. An individual application has to be considered base on its own properties to decide whether to use a Diels-Alder reaction or an oxy-Cope rearrangement in the synthesis of *cis*-decalins.

4.1.3 Roush's racemic synthesis of the cis-decalin unit of integramycin

When our study towards the synthesis of **4.1** was in progress, Roush reported a racemic synthesis of the *cis*-decalin unit of integramycin using an IMDA as the key step (Scheme 4.9).[12] The synthesis started with a Suzuki coupling of vinylboronic acid **4.24** and vinyl iodide **4.25**, which provided a diene **4.26** in a 60% yield. Installation of a hydroxyl group onto **4.26** with Davis' oxaziridine followed by a silyl protection afforded diene ester **4.27**. Ester **4.27** was then converted into a Weinreb amide **4.28**. Addition of vinyl lithium **4.29** onto **4.28** furnished triene **4.30** in 84% yield. Triene **4.30** underwent facile IMDA when treated with 0.6 eq of $MeAlCl_2$ in CH_2Cl_2 at -78 °C, providing the desired product **4.31** in an excellent 92% yield with >95:5 dr.



a) $Pd(PPh_3)_4$, Tl_2CO_3, THF-H_2O (3/1), 23 °C, 60%. b) KHMDS, THF; Davis' oxaziridine, 73%. c) TBDPSCl, imi, DMF, DMAP, ~90%. d) *i*-PrMgCl, Me(OMe)NH·HCl, THF, -20 °C, 83%. e) **4.29**, THF, -90 °C, 84%. f) $MeAlCl_2$ (0.6 eq), CH_2Cl_2, -78 °C, 15 min, 92%, >95:5 dr. g) Tebbe reagent, THF-toluene (1/1), -40 °C to 23 °C, 69%. h) HCl/MeOH. i) Dess-martin periodinane, 89% over 2 steps. j) K_2CO_3, MeOH/THF, 15 h, 100%. k) $NaClO_2$, NaH_2PO_4. l) TMS-CHN_2, 85% over 2 steps. m) NBSH, Et_3N, CH_2Cl_2, 23 °C, 68% (and 10% recovered **4.35**).

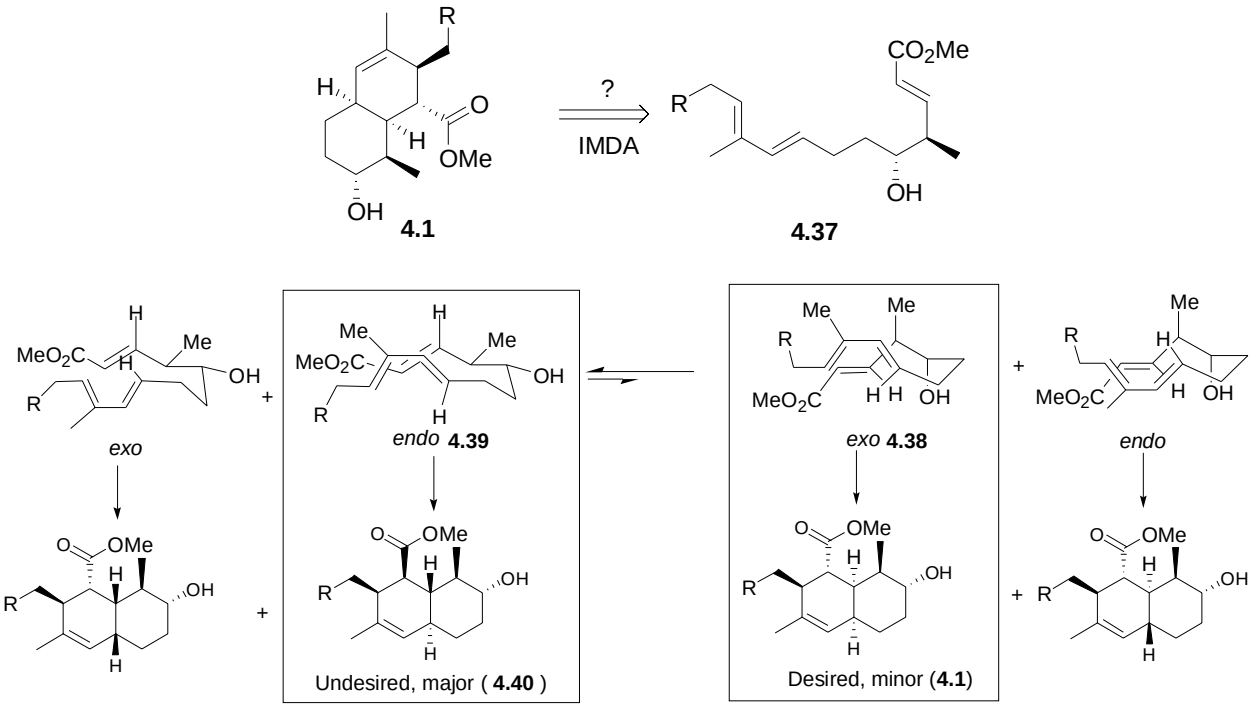
Scheme 4.9. Roush's racemic synthesis of the *cis*-decalin unit of integramycin.

To complete the synthesis, *cis*-decalin **4.31** was treated with Tebbe reagent to furnish olefin **4.32** in a 69% yield. The TBS ether of **4.32** was removed under acidic conditions, and the resulting alcohol was oxidized to an aldehyde which has an incorrect stereocenter at the α-carbon (**4.33**). The α-carbon stereocenter was then epimerized under basic conditions to afford the

desired stereochemical configuration. The resulting aldehyde **4.34** was converted to methyl ester **4.35** over two steps in 85% yield. Finally, the *exo*-cyclic olefin of **4.35** was reduced to a methyl group and gave the *cis*-decalin unit of integramycin **4.36** to complete the synthesis. Roush's sequence took 13 linear steps and provided ~9% overall yield. This is the only integramycin related synthesis reported to date other than our published synthesis of the C16-C35 fragment of integramycin as introduced in Chapter 3.

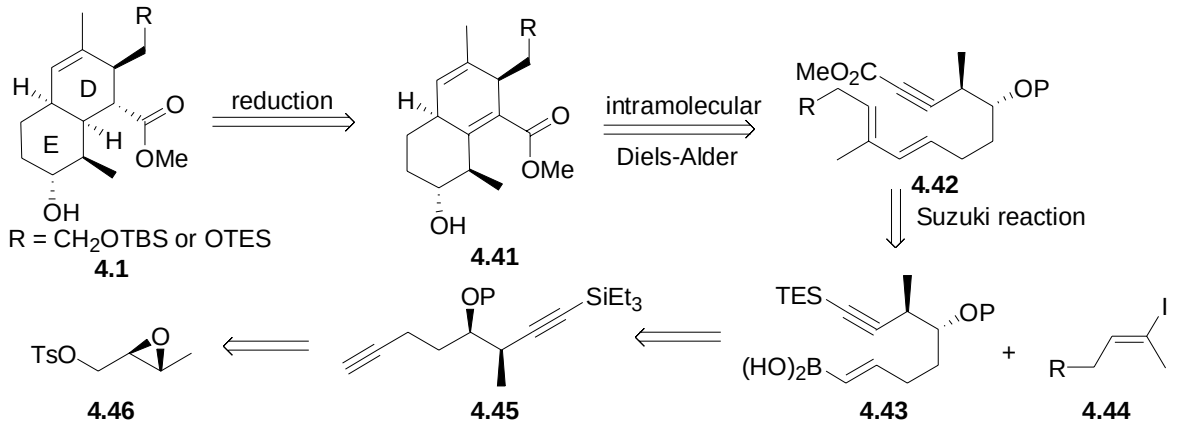
4.1.4 Retrosynthetic analysis

As summarized above, both oxy-Cope rearrangements and IMDA's are viable choices to synthesize the *cis*-decalin unit of integramycin, and an IMDA seems to be a relatively easier approach. Oikawa and Tokiwano proposed that the *cis*-decalin of **4.1** is an *exo*-adduct of an IMDA.[13] However, a close examination revealed that this reaction is unlikely to produce the *cis*-decalin product (Scheme 4.10). To yield the *cis*-decalin **4.1** with the correct stereocenters, a triene (**4.37**) needs to take an *exo* transition state and has the methyl and hydroxyl groups sit in pseudoaxial positions, which would be an unfavorable transition state (**4.38**). The *endo* transition state (**4.39**) with the two substituents sit in the pseudoequatorial positions will be more favorable, but it will afford the undesired *trans*-decalin **4.40**. Therefore, it is unlikely to obtain **4.1** from triene **4.37**. Unsuccessful attempts with *trans*-decalin as the major product can be found in Roush's report.[12]



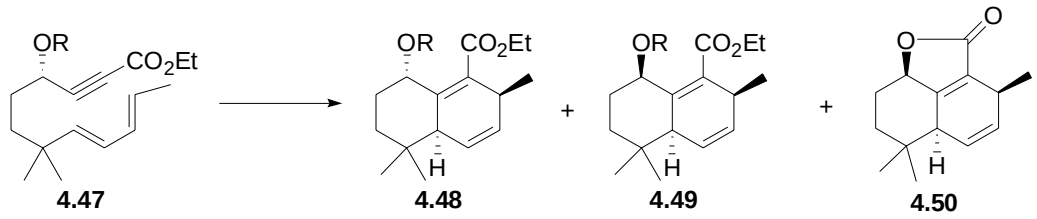
Scheme 4.10. Predicted stereochemical outcomes of an IMDA of triene **4.37**.

As an alternative, we anticipated that *cis*-decalin **4.1** could be generated through a reduction of *α,β*-unsaturated ester **4.41**, which is an IMDA product of dienyne **4.42** (Scheme 4.11). Because of the free hydroxyl group, it was expected that a reduction of **4.41** would have a formal hydride delivered from the hydroxyl side to afford a *cis*-decalin.[14] Many *α,β*-unsaturated ester reducing reagents that can chelate to a hydroxyl group are available, such as CuH[15] and Crabtree's catalyst[16] in the presence of H_2. Dissolving metals and SmI_2[17] are additional available choices. Moreover, in reductions using dissolving metals, changing metal species, solvents, and temperature was reported to affect the *trans*- and *cis*-decalin product ratios.[18]



Scheme 4.11. Retrosynthetic analysis of the *cis*-decalin unit of integramycin.

α,β-Unsaturated ester **4.41** can be prepared using an intramolecular Diels-Alder reaction of dienyne **4.42** (Scheme 4.11). Many methods have been established to cyclize a dienyne into a diene, including IMDA's under thermal conditions or catalyzed by Lewis acids[6] and cycloadditions using transition metal catalysts.[19] For example, Trost found that the IMDA of dienyne **4.47** provided a mixture of products with various ratios depending on the protecting group on the alcohol and the reaction conditions (Scheme 4.12).[20] IMDA of **4.47** with R = TMS under thermal conditions provided **4.48** as the only product (entry 1), while the same substrate solely afforded **4.50** under Lewis acid catalyzed conditions (entry 2). When R = TBDMS, $EtAlCl_2$ (1.1 eq) catalyzed IMDA furnished **4.49** as the only product (entry 3). When R = MOM, a mixture of products was obtained with ratios dependant on the reaction temperature (entries 4&5).



entry	R	Lewis acid	T	product	yield
1	TMS	-	170 °C	only **4.48**	75%
2	TMS	1.1 eq of $EtAlCl_2$	25 °C	only **4.50**	30%
3	TBDMS	1.1 eq of Et_2AlCl	25 °C	only **4.49**	80%
4	MOM	2 eq of Et_2AlCl	25 °C	4:1:0	50%
5	MOM	2 eq of Et_2AlCl	0 °C	6:1:0	50%

Scheme 4.12. Trost's IMDA of triene **4.47**.

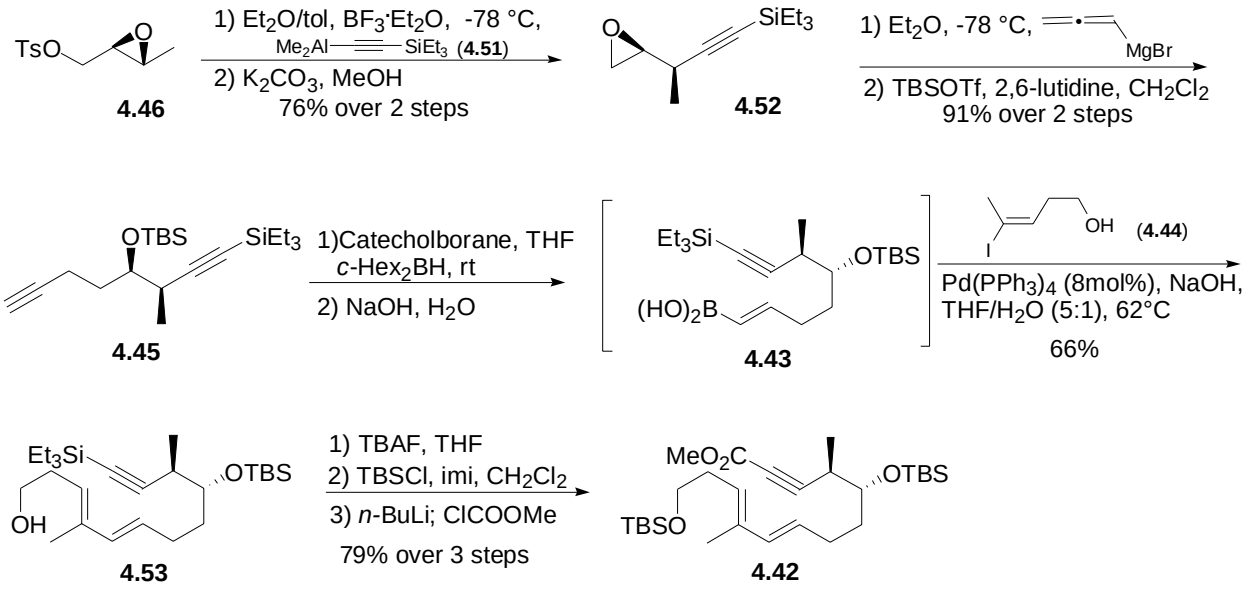
The dienyne **4.42** can be generated from a Suzuki coupling reaction of alkenylboronic acid **4.43** and vinyl iodide **4.44** (Scheme 4.11). Alkenylboronic acid **4.43** could be obtained *via* a sequence using a Sharpless asymmetric epoxidation as the key step. Iodide **4.44** is a known compound and can be synthesized using several protocols.[21]

4.2 Results

4.2.1 The synthesis of dienyne 4.42

The synthesis of dienyne **4.42** started from known compound **4.46** which was prepared from a Sharpless epoxidation[22] of *trans*-butenol followed by an in situ derivatization with TsCl in 71% yield and 98% ee (Scheme 4.13). The epoxide **4.46** was opened with acetylide **4.51** in the presence of $BF_3{\cdot}Et_2O$[23] and the resulting product was treated with K_2CO_3 in methanol to furnish epoxide **4.52**. Epoxide **4.52** was opened again with allenylmagnesium bromide[24] and the resulting alcohol was protected with a TBS ether to afford dialkyne **4.45**.

