Synthesis of Structurally and Stereochemically Diverse Tetrahydropyran Structures via DDQ-Mediated Oxidative Carbon–Hydrogen Bond Activation

by

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Submitted to the Graduate Faculty of

School of Arts and Sciences in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh

2011

UNIVERSITY OF PITTSBURGH

SCHOOL OF ARTS AND SCIENCES

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Synthesis of Structurally and Stereochemically Diverse Tetrahydropyran Structures via DDQ-Mediated Oxidative Carbon–Hydrogen Bond Activation

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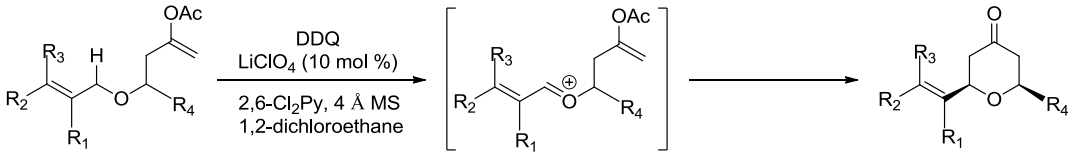
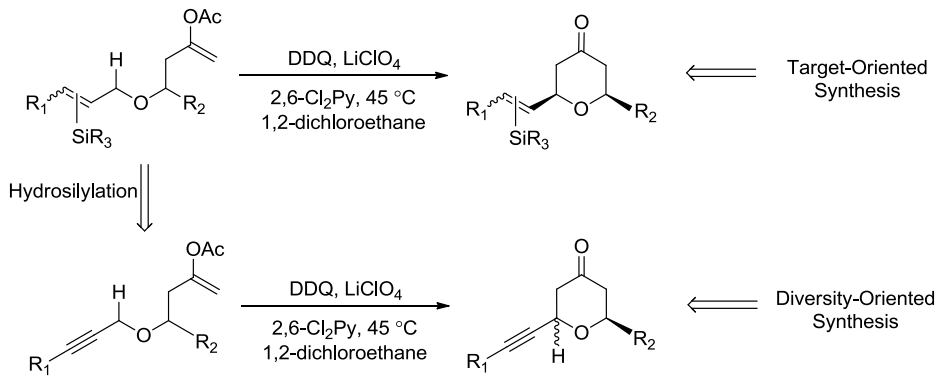
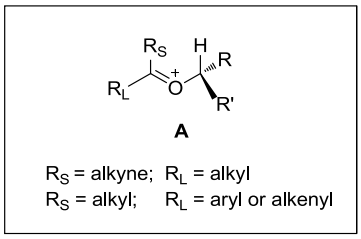
The 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)-mediated oxidative carbon–hydrogen bond cleavage of allylic ethers has been studied. The generated *α,β*-unsaturated oxocarbenium ions can be captured by appended enol acetate nucleophiles to stereoselectively provide *cis*-2,6-disubstituted tetrahydropyrones. Alkenes with a wide assortment of substitution patterns undergo oxidative cyclizations efficiently, and commonly encountered functional groups on either side of the ether linkage are well tolerated.

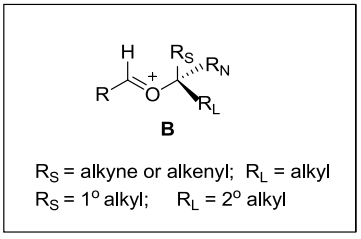


The scope of this method has successfully been expanded to (silyl)allylic and propargylic ethers. The generated vinylsilane-substituted tetrahydropyrans are versatile precursors for a wide range of functional group interconversions and stereocontrolled additions. The cyclization of (silyl)allylic ethers proceeds efficiently to generate *cis*-2,6-disubstituted tetrahydropyrones with excellent stereocontrol, and therefore is preferable for target-oriented syntheses. The cyclization of propargylic ethers results in a mixture of *cis*- and *trans*-2,6-disubstituted tetrahydropyrones, and it is applicable in diversity-oriented syntheses.

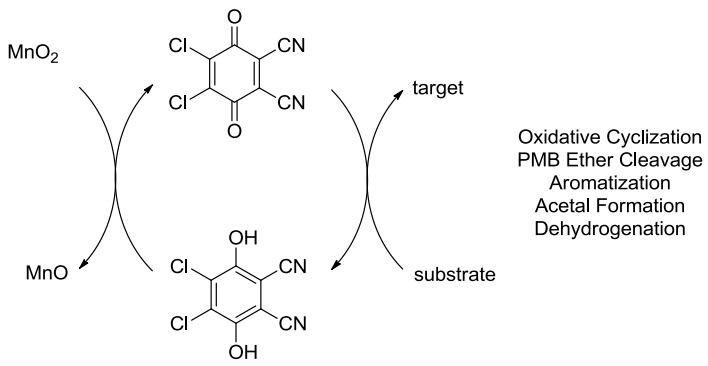


Two models of the geometries of 1,1-disubstituted oxocarbenium ions (A) and the conformations of oxocarbenium ions that contain a tertiary stereocenter (B) have been designed. Both models have been applied to highly stereoselective syntheses of tetrahydropyrans containing tertiary ethers.





DDQ-catalyzed oxidative cyclizations for tetrahydropyran synthesis have been achieved by using MnO_2 as an inexpensive and environmentally benign terminal oxidant. This catalytic system is also applicable to other commonly encountered DDQ-mediated reactions, such as PMB ether cleavages and dehydrogenations. The products are quite easy to purify, and the yields are comparable with the corresponding reactions using stoichiometric DDQ.


MnO2
MnO
target
substrate
Oxidative Cyclization
PMB Ether Cleavage
Aromatization
Acetal Formation
Dehydrogenation

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LIST OF ABBREVIATIONS

Ac	Acetyl
AIBN	Azobisisobutyronitrile
Bn	Benzyl
BOC	*tert*-Butyloxycarbonyl
CDC	Cross dehydrogenative coupling
coe	Cyclooctene
cod	1,5-Cyclooctadiene
Cp^*	Pentamethylcyclopentadienyl
cy	Cyclohexyl
dba	Dibenzylideneacetone
DCC	*N,N'*-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	Diisobutylaluminum hydride
DMAP	4-Dimethylaminopyridine
DMF	*N,N'*-Dimethylformamide
DMP	Dess-Martin periodinane
dr	Diastereomeric ratio
DMSO	Dimethylsulfoxide
DVDS	1,3-Divinyl-1,1,3,3-tetramethyldisiloxane
ee	Enantiomeric excess

EDG	Electron donating group
EI	Electron impact ionization
EWG	Electron withdrawing group
FG	Functional group
HRMS	High-resolution mass spectrometry
HMPA	Hexamethylphosphoramide
mCPBA	Meta-Chloroperoxybenzoic acid
MS	Methanesulfonyl
M.S.	Molecule sieves
NMO	*N*-Methylmorpholine-*N*-oxide
OTf	Trifluoromethanesulfonate
PG	Protecting group
PMB	*para*-Methoxybenzyl
Py	Pyridine
PPTS	Pyridine *p*-toluenesulfonate
PTSA	*p*-Toluenesulfonic acid

PREFACE

This is probably the best opportunity for me to express my appreciation to many people who have helped me. First and foremost I would like to thank my advisor Professor Paul E. Floreancig. Thanks for allowing me to join his group and sharing in the development of those challenging but rewarding projects. I appreciated all his contributions of time, ideas, and funding to make my Ph.D. experience productive and stimulating. The joy and enthusiasm he has for his research was contagious and motivational for me, and my whole life will benefit from this precious and wonderful experience working with him.

I would like to think Professor Peter Wipf, Kazunori Koide, and Xiang-Qun Xie for the guidance they gave me as my committee members, and thank Professor Dennis P. Curran for serving as my proposal mentor. Their help and advices are greatly appreciated.

To the past and present members of the Floreancig group, I wish to thank all of you for your friendship and for your help during my time in Pittsburgh. I would especially like to express my gratitude to Drs. Shuangyi Wan, Qing Xiao, Wangyang Tu, Hyung Hoon Jung and Michael E. Green for their help when I started in the Floreancig group and thereafter. Fanghui, Dane, Chunliang, yubo and Gudi, we encouraged each other and shared a lot of happy and rough times in the lab. Xun, Guangrong and Youwei, good luck and now it is up to you guys to make the group even stronger…

Last but not the least, I would like to thank my mom and dad. A lot has happened over the past four and half years to get me through my graduate career. Without the love and support you have shown me over the past 29 years, I would not be where I am today. Thank you for standing by me during the good times, and for helping me stay motivated through the tough times. This is for you!

1.0 CARBON–CARBON BOND CONSTRUCTION THROUGH OXIDATIVE CARBON–HYDROGEN BOND CLEAVAGE OF VINYL AND ALLYLIC ETHERS

1.1 INTRODUCTION OF C–H BOND ACTIVATION

Carbon–carbon bond formation is a fundamental transformation in organic synthesis. Over the past few decades, much effort has been made in the development of various metal-catalyzed coupling reactions, such as the Heck reaction, the Suzuki reaction, and olefin metathesis, which have greatly advanced modern organic synthesis.[1] However, most methods require that each reactant has a pre-existing functional group (Figure 1). Moreover, incorporating the functional group into a carbon skeleton typically involves multiple steps, thereby lengthening the synthetic sequence. C–C bond formation through C–H bond activation reactions has attracted great attention recently.[2] In such a process, a selective and direct one step formation of C–C bonds from C–H bonds allows straightforward and concise approaches to access target molecules with minimum intermediary functionalizations. Aside from the benefits concerning step economy,[3] this approach is also attractive in terms of atom economy.[4] Four representative types of C–H functionalization strategies for C–C bond formation and their application in complex molecule syntheses will be briefly discussed in this introduction.

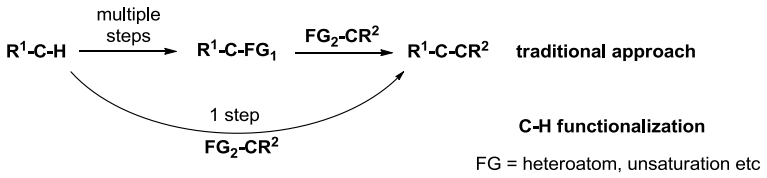
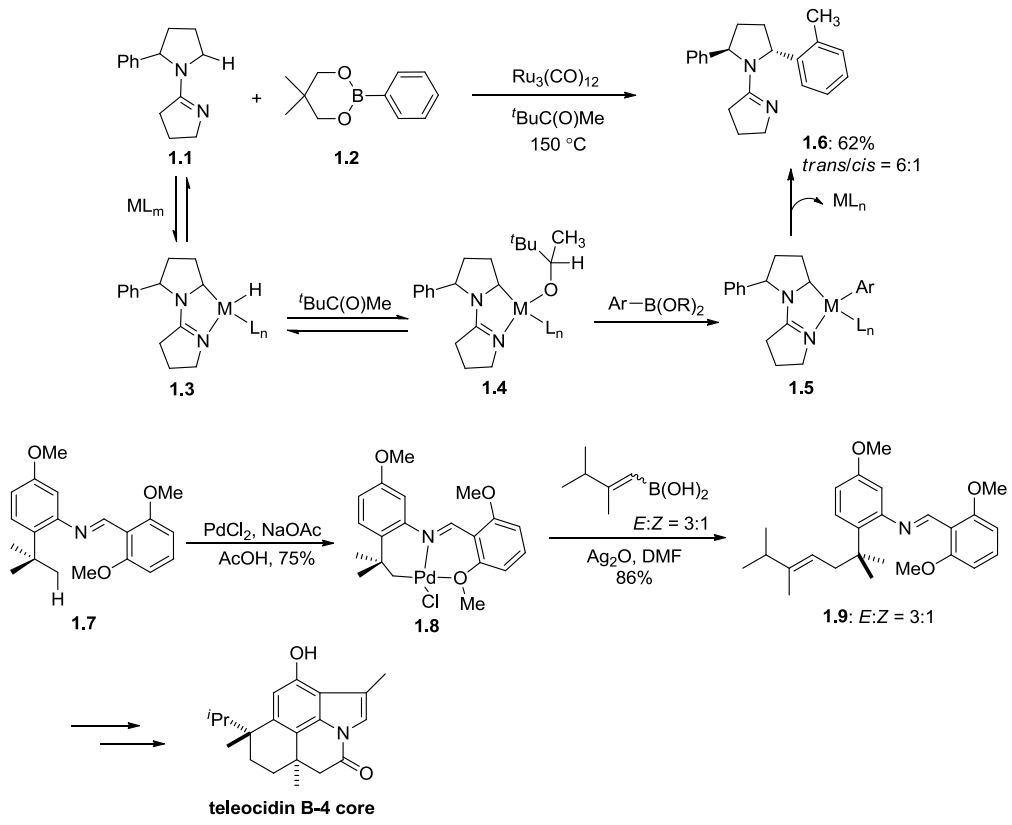


Figure 1. Synthetic efficiency of traditional approach and C–H functionalization

1.1.1 C–H activation through transition metal-catalyzed metallation

Transition metals insert into C–H bonds, and the resulting organometallic complex serves as a useful intermediate for C–C bond formation. A suitable Lewis basic group can direct the transformation with high regiospecificity, which is known as coordination-directed metallation.

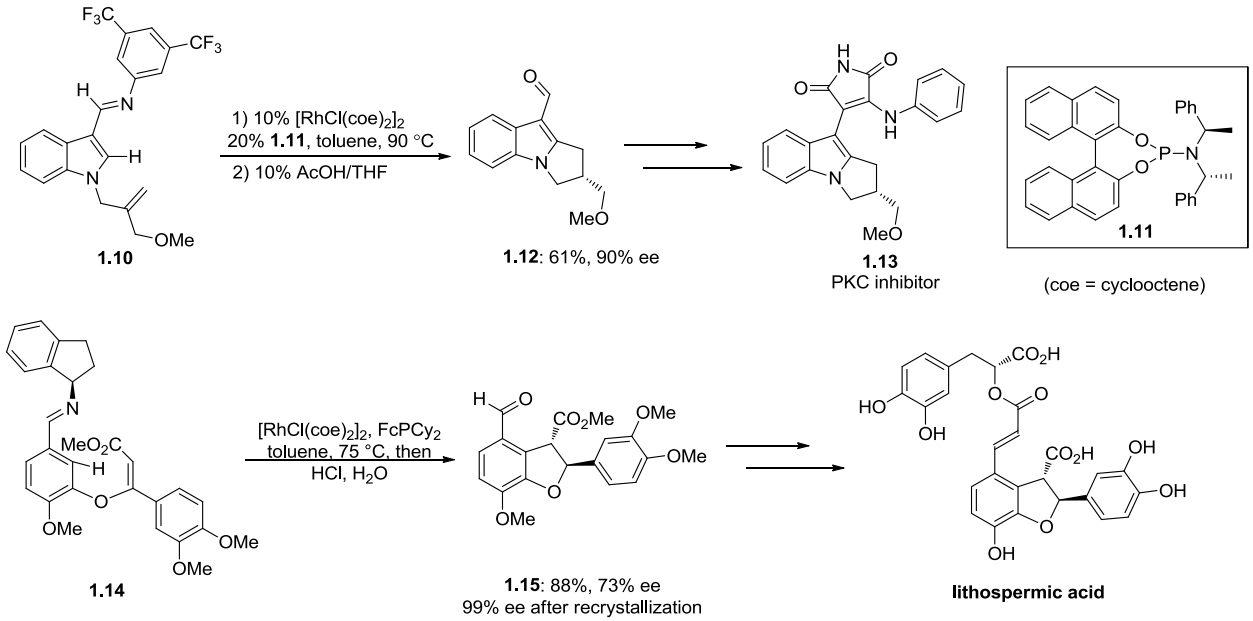
Sames disclosed an sp^3 C–H bond arylation of amidine-substituted pyrrolidines through directed metallation (Scheme 1).[5] The amidine **1.1** directs the insertion of $Ru_3(CO)_{12}$ into a C–H bond at 150 ^oC to generate metal hydride **1.3**, which is oxidized by pinacolone to give metal-alkoxide **1.4**. Intermediate **1.4** undergoes transmetalation with phenylboronate ester **1.2** affording metal-aryl **1.5**. The subsequent reductive elimination results in pyrrolidine **1.6** in 62% yield with the *trans*/*cis* ratio of 6:1. The directing group amidine can be removed in one step from the sterically hindered pyrrolidine with TFA and H_2NNH_2. Another interesting example is the teleocidin B-4 synthesis by the same group (Scheme 1).[6] The imine and methoxy group in **1.7** can direct $PdCl_2$ to insert into the C–H bond of methyl group forming stable palladacycle **1.8**, which undergoes transmetallation with an alkenylboronic acid to afford the alkene **1.9** in 86% yield. The non-traditional activation of less reactive C–H bond of highly functionalized substrates opens a new synthetic strategy for modern synthesis.



Scheme 1. Directed sp^3 C–H activation and the application in natural product synthesis

The coordination-directed metallation has also been applied to activate sp^2 C–H bonds. Bergman and Ellman reported a rhodium-chiral phorphoramidite-mediated enantioselective cyclization reaction via directed C–H activation (Scheme 2).[7] Substrate **1.10** reacts with $[RhCl(coe)_2]_2$ and chiral phosphoramidite **1.11** through a process involving imine-directed C–H activation, asymmetric hydrometallation, and reductive elimination to give dihydropyrroloindole **1.12** in 61% yield and 90% ee. This method is applied to the asymmetric synthesis of the potent protein kinase C inhibitor tricyclic indole **1.13**.[8] The method proved not to be applicable in the enantioselective total synthesis of the HIV-1 integrase inhibitor lithospermic acid; the yields and enantioselectivities are unsatisfactory. However, the problem is solved by using a chiral imine auxiliary **1.14** to direct a diastereoselective C–H insertion into the prochiral olefin (Scheme 2).[9]

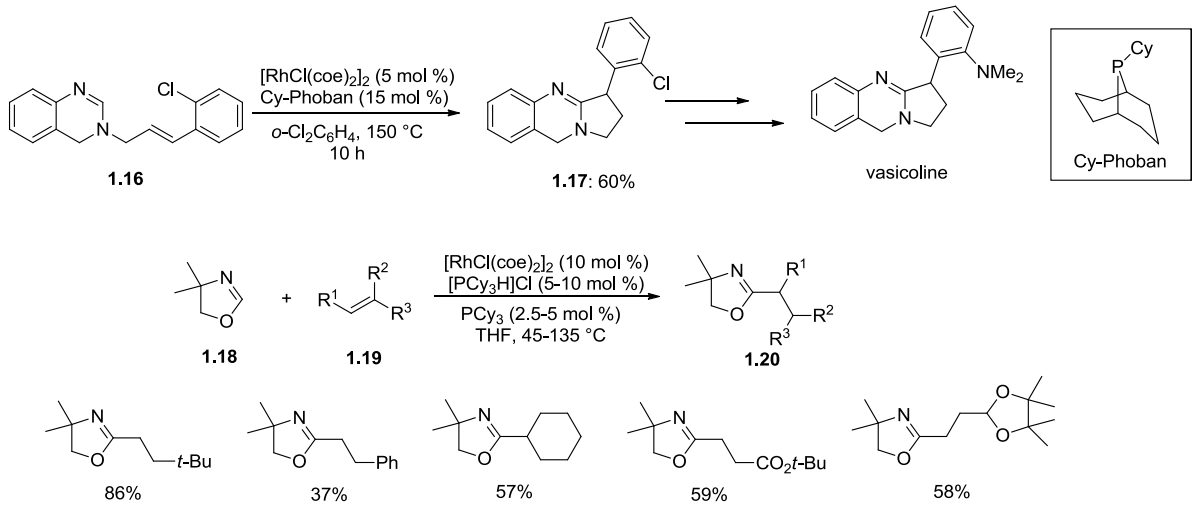
Chiral imine **1.14** reacts with $[RhCl(coe)_2]_2$ and $FcPCy_2$ to afford dihydrobenzofuran **1.15** in 88% yield and 73% ee, which is improved to 99% after recrystallization. Both syntheses are noteworthy because they provide much more efficient entries to these two inhibitors through C–H activation.



Scheme 2. Directed sp^2 C–H activation in natural product synthesis

Transition metals can also direct insert into C–H bonds of nitrogen heterocycles in the absence of directing groups, providing a powerful approach to regioselectively introducing various substituents onto the heterocycle scaffold. Bergman and Ellman reported a Rh-catalyzed intramolecular dihydroquinazoline alkylation yielding ring-fused pyrrolo[2,1-*b*]quinazolines, a common structural motif for biologically active natural products (Scheme 3).[10] Exposing dihydroquinazoline **1.16** to $[RhCl(coe)_2]_2$ and a conformationally rigid cyclohexylphoban ligand at 150 ^oC led to tricycle **1.17** in 60% yield. The intermediate was employed in a total synthesis of vasicoline. The alkylation of oxazolines was also achieved in the presence of Rh-phosphine

catalyst to furnish a variety of alkenes with a range of functionality.[11] These alkylated oxazolines can be converted to corresponding carboxylic acids or esters using known protocols.[12]

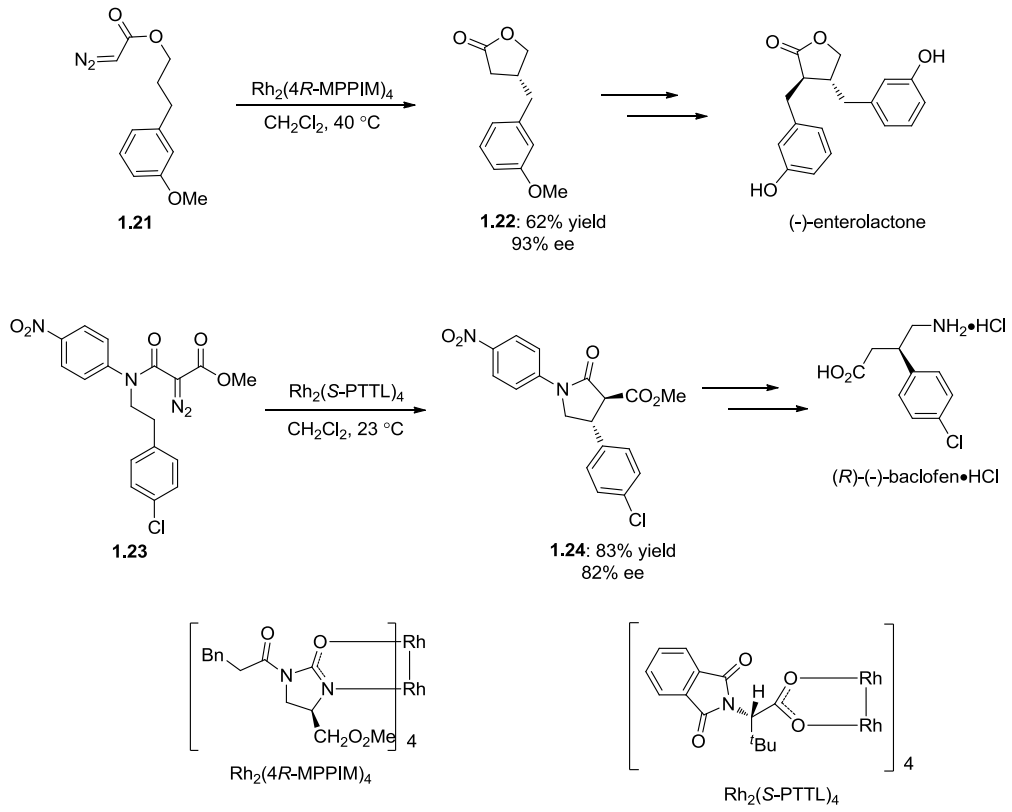


Scheme 3. Heterocycle metalation without directing groups

1.1.2 C–H activation through metal carbenoid insertion

Metal carbenoid insertion is a powerful strategy for C–H functionalization.[13] Intramolecular reactions have been extensively studied. Metal carbenoids, usually generated from diazo compounds by the use of a transition metal, insert directly into a proximal C–H bond to give cyclic ketones, lactones and lactams in one step, without the participation of the metal (Scheme 4).[14] In most of the precedents, the regioselectivity in intramolecular metal carbenoid insertions occurs to form 5-membered ring structures through 1,5-C–H insertion. Dirhodium complexes are efficient catalysts for the process, and good chemo-, diastereo- and enantioselectivity can be achieved by tuning the ligands on the metal.[13] As demonstrated in

natural product synthesis (Scheme 4), the unique and direct strategy is attractive in terms of its neutral reaction conditions, good functional compatibility and high stereoselectivity.



Scheme 4. Intramolecular metal carbenoid insertion in natural product synthesis

Compared with intramolecular reactions, intermolecular transformations would be more efficient because multistep substrate synthesis can be avoided. However, the control of regioselectivity of intermolecular process proves to be much more challenging than that of intramolecular process mainly due to the high reactivity of metal carbenoids commonly derived from acceptor-only substituted diazoacetates (Figure 2).[15] The major breakthroughs have been made to attenuate the carbenoid reactivity by incorporating a donor substituent like an aryl or

vinyl group into the carbenoid.[13,16] This modification is beneficial to suppress carbene dimerization byproducts as well as increase the regioselectivity for intermolecular processes.

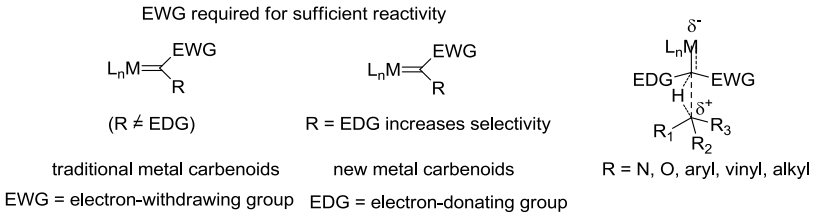
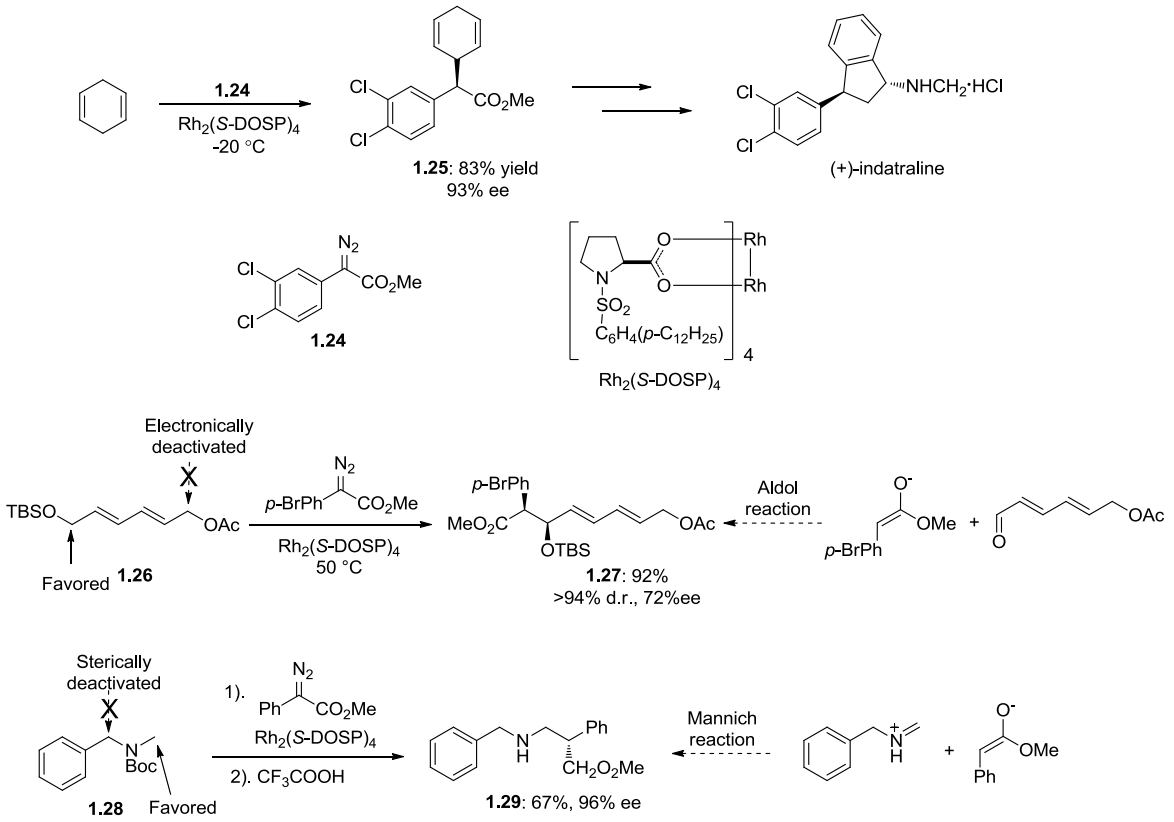


Figure 2. Controlling factors of carbenoid reactivity

The intermolecular donor/acceptor carbenoid C–H insertion has been successfully applied to a number of complex molecule syntheses, as demonstrated in the synthesis of the potent monoamine re-uptake inhibitor (+)-indatraline by Davies (Scheme 5).[17] The key step involved the allylic C–H activation of 1,4-cyclohexadiene by the rhodium-carbenoid derived from **1.24**, leading to **1.25** in 83% yield and 93% ee. In addition, this strategy can provide complementary approaches to give versatile structures such as **1.27** and **1.29**, as shown in Scheme 5.[18,19] These structures are usually synthesized by classic aldol and Mannich reactions, respectively.

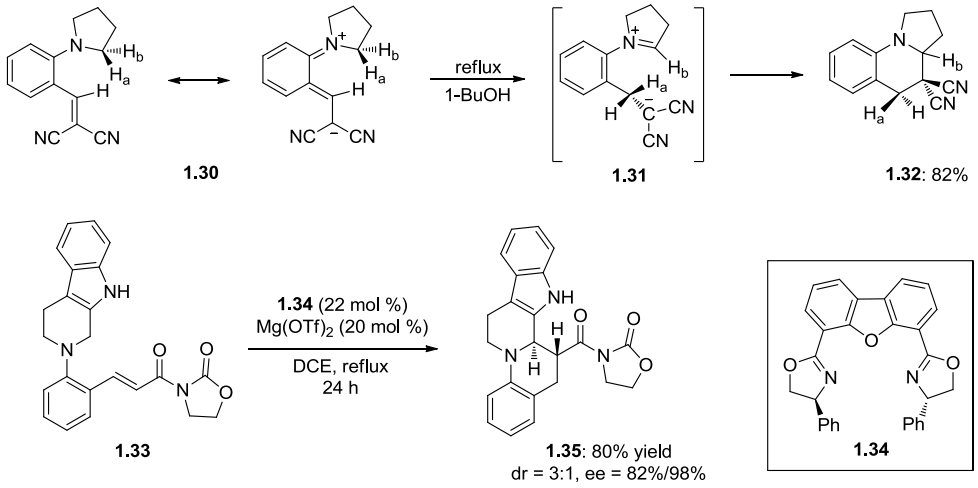


Scheme 5. Intermolecular carbenoid C–H insertions in synthesis

1.1.3 C–H activation through intramolecular hydride transfer

Intramolecular hydride transfer is another strategy for selective activation of a variety of C–H bonds. One of the most well studied examples is the "*tert*-amino effect" that involves the thermal cyclization of tertiary anilines bearing electron deficient alkenes to afford a 6-membered ring (Scheme 6).[20] Reinhoudt reported that when aryl pyrrolidine **1.30** in BuOH was heated to reflux, a 1,5-hydride transfer occurred to the dicyanovinyl moiety to afford **1.32** in 82% yield in 2 h.[21] The mechanistic study shows that the first, rate limiting step comprises hydrogen migration in a conformation in which the vinyl group points away from the amino group to give a dipolar

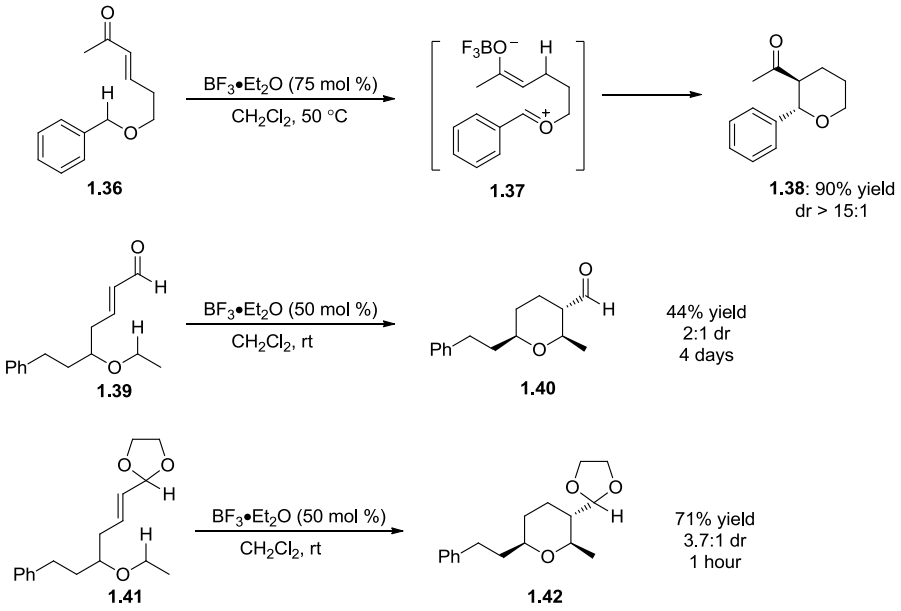
intermediate **1.31**; the migrating hydrogen atom (H_a) stays on the same face of the substrate. Seidel and co-workers described a first catalytic enantioselective variant of the reaction.[22] Substrate **1.33** was converted to ring-fused tetrahydroquinoline **1.35** in 80% yield with high enantioselectivity, though the diastereocontrol was moderate. The electrophilicity of *α,β*-unsaturated acyl oxazolidinone in **1.33** was enhanced by the catalysis of chiral Lewis acid formed from $Mg(OTf)_2$ and ligand **1.34**.



Scheme 6. C–H activations through *tert*-amino effect

Simple ethers can also undergo similar transformations to provide C–C bonds. Sames developed a Lewis acid-mediated intramolecular hydride transfer to generate oxygen-containing heterocycles with high diastereocontrol (Scheme 7).[23] The coordination of BF_3•Et_2O to the carbonyl oxygen of **1.36** activated the alkene to undergo a [1,5]-hydride transfer giving intermediate **1.37**; the resulting enolate reacted with the oxocarbenium ion to furnish tetrahydropyran **1.38** in 90% yield with a diastereomeric ratio of 15:1. Enals proved to be poor acceptor components in such transformations, illustrated by the reaction of **1.39**, in which the cyclization of **1.39** was very slow under similar conditions, taking four days to give **1.40** in 44%

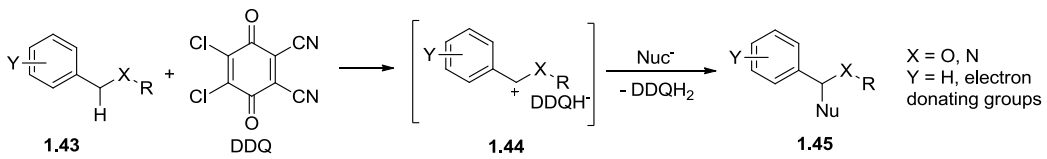
yield (Scheme 7).[24] The problem was addressed by converting aldehyde **1.39** to acetal **1.41**, with a dramatic improvement in reactivity, yield and stereocontrol.



Scheme 7. C–H activations through intramolecular hydride transfer to alkenes

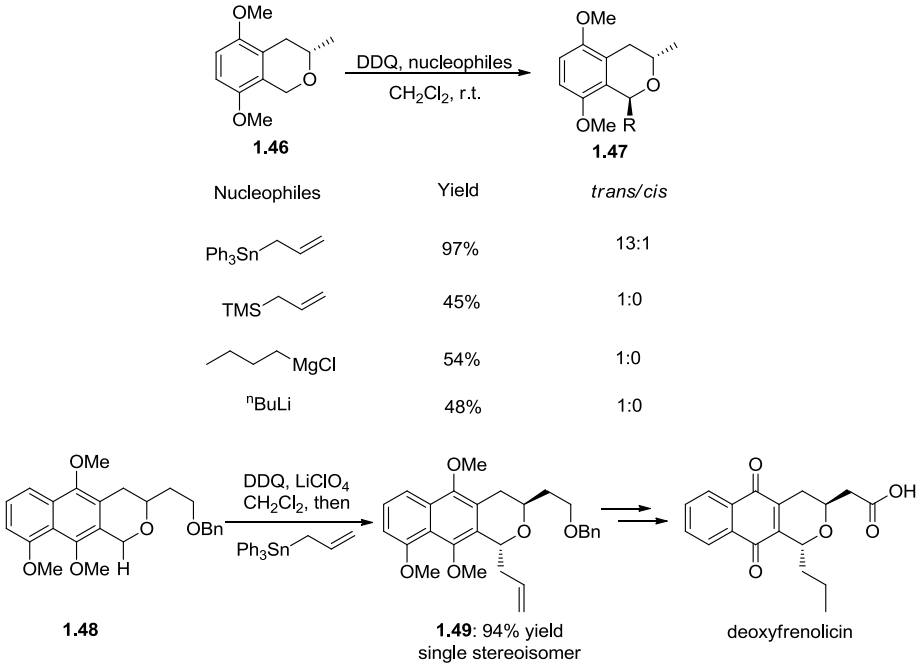
1.1.4 C–H activation through DDQ oxidation

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) can mediate oxidative C–H bond cleavage at benzylic positions.[25] Benzylic substrate **1.43** reacts with DDQ through the cleavage of the benzylic C–H bond to generate carbocation **1.44** (Scheme 8), which readily reacts with a variety of carbon nucleophiles to give **1.45**.



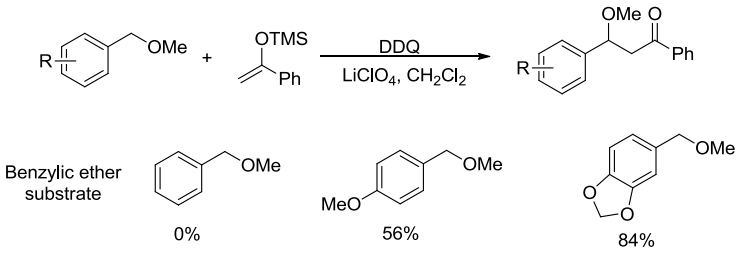
Scheme 8. DDQ induced oxidative transformation at the benzylic position

Xu and coworkers reported the C–H functionalization of isochroman substrates with a variety of carbon nucleophiles in high yields and with good stereochemical control (Scheme 9).[26] High *trans*-selectivity is observed for 3-substituted isochroman **1.46** especially with strong nucleophiles. This method was subsequently applied in a total synthesis of deoxyfrenolicin.[27] As depicted in scheme 9, **1.48** reacted with DDQ and allyl triphenyltin smoothly to provide **1.49** in 94% yields as a single stereoisomer. The synthesis was completed in five steps from the intermediate **1.49**.



Scheme 9. DDQ-mediated C–H functionalization of isochroman substrates

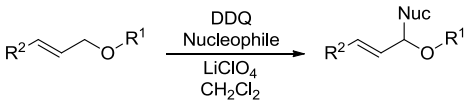
The DDQ-mediated C–H cleavage process was expanded to acyclic benzylic ether substrates (Scheme 10).[28] Electron rich benzylic ethers reacted readily with DDQ to yield the desired products; however, no reaction was observed for the non-substituted benzylic ethers under the same condition. The author's explanation was that in the non-substituted benzylic case the absence of the stabilizing group prevented the initial hydrogen abstraction.

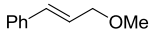
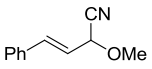
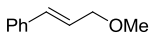
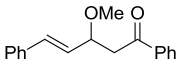
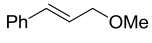
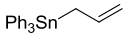
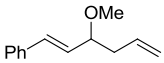
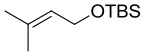
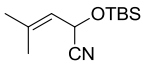


Scheme 10. DDQ-mediated oxidative C–H functionalization of acyclic benzylic ethers

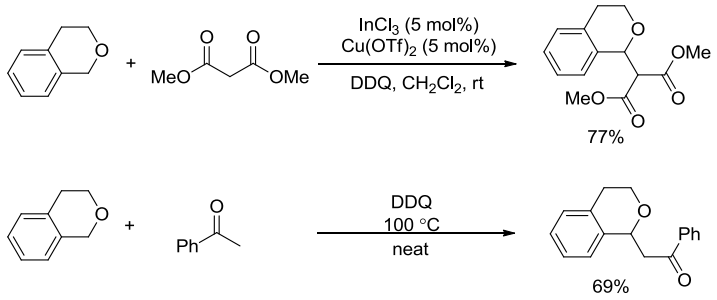
DDQ can also react with allylic ethers yielding similar carbocation intermediates. In 1987, Mukaiyama documented that the intermediate carbocations from allylic ether oxidation react with a variety of carbon nucleophiles to form new C–C bonds (Table 1).[29] The electron rich phenyl-substituted allylic ethers were excellent substrates for the process (entries 1-3, table 1), though reactions with simple alkyl-substituted allylic ethers did not work very well (entry 4, table 1). $LiClO_4$ proved to be pivotal for the high yields, presumably because it increased the electrophilicity of the carbocations by counter-ion exchanges. Because the carbon nucleophiles that they explored were not tolerant toward DDQ, the order of reagent addition is critical: excess carbon nucleophiles were added 1 h after DDQ was introduced to the reaction to ensure the complete conversion of all the substrates to intermediate carbocations. The complicated procedure dictated that the intermediate carbocations should be very stable, which limited the substrate scope.

Table 1. DDQ-mediated oxidative C–H cleavage of phenyl-substituted allylic ethers



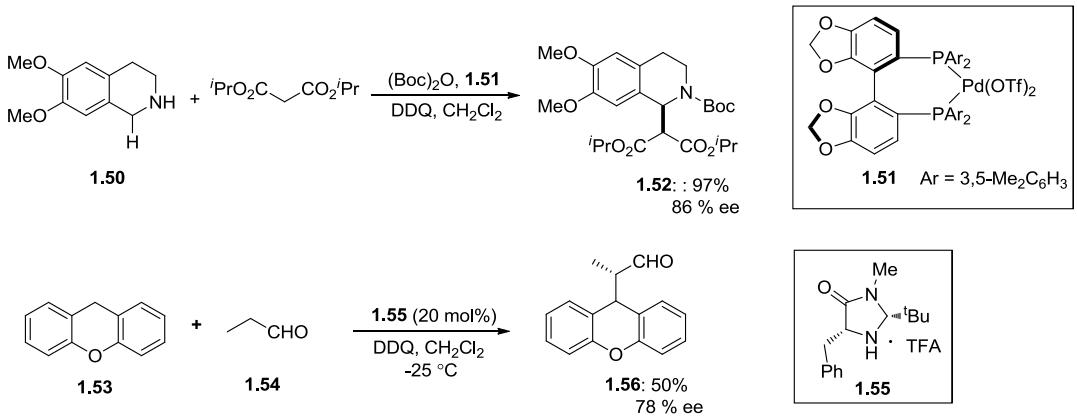
Entry	Substrate	Nucleophile	Product	Yield
1		TMSCN		82%
2				84%
3				79%
4		TMSCN		40%

As mentioned above, all the previously reported carbon nucleophiles were not stable toward DDQ, complicating the procedure and limiting the substrate scope. During the efforts in developing cross dehydrogenative coupling (CDC) reactions, Li explored the DDQ mediated coupling of a variety of dialkyl malonates with isochroman in the presence of $InCl_3$ and $Cu(OTf)_2$ as catalysts (Scheme 11).[31] The malonates were activated by the In/Cu catalyst to serve as the nucleophiles, which were found to be compatible with DDQ. Furthermore, simple ketones can also undergo similar CDC reactions with isochroman upon treatment with DDQ, though the reaction conditions were very harsh (neat at 100 ^{o}C).[32]



Scheme 11. DDQ-mediated CDC reactions using malonates or ketones as nucleophiles

Chiral nucleophiles were also employed to capture the oxidatively generated carbocations to functionalize the heterocyclic structures.[33] Sodeoka developed a catalytic asymmetric functionalization of tetrahydroisoquinoline (Scheme 12). Addition of **1.50** into the reaction system of $(Boc)_2O$, DDQ, diisopropyl malonate and chiral palladium catcalyst **1.51** gave **1.52** in 97% yield and 86% ee. This transformation was proposed to begin with amine acylation, followed by the oxidative generation of an acyliminium ion that was captured by a chiral palladium enolate through a Mannich-type reaction to form the C–C bond. Cozzi et al. reported a stereoselective alkylation of benzylic C–H combining an oxidative C–H cleavage with organocatalysis.[34] MacMillan-type catalyst **1.55** can promote stereoselective α-alkylation of aldehyde **1.54** based on oxidative C–H cleavage of substrate **1.53** to form **1.56** in 50% yield and 78% ee. While the ee was not excellent, this method demonstrated the potential that C–H activation can be coupled with stereoselective organocatalytic reactions, with the advantages of simple reaction conditions and absence of metal catalysts.



Scheme 12. Catalytic asymmetric reactions through oxidative C–H cleavage

While C–C bond formations through DDQ-mediated oxidative C–H bond cleavage of isochroman-related substrates have been well studied, many of them suffer from either limited substrate scope or poor diastereoselectivity. Our goals were to develop a diastereoselective tetrahydropyrone synthesis through intramolecular cyclizations initiated by DDQ-mediated oxidative C–H bond cleavage process, and apply the method to complex molecule synthesis.

Recently the Floreancig group developed a DDQ-mediated oxidative C–H bond cleavage of benzylic ethers leading to tetrahydropyrone synthesis through diastereoselective C–C bond formation (Figure 3).[34] In the presence of 2,6-dichloropyridine and powdered molecular sieves, PMB ether **1.57** readily reacted with DDQ at room temperature to provide tetrahydropyrone **1.58** in 77% yield as a single diastereomer. The mechanism for the C–H bond cleavage has not been unambiguously understood, though a reasonable mechanism proceeds through an electron transfer from PMB ether **1.57** to DDQ to form the radical-ion pair **1.59** followed by hydrogen atom abstraction to form oxocarbenium ion **1.60**. The incorporation of 2,6-dichloropyridine makes the reaction proceed more efficiently because it quenches the acylium ion that forms when the enol acetate group reacts with the oxocarbenium ion.

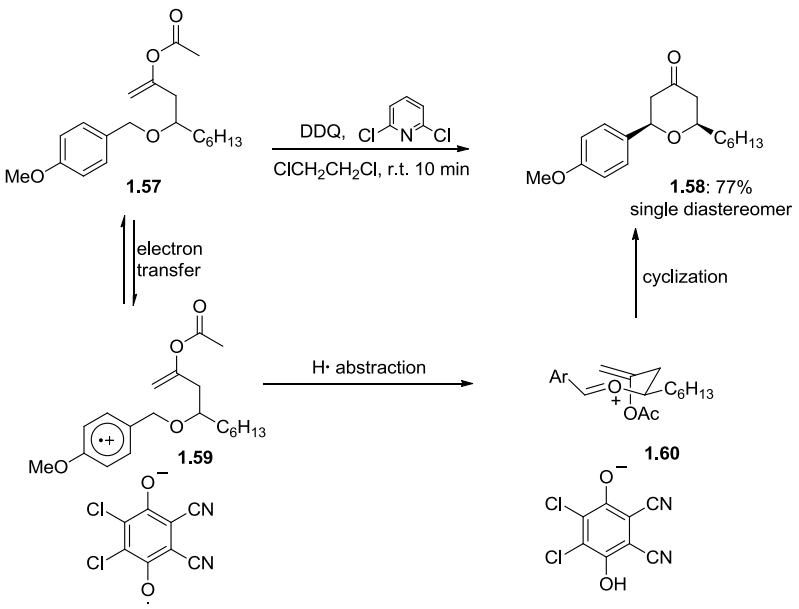
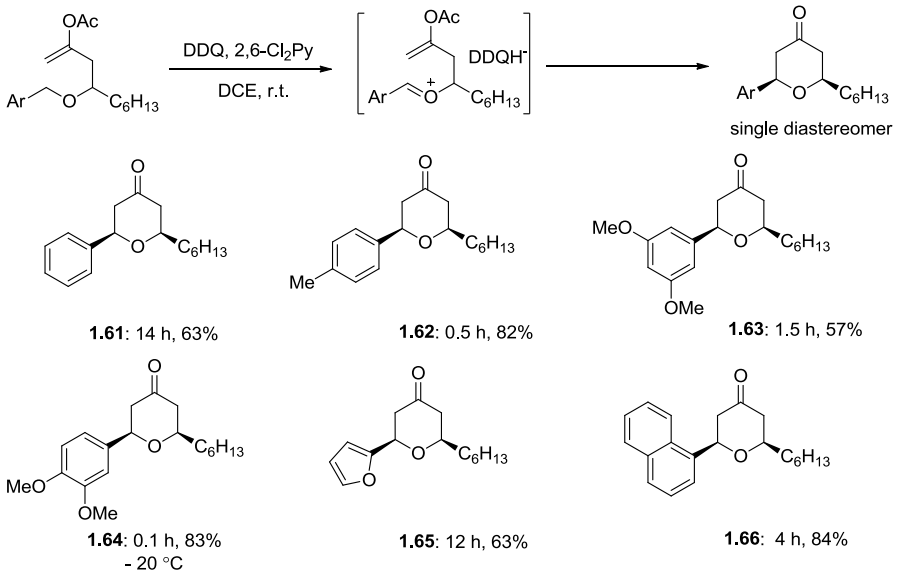


Figure 3. Diastereoselective tetrahydropyrone synthesis from PMB ether substrate

Moreover, the scope of aromatic and heteroaromatic rings with different substituents was also examined (Scheme 13). The desired tetrahydropyrone products were obtained in good to very good yields as single diastereomers. The substituents on the arene have significant influence on the rates of the reactions. The substrate with an electron-donating group reacted faster than that without an electron-donating group, which was explained by the difference of the oxidation potential (a measure of the tendency of a chemical species to lose electrons and thereby be oxidized) of the substrate and the stability of the intermediate oxocarbenium ion. The oxidation potential of *para*-methyl substituted arene is lower than that of simple phenyl ring, so the substrate of **1.62** is oxidized more easily by DDQ than that of **1.61**. The arene with 3,5-disubstituted methoxy groups has similar oxidation potential as that with 3,4-disubstituted methoxy groups, however, great reactivity difference is still observed during the formation of **1.63** and **1.64**. This can be attributed to the fact that *para*-methoxy group in **1.64** can stabilize the

intermediate oxocarbenium ions better than the *meta* one in **1.63**, facilitating the hydrogen atom abstraction process.



Scheme 13. Different substituent effects on aromatic rings

1.2 DEVELOPMENT OF DDQ-MEDIATED OXIDATIVE C–H CLEAVAGE OF VINYL AND ALLYLIC ETHERS

Cis-2,6-Disubstituted tetrahydropyrans occur in a wide array of biologically active natural products such as (+)-neopeltolide, leucascandrolide A and (+)-dactylolide (Figure 4).[35]

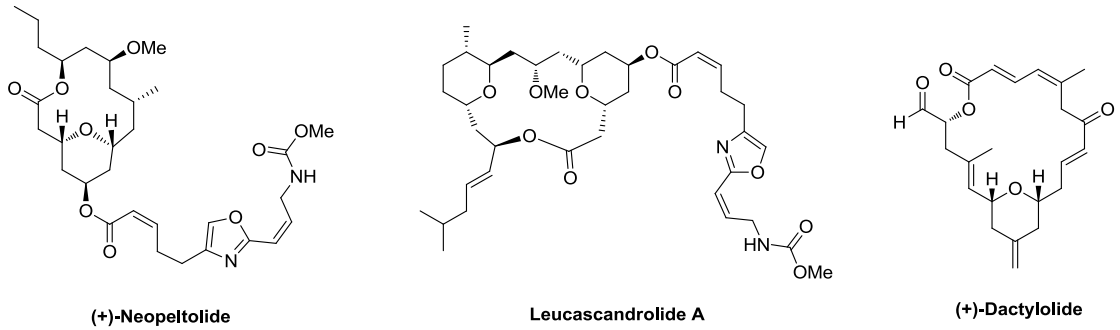


Figure 4. *cis*-2,6-Dialkyltetrahydropyran subunit in natural products

Cis-2,6-Disubstituted aryl tetrahydropyrones can be prepared through DDQ-mediated oxidative C–H bond cleavage reactions in moderate to good yields and with excellent stereocontrol. Considering the relatively low capability of the arene to be functionalized, however, we initiated a program directed toward broadening the scope of substrates that can be utilized in cyclization reactions by substituting the arene with other functional groups. After analyzing the structures of natural products shown in Figure 4, we believed that alkenes would be useful cation precursors because they can be converted to other functional groups through numerous transformations.