Dialkyne **4.45** was subjected to hydroboration conditions with catecholborane and a catalytic amount of dicyclohexylborane[25] followed by basic workup to give alkenylboronic acid **4.43**. Suzuki coupling of **4.43** with iodide **4.44** was not as straightforward as expected and required extensive optimization. Initially, alkenylboronic acid **4.43** was isolated and then subjected to Suzuki coupling conditions following literature procedures.[24,26] The reaction provided low yield especially on scales larger than 1 mmol. After extensive investigation, a one-pot protocol modified from Soderquist's procedure[27] was adopted. After the hydroboration of dialkyne **4.45** was completed, aqueous NaOH was added to the reaction mixture, followed by a mixture of palladium catalyst and iodide **4.44** in THF. Upon heating, the desired Suzuki coupling occurred and went to completion within 20 min at 62 °C, providing dienyne **4.53** in 60-70% yield (one-pot, two steps). Up to 6 mmol scale reactions were conducted without losing efficiency. Deoxygenating the solvents was found to be important for high yields.



Scheme 4.13. The synthesis of dienyne **4.42**.

The TES group on alkyne **4.53** has executed its masking role and needed to be removed. Treatment of **4.53** with a slight excess of TBAF in THF achieved the deprotection of the TES group with minimal effect on the secondary TBS ether. To mask the primary alcohol of **4.53**, we have examined several protective groups such as TBS, TES, and methyl carboxylate. It appeared that TBS was the best choice which generated minimal side reaction in the following steps. Therefore, **4.53** was converted to a TBS ether using TBSCl. Finally, deprotonation of the resulting terminal alkyne with *n*-BuLi followed by treatment with methyl chloroformate gave the methyl ester **4.42** in 79% yield over 3 steps. The Diels-Alder reaction substrate **4.42** with the desired olefin geometry and two stereocenters was now synthesized enantioselectively through a 9-step sequence in an efficient ~36% overall yield.

4.2.2 Cycloaddition of dienyne 4.42

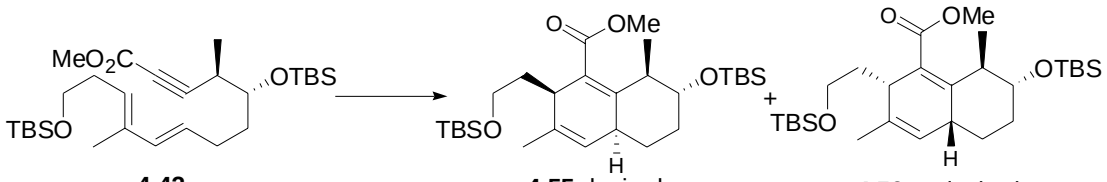
With dienyne **4.42** in hand, our attention turned to one of the key steps—the intramolecular Diels-Alder reaction. This reaction turned out to be very challenging and much effort was expended to obtain satisfactory diastereoselectivity. Initially, thermal conditions were tested, though the reaction did not occur in refluxing toluene. In refluxing *p*-cymene (160 °C) under slightly basic conditions, dienyne **4.42** underwent intramolecular Diels-Alder reaction, however, giving a 1:2 mixture of diastereomers with the undesired **4.56** (determined by 2-D NMR study) as the major product (Table 4.1, entry 1). More than a dozen of Lewis acids were then examined seeking to get better selectivity. However, these reagents either did not promote Diels-Alder reactions or gave complex products (Table 4.1, entry 2).

We then turned our attention to cycloadditions catalyzed by transition metals. Wender *et al.* have used Ni or Rh catalyzed cycloadditions to generate decalins.[28] The reaction conditions

using $Ni(acac)_2$ were tested on dienyne **4.42** (Table 4.1, entry 3). The reaction gave a reversed ratio with the desired isomer **4.55** as the major product but along with many other inseparable side products.

We then investigated cycloadditions using [(naphthalene)Rh(cod)]SbF_6 as the catalyst, which was also developed in the Wender group.[19a] This catalyst and its variants have been used by Wender and other groups in varieties of cycloadditions, and excellent reactivity and efficiency have been observed. Indeed, dienyne **4.42** underwent facile cycloaddition when treated with 5 mol% [(naph)Rh(cod)]SbF_6 in dichloroethane (DCE) at room temperature. The cycloaddition was complete in less than 1 h, albeit giving a dr of 1:1.7 still favoring the undesired product **4.56** (entry 4). However, its amazing reactivity interested us in consideration that the IMDA under thermal conditions at 160 °C took 4 h, while using this Rh catalyst, the reaction only took less than 1 h at rt. The excellent reactivity of the catalyst allows many reaction conditions such as temperature and solvent to be changed. Because the diastereomeric ratio of the reaction is only ~1:2, the energy difference between the two isomers and their transition states must be minimal and changing the reaction conditions may invert the ratio.

The reaction temperature was indeed observed to have influence on the product ratio. When elevating the reaction temperature to 45 °C, a 1:3.4 mixture of products was obtained further favoring the undesired diastereomer **4.56** (Table 4.1, entry 5). By lowering the reaction temperature to 0 °C, a mixture of 1:1 ratio was obtained (Table 4.1, entry 6), and the reaction still appeared to be very clean.



Entry	Conditions		Product (**4.55**:**4.56**)
1	*p*-cymene, TEA, 160 °C, 4 h		1:2
2	$BF_3{\cdot}Et_2O$, $TiCl_4$, $ZnCl_2$, $SnCl_4$, $AlCl_3$, $LiClO_4$ ...		No reaction or complex products
3	$Ni(acac)_2$, $P(O\text{-}^iC_3HF_6)_3$, $AlEt_3$, 50 °C, 20 h		Promising but complex products
4	[(naph)Rh(cod)]SbF_6 (5 mol%)	DCE, 25 °C, <1 h	1:1.7
5	[(naph)Rh(cod)]SbF_6 (5 mol%)	DCE, 45 °C, <15 min	1:3.4
6	[(naph)Rh(cod)]SbF_6 (5 mol%)	DCE, 0 °C, 2 h	1:1
7	[(naph)Rh(cod)]SbF_6 (5 mol%)	DCE, -5 °C, 2 h	1.1:1
8	[(naph)Rh(cod)]SbF_6 (5 mol%)	DCE, -12 °C, 4 h	1.8:1 (60% yield)
9	[(naph)Rh(cod)]SbF_6 (5 mol%)	acetone, -5 °C	1:2
10	[(naph)Rh(cod)]SbF_6 (5 mol%)	CH_2Cl_2, -5 °C	1:1.8

Table 4.1. Optimization of the diastereoselectivity of the IMDA of **4.42**.

Further lowering the reaction temperature to -12 °C, the dr was improved to 1.8:1 and the desired product **4.55** was obtained in a satisfactory 60% yield after purification by flash chromatography. Investigation of temperature-dr relationship revealed that at -15 °C, the reaction gave the best 2.1:1 dr favoring the desired **4.55** (Figure 4.1). When decreasing the reaction temperature to -18 °C and -24 °C, the dr went down to 2:1 and 1.3:1 respectively. Brief evaluation of other solvents such as acetone or CH_2Cl_2 did not improve the diastereoselectivity.

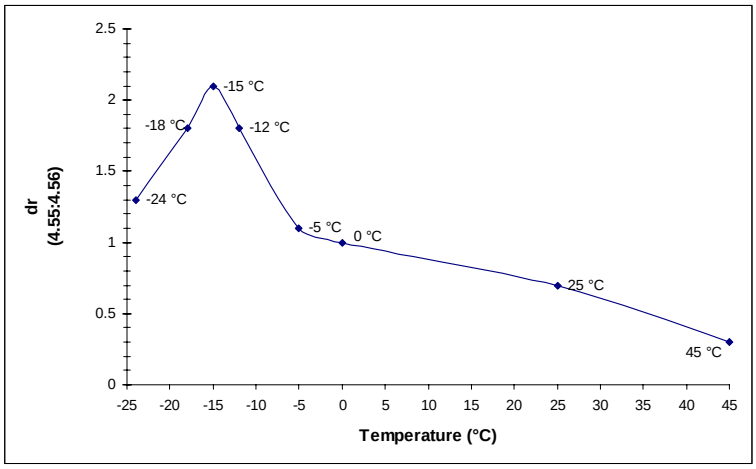
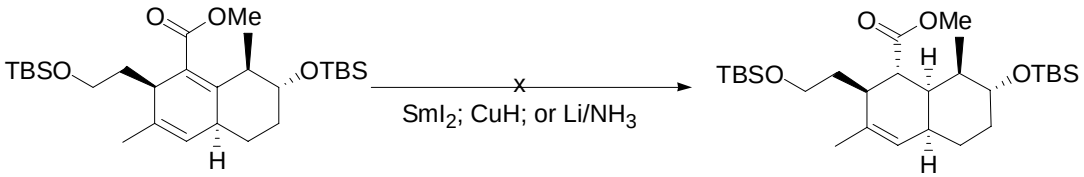


Figure 4.1. Temperature-dr relationship of the cycloaddition of **4.42**.

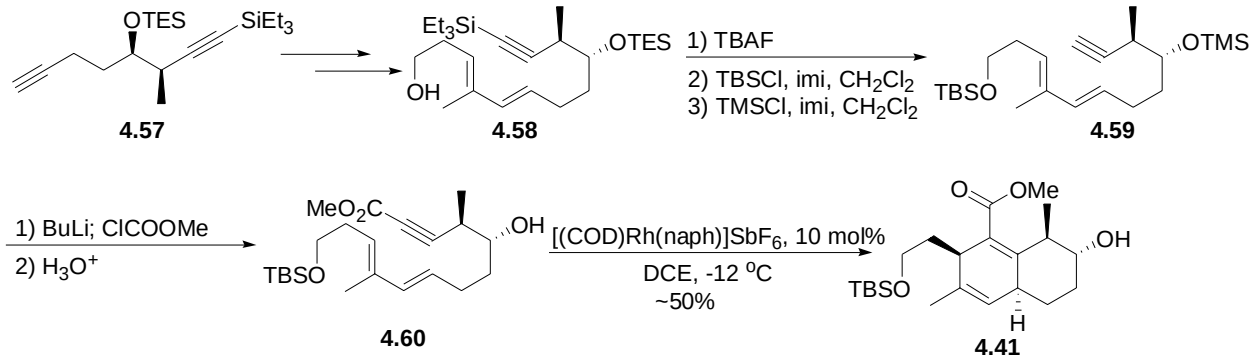
4.2.3 The challenge of reducing the α,β-unsaturated esters

Initially, reduction of *α,β*-unsaturated ester **4.55** was attempted (Scheme 4.14). Reduction of **4.55** with SmI_2 or CuH did not give any desired reaction even in refluxing THF. Reduction of **4.55** with Li/NH_3 produced the undesired *trans*-decalin product. It appeared that we needed to go back to the original design and synthesize ester **4.41**, which has a free secondary hydroxyl group that can provide a hydroxyl-assisting effect. However, removing the TBS groups on **4.55** turned out to be troublesome. The substrate underwent facile isomerization/aromatization and gave complex products when treated with TBAF or acids.



Scheme 4.14. Unsuccessful reduction of **4.55**.

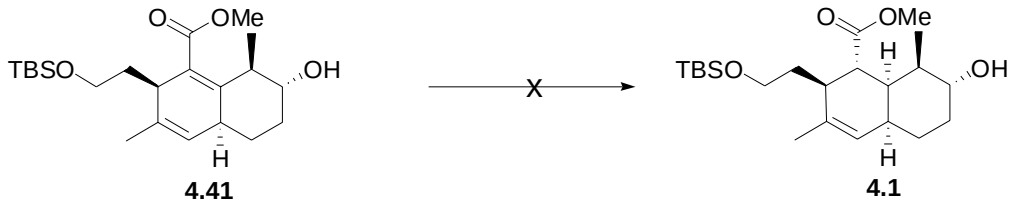
Eventually, *α,β*-Unsaturated ester **4.41** was synthesized using a sequence as shown in Scheme 4.15. Dialkyne **4.57**, which has a TES ether rather than a TBS ether, was subjected to hydroboration and Suzuki coupling reaction conditions to furnish dienyne **4.58**. Dienyne **4.58** was treated with TBAF in THF to remove both TES groups. Protection of the primary alcohol of the resulting product with a TBS ether and the secondary alcohol with a TMS ether provided **4.59**. Installation of a methyl ester onto alkyne **4.59** followed by a spontaneous removal of the TMS group upon acidic aqueous workup gave the desired ester **4.60**. The cycloaddition of **4.60** was sluggish, requiring 10 mol% of [(naph)Rh(cod)]SbF_6 catalyst and provided ~50% yield of **4.41**.