As shown in Figure 5, tetrahydropyrone (**1.67**) syntheses were designed to proceed with vinyl ethers (**1.68**) or allylic ethers (**1.69**), respectively. Precursors **1.68** and **1.69** can react with DDQ to provide the corresponding radical cations **1.70** and **1.71**, respectively. Following a hydrogen atom abstraction, both **1.70** and **1.71** will be converted to the same α,β-unsaturated oxocarbenium ion intermediates **1.72**, which are captured by enol acetate nucleophiles to furnish tetrahydropyrone **1.67**. In the following section, both vinyl and allylic ethers will be explored as substrates for the construction of vinyl tetrahydropyrones. The ability of a substrate to be oxidized by DDQ depends on its oxidation potential and the stability of the oxocarbenium ion (discussed in section **1.1**). Considering that **1.68** and **1.69** should form the same oxocarbenium

ion intermediate (**1.72**), we proposed that electron rich **1.68** would react more readily with DDQ than **1.69**. Thus we planned to test the vinyl ether substrate first.

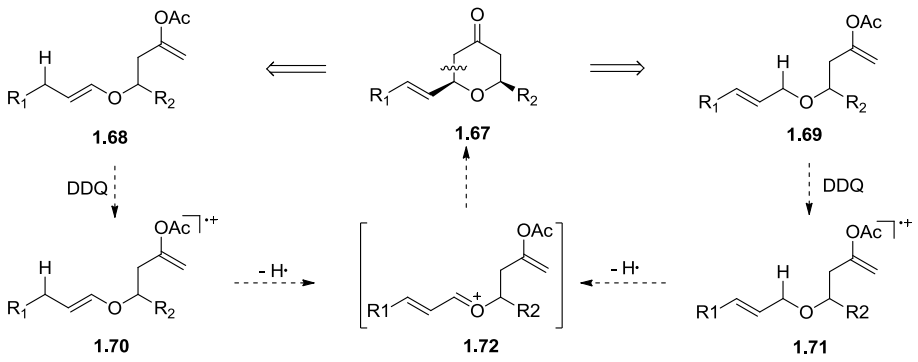
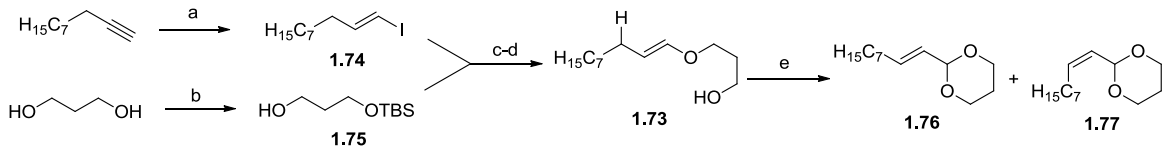


Figure 5. Retrosynthetic analysis of **1.67**

1.2.1 DDQ-mediated oxidative C–H activation of vinyl ether substrates

As an initial test of the hypothesis that *α,β*-unsaturated oxocarbenium ions can be generated through DDQ mediated C–H activation of vinyl ethers, substrate **1.73** bearing a primary alcohol as the nucleophile was prepared through the synthetic sequence shown in Scheme 14. Hydrozirconation of 1-decyne with Schwartz's reagent, followed by the addition of iodine gave *trans*-vinyl iodide **1.74** in 94% yield.[36] CuI-catalyzed cross coupling reaction[37] between **1.74** and alcohol **1.75** in the presence of 1,10-phenanthroline as a ligand, and Cs_2CO_3 as a base in toluene at 80 ^oC afforded the vinyl ether, which underwent desilylation with TBAF to provid the desired substrate **1.73** in 97% yield.



Reagents and conditions

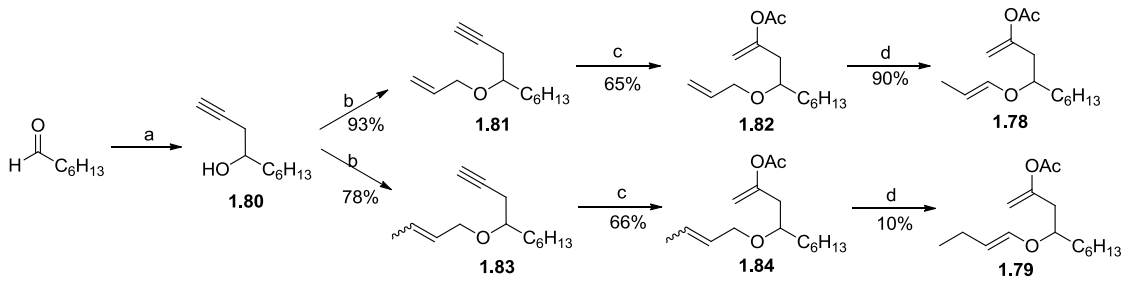
a) $Cp_2Zr(H)Cl$, DCM, 0 °C, then I_2, THF, 94%. b) TBSCl, imidazole, DMF, 53%. c) 1,10-phenanthroline, CuI, Cs_2CO_3, toluene, 80 °C, 37%. d) TBAF, THF, 97%. e) DDQ, 2,6-Cl_2Py, 4Å MS, DCE, -15°C, 85%, **1.76**:**1.77** = 11:1.

Scheme 14. The preparation of substrate **1.73** and its cyclization

Substrate **1.73** was subjected to DDQ with 1,2-dichloroethane (DCE) as the solvent, 4 Å molecular sieves as the water scavenger and 2,6-dichloropyridine as the base. At –15 °C, the cyclization was complete within 5 minutes, providing 2-vinyl-1,3-dioxane products **1.76** and **1.77** in 85% yield with an *E*:*Z* alkene ratio of 11:1. Thus, vinyl ethers are highly reactive substrates for DDQ-induced oxidative C–H activation. This successful cyclization paved the way for our further investigations of C–C bond construction using vinyl ethers as substrates.

Vinyl ethers **1.78** and **1.79** were synthesized to investigate the feasibility of C–C bond formations, considering that enol acetates proved to be compatible carbon nucleophiles in DDQ-induced oxidative cyclization reactions of benzylic ethers.[34] The preparation of **1.78** and **1.79** shared the similar synthetic sequence (Scheme 15). A Barbier reaction between heptanal and propargyl bromide yielded homopropargylic alcohol **1.80**,[38] which was alkylated with allyl bromide or crotyl bromide (where commercial available crotyl bromide is a *trans*- and *cis*- mixed alkene with a ratio of 4:1) to afford allylic ethers **1.81** and **1.83**, respectively. Ruthenium-catalyzed Markovnikov addition of AcOH across the terminal alkyne generated enol acetates **1.82** and **1.84** (where **1.84** are *trans*- and *cis*-alkene mixtures with a ratio of 4:1).[39] Vinyl ether substrate **1.78** was obtained through iridium-catalyzed (2 mol %) olefin isomerization as exclusively the *trans*-alkene in 90% yield.[40] While Ir(I) catalyzed (10 mol %) olefin

isomerization of **1.84** was very slow, and only 15% conversion was observed even after stirring at 45 ℃ overnight, enough *trans*-alkene **1.79** was obtained to test the reaction.

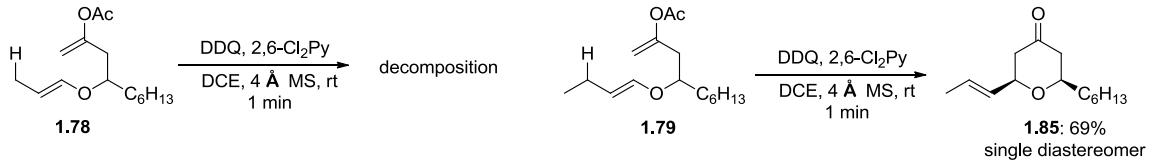


Reagents and conditions

a) Propargyl bromide, Zn, 1,2-diiodoethane, THF, 55%. b) allyl bromide or crotyl bromide, NaH, DMF. c) $[Ru(p\text{-cymene})Cl_2]_2$, $(2\text{-furyl})_3$phosphine, AcOH, Na_2CO_3, toluene, 80 °C. d) $[^c(C_8H_{14})_2IrCl]_2$, $NaBPh_4$, PCy_3, DCE/acetone.

Scheme 15. The preparation of substrate **1.78** and **1.79**

Substrate **1.78** was examined under the same conditions as the synthesis of 1,3-dioxane **1.76** (Scheme 16). The starting material was completely consumed in 1 minute, but no identifiable products were isolated. In contrast, the cyclization of substrate **1.79** proceeded smoothly at room temperature to provide *cis*-2,6-disubtituted tetrahydropyrone **1.85** in 69% yield as a single diastereomer.



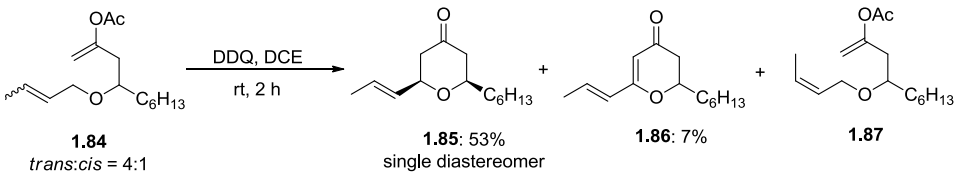
Scheme 16. Cyclization reactions of substrates **1.78** and **1.79**

Since vinyl tetrahydropyrones can be prepared through DDQ-mediated oxidative C–H cleavage of vinyl ethers and good yield and high diastereoselectivity were obtained, the only

problem left was how to efficiently prepare the vinyl ether substrates bearing enol acetates as nucleophiles. This problem could be avoided, however, if allylic ethers, precursors of vinyl ethers, proved to be sufficiently reactive to undergo cyclization through DDQ induced C–H activation.

1.2.2 DDQ-mediated oxidative C–H activation of allylic ether substrates

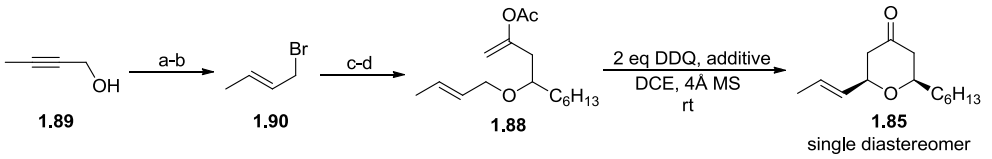
To examine whether allylic ether substrates could undergo same oxidation process as vinyl ethers, allylic ether **1.84**, the synthetic precursor of vinyl ether **1.79**, was subjected to the DDQ-mediated oxidation conditions. After 2 h in DCE at room temperature, about 80% conversion was achieved, and the desired tetrahydropyrone **1.85** was isolated in 53% yield as a single diastereomer (Scheme 17). In addition, the overoxidation product **1.86** was isolated in 7% yield. More interestingly, the starting material recovered from the reaction was exclusively the *cis*-alkene isomer **1.87**, which suggested that *cis*-allylic ethers reacted more slowly with DDQ than *trans*-allylic ethers.



Scheme 17. The cyclization of substrate **1.84**

To improve the conversion of starting materials, all *trans*-crotyl bromide **1.90** was synthesized and allylic ether **1.88** was accessed following the same procedure of the synthesis of **1.84** (Scheme 18).[41] With isomerically pure **1.88** in hand, we optimized reaction conditions. The

loading of DDQ (1.5 equiv to 3.0 equiv) did not affect the yield of **1.85**. When 2,6-dichloropyridine (2 equiv) was employed as a base, the yield of **1.85** was improved from 65% to 71%. In accord with Mukaiyama's protocol,[29] a catalytic amount of $LiClO_4$ (10 mol %) was found to be quite beneficial in suppressing the overoxidation pathway. Under the optimized conditions (a 0.1 M solution of DDQ (2 equiv), 2,6-dichloropyridine (2 equiv), $LiClO_4$ (10 mol %) and 4 Å molecule molecular sieves (2 equiv) in DCE at room temperature), 2,6-*cis*-disubstituted tetrahydropyrone **1.85** was obtained in 81% yield as a single diastereomer in 1 h.



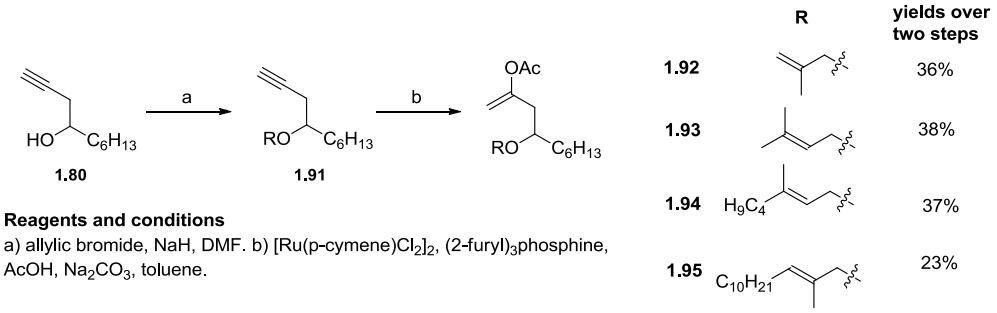
Reagents and conditions
a) $LiAlH_4$, DME, 61%. b) PBr_3, Et_2O, 0 °C. c) **1.80**, NaH, DMF, 47% over two steps.
d) $[Ru(p\text{-cymene})Cl_2]_2$, (2-furyl)$_3$phosphine, AcOH, Na_2CO_3, toluene, 80 °C, 65%.

additive	yield
none	65%
2,6-Cl_2Py	71%
2,6-Cl_2Py/ $LiClO_4$ (10 mol %)	82%

Scheme 18. The preparation of substrate **1.88** and its cyclization

I. Substituent effects on allylic ethers

After optimizing the reaction conditions for DDQ-mediated oxidative cyclization of allylic ethers, we examined the substituent effects of alkenes on reaction rate and efficiency. Therefore, a series of allylic ether substrates were synthesized following the sequence that was used to prepare substrate **1.88** (Scheme 19).

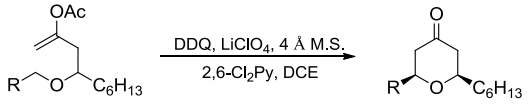


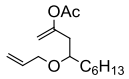
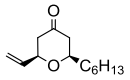
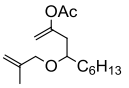
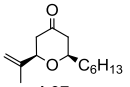
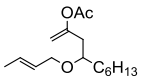
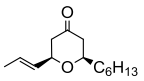
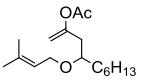
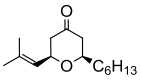
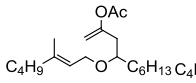
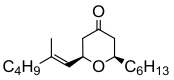
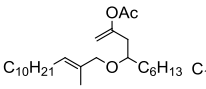
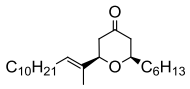
Scheme 19. The preparation of substrates **1.92-1.95**

The optimized reaction conditions were applied to these allylic ethers and the results are summarized in Table 2. All the reactions proceeded smoothly to generate the corresponding *cis*-2,6-disubstituted vinyl tetrahydropyrone products in very good chemical yields.

The reaction of monosubstituted allylic ether **1.82** was very slow at room temperature, and even at 45 ℃ it took 48 h to consume all the starting material (entry 1, table 2). Both disubstituted allylic ethers **1.92** and **1.88** reacted much faster than the monosubstituted alkene; however, a great reactivity difference between 1,1-disubstituted allylic ether **1.92** and (*E*)-1,2-disubstituted allylic ether **1.88** was still observed (entries 2 and 3, table 2). The cyclization of **1.88** went to completion in 1 h with only 2 equiv of DDQ, while complete consumption of **1.92** required 17 h and 4 equiv of DDQ at the same temperature. The cyclizations of trisubstituted allylic ethers were much faster than those of monosubstituted and disubstituted allylic ethers. When trisubstituted alkene **1.93** was subjected to the DDQ oxidation conditions at 0 ℃ , the reaction was complete in 1.5 h (entry 4, table 2). The reactions of another two trisubstituted alkene substrates **1.94** and **1.95** also proceeded smoothly at 0 ℃ , affording 82% and 85% yields, respectively (entries 5 and 6, table 2). Moreover, no olefin isomerization was observed during the cyclization process for these two substrates.

Table 2. DDQ-mediated oxidative C–H cleavage of allylic ethers[a]



Entry	Substrate	Product[b]	temp (°C)	DDQ (equiv)	t (h)	Yield(%)[c]
1	 **1.82**	 **1.96**	45	2.3	48	80
2	 **1.92**	 **1.97**	rt	4.0	17	77
3	 **1.88**	 **1.85**	rt	2.0	1	81
4	 **1.93**	 **1.98**	0	2.0	1.5	82
5	 **1.94**	 **1.99**	0	2.0	1.0	82
6	 **1.95**	 **1.100**	0	2.0	1.0	85

[a] Representative procedure: Substrate, 2,6-dichloropyridine (4 equiv), and 4 Å M.S. were stirred in DCE for 15 minutes. Then $LiClO_4$ (10 mol %) was added, and stirred for another 10 minutes. After that, DDQ (2-4 equiv) was added and reaction was stirred for the indicated time.

[b] Diastereomeric ratio determined by ^1H NMR spectroscopy.

[c] Yields refer to isolated, purified material.

II. Functional group compatibility

After examining the substituent effects on allylic ethers, we explored the tolerance of different functional groups to the reaction conditions to expand the range of structures that are accessible. Substrates **1.101-1.105** shown in Figure 6 were designed to test functional group

compatibility and to study the C–C bond formation in the presence of competitive heteroatom nucleophiles.

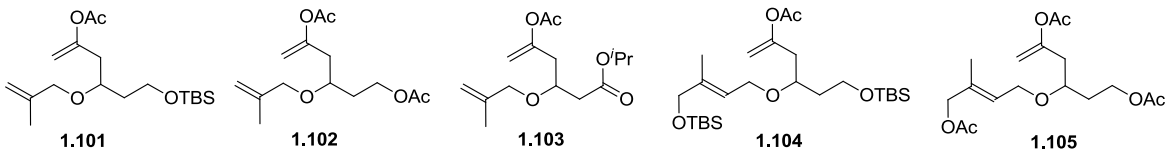
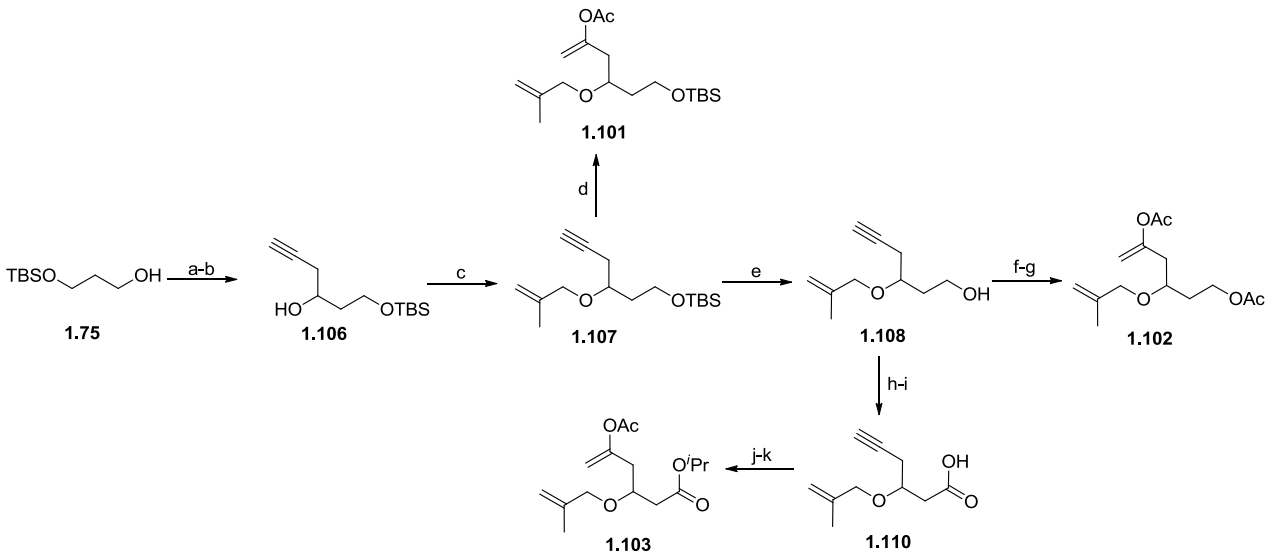


Figure 6. Substrates for the study of functional group compatibility

Substrates **1.101**-**1.103** were prepared as shown in Scheme 20. Alcohol **1.75** was oxidized under Parikh-Doering conditions and the resulting aldehyde was subjected to a Barbier reaction with propargyl bromide and zinc to afford homopropargylic alcohol **1.106**. Alkylation of **1.106** with methallyl chloride followed by a ruthenium-catalyzed enol acetate formation provided the desired substrate **1.101**. Desilylation of allylic ether **1.107** with TBAF, followed by an acylation and typical enol acetate formation gave substrate **1.102**. Substrate **1.103** was synthesized from intermediate **1.108** through Parikh-Doering oxidation of the alcohol to the aldehyde, which was then converted to carboxylic acid **1.110** in the presence of $NaClO_2$ and NaH_2PO_4.[42] Finally, the cyclization substrate **1.103** was prepared after an isopropyl ester formation and the enol acetate formation.

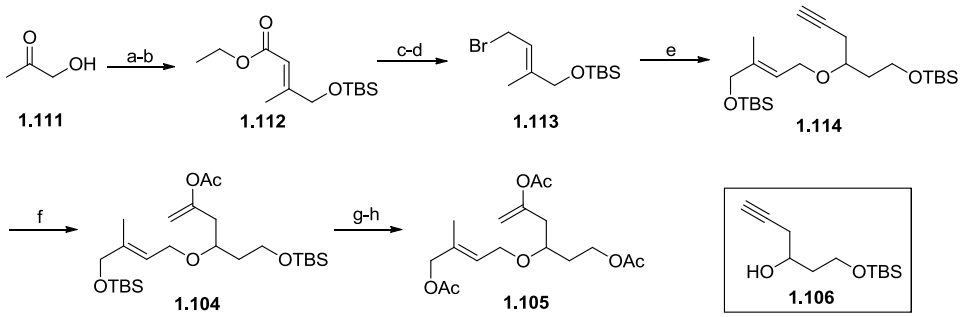


Reagents and conditions

a) Py•SO_3, DMSO, Et_3N, DCM, 70%. b)Propargyl bromide, Zn, 1,2-diiodoethane, THF, 49%. c) 3-chloro-2-methyl-1-propene, NaH, Bu_4NI, THF/DMF, 83%. d) $[Ru(p\text{-cymene})Cl_2]_2$, (2-furyl)$_3$phosphine, AcOH, Na_2CO_3, toluene, 63%. e) TBAF, THF, 80%; f) Ac_2O, Et_3N, DMAP, DCM, 97%. g) $[Ru(p\text{-cymene})Cl_2]_2$, (2-furyl)$_3$phosphine, AcOH, Na_2CO_3, toluene, 77%. h) Py•SO_3, DMSO, Et_3N, CH_2Cl_2; i) $NaClO_2$, NaH_2PO_4, ^{t}BuOH, 2-methyl-2-butene. j) 2-Propanol, DCC, DMAP, DCM, 54% over three steps. k) $[Ru(p\text{-cymene})Cl_2]_2$, (2-furyl)$_3$phosphine, AcOH, Na_2CO_3, toluene, 50%.

Scheme 20. The preparation of substrates **1.101-1.103**

Substrates **1.104** and **1.105** were synthesized following the procedures shown in Scheme 21. Protection of commercially available hydroxyacetone **1.111** as a TBS ether followed by Horner-Wadsworth-Emmons reaction with triethyl phosphonoacetate generated the α,β-unsaturated ester **1.112**.[43] The ester was reduced by DIBAL-H to form an allylic alcohol, which was then converted to the allylic bromide **1.113** in the presence of MsCl and LiBr.[44] Coupling the allylic bromide **1.113** with propargyl alcohol **1.106** yielded the allylic ether **1.114**, which was converted to substrate **1.104** through the typical enol acetate formation protocol. Substrate **1.105** was prepared from substrate **1.104** through desilylation of two TBS ethers with TBAF followed by the diacylation by Ac_2O.

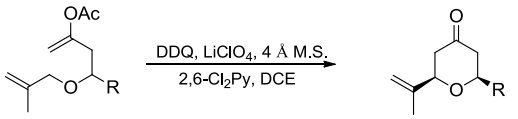


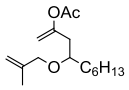
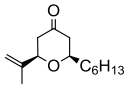
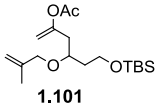
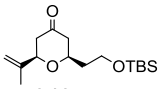
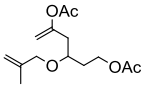
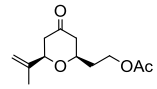
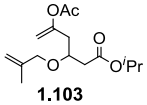
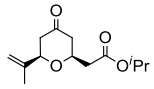
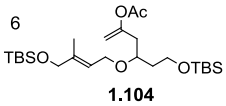
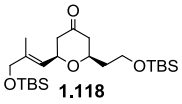
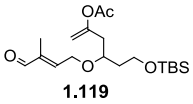
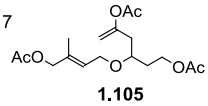
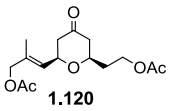
Reagents and conditions
a) TBSCl, imidazole, DMF, 70%. b) triethyl phosphonoacetate, NaH, THF, 85%. c) DIBAL-H, toluene. d) MsCl, Et_3N, LiBr, DCM/THF. e) **1.106**, Bu_4NI, NaH, THF/DMF, 49% over three steps. f) $[Ru(p\text{-cymene})Cl_2]_2$, $(2\text{-furyl})_3$phosphine, AcOH, Na_2CO_3, toluene, 80 °C, 41%. g) 3% HCl in Methol. h) Ac_2O, DMAP, pyridine, DCM, 72% over two steps.

Scheme 21. The preparation of substrates **1.104** and **1.105**

DDQ-mediated oxidative cyclizations of substrates **1.101-1.105** were examined, and the results are summarized in Table 3. Substrates **1.101-1.103**, bearing commonly encountered functional groups in the alkyl side chain, proceeded in comparable yields to those without functional groups in the alkyl side chain and stereocontrol remained high (entries 1-5, table 3), though the cyclizations proceeded somewhat more slowly than the parent model **1.92** without a functional group in the alkyl chain. Then we explored whether good selectivity could be obtained when two allylic ethers were installed in the same molecule. Under the standard DDQ oxidation conditions, the cyclization of **1.104** was complete in 45 minutes at room temperature, however, two tetrahydropyrone products (overall yield is 83%) were observed and the ratio of desired **1.118** and undesired **1.119** was 1.2:1 (entry 6, table 3). While the cyclization of diacetate **1.105** was much slower than that of **1.104** even at higher temperature, the desired product **1.120** was isolated in 80% yield with high selectivity (entry 7, table 3).

Table 3. Functional group compatibility with DDQ-mediated oxidative C–H cleavage[a]



Entry	Substrate	Product[b]	temp (°C)	DDQ (equiv)	t (h)	Yield(%)[c]
1	 **1.92**	 **1.97**	rt	4.0	17	77
2	 **1.101**	 **1.115**	rt	4.0	24	75
3	 **1.102**	 **1.116**	rt	4.0	30	73
4	 **1.103**	 **1.117**	rt	4.0	70	78
5	**1.103**	**1.117**	45	4.0	12	77
6	 **1.104**	 **1.118**  **1.119**	rt	2.0	0.75	45 38
7	 **1.105**	 **1.120**	45	4.0	5.5	80

[a] Representative procedure: Substrate, 2,6-dichloropyridine (4 equiv), and 4 Å M.S. were stirred in DCE for 15 minutes. Then $LiClO_4$ (10 mol %) was added, and stirred for another 10 minutes. After that, DDQ (2-4 equiv) was added and reaction was stirred for the indicated time.

[b] Diastereomeric ratio determined by ^1H NMR spectroscopy.

[c] Yields refer to isolated, purified material.

1.3 DISCUSSION

1.3.1 Vinyl ether substrates

Under the same reaction conditions, vinyl ether **1.79** and allylic ether **1.88** gave the same *cis*-2,6-disubstituted tetrahydropyrone product **1.85** (Figure 7). This result implies that they share the same α,β-unsaturated oxocarbenium ion intermediate **1.121**. Although vinyl ethers are more stable than allylic ethers,[45] the reaction of vinyl ether **1.79** is much faster than that of allylic ether **1.88**, suggesting that direct H^- abstraction is an unlikely mechanism. A proposed mechanism for

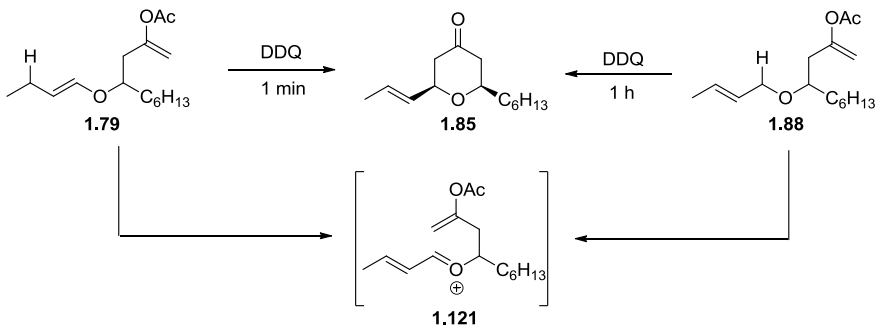


Figure 7. A comparison between vinyl ether **1.79** and allylic ether **1.88**

the reaction of vinyl ether with DDQ is shown in Figure 8. An electron transfer from vinyl ether **1.79** to DDQ gives rise to a radical cation **1.122** and hydroquinone radical anion **1.123**. Then a hydrogen atom transfer from **1.122** to **1.123** generates a α,β-unsaturated oxocarbenium ion **1.124**, which undergoes intramolecular cyclization through a chair transition state to provide *cis*-2,6-disubstituted tetrahydropyrone **1.85**. The resulting acylium ion was quenched by 2,6-dichloropyridine, facilitating the cyclization reaction.

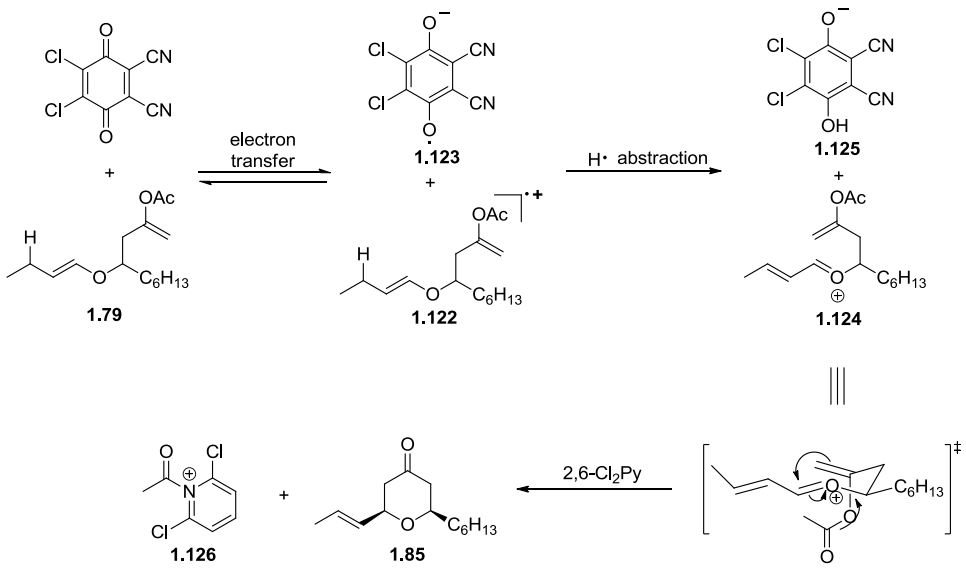


Figure 8. A proposed mechanism of DDQ-mediated C–H cleavage of vinyl ether **1.79**

Vinyl ether substrate **1.78** (Scheme 16) did not give any cyclization product under DDQ induced oxidation conditions, though it was consumed completely in 1 minute. I believe that the starting material consumption indicated the occurrence of vinyl ether oxidation by DDQ. As shown in Figure 9, the only difference between intermediate **1.124** generated from **1.79** and intermediate **1.127** from **1.78** is the presence of an extra methyl group in **1.124** that stabilizes the intermediate carbocation through hyperconjugation. The oxidation process was very fast, leading to a high concentration of highly reactive intermediate **1.127**, and decomposition of **1.127** might be faster than the nucleophilic addition step.

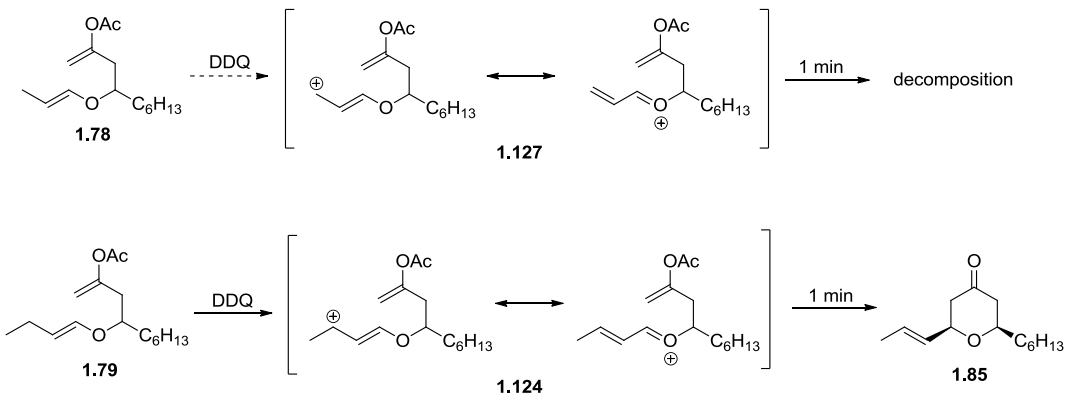


Figure 9. A comparison between the intermediates of vinyl ethers **1.78** and **1.79**

1.3.2 Allylic ether substrates

I. Proposed mechanism for allylic ether oxidation

We did not put too much effort in improving this process because readily accessible allylic ethers proved to be a better option for vinyl tetrahydropyrone syntheses. Similar to the oxidation of vinyl ethers, the reaction of allylic ethers with DDQ was proposed to be initiated by a single electron transfer between the substrates and DDQ (Figure 10). The radical cation **1.128** lose a hydrogen atom to give the α,β-unsaturated oxocarbenium ion intermediate **1.129**. The presence of catalytic amount of $LiClO_4$ (10 mol %) improved the yield of the reaction, though the origin of this curious but useful effect has not been elucidated. $LiClO_4$ might be beneficial to the stability of intermediate **1.129**. Intramolecular cyclization through a chair transition state afforded the desired product **1.85** along with the regeneration of $LiClO_4$.

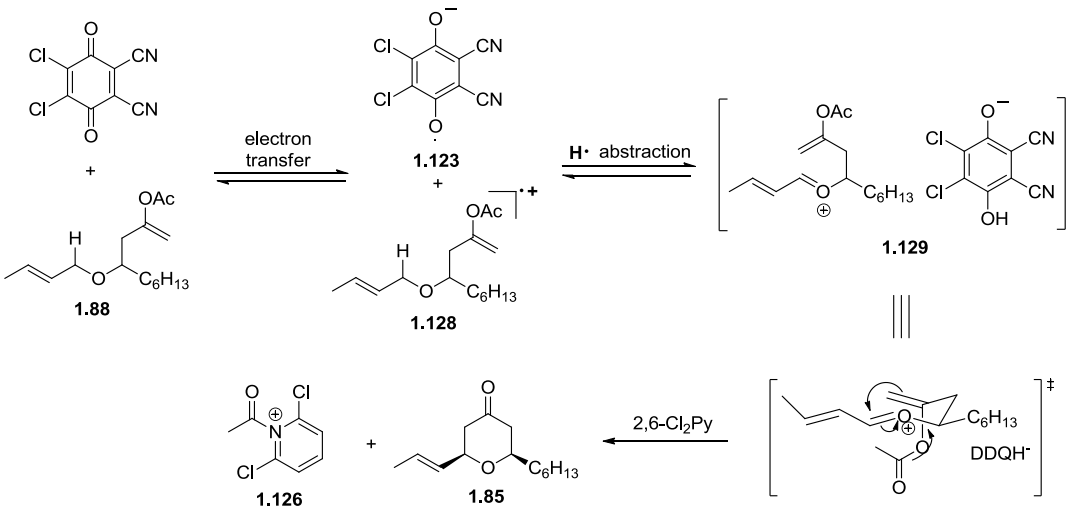


Figure 10. A proposed mechanism of DDQ-mediated C–H cleavage of allylic ether **1.88**

II. Reaction rate analysis

According to the analysis of kinetic isotope effects of DDQ-mediated oxidative C–H cleavage of benzylic and allylic ethers,[46] the rate determining step of the process was believed to be the hydrogen atom abstraction (Figure 11). Once the intermediate oxocarbenium ion was generated, the cyclization happeded readily to afford the product. A substrate with lower oxidation potential reacts with DDQ faster than that with higher oxidation potential, leading to a higher concentration of allylic ether radical cation. Moreover, a substrate with more stable intermediate oxocarbenium ion has a larger rate constant k_2 (Figure 11). Therefore, the reaction rate would depend on rate constant k_2, the concentration of the allylic ether radical cation and the concentration of hydroquinone radical anion ((*eq* 1), Figure 11). The equation will be useful to explain several interesting observations mentioned in the section **1.2.2**.

Figure 11. Reaction rate analysis

The only substrate that did not react with DDQ was the *cis*-allylic ether (Scheme 17). Considering that *cis*- and *trans*-allylic ethers should have similar oxidation potentials, the reactivity difference can be attributed to the stability of the respective oxocarbenium ions. DDQ-induced oxidation processes of *cis*- and *trans*-alkenes are shown in Figure 12. Intermediate **1.134** should be much less stable than **1.131** due to the steric interaction between methyl and hydrogen in **1.134**. This factor inhibits the hydrogen atom abstraction of **1.133** to form **1.134**, and thus *trans*-allylic ethers reacted faster than *cis*-isomers.

While the same steric interaction also exists in intermediate **1.136** of trisubstituted allylic ether **1.93**, the consumption of **1.93** is even faster than that of *trans*-disubstituted allylic ether **1.88**. The observation was attributed to the low oxidation potential of trisubstituted alkene that allows **1.93** to react with DDQ faster than disubstituted alkene **1.88**, leading to a higher concentration of radical cation **1.135** than that of **1.130**. Moreover, the extra methyl group in the trisubstituted alkene **1.93** stabilizes oxocarbenium ion **1.136** through the hyperconjugation, which offsets the destabilization of the steric interaction.

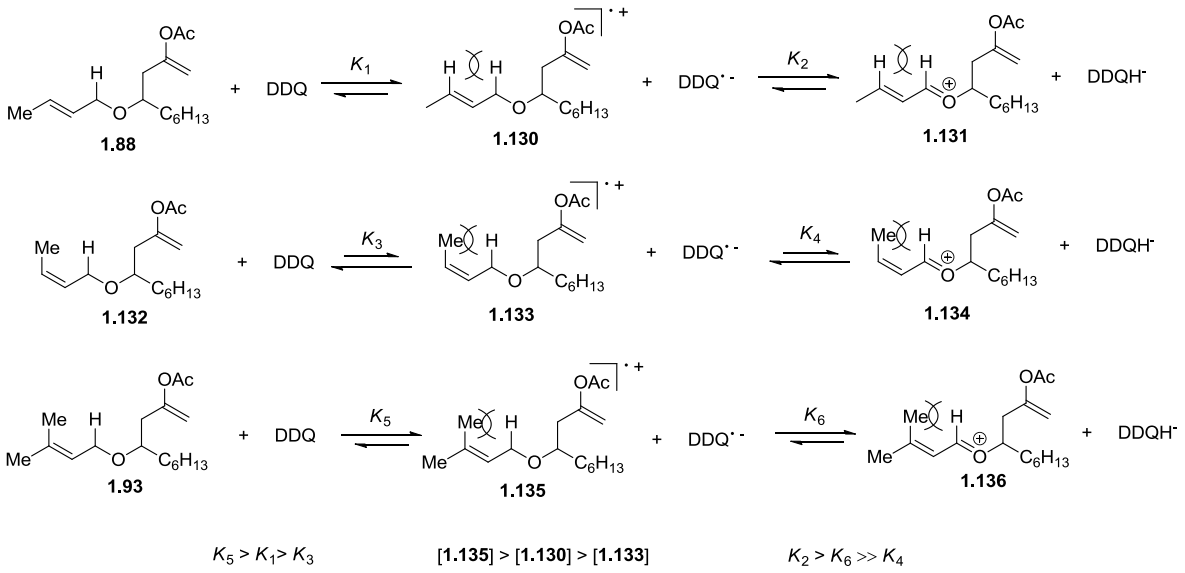


Figure 12. Comparisons of oxidations of **1.88**, **1.132** and **1.93**[46]

The 1,1-disubstituted allylic ether substrate **1.92** reacted more slowly than (*E*)-1,2-disubstituted allylic ether **1.88**, which can be attributed to the stabilities of corresponding oxocarbenium ion intermediates (Figure 13). The vinyl methyl group in **1.137** does not directly stabilize the intermediate cation, while the direct stabilization by methyl group exists in intermediate **1.124**, making **1.124** more stable than **1.137**.

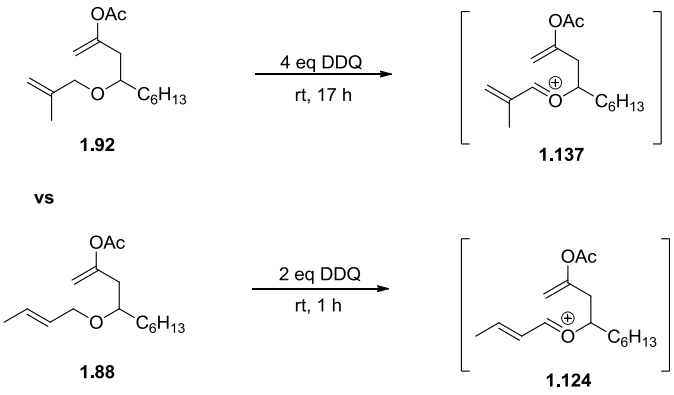


Figure 13. A comparison of stabilities of oxocarbenium ions **1.137** and **1.124**

DDQ oxidation of vinyl ether **1.78** did not afford any identifiable products (Scheme 16), which was attributed to the possibility that the lifetime of the intermediate cation was too short to be captured by the nucleophile due to the absence of stabilizing-factors. Considering that monosubstituted allylic ether **1.82** should have the same intermediate as **1.78**, the cyclization of **1.82** was supposed to be a challenge. Under forcing conditions, however, 77% was obtained with no loss of stereocontrol (entry 1, table 2). The different results between vinyl ether **1.78** and allylic ether **1.82** might be explained by the high reactivity of vinyl ether **1.78** that generated much higher concentration of highly reactive intermediate than allylic ether **1.82**. Considering that terminal alkenes are frequently employed in organic synthesis, such as cross metathesis, hydroboration followed by palladium-catalyzed cross-coupling reaction, and hydroformylation, this protocol should have potential application in the synthesis of many complex molecules containing tetrahydropyrone or related structures.

III. Conserved olefin geometry

The reactions of DDQ with trisubstituted alkenes **1.94** and **1.95** proceeded smoothly to provide the desired products in 82% and 85% yield, respectively, and no olefin isomerization was observed (entries 5 and 6, Table 2). This result suggests that at the stage of radical cation **1.138** or **1.140** (Figure 14), the hydrogen atom abstraction is faster than the rotation of C_2–C_3 bond. The potentially severe steric interaction between alkyl chain and hydrogen after the rotation of C_2–C_3 bond may also help to suppress the olefin isomerization pathway.

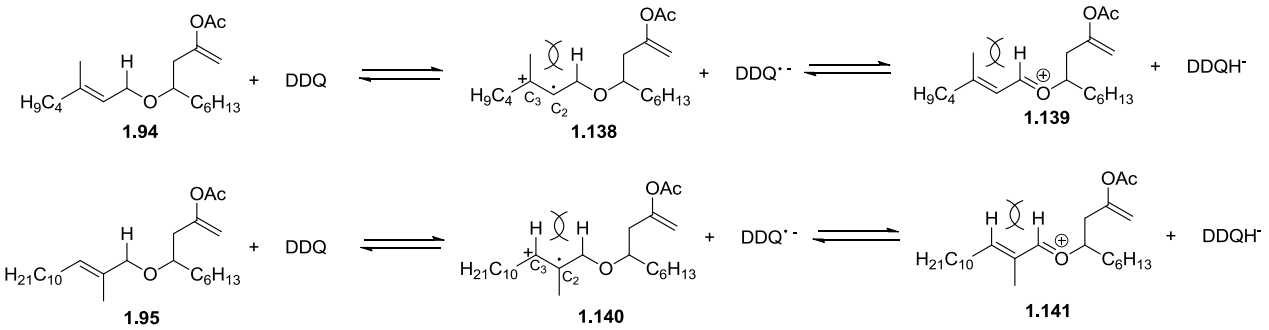


Figure 14. DDQ-mediated oxidation processes of **1.94** and **1.95**

IV. Functional group compatibility

Commonly encountered functional groups such as TBS ether, acetate and isopropyl ester are compatible with the DDQ oxidation process. The reactions proceeded somewhat more slowly than the parent model with a simple alkyl side chain (entries 1-5, Table 3), which was attributed to the inductive effect of the oxygen-containing groups destabilizing the intermediate oxocarbenium ions. Additionally, no C–O bond forming product was observed indicating that the C–C bond formation is still favored even though competitive heteroatom nucleophile exists in the same molecule (Figure 15).

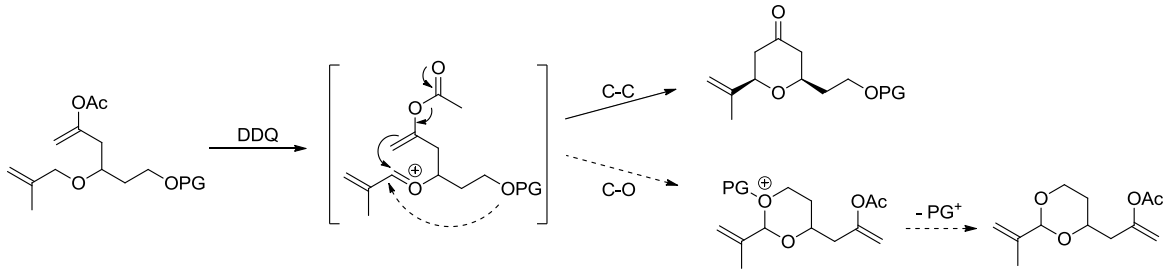


Figure 15. Competition between C–C and C–O bond formation

Almost no selectivity for the oxidation of two allylic ethers in **1.104** was observed (entry 6, table 3), which was attributed to the similar oxidation potential of two allylic ethers and comparable stability of intermediates **1.142** and **1.143** (Figure 16). When substituting the silyl ether with the electron-withdrawing acetate, the oxidation potential of allylic acetate was higher than that of the other allylic ether in **1.105** as shown in Figure 16; the stability of the undesired intermediate **1.145** also decreased due to the inductive effect. Therefore the undesired pathway B was blocked and a high selectivity was obtained.

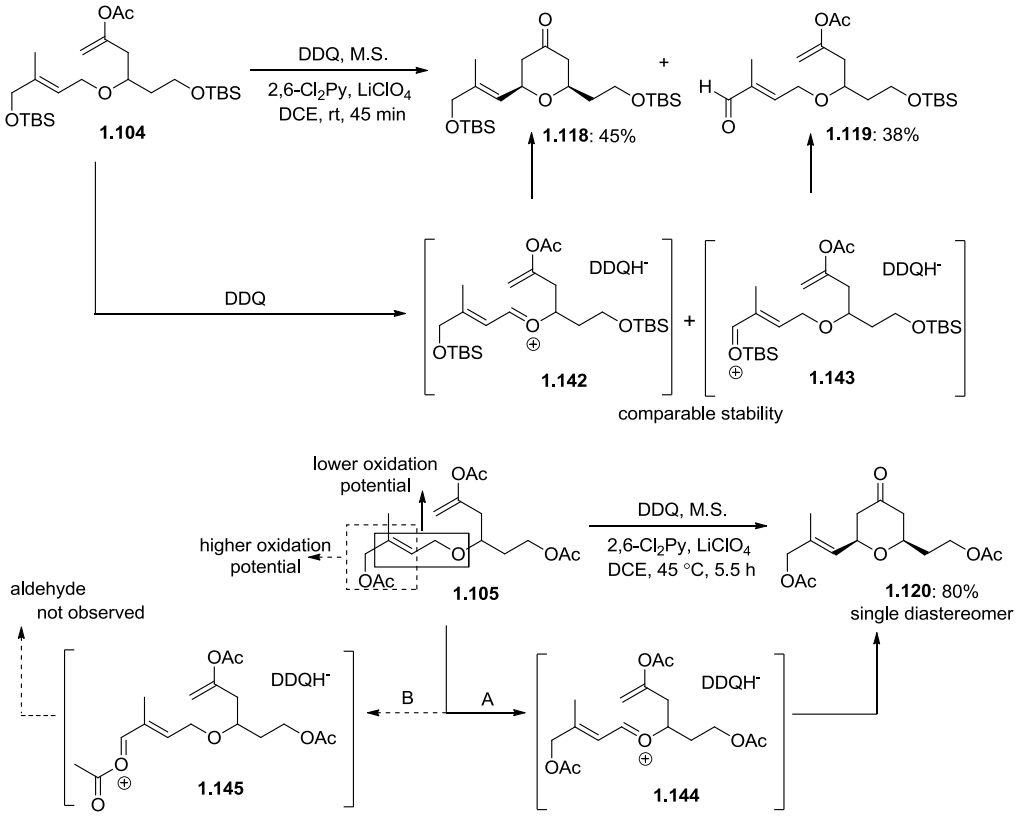


Figure 16. Reactivity analysis of substrates **1.104** and **1.105**

1.4 SUMMARY

We have demonstrated that DDQ-mediated oxidative C–H bond cleavage of a series of vinyl and allylic ethers containing enol acetate nucleophiles efficiently leads to *cis*-2,6-disubstituted tetrahedropyrone formation. The reaction is initiated by a single electron transfer from the substrate to DDQ to form a radical cation, which undergoes hydrogen atom cleavage to give the oxocarbenium ion intermediate. The intramolecular cyclizations occur through a chair transition state to afford the high diastereoselectivity. The reactivities of the substrates are correlated to the oxidation potential of substrates and stability of the oxocarbenium ions.