Scheme 4.15. The synthesis of dienyne **4.41**.

Many attempts were made to reduce the *α,β*-unsaturated ester **4.41**. The substrate, however, proved to have unusually low reactivity (Table 4.2). In refluxing THF, **4.41** did not react with SmI_2.[17] Reaction conditions using Mg in refluxing MeOH[29] did not provide reactivity either. Zn in refluxing acidic MeOH, which was successful in a reduction of a similar tetrasubstituted *α,β*-unsaturated ester by Overman,[30] also failed to provide any reaction. Dissolving metals such as Li

or Na in NH_3 or NH_3/THF yielded a *trans*-decalin. CuH in refluxing THF lead to the formation of complex products. Hydrogenation using Crabtree's catalyst and H_2 appeared to reduce the trisubstituted double bond.



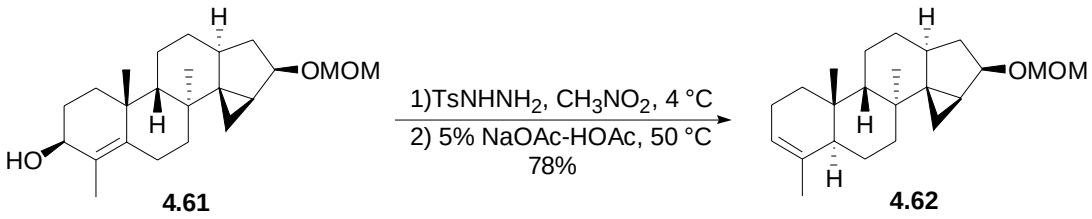
4.41 **4.1**

Entry	Conditions	Results
1	SmI_2/Δ, Mg/MeOH/Δ, or Zn/MeOH/H^+/Δ	No reaction
2	Li/NH_3 or Na/NH_3	*trans*-Decalin
3	CuH, Δ	Complex products
4	Crabtree's catalyst/H_2	Reduced the trisubstituted double bond

Table 4.2. The challenge of reducing the *α,β*-unsaturated ester **4.41**.

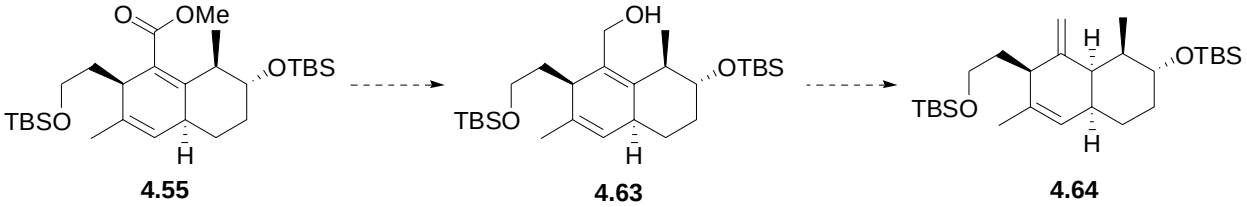
4.2.4 Alternative approach to the cis-decalin

After many unsuccessful attempts of reduction of *α,β*-unsaturated ester **4.41** and discovering its unusually low reactivity, we decided to bypass this difficulty by seeking alternatives such as an allylic rearrangement. Allylic rearrangements have been used by Corey in his synthesis of protosterol. A tetrasubstituted olefin **4.61** was transformed into a trisubstituted olefin **4.62** which could be manipulated more easily (Scheme 4.16).[31a]



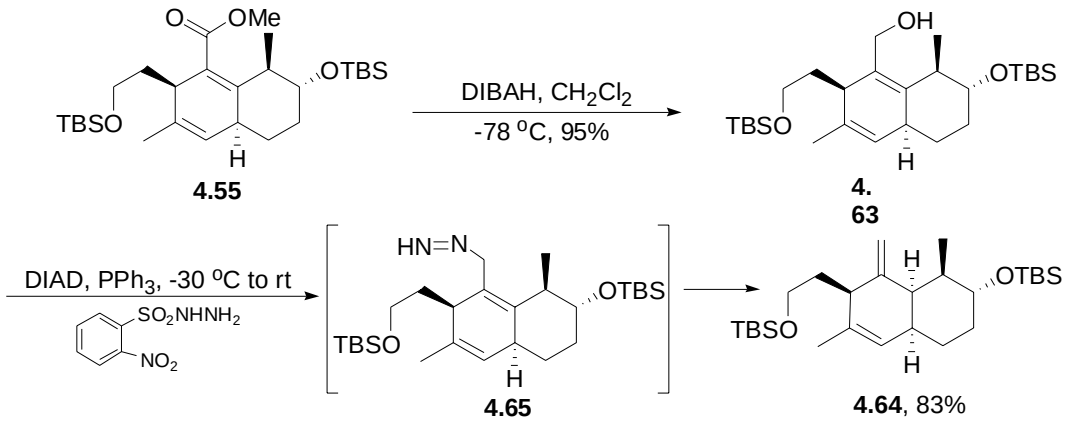
Scheme 4.16. Allylic rearrangement in Corey's synthesis of protosterol.

A similar strategy has been used by Schreiber[31b] in the synthesis of dynemicin A and by McIntosh[31c] in his synthesis of the core of eunicellin. We envisioned that ester **4.55** could be reduced into an allylic alcohol **4.63**, which would undergo an allylic rearrangement to produce *cis*-decalin **4.64** (Scheme 4.17). The exo-cyclic olefin of **4.64** can be transformed into a carbonyl functional group and eventually furnish **4.1**.



Scheme 4.17. Proposed synthesis of *cis*-decalin **4.64**.

To examine this idea, ester **4.55** was reduced with DIBAH to yield allylic alcohol **4.63** (Scheme 4.18). To our delight, upon subjecting **4.63** to Myers' reductive allylic transposition conditions,[32] desired *cis*-decalin **4.64** was obtained as the only diastereomer in 83% yield, through the diazene intermediate **4.65**. The *cis*-decalin configuration has been confirmed by 2D-NMR study of **4.67**, generated from **4.66** after removing the TES group under acidic conditions. The NOESY spectrum of **4.67** shows a characteristic correlation between H-8 and H-16. (Figure 4.2). One of the most challenging steps of the synthesis towards integramycin—the *cis*-decalin construction was thus achieved.



Scheme 4.18. Synthesis of *cis*-decalin **4.64**.

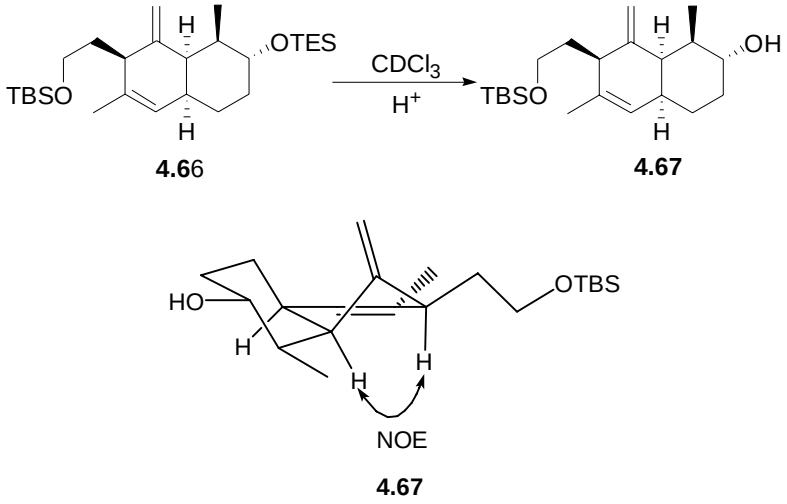


Figure 4.2. NOE correlation of *cis*-decalin **4.67**.

The allylic rearrangement proceeded with excellent diastereoselectivity. The proposed explanation is shown in Figure 4.3. The cyclohexadiene ring of the diazene intermediate **4.65** exists in a puckered transition state like a half-opened book. Approaching of the diazene to the double bond from the top face (the convex face) is hindered. Moreover, when approaching from the top face, the diazene comes to the vicinity of Me-37 and generate steric interactions with it. The bottom face is the concave face and there is no severe interaction between the diazene and Me-37. Thus this approach is favored and generates the *cis*-decalin.

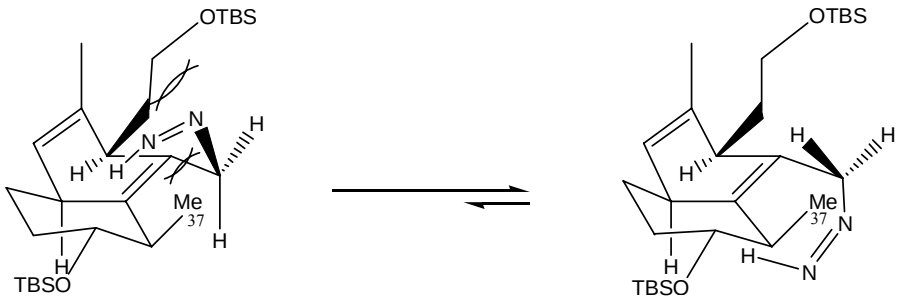
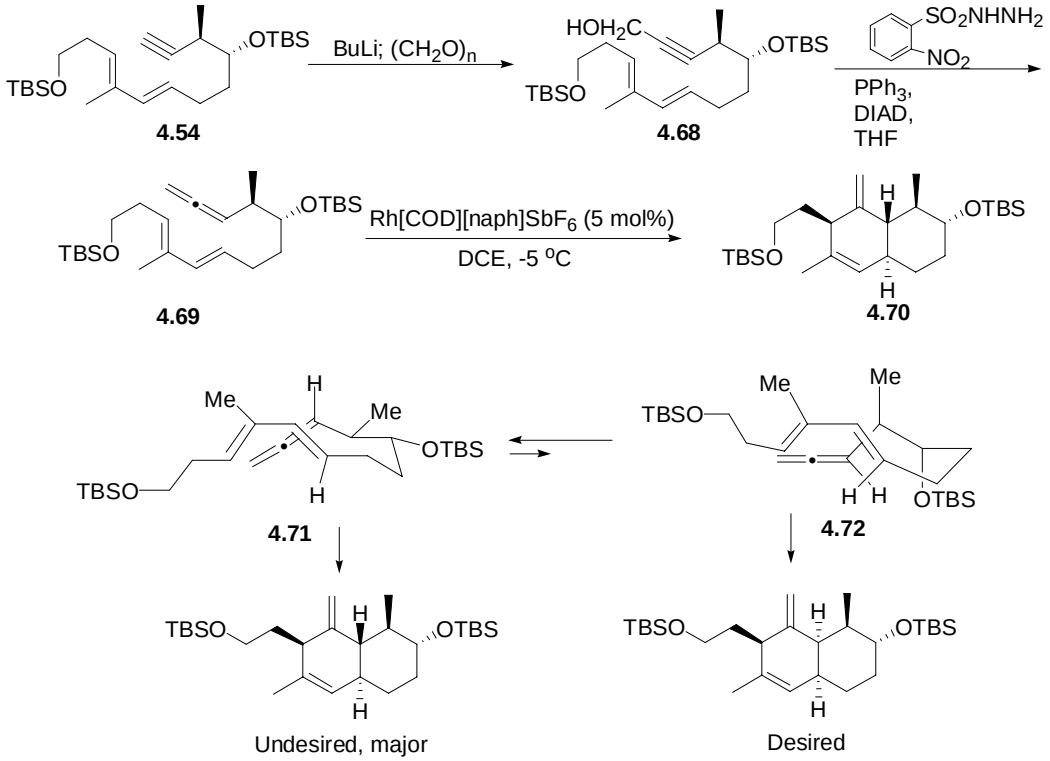


Figure 4.3. Proposed transition states of the *cis*-decalin formation.

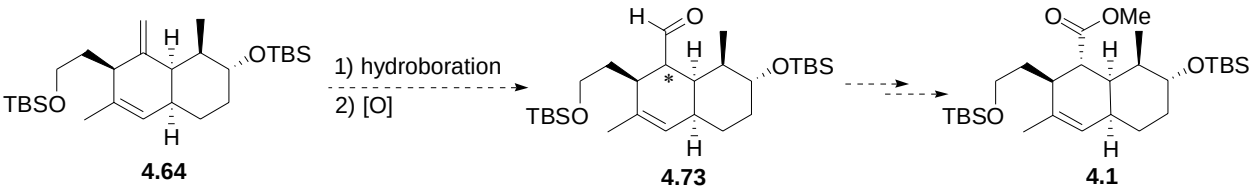
With the success of synthesizing **4.64** through an allylic rearrangement, we then sought ways to access the same intermediate in fewer steps. Dieneallene **4.69** was prepared through a two-step sequence from **4.54** (Scheme 4.19).[33] Though **4.69** underwent facile cycloaddition, the reaction gave a product that was consistent with *trans*-decalin **4.70**, presumably through the transition state of **6.71**. This reaction can be taken to support our previous assumption that a triene substrate **4.37** would not generate a *cis*-decalin *via* a Diels-Alder reaction.



Scheme 4.19. Cycloaddition of dienallene **4.70**.

4.4.5 Attempts to functionalize the exo-cyclic olefin of 4.64

With *cis*-decalin **4.64** in hand, it seemed that the completion of the *cis*-decalin unit of integramycin could be completed in a straightforward manner. As shown in Scheme 4.20, selective hydroboration of the *exo*-cyclic olefin of **4.64** followed by oxidation of the resulting alcohol to an aldehyde (**4.73**) was expected to furnish the carbonyl functional group and the last stereocenter. If necessary, the carbon center next to the carbonyl can be epimerized to give the desired stereochemistry. Aldehyde **4.73** could be transformed into **4.1** after oxidation and ester formation.

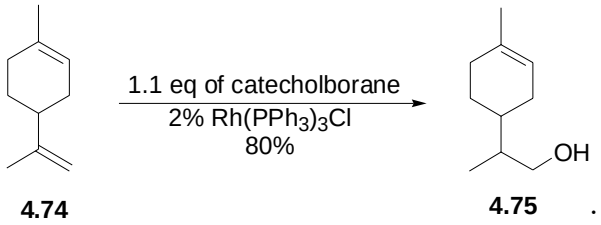


Scheme 4.20. Proposed transformation of **4.64** to **4.1**.

There are several methods in the literature that can selectively hydroborate an 1,1-disubstituted olefin in the presence of a trisubstituted olefin. The first conditions we tested were hydroboration of **4.64** using 9-BBN or disiamylborane at room temperature.[34] Surprisingly, no reaction was observed. Upon heating, the product obtained still contains the *exo*-cyclic olefin, with the trisubstituted double bond being more reactive and undergoing hydroboration.

Many researchers have demonstrated selective hydroborations using catecholborane catalyzed by transition metal catalysts.[35] For example, Evans and co-workers have shown that diene **4.74** underwent selective hydroboration with catecholborane in the presence of Wilkinson's catalyst to afford alcohol **4.75** (Scheme 4.21).[35a] The Evan's conditions were tested on **4.64**, however,

provided no reaction even upon heating. Hydroboration of **4.64** with BH_3·THF also failed. A diol was generated without showing any selectivity.



Scheme 4.21. Evan's selective hydroboration.

The reason of the low reactivity of the *exo*-cyclic olefin of **4.64**, after careful analysis, could be that the *exo*-cyclic olefin is buried in between the Me-37 group and the cyclohexane ring (Figure 4.4). Setting up stereocenters in this crowded environment can be very challenging.

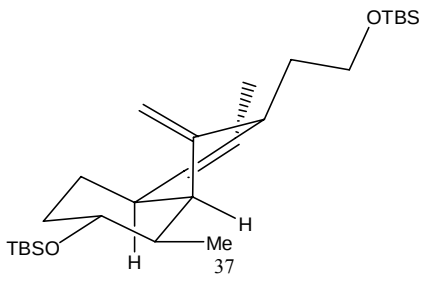
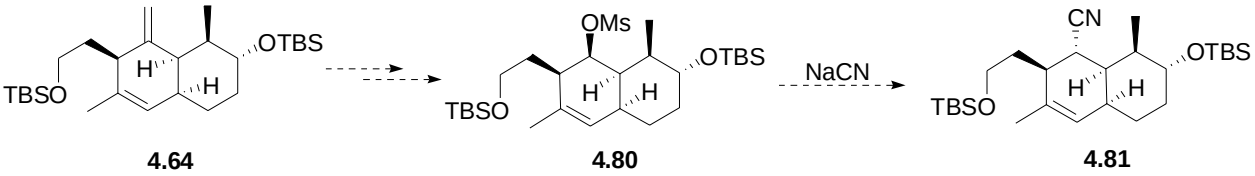


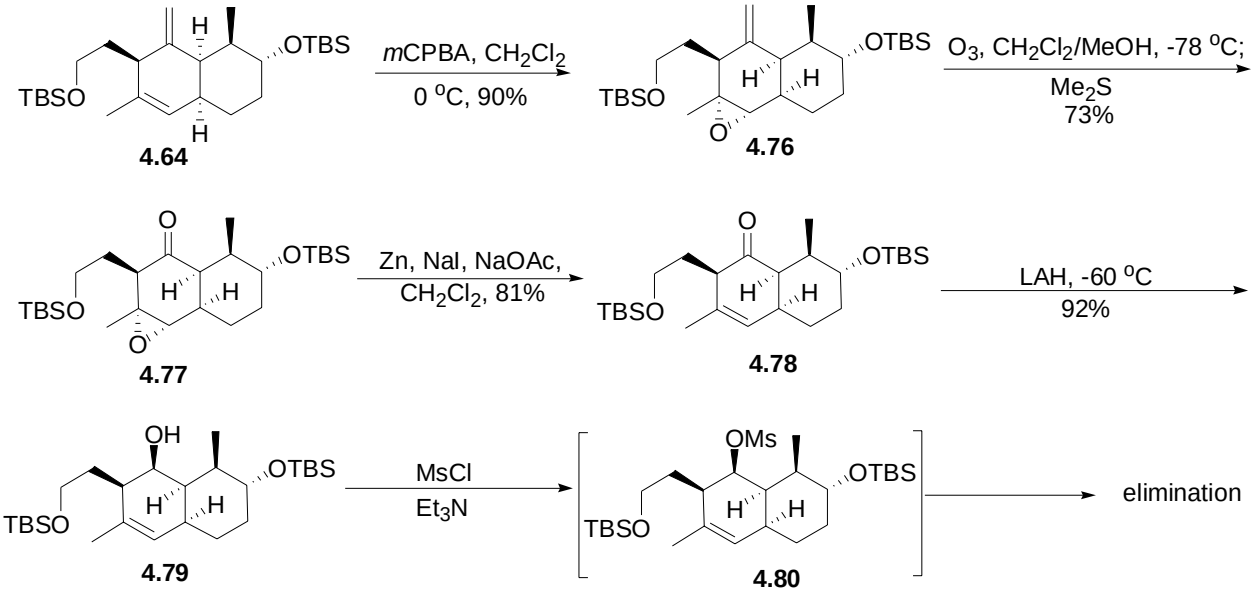
Figure 4.4. Possible conformation of *cis*-decalin **4.64**.

Knowing that the *exo*-cyclic olefin is actually less reactive than the internal trisubstituted olefin, we sought a strategy that can protect the internal olefin, after which the *exo*-cyclic olefin could be manipulated. For example, after protecting the internal olefin, the *exo*-cyclic olefin can be converted into an alcohol and thereafter a mesylate (**4.80**). Mesylate **4.80** would allow a displacement reaction with NaCN to provide cyanide **4.81**, which is synthetically equivalent to **4.1** (Scheme 4.22).



Scheme 4.22. Proposed cyanide formation.

Both electronically and sterically, the internal trisubstituted olefin should be more reactive towards epoxidation conditions than the *exo*-cyclic olefin. **4.64** was treated with *m*CPBA at 0 °C and the reaction indeed gave epoxide **4.76** as the only product, even when excess *m*CPBA was used (Scheme 4.23). Epoxide **4.76** was subjected to ozonolysis conditions[36] and provided ketone **4.77** in 73% yield. The epoxide has executed its masking function and was reduced back to an olefin using zinc metal[36] to provide **4.78** in 81% yield at 74% conversion. The ketone (**4.78**) was then reduced to its corresponding alcohol **4.79** with LAH in 92% yield.



Scheme 4.23. Functionalization of the *exo*-cyclic olefin of **4.64**.

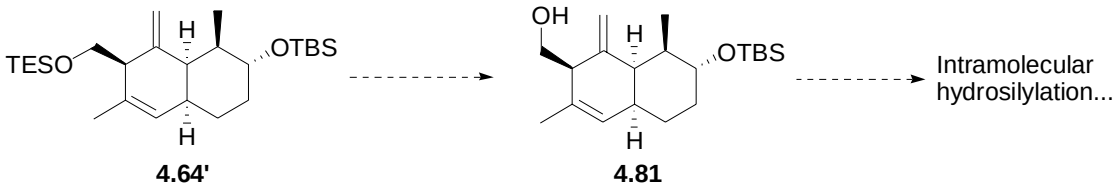
When alcohol **4.79** was treated with MsCl or TsCl in the presence of a base, mesylate or tosylate formation occurred but followed by an in situ elimination that resulted in a diene formation. Attempts to convert ketone **4.78** into an epoxide using Corey-Chaykovski reaction[37] lead to olefin isomerization and generated an enone. Addition of $LiCH_2I$[38a], $LiCH_2Br$[38b], or CH_2I_2/Sm[38c] onto the carbonyl also failed because of deprotonation under basic conditions to generate enone products.

4.3 Summary and project perspectives

The study directed towards the synthesis of the *cis*-decalin unit of integramycin has yielded several successes. *cis*-Decalin **4.64** has been prepared through a 12-step sequence in 15% overall yield. The highlights of the sequence include an efficient preparation of the dienyne substrate starting from a Sharpless asymmetric epoxidation, a rhodium-catalyzed cycloaddition whose diastereo-selectivity can be modified by changing the reaction temperature and solvent, and an allylic rearrangement that established the *cis*-decalin structure.

The functionalization of the *exo*-cyclic olefin of **4.64** proved to be difficult. Selective hydroboration of the *exo*-cyclic olefin under various conditions was not successful. Alternative attempts to establish a carbonyl functional group using alcohol **4.79** or ketone **4.78** were also unsuccessful. The results suggest that functionalizing the hindered *exo*-cyclic olefin using intermolecular reactions may be difficult. As an alternative, an intramolecular reaction can be

used which may provide better reactivity towards the *exo*-cyclic olefin. Compound **4.81** (Scheme 4.24), which has one less carbon on the alcohol side chain than **4.64**, may undergo chelate-controlled hydrosilylation,[39] hydrostannylation,[40] or hydroboration[13] to functionalize the *exo*-cyclic olefin.



Scheme 4.24. Functionalize the *exo*-cyclic olefin using intramolecular reactions.

4.4 References

(1) Evans, D. A.; Golob, A. M.; *J. Am. Chem. Soc.* **1975**, *97*, 4765-4766.

(2) Paquette, L. A.; Guevel, R.; Sakamoto, S.; Kim, I. H.; Crawford, J. *J. Org. Chem.* **2003**, *68*, 6096-6107.

(3) Hua, Z.; Yu, W.; Jin, Z. *Org. Lett.* **2005**, *7*, 1939-1942.

(4) Banwell, M. G.; Edwards, A. J.; McLeod, M. D.; Stewart, S. G. *Aust. J. Chem.* **2004**, *57*, 641-644.

(5) Paquette, L. A. *Tetrahedron* **1997**, *53*, 13971-14020.

(6) Fringuelli, F. *The Diels-Alder reaction: selected practical methods.* New York : Wiley, **2002**.

(7) Anderson, J. C.; Blake, A. J.; Graham, J. P.; Wilson, C. *Org. Biomol. Chem.* **2003**, *1*, 2877-2885.

(8) Miyaoka, H.; Shida, H.; Yamada, N.; Mitome, H.; Yamada, Y. *Tetrahedron Lett.* **2002**, *43*, 2227-2230.

(9) Taber, D. F.; Gunn, B. P. *J. Am. Chem. Soc.* **1979**, *101*, 3992-3993.

(10) Suzuki, T.; Usui, K.; Miyake, Y.; Namikoshi, M.; Nakada, M. *Org. Lett.* **2004**, *6*, 553-556.

(11) Roush, W. R.; Kageyama, M.; Riva, R.; Brown, B. B.; Warmus, J. S.; Moriarty, K. J. *J. Org. Chem.* **1991**, *56*, 1192-1210.

(12) Dineen, T. A.; Roush, W. R. *Org. Lett.* **2005**, *7*, 1355-1358.

(13) Oikawa, H.; Tokiwano, T. *Nat. Prod. Rep.* **2004**, *21*, 321-352.

(14) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307-1370.

(15) (a) Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291-293. (b) Appella, D. H.; Moritani, Y.; Shintani, R.; Ferreira, E. M.; Buchwald, S. L. *J. Am.*

Chem. Soc. **1999**, *121*, 9473-9474. (c) Yang, J.; Long, Y. O.; Paquette, L. A. *J. Am. Chem. Soc.* **2003**, *125*, 1567-1574.

(16) Crabtree, R. H.; Davis, M. W. *J. Org. Chem.* **1986**, *51*, 2655-2661.

(17) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693-2698.

(18) (a) Arth, G. E.; Poos, G. I.; Lukes, R. M.; Robinson, F. M.; Johns, W. F.; Feurer, M.; Sarett, L. H. *J. Am. Chem. Soc.* **1954**, *76*, 1715-1722. (b) Hall, S. E.; Roush, W. R. *J. Org. Chem.* **1982**, *47*, 4611-4621.

(19) (a) Wender, P. A.; Williams, T. J. *Angew. Chem. Int. Ed.* **2002**, *41*, 4550-4553. (b) Wang, B.; Cao, P.; Zhang, X. *Tetrahedron Lett.* **2000**, *41*, 8041-8044. (c) Paik, S.-J.; Son, S. U.; Chung, Y. K. *Org. Lett.* **1999**, *1*, 2045-2047.

(20) Trost, B. M.; Holcomb, R. C. *Tetrahedron Lett.* **1989**, *30*, 7157-7160.

(21) (a) Fargeas, V.; Le Ménez, P.; Berque, I.; Ardisson, J.; Pancrazi, A. *Tetrahedron*, **1996**, *52*, 6613-6634. (b) Commeiras, L.; Santelli, M.; Parrain, J.-L. *Org. Lett.* **2001**, *3*, 1713-1715. (c) Sato, F.; Yuichi, K. *Org. Synth.* **1990**, *69*, 106-113.