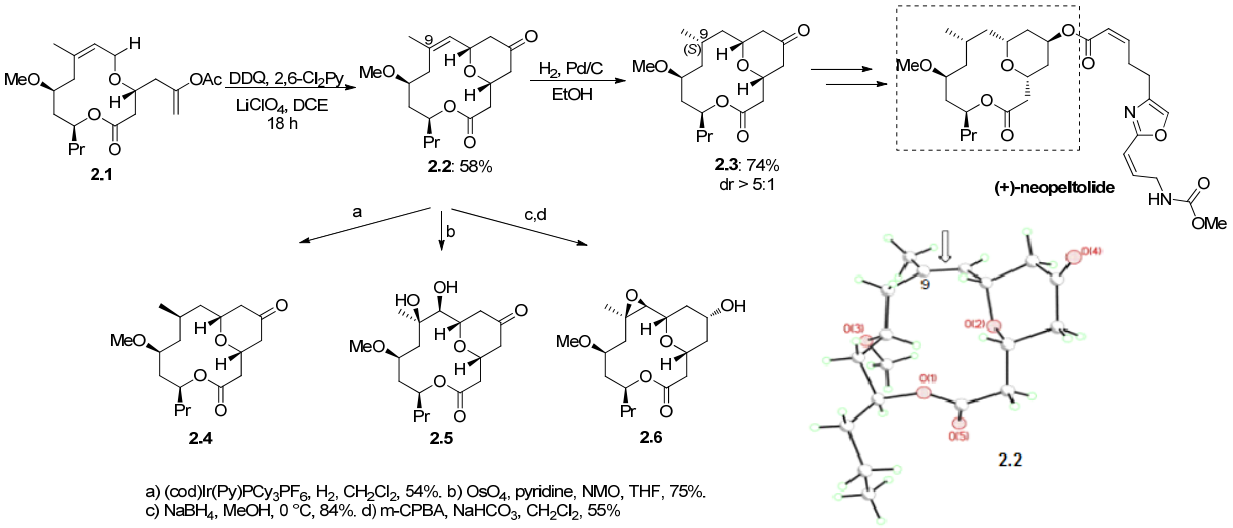
This method is highly supplementary to acid-mediated Prins-based methods in the preparation of tetrahydropyrans,[47] and the tolerance of acid labile functional groups on either side of ether linkage makes the methodology more applicable to complex molecule synthesis.

2.0 STRUCTURALLY AND STEREOCHEMICALLY DIVERSE TETRAHYDROPYRAN SYNTHESIS VIA OXIDATIVE C–H CLEAVAGE OF (SILYL)ALLYLIC AND PROPARGYLIC ETHERS

2.1 INTRODUCTION

In Chapter 1, I reported that *cis*-2,6-disubstituted tetrahydropyrones could be efficiently prepared through DDQ-mediated oxidative C–H cleavage of allylic ethers. The high stereoselectivity and good functional group compatibility suggest that the method should have the potential to be applied in the complex molecule synthesis. In 2009, Dr. Tu in the Floreancig group successfully applied this method to a total synthesis of the biologically active natural product (+)-neopeltolide (Scheme 22).[48] Trisubstituted allylic ether **2.1** was subjected to the standard DDQ oxidation conditions, and the desired neopeltolide macrocycle **2.2** was isolated in 58% yield as a single diastereomer. Consistent with predictions based on the X-ray structure of **2.2**, Pd/C catalyzed hydrogenation reaction took place with the hydrogen addition from outside of the macrocycle affording the desired 9*S* product **2.3** in 74% yields (dr > 5:1). The total synthesis was completed in 2 steps from **2.3**. Aside from the natural product, the unsaturated C8–C9 double bond afforded an excellent opportunity to prepare neopeltolide analogs. Several interesting analogs were achieved from **2.2** with high stereoselectivity and efficiency (Scheme 22).[48b] Considering the wide range of biological activities that tetrahydropyran-containing

molecules possess,[49] the next phase of my project was to further expand the DDQ-mediated C–H cleavage method to access 2,6-disubstituted tetrahydropyrones that contain modifiable unsaturations. These unsaturations should be able to provide a route towards a range of structurally and stereochemically diverse tetrahydropyran structures through post-cyclization manipulations. Vinylsilanes are excellent candidates for the purpose because of their ability to engage in numerous transformations[50] and to exist in easily-predicted conformational preferences.[51] Besides the comparable reactivities with alkyl-substituted alkenes, vinylsilanes have several unique characteristics that will be briefly discussed in this introduction.



Scheme 22. Total synthesis of neopeltolide and its analogues

2.1.1 Vinylsilanes in palladium-catalyzed cross-coupling reactions

Suitably functionalized vinylsilanes can participate in palladium-catalyzed cross-coupling reaction with organic halides to form new C–C bonds.[52] Its catalytic cycle starts from the

oxidative addition of an organic halide to the Pd(0)-species generating Pd(II) (Figure 17).[53] In the presence of TBAF, vinylsilane **2.7** is converted to a pentacoordinate silicate intermediate **2.8**, which undergoes transmetalation process with Pd(II) to provide **2.9**. After *trans-cis* isomerization and reductive elimination, cross-coupling product **2.11** is obtained with the regeneration of Pd(0) catalyst. Examples of vinylsilanes that participate in palladium-catalyzed cross-coupling reactions include silacyclobutanes **2.12**,[54] silanols **2.13**,[55] silanolates **2.14**,[56] siloxanes **2.15**,[57] benzylsilanes **2.16**,[58] allylsilanes **2.17**,[59] 2-thienylsilanes **2.18**[58] and 2-pyridylsilanes **2.19**[60] (Scheme 23). Hiyama and Hatanaka stated that the key for successful Hiyama coupling is the generation of reactive, pentacoordinate silicate intermediates to effect the rate-determining transmetalation.[61] Recently, Denmark's mechanistic studies demonstrated that in the presence of a fluoride activator such as TBAF and TASF, vinylsilanes are converted to corresponding vinylsilanols, which are the real intermediates for the cross-coupling.[62]

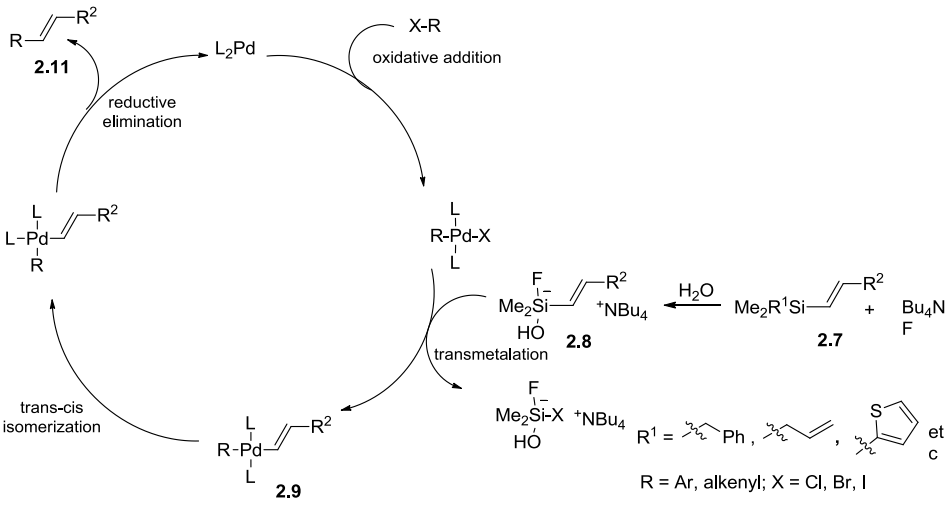
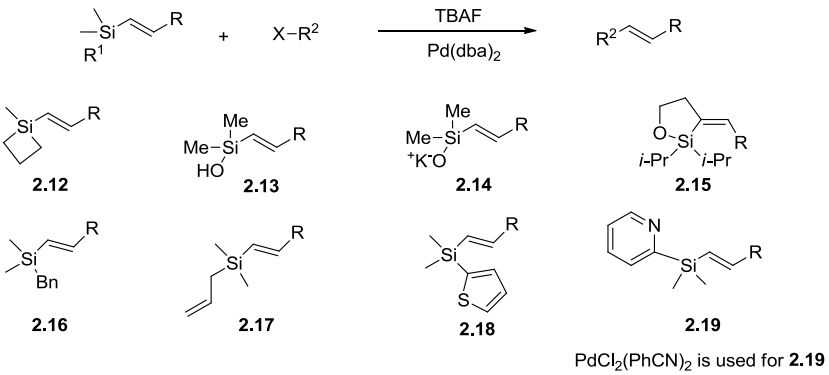
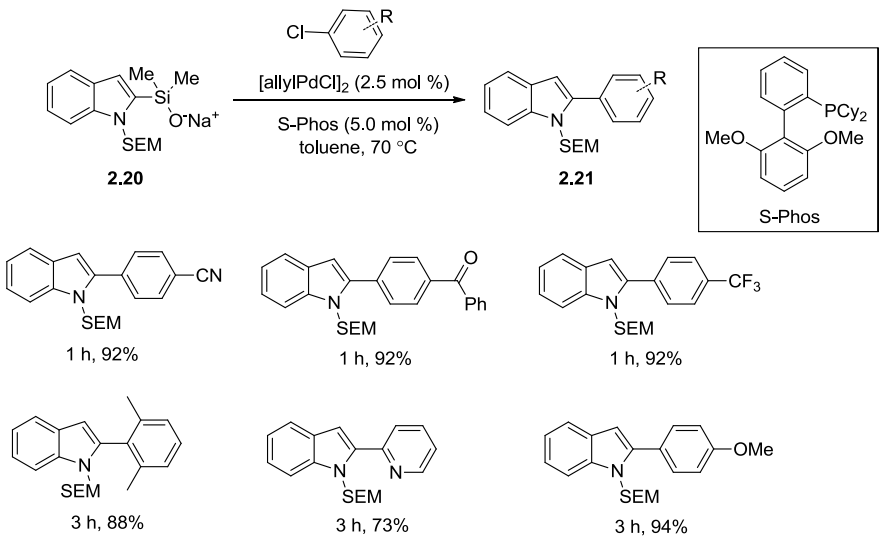


Figure 17. Catalytic cycle of Pd-catalyzed cross-coupling of vinylsilanes



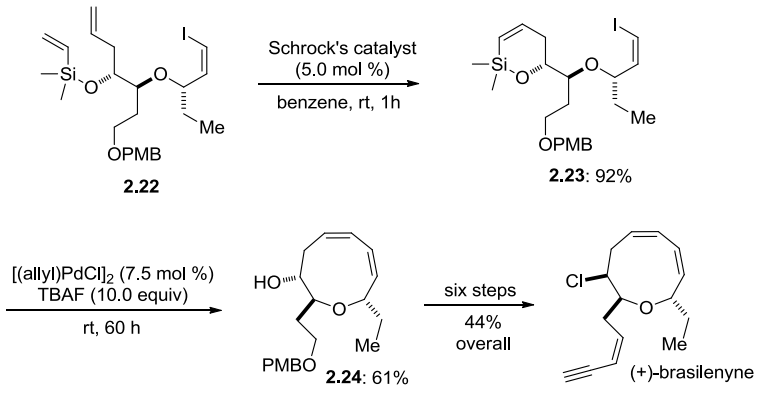
Scheme 23. Vinylsilanes in Pd-catalyzed cross-coupling reactions

The palladium-catalyzed cross coupling of vinylsilanes with organic halides allows vinylsilanes to function as versatile platforms for olefin synthesis, and provides convenient and robust methods for library syntheses. For example, Denmark disclosed that the cross-coupling of *N*-SEM-dimethyl(2-indolyl)silanolate (**2.20**) with a range of aryl chlorides proceeded smoothly to provide a library of 2-substituted indoles **2.21** in excellent yields (Scheme 24).[63]



Scheme 24. Cross-coupling of **2.20** with substituted aryl chlorides

In addition to diversity-oriented synthesis to construct chemical libraries, cross-coupling has also been widely applied to the target-oriented synthesis. One of the most illustrative examples is the synthesis of 9-membered cyclic ether (+)-brasilenyne by Denmark (Scheme 25).[64] The key step of the synthesis was to construct the difficult-to-access 1,3-*cis*-*cis*-diene **2.24**, which was realized through a tandem RCM/cross-coupling sequence from advanced intermediate **2.22**. The synthesis successfully illustrated the application of vinylsilanes in target-oriented synthesis of complex molecules, though a large scale of TBAF (10 equiv) is employed to consume all the siloxane **2.23**.

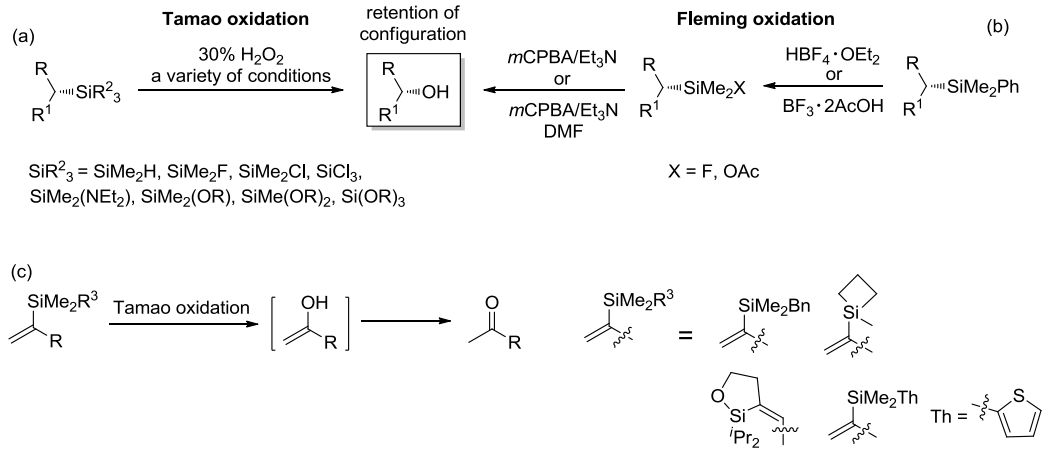


Scheme 25. Total synthesis of (+)-brasilenyne

2.1.2 Silyl groups as masked hydroxyl groups

The silyl group can also be replaced by a hydroxyl group to form a new C–O bond (Scheme 26(a)).[51] A silyl group can be introduced stereospecifically into a site of the substrate for a future hydroxyl group, and after a series of transformations, the silyl group is converted to a hydroxyl group, without having the hydroxyl group in all its attendant chemistry. Typically the

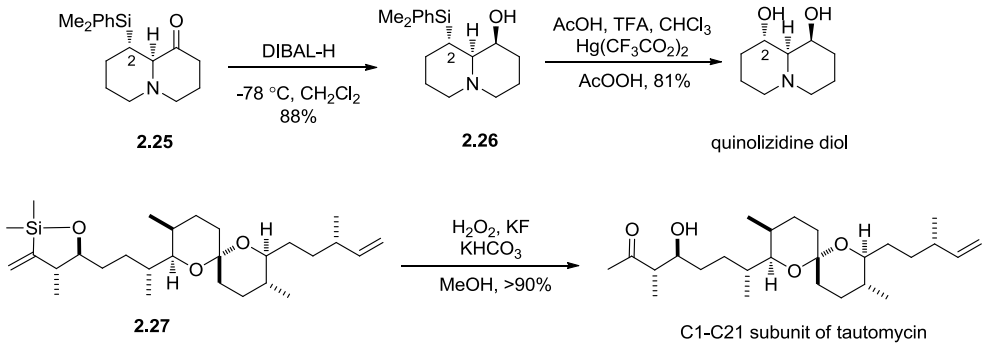
silyl group carrying a nucleofugal group, like a halogen, an alkoxyl group, or a hydrogen atom, can be oxidized by peroxides or peracids in the presence of a fluoride ion, which is known as Tamao oxidation (Scheme 26).[65] Under Tamao oxidation conditions, vinylsilanes are oxidized to form enols, which then tautomerize to the corresponding ketones (Scheme 26(c)). Phenylsilanes can also participate in this oxidation process. In this case, the benzene ring will first be removed, and replaced by a nucleofugal group such as a fluoride, which is known as Fleming oxidation (Scheme 26(b)).[66] This can be achieved by protodesilylation, mercuridesilylation or bromodesilylation. Aryl, heteroaryl and allyl substituents on the silicon atom also act as removable groups. Fleming-Tamao oxidations are stereospecific with retentions of original configurations (Scheme 26).



Scheme 26. Fleming-Tamao oxidation

The Fleming-Tamao oxidation conditions are sufficiently mild to tolerate a wide range of functional groups even in complex substrates. In West's synthesis of dihydroxyquinolizidine, the dimethylphenylsilyl group served as a surrogate for one of the hydroxyl groups in the product (Scheme 27).[67] Under Denmark's conditions, the Fleming oxidation proceeded smoothly to

furnish the target molecule in 81% yield with the retention of the configuration at C2 position; Baeyer-Villiger oxidation of ketone **2.25** was not observed. In Marshall's synthesis of the C1–C21 subunit of tautomycin, a 5-membered siloxane **2.27** was oxidized under Tamao conditions to afford an enol, which tautomerized spontaneously to the corresponding *β*-hydroxyl methyl ketone in high chemical yield (Scheme 27).[68]



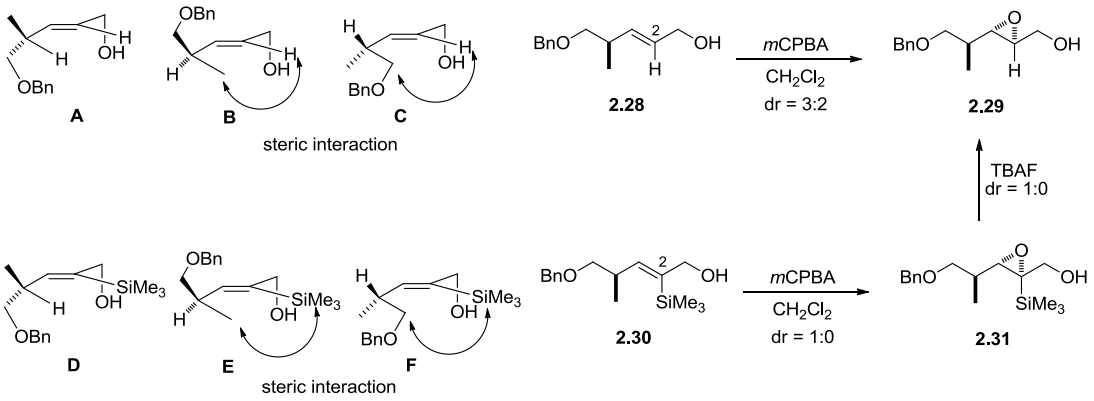
Scheme 27. Fleming-Tamao oxidation in natural product synthesis

2.1.3 Vinylsilanes as removable stereocontrol elements

The bulky silyl group in the vinylsilane can be used to control the conformations of substrates, without directly participating in the chemistry.[51] During stereochemistry-determining step, the reaction will selectively occur at one face of the molecule. Sometimes the stereochemistry will not exist without this conformational control element. After the silyl group finishes the job, it will be replaced by a proton through a desilylation process or a hydroxyl group through Fleming-Tamao oxidation, both of which retain the configuration of the molecule.

The epoxidation of allylic alcohol **2.28** with mCPBA yielded epoxide **2.29** as the major stereoisomer in a poor 3:2 ratio (Scheme 28).[69] Structures A, B and C are three possible

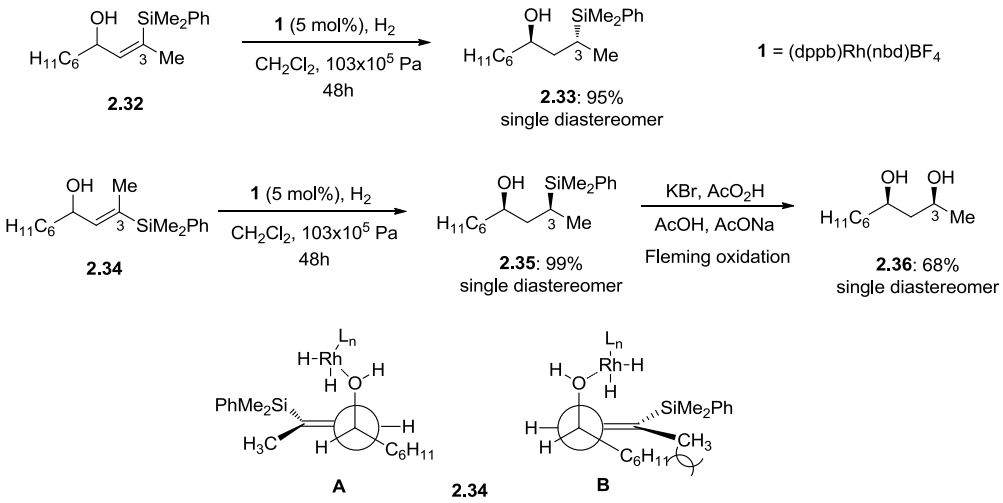
conformations of allylic alcohol **2.28**. Conformation A should be more stable than B and C due to the steric interaction between hydrogen and methyl group in B or methylene group in C. However, this stability difference is small, leading to the poor selectivity. After the hydrogen on C2 of **2.28** is replaced with a bulky trimethylsilyl group (A = 2.4 kcal/mol)[70] as shown in **2.30**, the potential steric interaction between trimethylsilyl group and methyl group in E or methylene group in F increases, making conformation D much more stable than the other two (E and F). In the preferred conformation D, both the hydroxyl and benzyloxy groups help to direct the epoxidation from the lower face, leading to the epoxide **2.31** as a single diastereomer. After the desilylation with TBAF, the desired epoxide **2.29** was isolated with the retention of its stereochemistry (Scheme 28).



Scheme 28. Vinylsilanes as stereocontrol elements in stereoselective epoxidations

In addition to epoxidations, excellent stereocontrol is observed in transition-metal mediated hydrogenation of alkenes because of the presence of the silyl group. Saturated silanes **2.33** and **2.35** were obtained by treating vinylsilanes **2.32** and **2.34** with rhodium catalyst **1** (5 mol %) in DCM under a high pressure of H_2 for 48 h, respectively (Scheme 29).[71] Exceptionally high yields and stereoselectivities were observed in both cases. The new chiral center at C3 can

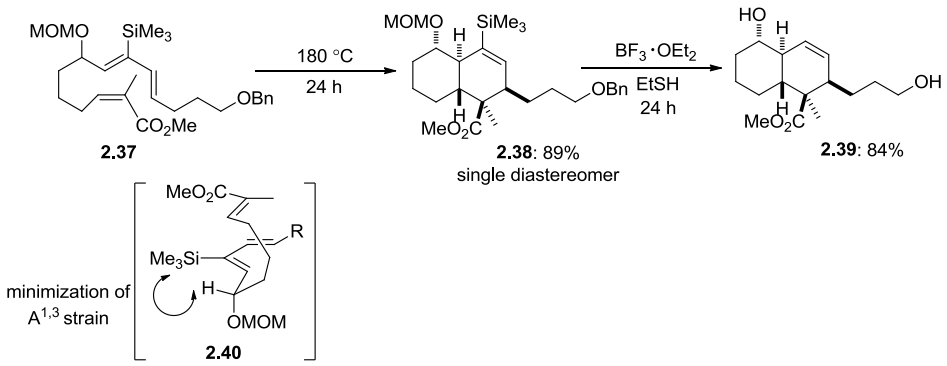
be controlled by the geometry of starting vinylsilanes. The stereochemistry of the hydrogenation of **2.34** was explained by the Newman projections **A** and **B**, the two most likely reactive conformations. The steric interaction between C_6H_{11} group and methyl group disfavored conformation **B**; the hydrogenation proceeded through **A** affording the observed product. After Fleming oxidation under a typical bromodesilylation condition, the *syn*-1,3-diol **2.36** was formed as a single diastereomer with retention of the stereochemistry at C3 position.



Scheme 29. Vinylsilanes as stereocontrol elements in stereoselective hydrogenations

In the intramolecular Diels-Alder reaction of triene **2.37**, a sterically demanding TMS group was employed as a removable stereocontrol element, leading to the *trans* ring product **2.38** as a single diastereomer (Scheme 30).[72] In the absence of the silyl group, four diastereomers were observed with the isomer corresponding to **2.38** only 15% of the mixture. The presence of the TMS group dramatically improved the stereoselectivity of the cycloaddition reaction, which can be attributed to the minimization of the steric interaction between TMS and hydrogen in **2.40**, making conformation **2.40** more stable than other conformations. Removal of the TMS

group together with the cleavage of the benzyl and methoxymethyl ethers provided **2.39** in 84% yield.

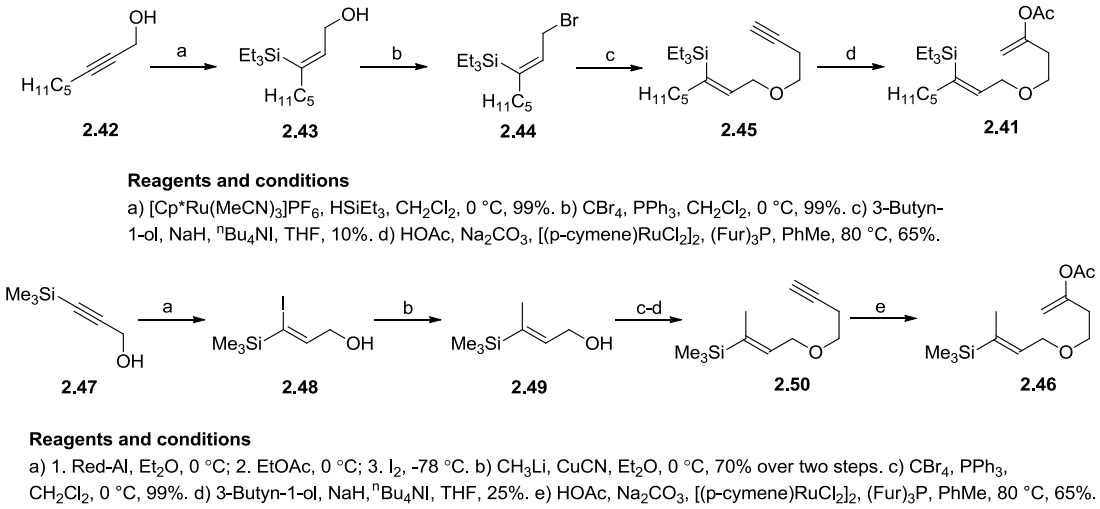


Scheme 30. Vinylsilanes as stereocontrol elements in intramolecular Diels-Alder reactions

2.2 DEVELOPMENT OF DDQ-MEDIATED OXIDATIVE C–H CLEAVAGE OF (SILYL)ALLYLIC ETHERS

As mentioned in the introduction section, a silyl group carrying a nucleofugal group, like a halogen, an alkoxyl group, or a hydrogen atom, can participate in numerous transformations. However, at the initial stage of the project, our concern was that these reactive nucleofugal groups would not be compatible with DDQ oxidation conditions. To exclude this uncertainty, simple (*Z*)- and (*E*)-trialkyl-substituted vinylsilanes **2.41** and **2.46** were prepared to examine whether (silyl)allylic ethers possess similar reactivities as simple allylic ethers towards the DDQ oxidation (Scheme 31). According to Trost's protocol,[73] ruthenium-mediated (5 mol %) hydrosilylation of propargylic alcohol **2.42** gave (silyl)allylic alcohol **2.43** in a quantitative yield with an *E*:*Z* alkene ratio of 9:1. In the presence of CBr_4 and PPh_3,[74] **2.43** was converted to allyl

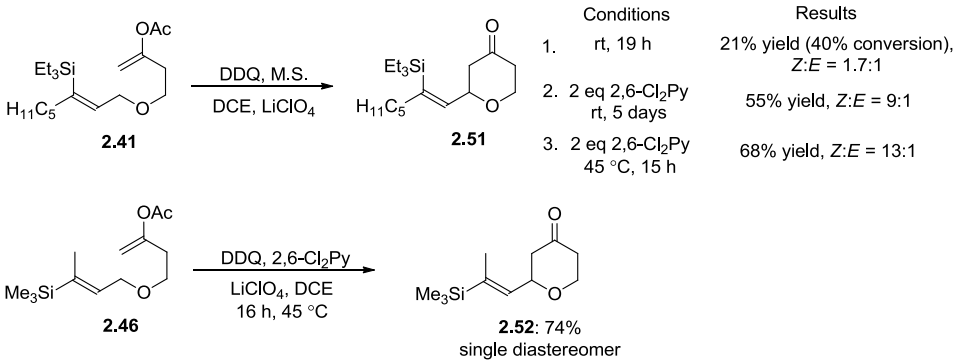
bromide **2.44**, which was coupled with 3-butyn-1-ol affording (silyl)allylic ether **2.45**. While the yield of ether formation was only 10%, the enol acetate formation reaction proceeded efficiently to provide us enough substrate **2.41** to test the hypothesis. The reduction of propargylic alcohol **2.47** with Red-Al, followed by the addition of iodine gave vinyl iodide **2.48**, which underwent copper-mediated cross-coupling with MeLi to generate (*E*)-(silyl)allylic alcohol **2.49** in 70% yields over 2 steps.[75] Following the same sequence as that from **2.43** to **2.41**, **2.49** was converted to substrate **2.46**.



Scheme 31. The preparation of substrates **2.41** and **2.46**

Substrate **2.41** was subjected to the standard oxidation condition using DDQ as the oxidant, DCE as the solvent and 4 Å molecular sieves as the water scavenger (Scheme 32). Even after 19 h at room temperature, the reaction did not proceed to completion (40% conversion), and the desired tetrahydropyrone **2.51** was obtained as the major isomer in a poor *Z*:*E* ratio of 1.7:1. The incorporation of 2,6-dichloropyridine proved to be beneficial in suppressing olefin isomerization, leading to product **2.51** in 55% yield with a *Z*:*E* ratio of 9:1 after 5 days at room

temperature. Reaction efficiency was enhanced by heating to 45 ℃ , and **2.51** was isolated in 68% yield with a *Z*:*E* ratio of 13:1 after 15 h. Under the optimized conditions, the cyclization of (*E*)-vinylsilane **2.46** was complete in 16 h providing tetrahydropyrone **2.52** in 74% yield as a single diastereomer.

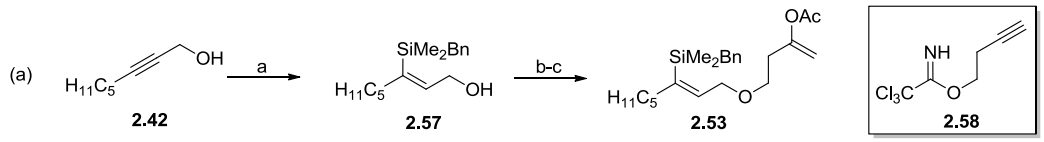


Scheme 32. Cyclizations of substrates **2.41** and **2.46**

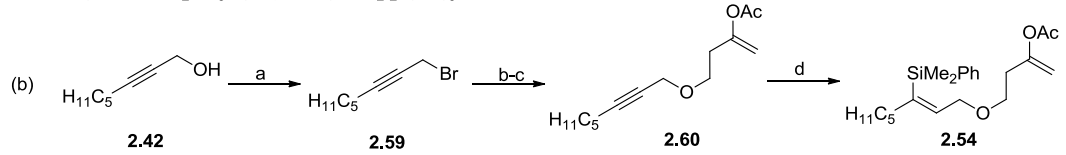
Since trialkyl-substituted vinylsilanes proved to be good substrates for the DDQ-induced oxidative C–H activation, next we planned to investigate the feasibility of cyclization reactions of vinylsilanes containing reactive nucleofugal groups. In accord with the precedents mentioned in Section 2.1, vinylsilanes **2.53**-**2.56** were studied in the DDQ oxidation process for the ultimate purpose of post-cyclization functionalizations.

The constructions of vinylsilanes in substrates **2.53**-**2.56** relied on transition-metal catalyzed hydrosilylation of alkynes (Scheme 33). TMSOTf-catalyzed etherification reaction of (silyl)allylic ether **2.57** and trichloroacetimidate **2.58** afforded the (silyl)allylic ether in 49% yields, which was then converted to enol acetate substrate **2.53** (Scheme 33(a)). Bromination of propargylic alcohol **2.42**, followed by ether formation and enol acetate formation provided propargylic ether **2.60** (Scheme 33(b)). Ruthenium-catalyzed hydrosilylation of **2.60** with

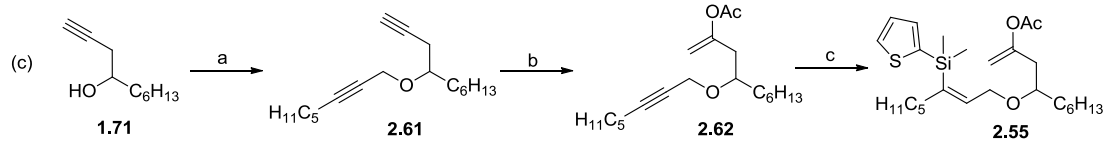
phenyldimethylsilane gave substrate **2.54**. 2-Thienylvinylsilane **2.55** was prepared following the same route as the synthesis of **2.54** (Scheme 33(c)). The preparation of vinylsiloxane **2.56** started from alkyne **2.63** (Scheme 33(d)). An addition of **2.63** onto paraformaldehyde followed by bromination gave propargylic bromide **2.64**.[76] After a sequence of etherification, enol acetate formation, desilylation and diisopropyl silyl ether formation to yield **2.66**, platinum-catalyzed intramolecular hydrosilylation proceeded smoothly to furnish siloxane **2.56** in quantitative yields.[57a]



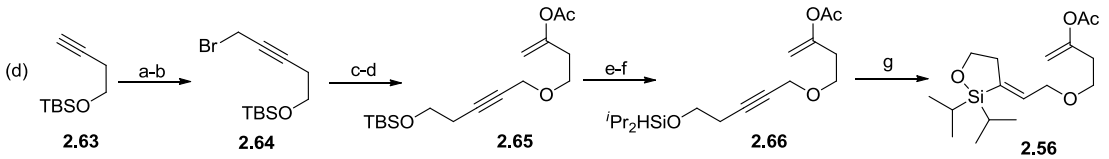
Reagents and conditions
a) $[Cp^*Ru(MeCN)_3]PF_6$, $HSiMe_2Bn$, acetone, 0 °C, 99%. b) **2.58**, TMSOTf, cyclohexane, 49%.
c) HOAc, Na_2CO_3, $[(p\text{-cymene})RuCl_2]_2$, $(Fur)_3P$, PhMe, 80 °C, 69%.



Reagents and conditions
a) CBr_4, PPh_3, CH_2Cl_2, 0 °C, 99%. b) 3-Butyn-1-ol, NaH, $^nBu_4NI$, THF, 84%. c) HOAc, Na_2CO_3, $[(p\text{-cymene})RuCl_2]_2$, $(Fur)_3P$, PhMe, 80 °C, 62%. d) $[Cp^*Ru(MeCN)_3]PF_6$, $HSiMe_2Ph$, acetone, 0 °C, 80%



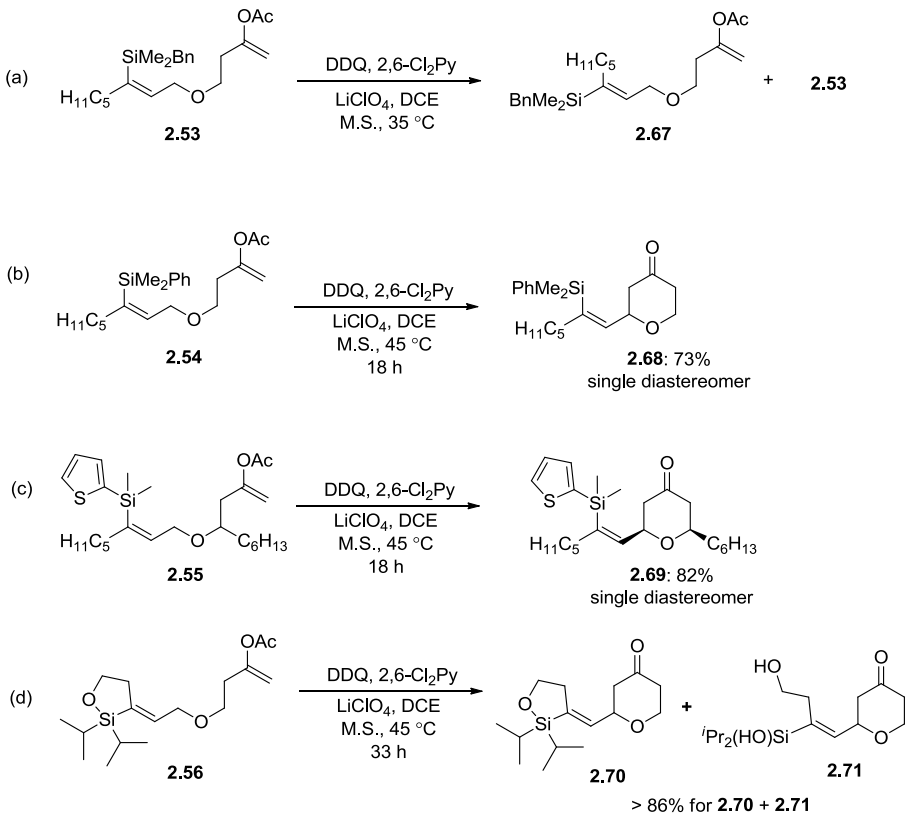
Reagents and conditions
a) NaH, **2.59**, $^nBu_4NI$, THF, 82%. b) HOAc, Na_2CO_3, $[(p\text{-cymene})RuCl_2]_2$, $(Fur)_3P$, PhMe, 80 °C, 74%.
c) $[Cp^*Ru(MeCN)_3]PF_6$, dimethyl(2-thienyl)silane, acetone, 0 °C, 99%.



Reagents and conditions
a) ^nBuLi, paraformaldehyde, THF, -78 °C to 0 °C, 75%. b) CBr_4, PPh_3, CH_2Cl_2, 99%. c) 3-Butyn-1-ol, NaH, $^nBu_4NI$, THF, 67%.
d) HOAc, Na_2CO_3, $[(p\text{-cymene})RuCl_2]_2$, $(Fur)_3P$, PhMe, 80 °C, 66%. e) 3% HCl in MeOH, 0 °C. f) chlorodiisopropylsilane, Et_3N, DMAP, CH_2Cl_2, 95%. g) Pt(DVDS), CH_2Cl_2/CH_3CN (1:1), 99%.

Scheme 33. The preparation of substrates **2.53-2.56**

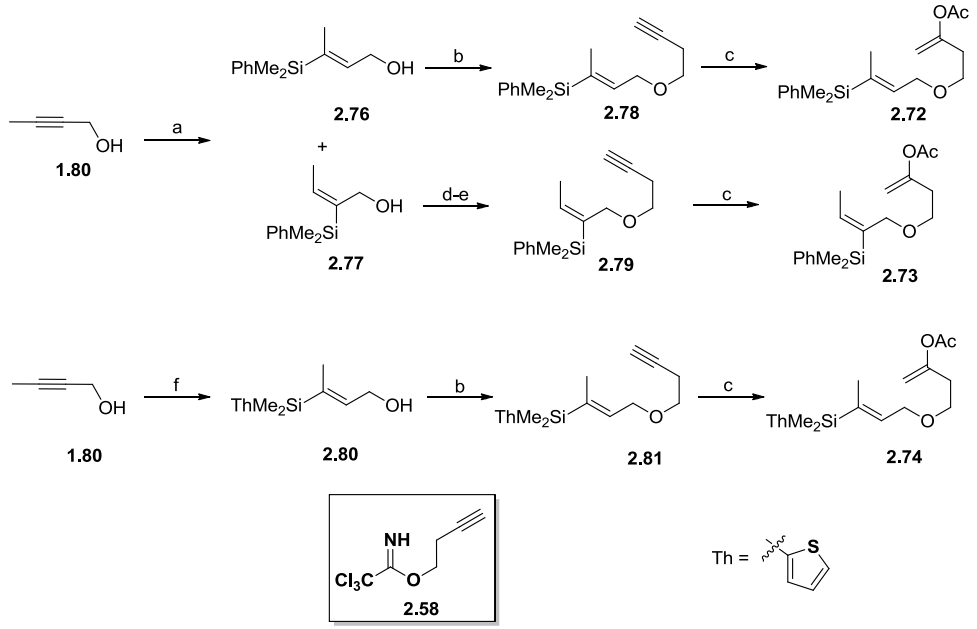
The results of DDQ-mediated oxidative cyclizations of substrates **2.53**-**2.56** are shown in Scheme 34. Once benzylsilane **2.53** was treated with DDQ at room temperature, the clear solution turned navy blue immediately. However, no reaction was observed and starting material was not consumed over a prolonged time. Raising the temperature to 35 ℃ led to the formation of olefin isomerization byproduct **2.67** (Scheme 34(a)). (*Z*)-3-Phenyldimethylsilane **2.54** reacted with DDQ smoothly to form tetrahydropyrone **2.68** in 73% yields and no olefin isomerization byproduct was observed (Scheme 34(b)). Hetero arylsilanes are also suitable substrates for the process as demonstrated by the cyclization of (*Z*)-3-(2-thienyl)dimethylsilane **2.55** to give **2.69** in 82% yield (Scheme 34(c)). Consistent with previous cyclizations of simple allylic ether substrates, vinylsilane substrates react exclusively to generate the 2,6-*cis* isomers. Vinylsiloxane **2.56** can also be oxidized by DDQ to provide the desired tetrahydropyrone **2.70** along with hydrated product **2.71** in over 86% yield. According to Denmark's studies, both **2.70** and **2.71** are expected to serve as substrates for cross-coupling and Fleming-Tamao oxidation, leading to same products.[52b]



Scheme 34. Cyclizations of substrates **2.53**-**2.56**

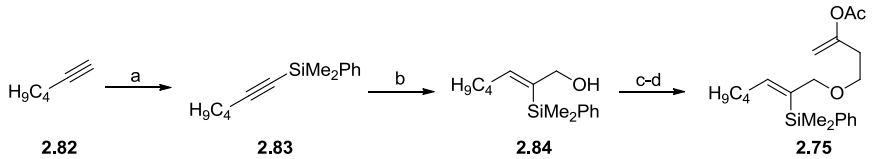
Since phenyldimethylsilane, (2-thienyl)dimethylsilane and diisopropyl siloxane groups proved to be compatible with the DDQ oxidations, (silyl)allylic ether substrates **2.72**-**2.75** were synthesized to examine the different substituent effects of vinylsilanes on the cyclizations (Scheme 35). The preparation of substrates **2.72**-**2.74** began from 2-butyn-1-ol (**1.80**) through a similar sequence as the synthesis of substrate **2.53** (Scheme 33(a)). Chloroplatinic acid-mediated hydrosilylations[77] of **1.80** with phenyldimethyisilane gave the corresponding (*E*)-3-trialkylsilyl allylic alcohol **2.76** and (*Z*)-2-trialkylsilyl allylic alcohol **2.77**. The known (silyl)allylic ether formations under acidic or basic conditions, followed by enol acetate formations afforded substrates **2.72**-**2.73**. The synthetic route to substrate **2.74** was same as that to **2.72**. Pt-mediated reactions were not highly regioselective but were sufficiently efficient to provide suitable

amounts of cyclization substrates for further studies. The (*Z*)-2-phenyldimethylsilyl allylic ether **2.75** was prepared through the well-known sequence from the corresponding alcohol **2.84**, which can be accessed by hydroalumination of silylalkyne **2.83** followed by the addition to the paraformaldehyde.[78]



Reagents and conditions

a) $H_2PtCl_6 \bullet 6H_2O$, $HSiMe_2Ph$, THF, 50 °C, 56% for **2.76,** 29% for **2.77.** b) **2.58,** TMSOTf, cyclohexane, 53% for **2.78,** 50% for **2.81.** c) HOAc, Na_2CO_3, $[(p\text{-cymene})RuCl_2]_2$, $(Fur)_3P$, PhMe, 80 °C, 69% for **2.72,** 70% for **2.73,** 68%% for **2.74.** d) PPh_3, CBr_4, CH_2Cl_2. e) 3-Butyn-1-ol, NaH, $^nBu_4NI$, THF, 32% over two steps. f) $H_2PtCl_6 \bullet 6H_2O$, dimethyl(2-thienyl)silane, THF, 50 °C, 51%.



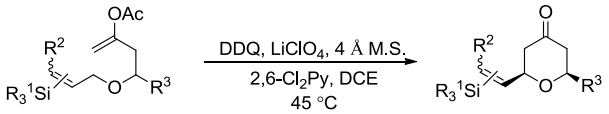
Reagents and conditions

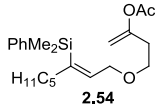
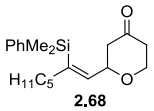
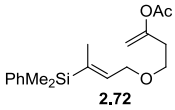
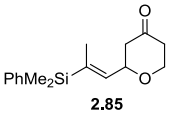
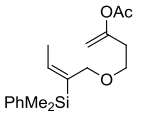
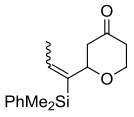
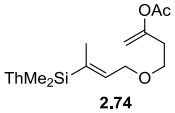
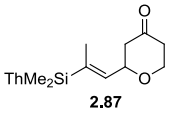
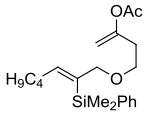
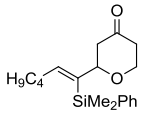
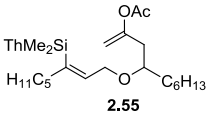
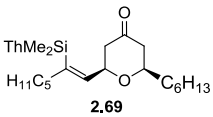
a) $PhMe_2SiCl$, ^nBuLi, THF, -78 °C, 99%. b) DIBAL-H, Et_2O, 0 °C, then MeLi, 0 °C, then paraformaldehyde, 83%. c) **2.58**, TMSOTf, cyclohexane, 54%. d) HOAc, Na_2CO_3, $[(p\text{-cymene})RuCl_2]_2$, $(Fur)_3P$, PhMe, 80 °C, 64%.

Scheme 35. The preparation of substrates **2.72-2.75**

(Silyl)allyl ethers **2.72-2.75** were studied under standard DDQ oxidation conditions and the results are summarized in Table 4. All the reactions proceeded smoothly to afford the desired tetrahydropyrone products in good yields, though alkene isomerization was observed for **2.73**, leading to **2.86** as a 1:1 mixture of alkene isomers (entry 3, table 4).

Table 4. DDQ-mediated C–H cleavage of substituted (silyl)allylic ethers[a]

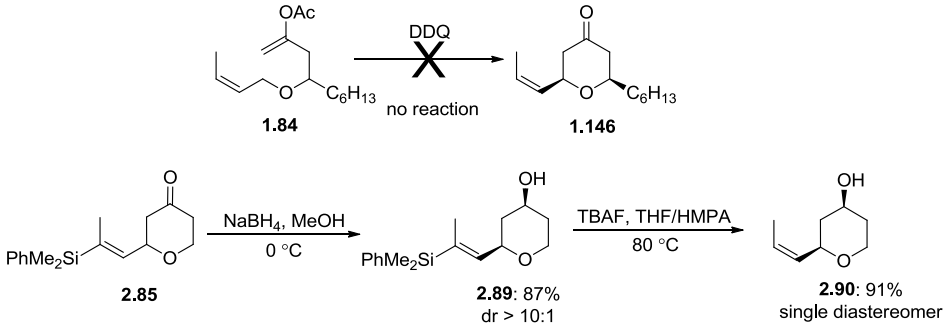


Entry	Substrate	Product	t (h)	Yield(%)
1	 **2.54**	 **2.68**	18	73
2	 **2.72**	 **2.85**	17	94
3	 **2.73**	 **2.86**	24	69 *E*:*Z* = 1:1
4	 **2.74**	 **2.87**	8	86
5	 **2.75**	 **2.88**	6	82
6	 **2.55**	 **2.69**	18	82

[a] Representative procedure: DDQ (4 equiv) was added to a solution (0.1 M) of the substrate, 2,6-dichloropyridine (4 equiv), $LiClO_4$ (0.2 equiv) and 4Å M.S in DCE. The reaction was stirred at 45 °C for the indicated time.

2.3 DIVERSE FUNCTIONALIZATION OF VINYLSILANE-SUBSTITUTED TETRAHYDROPYRONES

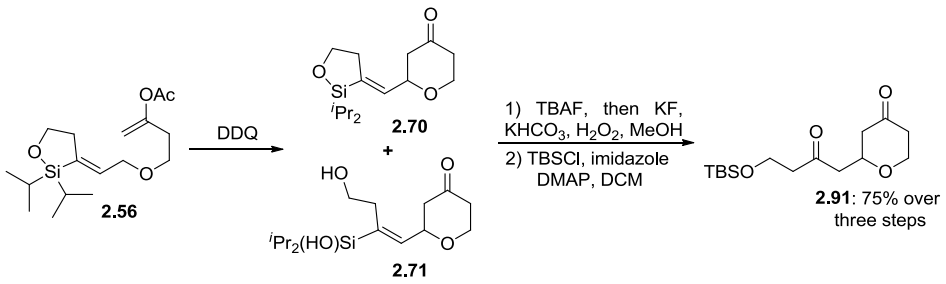
With a variety of vinylsilane-substituted tetrahydropyrones in hand, we started to functionalize the vinylilanes to give a range of structurally and stereochemically diverse tetrahydropyran structures. As mentioned in Chapter 1, (*Z*)-allylic ether **1.84** did not react with DDQ to give the tetrahydropyran **1.146** containing a *cis*-alkene. This gap can be filled by the desilylation of (*E*)-3-phenyldimethylsilane (Scheme 36). Because the ketone moiety was not compatible with the succedent desilylation conditions, it was stereoselectively reduced by $NaBH_4$ to give the alcohol **2.89**; **2.89** can efficiently undergo desilylation process with TBAF at 80 ℃ using THF and HMPA as co-solvents to provide the (*Z*)-vinyl tetrahydropyran **2.90** in 91% yield as a single diastereomer.[79]



Scheme 36. (*Z*)-Vinyl tetrahydropyran synthesis through desilylation of (*E*)-vinylsilanes

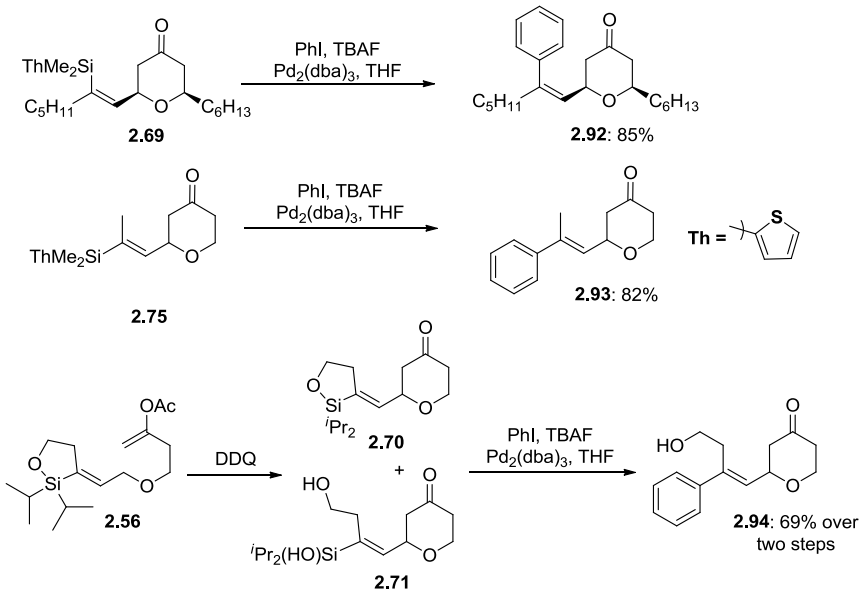
The Tamao oxidation of vinylsilanes was also examined (Scheme 37). After the DDQ-mediated oxidative cyclization of vinylsiloxane **2.56**, mixtures of vinylsiloxane **2.70** along with hydrated product **2.71** were subjected to the Tamao oxidation.[80] To facilitate the separation

through column chromatography, the product was converted to a TBS ether to yield diketone **2.91** in 75% yield over three steps.



Scheme 37. Conversion of vinylsilanes to ketones through Tamao oxidations

Vinylsilane tetrahydropyrans can serve as precursors to other alkenes through palladium-catalyzed cross-coupling reactions as shown in Scheme 38. The electron-rich 2-thienyl group was selected as the nucleofugal group in vinylsilanes to assure that the vinylsilane was not cleaved during the coupling.[81] Both (*Z*)-vinylsilane **2.69** and (*E*)-vinylsilane **2.75** reacted smoothly with iodobenzene in the presence of TBAF and $Pd_2(dba)_3$ to generate **2.92** (85%) and **2.93** (82%), respectively. Moreover, the mixture of **2.70** and **2.71** from the oxidative cyclization of **2.56** can also participate in the cross-coupling reactions, giving product **2.94** in 69% yields over two steps from the cyclization reaction. While this study was not exhaustive, these results demonstrate the capacity to prepare diverse tetrahydropyran structures by combining oxidative cyclization of vinylsilanes with palladium-catalyzed cross-coupling reactions.



Scheme 38. Vinylsilanes in cross-coupling reactions

As shown in Figure 18, several complex natural products share an interesting structural moiety that is 2-(2-hydroxyalkyl)tetrahydropyran-4-ol (**2.95**) containing four stereocenters.[82] Since **2.95** is frequently seen in natural products, we would like to develop a protocol to prepare the eight possible stereoisomers of **2.95** from vinylsilane-tetrahydropyrones. As depicted in Figure 19, **2.95** will be achieved from **2.96** through Fleming oxidation with the retention of the configuration at C2'. **2.96** will be prepared from oxidative cyclization product **2.97** through stereoselective hydrogenation. $A^{1,3}$ strain[83] dictates that **2.68** and **2.85** will strongly prefer to occupy conformers **2.98** and **2.99**, respectively (Figure 19). These conformers present opposite faces of the alkene for functionalization through directed hydrogen delivery from the tetrahydropyranyl oxygen, thus providing an opportunity to realize the stereoselective hydrogenation of vinylsilanes through reagent selection. After a detailed literature search, Crabtree's catalyst[84] was selected for the purpose.

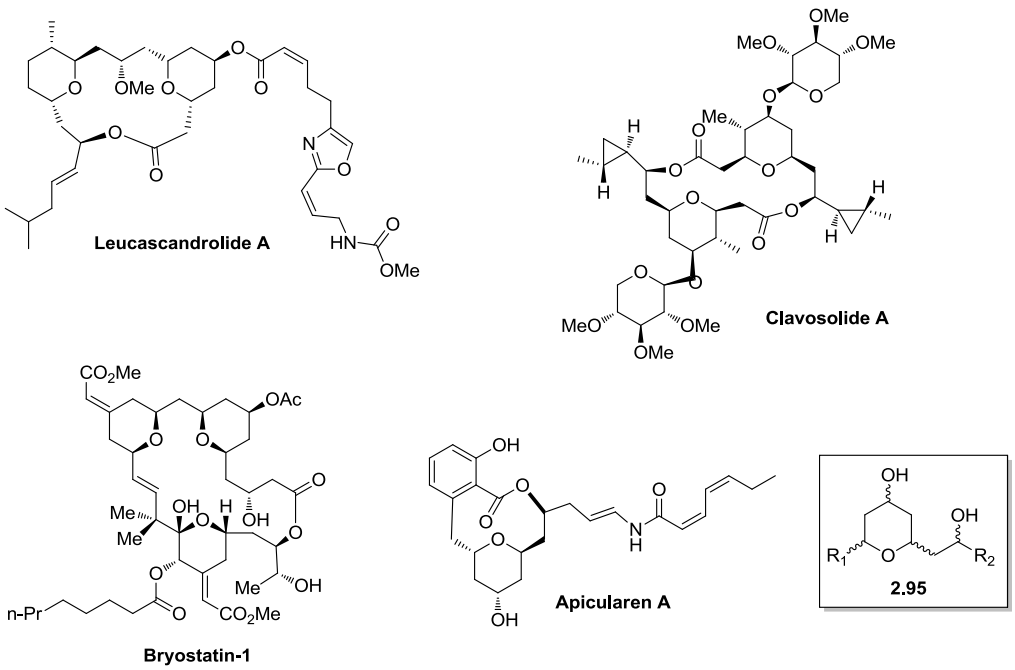


Figure 18. An interesting building block in several natural products

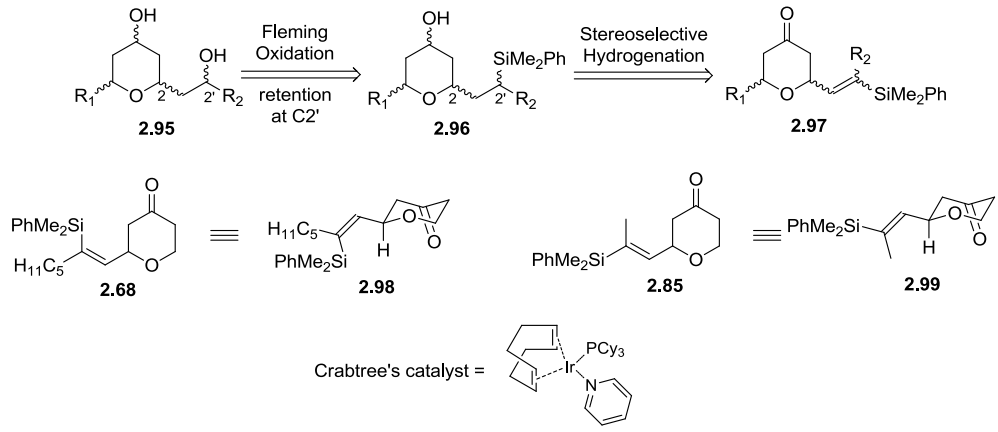
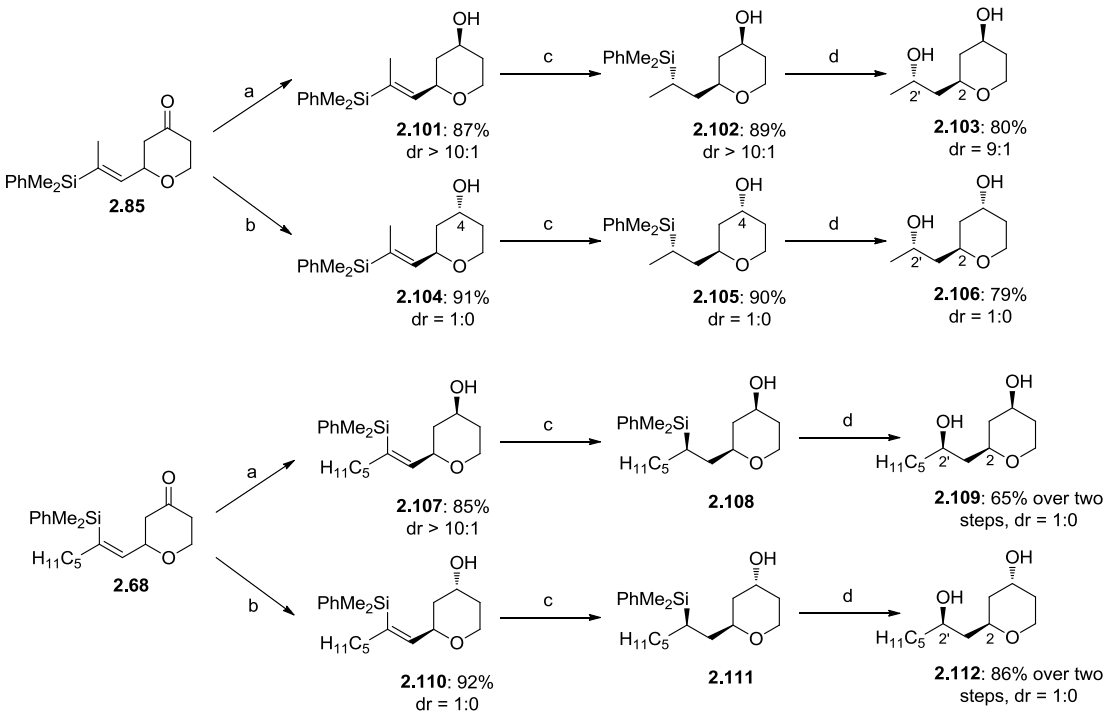


Figure 19. A retrosynthetic analysis of **2.95** and conformation analysis of **2.68** and **2.85**

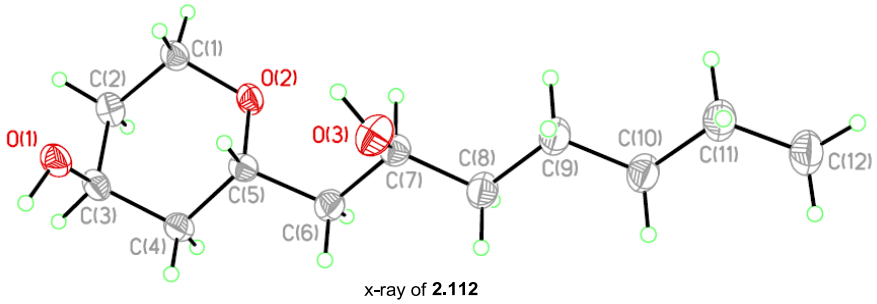
As shown in Scheme 39, exposing **2.85** to $NaBH_4$ afforded equatorial alcohol **2.101**, which underwent a hydrogenation mediated by Crabtree's catalyst to yield alkyl phenyldimethylsilane **2.102** in 89% yield with a diastereomeric ratio of > 10:1. After oxidation of the silane **2.102** under Fleming's conditions, the first dihydroxy isomer **2.103** was isolated in

80% yield with a diastereomeric ratio of 9:1. Tetrahydropyrone **2.85** was reduced by L-Selectride to give axial alcohol **2.104**. Changing the orientation of the hydroxyl group at C4 position of tetrahydropyran ring did not interfere with the hydrogenation process, and **2.105** was obtained in 90% yield as a single diastereomer. The stereocenter at C2' position of **2.103** and **2.106** can be reversed by changing the geometry of the vinylsilanes from *E* to *Z*, as demonstrated by the efficient synthesis of another two stereoisomers **2.109** and **2.112** with excellent stereocontrol. The hypotheses regarding the stereochemical outcomes of these reactions were confirmed by single crystal diffraction studies of **2.112** (Scheme 39).



Reagents and conditions

a) $NaBH_4$, MeOH, -10 °C. b) L-Selectride, THF, -90 °C. c) H_2, Crabtree's catalyst, CH_2Cl_2. d) CH_3CO_3H, KBr, NaOAc, HOAc.

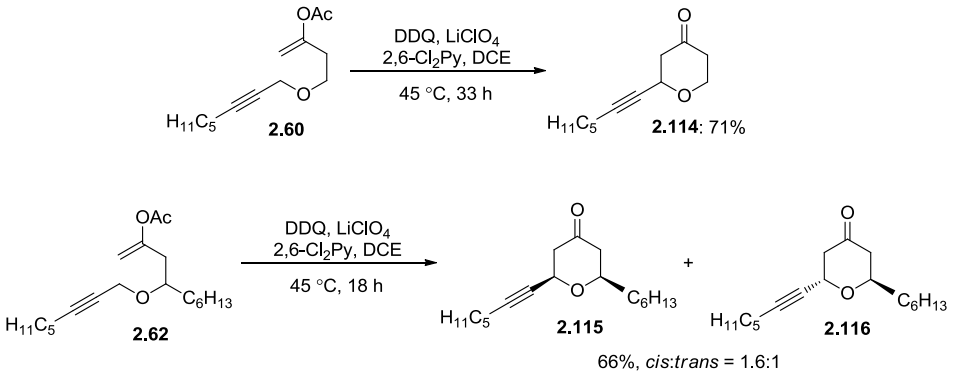


x-ray of **2.112**

Scheme 39. Target-oriented synthesis of four possible stereoisomers of 2-(2-hydroxyalkyl)tetrahydropyran-4-ol moiety from vinylsilanes

The use of alkyne hydrosilylation reactions to prepare vinylsilanes led us to study propargylic ethers as substrates for the oxidative cyclization reactions. Propargylic ethers are worth pursing also because alkynes would provide good opportunities for late stage diversification. Propargylic ethers proved to be similarly reactive relative to vinylsilane substrates (Scheme 40), with the DDQ-mediated cyclization of alkyne **2.60** to tetrahydropyran

2.114 proceeding in 71% yield after 33 h at 45 ℃ . The oxidative cyclization of **2.62** provided a 41% yield of *cis*-isomer **2.115** and a 25% yield of *trans*-isomer **2.116** after 18 h at the same temperature. While the stereocontrol (1.6:1) was moderate, the access to the rare *trans*-2,6-disubstituted tetrahydropyran moiety allow us to explore the preparation of eight possible stereoisomers of **2.95**.

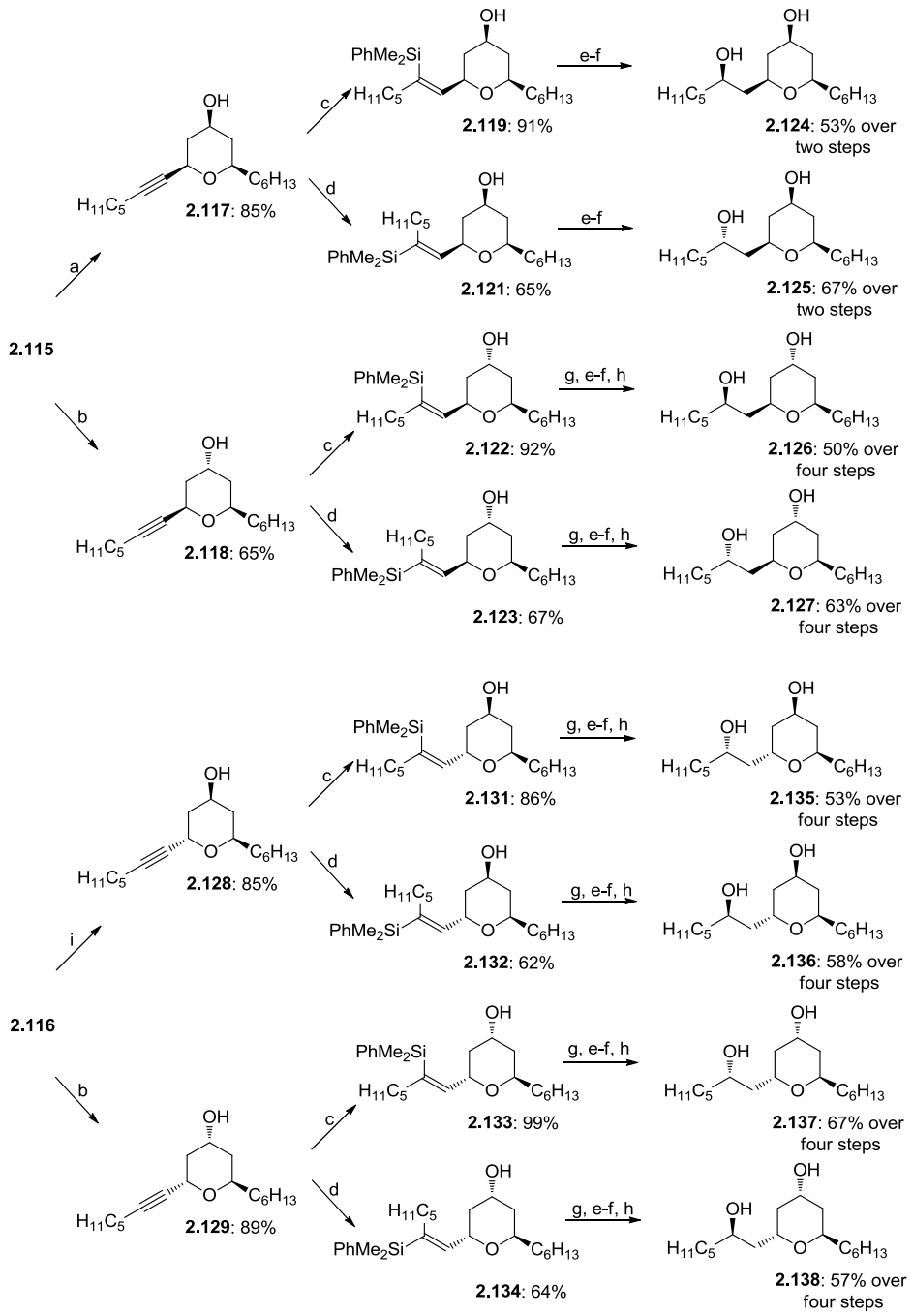


Scheme 40. Cyclizations of propargylic ether substrates **2.113** and **2.62**

A library that consisted of the eight possible stereoisomers of hydroxyalkyl tetrahydropyranyl alcohols (**2.95**) was prepared from propargylic ether substrate **2.62** (Scheme 41). The approach proceeded through the non-stereoselective cyclization of **2.62** to **2.115** and **2.116**. The products are separated and subjected to ketone reduction, hydrosilylation, reduction and Fleming oxidation to generate the full array of stereoisomers. As shown in Scheme 41, 2,6-*cis*-isomer **2.115** reacted with $NaBH_4$ and L-Selectride in a predictable manner to form alcohol **2.117** and **2.118**, respectively. Equatorial alcohol **2.117** proceeded through hydrosilylation with $PhMe_2SiH$ and $Cp^*Ru(CH_3CN)_3PF_6$ giving (*Z*)-vinylsilane **2.119** in 91% yield, while hydrosilylation with $PhMe_2SiH$ and $H_2PtCl_6{\bullet}6H_2O$ generating (*E*)-vinylsilane **2.121** in 65% yield. The regioselectivity of the Pt-mediated hydrosilylation was lower (~3:1) than that of the

Ru-catalyzed reaction, but the desired product was obtained in a suitable yield to complete the synthesis. The vinylsilanes were reduced through the Crabtree's catalyst mediated hydrogenation followed by oxidation under Fleming's conditions to provide tetrahydropyranols **2.124** and **2.125**. The application of the directed hydrogenation process to vinylsilanes **2.122** and **2.123** led to desired hydrogenated products, but poor diastereoselectivity was observed, which was attributed to axial hydroxyl groups as potential competitive coordination sites for Crabtree's catalyst. This problem was solved by protecting the hydroxyl groups of **2.122** and **2.123** as TBDMS ethers. The simple functionalization allowed the sequences to proceed readily to form **2.126** and **2.127**.

Reduction of **2.116** with SmI_2 and *i*PrOH formed equatorial alcohol **2.128** in 85% yield as a single isomer (Scheme 41).[85] Proceeding through the sequence of stereodivergent hydrosilylations, vinylsilane reduction and Fleming oxidation afforded **2.135** and **2.136**. Subjecting **2.116** to L-Selectride resulted in ketone reduction from an equatorial trajectory to form **2.129** with excellent stereocontrol, and the final two stereoisomers **2.137** and **2.138** were obtained with high selectivity following the same synthetic sequence.

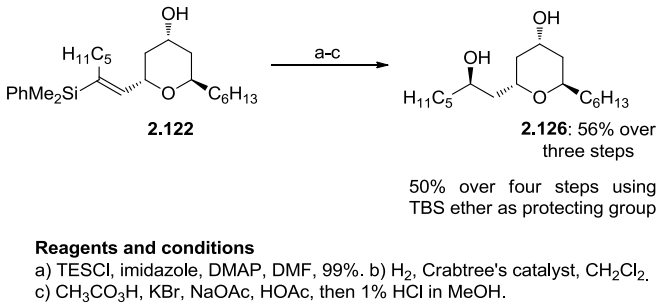


Reagents and conditions

a) $NaBH_4$, MeOH, -10 °C. b) L-Selectride, THF, -90 °C. c) $PhMe_2SiH$, $Cp^*Ru(NCCH_3)_3]PF_6$, acetone, 0 °C. d) $PhMe_2SiH$, $H_2PtCl_6 \bullet 6H_2O$, THF, 50 °C. e) H_2, Crabtree's catalyst, CH_2Cl_2. f) CH_3CO_3H, KBr, NaOAc, HOAc. g) TBSCl, imidazole, CH_2Cl_2, or DMF. h) Bu_4NF, THF. i) SmI_2, THF, *i*PrOH.

Scheme 41. Synthesis of a stereochemically diverse library

At last, triethylsilyl ethers were sufficiently stable to allow the sequences to proceed with similar efficiencies to those employing TBS ethers. Moreover, triethylsilyl ethers were advantageous because desilylation can be conducted in the same flask as Fleming oxidation (Scheme 42), thereby saving one step in the sequence.



Scheme 42. One step reduction using triethylsilyl ether as protecting group

2.4 DISCUSSION

2.4.1 Control of olefin geometry

In the oxidative cyclization of (*Z*)-triethyl(silyl)allylic ether **2.41**, stoichiometric amount of weak, soluble base 2,6-dichloropyridine was found to be beneficial in suppressing the olefin isomerization, and the *Z*:*E* ratio of **2.51** was improved from 1.7:1 to 13:1 (Scheme 32). Considering that the olefin isomerization was not observed in reactions of alkyl-substituted allylic ethers even in the absence of 2,6-dichloropyridine, it should be brought about by the increased interaction between bulky trialkylsilyl group and hydrogen atom on C1 carbon (Figure 20). To alleviate this interaction, the rotation of C2–C3 bond in **2.139** occurred ahead of

hydrogen atom abstraction. 2,6-Dichloropyridine would facilitate the hydrogen atom abstraction to give oxocarbenium ion intermediate **2.141**, thereby inhibiting the olefin isomerization process.

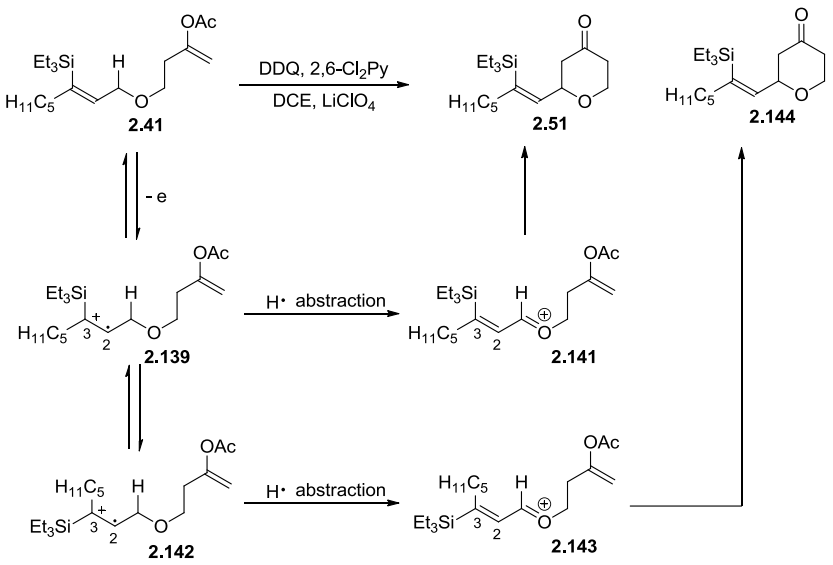


Figure 20. DDQ-mediated oxidation of **2.41**

2.4.2 Oxidation of benzylsilane substrate

Benzylsilane **2.53** was not converted to the cyclized product (Scheme 34), though the clear solution turned navy blue immediately upon treating **2.53** with DDQ at room temperature. The color change indicates the occurrence of DDQ-mediated oxidation process. The (silyl)allylic ether in **2.53** is oxidized by DDQ to form radical cation **2.145** (pathway A, Figure 21), which is quenched by the benzylsilane to afford the radical cation intermediate **2.146**; according to the known capacity of benzylsilanes to undergo single electron oxidation,[86] the benzylsilane in **2.53** can also be oxidized directly by DDQ to give **2.146** (pathway B, Figure 21). Either of these two pathways will block the hydrogen atom abstraction process.

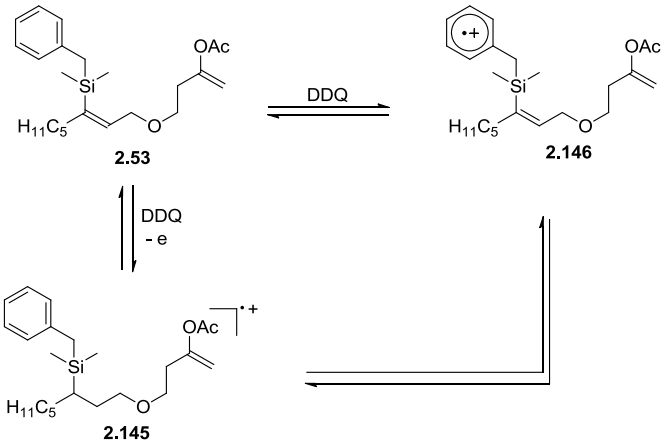


Figure 21. Possible pathways for the oxidation of **2.53**

2.4.3 Reaction rate analysis

Phenyl and 2-thienyl (silyl)allylic ethers proved to be good substrates for the DDQ-induced oxidative C–H activation (Table 4). However, these reactions were much slower than reactions of similarly substituted allylic ethers, requiring higher temperature and multiple hours for complete conversion. Trialkylsilyl groups are electron donating substituents, indicating that the origin of the difference should not be an electronic effect. Kochi has disclosed that sterically hindered arenes react with quinones much more slowly than sterically unhindered arenes with similar oxidation potentials because the rate of electron transfer is dependent on the ability of quinone to approach the arene.[87] The bulky trialkylsilyl group blocks the approach of DDQ towards the vinylsilane, and therefore the reaction was much slower.

2.4.4 Stereochemically diverse library syntheses

As shown in Scheme 39, an efficient protocol was developed to prepare the four possible stereoisomers of 2-(2-hydroxyalkyl)tetrahydropyran-4-ols. Each of the isomers can be accessed through a sequence of ketone reduction, hydrogenation and Fleming oxidation from the cyclization products of vinylsilane substrates. The ketone was reduced stereoselectively by $NaBH_4$ or L-Selectride to provide equatorial or axial alcohol, respectively. Reduction of the vinylsilane with H_2 and Crabtree's catalyst resulted in the corresponding alkyl phenyldimethylsilane with excellent stereocontrol due to catalyst coordination by the tetrahydropyranyl oxygen and conformational control as defined by $A^{1,3}$ strain (Figure 19). The orientation of the hydroxyl group at the 4-position of the tetrahydropyran did not influence the efficiency of the hydrogenation, and the stereocenter at C2' was controlled by the geometry of the vinylsilane. Fleming oxidation proceeded smoothly with the retention of the configuration at C2'.

Propargylic ethers can serve as substrates for DDQ-mediated oxidative cyclization reactions. Alkynes do not present the steric challenges of vinylsilanes, but are inferior cation-stabilizing groups, so the reactivity of the propargylic ether is comparable to that of the vinylsilane. Different from the complete diastereocontrol observed in all previous cyclization reactions, the stereocontrol in the cyclization of propargylic ether **2.62** was diminished (Scheme 40), which is attributed to the minimal energetic difference between the (*E*)- and (*Z*)-oxocarbenium ion intermediates due to the sterically undemanding alkynyl groups.

The access to the rare (*Z*)-oxocarbenium ion has been used to prepare the eight possible diastereomers of a 2-hydroxyalkyl-4-hydroxy-6-alkyltetrahydropyran structure through the established sequence (Scheme 41). Vinylsilanes **2.119** and **2.121** can be stereoselectively

reduced with H_2 and Crabtree's catalyst. However, the attempts to apply the same hydrogenation conditions to all other vinylsilanes resulted in poor stereoselectivities. We postulated that in the preferred conformations of stereoisomers **2.122**-**2.123** and **2.131**-**2.134** as shown in Figure 22, the axial hydroxyl groups served as competitive coordination sites for Crabtree's catalyst, leading to the hydrogen delivery from the undesired face. Protecting these hydroxyl groups as silyl ethers can eliminate the undesired coordination effect to provide the hydrogenation products with excellent stereocontrol.

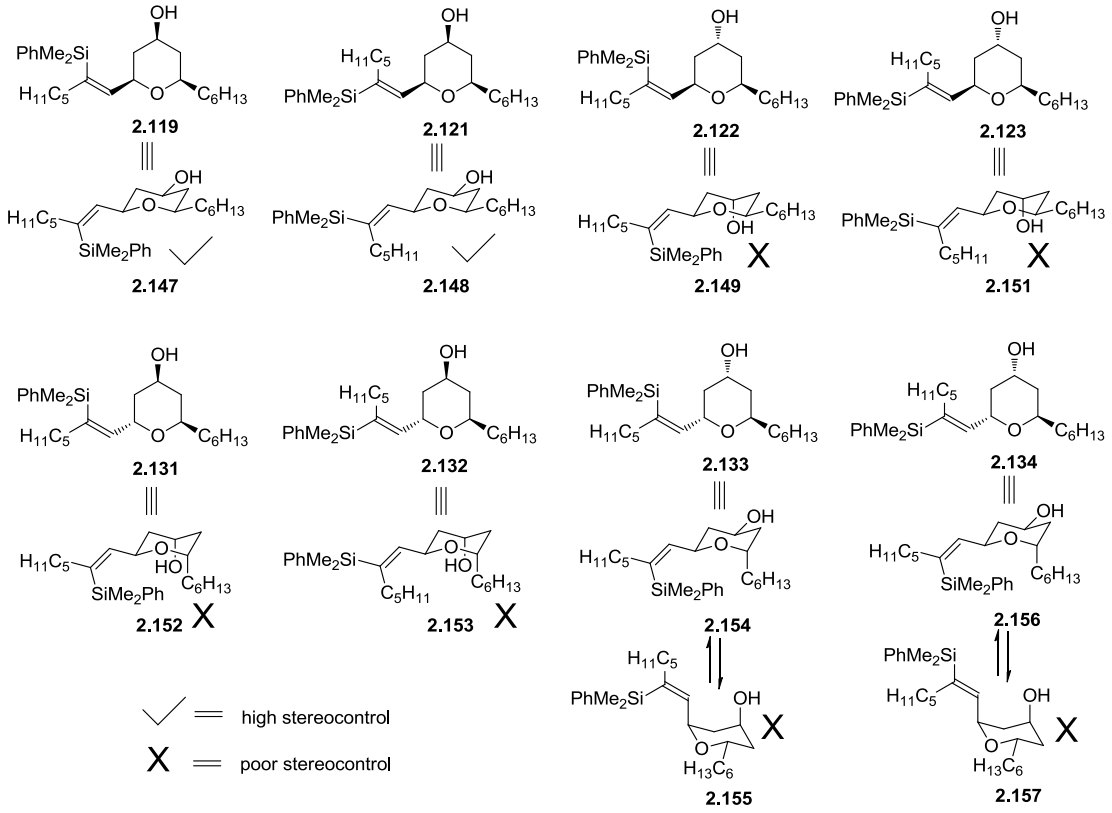


Figure 22. Conformation analysis of eight vinylsilanes for hydrogenation processes

Stereoselective reductions of *trans*-2,6-dialkyltetrahydropyran-4-ones are difficult when the alkyl substituents are sterically similar because the two possible chair conformations are

energetically similar.[88] However, due to the significantly different A-values of alkynyl and alkyl groups, the preferred chair conformation of 2-alkynyl-6-alkyltetrahydropyran-4-one (**2.116**) should be **2.158B** (Figure 23), in which the alkynyl group is axially oriented and the alkyl is equatorially oriented. L-Selectride delivered the hydride addition from an equatorial trajectory to give **2.129** as a single diastereomer. Reduction of **2.116** with $NaBH_4$, however, was unselective due to the block of the axial trajectory by the alkynyl group. The challenge was solved finally by employing SmI_2 and *i*PrOH affording **2.128** in 85% yields as a single isomer. The capacity to control the stereochemical outcome of the C4 carbonyl group in a tetrahydropyran-4-one in a completely selective and complementary manner illustrates that alkynyl-substitution should have broader application in the synthesis of *trans*-2,6-dialkyltetrahydropyrans.

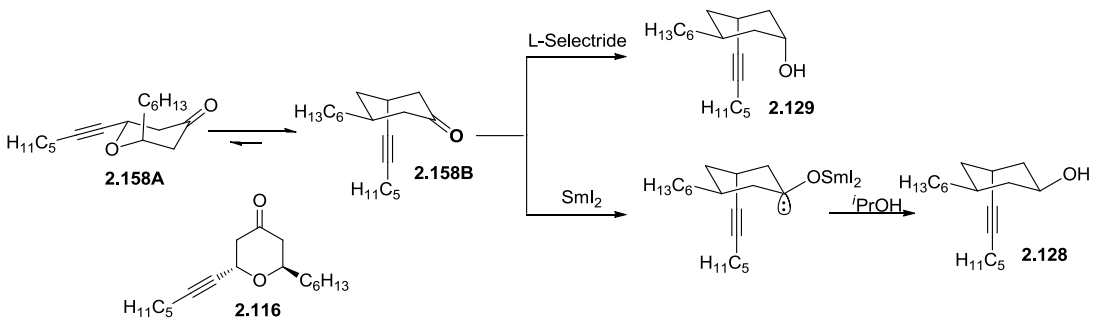


Figure 23. Stereocontrolled reduction of *trans*-2,6-disubstituted tetrahydropyran-4-ones

2.5 SUMMARY

We have shown that vinylsilane-substituted tetrahydropyrans, readily prepared through oxidative cyclization on (silyl)allylic ethers or on propargylic ethers followed by transition-metal catalyzed hydrosilylation, provide access to a broad range of structurally and stereochemically diverse tetrahydropyran products. The versatility arises from the ability of vinylsilanes to engage in numerous transformations, such as Pd-mediated cross-coupling reactions, desilylations and Fleming–Tamao oxidations, as well as their well-defined conformational preferences for stereoselective functionalization.

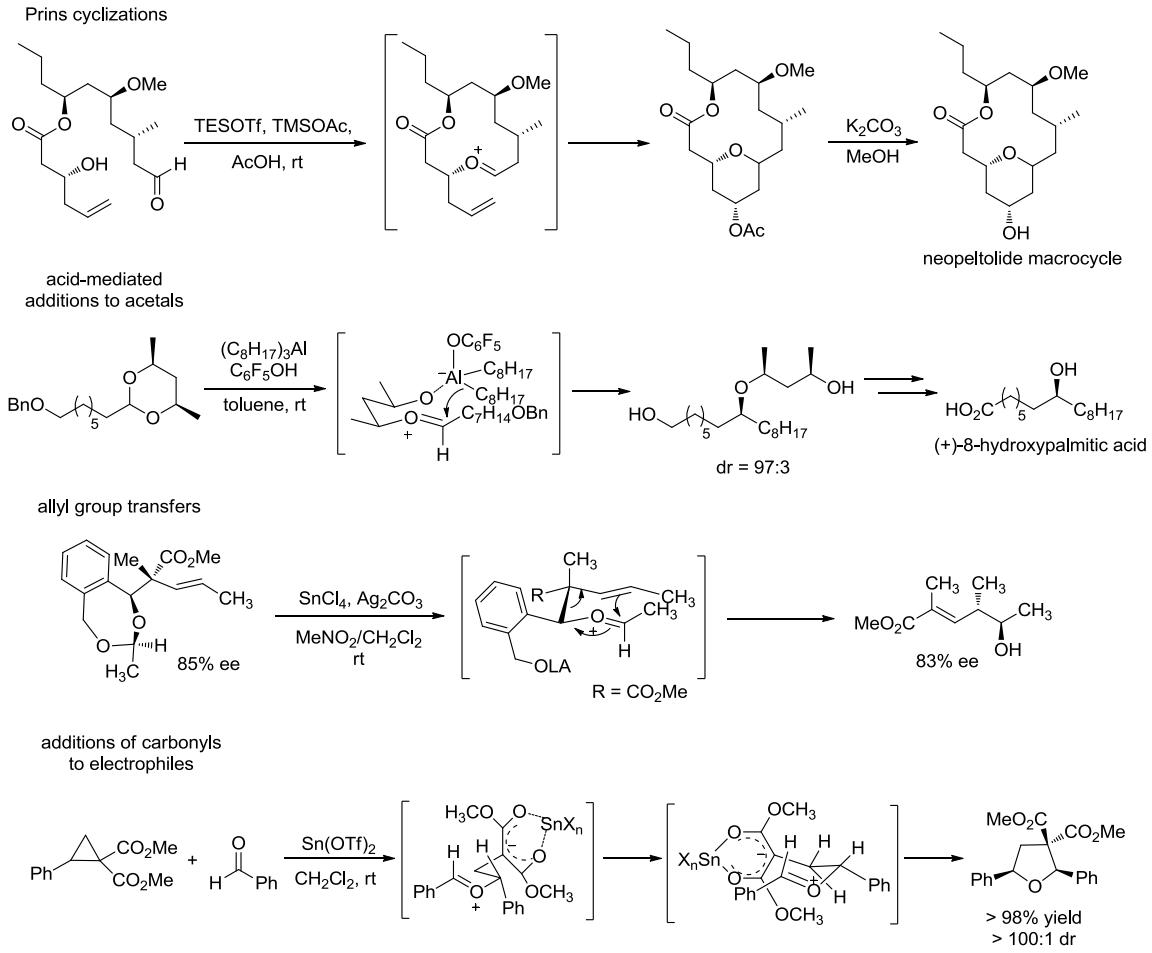
The cyclization of (silyl)allylic ethers proceeds efficiently to generate *cis*-2,6-disubstituted tetrahydropyrones with excellent stereocontrol, and therefore is preferable for target-oriented syntheses. Pd-mediated cross-coupling reactions were useful for the synthesis of complex alkene structures, and desilylation process afforded us an opportunity to access (*Z*)-vinyl tetrahydropyrans. Moreover, Tamao oxidations were employed to convert vinylsilanes to corresponding ketones. Coupling stereoselective ketone reduction, Crabtree's catalyst mediated hydrogenation and Fleming oxidation led to the formation of four diastereomers of a hydroxyl tetrahydropyranol structure.

The cyclization of propargylic ethers results in a mixture of *cis*- and *trans*-2,6-disubstituted tetrahydropyrones due to the similar energies of the *E*- and *Z*-oxocarbenium ion intermediates. The access to the *trans*-2,6-disubstituted tetrahydropyrans was employed to prepare the eight possible stereoisomers of a 2-hydroxyalkyl-4-hydroxy-6-alkyltetrahydropyran structure. The approach outlined herein will have broad applications in natural product and libraries synthesis when coupled with the growing number of protocols that utilize vinylsilanes as substrates for new chemical bond forming reactions.

3.0 STEREOSELECTIVE SYNTHESIS OF TERTIARY ETHERS THROUGH GEOMETRIC CONTROL OF HIGHLY SUBSTITUTED OXOCARBENIUM IONS

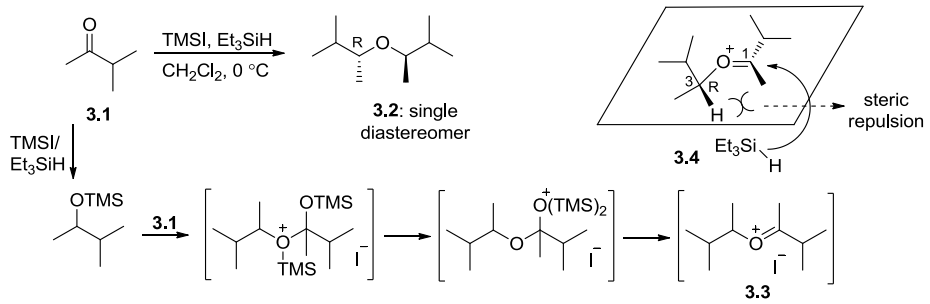
3.1 INTRODUCTION OF 1,1-DISUBSTITUTED OXOCARBENIUM IONS AS REACTION INTERMEDIATES

Oxocarbenium ions are important reactive intermediates in synthetic organic chemistry. Numerous methods for highly diastereoselective additions of carbon or heteroatom nucleophiles to mono-substituted oxocarbenium ions have been identified, such as Prins cyclizations,[47,89] acid-mediated additions to acetals,[90] allyl group transfers,[91] and additions of carbonyls to electrophiles (Scheme 43).[92] The excellent stereoselectivities in these reactions are attributed to the strong preference of mono-substituted oxocarbenium ions for (*E*)-configurations, which are calculated at approximately 2 kcal/mol^{-1} more stable than the corresponding (*Z*)-isomers.[93] On the other hand, stereoselective additions to 1,1-disubtituted oxocarbenium ions are not well developed. This challenge arises from the fact that the two possible chair conformations are energetically similar.



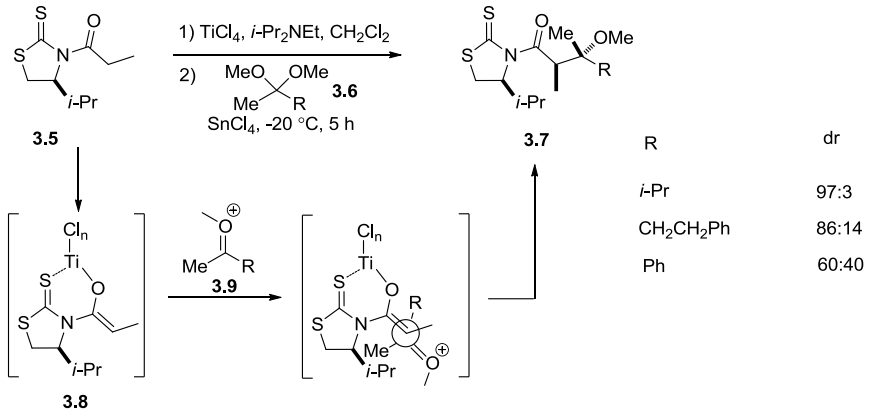
Scheme 43. Oxocarbenium ion intermediates in organic transformations

In 1987, Olah reported that TMSI-catalyzed reductive coupling of ketone **3.1** with Et_3SiH gave symmetrical ether **3.2** as a single diastereomer (Scheme 44).[94] The stereoselectivity in the step of 1,1-disubstituted oxocarbenium ion **3.3** reduction with Et_3SiH resulted from the substitution at the α-carbon of **3.1**. The steric repulsion between the methyl group on C_1 and the hydrogen atom on C_3 dictated that **3.3** would strongly prefer to adopt a conformation shown in **3.4**. The bulky Et_3SiH selectively attacked the oxocarbenium ion from the bottom face, since the top face was blocked by ^{i}Pr group on C_3 carbon.



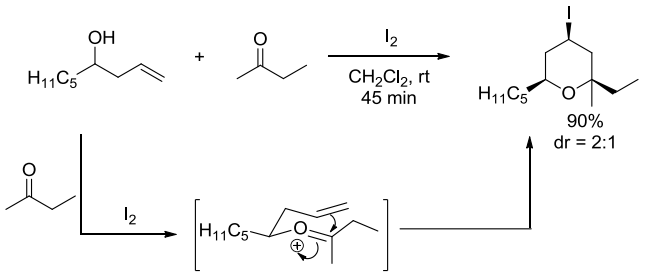
Scheme 44. TMSI catalyzed reductive coupling of ketones with Et_3SiH

In 2009, Romea and Urpí disclosed a $SnCl_4$-mediated addition of titanium enolate **3.8** from **3.5** to dimethyl ketals **3.6** furnishing tertiary methyl ethers **3.7** with moderate to excellent stereoselectivity (Scheme 45).[95] The stereogenic center formation step was believed to involve nucleophilic additions on 1,1-disubstituted oxocarbenium ions **3.9**. When the substrate was the ketal derived from methyl isopropyl ketone, excellent stereocontrol (97:3) was observed. However, when the ketal with no substitution at the α-carbon was used, the stereoselectivity decreased to 86:14. Almost no selectivity was observed for ketal prepared from acetophenone.



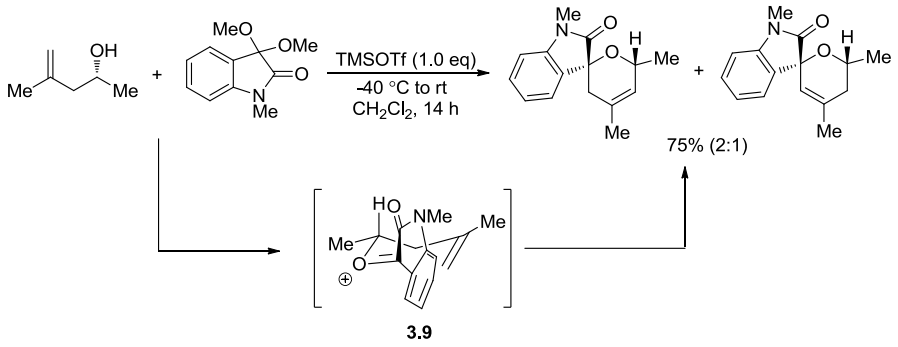
Scheme 45. Tertiary methyl ether synthesis through additions onto E-oxocarbenium ions **3.8**

1,1-Disubstituted oxocarbenium ions also served as reactive intermediates for intramolecular cyclizations. Yadav realized an iodine-promoted Prins-cyclization of symmetric ketones affording 4-iodo-tetrahydropyrans bearing quaternary carbon centers in high yields (Scheme 46).[96] However, when asymmetric methyl ethyl ketone was used, poor diastereoselectivity (2:1) was obtained, which was attributed to the small energy difference between the two possible chair conformations.



Scheme 46. I_2-promoted Prins-cyclization of ketones

Porco documented that enantiopure spirocyclic oxindole pyrans can be efficiently prepared by highly stereoselective Prins-type cyclizations of homoallylic alcohols and isatin ketals (Scheme 47).[97] The transformation was proposed to proceed through an *E*-1,1-disubstituted oxocarbenium ion **3.9** in which the larger aryl substituent of the oxindole moiety adopted a *pseudo*-equatorial orientation.



Scheme 47. Stereoselective synthesis of spirocyclic oxindoles via Prins cyclization

Despite a few precedents involving nucleophilic additions on 1,1-disubstituted oxocarbenium ions have been developed with moderate to high stereocontrol, there was no systematical study on the geometry of disubstituted oxocarbenium ions. Therefore in this project, our key objective is to devise a more general model that can be applied to predict the conformational properties of disubstituted oxocarbenium ions, and to design synthesis of natural products or other complex molecules containing tertiary ethers.

3.2 A MODEL STUDY ON THE GEOMETRIES OF 1,1-DISUBSTITUTED OXOCARBENIUM IONS

The observed 1.6:1 ratio of *cis*:*trans* isomers from the cyclization of **2.62** (Scheme 40, Chapter 2) can be explained by the nearly identical energies of the intermediate (*E*) and (*Z*)-oxocarbenium ions (*eq* 2, Figure 24), resulting from the small steric difference between an alkynyl group and a hydrogen atom.[98] Provided that the cyclization product distribution is attributed to the energetic difference between (*E*)- and (*Z*)-isomers of alkynyl-substituted

oxocarbenium ions (**B1** and **B2**, Figure 24), the difference is approximately 0.3 kcal/mol^{-1}. The strong preference for the (*E*)-dialkyl oxocarbenium ion **A1** and the small energetic penalty for the (*Z*)-orientation of the alkyl and alkynyl group (**B1**) suggest that 1,1-disubstituted oxocarbenium ions containing an alkyl group and an alkynyl group on the cationic carbon will prefer the conformation that places the alkyl groups in an (*E*)-orientation (**C1**) (*eq* 3, Figure 24).

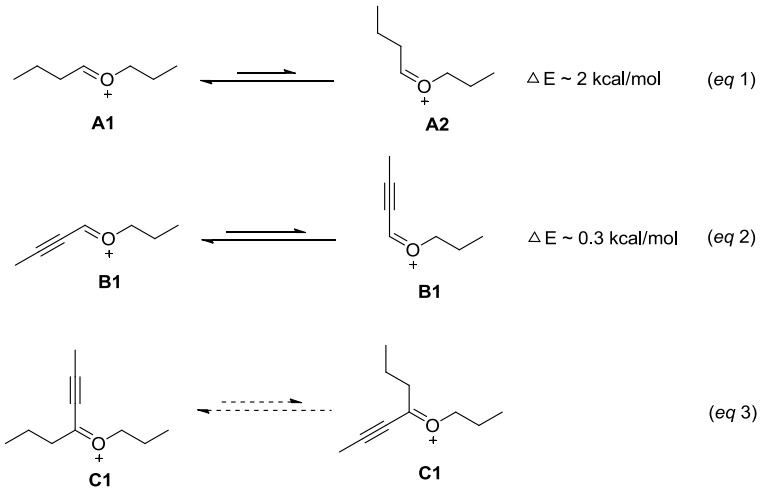
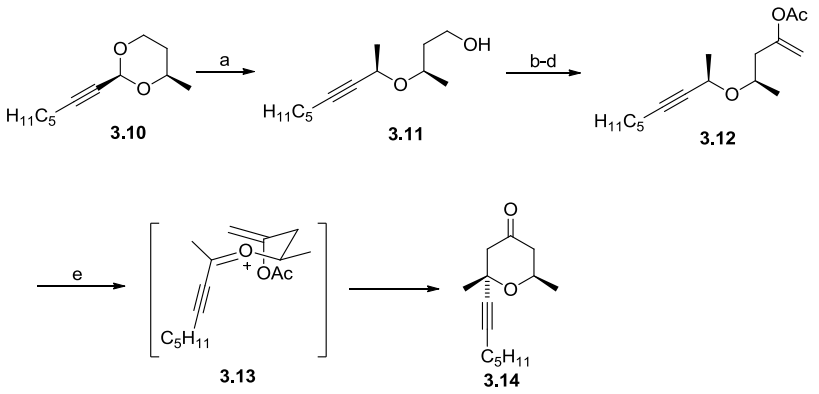


Figure 24. Alkyl- or alkynyl-substituted oxocarbenium ions

Since oxocarbenium ions can be efficiently accessed through DDQ-mediated oxidative C–H activation of propargylic ethers (Scheme 40, Chapter 2),[98] this protocol was employed for 1,1-disubstituted oxocarbenium ion formation to test the hypothesis. Substrate **3.12** was prepared starting from alkynyl acetal **3.10** as shown in Scheme 48. The construction of the ether linkage between two secondary carbon atoms in **3.11** was realized by using Yamamoto's Me_3Al-mediated acetal opening protocol[99] to **3.10** with excellent stereocontrol. Parikh-Doering oxidation of **3.11**, followed by Seyferth-Gilbert homologation[100] and enol acetate formation[39] afforded the cyclization substrate **3.12**. Exposing **3.12** to DDQ at room temperature provided

tetrahydropyran **3.14** in 72% yield as a single diastereomer after 18 h. The result validated our hypothesis that oxocarbenium ions containing an alkyl group and an alkynyl group exist in a predictable (*E*)-dialkyl conformation as depicted in **3.13**.



Reagents and conditions
a) $AlMe_3$, toluene, 75%. b) Py•SO_3, Et_3N, DMSO, 92%. c) $(MeO)_2P(O)C(N_2)C(O)CH_3$, K_2CO_3, MeOH.
d) $[(p\text{-cymene})RuCl_2]_2$, Fur_3P, Na_2CO_3 AcOH, 65%. e) DDQ, 2,6-Cl_2Py, DCE, 17 h, 72%, dr = 1:0.