(22) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765-5780.

(23) Chouteau, F.; Addi, K.; Bénéchie, M.; Prangé, T.; Khuong-Huu, F. *Tetrahedron* **2001**, *57*, 6229-6238.

(24) Nicolaou, K. C.; Fylaktakidou, K. C.; Monenschein, H.; Li, Y.; Weyershausen, B.; Mitchell, H. J.; Wei, H.; Guntupalli, P.; Hepworth, D.; Sugita, K. *J. Am. Chem. Soc.* **2003**, *125*, 15433-15442.

(25) Arase, A.; Hoshi, M.; Mijin, A.; Nishi, K. *Synth. Commun.* **1995**, *25*, 1957-1962.

(26) Roush, W. R.; Sciotti, R. J. *J. Org. Chem.* **1998**, *63*, 5473-5482.

(27) Rivera, I.; Soderquist, J. A. *Tetrahedron Lett.* **1991**, *32*, 2311-2314.

(28) (a) Wender, P. A.; Smith, T. E. *J. Org. Chem.* **1995**, *60*, 2962-2963. (b) Wender, P. A.; Smith, T. E. *J. Org. Chem.* **1996**, *61*, 824-825. (c) Wender, P. A.; Jenkins, T. E.; Suzuki, S. *J. Am. Chem. Soc.* **1995**, *117*, 1843-1844.

(29) (a) Paquette, L. A.; Dyck, B. *J. Am. Chem. Soc.* **1993**, *120*, 5953-5960. (b) Hudlicky, T.; Natchus, M. G.; Sinai-Zingde, G. *J. Org. Chem.* **1987**, *52*, 4641-4644.

(30) Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1993**, *115*, 9293-9294.

(31) (a) Corey, E. J.; Virgil, S. C. *J. Am. Chem. Soc.* **1990,** *112,* 6429-6431. (b) Wood, J. L.; Porco, J. A.; Taunton, J.; Lee, A. Y.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992,** *114***,** 5898-5900. (c) Chai, Y.; Vicic, D. A.; McIntosh, M. C. *Org. Lett.* **2003**, *5*, 1039-1042.

(32) Myers, A. G.; Zheng, B. *Tetrahedron Lett.* **1996***, 37,* 4841-4844.

(33) Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492-4493.

(34) (a) Brown, H. C.; Chandrasekharan, J. *J. Org. Chem.* **1983**, *48*, 5080-5082 and references therein. (b) Kanth, J. V. B.; Brown, H. C. *J. Org. Chem.* **2001**, *66*, 5359-5365.

(35) (a) Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1992**, *114*, 6671-6679. (b) Renaud, P.; Ollivier, C.; Weber, V. *J. Org. Chem.* **2003**, *68*, 5769-5772.

(36) Cane, D. E.; Yang, G.; Coates, R. M.; Pyun, H.-J.; Hohn, T. *J. Org. Chem.* **1992**, *57*, 3454-3462.

(37) (a) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1962**, *84*, 867-868. (b) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353-1364. (c) Gololobov, Y. G.; Nesmeyanov, A. N.; Lysenko, V. P.; Boldeskul, I. E. *Tetrahedron* **1987**, *43*, 2609-2651.

(38) (a) Bessieres, B.; Morin, C. *J. Org. Chem.* **2003**, *68*, 4100-4103. (b) Michnick, T. J.; Matteson, D. S. *Synlett* **1991**, 631-632. (c) Imamoto, T.; Takeyama, T.; Koto, H. *Tetrahedron Lett.* **1986**, *27*, 3243-3246.

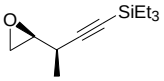
(39) (a) Barton, D. H. R.; Subramanian, R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1718-1723. (b) Lautens, M.; Colucci, J. T.; Hiebert, S.; Smith, N. D.; Bouchain, G. *Org. Lett.* **2002**, *4*, 1879-1882.

(40) Widenhoefer, R. A.; Krzyzanowska, B.; Webb-Wood, G. *Organometallics* **1998**, *17*, 5124-5127.

(41) Miura, K.; Wang, D.; Hosomi, A. *J. Am. Chem. Soc.* **2005**, *127*, 9366-9367.

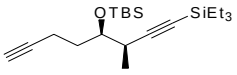
4.5 Experimental

Triethyl-(3-oxiranylbut-1-ynyl)silane (4.52)



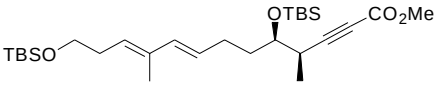
Butyllithium (1.6 M in hexane, 21.6 mL, 34.5 mmol) was added to a stirring solution of triethylsilylacetylene (5 g, 34.5 mmol) in Et_2O (100 mL) at -78 °C. The reaction mixture was stirred for 15 min, and $AlMe_3$ (2 M in toluene, 18.3 mL, 36.6 mmol) was added. The resulting mixture was stirred at -40 °C for 1 h, then was cooled to -78 °C. Epoxide **4.46** (5 g, 20.6 mmol) in toluene (100 mL) was added, followed by $BF_3{\cdot}Et_2O$ (4.9 g, 34.5 mmol). The reaction mixture was stirred at -78 °C for 1.5 h, and was quenched with saturated sodium potassium tartrate (50 mL). The resulting mixture was warmed to room temperature and was stirred until the emulsion was broken down. The organic layer was separated, and the aqueous layer was extracted with ether (3×). The organic layers were combined, washed with water and brine, then were dried over Na_2SO_4, filtered, and concentrated. The resulting residue was dissolved in MeOH (250 mL). Anhydrous K_2CO_3 (10 g) was added. The reaction mixture was stirred at rt for 20 min, diluted with ether (200 mL), and was filtered. The filtrate was concentrated to remove most of the solvents. The resulting residue was dissolved in ether and washed with saturated NH_4Cl and brine, then dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by flash chromatography (10→15→20% EtOAc in hexanes) to give the desired product (3.3 g, 76% over 2 steps): $[\alpha]^{23}_D$ +64.4º (*c* = 1.09, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.82 (ddd, J = 2.5, 3.8, 6.3 Hz, 1H), 2.70 (dd, J = 3.8, 5.2 Hz, 1H), 2.62 (dd, J = 2.6, 4.9 Hz, 1H), 2.34 (app p, J = 6.8 Hz, 1H), 1.24 (d, J = 6.9 Hz, 3H), 0.93 (t, J = 7.8 Hz, 9H), 0.49 (q, J = 7.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 107.2, 83.7, 54.8, 46.1, 30.3, 18.2, 7.4, 4.5; IR (neat) 939, 1013, 1458, 2161, 2872 cm^{-1}.

4-(*tert*-Butyldimethylsilyloxy)-3-methyl-1-triethylsilyl-octa-1,7-diyne (4.45)



To a solution of epoxide **4.52** (3.3 g, 15.7 mmol) in ether (150 mL) at -78 °C was added allenylmagnesium bromide (2 M in ether, 25 mL, 50 mmol). The reaction mixture was stirred at -78 °C for 5 min, warmed to 0 °C for 1 h, then was quenched with saturated sodium potassium tartrate (20 mL). The resulting mixture was stirred until the cloudy emulsion separated into two layers. The organic layer was separated, and the aqueous layer was extracted with ether (3×). The organic layers were combined, washed with water and brine, then were dried over Na_2SO_4, filtered, and concentrated. The resulting residue was dissolved in CH_2Cl_2 (50 mL) and the resultant solution was cooled to 0 °C. 2,6-Lutidine (3.3 mL, 28.3 mmol) was added, followed by TBSOTf (4 mL, 17.3 mmol) dropwise. The reaction mixture was stirred at rt for 1.5 h then was quenched with saturated NH_4Cl (10 mL) and water (10 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×). The organic layers were combined, washed with water and brine, then were dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by flash chromatography (2→4→5% EtOAc in hexanes) to give the desired product (5.2 g, 91% over 2 steps): $[\alpha]^{23}_D$ +34.6º (*c* = 1.74, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.65 (dt, J = 3.6, 6.5 Hz, 1H), 2.51 (app p, J = 6.3 Hz, 1H), 2.24-2.35 (m, 2H), 1.91 (t, J = 2.6 Hz, 1H), 1.89-2.00 (m, 1H), 1.69-1.79 (m, 1H), 1.13 (d, J = 7.0 Hz, 3H), 0.99 (t, J = 7.4 Hz, 9H), 0.90 (s, 9H), 0.53 (q, J = 7.8 Hz, 6H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 110.3, 84.6, 83.3, 73.9, 68.5, 33.7, 33.1, 26.0, 18.3, 17.7, 14.2, 7.7, 14.2, 7.7, 4.8, -4.7; IR (neat) 1082, 1249, 1429, 2165, 2953 cm^{-1}; HRMS-EI (m/z) calcd for $C_{19}H_{35}OSi$ [M – C_2H_5]$^+$ 335.2226, found 335.2233.

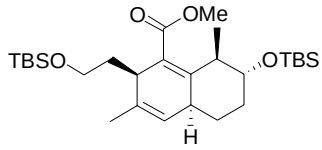
5,13-Bis-(*tert*-butyldimethylsilyloxy)-4,10-dimethyltrideca-8,10-dien-2-ynoic acid methyl ester (4.42)



To a solution of alkyne **4.45** (730 mg, 2 mmol) in THF (10 mL) at rt were added catecholborane (288 mg, 2.4 mmol) and freshly made dicyclohexylborane (0.5 M in THF, 0.2 mL, 0.1 mmol). After 2 h, additional catecholborane (0.05 mL) and dicyclohexylborane (0.1 mL) were added. The reaction mixture was stirred for another 1 h, and a solution of NaOH (440 mg, 11 mmol) in water (degassed by bubbling with N_2, 3 mL) was added dropwise. The reaction mixture was stirred for 5 min and a mixture of *trans*-4-iodo-pent-3-en-1-ol (475 mg, 2.4 mmol), $Pd(PPh_3)_3$ (185 mg, 0.16 mmol), and degassed THF (4 mL) was added. The reaction mixture was heated to 62 °C over 5 min and was stirred at that temperature for 20 min. The reaction mixture was cooled to rt then was quenched with water. The organic layer was separated and the aqueous layer was extracted with ether (3×). The organic layers were combined, washed with water and brine, then were dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by flash chromatography (10→15% EtOAc in hexanes) to give the desired product **4.53**, which was dissolved in THF (20 mL), and TBAF (391 mg, 1.5 mmol) was added. The reaction mixture was stirred for 15 min and was quenched with water. The resulting mixture was extracted with ether (3×). The organic layers were combined, washed with water and brine, then were dried over Na_2SO_4, filtered, and concentrated. The resulting residue was dissolved in CH_2Cl_2 (10 mL), cooled to 0 °C, and 2,6-lutidine (0.58 mL, 5.0 mmol) and TBSOTf (0.52 mL, 2.25 mmol) were added successively. The reaction mixture was stirred for 1 h and was quenched with saturated NH_4Cl (1 mL) and water (1 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×). The organic layers were combined, washed with water and brine, then were dried over Na_2SO_4, filtered, and concentrated.

The resulting residue was purified by flash chromatography (0→4% EtOAc in hexanes) to give the desired product, which was dissolved in THF (10 mL). To the resulting solution at -78 °C was added butyllithium (1.56 M in hexane, 2.3 mL, 3.7 mmol) dropwise. The reaction mixture was stirred at -78 °C for 10 min and methyl chloroformate (0.58 mL, 7.5 mmol) was added dropwise. The cold bath was removed and the reaction mixture was further stirred for 15 min. Saturated NH_4Cl (1 mL) and water (1 mL) were added. The organic layer was separated and the aqueous layer was extracted with ether (3×). The organic layers were combined, washed with water and brine, then were dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by flash chromatography (0→1→1.5% EtOAc in hexanes) to give the desired product (496 mg, 52% over 4 steps): $[\alpha]^{23}_D$ +12.7º (*c* = 0.29, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.05 (d, J = 15.6 Hz, 1H), 5.51 (dt, J = 14.3, 6.9 Hz, 1H), 5.35 (t, J = 7.5 Hz, 1H), 3.76 (s, 3H), 3.67-3.73 (m, 1H), 3.60 (t, J = 7.1 Hz, 2H), 2.65 (p, J =6.8 Hz, 1H), 2.33 (q, J = 7.0 Hz, 2H), 2.02-2.21 (m, 2H), 1.74 (s, 3H), 1.70-1.82 (m, 1H), 1.56-1.66 (m, 1H), 1.19 (d, J = 7.1 Hz, 3H), 0.91 (s, 9H), 0.90 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.3, 127.4, 126.7, 91.9, 74.1, 63.1, 52.7, 34.7, 32.4, 32.3, 29.9, 28.2, 26.2, 26.1, 18.6, 15.8, 12.8, -4.1, -4.3, -5.0; IR (neat) 829, 1098, 1254, 1719, 2234, 2917 cm^{-1}; HRMS-ESI (m/z) calcd for $C_{28}H_{52}O_4Si_2Na$ $[M + Na]^+$ 531.3302, found 531.3266.

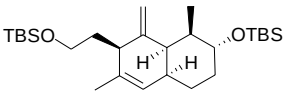
7-(*tert*-Butyldimethylsilyloxy)-2-[2-(*tert*-butyldimethylsilyloxy)-ethyl]-3,8-dimethyl-2,4a,5,6,7,8-hexahydronaphthalene-1-carboxylic acid methyl ester (4.55)



To dienyne **4.42** (2.2 g, 4.3 mmol) in DCE (100 mL) at -12 °C was added $[(COD)Rh(naph)]SbF_6$ (124 mg, 0.2 mmol) in one portion. The reaction mixture was stirred at -12 °C for 1.5 h and

additional catalyst (20 mg) was added. The reaction mixture was stirred for another 1 h then was concentrated. The resulting residue was purified by flash chromatography (long silica gel plug, 2% EtOAc in hexanes) to give the desired product (1.3 g, ~60%): $[\alpha]^{23}_{D}$ -35.0º (*c* = 0.40, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.31 (d, J = 3.3 Hz, 1H), 3.74 (s, 3H), 3.56 (dt, J = 5.5, 11.0 Hz, 3H), 3.36-3.46 (m, 2H), 3.04 (d, J = 3.3 Hz, 1H), 2.45 (dd, J = 3.8, 11.5 Hz, 1H), 2.10-2.20 (m, 1H), 1.86-2.01 (m, 2H), 1.70 (s, 3H), 1.45-1.60 (m, 2H), 1.08 (d, J = 6.6 Hz, 3H), 0.89 (s, 18 H), 0.05-0.06 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 139.7, 131.6, 125.3, 124.5, 74.5, 60.5, 51.5, 47.8, 42.2, 40.9, 36.6, 33.2, 32.3, 26.2, 26.1, 21.0, 18.3, 13.4, -4.1, -4.4, -5.0, -5.1; IR (neat) 1245, 1728 cm^{-1}; HRMS-ESI (m/z) calcd for $C_{28}H_{52}O_4Si_2Na^+$ $[M + Na]^+$ 531.3302, found 531.3325.

3-(*tert*-Butyldimethylsilyloxy)-6-[2-(*tert*-Butyldimethylsilyloxy)ethyl]-4,7-dimethyl-5-methylene-1,2,3,4,4a,5,6,8a-octahydronaphthalene (4.64)

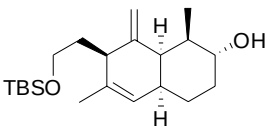


To a solution of ester **4.55** (1.2 g, 2.4 mmol) in CH_2Cl_2 (50 mL) at -78 °C was added DIBAH (1 M in hexanes, 10 mL, 10 mmol) dropwise. The reaction mixture was warmed to -20 °C over 2 h. Saturated sodium potassium tartrate (20 mL) was added slowly. The resulting emulsion was stirred at rt until layer separation occurred. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×). The organic layers were combined, washed with water and brine, then were dried over Na_2SO_4, filtered, and concentrated. The resulting residue was filtered through a short silica gel column. The filtrate was concentrated to give allylic alcohol **4.63**.

In another flask, to a solution of PPh_3 (810 mg, 3.1 mmol) in THF (45 mL) at -30 ° was added DIAD (0.57 mL, 2.8 mmol) dropwise. After 5 min, the above allylic alcohol **4.63** in THF (9 mL)

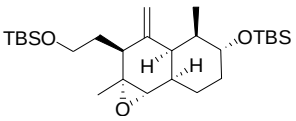
was added. After 10 min, NBSH (651 mg, 2.6 mmol) was added in one portion. The reaction mixture was stirred at -30 °C for 45 min, warmed to rt for 30 min, and was poured into a mixture of ether (30 mL) and water (30 mL). The organic layer was separated and the aqueous layer was extracted with ether (3×). The organic layers were combined, washed with water and brine, then were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (1→2% EtOAc in hexanes) to give the desired product (763 mg, 70% over 2 steps): $[\alpha]^{23}_D$ -14.8º (*c* = 1.28, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.40 (dd, J = 1.5, 3.2 Hz, 1H), 5.11 (s, 1H), 4.89 (s, 1H), 3.93 (dt, J = 4.7, 10.3 Hz, 1H), 3.63-3.70 (m, 1H), 3.49 (dt, J = 4.8, 9.1 Hz, 1H), 2.78 (s, 1H), 2.56 (t, J = 4.6 Hz, 1H), 2.07-2.17 (m, 2H), 1.84-1.91 (m, 2H), 1.72-1.82 (m, 1H), 1.69 (s, 3H), 1.47-1.52 (m, 1H), 1.13 (d, J = 7.2 Hz, 3H), 1.05-1.15 (m, 1H), 0.80-0.90 (m, 1H), 0.91 (s, 9H), 0.90 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.5, 135.6, 128.5, 109.2, 71.4, 60.6, 48.2, 44.3, 43.7, 42.0, 36.9, 31.0, 26.24, 26.19, 21.8, 15.8, -3.7, -4.3, -4.9; IR (neat) 767, 833, 1074, 1254, 1466, 2851 cm^{-1}; HRMS-EI (m/z) calcd for $C_{27}H_{52}O_2Si_2$ [M^+] 464.3506, found 464.3498.

7-[2-(*tert*-Butyldimethylsilyloxy)ethyl]-1,6-dimethyl-8-methylene-1,2,3,4,4a,7,8,8a-octahydro-naphthalen-2-ol (4.67)



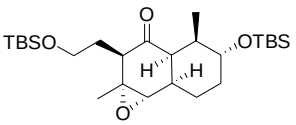
^{1}H NMR (300 MHz, C_6D_6) δ 5.30 (d, J = 4.9 Hz, 1H), 5.14 (s, 1H), 4.84 (s, 1H), 3.72-3.80 (m, 2H), 3.56 (td, J = 4.9, 9.3 Hz, 1H), 2.70 (d, J = 3.8 Hz, 1H), 2.37 (t, J = 4.5 Hz, 1H), 2.10-2.20 (m, 1H), 1.75-1.95 (m, 3H), 1.62 (s, 3H), 1.50-1.54 (m, 1H), 1.25-1.40 (m, 2H), 1.18 (d, J = 7.1 Hz, 3H), 1.00-1.12 (m, 1H), 0.99 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.0, 135.8, 128.2, 109.4, 70.9, 60.5, 48.1, 44.3, 43.6, 42.1, 30.9, 29.9, 27.8, 26.2, 21.8, 15.1, -5.0.

6-(*tert*-Butyldimethylsilyloxy)-3-[2-(*tert*-butyldimethylsilyloxy)ethyl]-2,5-dimethyl-4-methylenedecahydronaphthalen-2-ol (4.76)



To diene **4.64** (400 mg, 0.86 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added *m*CPBA (300 mg, ~1.7 mmol). The reaction mixture was stirred at 0 °C for 65 min, and was purified using a short silica gel column (eluting with 0→5→8→10% EtOAc in hexanes). The fractions of the filtrate containing the product were combined and concentrated to give the desired product (370 mg, 90%): $[\alpha]^{23}_D$ -1.3º (*c* = 0.77, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.03 (s, 1H), 4.89 (s, 1H), 3.76-3.88 (m, 2H), 3.61-3.70 (m, 1H), 2.92 (d, J = 5.5 Hz, 1H), 2.42 (d, J = 8.9 Hz, 1H), 2.36 (t, J = 5.6 Hz, 1H), 1.84-2.11 (m, 4H), 1.41-1.71 (m, 4H), 1.34 (s, 3H), 1.18-1.30 (m, 2H), 1.02 (d, J = 7.1 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.04-0.06 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.0, 111.8, 71.4, 64.2, 63.5, 62.6, 48.0, 45.4, 42.8, 40.5, 39.1, 36.3, 29.8, 26.2, 26.1, 22.5, 21.5, 18.5, 18.3, 15.2, -3.8, -4.4, -5.0, -5.1; IR (neat) 829, 1074, 1254, 1470, 2855, 2929, 2958 cm^{-1}; HRMS-EI (m/z) calcd for $C_{27}H_{52}O_3Si_2$ [M^+] 480.3455, found 480.3434.

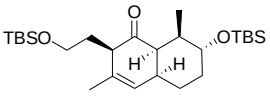
5-(*tert*-Butyldimethylsilyloxy)-2-[2-(*tert*-Butyldimethylsilyloxy)-ethyl]-1a,4-dimethyl-octahydro-1-oxacyclopropa[a]naphthalen-3-one (4.77)



To a solution of olefin **4.76** (130 mg, 0.27 mmol) in CH_2Cl_2 (10 mL) and MeOH (0.33 mL) at -78 °C was introduced O_3 until a blue color showed up and sustained. The reaction mixture was further stirred for 3 min, and Me_2S (1 mL) was added. The reaction mixture was warmed to rt and stirred at rt for 1 h. The reaction mixture was concentrated and the resulting residue was purified by flash chromatography (4→6→10% EtOAc in hexanes) to give the desired product (95 mg, 73%): $[\alpha]^{23}_D$ +13.8º (*c* = 1.03, CH_2Cl_2);

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.90 (dt, J = 4.4, 10.0 Hz, 1H), 3.73 (ddd, J = 3.9, 5.8, 9.9 Hz, 1H), 3.54 (dt, J = 4.3, 9.7 Hz, 1H), 3.13 (d, J = 5.6 Hz, 1H), 2.96 (dd, J = 4.2, 6.9 Hz, 1H), 2.83 (dd, J = 1.2, 8.8 Hz, 1H), 2.41-2.50 (m, 1H), 2.02-2.12 (m, 1H), 1.84-1.93 (m, 1H), 1.64-1.75 (m, 2H), 1.41 (s, 3H), 1.12-1.33 (m, 3H), 0.97 (d, J = 5.9 Hz, 3H), 0.87 (s, 18H), 0.00-0.07 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.7, 70.83, 66.6, 62.9, 61.4, 52.6, 51.0, 41.0, 40.1, 35.4, 27.7, 26.1, 23.6, 24.1, 18.4, 18.3, 15.3, -4.0, -4.4, -5.1, -5.2; IR (neat) 829, 1074, 1098, 1254, 1466, 1720, 2921 cm^{-1}; HRMS-EI (m/z) calcd for $C_{26}H_{50}O_4Si_2$ [M^+] 482.3248, found 482.3216.

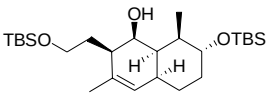
7-(*tert*-Butyldimethylsilyloxy)-2-[2-(*tert*-butyldimethylsilyloxy)-ethyl]-3,8-dimethyl-



4a,5,6,7,8,8a-hexahydro-2H-naphthalen-1-one (4.78)

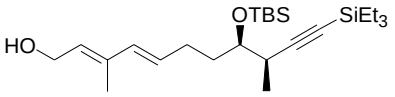
To a mixture of NaOAc (200 mg), NaI (600 mg), and Zn (400 mg) under Ar was added HOAc (1 mL). A solution of epoxide **4.77** (80 mg, 0.16 mmol) in CH_2Cl_2 (5 mL) was added to the above mixture. The reaction mixture was stirred vigorously for 3 h then was directly loaded onto silica gel column, eluting with 2→8% EtOAc in hexanes to give the desired product (46 mg, 81% yield at 74% conversion) and unreacted starting material (21 mg): $[\alpha]^{23}_D$ -6.7º (*c* = 0.51, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.56-5.58 (m, 1H), 3.99 (dt, J = 4.7, 10.4 Hz, 1H), 3.56 (t, J = 7.4 Hz, 2H), 2.98-2.99 (m, 2H), 2.40-2.46 (m, 1H), 1.73 (s, 3H), 1.63-2.00 (m, 4H), 1.41-1.53 (m, 1H), 1.16-1.25 (m, 2H), 1.10 (d, J = 6.9 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.11 (s, 3H), 0.07 (s, 3H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.6, 135.4, 127.7, 71.1, 61.3, 54.2, 42.7, 41.8, 36.2, 29.8, 29.5, 26.2, 21.5, 18.5, 18.3, 15.9, -3.9, -4.3, -5.0; IR (neat) 837, 1078, 1249, 1470, 1711 cm^{-1}; HRMS-EI (m/z) calcd for $C_{26}H_{50}O_3Si_2$ [M^+] 466.3299, found 466.3276.

7-(*tert*-Butyldimethylsilyloxy)-2-[2-(*tert*-Butyldimethylsilyloxy)-ethyl]-3,8-dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-ol (4.79)



To ketone **4.78** (39 mg, 0.08 mmol) in ether (3 mL) at -60 °C was added LAH (1 M in ether, 0.7 ml, 0.7 mmol). The reaction mixture was warmed to -20 °C over 2 h, and was quenched with water (three drops). The resulting mixture was directly loaded onto silica gel column, eluting with 2% EtOAc in hexanes to give the desired product (36 mg, 92%): $[\alpha]^{23}_{D}$ -1.4º (*c* = 1.17, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.47-5.48 (m, 1H), 4.23 (s, 1H), 3.95 (dt, J = 4.1, 10.1 Hz, 1H), 3.86-3.91 (m, 1H), 3.65 (t, J = 9.9 Hz, 1H), 3.12 (d, J = 4.4 Hz, 1H), 1.85-2.15 (m, 4H), 1.77 (t, J = 5.5 Hz, 1H), 1.53-1.73 (m, 2H), 1.63 (s, 3H), 1.21-1.29 (m, 2H), 1.07 (d, J = 6.9 Hz, 3H), 0.92 (s, 9H), 0.90 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.5, 128.3, 73.6, 66.0, 63.0, 45.8, 43.4, 42.7, 37.3, 36.3, 31.3, 29.9, 26.3, 26.1, 21.8, 18.4, 18.3, 15.9, -3.8, -4.4, -5.4, -5.5; IR (neat) 820, 1070, 1254, 3489 cm^{-1}; HRMS-ESI (m/z) calcd for $C_{26}H_{52}O_3Si_2Na$ $[M + Na]^+$ 491.3353, found 491.3379.