Scheme 48. The preparation of substrate **3.12** and its cyclization

The result led us to design a generalized model for 1,1-disubstituted oxocarbenium ion geometry to guide substrate design for stereoselective cyclic tertiary ether synthesis. The model (model A, Figure 25) places the smaller group (R_S) in a *cis*-relationship with the opposite ether linkage, and the larger group (R_L) in a *trans*-relationship. The result in Scheme 48 showed that alkynyl groups act as R_S substituents when compared with alkyl groups in model A. Then we investigated what R_L should be if R_S was the alkyl group. We noticed that this model was similar to the reactive conformation for the well-studied Corey-Bakshi-Shibata (CBS) ketone reduction (model C, Figure 25),[101] and therefore, the substrate scope of CBS reduction can be used as guidance for substrate design in the project. It was reported that CBS reduction of aryl-alkyl or alkenyl-alkyl ketones at –78 ℃ resulted in secondary alcohols with excellent ee, and aryl or alkenyl substituents served as R_L groups in model C.

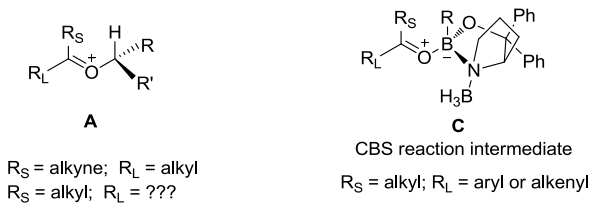


Figure 25. Models for 1,1-disubstituted oxocarbenium ion and CBS reduction

Therefore, allylic ethers **3.15-3.20** and benzylic ethers **3.21-3.25** were designed for the stereoselective synthesis of cyclic tertiary ethers (Figure 26). The investigation began with the oxidation of substrate **3.15** by DDQ, on which reaction condition optimizations would be performed to pursue high chemical yields and stereoselectivity.

The synthesis of substrates **3.15-3.17** and **3.19-3.21** shared the same synthetic route (Scheme 49). Various enals reacted with 1,3-butanediol and PPTs in refluxing benzene to afford the corresponding *cis*-acetals **3.26**. Exposing **3.26** to Me_3Al provided acetal opening products **3.27**, which underwent the sequence of Parikh-Doering oxidation, Seyferth-Gilbert homologation and enol acetate formation to furnish substrates **3.15-3.17** and **3.19-3.21**.

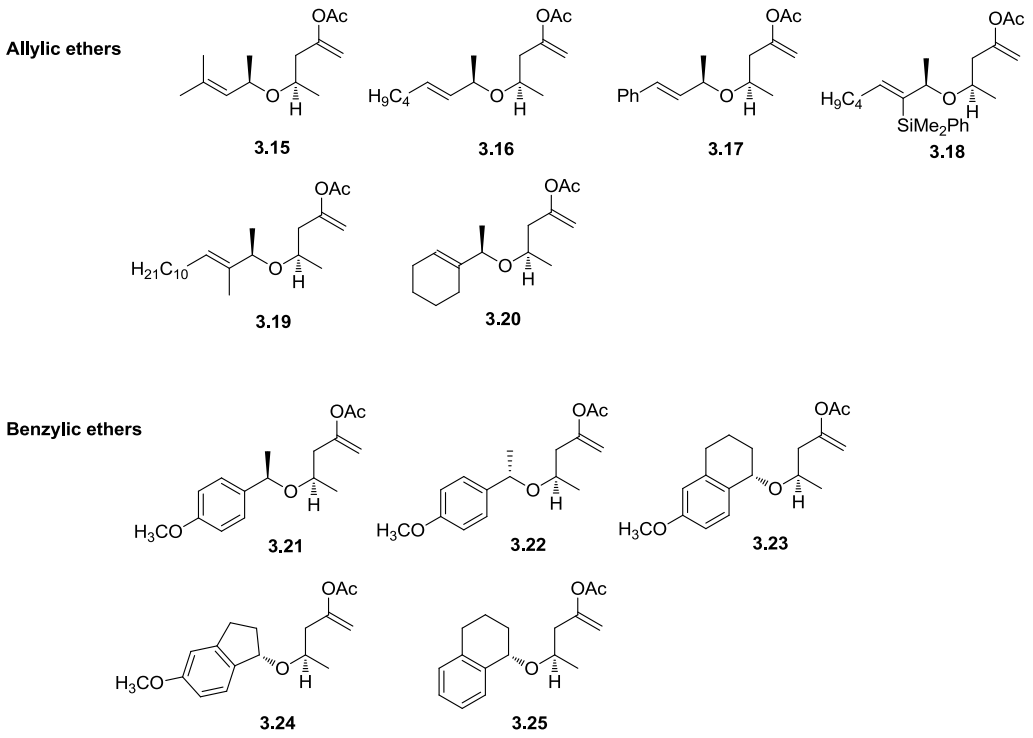
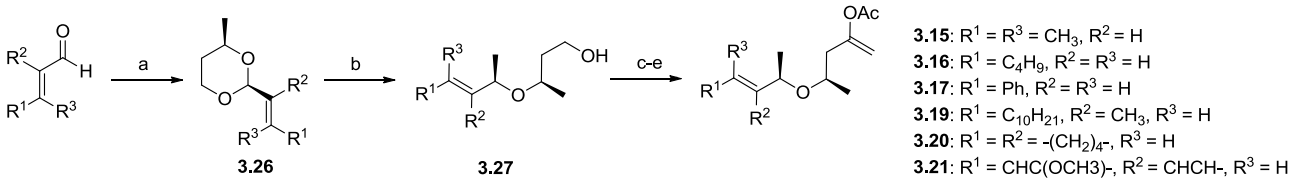


Figure 26. Substrates for the study of model A



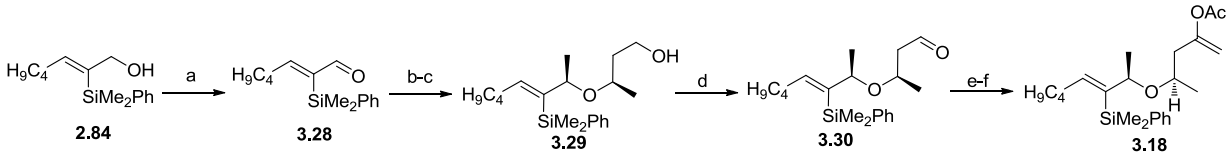
Reagents and conditions

a) 1,3-butanediol, PPTs, benzene, reflux (Dean-Stark), 99% for **3.15**, 92% for **3.16**, 70% for **3.17**, 82% for **3.19**, 99% for **3.20**, 95% for **3.21**. b) $AlMe_3$, toluene, 92% for **3.15**, 95% for **3.16**, 97% for **3.17**, 92% for **3.19**, 94% for **3.20**, 75% for **3.21**. c) SO_3•Py, DMSO, Et_3N, CH_2Cl_2, 93% for **3.15**, 88% for **3.16**, 60% for **3.17**, 92% for **3.19**, 94% for **3.20**, 87% for **3.21**. d)$(MeO)_2P(O)C(N_2)C(O)CH_3$, K_2CO_3, MeOH, 99% for **3.15**, 81% for **3.16**, 74% for **3.17**, 83% for **3.19**, 95% for **3.20**, 53% for **3.21**. e) HOAc, $[(p\text{-cymene})RuCl_2]_2$, Fur_3P, Na_2CO_3, PhMe, 65% for **3.15**, 72% for **3.16**, 52% for **3.17**, 94% for **3.19**, 64% for **3.20**, 87% for **3.21**.

Scheme 49. Syntheses of substrates **3.15-3.17** and **3.19-3.21**

Dess-Martin periodinane (DMP) oxidation of known (silyl)allyl alcohol **2.84** to **3.28**, followed by acetal formation with 1,3-butanediol, and acetal opening with Me_3Al gave alcohol

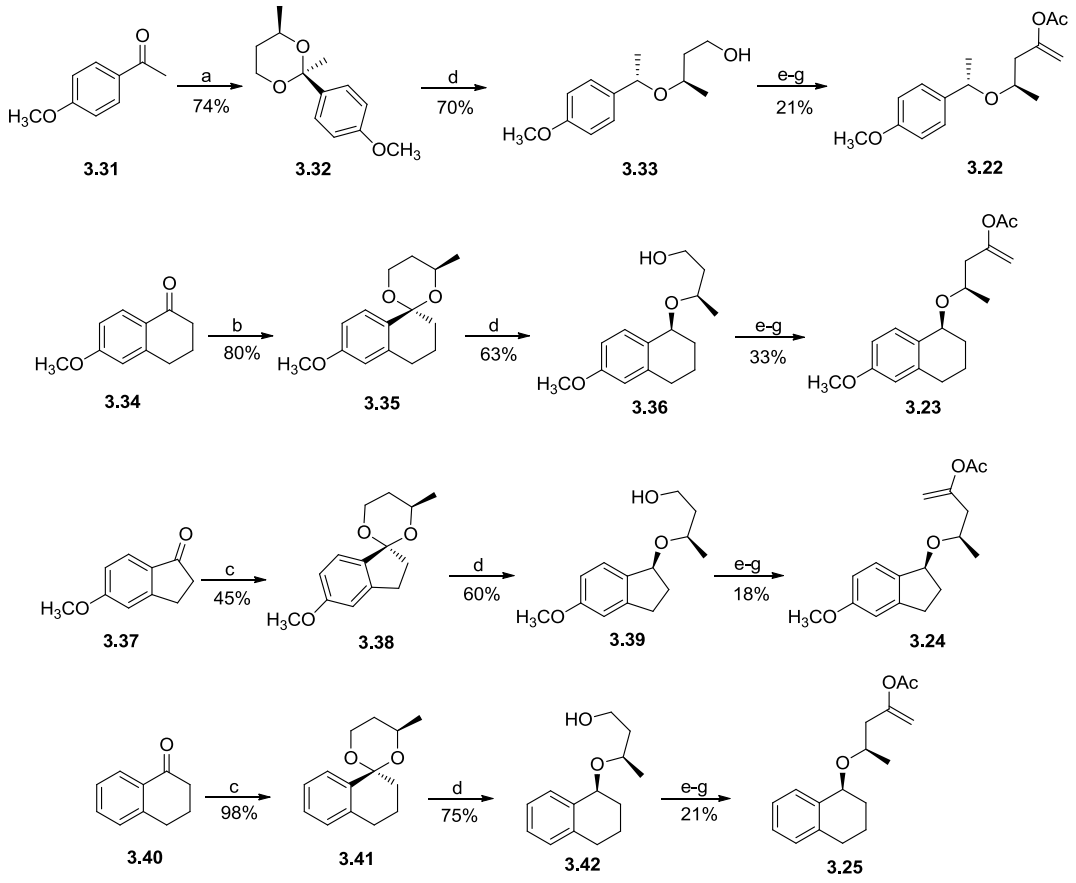
3.29 in 35% yield (Scheme 50). Another DMP oxidation of **3.29**, followed by Seyferth-Gilbert homologation and enol acetate formation generated substrate **3.18**.



Reagents and conditions
a) DMP, CH_2Cl_2, 99%. b) 1,3-butanediol, PPTs, benzene, reflux (Dean-Stark), 87%. c) $AlMe_3$, toluene, 35%. d) DMP, CH_2Cl_2, 87%. e) $(MeO)_2P(O)C(N_2)C(O)CH_3$, K_2CO_3, MeOH, 86%. f) HOAc, $[(p\text{-cymene})RuCl_2]_2$, Fur_3P, Na_2CO_3, PhMe, 80 °C, 79%.

Scheme 50. The preparation of substrate **3.18**

p-Toluenesulfonic acid-catalyzed reaction of ketone **3.31** and 1,3-butanediol yielded ketal **3.32** in 74% yield, which was opened by DIBAL-H[102] to provide alcohol **3.33** in 70% yield as a single diastereomer (Scheme 51). An uneventful sequence of Parikh-Doering oxidation, Seyferth-Gilbert homologation and typical enol acetate formation, was executed for the conversion of **3.33** to substrate **3.22**. The preparation of substrates **3.23**-**3.25** followed the same sequence as that of **3.22** except the ketal formation step. The transformation from **3.34** to **3.35** was achieved in two steps. **3.34** first reacted with trimethyl orthoformate in MeOH yielding a dimethyl ketal derivative, which then reacted with 1,3-butanediol to provide the cyclic ketal **3.35** in 80% yield. A one-step protocol for the synthesis of cyclic ketals **3.38** and **3.41** was employed by simply combining corresponding ketone **3.37** or **3.40**, 1,3-butanediol, trimethyl orthoformate and conc. H_2SO_4 in the same flask.[103] Following the same sequence from **3.32** to **3.22**, ketals **3.35**, **3.38** and **3.41** were converted to corresponding substrates **3.23**, **3.24** and **3.25**.



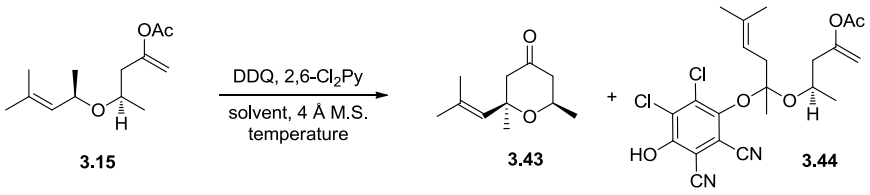
Reagents and conditions
a) 1,3-butanediol, PTSA, benzene, reflux (Dean-Stark). b) 1. trimethyl orthoformate, PTSA, MeOH; 2. 1,3-butanediol, PPTs, benzene, reflux. c) 1,3-butanediol, trimethyl orthoformate, conc. H_2SO_4. d) DIBAL-H, CH_2Cl_2, 70%. e) SO_3•Py, DMSO, Et_3N, CH_2Cl_2. f) $(MeO)_2P(O)C(N_2)C(O)CH_3$, K_2CO_3, MeOH. g) HOAc, $[(p\text{-cymene})RuCl_2]_2$, Fur_3P, Na_2CO_3, PhMe.

Scheme 51. The preparation of substrates **3.22-3.25**

Different reaction conditions for the formation of tetrahydropyran **3.43** were screened and the results are summarized in Table 5. Initially, **3.15** was subjected to the standard oxidation conditions using DDQ as the oxidant, 1,2-dichloroethane (DCE) as the solvent, 4 Å molecular sieves as the water scavenger and 2,6-dichloropyridine as the base. After 3 h at rt, all the starting material was converted to a polar compound based on TLC (entry 1, table 5). However, this compound decomposed during the purification through column chromatography. We believed that it should be **3.44** resulting from the addition of $DDQH_2$ onto the intermediate oxocarbenium ion. A catalytic amount of $LiClO_4$ (30 mol%) was found to be quite beneficial in suppressing the

$DDQH_2$-adduct formation, and the desired tetrahydropyran **3.43** was isolated in 30% yield with the *cis*:*trans* ratio of 2:1 (entry 2, table 5). Different reaction temperatures, the $LiClO_4$ loadings, and different solvents were screened to improve the yield and stereoselectivity of the reaction. The reaction was very slow at 0 ℃ , and only about 15% conversion was observed even after 24 h (entry 3, table 5); at 45 ℃ the reaction afforded lower yields and selectivities than those at room temperature (entries 2 and 4, table 5). The dr of **3.43** decreased from 2:1 to 1.4:1 when $LiClO_4$ loadings were increased from 30 mol % to 100 mol % (entries 2 and 5, table 5). The reaction was strongly influenced by solvents. Et_2O made the transformation sluggish, though a better dr was obtained (entry 6); CH_3NO_2 was the best solvent, affording **3.43** in 52% yield with a diastereomeric ratio of 3:1, though the reaction was slower than that in DCE (entry 8).

Table 5. Optimizing the synthesis of tetrahydropyran **3.43**



3.15 **3.43** **3.44**

	solvent	temperature (°C)	additive (mol %)	yield(**3.43**)[b]	dr[c] (*cis*/*trans*)	time (h)
1.	DCE	rt	–	0%	NA	NA
2.	DCE	rt	$LiClO_4$ (30)	30%	2:1	6
3.	DCE	0	$LiClO_4$ (30)	~15% conversion	NA	24
4.	DCE	45	$LiClO_4$ (30)	25%	1.7:1	3
5.	DCE	rt	$LiClO_4$ (100)	27%	1.4:1	6
6.	Et_2O	rt	$LiClO_4$ (30)	~10% conversion	3.2:1	10
7.	CH_3CN	rt	$LiClO_4$ (30)	25%	1.3:1	6
8.	CH_3NO_2	rt	$LiClO_4$ (30)	52%	3:1	10

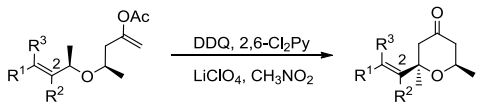
[a] Representative procedure: **3.15**, 2,6-Cl_2Py (2 equiv), and 4 Å M.S. were stirred in dry solvent for 15 minutes. Then additive was added, and stirred for another 5 minutes. After that, DDQ (2.0 equiv) was added and the reaction was monitored by TLC.

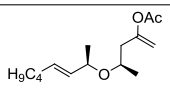
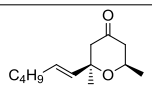
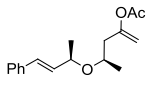
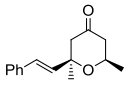
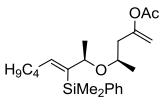
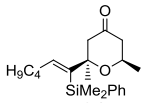
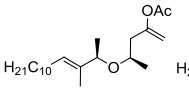
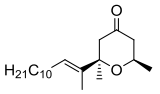
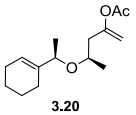
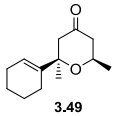
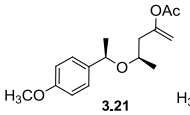
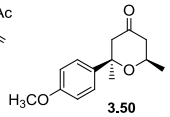
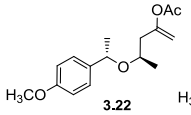
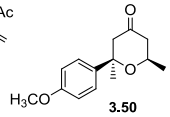
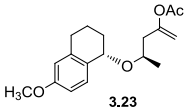
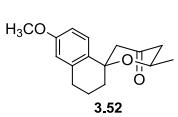
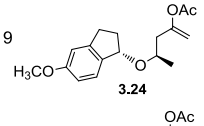
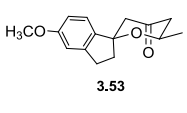
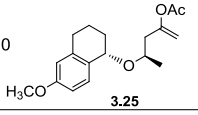
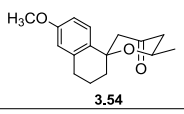
[b] Yields refer to isolated, purified material.

[c] dr is determined on crude reaction mixtures by 1H NMR spectroscopy.

Substrates **3.16-3.25** were subjected to the optimized conditions using 30 mol % $LiClO_4$ as the additive and CH_3NO_2 as the solvent, and the results are summaried in Table 6. (*E*)-1,2-Disubstituted allylic ether **3.16** reacted with DDQ more efficiently than trisubstituted allylic ether **3.15**, though the diastereocontrol was still 3:1 (entry 1, table 6). However, the diastereomers were separable, affording the major isomer of **3.45** in good yield. Cinnamyl ethers were significantly more reactive than allylic ethers, allowing the reaction of **3.17** to be performed at –60 °C in nitroethane to yield **3.46** in 82% yield as a 10:1 mixture of diastereomers in 4 h (entry 2, table 6). No reaction was observed for (*Z*)-2-(silyl)allylic ether **3.18** at room temperature and the starting material decomposed when performed at 45 °C (entry 3, table 6). 2-Alkyl-substituted allylic ethers **3.19** and **3.20** reacted efficiently to provide tetrahydropyrans **3.48** and **3.49** with high stereocontrol (entries 4 and 5, table 6). Benzylic ether analogues were excellent substrates for quaternary center formation, with diastereomeric substrates **3.21** and **3.22** generating the same isomer **3.50** as a single diastereomer (entries 6 and 7, table 6). Spirocyclic ethers **3.52**, **3.53** and **3.54** were also accessible through oxidative cyclizations as shown in entries 8, 9, and 10 of Table 6. The transformations were quite fast and extremely stereoselective.

Table 6. Tertiary ether synthesis from allylic and benzylic ethers[a]



Entry	Substrate	Product	temperature (°C)	t (h)	Yield (%)[b]	dr[c]
1	 **3.16**	 **3.45**	rt	5.5	85	3:1
2	 **3.17**	 **3.46**	-60	4	82[d]	10:1[e]
3	 **3.18**	 **3.47**	45	15	—	—
4	 **3.19**	 **3.48**	rt	12	82	26:1
5	 **3.20**	 **3.49**	rt	2.5	86	1:0
6	 **3.21**	 **3.50**	rt	2	78	1:0
7	 **3.22**	 **3.50**	rt	2	74	1:0
8	 **3.23**	 **3.52**	rt	0.67	82	1:0
9	 **3.24**	 **3.53**	rt	0.5	84	1:0
10	 **3.25**	 **3.54**	rt	7	67	1:0

[a] Typical procedure: a 0.1 M solution of the substrate, 2,6-dichloropyridine, 4 Å M.S. and $LiClO_4$ (30 mol %) in $MeNO_2$ was treated with DDQ (2 equiv) for the indicated time period.

b Yields refer to isolated, purified material.

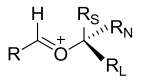
c dr was determined on crude reaction mixtures by 1H NMR spectroscopy.

d $C_2H_5NO_2$ was employed as the solvent.

e A dr of 4.6:1 was obtained at room temperature.

3.3 A MODEL STUDY ON THE CONFORMATIONS OF OXOCARBENIUM IONS WITH PREEXISTING TERTIARY STEREOCENTERS

The success of model A for the geometry of 1,1-disubstituted oxocarbenium ions led us to explore another model, in which preexisting tertiary stereocenters will influence the sense of nucleophilic addition onto oxocarbenium ions (model B, Figure 27). To minimize steric repulsion between the hydrogen on the cationic carbon and the substituent on the tertiary ether, the R_S group will occupy an eclipsed orientation with the hydrogen atom on the cationic carbon.



B

The large, small, and nucleophilic groups on the tertiary ether are labeled as R_L, R_S, and R_N, respectively.

Figure 27. A model for oxocarbenium ions with preexisting tertiary stereocenters

Substrates **3.55**-**3.60** were designed as shown in Figure 28 to test the generality of model B. Prenyl ethers were employed in theses substrates due to their high efficiency in DDQ-mediated oxidation process. The preexisting tertiary ethers contained unsaturations, such as alkynes (**3.55** and **3.60**) and alkenes (**3.56** and **3.57**), as well as saturated alkyl groups (**3.58** and **3.59**).

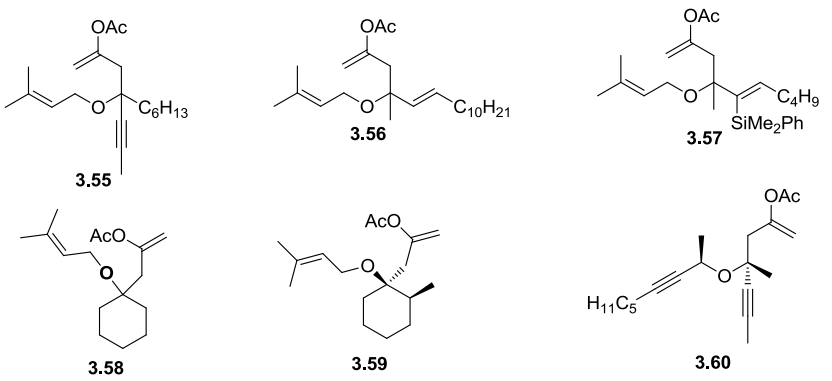
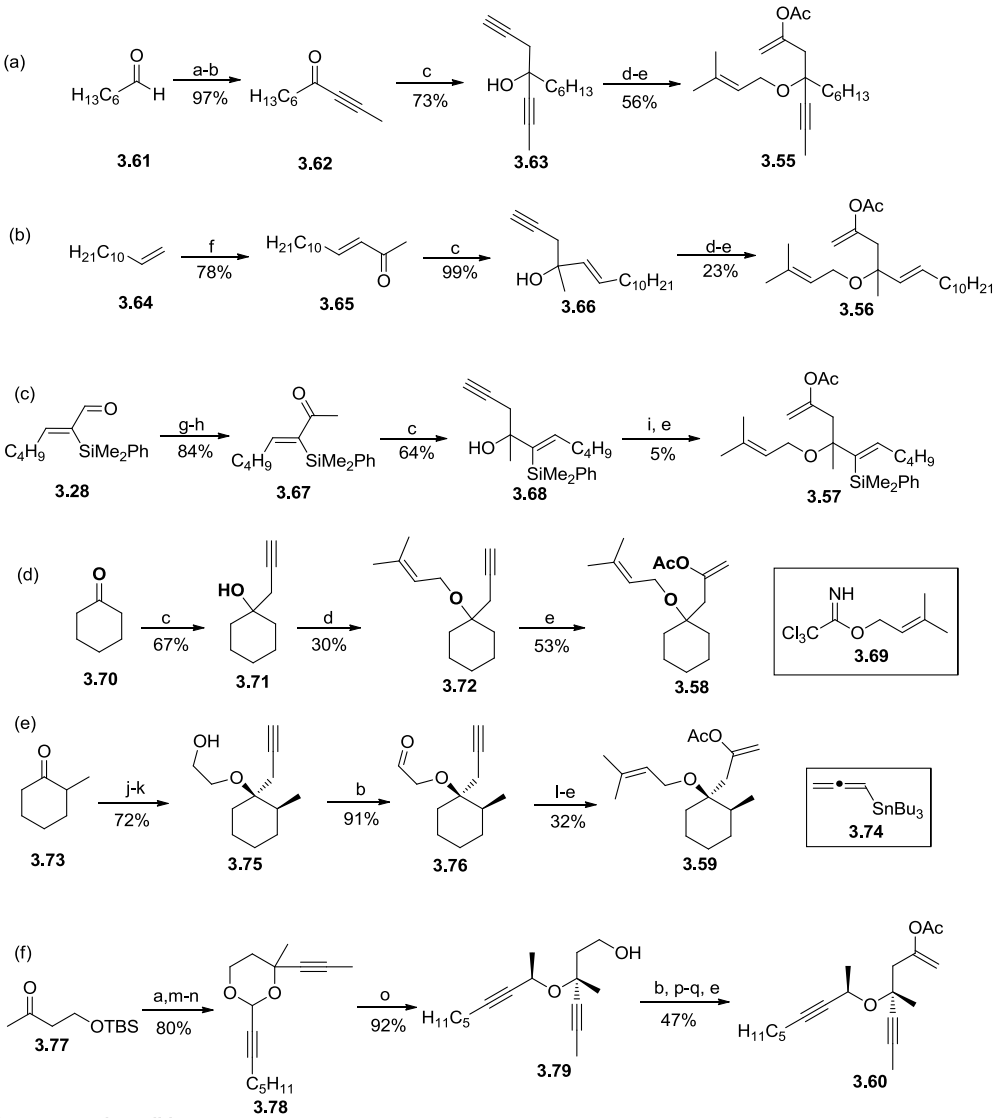


Figure 28. Substrates for the study of model B

Substrates **3.55-3.60** were prepared as depicted in Scheme 52. Substrate **3.55** was synthesized from aldehyde **3.61** in 5 steps (Scheme52(a)). Propynyl magnesium bromide addition to **3.61**, followed by Parikh-Doering oxidation afforded ketone **3.62**. Propargylation of **3.62** with propargyl magnesium bromide gave **3.63**, which underwent a sequence of prenyl ether formation and enol acetate formation to provide substrate **3.55**. A cross metathesis between alkene **3.64** and 3-buten-2-one yielded enone **3.65** in 78% yields, which was then converted to substrate **3.56** following the same synthetic route as that from **3.62** to **3.55** (Scheme 52(b)). The preparation of substrate **3.57** started with a methyl Grignard addition to the known enal **3.28**, followed by a DMP oxidation to afford enone **3.67** (Scheme 52(c)). Propargylation of **3.67** generated propargylic alcohol **3.68**, followed by TMSOTf-catalyzed coupling between **3.68** and **3.69**, and enol acetate formation provided substrate **3.57**.

Propargylation of cyclohexanone **3.70**, followed by prenyl ether formation and enol acetate formation gave substrate **3.58** (Scheme 52(d)). The preparation of substrate **3.59** started with the reaction of ketone **3.73** with ethylene glycol yielding a ketal, which underwent a $TiCl_4$-catalyzed ketal opening with allenyl(tributyl)tin **3.74** afford alcohol **3.75** (Scheme 52(e)).[104] A sequence of DMP oxidation, Wittig olefination[105] and enol acetate formation gave substrate **3.59**.

Propynylmagnesium bromide addition to methyl ketone **3.77**, followed by desilylation and acetal formation generated **3.78** (Scheme 52(f)). Me_3Al-mediated acetal opening of **3.78** yielded alcohol **3.79** with excellent stereocontrol. A DMP oxidation of **3.79**, followed by a Corey-Fuchs reaction[106] afforded an alkyne, which underwent regioselective AcOH addition to the terminal alkyne to furnish substrate **3.60**.



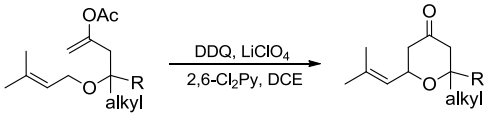
Reagents and conditions

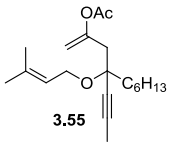
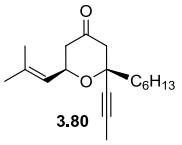
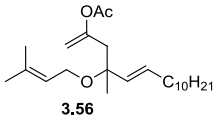
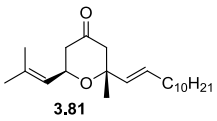
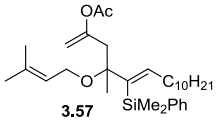
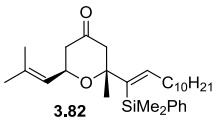
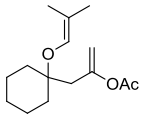
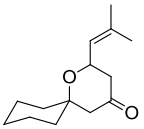
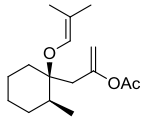
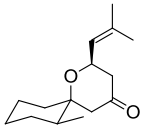
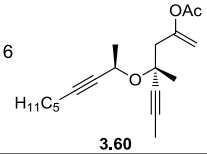
a) 1-propynylmagnesium bromide, Et_2O. b) SO_3•Py, DMSO, Et_3N, CH_2Cl_2. c) propargyl bromide, Mg, $HgCl_2$, THF. d) 3,3-dimethylallyl bromide, NaH, tetrabutylammonium iodide, DMF. e) HOAc, [(*p*-cymene)$RuCl_2]_2$, Fur_3P, Na_2CO_3, PhMe. f) 3-buten-2-one, Grubbs catalyst, 2nd generation, CH_2Cl_2, reflux. g) MeMgBr, Et_2O, 93%. h) Dess-Martin periodinane, CH_2Cl_2, 90%. i) **3.69**, TMSOTf, cyclohexane, 21%. j) ethylene glycol, PTSA, benzene, reflux, 99%. k) **3.74**, $TiCl_4$, CH_2Cl_2, -78 °C, 73%. l) $Ph_3PCH(CH_3)_2I$, nBuLi, - 78 °C, 64%. m) Bu_4NF, THF, 90%. n) 2-octynal, PPTs, benzene, 89%. o) $AlMe_3$, toluene, 40 °C, 92%. p) CBr_4, PPh_3, Et_3N, CH_2Cl_2, 88%. q) ^{n}BuLi, THF, - 78 °C, 97%.

Scheme 52. The preparation of substrates **3.55-3.60**

These substrates were applied to the DDQ oxidation process, and the results are summarized in Table 7. Propargylic ether **3.55** reacted smoothly with DDQ to afford **3.80** as a single diastereomer (entry 1, table 7). In this reaction, alkynyl group served as the R_S substituent. Allylic ether **3.56** and (silyl)allyl ether **3.57** were oxidized by DDQ to give corresponding tetrahydropyrans **3.81** and **3.82** in high efficiency, respectively (entries 2 and 3, table 7). Alkenyl groups were also found to serve as R_S substituent in both reactions. Saturated spirocyclic ethers can be accessed through model B, and the cyclization of **3.58** yielded spirocycle **3.83** in 88% yield, in which the alkyl group occupied the R_S position (entry 4, table 7). Excellent stereocontrol was observed during the cyclization of **3.59** to **3.84** (entry 5, table 7), in which the unbranched group was the R_S substituent and the branched group was the R_L substituent. Our attempt to synthesize tetrahydropyrans with two tertiary ethers failed, as demonstrated by the oxidation of **3.60** (entry 6, table 7). No reaction was observed when performed at room temperature and decomposition of the starting material happened at 45 ℃ . We postulated that even the 1,3-diaxial interaction between two alkynyl groups was too significant to be overcome in such a transformation.

Table 7. Tertiary ether synthesis from prenyl ethers **3.55-3.60**[a]

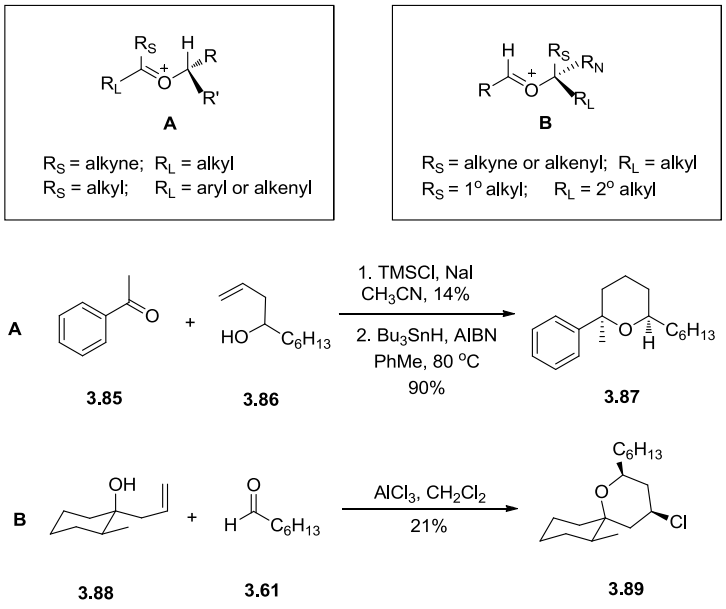


Entry	Substrate	Product	temperature (°C)	t (h)	Yield (%)[b]	dr[c]
1	 **3.55**	 **3.80**	0	2.5	79	1:0
2	 **3.56**	 **3.81**	0	2	95	15.7:1
3	 **3.57**	 **3.82**	0	0.5	76	1:0
4	 **3.58**	 **3.83**	0	0.3	88	—
5	 **3.59**	 **3.84**	-30	5	81	1:0
6	 **3.60**	—	—	—	—	—

[a] Typical procedure: a 0.1 M solution of the substrate, 2,6-dichloropyridine, 4 Å M.S. and $LiClO_4$ (30 mol %) in 1,2-dichloroethane was treated with DDQ (2 equiv) for the indicated time period.
[b] Yields refer to isolated, purified material.
[c] dr is determined on crude reaction mixtures by 1H NMR spectroscopy.

According to the results in Tables 6 and 7, the generalized model for 1,1-disubstituted oxocarbenium ion geometry (model A) and the model in which preexisting tertiary stereocenters influence the sense of nucleophilic addition onto monosubstituted oxocarbenium ions (model B) are summarized in Scheme 53. The applications of models A and B to other reactions sharing

same oxocarbenium ion intermediates are also explored (Scheme 53). TMSI-mediated Prins reaction[107] of acetophenone (**3.85**) with homoallylic alcohol **3.86**, followed by radical-mediated removal of iodide provided tetrahydropyran **3.87** as a single diastereomer (application of model A). The condensation of heptanal (**3.61**) with tertiary alcohol **3.88** in the presence of $AlCl_3$[108] gave chlorotetrahydropyran **3.89**, also as a single diastereomer (application of model B). The yields of these transformations were quite low due to the competitive ionization and the oxonia-Cope rearrangement[109]. However, these conditions were not optimized because we are mainly interested in the stereoselecticities of the transformations.



Scheme 53. Applications of models A and B to acid-mediated Prins reactions

3.4 DISCUSSION

As shown in Figure 29, the reaction of secondary propargylic ether **3.12** (17 h, room temperature) occurred more rapidly than that of primary propargylic ether **2.62** (18 h, 45 ℃). This observation indicated that cation stabilization by the methyl group through hyperconjugation in **3.91** became a dominant factor that influences the reaction rate. Alkynes are inferior cation-stabilizing groups, thus the extra methyl group dramatically increased the stability of the cation. Compared with **3.90A**, an increased steric hindrance between alkynyl and hydrogen atom existed in **3.91**. However, this destabilization was not a big issue due to the sterically undemanding property of alkynes as well as the existence of a similar interaction in **3.90B**.

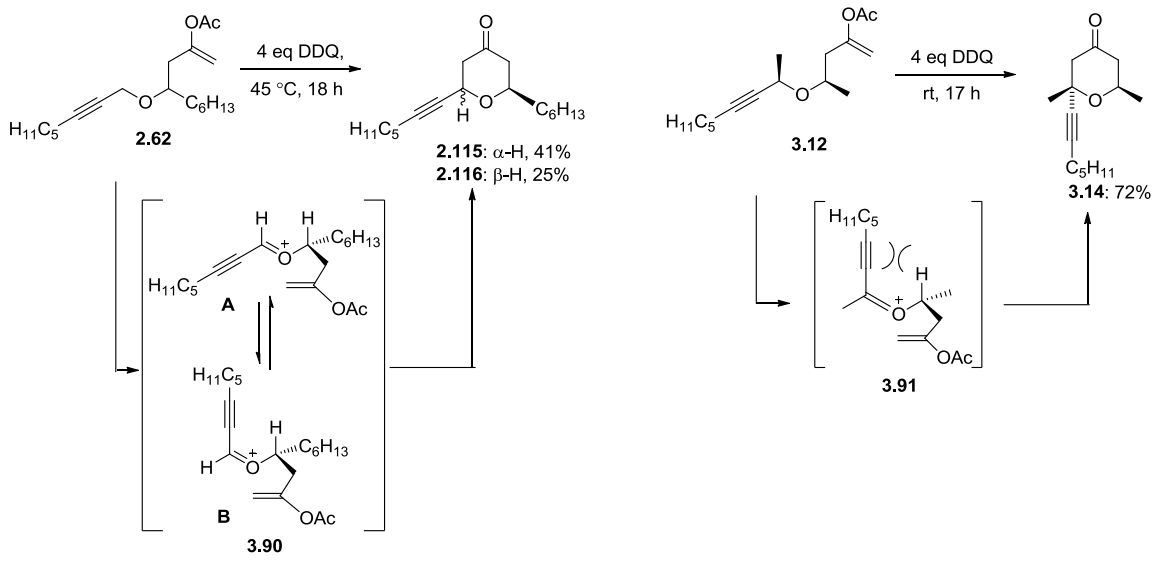


Figure 29. Reaction rate comparisons between primary and secondary propargylic ethers

Two possible geometric oxocarbenium ion intermediates (**C** and **D**) for the oxidation of secondary allylic or benzylic ethers are depicted in Figure 30. A methyl group acted as the R_S

substituent in **C** while an alkene group acted as the R_S substituent in **D**. In both **C** and **D**, the steric repulsion between alkyl group on C_1 and hydrogen on $C_{1'}$ existed. However, the conjugation between the alkene and the oxocarbenium ion in **D** forced the R^2 group to project across the ether linkage. The additional steric repulsion between R^2 and hydrogen on $C_{1'}$ disfavored **D**, and therefore, the subsequent cyclization proceeded through geometric intermediate **C** leading to the observed product.

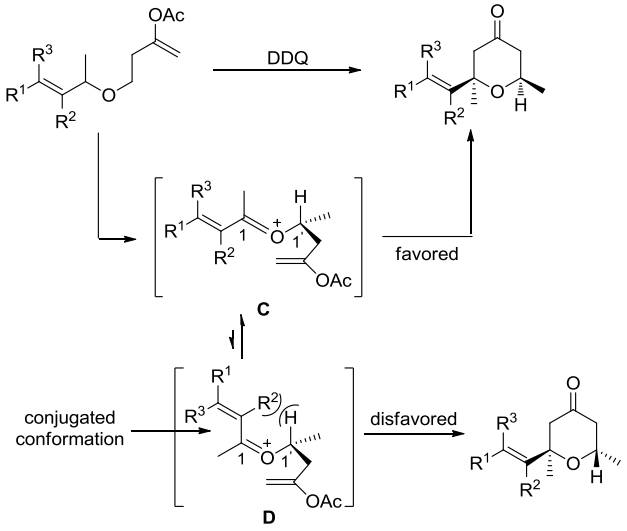


Figure 30. Stereoselectivity in oxidation of secondary allylic ethers

In contrast to propargylic ether substrates, secondary allylic or benzylic ethers reacted with DDQ much more slowly than those of corresponding primary ethers (Figure 31). This trend suggested that the steric repulsion between methyl group on C_1 and hydrogen on $C_{1'}$ in **3.92** should play a dominant cation-destabilization role over cation-stabilization by methyl group on the reaction rate.

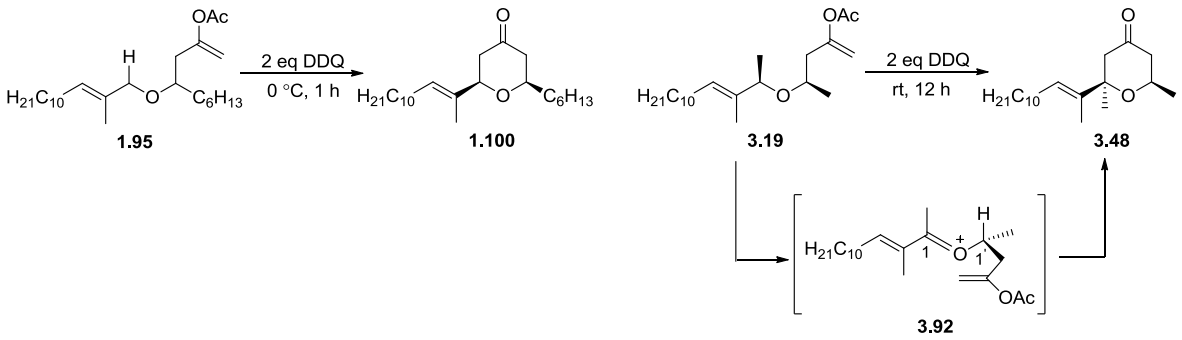


Figure 31. Reaction rate comparison between primary and secondary allylic ethers

The cyclization of trisubstituted allylic ether **3.15** afforded product **3.43** in 52% yield (Figure 32). The modest yield was attributed to the $A^{1,3}$ strain between methyl groups as shown in **3.93**. The strain destabilized **3.93**, leading to a decomposition before the cyclization.

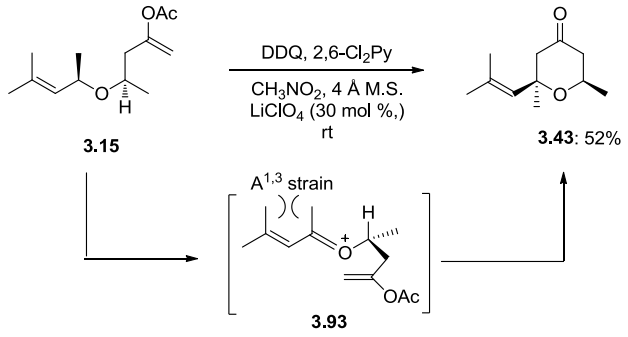


Figure 32. The reaction of DDQ and **3.15**

Disubstituted allylic ether **3.16** only provided **3.45** with a modest stereocontrol (3:1) at room temperature (entry 1, table 6). A similar stereocontrol (4.6:1) was also observed for the cyclization of cinnamyl ether **3.17** at room temperature. However, the low oxidation potential of **3.17** allowed the reaction to be conducted at –60 ℃ , and the stereoselectivity was improved to 10:1 (entry 2, table 6). The improvement suggested that the steric difference between the alkene group and alkyl group could be amplified by lowering the reaction temperature, and better

stereocontrol should be obtained. Reactions of simple alkyl-substituted allylic and benzylic ethers proved to be difficult when performed at low temperature due to the issues of oxidation potential and intermediate stability. However, model A should have broad application in other temperature insensitive reactions.

When the substituent at 2-position of the allylic ether is an alkyl group (R^2 = alkyl), excellent stereoselectivity was achieved (entries 4 and 5, Table 6). The observation can be explained by the increased steric repulsion between R^2 and hydrogen in intermediate **D** in Figure 29. The replusion made intermediate **C** more favored, resulting in excellent stereocontrol. Single diastereomeric products were obtained for cyclizations of benzylic ether substrates (entries 6-10, table 6), arising from the same origin as 2-substituted allylic ethers.

Like model A, the alkynyl group still served as the R_S substituent in model B (entry 1, table 7). In contrast to model A, however, alkenyl groups or even bulky vinylsilane groups acted as the R_S substituent in model B (entries 2 and 3, table 7). The twisted conformation of tertiary ether in model B allowed the alkenyl groups to orient their sterically undemanding flat faces toward the substituents across the ether linkage to minimize steric interactions (Figure 33). An electrostatic attraction between the π electrons and the electron deficient formyl hydrogen atom[110] could further stabilize this conformation. The fact that alkenyl groups act as the small substituent in model B demonstrates that stereochemically complementary 2,2,6-trisubstituted tetrahydropyrans can be accessed based on models A and B.

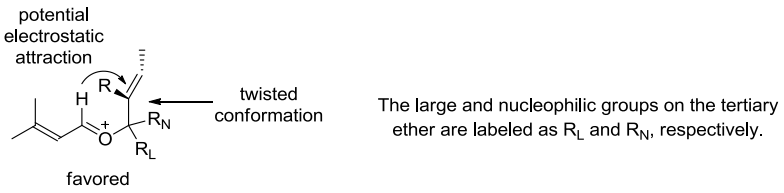


Figure 33. Explanation for oxocarbenium ion geometry in model B

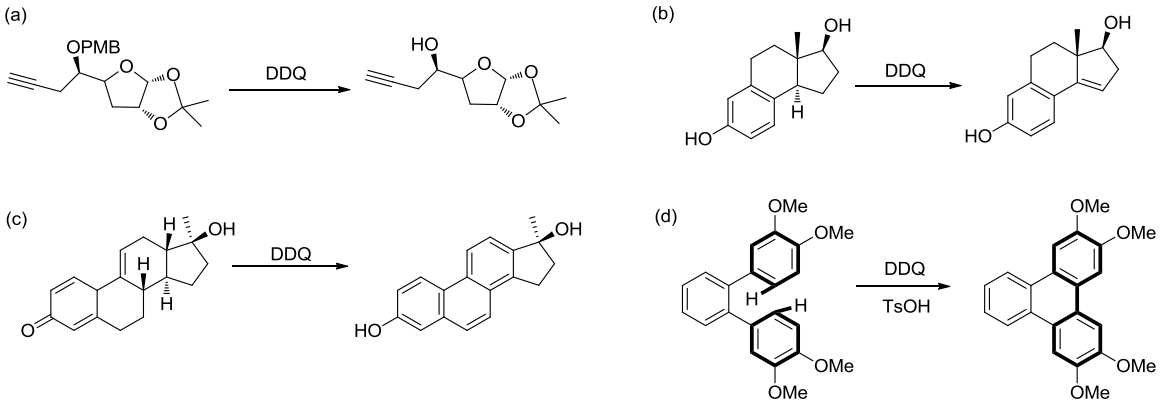
3.5 SUMMARY

In this project, two generalized models for oxocarbenium ion geometry have been extensively studied by means of our DDQ-mediated oxidative C–H activation of secondary propargylic, allylic and benzylic ether substrates. Tetrahydropyrans containing tertiary ethers were synthesized with excellent stereocontrol. In model A, the geometry of 1,1-disubstituted oxocarbenium ions can be predicted based on the steric difference between two substituents. Oxocarbenium ions containing an alkyl group and an alkynyl group on the cationic carbon, place the alkynyl group (R_S) in a *cis*-relationship with the opposite ether linkage, and the alkyl group (R_L) in a *trans*-relationship. Oxocarbenium ions containing an alkyl group and an alkenyl or aryl group on the cationic carbon, places the alkyl group (R_S) in a *cis*-conformation with the ether linkage. Model B uses the preexisting quaternary center to control the geometry of oxocarbenium ion, resulting in a new stereocenter with exceptionally diastereoselectivity. These two models are successfully applied to oxocarbenium ions derived from other processes like the acid-mediated Prins reactions, with excellent stereoselectivity. The generality of models A and B indicates that they will serve as guidance for reactions proceeding through highly substituted oxocarbenium ions.

4.0 DDQ-CATALYZED REACTIONS USING MANGANESE DIOXIDE AS A TERMINAL OXIDANT

4.1 INTRODUCTION OF PROTOCOLS FOR DDQ-REGENERATION FROM $DDQH_2$

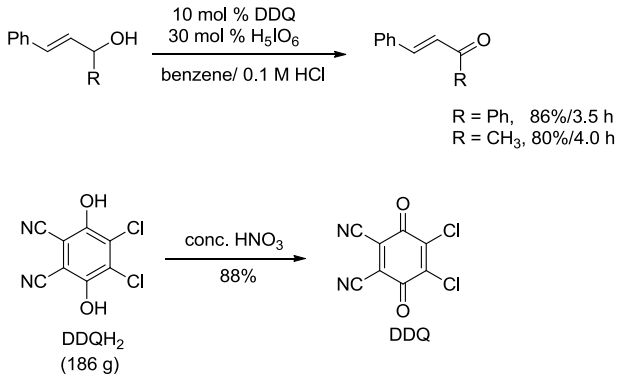
In Chapters 1-3, DDQ was shown to be a powerful reagent for selective oxidation of various compounds with high efficiency, such as vinyl ethers, allylic ethers, and propargylic ethers. In addition to these transformations, DDQ is a highly effective oxidant for a wide range of organic transformations including protecting group removal (Scheme 54(a)), dehydrogenation (Scheme 54(b)), aromatization (Scheme 54(c)), and biaryl construction (Scheme 54(d)).[111]



Scheme 54. DDQ in organic synthesis

However, the stoichiometric use of DDQ can result in difficulty in removing the reduced byproduct, $DDQH_2$ (2,3-dichloro-5,6-dicyanohydroquinone). Moreover, DDQ is moderately expensive with a cost of $526/mol according to the 2009-2010 Aldrich catalog.[112] The toxicity of DDQ is another problem. DDQ poses modest toxicity concerns, with an LD_{50} of 82 mg/kg[113] and the potential for HCN generation upon exposure to H_2O. To address such issues, some efforts have been made to discover co-oxidants that regenerate DDQ from $DDQH_2$.

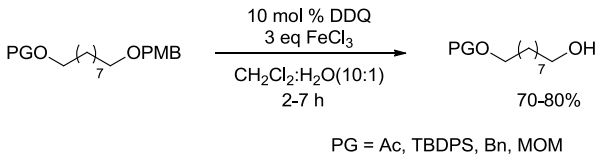
Strong acids were reported for the purpose (Scheme 55). DDQ-catalyzed allylic alcohol oxidations were realized by using H_5IO_6[114] as the terminal oxidant to afford enones in high yields. In addition, concentrated nitric acid[115] was also a good oxidant to promote the transformation of $DDQH_2$ to DDQ in large scale. However, their strong acidities are not compatible with functionalized organic compounds.