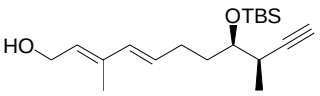
8-(*tert*-Butyldimethylsilyloxy)-3,9-dimethyl-11-triethylsilylundeca-2,4-dien-10-yn-1-ol



$[\alpha]^{23}_{D}$ +21.6º (*c* = 1.25, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.06 (d, J = 15.6 Hz, 1H), 5.66 (dt, J = 14.1, 6.9 Hz, 1H), 5.55 (t, J = 6.9 Hz, 1H), 4.27 (d, J = 6.9 Hz, 2H), 3.57 (dd, J = 6.0, 10.4 Hz, 1H), 2.54 (p, J = 6.9 Hz, 1H), 2.10-2.25 (m, 2H), 1.82-1.92 (m, 1H), 1.79 (s, 3H), 1.54-1.68 (m, 2H), 1.14 (d, J = 7.0 Hz, 3H), 0.96 (t, J = 8.1 Hz, 9H), 0.90 (s, 9H), 0.53 (q, J = 8.1 Hz, 6H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.7, 134.3, 130.6, 128.0, 111.0, 83.0, 75.2, 66.2, 59.5, 34.6, 33.5, 28.0, 26.3, 26.2, 18.4, 17.8, 15.5, 12.8, 7.8, 4.8, 4.5, -4.0, -4.2; IR (neat) 722, 771,

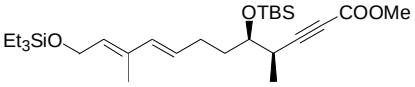
837, 1000, 1090, 1249, 1446, 2161, 2868, 2925 cm^{-1}; HRMS-EI (m/z) calcd for $C_{25}H_{46}OSi_2$ [M – H_2O]$^+$ 418.3087, found 418.3074.

8-(*tert*-Butyldimethylsilyloxy)-3,9-dimethylundeca-2,4-dien-10-yn-1-ol



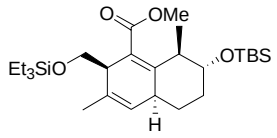
$[\alpha]^{23}_D$ +16.9º (*c* = 1.35, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.08 (d, J = 15.6 Hz, 1H), 5.69 (td, J = 6.8, 14.0 Hz, 1H), 5.56 (t, J = 6.8 Hz, 1H), 4.27 (d, J = 6.8 Hz, 2H), 3.60 (dd, J = 6.0, 10.2 Hz, 1H), 2.51 (dq, J = 2.3, 6.8 Hz, 1H), 2.10-2.28 (m, 2H), 2.05 (d, J = 3.2 Hz, 1H), 1.77-1.87 (m, 1H), 1.80 (s, 3H), 1.56-1.65 (m, 2H), 1.12 (d, J = 7.0 Hz, 3H), 0.88 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.5, 134.9, 130.3, 128.0, 86.9, 74.7, 69.9, 59.4, 34.2, 32.1, 28.0, 26.1, 18.3, 17.3, 12.7, -4.1, -4.3; IR (neat) 767, 833, 1094, 1249, 1466, 2361, 2847, 2925, 3313 cm^{-1}; HRMS-ESI (m/z) calcd for $C_{19}H_{34}O_2SiNa$ [M + Na]$^+$ 345.2226, found 345.2220.

5-(*tert*-Butyldimethylsilyloxy)-4,10-dimethyl-12-triethylsilyloxydodeca-8,10-dien-2-ynoic acid methyl ester



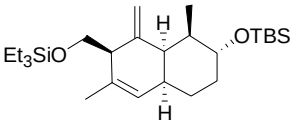
$[\alpha]^{23}_D$ +24.0º (*c* = 0.87, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.05 (d, J = 15.6 Hz, 1H), 5.57 (dt, J = 6.8, 14.0 Hz, 1H), 5.48 (t, J = 6.2 Hz, 1H), 4.28 (d, J = 6.4 Hz, 2H), 3.75 (s, 3H), 3.66-3.75 (m, 1H), 2.65 (p, J = 6.8 Hz, 1H), 2.10-2.22 (m, 2H), 1.73 (s, 3H), 1.56-1.80 (m, 3H), 1.18 (d, J = 7.8 Hz, 3H), 0.94 (t, J = 7.9 Hz, 9H), 0.90 (s, 9H), 0.57 (q, J = 7.9 Hz, 6H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.9, 134.5, 129.7, 128.8, 91.8, 74.4, 74.1, 60.0, 52.7, 34.6, 32.5, 28.2, 26.1, 18.4, 15.9, 12.9, 7.0, 4.8, -4.0, -4.3; IR (neat) 1098, 1245, 1715, 2234, 2953 cm^{-1}; HRMS-ESI (m/z) calcd for $C_{27}H_{50}O_4Si_2Na$ [M + Na]$^+$ 517.3145, found 517.3145.

7-(*tert*-Butyldimethylsilyloxy)-3,8-dimethyl-2-triethylsilyloxymethyl-2,4a,5,6,7,8-hexahydronaphthalene-1-carboxylic acid methyl ester



$[\alpha]^{23}_{D}$ -60.9º (*c* = 0.59, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.41 (d, J = 3.8 Hz, 1H), 3.71 (s, 3H), 3.64-3.70 (m, 1H), 3.45-3.54 (m, 2H), 2.91 (d, J = 3.6 Hz, 1H), 2.14-2.53 (m, 1H), 2.14-2.22 (m, 1H), 1.94-2.00 (m, 1H), 1.84-1.89 (m, 1H),1.74 (s, 3H), 1.48-1.56 (m, 1H), 1.14-1.28 (m, 2H), 1.08 (d, J = 7.1 Hz, 3H), 0.92 (t, J = 8.0 Hz, 9H), 0.89 (s, 9H), 0.53 (q, J = 7.4 Hz, 6H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 141.7, 131.4, 125.6, 124.2, 77.9, 64.0, 51.4, 48.2, 47.5, 43.3, 37.0, 34.2, 26.3, 21.6, 18.5, 13.7, 7.1, 4.7, -3.9, -4.3; IR (neat) cm^{-1}; HRMS-EI (m/z) calcd for $C_{26}H_{47}O_4Si_2$ [M – CH_3]$^+$ 479.3013, found 479.2996.

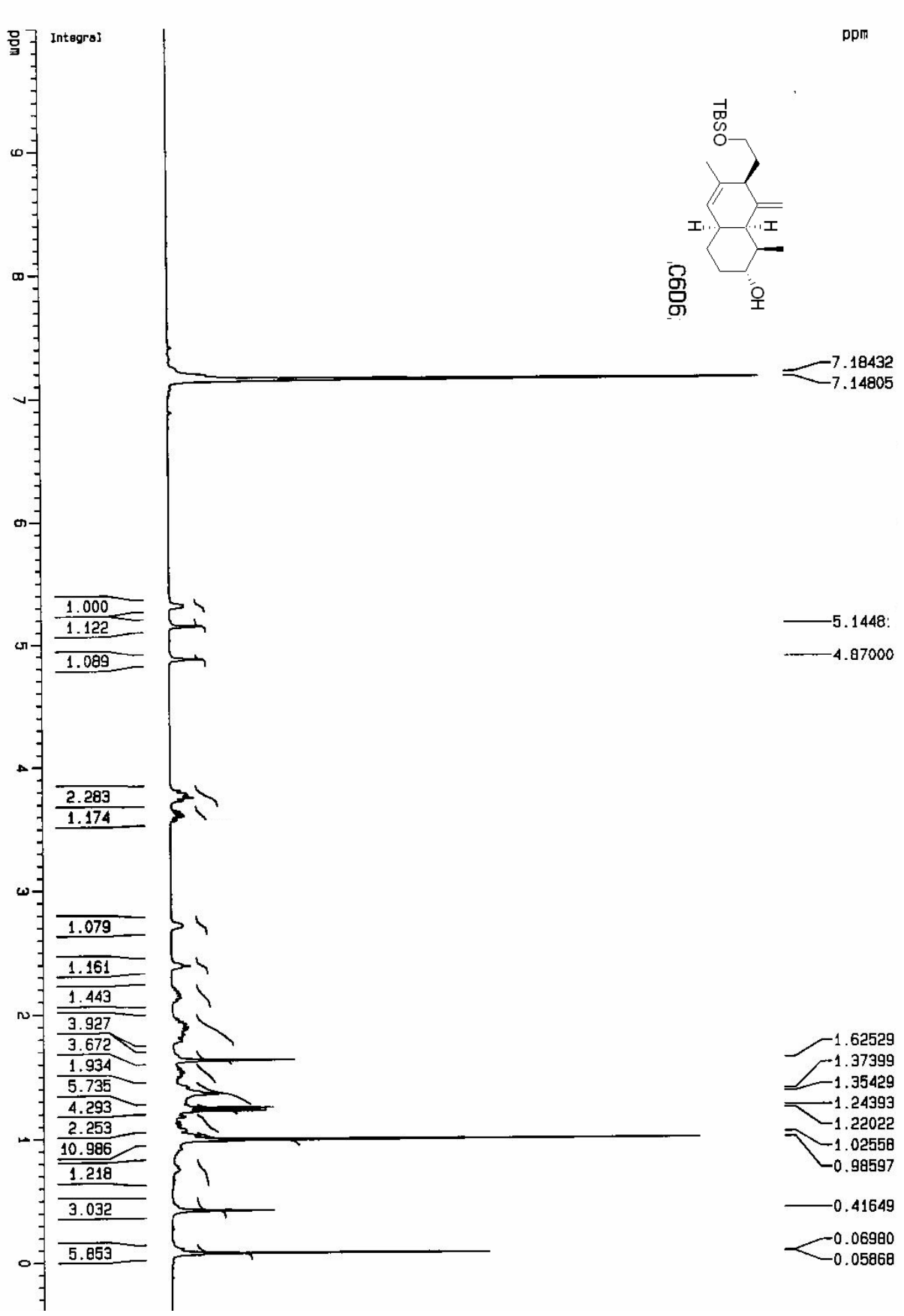
3-(*tert*-Butyldimethylsilyloxy)-4,7-dimethyl-5-methylene-6-triethylsilyloxymethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalene (4.64′)