Scheme 55. Strong acids as oxidants for DDQ regeneration

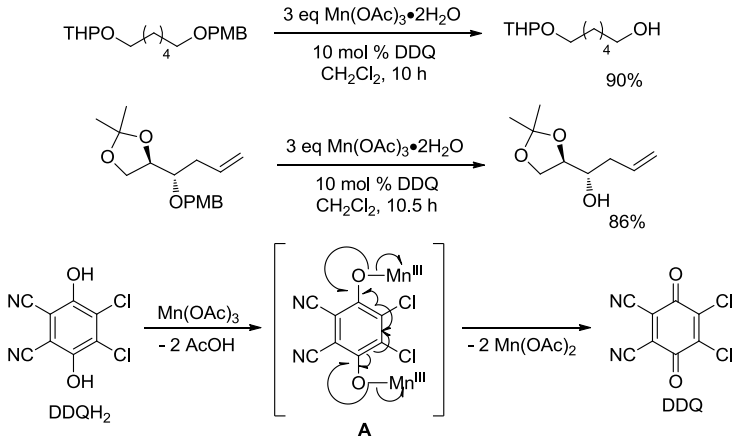
Chandrasekhar disclosed that oxidative cleavage of PMB ethers can be achieved by the employment of catalytic amount of DDQ with $FeCl_3$ serving as the stoichiometric oxidant (Scheme 56).[116] This system is quite economical and environmentally benign because $FeCl_3$ only costs $41/mol, and because $FeCl_3$ has a higher LD_{50} (450 mg/kg) than DDQ. Some protecting

groups such as acetates, benzyl ethers, and silyl ethers, were found to be compatible with the process. However, the Lewis acidity makes it incompatible with many other functional groups like THP ethers.



Scheme 56. $FeCl_3$ as terminal oxidant for DDQ-catalyzed PMB ether cleavage

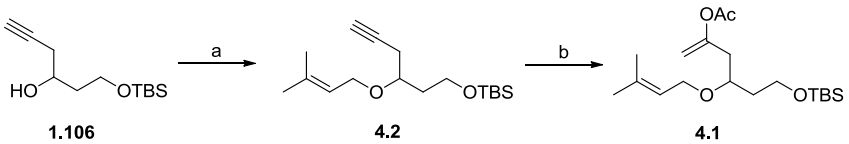
$Mn(OAc)_3$ proved to be an effective reagent for DDQ regeneration as demonstrated in the deprotection of PMB ethers.[117] A proposed mechanism for the regeneration of DDQ from $DDQH_2$ is shown in Scheme 57. $DDQH_2$ reacted with $Mn(OAc)_3$ to form Mn(III) complex **A**, the decomposition of which led to the formation of DDQ. $Mn(OAc)_3$ does not exhibit strong Lewis acidity, and commonly encountered functional groups such as THP ethers, acetals, alkenes, and alkynes are compatible with the process. However, the price of $Mn(OAc)_3 \cdot 2H_2O$ ($647/mol) is actually more expensive than DDQ. Therefore, the development of economical and environmentally benign oxidants that regenerate DDQ from its reduced $DDQH_2$ is still a worthwhile project.



Scheme 57. $Mn(OAc)_3$ as terminal oxidant for DDQ-catalyzed PMB ether cleavage

4.2 RESULTS AND DISCUSSION

The initial objective was to search for a terminal oxidant to promote our DDQ-catalyzed C–H bond activation processes. Terminal oxidants ($FeCl_3$, $Mn(OAc)_3$) that regenerate DDQ from $DDQH_2$, as well as metal oxides (PbO_2,[118] MnO_2,[119] $Mn(acac)_3$[120]) that are known to promote phenol oxidations, were applied to DDQ-catalyzed oxidative cyclization of allylic ether **4.1** (Table 8). Substrate **4.1** was readily synthesized from known alcohol **1.106** through ether formation and enol acetate formation (Scheme 58).



Reagents and conditions
a) 3,3-dimethylallyl bromide, NaH, tetrabutylammonium iodide, DMF, 81%.
B) HOAc, $[(p\text{-cymene})RuCl_2]_2$, Fur_3P, Na_2CO_3, PhMe, 55%.

Scheme 58. The preparation of substrate **4.1**

The starting material decomposed immediately upon treating **4.1** with $FeCl_3$ or $Mn(acac)_3$, most likely due to their strong Lewis acidities (entries 1 and 4, table 8). $Mn(OAc)_3$ and PbO_2 proved to be effective terminal oxidants to promote DDQ-regeneration process, and 70% and 72% yields were obtained after 48 h (entries 2 and 3, table 8). However, the cost concern for both $Mn(OAc)_3$ ($647/mol) and PbO_2 ($117/mol), combined with the toxicity issue of PbO_2 (LD_{50} = 220 mg/kg) led us to explore the feasibility of MnO_2 ($28/mol, LD_{50} = 3478 mg/kg) as the stoichiometric oxidant.

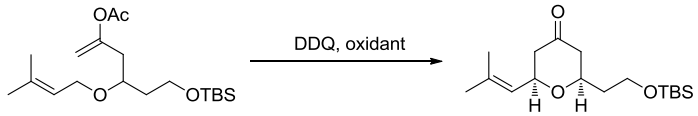
Exposing **4.1** to DDQ (40 mol %) and MnO_2 in CH_3NO_2 afforded **4.3** in 66% yield after 48 h (entry 5, tale 8). No conversion of **4.1** to **4.3** was observed when MnO_2 was used in the absence of DDQ (entry 6, table 8), suggesting that the reaction should be mediated by DDQ. Moreover, DDQ regeneration was confirmed through ^{13}C NMR spectroscopy by treating $DDQH_2$[121] with MnO_2 in CH_3NO_2.

Different solvents were screened to improve the reaction efficiency. The starting material was completely consumed in 60 h and a 45% yield of **4.3** was obtained when the reaction was performed in DCE (entry 7, table 8); decomposition to an unidentified byproduct was the major side pathway. The transformation was sluggish in CH_3CN (entry 8, table 8). Polar solvents, such as EtOAc and DMF, were not good options even for the DDQ oxidation process, and no reactions were observed (entries 9 and 10, table 8). Typically, oxidative cyclizations are slower in CH_3NO_2 than in less polar solvents, such as DCE. However, the regeneration of DDQ was faster in CH_3NO_2, making it the best solvent for the process.

The yield was improved from 66% to 80% by the incorporation of $NaHCO_3$ as a base (entry 11, table 8). Employing 2,6-dichloropyridine made the transformation proceed more efficiently (entry 12, table 8) probably because it acted as a soluble base and quenched the

acylium ion formed when the enol acetate nucleophile attacks the oxocarbenium ion. Increased temperature or sonication condition proved not to be beneficial to the reaction rate (entries 13 and 14, table 8). Lowering DDQ loadings from 40 mol % to 15 mol % did not result in a loss of yield, though the reaction required an additional 12 h to go to completion (entry 15, table 8). The purification step was quite easy, with the removal of the excess MnO_2 and metal-containing byproduct through a simple filtration over silica gel.

Table 8. Terminal oxidant screen and reaction condition optimization[a]



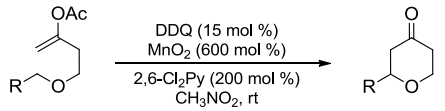
4.1 **4.3**

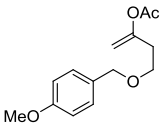
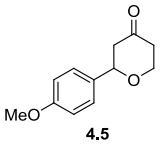
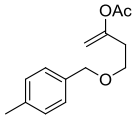
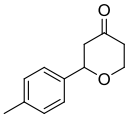
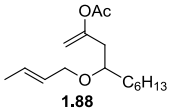
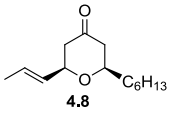
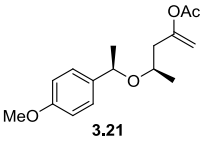
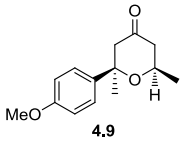
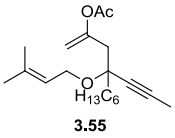
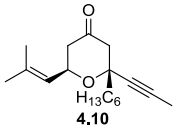
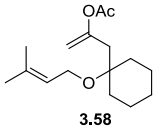
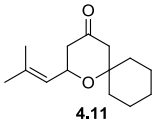
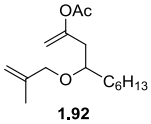
	oxidant (eq)	solvent	base (eq)	DDQ (mol%)	time (h)	yield (%)[b]
1.	$FeCl_3$ (3)	DCE	—	—	0.02	decomposition
2.	$Mn(OAc)_3$ (3)	CH_3NO_2	—	40	48	70
3.	PbO_2 (8)	CH_3NO_2	—	40	48	72
4.	$Mn(AcAc)_3$ (3)	CH_3NO_2	—	—	0.02	decomposition
5.	MnO_2 (6)	CH_3NO_2	—	40	48	66
6.	MnO_2 (6)	DCE	—	—	10	no reaction
7.	MnO_2 (6)	DCE	—	40	60	45
8.	MnO_2 (6)	CH_3CN	—	40	48	~ 30% conversion
9.	MnO_2 (6)	EtOAc	—	40	10	no reaction
10.	MnO_2 (6)	DMF	—	40	10	no reaction
11.	MnO_2 (6)	CH_3NO_2	$NaHCO_3$	40	48	80
12.	MnO_2 (6)	CH_3NO_2	2,6-Cl_2Py	40	32	82
13.[c]	MnO_2 (6)	CH_3NO_2	2,6-Cl_2Py	40	36	~ 70% conversion
14.[d]	MnO_2 (6)	CH_3NO_2	2,6-Cl_2Py	40	16	~ 45% conversion
15.	MnO_2 (6)	CH_3NO_2	2,6-Cl_2Py	15	48	79

[a] Representative procedure: DDQ was added in three equal portions over the course of the reaction to a suspension of **4.1**, base (2 equiv), and oxidant. The reaction was stirred at room temperature for the indicated period of time.
[b] Yields refer to isolated, purified material.
[c] reaction was performed at 45 °C.
[d] reaction was performed under sonication condition.

After suitable reaction conditions were identified, a variety of allylic and benzylic ethers that worked in stoichiometric DDQ-mediated oxidation reactions were subjected to this catalytic process. The results are summarized in Table 9. Cyclizations of benzylic and allylic ethers proceeded smoothly to provide the corresponding tetrahydropyrans (entries 1-3, table 9). Quaternary centers can be formed through the catalytic system by using sterically hindered ethers **3.21** and **3.55** as substrates (entries 4 and 5, table 9). The cyclization of substrate **3.58** provided spirocyclic ether **4.11** in 81% yield (entry 6, table 8). Generally speaking, the yields of the reactions were within approximately 10% of the yields for the corresponding reactions using stoichiometric DDQ. The reaction rates roughly correlated with the substrate's oxidation potential and the oxocarbenium ion's stability, though the reaction time difference between the most and least reactive substrates was quite small (entries 1 and 3, table 8). This observation indicated that the hydroquinone oxidation should be the rate limiting step. No reaction was observed for substrate **1.92**. This challenge can be attributed to the low reaction rate even when using stoichiometric DDQ in DCE (entry 2, table 2, Chapter 1), and the change in solvent, since oxidative cyclizations are slower in CH_3NO_2 than in DCE.

Table 9. DDQ-catalyzed oxidative cyclization reactions[a]



Entry	Substrate	Product	t (h)	Yield (%)[b]
1	 **4.4**	 **4.5**	41	76
2	 **4.6**	 **4.7**	44	83
3	 **1.88**	 **4.8**	40	92
4[c]	 **3.21**	 **4.9**	48	75
5	 **3.55**	 **4.10**	40	70
6	 **3.58**	 **4.11**	30	81
7	 **1.92**	—	—	—

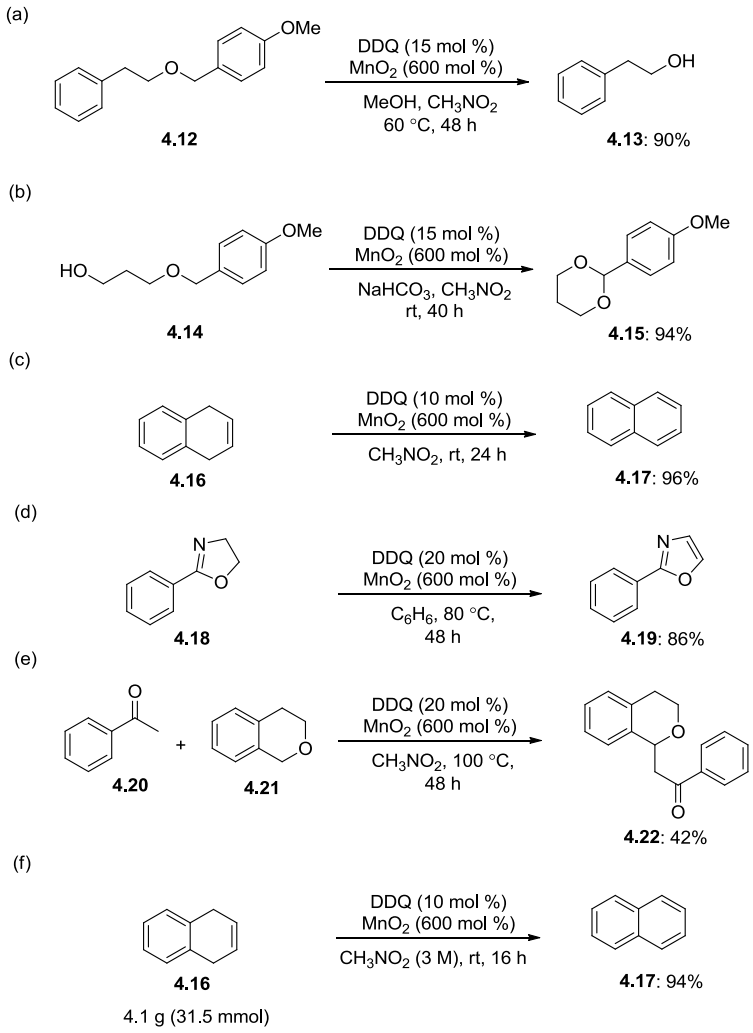
[a] Representative procedure: DDQ was added in three equal portions over the course of the reaction to a suspension of the substrate, 2,6-dichloropyridine (2 equiv), and activated MnO_2 (6 equiv) in CH_3NO_2 (0.1 M). The reaction was stirred at room temperature for the indicated period of time.

[b] Yields refer to isolated, purified material.

[c] reaction required 0.2 equiv of DDQ.

We also investigated the applicability of MnO_2 as a stoichiometric oxidant in other commonly encountered DDQ-mediated reactions (Scheme 59). The oxidative cleavage of PMB ether **4.12** proceeded efficiently to afford alcohol **4.13** in 90% yield (Scheme 59(a)). H_2O proved

to deactivate MnO_2, so MeOH was employed as the nucleophile in the transformation. An intramolecular variant of the reaction provided cyclic acetal **4.15** in 94% yield using $NaHCO_3$ as a base (Scheme 59(b)). Dehydrogenation reactions also worked pretty well, with dihydronaphthalene (**4.16**) being oxidized to naphthalene (**4.17**) in 96% yield (Scheme 59(c)), and with oxazoline **4.18** being oxidized to oxazole **4.19** in 86% yield (Scheme 59(d)). The protocol was also applicable to Li's cross-dehydrogenative coupling (CDC)[122] of acetophenone (**4.20**) and isochroman **4.21** forming **4.22** in 42% yield (Scheme 59(e)). While the yield was not satisfactory, this example demonstrated that intermolecular C–C bond formation can be achieved by employing MnO_2 as the terminal oxidant. When the amount of **4.16** in transformation (c) was scaled up from 50 mg to 4.1 g (31.5 mmol), the reaction proceeded more rapidly than that of the smaller scale (16 h vs 24 h) and provided a comparable yield (Scheme 60(f)). The rate enhancement was attributed to the increase of concentration from 0.1 M in the smaller scale transformation to 3 M in the larger scale. The ability to perform large-scale transformations indicates that this protocol might have potential application in process chemistry.



Scheme 59. MnO_2-mediated DDQ-catalyzed reactions

4.3 SUMMARY

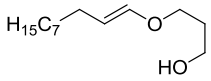
We have demonstrated that DDQ-catalyzed oxidative C–H functionalization of benzylic and allylic ethers for tetrahydropyran synthesis can be achieved by using MnO_2 as an inexpensive and environmentally benign terminal oxidant. This catalytic system is also applicable to other commonly encountered DDQ-mediated reactions, such as PMB ether cleavages, dehydrogenations, and cross-dehydrogenative couplings. The processes are comparable with respect to yield and stereocontrol, though these reactions are significantly slower than the corresponding reactions using stoichiometric DDQ. Moreover, the products are quite easy to purify. Substrates with low reactivities toward DDQ oxidation are not compatible with this system. The success of gram-scale transformation suggests that the protocol should have potential application in process chemistry due to the benefits of MnO_2's low price and negligible toxicity.

APPENDIX A

CARBON–CARBON BOND CONSTRUCTION THROUGH OXIDATIVE CARBON–HYDROGEN BOND CLEAVAGE OF VINYL AND ALLYLIC ETHERS

General Experimental Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on Bruker Avance 300 spectrometer 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 was used as a reference value, for ^{1}H NMR: $CDCl_3$ = 7.26 ppm, for ^{13}C NMR: $CDCl_3$ = 77.23. Data are reported as follows: (s = singlet; d = doublet; t = triplet; q = quartet; dd = doublet of doublets; dt = doublet of triplets; br = broad). High resolution and low resolution mass spectra were recorded on a VG 7070 spectrometer. Infrared (IR) spectra were collected on a Mattson Cygnus 100 spectrometer. Samples for IR were prepared as a thin film on a NaCl plate by dissolving the compound in CH_2Cl_2 and then evaporating the CH_2Cl_2. Analytical TLC was performed on E. Merck pre-coated (25 mm) silica gel 60F-254 plates. Visualization was done under UV light (254 nm). Flash chromatography was done using ICN SiliTech 32-63 60 Å silica gel. Methylene chloride was distilled under N_2 from CaH_2, and 1,2–dichloroethane was dried over 4Å molecular sieves. Reagent grade ethyl acetate, diethyl ether, pentane and hexanes were purchased from EM Science and used as purchased for chromatography. Tetrahydrofuran and

diethyl ether were dried by passage through an activated alumina column under positive N_2 pressure. Anhydrous (*N*,*N*)-dimthylformamide (DMF), methanol (MeOH), dimethyl sulfoxide (DMSO), acetone were purchased from Aldrich and used as it is. Activated 4 Å molecular sieves were obtained through drying in oven at 150 °C overnight. All reactions were performed in oven or flame-dried glassware under a positive pressure of N_2 with magnetic stirring unless otherwise noted.



(*E*)-3-(Dec-1-enyloxy)propan-1-ol (1.73)

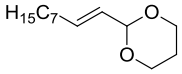
The mixture of vinyl iodide **1.74** (2.09 g, 7.88 mmol), alcohol **1.75** (3.00 g, 15.8 mmol), 1,10-phenanthroline (284 mg, 1.58 mmol), Cs_2CO_3 (3.85 g, 11.8 mmol) and CuI (150 mg, 0.790 mmol) in 4 mL toluene was heated to 80 ^oC for 3 days.[1] The reaction mixture was filtered through a short plug of silica gel. After concentration, the resulting residue was purified by flash chromatography (20% CH_2Cl_2 in pentane) to give desired (*E*)-*tert*-butyl(3-(dec-1-en-1-yloxy)propoxy)dimethylsilane (951 mg, 37%).

To (*E*)-*tert*-butyl(3-(dec-1-en-1-yloxy)propoxy)dimethylsilane (130 mg, 0.400 mmol) in 4 mL THF was added TBAF (414 mg, 1.60 mmol) in one portion at 0 ^oC. The reaction was stirred at that temperature for 2 h before H_2O was added. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (20% EtOAc in hexane) to afford the desired **1.73** (84 mg, 99%). ^1H NMR (300 MHz, $CDCl_3$) δ 6.19 (d, *J* = 12.6 Hz, 1H), 4.77 (dt, *J* = 7.4, 12.6, 14.6 Hz, 1H), 3.78-3.70 (m, 4H), 2.46 (s, 1H), 1.89-1.81 (m, 4H), 1.25 (br, 12H), 0.86 (t, *J* =6.9 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 145.9, 104.9, 70.0, 60.5, 32.1, 32.0, 30.8, 29.6, 29.5, 29.2, 27.9, 22.8, 14.2; IR (neat)

3350, 2954, 2924, 2853, 1671, 1653, 1465, 1159, 1057, 931 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{26}O_2$ (M^+) 214.1933, found 214.1936.

General procedure for the cyclization reaction:

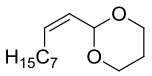
Substrate (1 eq), 2,6-dichloropyridine (2 eq) and 4 Å molecular sieves (2 mass eq) were dissolved in anhydrous 1,2-dichloroethane to give a ~0.1 M solution. The mixture was stirred at room temperature for 15 minutes, followed by addition of $LiClO_4$ (0.1 eq). After 5 minutes, DDQ (2 eq) was added. The reaction was monitored by TLC at room temperature unless specified and, upon starting material consumption, was quenched by Et_3N. The resulting mixture was loaded directly onto a short plug of silica gel and eluted with dichloromethane. The filtrate was concentrated and purified by flash chromatography to give the desired product.



(*E*)-2-(Non-1-enyl)-1,3-dioxane (1.76)

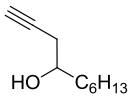
The general procedure for cyclization reaction was followed: **1.73** (109 mg, 0.509 mmol), 2,6-dichloropyridine (301 mg, 2.03 mmol) and 4 Å molecular sieves (218 mg) were dissolved in 5.0 mL anhydrous 1,2-dichloroethane, and the mixture was stirred at room temperature for 15 minutes. After that, the mixture was cooled to –15 °C, and DDQ powder (230 mg, 1.01 mmol) was added in one portion. The reaction was stirred at that temperature for 1 minute and then quenched by Et_3N. It was loaded onto a short plug of silica gel and washed off with dichloromethane. The filtrate was concentrated and purified by flash chromatography (50% CH_2Cl_2 in hexane) to give desired products (91.3 mg, 85%, **1.76**:**1.77** = 11.4:1). ^1H NMR (300 MHz, $CDCl_3$) δ 5.91 (dt, *J* = 6.6, 15.6 Hz, 1H), 5.50 (dd, *J* = 5.1, 15.6 Hz, 1H), 4.93 (d, *J* = 5.1 Hz, 1H), 4.14 (dd, *J* = 4.9, 10.8 Hz, 2H), 3.85 (dd, *J* = 2.3, 12.3 Hz, 1H), 3.81 (dd, *J* = 2.2, 12.2

Hz, 1H), 2.20-2.02 (m, 3H), 1.41-1.26 (m, 11H), 0.87 (t, J = 6.9 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 135.9, 127.1, 101.4, 67.1, 32.3, 32.0, 29.4, 29.3, 28.9, 25.9, 22.8, 14.3; IR (neat) 2958, 2927, 2853, 1466, 1378, 1279, 1237, 1146, 1092, 997, 967 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{24}O_2$ (M^+) 212.1776, found 212.1766.



(*Z*)-2-(Non-1-enyl)-1,3-dioxane (1.77)

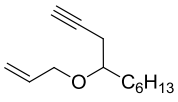
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.64 (dt, J = 7.5, 11.0 Hz, 1H), 5.44 (dd, J = 6.4, 11.1 Hz, 1H), 5.24 (d, J = 6.4 Hz, 1H), 4.14 (dd, J = 4.9, 10.7 Hz, 2H), 3.87 (dd, J = 2.3, 12.3 Hz, 1H), 3.82 (dd, J = 2.3, 12.2 Hz, 1H), 2.21-2.02 (m, 3H), 1.38-1.28 (m, 11H), 0.89 (t, J = 6.9 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 136.0, 127.0, 98.2, 67.1, 32.0, 29.6, 29.4, 29.3, 28.4, 25.9, 22.9, 14.3; IR (neat) 2956, 2925, 2853, 1465, 1238, 1139, 1118, 996, 929 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{24}O_2$ (M^+) 212.1776, found 212.1775.



Dec-1-yn-4-ol (1.80)

The heptaldehyde (4.00 g, 35.5 mmol), zinc powder (11.5 g, 175 mmol), 1,2-diiodoethane (9.87 g, 35.0 mmol) and 3-bromo-1-propyne (7.81 g, 52.5 mmol) were mixed in a 250 mL RBF with 175 mL anhydrous THF. The reaction was sonicated for 2.5 h, and then quenched by adding 70 mL 2.0 M HCl (aq). The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic phase was washed with saturated aqueous $Na_2S_2O_3$ to remove the iodine from the crude product. The organic layer was then dried over $MgSO_4$, filtrated and concentrated. The resulting residue was purified by chromatography (10% EtOAc in hexane) to give **1.80** (2.97 g, 55%). The spectrum is consistent with the data reported by literature.[2] ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.71-.3.79 (m, 1H), 3.44 (ddd, J = 3.0, 4.5, 16.8 Hz,

1H), 2.31 (ddd, *J* = 2.1, 6.3, 16.8 Hz, 1H), 2.06 (t, *J* = 2.1 Hz, 1H), 1.86 (d, *J* = 5.1 Hz, 1H), 1.56-1.50 (m, 2H), 1.49-1.14 (m, 8H), 0.88 (t, *J* = 6.6 Hz, 3H).



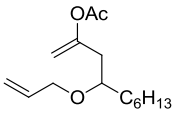
4-(Allyloxy)dec-1-yne (1.81)

To **1.80** (517 mg, 3.36 mmol) in 10 mL DMF at 0 °C was added NaH (60%, dispersed in mineral oil, 201 mg, 5.03 mmol) in one portion. The mixture was stirred at that temperature for 30 minutes before 3-bromo-1-propene (440 uL, 5.00 mmol) was added. The reaction was allowed to warm to room temperature and stirred for another 5 h. The reaction was quenched by H_2O at 0 °C, followed by excess amount of EtOAc. After the organic layer was washed with brine, the mixture was dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (10% EtOAc in hexane) to provide **1.81** (606 mg, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.99-5.86 (m, 1H), 5.28 (ddd, *J* = 1.6, 3.2, 17.2 Hz, 1H), 5.16 (dd, *J* = 1.6, 10.3 Hz, 1H), 4.11 (ddt, *J* = 1.2, 5.4, 12.6 Hz, 1H), 3.99 (ddt, *J* = 1.2, 5.7, 12.6 Hz, 1H), 3.50-3.42 (m, 1H), 2.47-2.31 (m, 2H), 1.99 (t, *J* = 2.7 Hz, 1H), 1.46-1.59 (m, 2H), 1.43-1.29 (m, 8H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 135.3, 117.0, 81.5, 77.4, 70.6, 70.0, 34.2, 32.0, 29.5, 25.4, 24.0, 22.8, 14.3; IR (neat) 3311, 2859, 2360, 2340, 1648, 1458, 1428, 1376, 1341, 1129, 1092, 995, 923 cm^{-1}; HRMS (EI) calcd for $C_{10}H_{19}O$ $(M\text{-}C_3H_3)^+$ 155.1436, found 155.1443.

General procedure for the enol acetate preparation:[3]

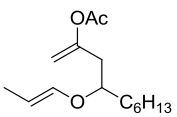
A mixture of Na_2CO_3 (15%), $[(p\text{-cymene})RuCl_2]_2$ (0.04 eq), tri(2-furyl)phosphine (0.08 eq), acetic acid (2.0 eq), and 1-decyne (0.5 eq) in toluene was heated to 80 °C and stirred for 1 h. Another portion of acetic acid (2.0 eq) and the alkyne substrate (1.0 eq) were dissolved in

toluene and added to the mixture (~0.15 M final substrate concentration). The reaction was stirred at 80 °C overnight. Then crude mixture was concentrated on a rotary evaporator and purified by chromatography to give the desired enol acetate product.



4-(Allyloxy)dec-1-en-2-yl acetate (1.82)

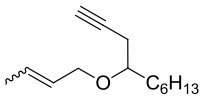
A 50 mL RBF was charged with Na_2CO_3 (48.9 mg, 0.461 mmol), dichloro(p-cymene)ruthenium(II) dimer (75 mg, 0.12 mmol), tri(2-furyl)phosphine (57.1 mg, 0.246 mmol). Then 10 mL toluene was added into the flask, followed by acetic acid (352 uL, 6.20 mmol) and 1-decyne (554 uL, 2.97 mmol). The mixture was then heated to 80 °C and stirred for 1 h. Another 352 uL of acetic acid and **1.80** derived from previous step were dissolved in 10 mL toluene and added into the reaction through syringe. The reaction was stirred at the same temperature overnight. Then crude mixture was loaded onto a short plug of silica gel and washed off with Et_2O. The residue was concentrated on a rotary evaporator and purified by chromatography (2% EtOAc in hexane) to give the desired product (503 mg, 65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95-5.84 (m, 1H), 5.26 (ddd, *J* = 1.6, 5.1, 17.3 Hz, 1H), 5.15 (ddd, *J* = 1.2, 2.8, 10.2 Hz, 1H), 4.80 (s, 2H), 4.04-3.97 (m, 2H), 3.50-3.44 (m, 1H), 2.50-2.35 (m, 2H), 2.13 (s, 3H), 1.53-1.28 (m, 10H), 0.89 (t, *J* = 6.4 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 169.3, 153.9, 135.5, 116.8, 103.8, 76.7, 70.4, 38.6, 34.3, 32.0, 29.6, 25.5, 22.8, 21.3, 14.3; IR (neat) 2930, 2858, 2360, 2340, 1758, 1717, 1666, 1459, 1429, 1370, 1195, 1130, 1081, 1020, 965, 921, 872 cm^{-1}; HRMS(ESI) calcd for $C_{15}H_{26}O_3Na$ $(M+Na)^+$ 277.1780, found 277.1760.



(*E*)-4-(Prop-1-enyloxy)dec-1-en-2-yl acetate (1.78)

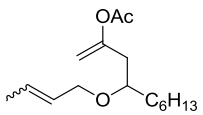
To a solution of $[(^cC_8H_{14})_2IrCl]_2$ (24 mg, 0.030 mmol) and PCy_3 (44 mg, 0.16

mmol) in 1 mL anhydrous 1,2-dichloroethane was added to a solution of $NaBPh_4$ (18 mg, 0.053 mmol) in 1 mL DCE/acetone (25/1).[4] The yellow mixture was stirred at room temperature for 5 minutes, and then allylic ether **1.82** (338 mg, 1.33 mmol) was added. The mixture was stirred for 30 minutes under N_2, and purified by flash chromatography (florisil, 1% EtOAc in hexane) to give **1.78** (305 mg, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.03 (dd, *J* = 1.3, 12.3 Hz, 1H), 4.90-4.81 (m, 1H), 4.80 (s, 1H), 4.77 (s, 1H), 3.76-3.68 (m, 1H), 2.48 (dd, *J* = 6.5, 15.1 Hz, 1H), 2.38 (dd, *J* = 5.6, 15.0 Hz, 1H), 2.12 (s, 3H), 1.52 (dd, *J* = 1.3, 6.7 Hz, 3H), 1.38-1.26 (m, 10H), 0.88 (t, *J* = 5.2 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 169.0, 153.0, 145.6, 103.8, 100.7, 77.6, 38.3, 34.0, 31.7, 29.2, 25.1, 22.5, 21.0, 14.0, 12.4; IR (neat) 2929, 2859, 1760, 1673, 1370, 1197, 1164, 1019, 922, 875 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{26}O_3$ $(M)^+$ 254.1882, found 254.1881.



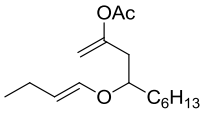
4-(But-2-enyloxy)dec-1-yne (1.83)

The same procedure for the synthesis of **1.81** was followed employing **1.80** (530 mg, 3.40 mmol), NaH (206 mg, 60% in mineral oil) and crotyl bromide (530 uL, 5.20 mmol) in 10 mL DMF. The resulting residue was purified by chromatography (4% EtOAc in hexane) to give desired **1.81** (560 mg, 78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.72-5.53 (m, 2H), 4.15-3.99 (m, 1H), 3.94-3.77 (m, 1H), 3.48-3.40 (m, 1H), 2.46-2.29 (m, 2H), 1.99-1.96 (m, 1H), 1.72-1.69 (m, 3H), 1.68-1.55 (m, 2H), 1.43-1.23 (m, 8H), 0.91-0.86 (m, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 129.4, 128.1, 81.6, 77.0, 70.4, 69.9, 34.2, 32.0, 29.5, 25.4, 24.1, 22.8, 17.9, 14.2; IR (neat) 3312, 3012, 2955, 2930, 2857, 2120, 1456, 1377, 1347, 1304, 1247, 1126, 1096, 1051, 967, 907 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{24}O$ $(M)^+$ 208.1827, found 208.1829.



4-(But-2-enyloxy)dec-1-en-2-yl acetate (1.84)

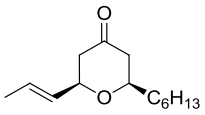
General procedure for enol acetate preparation was followed employing Na_2CO_3 (42.7 mg, 0.403 mmol), [(*p*-cymene)$RuCl_2$]$_2$ (33 mg, 0.054 mmol), tri(2-furyl)phosphine (25 mg, 0.11 mmol), acetic acid (310 μL, 5.40 mmol) and **1.83** (560 mg, 2.70 mmol) in 18 mL toluene at 80 °C for 17 h. Then crude mixture was concentrated on a rotary evaporator and purified by flash chromatography (1% EtOAc in hexane) to give **1.84** (476 mg, 66%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.75-5.51 (m, 2H), 4.79 (s, 2H), 4.07-3.85 (m, 2H), 3.47-3.39 (m, 1H), 2.50-2.33 (m, 2H), 2.14 (s, 3H), 1.71-1.64 (m, 3H), 1.51-1.47 (m, 2H), 1.44-1.20 (m, 8H), 0.88 (t, *J* = 6.5 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 169.3, 153.9, 129.3, 128.2, 103.7, 76.3, 70.2, 38.6, 34.3, 32.0, 29.5, 25.4, 22.8, 21.3, 17.9, 14.3; IR (neat) 2930, 2857, 2360, 2340, 1758, 1666, 1456, 1370, 1195, 1127, 1093, 1046, 1021, 966, 872 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{28}O_3Na$ $(M+Na)^+$ 291.1936, found 291.1934.



(*E*)-4-(But-1-enyloxy)dec-1-en-2-yl acetate (1.79)

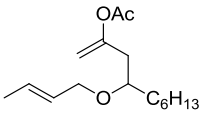
To a solution of [(^{c}C_8H_{14})$_2$IrCl]$_2$ (32 mg, 0.040 mmol) and PCy_3 (59 mg, 0.21 mmol) in 1 mL anhydrous 1,2-dichloroethane was added to a solution of $NaBPh_4$ (24.3 mg, 0.071 mmol) in 1 mL DCE/acetone (25/1). The yellow mixture was stirred at room temperature for 5 minutes, and then allylic ether **1.84** (475 mg, 1.77 mmol) was added. The mixture was stirred at 40 °C overnight, and purified by chromatography (florisil, 2% EtOAc in hexane) to give the desired product (47 mg, 10%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.06 (dt, *J* = 1.2, 12.3 Hz, 1H), 4.95-4.80 (m, 3H), 3.79-3.69 (m, 1H), 2.51 (dd, *J* = 6.6, 15.1 Hz, 1H), 2.40 (dd, *J* = 5.6, 15.1 Hz, 1H), 2.15 (s, 3H), 1.98-1.88 (m, 2H), 1.59-1.53 (m, 2H), 1.40-1.20 (m, 8H), 0.97 (t, *J* = 7.4 Hz, 3H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 169.3, 153.9, 144.8, 108.6, 104.2, 77.8, 38.5, 34.3, 32.0, 29.4, 25.3, 22.8, 21.3, 21.2, 15.4, 14.3; IR (neat) 2958, 2929, 2857, 1759,

1664, 1370, 1195, 1090, 1019 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{28}O_3Na$ $(M+Na)^+$ 291.1936, found 291.1933.



2-Hexyl-6-((*E*)-prop-1-enyl)dihydro-2*H*-pyran-4(3*H*)-one (1.85)

The general procedure for the cyclization reaction was followed: **1.79** (50 mg, 0.19 mmol), 2,6-dichloropyridine (110 mg, 0.743 mmol) and 4 Å molecular sieves (100 mg) were dissolved in 1.9 mL anhydrous 1,2-dichloroethane, followed by $LiClO_4$ (4.0 mg, 0.037 mmol) and DDQ (44.3 mg, 0.195 mmol). The reaction was stirred for 2 minutes at room temperature before quenched by Et_3N. The mixture was loaded onto a short plug of silica gel and washed off with dichloromethane. The filtrate was concentrated and purified by flash chromatography (4% EtOAc in hexane) to give **1.85** (28.7 mg, 69%). ^1H NMR (300 MHz, $CDCl_3$) δ 5.74 (ddq, *J* = 0.9, 12.8, 15.4 Hz, 1H), 5.54 (ddq, *J* = 1.5, 6.1, 15.3 Hz, 1H), 4.06-3.99 (m, 1H), 3.58 (ddt, *J* = 2.7, 6.9, 14.3 Hz, 1H), 2.37-2.33 (m, 3H), 2.28-2.18 (m, 1H), 1.72-1.66 (m, 3H), 1.54-1.27 (m, 10H), 0.87 (t, *J* = 6.6 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 207.4, 130.7, 128.4, 77.5, 77.2, 48.0, 47.9, 36.6, 31.9, 29.3, 25.4, 22.7, 17.9, 14.2; IR (neat) 2927, 2856, 2362, 2342, 1719, 1458, 1408, 1377, 1349, 1320, 1280, 1247, 1154, 1112, 1053, 964, 936, 891, 841, 724 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{24}O_2$ $(M)^+$ 224.1776, found 224.1782.



(*E*)-4-(But-2-enyloxy)dec-1-en-2-yl acetate (1.88)

To a suspension of LAH (2.25 g, 58.9 mmol) in DME (60 ml) at 0 °C was added **1.89** (3.45 g, 49.3 mmol) dropwise. The ice bath was then removed and the reaction mixture was stirred at room temperature for 38 h. Then the reaction was quenched by addition of H_2O (6 mL), and washed with 6 mL 14% NaOH (aq) and 6 mL H_2O. The gray precipitate was

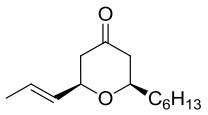
filtered through Celite. The residue was washed with dry ether and the combined filtrates were dried over $MgSO_4$. Evaporation of the solvent at atmospheric pressure left the crude alcohol, distillation of which at reduced pressure afforded (*E*)-2-butenol as a colourless liquid (2.15 g, 61%), b.p. 45-48 °C, 30-40 Torr.[5]

The (*E*)-2-butenol (1.00 g, 13.9 mmol) in dry Et_2O (6 mL) at 0 °C under nitrogen was treated dropwise with freshly distilled phosphorus tribromide (0.67 mL, 7.1 mmol). The mixture was stirred for 3 h at 0 °C before it was poured onto ice (15 g). The organic phase was washed successively with water, saturated aqueous K_2CO_3, and brine, and then dried over $MgSO_4$. Ether was removed by distillation at atmospheric pressure to afford the crude (*E*)-1-Bromo-2-butene (**1.90**) as a pale orange liquid (1.15 g, 60%), which was used as such.

To dec-1-yn-4-ol (**1.80**) (848 mg, 5.5 mmol) in 15 mL DMF at 0 °C was added NaH (60%, dispersed in mineral oil, 352 mg) in one portion. The mixture was stirred at that temperature for 30 minutes before **1.90** (1.15 g, 8.50 mmol) was added in. The reaction was warmed to room temperature and stirred overnight. The reaction was then quenched by H_2O at 0 °C, followed by excess amount of EtOAc. After the organic layer was washed with brine, it was dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (10% EtOAc in hexane) to give the (*E*)-4-(but-2-enyloxy)dec-1-yne (896 mg, 78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.77-5.65 (m, 1H), 5.62-5.53 (m, 1H), 4.03 (dd, J = 6.1, 11.6 Hz, 1H), 3.90 (dd, J = 6.2, 11.6 Hz, 1H), 3.49-3.40 (m, 1H), 2.46-2.29 (m, 2H), 1.98 (t, J = 2.5 Hz, 1H), 1.70 (dd, J = 0.9, 6.0 Hz, 3H), 1.62-1.57 (m, 2H), 1.42-1.28 (m, 8H), 0.88 (t, J = 6.3 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 129.2, 127.9, 81.4, 77.4, 70.1, 69.7, 34.0, 31.8, 29.3, 25.2, 23.8, 22.6, 17.7, 14.0; IR (neat) 3312, 3012, 2955, 2930, 2857, 2120, 1456, 1377, 1347, 1304,

1247, 1126, 1096, 1051, 967, 907 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{24}O$ (M^+) 208.1827, found 208.1829.

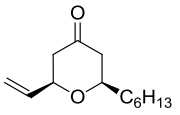
General procedure for enol acetate preparation was followed employing Na_2CO_3 (68.2 mg, 0.643 mmol), [(*p*-cymene)$RuCl_2$]$_2$ (52.5 mg, 0.0860 mmol), tri(2-furyl)phosphine (39.8 mg, 0.171 mmol), acetic acid (490 μL, 8.56 mmol) and (*E*)-4-(but-2-enyloxy)dec-1-yne (893 mg, 4.29 mmol) in 26 mL toluene at 80 °C for 12 h. Then crude mixture was concentrated on a rotary evaporator and purified by flash chromatography (1% EtOAc in hexane) to give **1.88** (738 mg, 65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.76-5.47 (m, 2H), 4.80 (s, 2H), 3.98-3.86 (m, 2H), 3.48-3.40 (m, 1H), 2.50-2.34 (m, 2H), 2.14 (s, 3H), 1.71 (dd, *J* = 1.0, 6.1 Hz, 3H), 1.52-1.48 (m, 2H), 1.44-1.29 (m, 8H), 0.89 (t, *J* = 6.4 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 169.3, 153.9, 129.3, 128.2, 103.7, 76.3, 70.2, 38.6, 34.3, 32.0, 29.6, 25.5, 22.8, 21.3, 17.9, 14.3; IR (neat) 2930, 2857, 2360, 2340, 1758, 1666, 1456, 1370, 1195, 1127, 1093, 1046, 1021, 966, 872 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{28}O_3Na$ $(M+Na)^+$ 291.1936, found 291.1934.



2-Hexyl-6-((*E*)-prop-1-enyl)dihydro-2*H*-pyran-4(3*H*)-one (1.85)

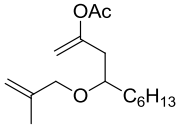
The general procedure for the cyclization reaction was followed: **1.88** (130 mg, 0.484 mmol), 2,6-dichloropyridine (288 mg, 1.95 mmol) and 4 Å molecular sieves (240 mg) were dissolved in 5 mL anhydrous 1,2-dichloroethane, followed by $LiClO_4$ (5.2 mg, 0.049 mmol) and DDQ (221 mg, 0.974 mmol). The reaction was stirred for 17 h at room temperature then quenched by Et_3N. The mixture was loaded onto a short plug of silica gel and washed off with dichloromethane. The filtrate was concentrated and purified by flash chromatography (40% hexane in DCM then 6% EtOAc in hexane) to furnish the desired product (88.4 mg, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.74 (ddq, *J* = 0.9, 12.8, 15.4 Hz, 1H), 5.54 (ddq, *J* = 1.5, 6.1, 15.3

Hz, 1H), 4.06-3.99 (m, 1H), 3.58 (ddt, *J* = 2.7, 6.9, 14.3 Hz, 1H), 2.37-2.33 (m, 3H), 2.28-2.18 (m, 1H), 1.72-1.66 (m, 3H), 1.54-1.27 (m, 10H), 0.87 (t, *J* = 6.6 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 207.4, 130.7, 128.4, 77.5, 77.2, 48.0, 47.9, 36.6, 31.9, 29.3, 25.4, 22.7, 17.9, 14.2; IR (neat) 2927, 2856, 2362, 2342, 1719, 1458, 1408, 1377, 1349, 1320, 1280, 1247, 1154, 1112, 1053, 964, 936, 891, 841, 724 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{24}O_2$ (M^+) 224.1776, found 224.1782.



2-Hexyl-6-vinyldihydro-2*H*-pyran-4(3*H*)-one (1.96)

The general procedure for the cyclization reaction was followed: **1.82** (59 mg, 0.23 mmol), 2,6-dichloropyridine (137 mg, 0.926 mmol) and 4 Å molecular sieves (120 mg) were dissolved in 2.4 mL anhydrous 1,2-dichloroethane, followed by $LiClO_4$ (2.5 mg, 0.024 mmol) and DDQ (34.3 mg, 0.151 mmol). The reaction was stirred for 48 h at 45 °C then quenched by Et_3N. The mixture was loaded onto a short plug of silica gel and washed off with dichloromethane. The filtrate was concentrated and purified by flash chromatography (40% hexane in CH_2Cl_2 then 6% EtOAc in hexane) to give the desired product (39.1 mg, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.92 (ddd, *J* = 5.4, 10.5, 17.2 Hz, 1H), 5.32 (dt, *J* = 1.3, 17.3 Hz, 1H), 5.21 (dt, *J* = 1.3, 10.5 Hz, 1H), 4.13-4.07 (m, 1H), 3.67-3.59 (m, 1H), 2.43-2.22 (m, 4H), 1.58-1.26 (m, 10H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 207.3, 137.5, 116.2, 77.5, 77.3, 48.0, 47.7, 36.6, 31.9, 29.4, 25.4, 22.8, 14.3; IR (neat) 2956, 2928, 2857, 1722, 1464, 1410, 1327, 1255, 1221, 1157, 1060, 988, 926 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{22}O_2$ (M^+) 211.1698, found 211.1704.



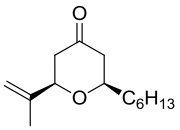
4-(2-Methylallyloxy)dec-1-en-2-yl acetate (1.92)

To dec-1-yn-4-ol (**1.80**) (463 mg, 300 mmol) in 8 mL DMF at 0 °C was added

NaH (60%, dispersed in mineral oil, 216 mg) in one portion. The mixture was stirred at that temperature for 30 minutes before 3-chloro-2-methyl-1-propene (529 μL , 5.40 mmol) was added in. The reaction was warmed to room temperature and stirred overnight. The reaction was then quenched by H_2O at 0 °C, followed by excess amount of EtOAc. After the organic layer was washed with brine, it was dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (1% EtOAc in hexane) to give the 4-((2-methylallyl)oxy)dec-1-yne (382 mg, 61%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.99 (s, 1H), 4.89 (s, 1H), 4.00 (d, *J* = 12.3 Hz, 1H), 3.89 (d, *J* = 12.2 Hz, 1H), 3.49-3.42 (m, 1H), 2.49-2.33 (m, 2H), 1.99 (t, *J* = 2.7 Hz, 1H), 1.77 (s, 3H), 1.64-1.60 (m, 2H), 1.44-1.30 (m, 8H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 142.8, 112.5, 81.6, 77.3, 73.6, 70.0, 34.1, 32.0, 29.5, 25.5, 23.9, 22.8, 19.8, 14.3; IR (neat) 2929, 2858, 1458, 1375, 1344, 1099, 900 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{21}O$ $(M-C_3H_3)^+$ 169.1952, found 169.1954.

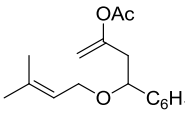
General procedure for enol acetate preparation was followed employing Na_2CO_3 (29.2 mg, 0.275 mmol), $[(p\text{-cymene})RuCl_2]_2$ (45 mg, 0.073 mmol), tri(2-furyl)phosphine (34 mg, 0.15 mmol), acetic acid (420 μL, 7.34 mmol), 1-decyne (331 μL, 1.80 mmol) and 4-((2-methylallyl)oxy)dec-1-yne (382 mg, 1.83 mmol) in 12 mL toluene at 80 °C for 18 h. Then crude mixture was concentrated on a rotary evaporator and purified by flash chromatography (1% EtOAc in hexane) to give **1.92** (286 mg, 58%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.96 (s, 1H), 4.86 (s, 1H), 4.79 (s, 2H), 3.91 (d, *J* = 12.2 Hz, 1H), 3.85 (d, *J* = 12.2 Hz, 1H), 3.48-3.40 (m, 1H), 2.48 (dd, *J* = 6.3, 14.9 Hz, 1H), 2.38 (dd, *J* = 5.8, 14.8 Hz, 1H), 2.13 (s, 3H), 1.74 (s, 3H), 1.54-1.49 (m, 2H), 1.40-1.28 (m, 8H), 0.88 (t, *J* = 6.6 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 169.3, 153.9, 142.9, 112.2, 103.7, 76.6, 73.3, 38.4, 34.1, 32.0, 29.6, 25.4, 22.8, 21.3, 19.9, 14.3; IR (neat) 2929, 2858, 1759, 1665,

1457, 1370, 1195, 1092, 1020, 899, 873 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{28}O_3Na$ $(M+Na)^+$ 291.1936, found 291.1934.



2-Hexyl-6-(prop-1-en-2-yl)dihydro-2*H*-pyran-4(3*H*)-one (1.97)

The general procedure for the cyclization reaction was followed: **1.92** (37 mg, 0.14 mmol), 2,6-dichloropyridine (82 mg, 0.55 mmol) and 4 Å molecular sieves (70 mg) were dissolved in 1.4 mL anhydrous 1,2-dichloroethane, followed by $LiClO_4$ (1.5 mg, 0.014 mmol) and DDQ (126 mg, 0.555 mmol). The reaction was stirred for 17 h at room temperature then quenched by Et_3N. The mixture was loaded onto a short plug of silica gel and washed off with dichloromethane. The filtrate was concentrated and purified by flash chromatography (40% hexane in CH_2Cl_2 then 6% EtOAc in hexane) to give the desired product (24.1 mg, 77%). ^1H NMR (300 MHz, $CDCl_3$) δ 5.03 (d, *J* = 0.6 Hz, 1H), 4.92 (d, *J* = 0.6 Hz, 1H), 3.99 (dd, *J* = 3.9, 10.5 Hz, 1H), 3.67-3.58 (m, 1H), 2.50-2.36 (m, 3H), 2.31-2.22 (m, 1H), 1.80 (s, 3H), 1.61-1.38 (m, 4H), 1.36-1.26 (m, 6H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 207.9, 144.3, 111.7, 79.7, 77.3, 48.1, 46.7, 36.6, 31.9, 29.4, 25.4, 22.8, 18.8, 14.3; IR (neat) 2929, 2857, 2360, 2340, 1722, 1652, 1456, 1316, 1250, 1152, 1060, 902 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{24}O_2$ (M^+) 224.1776, found 224.1779.

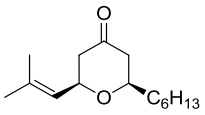


4-(3-Methylbut-2-enyloxy)dec-1-en-2-yl acetate (1.93)

To dec-1-yn-4-ol (**1.80**) (617 mg, 4.00 mmol) in 11 mL DMF at 0 °C was added NaH (60%, dispersed in mineral oil, 320 mg) in one portion. The mixture was stirred at that temperature for 30 minutes before 1-bromo-3-methyl-2-butene (924 μL, 7.87 mmol) was added in. The reaction was warmed to room temperature and stirred overnight. The reaction was

then quenched by H_2O at 0 °C, followed by excess amount of EtOAc. After the organic layer was washed with brine, it was dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (1% EtOAc in hexane) to give the 4-((3-methylbut-2-en-1-yl)oxy)dec-1-yne (not very pure).

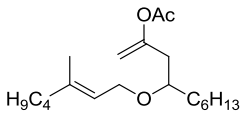
General procedure for enol acetate preparation was followed employing Na_2CO_3 (57.2 mg, 0.539 mmol), [(*p*-cymene)$RuCl_2$]$_2$ (88 mg, 0.14 mmol), tri(2-furyl)phosphine (66.8 mg, 0.288 mmol), acetic acid (824 µL, 14.4 mmol), 1-decyne (649 µL, 3.57 mmol) and 4-((3-methylbut-2-en-1-yl)oxy)dec-1-yne (from last step) in 24 mL toluene at 80 °C for 18 h. Then crude mixture was concentrated on a rotary evaporator and purified by flash chromatography (1% EtOAc in hexane) to give **1.93** (433 mg, 38% over two steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.36-5.30 (m, 1H), 4.80 (s, 2H), 4.03-3.91 (m, 2H), 3.46-3.38 (m, 1H), 2.46 (dd, *J* = 6.6, 15 Hz, 1H), 2.37 (dd, *J* = 5.7, 15 Hz, 1H), 1.74 (s, 3H), 1.67 (s, 3H), 1.52-1.28 (m, 10H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 169.3, 154.0, 136.8, 121.7, 103.6, 76.3, 65.8, 38.7, 34.4, 32.0, 29.6, 26.0, 25.5, 22.8, 21.3, 18.2, 14.3; IR (neat) 2928, 2857, 2360, 2340, 1758, 1666, 1455, 1370, 1196, 1063, 1021, 871 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{30}O_3Na$ $(M+Na)^+$ 305.2093, found 305.2089.



2-Hexyl-6-(2-methylprop-1-enyl)dihydro-2*H*-pyran-4(3*H*)-one (1.98)

The general procedure for the cyclization reaction was followed: **1.93** (66.4 mg, 0.235 mmol), 2,6-dichloropyridine (139 mg, 0.939 mmol) and 4 Å molecular sieves (120 mg) were dissolved in 2.5 mL anhydrous 1,2-dichloroethane, followed by $LiClO_4$ (2.5 mg, 0.024 mmol) and DDQ (107 mg, 0.471 mmol). The reaction was stirred for 1.5 h at 0 °C then quenched by Et_3N. The mixture was loaded onto a short plug of silica gel and washed off with dichloromethane. The filtrate was concentrated and purified by flash chromatography (40%

hexane in CH_2Cl_2 then 6% EtOAc in hexane) to give the desired product (46 mg, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.25 (dt, *J* = 1.5, 8.1 Hz, 1H), 4.36-4.23 (m, 1H), 3.62 (ddt, *J* = 2.7, 6.9, 14.4 Hz, 1H), 2.43-2.33 (m, 3H), 2.29-2.20 (m, 1H), 1.76 (d, *J* = 0.9 Hz, 3H), 1.69 (d, *J* = 0.9 Hz, 3H), 1.58-1.23 (m, 10H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C (75 MHz, C_6D_6) δ 205.4, 135.6, 126.3, 77.2, 74.7, 48.5, 48.3, 37.1, 32.4, 29.8, 25.9, 25.8, 23.2, 18.5, 14.6; IR (neat) 2957, 2928, 2858, 1721, 1453, 1409, 1377, 1352, 1316, 1258, 1196, 1131, 1053 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{26}O_2$ (M^+) 238.1933, found 238.1938.



(*E*)-4-(3-methylhept-2-enyloxy)dec-1-en-2-yl acetate (1.94)

To a white slurry solution of zirconocene dichloride (5.85 g, 20.0 mmol) in 50 mL of DCE was added $AlMe_3$ (20 mL, 2 M in hexanes, 40 mmol) at 0 °C. After stirring at that temperature for 45 minutes, it was warmed to room temperature for 2 h. To this lemon-yellow solution was added 1-hexyne (2.3 mL, 20 mmol) dissolved in 10 mL of DCE at room temperature. The reaction was allowed to stir at room temperature for 4.5 h. The volatile components were evaporated under reduced pressure for 1 h (maximum 50 °C, 0.3 mm Hg). The remaining orange-yellow organic residue was extracted with dry hexane (4 x 30 mL), and the yellow extract was transferred to a 500 mL round-bottom flask via a cannula. To this was added ^{n}BuLi (8 mL, 2.5 M in hexane, 20 mmol) at 0 °C. This orange-yellow slurry solution was stirred from 0 °C to room temperature for 1.5 h, and then THF (40 mL) was added to dissolve the precipitate. The resulting solution (homogeneous, brown-yellow color) was cannulated to a suspension of paraformaldehyde (3 g, 100 mmol) in THF (60 mL) under an argon atmosphere. This orange-yellow suspension was allowed to stir at room temperature for 21 h before it was cooled to 0 °C (ice-water bath). Ice was added to dilute the reaction, and then saturated NH_4Cl

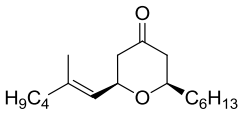
(aq) was added. The ice bath was removed, and the reaction was further acidified with 3 M HCl (aq) until the reaction turned to a clear yellow (homogeneous) solution. At this time, the reaction pH was measured 2-3. The organic layer was separated, and the aqueous layer was extracted with ether. The organic extracts were combined, washed with a saturated $NaHCO_3$ (aq), and then dried with $MgSO_4$, filtered, and concentrated under reduced pressure to provide crude allylic alcohol. The crude product was purified by flash chromatography (10% EtOAc in hexane) to afford (*E*)-3-methylhept-2-en-1-ol (1.8 g, 70% yield) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.41-5.37 (m, 1H), 4.16 (t, *J* = 5.1 Hz, 2H), 2.02 (t, *J* = 7.8 Hz, 2H), 1.67 (s, 3H), 1.46-1.19 (m, 4H), 0.91 (t, *J* = 7.2 Hz, 3H).[6]

(*E*)-3-Methylhept-2-en-1-ol (1.05 g, 8.2 mmol) was dissolved in Et_2O, and PBr_3 (386 uL, 4.10 mmol) was added dropwise at 0 °C. The reaction was stirred at that temperature for 4 h, and poured into ice (10 g). The mixture was extracted three times with Et_2O, and combined organic layers were washed with saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude (*E*)-1-bromo-3-methylhept-2-ene, which was used as such. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.54 (dt, *J* = 1.2, 8.4 Hz, 1H), 4.04 (d, *J* = 8.4 Hz, 2H), 2.06 (t, *J* = 7.2 Hz, 2H), 1.73 (d, *J* = 0.6 Hz, 3H), 1.48-1.19 (m, 4H), 0.91 (t, *J* = 7.2 Hz, 3H).[7]

To **1.80** (771 mg, 5.00 mmol) in 10 mL DMF at 0 °C was added NaH (60%, dispersed in mineral oil, 400 mg) in one portion. The mixture was stirred at the same temperature for 30 minutes, and then the crude (*E*)-1-bromo-3-methylhept-2-ene from last step was added in. The reaction was allowed to warm to room temperature and stirred overnight. The reaction was then quenched by H_2O at 0 °C, followed by excess amount of EtOAc. After the organic layer was washed with brine, it was dried over $MgSO_4$, filtrated and concentrated. The resulting residue was purified by

flash chromatography (1% EtOAc in hexane) to give (*E*)-4-((3-methylhept-2-en-1-yl)oxy)dec-1-yne (not very pure).

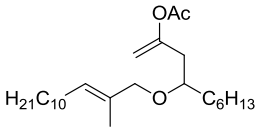
General procedure for enol acetate preparation was followed employing Na_2CO_3 (50.3 mg, 0.475 mmol), $[(p\text{-cymene})RuCl_2]_2$ (58.2 mg, 0.0950 mmol), tri(2-furyl)phosphine (44.1 mg, 0.190 mmol), acetic acid (363 μL, 6.34 mmol) and (*E*)-4-((3-methylhept-2-en-1-yl)oxy)dec-1-yne (from last step) in 24 mL toluene at 80 °C for 18 h. Then crude mixture was concentrated on a rotary evaporator and purified by flash chromatography (1% EtOAc in hexane) to give **1.94** (957 mg, 59% over two steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.35-5.30 (m, 1H), 4.80 (s, 2H), 4.06-3.94 (m, 2H), 3.46-3.39 (m, 1H), 2.47 (dd, *J* = 6.4, 14.9 Hz, 1H), 2.37 (dd, *J* = 5.7, 14.9 Hz, 1H), 2.14 (s, 3H), 2.04-1.99 (m, 2H), 1.65 (s, 3H), 1.52-1.24 (m, 14H), 0.92-0.87 (m, 6H); ^{13}C (75 MHz, $CDCl_3$) δ 169.3, 154.0, 140.3, 121.2, 103.7, 76.3, 65.9, 39.5, 38.7, 34.4, 32.1, 30.1, 29.6, 25.6, 22.8, 22.6, 21.3, 16.6, 14.3, 14.2; IR (neat) 2955, 2927, 1758, 1664, 1455, 1368, 1194, 1087, 1056, 1019 cm^{-1}; HRMS(ESI) calcd for $C_{20}H_{36}O_3Na$ $(M+Na)^+$ 347.2562, found 347.2566.



2-Hexyl-6-((*E*)-2-methylhex-1-enyl)dihydro-2*H*-pyran-4(3*H*)-one (1.99)

The general procedure for the cyclization reaction was followed: **1.94** (45 mg, 0.14 mmol), 2,6-dichloropyridine (82 mg, 0.56 mmol) and 4 Å molecular sieves (90 mg) were dissolved in 1.5 mL anhydrous 1,2-dichloroethane, followed by $LiClO_4$ (1.5 mg, 0.014 mmol) and DDQ (63 mg, 0.28 mmol). The reaction was stirred for 1 h at 0 °C before quenched by Et_3N. The mixture was loaded onto a short plug of silica gel and washed off with dichloromethane. The filtrate was concentrated and purified by flash chromatography (40% hexane in CH_2Cl_2 then 6% EtOAc in hexane) to give the desired product (32.1 mg, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.25 (ddd, *J* = 1.2, 2.4, 7.6 Hz, 1H), 4.35-4.27 (m, 1H), 3.62 (ddt, *J* =

2.6, 7.0, 14.4 Hz, 1H), 2.41-2.33 (m, 3H), 2.29-2.20 (m, 1H), 1.67 (d, *J* = 1.2 Hz, 3H), 2.03 (t, *J* = 7.1 Hz, 2H), 1.55-1.28 (m, 14H), 0.93-0.86 (m, 6H); ^{13}C (75 MHz, $CDCl_3$) δ 207.9, 141.2, 124.2, 74.5, 48.3, 48.1, 39.3, 36.7, 32.0, 30.0, 29.4, 25.5, 22.8, 22.6, 17.1, 14.3, 14.2; IR (neat) 2955, 2927, 2858, 1720, 1455, 1353, 1315, 1255, 1050 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{32}O_2$ (M^+) 280.2402, found 280.2403.

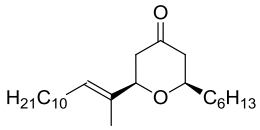


(*E*)-4-(2-Methyltridec-2-enyloxy)dec-1-en-2-yl acetate (1.95)

To **1.80** (394 mg, 2.55 mmol) in 8 mL DMF at 0 °C was added NaH (60%, dispersed in mineral oil, 400 mg) in one portion. The mixture was stirred at the same temperature for 30 minutes, and then (*E*)-1-bromo-2-methyltridec-2-ene[7] (914 mg, 3.32 mmol) was added in. The reaction was allowed to warm to room temperature and stirred overnight. The reaction was then quenched by H_2O at 0 °C, followed by excess amount of EtOAc. After the organic layer was washed with brine, it was dried over $MgSO_4$, filtrated and concentrated. The resulting residue was purified by flash chromatography (20% CH_2Cl_2 in hexane) to give (*E*)-1-(dec-1-yn-4-yloxy)-2-methyltridec-2-ene (390 mg, 44%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.44-5.39 (m, 1H), 3.96 (d, *J* = 11.2 Hz, 1H), 3.85 (d, *J* = 11.2 Hz, 1H), 3.46-3.38 (m, 1H), 2.47-2.31 (m, 2H), 2.06-2.02 (m, 2H), 1.99 (t, *J* = 2.6 Hz, 1H), 1.67 (s, 3H), 1.62-1.59 (m, 2H), 1.29-1.27 (m, 24H), 0.91-0.87 (m, 6H); ^{13}C (75 MHz, $CDCl_3$) δ 132.4, 129.2, 81.7, 76.5, 75.9, 69.9, 34.1, 32.1, 32.0, 31.8, 29.9, 29.8, 29.7, 29.58, 29.56, 29.5, 27.9, 25.5, 23.9, 22.9, 22.8, 14.3 14.28; IR (neat) 3314, 2925, 2855, 1462, 1343, 1062 cm^{-1}; HRMS (EI) calcd for $C_{24}H_{44}O$ (M^+) 348.3392, found 348.3386.

General procedure for enol acetate preparation was followed employing Na_2CO_3 (17.8 mg, 0.168 mmol), [(*p*-cymene)$RuCl_2$]$_2$ (20.5 mg, 0.0335 mmol), tri(2-furyl)phosphine (15.6 mg, 0.0672

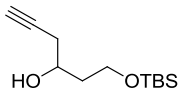
mmol), acetic acid (128 μL, 2.24 mmol) and (*E*)-1-(dec-1-yn-4-yloxy)-2-methyltridec-2-ene (390 mg, 1.12 mmol) in 12 mL toluene at 80 °C for 15 h. Then crude mixture was concentrated on a rotary evaporator and purified by flash chromatography (2% Et_2O in hexane) to give **1.95** (234 mg, 51%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.42-5.37 (m, 1H), 4.79 (s, 2H), 3.88 (d, *J* = 11.0 Hz, 1H), 3.81 (d, *J* = 11.0 Hz, 1H), 3.45-3.38 (m, 1H), 2.47 (dd, *J* = 6.2, 14.9 Hz, 1H), 2.37 (dd, *J* = 5.8, 14.9 Hz, 1H), 2.13 (s, 3H), 2.05-1.98 (m, 2H), 1.65 (s, 3H), 1.52-1.27 (m, 26H), 0.98-0.86 (m, 6H); ^{13}C (75 MHz, $CDCl_3$) δ 169.2, 154.0, 132.5, 128.9, 103.7, 75.9, 75.7, 38.5, 34.2, 32.1, 32.0, 29.9, 29.8, 29.7, 29.6, 29.57, 29.55, 27.9, 25.5, 22.9, 22.8, 21.3, 14.3, 14.27; IR (neat) 2925, 2855, 1760, 1666, 1461, 1369, 1195, 1062, 1021, 869 cm^{-1}; HRMS (EI) calcd for $C_{26}H_{48}O_3$ (M^+) 408.3603, found 408.3604.



2-Hexyl-6-((*E*)-tridec-2-en-2-yl)dihydro-2*H*-pyran-4(3*H*)-one (1.100)

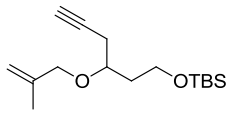
The general procedure for the cyclization reaction was followed: **1.95** (53.7 mg, 0.131 mmol), 2,6-dichloropyridine (77.8 mg, 0.526 mmol) and 4 Å molecular sieves (110 mg) were dissolved in 1.4 mL anhydrous 1,2-dichloroethane, followed by $LiClO_4$ (1.4 mg, 0.013 mmol) and DDQ (59.7 mg, 0.263 mmol). The reaction was stirred for 1 h at 0 °C and then quenched by Et_3N. The mixture was loaded onto a short plug of silica gel and washed off with dichloromethane. The filtrate was concentrated and purified by flash chromatography (40% hexane in CH_2Cl_2 then 6% EtOAc in hexane) to give the desired product (40.7 mg, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.45 (t, *J* = 7.0 Hz, 1H), 3.93 (dd, *J* = 2.4, 11.0 Hz, 1H), 3.60 (ddt, *J* = 2.6, 6.8, 14.1 Hz, 1H), 2.50-2.32 (m, 3H), 2.28-2.20 (m, 1H), 2.07-2.00 (m, 2H), 1.68 (s, 3H), 1.64-1.27 (m, 26H), 0.89 (m, 6H); ^{13}C (75 MHz, C_6D_6) δ 205.4, 134.7, 126.9, 82.0, 77.0, 48.0, 47.0, 36.8, 32.4, 32.2, 30.1, 30.0, 29.9, 29.8, 29.79, 29.6, 27.9, 25.6, 23.2, 23.0, 14.4, 14.3, 12.3;

IR (neat) 2925, 2854, 1721, 1459, 1337, 1250, 1150, 1052 cm^{-1}; HRMS (EI) calcd for $C_{24}H_{44}O_2$ (M^+) 364.3341, found 364.3335.



1-(*tert*-Butyldimethylsilyloxy)hex-5-yn-3-ol (1.106)

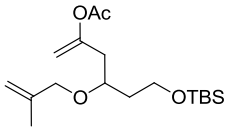
The 3-(*tert*-butyldimethylsilyloxy)propanal (7.89 g, 41.9 mmol), zinc powder (13.7 g, 209 mmol), 1,2-diiodoethane (11.8 g, 41.9 mmol) and 3-bromo-1-propyne (9.35 g, 62.9 mmol, 80% wt in toluene) were mixed in a 250 mL RBF with 130 mL anhydrous THF. The reaction was sonicated for 1 h, and then filtered through a short pad of celite with EtOAc, and concentrated. Then Et_2O was added, and the mixture was filtered. The organic mixture was concentrated and purified by chromatography (5% to 10% EtOAc in hexane) to give **1.106** (4.7 g, 49%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.55-3.80 (m, 3H), 3.61 (d, *J* = 3.0 Hz, 1H), 2.50-2.31 (m, 2H), 2.03 (t, *J* = 2.7 Hz, 1H), 1.88-1.70 (m, 2H), 0.90 (s, 9H), 0.09 (s, 6H).[8]



***tert*-Butyldimethyl(3-(2-methylallyloxy)hex-5-ynyloxy)silane (1.107)**

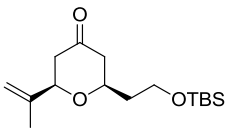
To 1-(*tert*-Butyldimethylsilyloxy)hex-5-yn-3-ol **(1.106)** (411 mg, 1.80 mmol) in 6 mL DMF at 0 °C was added NaH (60%, dispersed in mineral oil, 108 mg) in one portion. The mixture was stirred at that temperature for 30 minutes before 3-chloro-2-methyl-1-propene (317 μL , 3.20 mmol) was added in. The reaction was warmed to room temperature and stirred overnight. The reaction was then quenched by H_2O at 0 °C, followed by excess amount of EtOAc. After the organic layer was washed with brine, it was dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (4% Et_2O in hexane) to give **1.107** (360 mg, 71%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.98 (s, 1H), 4.88 (s, 1H), 4.02 (d, *J* = 12.2 Hz, 1H), 3.89 (d, *J* = 12.3 Hz, 1H), 3.79-3.67 (m,

3H), 2.52-2.34 (m, 2H), 2.00 (t, J = 2.7 Hz, 1H), 1.88-1.79 (m, 2H), 1.77 (s, 3H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C (75 MHz, $CDCl_3$) δ 142.7, 112.5, 81.4, 74.2, 73.7, 70.2, 59.6, 37.4, 26.1, 24.1, 19.8, 18.5, -5.12, -5.16; IR (neat) 3312, 2953, 2926, 2855, 1462, 1254, 1097, 835, 775 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{27}O_2Si$ $(M-C_3H_3)^+$ 243.1780, found 243.1784.



6-(*tert*-Butyldimethylsilyloxy)-4-(2-methylallyloxy)hex-1-en-2-yl acetate (1.101)

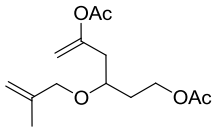
General procedure for enol acetate preparation was followed employing Na_2CO_3 (20.2 mg, 0.191 mmol), [(*p*-cymene)$RuCl_2$]$_2$ (31 mg, 0.051 mmol), tri(2-furyl)phosphine (23.6 mg, 0.102 mmol), acetic acid (290 μL, 5.07 mmol), 1-decyne (160 μL, 0.886 mmol) and **1.107** (360 mg, 1.27 mmol) in 12 mL toluene at 80 °C for 11 h. Then crude mixture was concentrated on a rotary evaporator and purified by flash chromatography (2% EtOAc in hexane) to give **1.101** (274 mg, 63%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.95 (s, 1H), 4.86 (s, 1H), 4.81 (s, 2H), 3.95 (d, J = 12.0 Hz, 1H), 3.85 (d, J = 12.0 Hz, 1H) 3.75-3.64 (m, 3H), 2.55-2.38 (m, 2H), 2.12 (s, 3H), 1.77-1.71 (m, 5H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C (75 MHz, $CDCl_3$) δ 169.3, 153.7, 142.8, 112.2, 103.9, 73.6, 73.4, 59.6, 38.5, 37.6, 26.1, 26.0, 21.3, 19.9, 18.4, -5.1, -5.2; IR (neat) 2929, 2858, 1759, 1650, 1254, 1200, 1095, 1019, 836, 775 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{34}O_4SiNa$ $(M+Na)^+$ 365.2124, found 365.2123.



2-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-6-(prop-1-en-2-yl)dihydro-2*H*-pyran-4(3*H*)-one (1.115)

The general procedure for the cyclization reaction was followed: **1.101** (59 mg, 0.17 mmol), 2,6-dichloropyridine (103 mg, 0.696 mmol) and 4 Å molecular sieves (78 mg) were dissolved in 1.7

mL anhydrous DCE followed by $LiClO_4$ (1.8 mg, 0.017 mmol) and DDQ (157 mg, 0.692 mmol). The reaction was stirred for 24 h at room temperature and then quenched by Et_3N. The mixture was loaded onto a short plug of silica gel and washed off with dichloromethane. The filtrate was concentrated and purified by flash chromatography (10% EtOAc in hexane) to give the desired product (38.9 mg, 75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.01 (s, 1H), 4.92-4.91 (m, 1H), 3.99 (dd, *J* = 3.3, 10.6 Hz, 1H), 3.87-3.72 (m, 3H), 2.50-2.27 (m, 4H), 1.93-1.82 (m, 1H), 1.79 (s, 3H), 1.78-1.71 (m, 1H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C (75 MHz, $CDCl_3$) δ 207.7, 144.2, 111.7, 79.7, 73.8, 59.2, 48.1, 46.7, 39.5, 26.1, 18.7, 18.5, -5.1, -5.2; IR (neat) 2954, 2929, 2858, 1724, 1469, 1388, 1362, 1325, 1254, 1145, 1096, 1027, 941, 903, 838, 777 cm^{-1}; HRMS(EI) calcd for $C_{16}H_{30}O_3Si$ (M^+) 298.1964, found 298.1969.



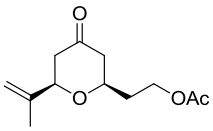
3-(2-Methylallyloxy)hex-5-ene-1,5-diyl diacetate (1.102)

To **1.107** (2.0 g, 7.2 mmol) in 25 mL THF at 0 ℃ under N_2 was added TBAF (1 M in THF, 21.7 mL) dropwise. After stirring at room temperature for 4 h, the mixture was concentrated and purified by flash chromatography (30% EtOAc in hexane) to afford 3-((2-methylallyl)oxy)hex-5-yn-1-ol (**1.108**).

To a solution of **1.108** (300 mg, 1.78 mmol) and DMAP (10.9 mg, 0.0892 mmol) in 6.5 mL DCM was added Et_3N (1.49 mL, 10.7 mmol) and Ac_2O (2.52 mL, 26.7 mmol) at 0 °C. The mixture was stirred at room temperature for 3 h. Then it was poured into H_2O, and extracted with DCM. Organic layer was washed with brine and dried over $MgSO_4$. The crude mixture was concentrated and purified by flash chromatography (10% EtOAc in hexane) to give 3-(2-methylallyloxy)hex-5-ynyl acetate (365 mg, 97%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.97 (s, 1H), 4.89 (s, 1H), 4.23-4.18 (m, 2H), 4.01 (d, *J* = 12.1 Hz, 1H), 3.87 (d, *J* = 12.1 Hz, 1H), 3.63-3.58

(m, 1H), 2.53-2.37 (m, 2H), 2.05 (s, 3H), 2.03-1.89 (m, 3H), 1.75 (s, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 171.2, 142.3, 112.8, 80.7, 74.1, 73.7, 70.6, 61.4, 33.3, 23.9, 21.2, 19.8; IR (neat) 3294, 2919, 1739, 1657, 1454, 1369, 1242, 1105, 1047, 903 cm^{-1}; HRMS (EI) calcd for $C_9H_{15}O_3$ $(M-C_3H_3)^+$ 171.1021, found 171.1028.

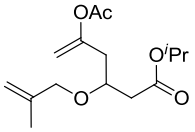
General procedure for enol acetate preparation was followed employing Na_2CO_3 (27.6 mg, 0.260 mmol), [(*p*-cymene)$RuCl_2$]$_2$ (42.5 mg, 0.0694 mmol), tri(2-furyl)phosphine (32.2 mg, 0.139 mmol), acetic acid (398 μL, 6.95 mmol), 1-decyne (219 μL, 1.15 mmol) and 3-(2-methylallyloxy)hex-5-ynyl acetate (365 mg, 1.74 mmol) in 12 mL toluene at 80 °C for 18 h. Then crude mixture was concentrated on a rotary evaporator and purified by flash chromatography (10% EtOAc in hexane) to give **1.102** (360 mg, 77%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.94 (s, 1H), 4.87 (s, 1H), 4.82 (t, *J* = 2.0 Hz, 2H), 4.20-4.15 (m, 2H), 3.94 (d, *J* = 12.0 Hz, 1H), 3.82 (d, *J* = 11.9 Hz, 1H) 3.61-3.57 (m, 1H), 2.54 (dd, *J* = 5.8, 14.9 Hz, 1H), 2.41 (dd, *J* = 6.2, 14.9 Hz, 1H), 2.13 (s, 3H), 2.04 (s, 3H), 1.95-1.81 (m, 2H), 1.73 (s, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 171.2, 169.2, 153.1, 142.4, 112.6, 104.3, 73.5, 73.4, 61.5, 38.3, 33.3, 21.3, 21.2, 19.8; IR (neat) 2926, 1740, 1665, 1434, 1369, 1239, 1199, 1102, 1045, 1022, 966, 901 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{22}O_5Na$ $(M+Na)^+$ 293.1365, found 293.1358.



2-(4-Oxo-6-(prop-1-en-2-yl)tetrahydro-2*H*-pyran-2-yl)ethyl acetate (1.116)

The general procedure for the cyclization reaction was followed: **1.102** (67 mg, 0.25 mmol), 2,6-dichloropyridine (146 mg, 0.987 mmol) and 4 Å molecular sieves (100 mg) were dissolved in 2.5 mL anhydrous 1,2-dichloroethane followed by $LiClO_4$ (2.6 mg, 0.025 mmol) and DDQ (225 mg, 0.991 mmol). The reaction was stirred for 30 h at room temperature and then quenched by Et_3N.

The mixture was loaded onto a short plug of silica gel and washed off with dichloromethane. The filtrate was concentrated and purified by flash chromatography (2% EtOAc in hexane) to give the desired product (40.7 mg, 73%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.01 (d, J = 0.81 Hz, 1H), 4.92 (d, J = 0.63 Hz, 1H), 4.28-4.22 (m, 2H), 4.00 (dd, J = 3.3, 10.7 Hz, 1H), 3.82-3.76 (m, 1H), 2.51-2.27 (m, 4H), 2.05 (s, 3H), 2.03-1.84 (m, 2H), 1.78 (s, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 206.9, 171.2, 143.9, 111.9, 79.8, 74.0, 61.0, 47.9, 46.6, 35.5, 21.2, 18.7; IR (neat) 2969, 2919, 2856, 1736, 1653, 1452, 1368, 1233, 1150, 1127, 1048, 904 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{18}O_4Na$ $(M+Na)^+$ 249.1103, found 249.1127.



Isopropyl 5-acetoxy-3-(2-methylallyloxy)hex-5-enoate (1.103)

To a solution of alcohol **1.108** (570 mg, 3.40 mmol) in CH_2Cl_2 (8 mL) was added DMSO (4.8 mL) and Et_3N (1.4 mL, 10.2 mmol) at 0 °C, followed by the addition of SO_3•Py complex (809 mg, 5.08 mmol). The mixture was stirred at room temperature for 3.5 h, before it was quenched by H_2O, and extracted with Et_2O. The combined organic layers were washed with H_2O and dried over $MgSO_4$. After filtration and concentration, it was purified by flash chromatography (10% EtOAc in hexane) to give desired aldehyde **1.110** (>507 mg, >90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.83 (t, J = 1.8 Hz, 1H), 4.97 (s, 1H), 4.90 (s, 1H), 4.07-3.89 (m, 3H), 2.78 (dd, J = 1.8, 6.2 Hz, 2H), 2.61-2.42 (m, 2H), 2.04 (t, J = 2.7 Hz, 1H), 1.73 (s, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 200.8, 142.0, 113.1, 80.1, 73.8, 72.5, 71.3, 48.1, 23.9, 19.7; IR (neat) 3292, 3078, 2975, 2915, 2850, 2731, 1724, 1659, 1454, 1431, 1346, 1297, 1229, 1184, 1102, 1051, 904 cm^{-1}; HRMS(EI) calcd for $C_7H_{11}O_2$ $(M-C_3H_3)^+$ 127.0759, found 127.0761.

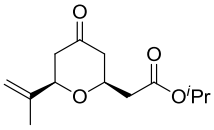
To a solution of **1.110** (from last step) and 2-methyl-2-butene (11.9 g, 169 mmol) in 15 mL ^{t}BuOH at 0 °C was added a solution of $NaClO_2$ (2.76 g, 30.5 mmol) and NaH_2PO_4•H_2O (3.28 g,

23.7 mmol) in 10 mL H_2O dropwise. The mixture was warmed to room temperature for 5 h before acidification the reaction to PH~4. The mixture was extracted with EtOAc, and the combined organic layers were washed with brine and dried over $MgSO_4$. After filtration and concentration, the crude acid was used as such for next step.

To a solution of the carboxylic acid from last step, DCC (2.1 g, 10 mmol) and DMAP (83 mg, 0.68 mmol) in DCM at room temperature was added ^{i}PrOH (519 uL, 6.80 mmol) dropwise. After 10 minutes, the reaction was quenched by H_2O and the mixture was extracted with DCM. Combined organic phase was washed with brine, and dried over $MgSO_4$. The crude mixture was concentrated and purified by flash chromatography (3% EtOAc in hexane) to give isopropyl 3-(2-methylallyloxy)hex-5-ynoate (410 mg, 54% over three steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.06-5.00 (m, 1H), 4.96 (s, 1H), 4.87 (s, 1H), 4.02-3.90 (m, 3H), 2.71-2.56 (m, 2H), 2.55-2.40 (m, 2H), 2.03-2.01 (m, 1H), 1.73 (s, 3H), 1.25 (s, 3H), 1.23 (s, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 171.0, 142.2, 112.8, 80.4, 74.2, 74.0, 70.8, 68.1, 39.9, 23.9, 22.0, 21.9, 19.7; IR (neat) 3296, 2981, 2934, 2119, 1731, 1455, 1375, 1310, 1263, 1215, 1163, 1108, 968, 901 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{20}O_3$ (M^+) 224.1412, found 224.1421.

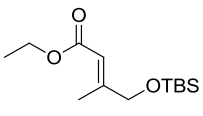
General procedure for enol acetate preparation was followed employing Na_2CO_3 (29 mg, 0.27 mmol), [(*p*-cymene)$RuCl_2$]$_2$ (44.8 mg, 0.0732 mmol), tri(2-furyl)phosphine (34 mg, 0.15 mmol), acetic acid (418 μL, 7.30 mmol), 1-decyne (231 μL, 1.28 mmol) and isopropyl 3-(2-methylallyloxy)hex-5-ynoate (410 mg, 1.83 mmol) in 12 mL toluene at 80 °C for 18 h. Then crude mixture was concentrated on a rotary evaporator and purified by flash chromatography (10% EtOAc in hexane) to give the isopropyl 5-acetoxy-3-(2-methylallyloxy)hex-5-enoate (260 mg, 50%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.06-4.98 (m, 1H), 4.95 (s, 1H), 4.86 (s, 1H), 4.84-4.82 (m, 2H), 3.99-3.85 (m, 3H), 2.60-2.41 (m, 4H), 2.14 (d, J = 1.7 Hz, 3H), 1.72 (s, 3H), 1.25

(s, 3H), 1.23 (s, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 171.0, 169.2, 152.9, 142.3, 112.4, 104.5, 73.9, 73.7, 68.1, 40.0, 38.4, 22.0, 21.9, 21.3, 19.7; IR (neat) 2981, 2936, 1758, 1731, 1666, 1454, 1372, 1193, 1108, 1045, 1022, 967, 899 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{24}O_5Na$ $(M+Na)^+$ 307.1521, found 307.1516.



Isopropyl 2-(4-oxo-6-(prop-1-en-2-yl)tetrahydro-2*H*-pyran-2-yl)acetate (1.117)

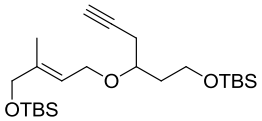
The general procedure for the cyclization reaction was followed: **1.103** (54 mg, 0.19 mmol), 2,6-dichloropyridine (113 mg, 0.764 mmol) and 4 Å molecular sieves (80 mg) were dissolved in 1.8 mL anhydrous 1,2-dichloroethane followed by $LiClO_4$ (2.0 mg, 0.019 mmol) and DDQ (173 mg, 0.762 mmol). The reaction was stirred for 12 h at 45 °C and then quenched by Et_3N. The mixture was loaded onto a short plug of silica gel and washed off with dichloromethane. The filtrate was concentrated and purified by flash chromatography (15% EtOAc in hexane) to give the desired product (35.2 mg, 77%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.11-5.02 (m, 1H), 5.00 (s, 1H), 4.91 (s, 1H), 4.16-4.07 (m, 1H), 4.06-4.02 (m, 1H), 2.70 (dd, *J* = 7.4, 15.2 Hz, 1H), 2.52 (dd, *J* = 5.4, 15.2 Hz, 1H), 2.47-2.31 (m, 4H), 1.77 (s, 3H), 1.25 (d, *J* = 1.5 Hz, 3H), 1.23 (d, *J* = 1.5 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 206.4, 169.9, 143.8, 112.0, 79.6, 73.6, 68.4, 47.2, 46.2, 41.8, 22.0, 21.9, 18.7; IR (neat) 2980, 1727, 1654, 1453, 1373, 1320, 1253, 1218, 1182, 1108, 1077, 964, 903, 828 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{20}O_4$ (M^+) 240.1362, found 240.1364.



(*E*)-Ethyl 4-(*tert*-butyldimethylsilyloxy)-3-methylbut-2-enoate (1.112)

To NaH (702 mg, 17.6 mmol, 60% in mineral oil) suspended in 40 mL THF at 0 °C was added triethyl phosphonoacetate (3.32 mL, 16.3 mmol) dropwise. After stirring at 0 °C

for 1 h until the end of hydrogen formation, ketone (2.45 g, 13.0 mmol) in 8 mL THF was added slowly. After another 1 h at room temperature, it was poured onto H_2O and extracted with Et_2O. Combined organic phase was washed with brine, and dried over $MgSO_4$. The crude mixture was concentrated and purified by flash chromatography (3% Et_2O in hexane) to give desired product (2.8 g, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.99 (s, 1H), 4.16 (q, J = 7.2 Hz, 2H), 4.11 (s, 2H), 2.05 (s, 3H), 1.28 (t, J = 6.9 Hz, 3H), 0.92 (s, 9H), 0.08 (s, 6H).[9]

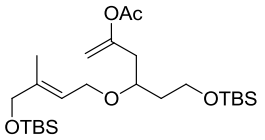


(*E*)-2,2,3,3,11,14,14,15,15-Nonamethyl-7-(prop-2-ynyl)-4,8,13-trioxa-3,14-disilahexadec-10-ene (1.114)

To a solution of **1.112** (982 mg, 3.80 mmol) in 5 mL toluene at –78 ℃ was added DIBAL-H (1 M in hexane, 8.4 mL) dropwise. After stirring at room temperature for 5 h, the reaction was cooled to 0 ℃ and quenched by saturated NH_4Cl (aq). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. Combined organic layers were dried over $MgSO_4$. After filtration and concentration, crude (*E*)-4-((tert-butyldimethylsilyl)oxy)-3-methylbut-2-en-1-ol was obtained which was used as such for next step.

To a solution of (*E*)-4-((tert-butyldimethylsilyl)oxy)-3-methylbut-2-en-1-ol (from last step) and Et_3N (726 μL, 5.21 mmol) in 20 mL CH_2Cl_2 at –40 ℃ was added MsCl (364 μL, 4.70 mmol) dropwise. After 30 minutes at that temperature, LiBr (938 mg, 10.8 mmol) was added in one portion followed by 20 mL THF. After stirring at 0 ℃ for 1.5 h, the reaction was diluted with hexane and washed with H_2O and brine. The mixture was dried over $MgSO_4$, filtrated and concentrated to afford crude (*E*)-((4-bromo-2-methylbut-2-en-1-yl)oxy)(tert-butyl)dimethylsilane for next step.

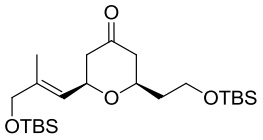
To 1-(*tert*-Butyldimethylsilyloxy)hex-5-yn-3-ol **(1.106)** (822 mg, 3.60 mmol) in 4 mL DMF and 10 mL THF at 0 °C was added NaH (60%, dispersed in mineral oil, 259 mg) in one portion. The mixture was stirred at that temperature for 30 minutes before (*E*)-((4-bromo-2-methylbut-2-en-1-yl)oxy)(tert-butyl)dimethylsilane from last step was added in. The reaction was warmed to room temperature and stirred for 27 h. The reaction was then quenched by H_2O at 0 °C, followed by excess amount of EtOAc. After the organic layer was washed with brine, it was dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (3% EtOAc in hexane) to give desired **1.114** (859 mg, 49% over three steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.62 (t, *J* = 6.0 Hz, 1H), 4.24-4.18 (m, 1H), 4.06-4.00 (m, 3H), 3.77-3.61 (m, 3H), 2.46-2.42 (m, 2H), 2.00 (t, *J* = 2.4 Hz, 1H), 1.87-1.77 (m, 2H), 1.65 (s, 3H), 0.92-0.86 (m, 18H), 0.10-0.05 (m, 12H); ^{13}C (75 MHz, $CDCl_3$) δ 138.8, 120.9, 81.4, 77.4, 74.1, 70.1, 68.1, 65.9, 59.6, 37.5, 26.1, 24.2, 18.6, 18.5, 13.9, -5.1; IR (neat) 2954, 2929, 2886, 2857, 1472, 1254, 1100, 836, 775 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{46}O_3Si_2Na$ $(M+Na)^+$ 449.2883, found 449.2877.



(*E*)-6-(*tert*-Butyldimethylsilyloxy)-4-(4-(*tert*-butyldimethylsilyloxy)-3-methylbut-2-enyloxy)hex-1-en-2-yl acetate (1.104)

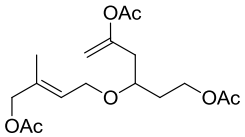
General procedure for enol acetate preparation was followed employing Na_2CO_3 (31.6 mg, 0.298 mmol), [(*p*-cymene)$RuCl_2$]$_2$ (48.7 mg, 0.0795 mmol), tri(2-furyl)phosphine (36.9 mg, 0.159 mmol), acetic acid (454 μL, 7.93 mmol), 1-decyne (250 μL, 1.39 mmol) and **1.114** (848 mg, 1.99 mmol) in 13 mL toluene at 80 °C for 13 h. Then crude mixture was concentrated on a rotary evaporator and purified by flash chromatography (4% EtOAc in hexane) to give the desired product (397 mg, 41%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.61-5.57 (m, 1H), 4.80 (s, 2H), 4.15-

3.97 (m, 4H), 3.77-3.71 (m, 3H), 2.53-2.35 (m, 2H), 2.12 (s, 3H), 1.75-1.68 (m, 2H), 1.63 (s, 3H), 0.91 (s, 9H), 0.89 (s, 9H), 0.06 (s, 6H), 0.05 (s, 6H); ^{13}C (75 MHz, $CDCl_3$) δ 169.3, 153.7, 138.6, 120.9, 103.8, 73.4, 68.1, 65.8, 59.6, 38.7, 37.7, 26.1, 21.3, 18.6, 18.4, 13.8, -5.1, -5.2; IR (neat) 2931, 2858, 1760, 1666, 1469, 1435, 1368, 1254, 1202, 1097, 963, 940, 838, 777 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{50}O_5Si_2Na$ $(M+Na)^+$ 509.3095, found 509.3102.



2-((*E*)-3-(*tert*-Butyldimethylsilyloxy)-2-methylprop-1-enyl)-6-(2-(*tert*-butyldimethylsilyloxy)ethyl)dihydro-2*H*-pyran-4(3*H*)-one (1.118)

The general procedure of cyclization reaction was followed: **1.104** (54.4 mg, 0.112 mmol), 2,6-dichloropyridine (66.2 mg, 0.447 mmol) and 4 Å molecular sieves (80 mg) were dissolved in 1.1 mL anhydrous 1,2-dichloroethane, followed by $LiClO_4$ (1.2 mg, 0.011 mmol) and DDQ (50.7 mg, 0.223 mmol). The reaction was stirred for 45 minutes at room temperature before quenched by Et_3N. The mixture was loaded onto a short plug of silica gel and washed off with dichloromethane. The filtrate was concentrated and purified by flash chromatography (10% EtOAc in hexane) to give the desired product **1.118** (22.4 mg, 45%) and aldehyde **1.119** (16.2 mg, 38%). ^1H NMR (300 MHz, $CDCl_3$) δ 5.52 (dd, J = 1.2, 7.8 Hz, 1H), 4.36 (dd, J = 8.4, 14.7 Hz, 1H), 4.04 (s, 2H), 3.88-3.67 (m, 3H), 2.43-2.90 (m, 4H), 1.91-1.71 (m, 2H), 1.64 (s, 3H), 0.89 (s, 9H), 0.92(s, 9H), 0.09 (s, 6H), 0.06 (s, 6H).

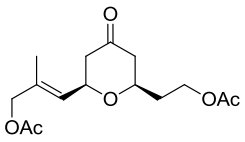


(*E*)-3-(4-Acetoxy-3-methylbut-2-enyloxy)hex-5-ene-1,5-diyl diacetate (1.105)

A solution of **1.118** (260 mg, 0.587 mmol) in 5 mL MeOH was added 3% HCl in MeOH (15 mL) at 0 °C. After 25 min at that temperature, the reaction was quenched by saturated $NaHCO_3$

(aq), and extracted with EtOAc for 4 times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated and concentrated to afford crude (*E*)-6-hydroxy-4-((4-hydroxy-3-methylbut-2-en-1-yl)oxy)hex-1-en-2-yl acetate for next step.

To (*E*)-6-hydroxy-4-((4-hydroxy-3-methylbut-2-en-1-yl)oxy)hex-1-en-2-yl acetate from last step and DMAP (3.3 mg, 0.027 mmol) in 5 mL CH_2Cl_2 at 0 °C was added pyridine (260 μL, 3.23 mmol) and Ac_2O (760 μL, 8.05 mmol). After stirring at room temperature for 3 h, the reaction was quenched by H_2O, and the mixture was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with H_2O, brine, and dried over $MgSO_4$. After filtration and concentration, the residue was purified by flash chromatography (30% EtOAc in hexane) to give the desired product (131 mg, 71% over two steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.62-5.57 (m, 1H), 4.84-4.82 (m, 2H), 4.49 (s, 2H), 4.21-4.15 (m, 2H), 4.13-3.97 (m, 2H), 3.61-3.52 (m, 1H), 2.56-2.36 (m, 2H), 2.15 (s, 3H), 2.09 (s, 3H), 2.06 (s, 3H), 1.96-1.75 (m, 2H), 1.70 (s, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 171.2, 171.0, 169.2, 153.1, 134.2, 124.8, 104.4, 73.8, 69.1, 65.6, 61.4, 38.6, 33.5, 21.3, 21.2, 21.1, 14.4; IR (neat) 2925, 1739, 1667, 1436, 1370, 1230, 1049 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{26}O_7Na$ $(M+Na)^+$ 365.1576, found 365.1579.



2-((2*R*,6*R*)-6-((*E*)-3-Acetoxy-2-methylprop-1-enyl)-4-oxotetrahydro-2*H*-pyran-2-yl)ethyl acetate (1.120)

The general procedure for the cyclization reaction was followed: **1.105** (31 mg, 0.091 mmol), 2,6-dichloropyridine (53.6 mg, 0.362 mmol) and 4 Å molecular sieves (50 mg) were dissolved in 0.9 mL anhydrous 1,2-dichloroethane, followed by $LiClO_4$ (1.0 mg, 0.0095 mmol) and DDQ (82.2 mg, 0.362 mmol). The reaction was stirred for 5.5 h at 40 °C then quenched by Et_3N. The mixture was loaded onto a short plug of silica gel and washed off with dichloromethane. The

filtrate was concentrated and purified by flash chromatography (30% EtOAc in hexane) to give the desired product (21.6 mg, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.53 (ddd, *J* = 1.2, 2.7, 7.5 Hz, 1H), 4.49 (s, 2H), 4.37 (dd, *J* = 7.5, 14.4 Hz, 1H), 4.29-4.16 (m, 2H), 3.83-3.74 (m, 1H), 2.44-2.31 (m, 4H), 2.10 (s, 3H), 2.05 (s, 3H),2.00-1.82 (m, 2H), 1.71 (d, *J* = 1.2 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 206.2, 171.2, 170.9, 134.7, 127.0, 77.4, 74.2, 73.9, 68.6, 60.9, 47.8, 47.6, 35.5, 21.1, 14.7; IR (neat) 2922, 1737, 1370, 1320, 1232, 1148, 1055, 887 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{22}O_6K$ $(M+K)^+$ 337.1053, found 337.1060.

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APPENDIX B

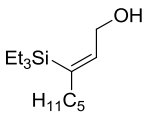
STRUCTURALLY AND STEREOCHEMICALLY DIVERSE TETRAHYDROPYRAN SYNTHESIS VIA OXIDATIVE C–H CLEAVAGE OF (SILYL)ALLYLIC AND PROPARGYLIC ETHERS

General Experimental Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on a Bruker Avance 300 spectrometer at 300 MHz and 75 MHz, a Bruker Avance 400 spectrometer at 400 MHz and 100 MHz, a Bruker Avance 500 spectrometer at 500 MHz and 125 MHz, a Bruker Avance 600 spectrometer at 600 MHz and 151 MHz if specified. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. The solvent peak was used as a reference value, for ^{1}H NMR: $CDCl_3$ = 7.26 ppm, for ^{13}C NMR: $CDCl_3$ = 77.23. Data are reported as follows: s = singlet; d = doublet; t = triplet; q = quartet; dd = doublet of doublets; dt = doublet of triplets; br = broad. High resolution and low resolution mass spectra were recorded on a VG 7070 spectrometer. Infrared (IR) spectra were collected on a Mattson Cygnus 100 spectrometer. Samples for IR were prepared as a thin film on a NaCl plate by dissolving the compound in CH_2Cl_2 and then evaporating the CH_2Cl_2. Analytical TLC was performed on E. Merck pre-coated (25 mm) silica gel 60F-254 plates. Visualization was done under UV light (254 nm). Flash chromatography was done using ICN SiliTech 32-63 60 Å silica

gel. Methylene chloride was distilled under N_2 from CaH_2, and 1,2–dichloroethane was dried over 4Å molecular sieves. Reagent grade ethyl acetate, diethyl ether, pentane and hexanes were purchased from EM Science and used as purchased for chromatography. Tetrahydrofuran and diethyl ether were dried by passage through an activated alumina column under positive N_2 pressure. Anhydrous (*N*,*N*)-dimthylformamide (DMF), methanol (MeOH), dimethyl sulfoxide (DMSO), acetone were purchased from Aldrich and used as it is. Activated 4 Å molecular sieves were obtained through drying in oven at 150 °C overnight. All reactions were performed in oven or flame-dried glassware under a positive pressure of N_2 with magnetic stirring unless otherwise noted.

General procedure for [Cp*Ru(MeCN)$_3$]PF$_6$ catalyzed alkyne hydrosilylation:[1]

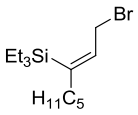
Alkyne (1 eq) and silane (1.2 eq) were dissolved in acetone to give an ~0.5 M solution. [Cp*Ru(MeCN)$_3$]PF$_6$ (0.02 eq) was added to the mixture at 0 °C. The reaction was monitored by TLC at 0 °C and, upon starting material consumption, was concentrated and purified by flash chromatography to give the (*Z*)-vinylsilane.



(*Z*)-3-(Triethylsilyl)oct-2-en-1-ol (2.43)

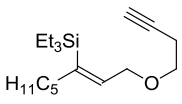
The general procedure for [Cp*Ru(MeCN)$_3$]PF$_6$ catalyzed alkyne hydrosilylation was followed: to a solution of 2-octyn-1-ol (717 μL, 5.00 mmol) in 10 mL CH_2Cl_2 was added Et_3SiH (958 μL, 6.00 mmol) and [Cp*Ru(MeCN)$_3$]PF$_6$ (25 mg, 0.050 mmol) at 0 °C. After 30 minutes at that temperature, the reaction was concentrated and the resulting residue was purified by flash chromatography (8% EtOAc in hexane) to give **2.43** (1.2 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.17 (tt, *J* = 1.1, 6.8 Hz, 1H), 4.15 (d, *J* = 6.8 Hz, 2H), 2.03 (t, *J* = 6.7 Hz, 2H), 1.84

(br, 1H), 1.37-1.23 (m, 6H), 0.98-0.86 (m, 12H), 0.67-0.61 (m, 6H); ^{13}C (100 MHz, $CDCl_3$) δ 141.4, 62.4, 38.2, 32.0, 30.4, 22.7, 14.2, 7.7, 4.5; IR (neat) 3301, 2954, 1461, 1416, 1378, 1236, 1074, 1004, 849, 731 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{30}O_2Si$ (M^+) 242.2066, found 242.2071.



(*Z*)-(1-Bromooct-2-en-3-yl)triethylsilane (2.44)

To a solution of **2.43** (1.2 g, 4.95 mmol) in 50 mL CH_2Cl_2 at 0 °C was added CBr_4 (1.8 g, 5.5 mmol) and PPh_3 (1.8 g, 6.9 mmol). After stirring at that temperature for 5 minutes, the reaction was concentrated, and the resulting residue was purified by flash chromatography (pentane) to afford **2.44** (1.53 g, 99%). ^1H NMR (400 MHz, $CDCl_3$) δ 6.24 (t, *J* = 11.4 Hz, 1H), 4.06 (d, *J* = 11.3 Hz, 2H), 2.07 (t, *J* = 8.7 Hz, 2H), 1.40-1.27 (m, 6H), 0.99-0.88 (m, 12H), 0.75-0.67 (m, 6H); ^{13}C (100 MHz, $CDCl_3$) δ 144.8, 137.8, 38.0, 32.9, 31.9, 30.1, 22.8, 14.3, 7.8, 4.4; IR (neat) 2956, 1461, 1416, 1378, 1237, 1199, 1074, 1004, 972, 890, 731 cm^{-1}.