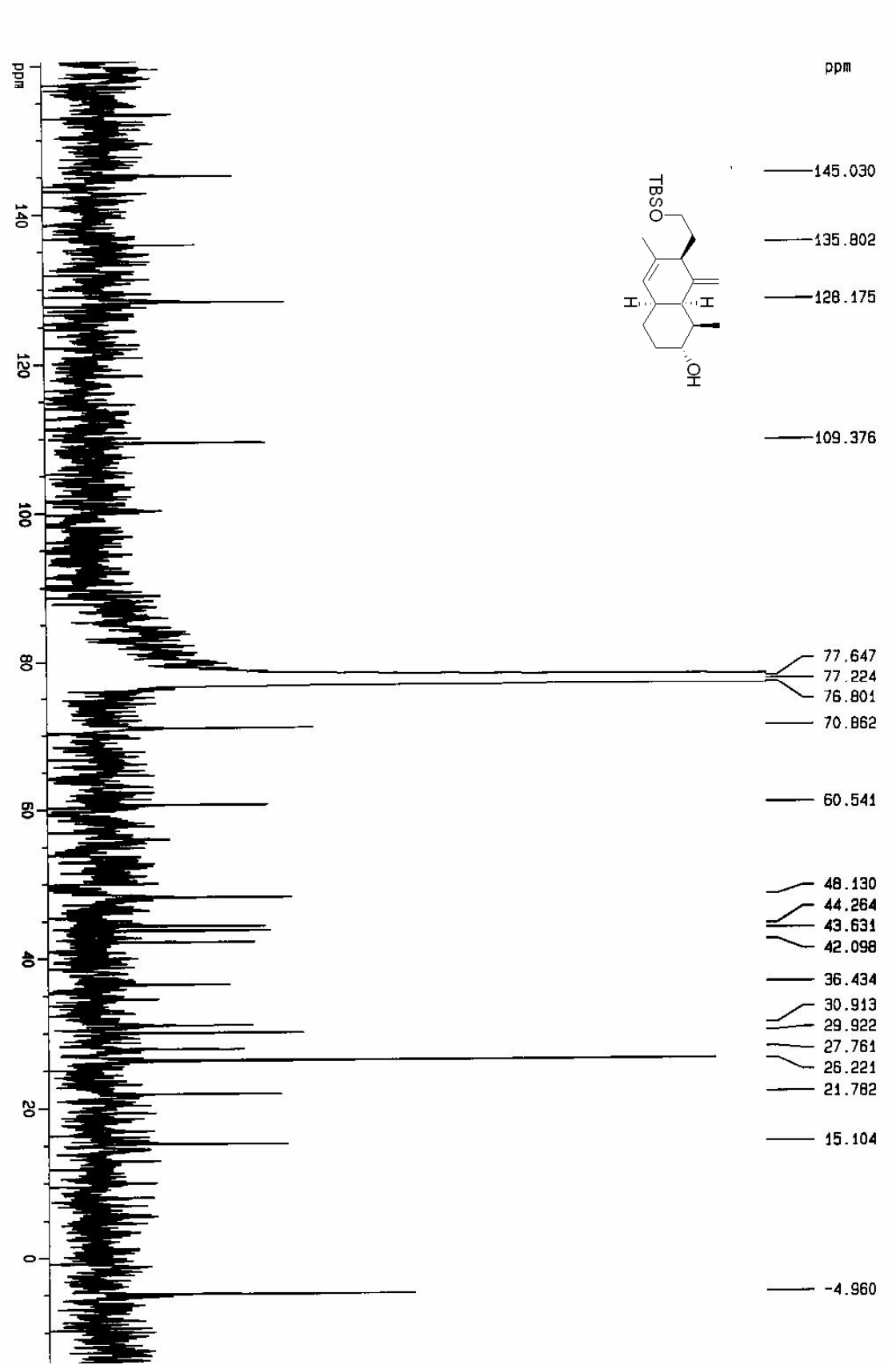


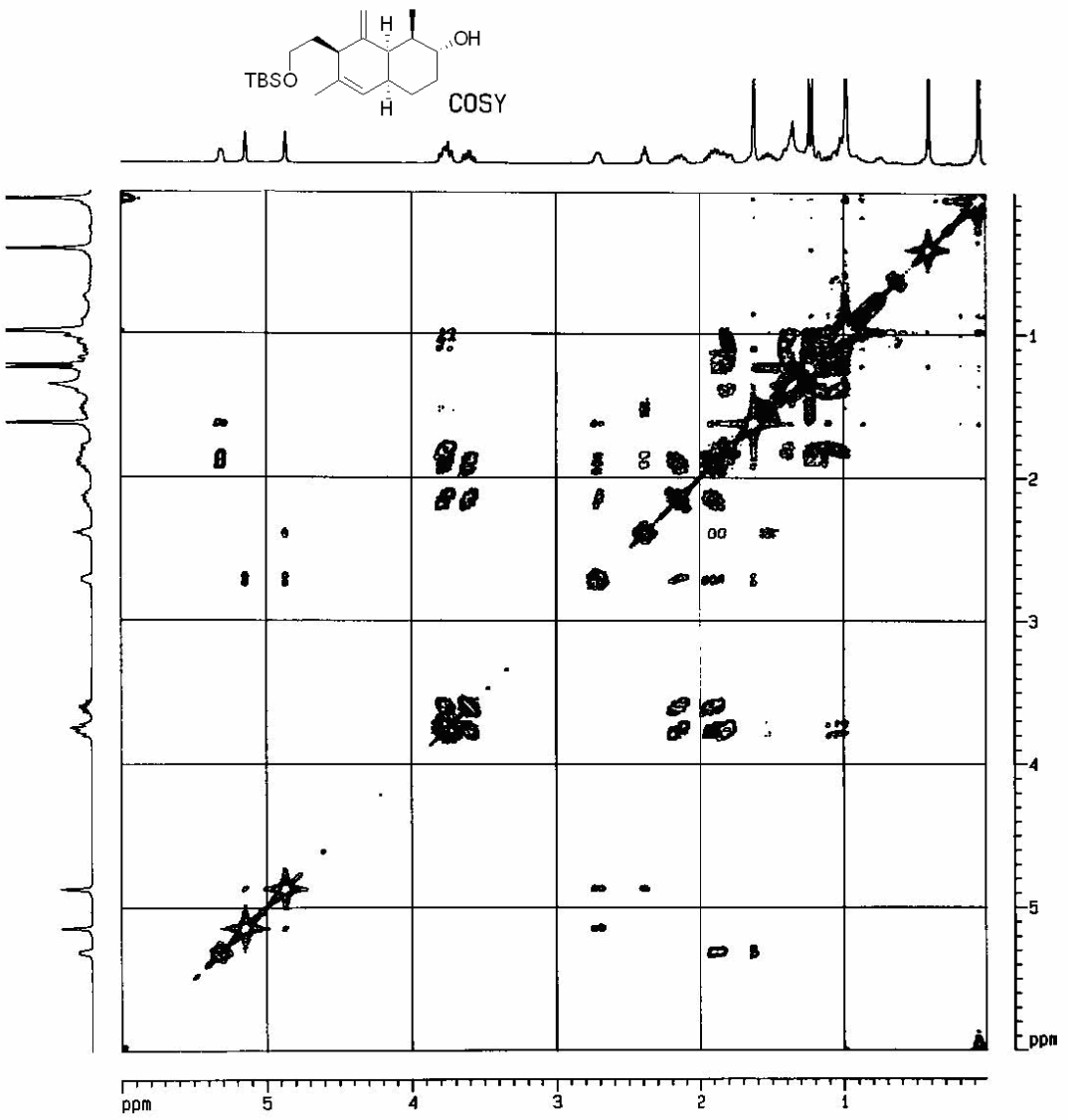
$[\alpha]^{23}_{D}$ -19.2º (*c* = 0.85, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.42 (dd, J = 1.5, 2.9 Hz, 1H), 5.25 (s, 1H), 4.88 (s, 1H), 3.91-4.02 (m, 2H), 3.80 (dd, J = 7.4, 10.5 Hz, 1H), 2.71 (s, 1H), 2.58 (t, J = 4.7 Hz, 1H), 2.05-2.15 (m, 1H), 1.82-1.91 (m, 1H), 1.68-1.80 (m, 1H), 1.72 (s, 3H), 1.42-1.53 (m, 1H), 1.20-1.30 (m, 2H), 1.14 (d, J = 7.2 Hz, 3H), 0.95 (t, J = 7.7 Hz, 9H), 0.90 (s, 9H), 0.57 (q, J = 7.5 Hz, 6H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.5, 134.3, 129.2, 109.6, 71.5, 61.6, 49.8, 48.0, 43.7, 41.9, 36.6, 29.9, 27.8, 26.2, 21.5, 18.4, 15.8, 7.1, 4.7, -3.8, -4.3; IR (neat) 767, 1078, 1249, 1458, 2876, 2953 cm^{-1}; HRMS-EI (m/z) calcd for $C_{26}H_{50}O_2Si_2$ [M^+] 450.3349, found 450.3344.

APPENDIX

Supporting information of Chapter 4: study towards the synthesis of the *cis*-decalin unit of integramycin


Integral
ppm
TBSO
H
H
OH
C6D6
7.18432
7.14805
5.14481
4.87000
1.62529
1.37399
1.35429
1.24393
1.22022
1.02558
0.98597
0.41649
0.06980
0.05868
1.000
1.122
1.089
2.283
1.174
1.079
1.161
1.443
3.927
3.672
1.934
5.735
4.293
2.253
10.986
1.218
3.032
5.853


ppm
140
120
100
80
60
40
20
0
TBSO
H
H
OH
ppm
145.030
135.802
128.175
109.376
77.647
77.224
76.801
70.862
60.541
48.130
44.264
43.631
42.098
36.434
30.913
29.922
27.761
26.221
21.782
15.104
-4.960



Current Data Parameters

NAME	lw09240402
EXPNO	111
PROCNO	1

F2 - Acquisition Parameters

Date_	20040924
Time	19.29
INSTRUM	spect
PROBHD	5 mm QNP 1H
PULPROG	cosy
TD	1024
SOLVENT	MeOH
NS	16
DS	16
SWH	1795.977 Hz
FIDRES	1.753884 Hz
AQ	0.2851316 sec
RG	256
DW	278.400 usec
DE	6.00 usec
TE	300.0 K
d0	0.00000300 sec
D1	1.00000000 sec
IN0	0.00055680 sec

CHANNEL f1

NUC1	1H
P0	11.00 usec
P1	7.10 usec
PL1	-6.00 dB
SFO1	300.1309004 MHz

F1 - Acquisition parameters

MDD	1
TD	256
SFO1	300.1309 MHz
FIDRES	7.015535 Hz
SW	5.984 ppm

F2 - Processing parameters

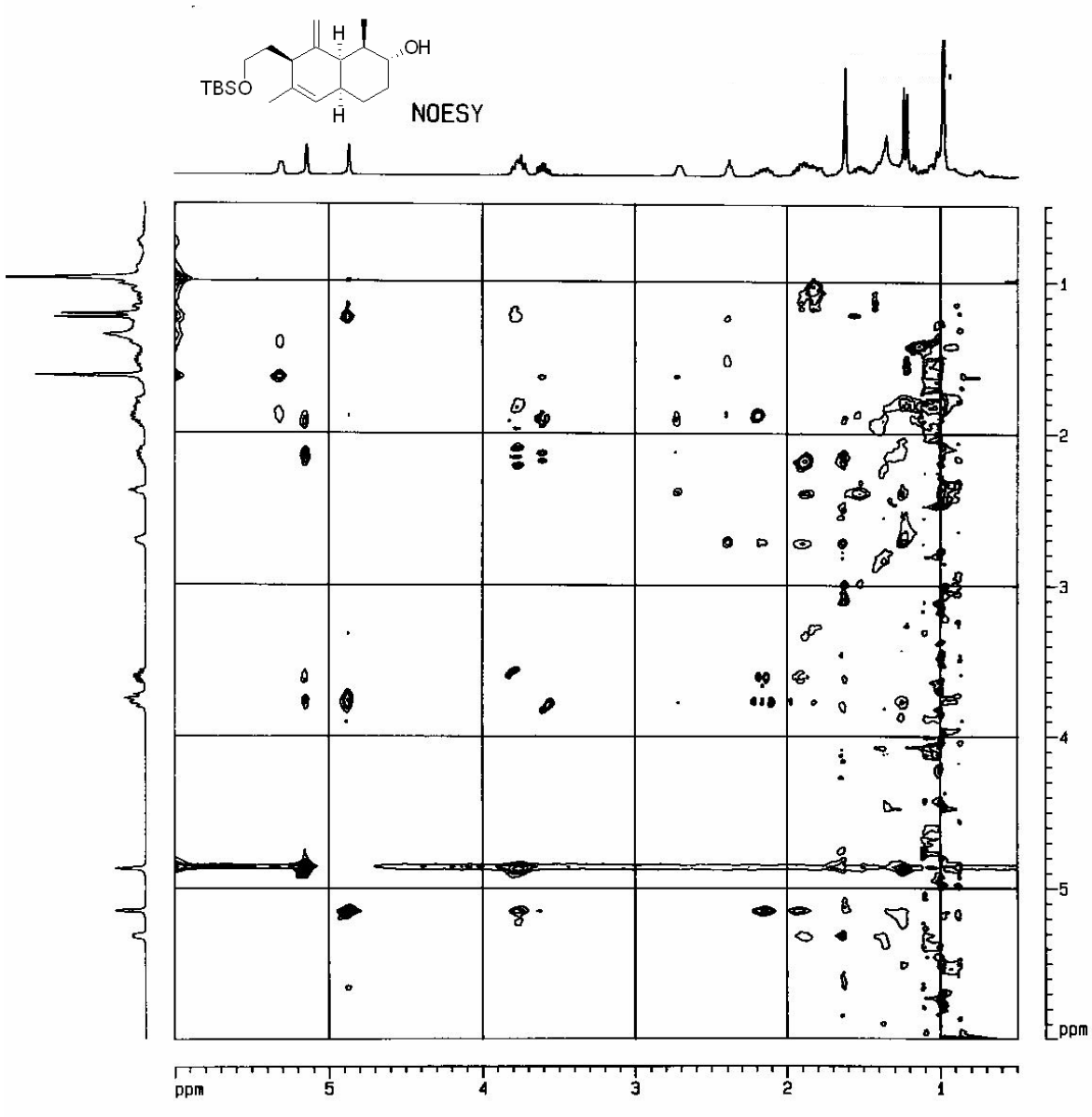
SI	512
SF	300.1299999 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0
PC	1.00

F1 - Processing parameters

SI	1024
MC2	QF
SF	300.1299971 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0

2D NMR plot parameters

CX2	15.00 cm
CX1	15.00 cm
F2PLO	6.002 ppm
F2LO	1801.47 Hz
F2PHI	0.018 ppm
F2HI	5.49 Hz
F1PLO	6.002 ppm
F1LO	1801.28 Hz
F1PHI	0.018 ppm
F1HI	5.30 Hz
F2PPMCM	0.39893 ppm/cm
F2HZCM	119.73180 Hz/cm
F1PPMCM	0.39893 ppm/cm
F1HZCM	119.73180 Hz/cm



Current Data Parameters

NAME	lw09240402
EXPNO	1111
PROCNO	1

F2 - Acquisition Parameters

Date_	20040924
Time	21.03
INSTRUM	spect
PROBHD	5 mm QNP 1H
PULPROG	noesytp
TD	1024
SOLVENT	MeOH
NS	32
DS	16
SWH	1795.977 Hz
FIDRES	1.753884 Hz
AQ	0.2851316 sec
RG	300
DW	278.400 usec
DE	6.00 usec
TE	300.0 K
d0	0.00000300 sec
D1	1.00000000 sec
D8	0.34999998 sec
IN0	0.00027840 sec

CHANNEL f1

NUC1	1H
P1	7.10 usec
PL1	-6.00 dB
SFO1	300.1309004 MHz

F1 - Acquisition parameters

NDO	2
TD	781
SFO1	300.1309 MHz
FIDRES	2.299587 Hz
SW	5.984 ppm

F2 - Processing parameters

SI	1024
SF	300.1299951 MHz
WDW	EM
SSB	0
LB	7.00 Hz
GB	0
PC	1.40

F1 - Processing parameters

SI	1024
MC2	TPPI
SF	300.1299955 MHz
WDW	EM
SSB	0
LB	7.00 Hz
GB	0

2D NMR plot parameters

CX2	15.00 cm
CX1	15.00 cm
F2PLO	8.002 ppm
F2LO	1801.49 Hz
F2PHI	0.498 ppm
F2HI	149.33 Hz
F1PLO	8.001 ppm
F1LO	1801.10 Hz
F1PHI	0.498 ppm
F1HI	148.94 Hz
F2PPMCM	0.36699 ppm/cm
F2HZCM	110.14391 Hz/cm
F1PPMCM	0.36699 ppm/cm
F1HZCM	110.14391 Hz/cm