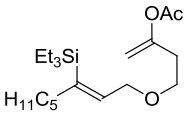
(*Z*)-(1-(But-3-yn-1-yloxy)oct-2-en-3-yl)triethylsilane (2.45)

To a solution of 3-butyn-1-ol (381 μL, 5.03 mmol) in 10 mL THF at 0 °C was added NaH (60%, dispersed in mineral oil, 231 mg, 5.78 mmol) in one portion. The mixture was stirred at that temperature for 30 minutes before **2.44** (1.69 g, 5.53 mmol) was added. The reaction was allowed to warm to room temperature and stirred for another 2 h. The reaction was quenched by H_2O at 0 °C, followed by excess amount of EtOAc. After the organic layer was washed with brine, the mixture was dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (5% EtOAc in hexane) to provide **2.45** (147 mg, 10%). ^1H NMR (400 MHz, $CDCl_3$) δ 6.15 (tt, *J* = 1.1, 6.5 Hz, 1H), 4.06 (d, *J* = 6.6 Hz, 2H), 3.57 (t, *J* = 7.0 Hz, 2H), 2.48 (dt, *J* = 2.7, 7.0 Hz, 2H), 2.05 (t, *J* = 6.9 Hz,

2H), 1.98 (t, J = 2.7 Hz, 1H), 1.39-1.22 (m, 6H), 0.96-0.87 (m, 12H), 0.69-0.63 (m, 6H); ^{13}C (100 MHz, $CDCl_3$) δ 141.9, 139.1, 81.5, 70.5, 69.4, 68.5, 38.3, 32.0, 30.3, 22.8, 20.1, 14.3, 7.7, 4.4; IR (neat) 3313, 2955, 2928, 2874, 1462, 1418, 1377, 1358, 1237, 1108, 1058, 1005, 971, 732 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{34}OSi$ (M^+) 294.2379, found 294.2383.

General procedure for the enol acetate preparation:[2]

A mixture of Na_2CO_3 (15%), $[(p\text{-cymene})RuCl_2]_2$ (0.04 eq), tri(2-furyl)phosphine (0.08 eq), acetic acid (2.0 eq), and 1-decyne (0.5 eq) in toluene was heated to 80 °C and stirred for 1 h. Another portion of acetic acid (2.0 eq) and the alkyne substrate (1.0 eq) were dissolved in toluene and added to the mixture (~0.15 M final substrate concentration). The reaction was stirred at 80 °C overnight. Then crude mixture was concentrated on a rotary evaporator and purified by flash chromatography to give the desired enol acetate product.



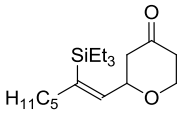
(*Z*)-4-((3-(Triethylsilyl)oct-2-en-1-yl)oxy)but-1-en-2-yl acetate (2.41)

The general procedure for the preparation of enol acetate was followed: A 50 mL RBF was charged with Na_2CO_3 (8.7 mg, 0.082 mmol), dichloro(p-cymene)ruthenium(II) dimer (13.4 mg, 0.0219 mmol), tri(2-furyl)phosphine (10.1 mg, 0.0435 mmol). Then 3.0 mL toluene was added into the flask, followed by acetic acid (125 uL, 2.18 mmol) and 1-decyne (49 uL, 0.27 mmol). The mixture was then heated to 80 °C and stirred for 1 h. Then **2.45** (160 mg, 0.550 mmol) in 1 mL toluene was added into the reaction through syringe. The reaction was stirred at the same temperature overnight. Then crude mixture was loaded onto a short plug of silica gel and washed off with Et_2O. The residue was concentrated on a rotary evaporator and purified by chromatography (3% EtOAc in hexane) to give the desired product (125 mg, 65%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.14 (tt, *J* = 1.2, 6.5 Hz, 1H), 4.82-4.80 (m, 2H), 4.03 (d, *J* = 6.5 Hz, 2H), 3.56 (t, *J* = 6.6 Hz, 2H), 2.53 (t, *J* = 6.7 Hz, 2H), 2.15 (s, 3H), 2.05 (t, *J* = 6.5 Hz, 2H), 1.41-1.25 (m, 6H), 0.97-0.87 (m, 12H), 0.70-0.62 (m, 6H); ^{13}C (75 MHz, $CDCl_3$) δ 169.4, 153.7, 141.7, 139.3, 103.1, 70.5, 67.3, 38.3, 34.3, 32.0, 30.4, 22.8, 21.3, 14.3, 7.8, 4.4; IR (neat) 2954, 2927, 2874, 1759, 1669, 1458, 1367, 1212, 1184, 1105, 1017 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{38}O_3Si$ (M^+) 354.2590, found 354.2605.

General procedure for the cyclization reactions:

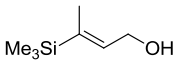
Substrate (1 eq), 2,6-dichloropyridine (2 eq) and 4 Å molecular sieves (2 mass eq) were dissolved in anhydrous 1,2-dichloroethane to give a ~0.1 M solution. The mixture was stirred at room temperature for 15 minutes, followed by addition of $LiClO_4$ (0.2 eq). After 5 minutes, DDQ (4 eq) was added. The reaction was monitored by TLC at 45 °C unless specified and, upon starting material consumption, was quenched by 5% aqueous $NaHCO_3$. The mixture was extracted with CH_2Cl_2 three times, and combined organic layers were dried over $MgSO_4$. The filtrate was concentrated and purified by flash chromatography to give the desired product.



(*Z*)-2-(2-(Triethylsilyl)hept-1-en-1-yl)dihydro-2*H*-pyran-4(3*H*)-one (2.51)

The general procedure for the cyclization reaction was followed: **2.41** (35 mg, 0.10 mmol), 2,6-dichloropyridine (29 mg, 0.20 mmol) and 4 Å molecular sieves (70 mg) were dissolved in 1.0 mL anhydrous 1,2-dichloroethane, followed by $LiClO_4$ (3.2 mg, 0.030 mmol) and DDQ (91 mg, 0.40 mmol). The reaction was stirred at 45 °C for 15 h and then quenched by 5% aqueous $NaHCO_3$. The crude mixture was extracted with CH_2Cl_2, concentrated, and purified by flash chromatography (6% EtOAc in hexane) to give the desired product (21 mg, 68%, *Z*:*E* =

13:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.00 (dd, *J* = 1.1, 9.1 Hz, 1H), 4.31 (dd, *J* = 7.5, 11.5 Hz, 1H), 5.25-4.20 (m, 1H), 3.71-3.65 (m, 1H), 2.65-2.59 (m, 1H), 2.45-2.32 (m, 3H), 2.07-2.04 (m, 2H), 1.43-1.25 (m, 5H), 0.99-0.92 (m, 9H), 0.90-0.87 (m, 3H), 0.69-0.59 (m, 7H); ^{13}C (75 MHz, $CDCl_3$) δ 206.8, 144.0, 140.6, 77.6, 66.5, 48.9, 42.4, 38.1, 31.9, 30.1, 22.7, 14.3, 7.7, 4.6; IR (neat) 2954, 1722, 1249, 1160, 1083, 1016, 838, 751 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{34}O_2Si$ (M^+) 310.2128, found 310.2119.

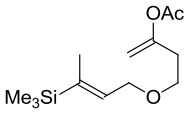


(*E*)-3-(Trimethylsilyl)but-2-en-1-ol (**2.49**)

To a solution of Red-Al (70% wt in toluene, 8.9 mL, 32 mmol) in 12 mL Et_2O at 0 °C was added **2.47** (2.6 g, 20 mmol) in 12 mL Et_2O dropwise over 20 minutes. After another 10 minutes, the reaction was warmed to room temperature for 2.5 h. Then the solution was recooled to 0 °C, and EtOAc (3.9 mL, 40 mmol) was added. 10 minutes later, the reaction was cooled to –78 °C and I_2 (15.2 g, 59.9 mmol) was added in several portions. After that, the reaction was warmed to room temperature for 2 h before it was quenched with H_2O and saturated Na-K tartrate, and it stirred vigorously for 1 h. The organic layer was washed with $Na_2S_2O_3$, and dried over $MgSO_4$. After filtration and concentration, the resulting residue was purified by flash chromatography (20% Et_2O in hexane) to give **2.48**.[3]

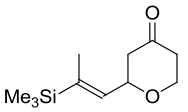
To a solution of CuCN (3.9 g, 44 mmol) in 15 mL Et_2O was added CH_3Li (3 M in hexane, 29 mL) dropwise at 0 °C. After 2 h at that temperature, **2.48** from last step in 20 mL Et_2O was added and the mixture was allowed to warm to room temperature for 8 h. It was quenched by saturated NH_4Cl (aq), and extracted with Et_2O. The organic layer was washed with H_2O, K_2CO_3 (aq) and then dried over $MgSO_4$. After filtration and concentration, the resulting residue was purified by flash chromatography ((20% Et_2O in hexane) to afford **2.49** (2 g, 70% over two

steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95-5.84 (m, 1H), 4.26 (d, *J* = 5.7 Hz, 2H), 1.69 (d, *J* = 0.9 Hz, 3H), 1.60 (br, 1H), 0.06 (s, 9H).[3]



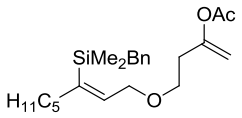
(*E*)-4-((3-(Trimethylsilyl)but-2-en-1-yl)oxy)but-1-en-2-yl acetate (2.46)

Compound **2.46** was prepared from **2.49** following the same protocol for converting **2.43** to **2.41**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86-5.81 (m, 1H), 4.82-4.81 (m, 2H), 4.10 (dd, *J* = 0.6, 5.8 Hz, 2H), 3.58 (t, *J* = 6.7 Hz, 2H), 2.54 (t, *J* = 6.6 Hz, 2H), 2.15 (s, 3H), 1.70 (s, 3H), 0.07 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 169.3, 153.7, 140.1, 135.2, 103.1, 67.9, 67.5, 34.1, 21.2, 15.0, 2.1; IR (neat) 2955, 2859, 1758, 1369, 1248, 1213, 1185, 1108, 1019, 838 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{24}O_3Si$ (M^+) 256.1495, found 256.1489.



(*E*)-2-(2-(Trimethylsilyl)prop-1-en-1-yl)dihydro-2*H*-pyran-4(3*H*)-one (2.52)

The general cyclization reaction procedure was followed with **2.46** (36 mg, 0.14 mmol), 2,6-dichloropyridine (41 mg, 0.28 mmol), 4 Å molecular sieves (72 mg), 1,2-dichloroethane (1.4 mL), $LiClO_4$ (4.5 mg, 0.042 mmol), and DDQ (63 mg, 0.28 mmol). The reaction was stirred at 45 °C for 16 h and then quenched by 5% aqueous $NaHCO_3$. The crude mixture was extracted with CH_2Cl_2, concentrated, and purified by flash chromatography (10% EtOAc in hexane) to give the desired product (22 mg, 74%, *Z*:*E* > 20:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.74 (dd, *J* = 1.5, 7.3 Hz, 1H), 4.48 (ddd, *J* = 4.2, 7.4, 10.7 Hz, 1H), 4.33 (dd, *J* = 7.3, 11.5 Hz, 1H), 3.75 (dt, *J* = 2.8, 12.3 Hz, 1H), 2.64 (ddd, *J* = 7.5, 12.5, 14.5 Hz, 1H), 2.41-2.33 (m, 3H), 1.73 (d, *J* = 1.5 Hz, 3H), 0.08 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 206.8, 141.4, 136.9, 75.0, 66.8, 48.1, 42.5, 15.3, -2.2; IR (neat) 2956, 1721, 1248, 1159, 1084, 1016, 838, 751 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{20}O_2Si$ (M^+) 212.1233, found 212.1240.



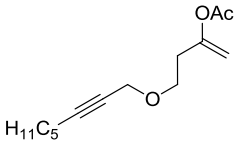
(*Z*)-4-((3-(Benzyldimethylsilyl)oct-2-en-1-yl)oxy)but-1-en-2-yl acetate (2.53)

The general procedure for $[Cp^*Ru(MeCN)_3]PF_6$ catalyzed alkyne hydrosilylation was followed with 2-octyn-1-ol (288 μL, 2.00 mmol), dimethylbenzylsilane (380 μL, 2.40 mmol), $[Cp^*Ru(MeCN)_3]PF_6$ (10 mg, 0.040 mmol) and acetone (4 mL). The reaction was stirred at 0 °C for 10 minutes and then concentrated under reduced pressure. The resulting residue was purified by flash chromatography (10% EtOAc in hexane) to give the (*Z*)-3-(benzyldimethylsilyl)oct-2-en-1-ol (555 mg, >99%).

To a solution of (*Z*)-3-(benzyldimethylsilyl)oct-2-en-1-ol (555 mg, 2.00 mmol) and **2.58** (343 mg, 1.60 mmol) in 25 mL cyclohexane was added TMSOTf (18 μL, 0.10 mmol) dropwise at 0 °C. After 1 h at that temperature, the mixture went through a short pad of Celit with hexane, and the filtrate was concentrated. The residue was purified by flash chromatography (30% CH_2Cl_2 in hexane to 3% Et_2O in hexane) to afford (*Z*)-benzyl(1-(but-3-yn-1-yloxy)oct-2-en-3-yl)dimethylsilane (324 mg, 49%).

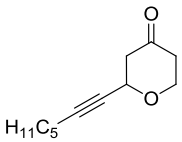
The general procedure for enol acetate formation was followed with alkyne (135 mg, 0.410 mmol), Na_2CO_3 (6.5 mg, 0.061 mmol), dichloro(p-cymene)ruthenium(II) dimer (10 mg, 0.016 mmol), tri(2-furyl)phosphine (7.6 mg, 0.033 mmol), toluene (10 mL), acetic acid (70 uL, 1.2 mmol) and 1-decyne (35 uL, 0.21 mmol). The mixture was stirred at 80 °C overnight. Then crude mixture was loaded onto a short plug of silica gel and washed off with Et_2O. The residue was concentrated on a rotary evaporator and purified by chromatography (4% EtOAc in hexane) to give the desired product (110 mg, 69%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.21 (t, J = 7.4 Hz, 2H), 7.1 (t, J = 7.3 Hz, 1H), 7.00 (d, J = 7.5 Hz, 2H), 6.11 (t, J = 6.5 Hz, 1H), 4.82 (s, 1H), 4.80 (s, 1H), 3.88 (d, J = 6.5 Hz, 2H), 3.50 (t, J = 6.6 Hz, 2H), 2.51 (t, J = 6.5 Hz, 2H), 2.20 (s, 2H),

2.14 (s, 3H), 2.06-2.02 (m, 2H), 1.33-1.22 (m, 6H), 0.88 (t, J = 7.1 Hz, 3H), 0.12 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.4, 153.6, 142.8, 139.9, 139.2, 128.5, 128.4, 124.3, 103.1, 70.3, 67.4, 38.5, 34.2, 32.0, 30.2, 26.8, 22.8, 21.3, 14.3, -1.6; IR (neat) 2957, 2859, 1756, 1667, 1429, 1370, 1213, 1186 cm^{-1}; HRMS (EI) calcd for $C_{23}H_{36}O_3Si$ (M^+) 388.2434, found 388.2429.



4-(Oct-2-yn-1-yloxy)but-1-en-2-yl acetate (2.60)

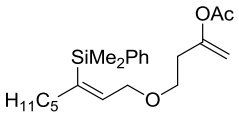
Compound **2.60** was prepared from **2.42** following the same protocol for converting **2.43** to **2.41**. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.84 (d, J = 1.2 Hz, 1H), 4.81 (d, J = 1.4 Hz, 1H), 4.15 (t, J = 2.1 Hz, 2H), 3.64 (t, J = 6.5 Hz, 2H), 2.54 (t, J = 6.5 Hz, 2H), 2.22 (tt, J = 2.1, 7.1 Hz, 2H), 2.15 (s, 3H), 1.52 (p, J = 7.0 Hz, 2H), 1.39-1.29 (m, 4H), 0.90 (t, J = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.2, 153.3, 103.0, 87.3, 75.7, 66.4, 58.7, 33.7, 31.1, 28.3, 22.2, 21.1, 18.7, 14.0; IR (neat) 2956, 2931, 2858, 1758, 1367, 1193, 1066, 1019 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{22}O_3Na$ $(M+Na)^+$ 261.1467, found 261.1460.



2-(Hept-1-ynyl)dihydro-2*H*-pyran-4(3*H*)-one (2.114)

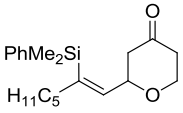
The general procedure of cyclization reaction was followed: **2.60** (75 mg, 0.31 mmol), 2,6-dichloropyridine (93 mg, 0.62 mmol) and 4 Å molecular sieves (150 mg) were dissolved in 3.2 mL anhydrous 1,2-dichloroethane, followed by $LiClO_4$ (10 mg, 0.094 mmol) and DDQ (285 mg, 1.26 mmol). The reaction was stirred at 45 °C for 33 h and then quenched by 5% aqueous $NaHCO_3$. The crude mixture was extracted with CH_2Cl_2. After concentration, it was purified by flash chromatography (9% EtOAc in hexane) to give the desired product (43 mg, 71%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.72-4.67 (m, 1H), 4.30 (dt, J = 5.9, 11.7 Hz, 1H), 3.88 (dt, J = 6.1, 12.0 Hz, 1H), 2.71 (dd, J = 4.8, 15.1 Hz, 1H), 2.57 (dd, J = 6.8, 14.3 Hz, 1H), 2.51-2.46

(m, 2H), 2.23 (dt, J = 2.0, 7.1 Hz, 2H), 1.54-1.47 (m, 2H), 1.38-1.26 (m, 4H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 205.0, 89.1, 76.6, 67.4, 64.2, 48.4, 42.1, 31.0, 28.1, 22.1, 18.6, 13.9; IR (neat) 2957, 2931, 2860, 1797, 1723, 1416, 1365, 1223, 1168, 1152, 1081, 1017 cm^{-1}; HRMS(EI) calcd for $C_{12}H_{18}O_2$ (M^+) 194.1307, found 194.1306.



(*Z*)-4-((3-(Dimethyl(phenyl)silyl)oct-2-en-1-yl)oxy)but-1-en-2-yl acetate (2.54)

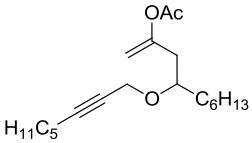
The general procedure for [Cp*Ru(MeCN)$_3$]PF$_6$ catalyzed alkyne hydrosilylation was followed with **2.60** (72 mg, 0.30 mmol), HSiMe$_2$Ph (56 μL, 0.36 mmol), [Cp*Ru(MeCN)$_3$]PF$_6$ (1.5 mg, 0.0030 mmol) and acetone (0.6 mL). After stirring for 2 h, the mixture was concentrated, and purified by flash chromatography (3% EtOAc in hexane) to give **2.54** (90 mg, 80%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53-7.51 (m, 2H), 7.35-7.34 (m, 3H), 6.17 (dt, J = 0.8, 6.7 Hz, 1H), 4.76 (d, J = 1.3 Hz, 1H), 4.73 (s, 1H), 3.82 (d, J = 6.6 Hz, 2H), 3.29 (t, J = 6.7 Hz, 2H), 2.38 (t, J = 6.7 Hz, 2H), 2.16 (t, J = 7.5 Hz, 2H), 2.12 (s, 3H), 1.37 (p, J = 7.8 Hz, 2H), 1.32-1.21 (m, 4H), 0.87 (t, J = 6.7 Hz, 3H), 0.40 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 153.4, 142.2, 139.6, 139.2, 133.7, 128.9, 127.8, 102.7, 70.1, 66.9, 38.3, 33.9, 31.7, 30.1, 22.5, 21.0, 14.1, -1.0; IR (neat) 2957, 2927, 2857, 1758,1250, 1213, 1185, 1109, 833, 817 cm^{-1}; HRMS (EI) calcd for $C_{22}H_{34}O_3Si$ (M^+) 374.2277, found 374.2277.



(*Z*)-2-(2-(Dimethyl(phenyl)silyl)hept-1-en-1-yl)dihydro-2*H*-pyran-4(3*H*)-one (2.68)

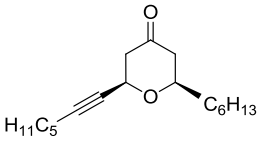
The general cyclization reaction procedure was followed with **2.54** (65 mg, 0.17 mmol), 2,6-dichloropyridine (51 mg, 0.35 mmol), 4 Å molecular sieves (130 mg), 1,2-dichloroethane (1.7

mL), $LiClO_4$ (5.5 mg, 0.052 mmol), and DDQ (158 mg, 0.696 mmol). The reaction was stirred at 45 °C for 10 h and then quenched by 5% aqueous $NaHCO_3$. The crude mixture was extracted with CH_2Cl_2, concentrated, and purified by flash chromatography (9% EtOAc in hexane) to give the desired product (38 mg, 73%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52-7.51 (m, 2H), 7.37-7.34 (m, 3H), 6.02 (d, *J* = 8.8 Hz, 1H), 4.09 (ddd, *J* = 0.9, 6.7, 11.7 Hz, 1H), 3.97 (ddd, *J* = 2.6, 8.8, 11.3 Hz, 1H), 3.13 (dt, *J* = 2.6, 12.1 Hz, 1H), 2.48 (ddd, *J* = 7.4, 12.5, 14.6 Hz, 1H), 2.30 (dd, *J* = 11.0, 14.3 Hz, 1H), 2.19-2.13 (m, 4H), 1.45-1.34 (m, 2H), 1.33-1.23 (m, 4H), 0.88 (t, *J* = 6.9 Hz, 3H), 0.41 (s, 3H), 0.39 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 206.6, 144.6, 140.9, 139.0, 133.9, 129.4, 128.1, 66.1, 48.2, 42.1, 38.4, 31.9, 30.1, 22.7, 14.3, -0.6, -0.9; IR (neat) 2957, 2927, 2856, 1719, 1248, 1153, 1110, 1080, 815 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{30}O_2Si$ (M^+) 330.2015, found 330.2015.



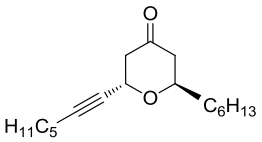
4-(Oct-2-yn-1-yloxy)dec-1-en-2-yl acetate (2.62)

Compound **2.62** was prepared from **1.71** following the same protocol for converting **2.42** to **2.60**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.82 (s, 1H), 4.81 (s, 1H), 4.19-4.12 (m, 2H), 3.62 (p, *J* = 5.9 Hz, 1H), 2.47 (dd, *J* = 6.3, 15.0 Hz, 1H), 2.39 (dd, *J* = 5.6, 15.0 Hz, 1H), 2.22-2.19 (m, 2H), 2.15 (s, 3H), 1.55-1.49 (m, 4H), 1.41-1.29 (m, 12H), 0.90 (t, *J* = 7.2 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.1, 153.5, 103.6, 86.5, 76.3, 75.8, 57.0, 38.1, 33.9, 31.8, 31.1, 29.4, 28.3, 25.2, 22.6, 22.2, 21.1, 18.8, 14.1, 14.0; IR (neat) 2956, 2930, 2858, 1758, 1369, 1194, 1067, 1020 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{34}O_3Na$ $(M+Na)^+$ 345.2406, found 345.2428.



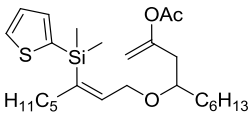
(2*R*,6*R*)-2-(Hept-1-ynyl)-6-hexyldihydro-2*H*-pyran-4(3*H*)-one (2.115)

The general cyclization reaction procedure was followed with **2.62** (75 mg, 0.23 mmol), 2,6-dichloropyridine (69 mg, 0.47 mmol), 4 Å molecular sieves (150 mg), 1,2-dichloroethane (2.4 mL), $LiClO_4$ (7 mg, 0.07 mmol), and DDQ (185 mg, 0.815 mmol). The reaction was stirred at 40 °C for 18 h and then quenched by 5% aqueous $NaHCO_3$. The crude mixture was extracted with CH_2Cl_2. After concentration, it was purified by flash chromatography (30% CH_2Cl_2 in hexane to 8% Et_2O in hexane) to give the desired products **2.115** and **2.116** (**2.115**, 27 mg, 41%; **2.116**, 16 mg, 25%). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 4.34 (tdd, *J* = 1.9, 4.0, 10.4 Hz, 1H), 3.61-3.52 (m, 1H), 2.67-2.52 (m, 2H), 2.39 (ddd, *J* = 1.6, 2.7, 14.6 Hz, 1H), 2.31-2.21 (m, 3H), 1.79-1.68 (m, 1H), 1.54-1.44 (m, 3H), 1.41-1.20 (m, 12H), 0.93-0.87 (m, 6H); ^{13}C NMR (75 MHz, CDCl3) δ 206.0, 87.6, 77.8, 77.4, 67.5, 48.6, 47.8, 36.6, 31.9, 31.3, 29.3, 28.3, 25.4, 22.8, 22.4, 19.0, 14.3, 14.2; IR (neat) 2956, 2930, 2858, 1723, 1464, 1346, 1056 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{30}O_2$ (M^+) 278.2246, found 278.2242.



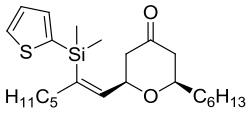
(2*R*,6*S*)-2-(Hept-1-ynyl)-6-hexyldihydro-2*H*-pyran-4(3*H*)-one (2.116)

^{1}H NMR (300 MHz, CD_2Cl_2) δ 5.06 (qd, *J* = 1.8, 6.9 Hz, 1H), 4.27-4.19 (m, 1H), 2.75 (ddd, *J* = 1.0, 6.9, 14.6 Hz, 1H), 2.46-2.37 (m, 2H), 2.27-2.16 (m, 3H), 1.73-1.63 (m, 1H), 1.57-1.44 (m, 3H), 1.43-1.30 (m, 12H), 0.92-0.87 (m, 6H); ^{13}C (75 MHz, $CDCl_3$) δ 205.9, 90.1, 72.1, 65.6, 48.3, 47.6, 36.2, 31.9, 31.2, 29.2, 28.4, 25.3, 22.8, 22.3, 18.8, 14.3, 14.2; IR (neat) 2956, 2929, 2858, 1723 cm^{-1}; HRMS(EI) calcd for $C_{18}H_{30}O_2$ (M^+) 278.2246, found 278.2256.



(*Z*)-4-(3-(Dimethyl(thiophen-2-yl)silyl)oct-2-enyloxy)dec-1-en-2-yl acetate (2.55)

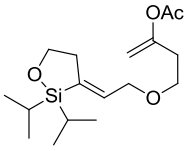
The general procedure for $[Cp^*Ru(MeCN)_3]PF_6$ catalyzed alkyne hydrosilylation was followed with **2.62** (105 mg, 0.330 mmol), $HSiMe_2Ph$ (70 μL, 0.39 mmol), $[Cp^*Ru(MeCN)_3]PF_6$ (3 mg, 0.006 mmol) and acetone (0.7 mL). After stirring for 30 minutes, the mixture was concentrated, and purified by flash chromatography (3% EtOAc in hexane) to give **2.54** (160 mg, 99%). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.61 (dd, *J* = 0.8, 4.7 Hz, 1H), 7.28 (dd, *J* = 0.9, 3.4 Hz, 1H), 7.18 (dd, *J* = 3.4, 4.6 Hz, 1H), 6.14 (t, *J* = 6.5 Hz, 1H), 4.72 (d, *J* = 1.3 Hz, 1H), 4.70 (s, 1H), 3.93-3.90 (m, 2H), 3.29 (p, *J* = 5.8 Hz, 1H), 2.28 (dd, *J* = 3.9, 5.8 Hz, 2H), 2.17-2.12 (m, 2H), 2.07 (s, 3H), 1.41-1.26 (m, 16H), 0.91-0.85 (m, 6H), 0.44 (s, 6H); ^{13}C (75 MHz, CD_2Cl_2) δ 169.4, 154.6, 141.8, 140.9, 135.5, 131.4, 128.7, 103.5, 77.2, 69.1, 38.8, 38.7, 34.5, 32.4, 32.3, 30.9, 30.0, 25.7, 23.2, 23.1, 21.5, 14.5, 14.4, 0.5; IR (neat) 2956, 2927, 2856, 1758, 1212, 1194, 1086, 832, 810 cm^{-1}; HRMS(ESI) calcd for $C_{26}H_{44}O_3SiSNa$ $(M+Na)^+$ 487.2678, found 487.2656.



(2*R*,6*R*)-2-((*Z*)-2-(Dimethyl(thiophen-2-yl)silyl)hept-1-enyl)-6-hexyldihydro-2*H*-pyran-4(3*H*)-one (2.69)

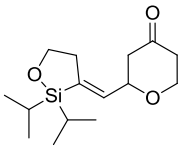
The general procedure of cyclization reaction was followed: **2.55** (50 mg, 0.11 mmol), 2,6-dichloropyridine (32 mg, 0.21 mmol) and 4 Å molecular sieves (100 mg) were dissolved in 1.1 mL anhydrous 1,2-dichloroethane, followed by $LiClO_4$ (4 mg, 0.03 mmol) and DDQ (97 mg, 0.43 mmol). The reaction was stirred at 45 °C for 18 h and then quenched by 5% aqueous $NaHCO_3$. The crude mixture was extracted with CH_2Cl_2. After concentration, it was purified by flash chromatography (5% Et_2O in hexane to 7% EtOAc in hexane) to give the desired product (37 mg, 82%). ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.62 (d, *J* = 4.5 Hz, 1H), 7.28 (dd, *J* = 0.6, 3.4 Hz,

1H), 7.17 (dd, *J* = 3.4, 4.6 Hz, 1H), 6.01 (dd, *J* = 9.2 Hz, 1H), 4.11 (ddd, *J* = 2.7, 9.2, 11.5 Hz, 1H), 3.29-3.24 (m, 1H), 2.34-2.09 (m, 6H), 1.47-1.35 (m, 4H), 1.34-1.16 (m, 12H), 0.89 (t, *J* = 6.8 Hz, 3H), 0.88 (t, *J* = 7.1 Hz, 3H), 0.46 (s, 3H), 0.43 (s, 3H); ^{13}C (125 MHz, $CDCl_3$) δ 206.9, 143.6, 142.5, 139.0, 135.7, 131.6, 128.7, 77.3, 76.5, 48.1, 48.0, 38.5, 37.0, 32.4, 32.1, 30.5, 29.8, 25.9, 23.2, 23.1, 14.5, 14.4, 0.7, 0.5; IR (neat) 2956, 2927, 2856, 1721, 1409, 1349, 1252, 1049, 992, 810 cm^{-1}; HRMS(ESI) calcd for $C_{24}H_{40}O_2SiSNa$ $(M+Na)^+$ 443.2416, found 443.2436.



(*E*)-4-(2-(2,2-Diisopropyl-1,2-oxasilolan-3-ylidene)ethoxy)but-1-en-2-yl acetate (2.56)[4,5]

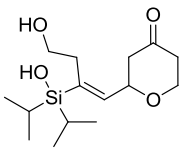
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.96 (tt, *J* = 2.7, 5.4 Hz, 1H), 4.82-4.81 (m, 2H), 4.11 (d, *J* = 5.2 Hz, 2H), 4.01 (t, *J* = 6.5 Hz, 2H), 3.58 (t, *J* = 6.5 Hz, 2H), 2.53 (t, *J* = 6.5 Hz, 2H), 2.48 (t, *J* = 6.6 Hz, 2H), 2.14 (s, 3H), 1.09-0.93 (m, 14H); ^{13}C (75 MHz, $CDCl_3$) δ 169.3, 153.6, 139.1, 135.2, 103.2, 69.6, 67.4, 67.2, 34.2, 32.9, 21.3, 17.3, 17.2, 12.5; IR (neat) 2940, 2865, 1758, 1213, 1184, 1105, 1020, 783 cm^{-1}; HRMS(EI) calcd for $C_{14}H_{23}O_4Si$ $(M^+-C_3H_7)$ 283.1366, found 283.1364.



(*E*)-2-((2,2-Diisopropyl-1,2-oxasilolan-3-ylidene)methyl)dihydro-*2H*-pyran-4(3*H*)-one (2.70)

The general procedure of cyclization reaction was followed: **2.56** (37 mg, 0.11 mmol), 2,6-dichloropyridine (28 mg, 0.19 mmol) and 4 Å molecular sieves (70 mg) were dissolved in 1.3 mL anhydrous 1,2-dichloroethane, followed by $LiClO_4$ (3 mg, 0.03 mmol) and DDQ (85 mg, 0.38 mmol). The reaction was stirred at 45 °C for 33 h and then quenched by 5% aqueous $NaHCO_3$. The crude mixture was extracted with CH_2Cl_2. After concentration, it was

purified by flash chromatography (20% to 30% to 60% EtOAc in hexane) to give the desired products **2.70** and **2.71** (29 mg, > 86%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.91 (td, *J* = 2.6, 6.7 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 1H), 4.36-4.33 (m, 1H), 4.05 (ddd, *J* = 5.2, 7.4, 9.3 Hz, 1H), 3.98 (td, *J* = 7.0, 9.1 Hz, 1H), 3.75 (dt, *J* = 2.8, 12.1 Hz, 1H), 2.65 (ddd, *J* = 7.3, 12.3, 14.4 Hz, 1H), 2.61-2.56 (m, 1H), 2.46-2.41 (m, 3H), 2.39-2.36 (m, 1H), 1.07-0.98 (m, 14H); ^{13}C (151 MHz, $CDCl_3$) δ 206.5, 139.8, 136.7, 77.1, 67.1, 66.8, 47.8, 42.5, 33.1, 17.3, 17.3, 17.3, 17.2, 12.6, 12.5; IR (neat) 2941, 2865, 1720, 1463, 1247, 1154, 1061, 1023, 783 cm^{-1}; HRMS(EI) calcd for $C_{15}H_{26}O_3Si$ (M^+) 282.1651, found 282.1655.

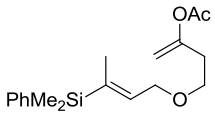


(*E*)-2-(4-Hydroxy-2-(hydroxydiisopropylsilyl)but-1-enyl)dihydro-2*H*-pyran-4(3*H*)-one (2.71)

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.90 (d, *J* = 7.6 Hz, 1H), 4.50 (ddd, *J* = 3.1, 7.6, 10.7 Hz, 1H), 4.33 (dd, *J* = 6.5, 10.7 Hz, 1H), 3.79-3.73 (m, 2H), 3.71-3.66 (m, 1H), 2.88 (br, 1H), 2.64 (ddd, *J* = 7.4, 12.5, 14.5 Hz, 1H), 2.54-2.36 (m, 6H), 1.06-0.98 (m, 14H); IR (neat) 3385, 2927, 2864, 1716, 1460, 1247, 1058, 1020, 881 cm^{-1}; HRMS(ESI) calcd for $C_{12}H_{19}O_3Si$ (M^+-C_3H_7-H_2O) 239.1103, found 239.1100.

General procedure for H_2PtCl_6•$6H_2O$ catalyzed hydrosilylation of alkyne:[6]

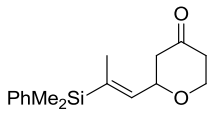
To a stirred solution of alkyne (1 eq) in THF was added dimethylphenylsilane (1.1 eq) and a 0.001 M solution of H_2PtCl_6•$6H_2O$ (0.001 eq) in THF (~0.53 M final substrate concentration). The mixture was heated at 50 °C for 5 h unless specified, cooled and filtered through Celite with Et_2O. The solvent was removed under vacuum and purified by flash chromatography to give the (*E*)-vinyl silane.



(*E*)-4-(3-(Dimethyl(phenyl)silyl)but-2-enyloxy)but-1-en-2-yl acetate (2.72)

The general procedure for H_2PtCl_6•$6H_2O$ catalyzed hydrosilylation of alkyne was followed with **1.80** (76 μL, 1.0 mmol), $HSiMe_2Ph$ (311 μL, 2.00 mmol), H_2PtCl_6•$6H_2O$ (0.001 M THF solution, 0.5 mL) and THF (0.95 mL). After 4 h at 50 °C, the mixture was cooled to 0 °C, and 0.5 mL HCl (1% solution in methol) was added dropwise. After 5 minutes, the reaction was quenched with saturated $NaHCO_3$ (aq), and extracted with EtOAc. The organic layer was dried over $MgSO_4$, and filtered. After concentration, it was purified by flash chromatography (10% EtOAc in hexane) to give **2.76** (115 mg, 56%) and **2.77** (59 mg, 29%).

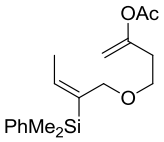
Compound **2.72** was prepared following the same synthetic route to **2.53**. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51-7.50 (m, 2H), 7.37-7.34 (m, 3H), 5.94 (qt, *J* = 1.7, 5.7 Hz, 1H), 4.82 (s, 1H), 4.81 (d, *J* = 1.4 Hz, 1H), 4.13 (d, *J* = 5.7 Hz, 2H), 3.58 (t, *J* = 6.6 Hz, 2H), 2.54 (t, *J* = 6.5 Hz, 2H), 2.13 (s, 3H), 1.69 (t, *J* = 0.7 Hz, 3H), 0.36 (s, 6H); ^{13}C (151 MHz, $CDCl_3$) δ 169.4, 153.7, 138.1, 138.1, 137.5, 134.2, 129.2, 128.0, 103.2, 68.1, 67.6, 34.1, 21.3, 15.4, -3.4; IR (neat) 2956, 2857, 1755, 1667, 1427, 1368, 1212, 1183, 1109, 1018 cm^{-1}; HRMS(EI) calcd for $C_{18}H_{26}O_3Si$ (M^+) 318.1651, found 318.1649.



(*E*)-2-(2-(Dimethyl(phenyl)silyl)prop-1-enyl)dihydro-2*H*-pyran-4(3*H*)-one (2.85)

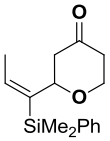
The general procedure of cyclization reaction was followed: **2.72** (72 mg, 0.23 mmol), 2,6-dichloropyridine (67 mg, 0.46 mmol) and 4 Å molecular sieves (140 mg) were dissolved in 2.3 mL anhydrous 1,2-dichloroethane, followed by $LiClO_4$ (7.2 mg, 0.068 mmol) and DDQ (154 mg, 0.678 mmol). The reaction was stirred at 45 °C for 17 h and then quenched by 5% aqueous $NaHCO_3$. The crude mixture was extracted with CH_2Cl_2. After concentration, it was purified by

flash chromatography (10%-15% EtOAc in hexane) to give the desired product (58 mg, 94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51-7.48 (m, 2H), 7.38-7.35 (m, 3H), 5.84 (qd, *J* = 1.7, 7.2 Hz, 1H), 4.55-4.48 (m, 1H), 4.33 (ddd, *J* = 1.4, 7.3, 11.4 Hz, 1H), 3.75 (dt, *J* = 2.7, 12.1 Hz, 1H), 2.64 (ddd, *J* = 7.3, 12.2, 14.5 Hz, 1H), 2.42-2.32 (m, 3H), 1.72 (d, *J* = 1.7 Hz, 3H), 0.38 (s, 6H); ^{13}C (75 MHz, $CDCl_3$) δ 206.7, 139.3, 139.0, 137.5, 134.2, 129.4, 128.1, 75.2, 66.8, 48.0, 42.5, 15.6, -3.5, -3.6; IR (neat) 2956, 2918, 2850, 1717, 1247, 1157, 1111, 1082 cm^{-1}; HRMS(EI) calcd for $C_{16}H_{22}O_2Si$ (M^+) 274.1389, found 274.1388.



(*E*)-4-(2-(Dimethyl(phenyl)silyl)but-2-enyloxy)but-1-en-2-yl acetate (2.73)

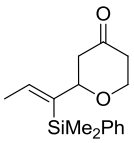
Compound **2.73** was prepared following the same synthetic route to **2.72**. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53-7.52 (m, 2H), 7.35-7.33 (m, 3H), 5.99 (tq, *J* = 1.3, 6.7 Hz, 1H), 4.76 (s, 1H), 4.73 (s, 1H), 4.12 (s, 2H), 3.41 (t, *J* = 6.8 Hz, 2H), 2.40 (t, *J* = 6.7 Hz, 2H), 2.13 (s, 3H), 1.74 (d, *J* = 6.8 Hz, 3H), 0.38 (s, 6H); ^{13}C (151 MHz, $CDCl_3$) δ 169.4, 153.7, 139.2, 139.1, 138.0, 134.3, 128.9, 127.8, 103.1, 69.3, 67.5, 34.1, 21.3, 15.2, -2.2; IR (neat) 2956, 2858, 1756, 1427, 1368, 1212, 1182, 1108 cm^{-1}; HRMS(ESI) calcd for $C_{18}H_{26}O_3SiNa$ $(M+Na)^+$ 341.1549, found 341.1556.



(*E*)-2-(1-(Dimethyl(phenyl)silyl)prop-1-enyl)dihydro-2*H*-pyran-4(3*H*)-one (*E*-2.86)

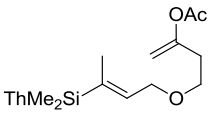
The general procedure of cyclization reaction was followed: **2.73** (49 mg, 0.15 mmol), 2,6-dichloropyridine (46 mg, 0.31 mmol) and 4 Å molecular sieves (100 mg) were dissolved in 1.5 mL anhydrous 1,2-dichloroethane, followed by $LiClO_4$ (5 mg, 0.05 mmol) and DDQ (140 mg, 0.617 mmol). The reaction was stirred at 45 °C for 24 h and then quenched by 5% aqueous

$NaHCO_3$. The crude mixture was extracted with CH_2Cl_2. After concentration, it was purified by flash chromatography (30% CH_2Cl_2 in hexane then 5% EtOAc in hexane) to give the desired product (29 mg, 69%, *E*:*Z* = 1.1:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59-7.57 (m, 2H), 7.35-7.33 (m, 3H), 5.85 (dq, *J* = 1.3, 6.8 Hz, 1H), 4.60 (dd, *J* = 2.1, 11.4 Hz, 1H), 4.30 (dd, *J* = 7.3, 11.4 Hz, 1H), 3.63 (dt, *J* = 2.4, 12.4 Hz, 1H), 2.41 (ddd, *J* = 7.4, 13.7, 13.7 Hz, 1H), 2.25-2.12 (m, 3H), 1.67 (d, *J* = 6.8 Hz, 3H), 0.47 (s, 3H), 0.44 (s, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 207.0, 141.8, 139.4, 136.3, 134.3, 128.8, 127.5, 79.4, 66.4, 47.7, 42.3, 15.2, -1.0, -1.5; IR (neat) 2959, 2920, 2852, 1719, 1247, 1157, 1108, 817 cm^{-1}; HRMS(EI) calcd for $C_{15}H_{19}O_2Si$ (M^+-CH_3) 259.1154, found 259.1146.



(*Z*)-2-(1-(Dimethyl(phenyl)silyl)prop-1-enyl)dihydro-2*H*-pyran-4(3*H*)-one (*Z*-2.86)

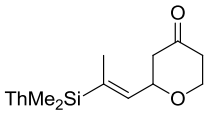
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56-7.54 (m, 2H), 7.36-7.35 (m, 3H), 6.44 (dq, *J* = 1.0, 7.0 Hz, 1H), 4.25 (ddd, *J* = 1.4, 7.4, 11.4 Hz, 1H), 4.10-4.08 (m, 1H), 3,53 (dt, *J* = 2.9, 11.8 Hz, 1H), 2.58-2.52 (m, 2H), 2.43 (td, *J* = 2.3, 14.2 Hz, 1H), 2.32-2.28 (m, 1H), 1.69 (d, *J* = 6.7, 3H), 0.48 (s, 3H), 0.46 (s, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 207.6, 139.7, 138.9, 138.1, 133.8, 128.9, 127.8, 81.6, 66.2, 48.2, 42.2, 18.0, -0.8, -0.9; IR (neat) 2958, 2919, 2852, 1719, 1243, 1156, 1110, 816 cm^{-1}; HRMS(EI) calcd for $C_{15}H_{19}O_2Si$ (M^+-CH_3) 259.1154, found 259.1151.



(*E*)-4-(3-(Dimethyl(thiophen-2-yl)silyl)but-2-enyloxy)but-1-en-2-yl acetate (2.74)

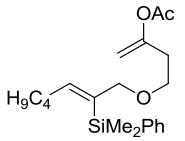
Compound **2.74** was prepared from **1.80** following the same synthetic route to substrate **2.72**.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 0.8, 4.6 Hz, 1H), 7.27-7.26 (m, 1H), 7.19 (dd, *J* = 3.3, 4.6 Hz, 1H), 5.97 (qt, *J* = 1.7, 5.6 Hz, 1H), 4.82 (s, 1H), 4.81 (d, *J* = 1.5 Hz, 1H), 4.13 (dd, *J* = 0.9, 5.6 Hz, 2H), 3.58 (t, *J* = 6.6 Hz, 2H), 2.53 (t, *J* = 6.5 Hz, 2H), 2.13 (s, 3H), 1.73-1.72 (m, 3H), 0.41 (s, 6H); ^{13}C (75 MHz, $CDCl_3$) δ 169.4, 153.7, 137.7, 135.1, 131.1, 128.4, 103.2, 68.1, 67.6, 34.1, 21.3, 15.3, -2.3; IR (neat) 2957, 2917, 2853, 1756, 1666, 1368, 1250, 1213, 1183, 1107, 991 cm^{-1}; HRMS(EI) calcd for $C_{16}H_{24}O_3SiS$ (M^+) 324.1219, found 324.1215.



(*E*)-2-(2-(Dimethyl(thiophen-2-yl)silyl)prop-1-enyl)dihydro-2*H*-pyran-4(3*H*)-one (2.87)

The general procedure of cyclization reaction was followed: **2.74** (38 mg, 0.12 mmol), 2,6-dichloropyridine (35 mg, 0.24 mmol) and 4 Å molecular sieves (75 mg) were dissolved in 1.2 mL anhydrous 1,2-dichloroethane, followed by $LiClO_4$ (4 mg, 0.04 mmol) and DDQ (107 mg, 0.471 mmol). The reaction was stirred at 45 °C for 8 h and then quenched by 5% aqueous $NaHCO_3$. The crude mixture was extracted with CH_2Cl_2. After concentration, it was purified by flash chromatography (15% EtOAc in hexane) to give the desired product (28 mg, 86%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.63 (d, *J* = 4.7 Hz, 1H), 7.27 (d, *J* = 3.2 Hz, 1H), 7.20 (dd, *J* = 3.4, 4.5 Hz, 1H), 5.87 (qd, *J* = 1.6, 7.2 Hz, 1H), 4.50 (ddd, *J* = 5.2, 7.3, 8.7 Hz, 1H), 4.33 (ddd, *J* = 1.0, 7.4, 11.5 Hz, 1H), 3.75 (dt, *J* = 2.7, 12.1 Hz, 1H), 2.64 (ddd, *J* = 7.4, 12.5, 14.4 Hz, 1H), 2.42-2.40 (m, 2H), 2.37-2.34 (m, 1H), 1.76 (d, *J* = 1.6 Hz, 3H), 0.42 (s, 6H); ^{13}C (151 MHz, $CDCl_3$) δ 206.7, 139.1, 138.8, 137.0, 135.3, 131.3, 128.4, 75.1, 66.8, 47.8, 42.5, 15.5, -2.3, -2.4; IR (neat) 2959, 2920, 2852, 1718, 1249, 990, 807 cm^{-1}; HRMS(EI) calcd for $C_{14}H_{20}O_2SiS$ (M^+) 280.0953, found 280.0948.



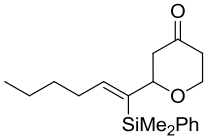
(*Z*)-4-(2-(Dimethyl(phenyl)silyl)hept-2-enyloxy)but-1-en-2-yl acetate (2.75)

To a solution of **2.82** (1.2 mL, 10 mmol) in THF (20 mL) was added ^{n}BuLi (1.6 M, 6.9 mL) dropwise at –78 °C. After 1 h at that temperature, $PhMe_2SiCl$ (1.7 mL, 10 mmol) was added and the mixture was stirred from –78 °C to room temperature for 3 h. The reaction was quenched with saturated NH_4Cl (aq), and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and filtered. After concentration, the residue was purified by flash chromatography (3% EtOAc in hexane) to give **2.83** (2.3 g, >99%).

To a solution of DIBAL-H (1 M solution in hexane, 11.7 mL) in Et_2O (4 mL) was added **2.83** (2.30 g, 10.6 mmol) in Et_2O (4 mL) dropwise at 0 °C. After stirring at room temperature for 3 h, it was cooled to 0 °C, and MeLi (1.6 M in hexane, 7.3 mL) was added. After another 1 h, the solution was transferred via cannula to para-formaldehyde in Et_2O (6 mL) at 0 °C, and the mixture was stirred at room temperature overnight. The mixture was quenched by 1 M HCl at 0 °C, and extracted with Et_2O. The organic layer was dried over $MgSO_4$, and filtrated. After concentration, it was purified by flash chromatography (8% EtOAc in hexane) to afford **2.84** (2.18 g, 83%).

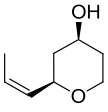
Compound **2.75** was prepared from **2.84** following the same synthetic route to substrate **2.72**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56-7.54 (m, 2H), 7.34-7.32 (m, 3H), 6.27 (t, *J* = 7.5 Hz, 1H), 4.78 (s, 2H), 3.99 (s, 2H), 3.44 (t, *J* = 6.9 Hz, 2H), 2.48 (t, *J* = 6.8 Hz, 2H), 2.13 (s, 3H), 1.98 (q, *J* = 7.3 Hz, 2H), 1.23-1.12 (m, 4H), 0.77 (t, *J* = 7.2 Hz, 3H), 0.42 (s, 6H); ^{13}C (125 MHz, $CDCl_3$) δ 169.4, 153.8, 148.2, 139.7, 134.2, 134.0, 128.9, 127.8, 103.1, 77.9, 66.8, 34.2, 32.0, 31.8, 22.6, 21.3, 14.1, -1.2; IR (neat) 2956, 2927, 2856, 1757, 1368, 1211, 1183, 1106, 817 cm^{-1}; HRMS(ESI) calcd for $C_{21}H_{32}O_3SiNa$ $(M+Na)^+$ 383.2018, found 383.20175.



(*Z*)-2-(1-(Dimethyl(phenyl)silyl)hex-1-enyl)dihydro-2*H*-pyran-4(3*H*)-one (2.88)

The general procedure of cyclization reaction was followed: **2.75** (40 mg, 0.11 mmol), 2,6-dichloropyridine (33 mg, 0.22 mmol) and 4 Å molecular sieves (80 mg) were dissolved in 1.1 mL anhydrous 1,2-dichloroethane, followed by $LiClO_4$ (3.5 mg, 0.033 mmol) and DDQ (100 mg, 0.44 mmol). The reaction was stirred at 40 °C for 5.5 h and then quenched by 5% aqueous $NaHCO_3$. The crude mixture was extracted with CH_2Cl_2. After concentration, it was purified by flash chromatography (10% EtOAc in hexane) to give the desired product (29 mg, 82%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.55-7.54 (m, 2H), 7.35-7.34 (m, 3H), 6.30 (t, *J* = 7.4 Hz, 1H), 4.26 (ddd, *J* = 1.1, 7.6, 11.3 Hz, 1H), 4.08 (d, *J* = 9.9 Hz, 1H), 3.54 (dt, *J* = 2.9, 11.8 Hz, 1H), 2.58-2.52 (m, 2H), 2.44 (td, *J* = 2.2, 14.2 Hz, 1H), 2.32-2.29 (m, 1H), 2.01 (q, *J* = 7.4 Hz, 2H), 1.26-1.14 (m, 4H), 0.78 (t, *J* = 7.3 Hz, 3H), 0.46 (s, 3H), 0.45 (s, 3H); ^{13}C (151 MHz, $CDCl_3$) δ 207.8, 145.7, 139.4, 137.0, 134.0, 129.1, 127.9, 81.8, 66.4, 48.5, 42.4, 32.0, 31.7, 22.5, 14.1, -0.4, -0.6; IR (neat) 2958, 2926, 2854, 1720, 1246, 1110, 816 cm^{-1}; HRMS(EI) calcd for $C_{19}H_{28}O_2Si$ (M^+) 316.1859, found 316.1852.

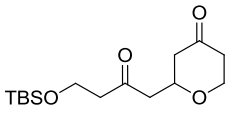


2-((*Z*)-Prop-1-en-1-yl)tetrahydro-2*H*-pyran-4-ol (2.90)

To **2.85** (40 mg, 0.15 mmol) in 1.4 mL MeOH at –10 °C was added $NaBH_4$ (4.0 mg, 0.11 mmol) in one portion. The mixture was stirred at that temperature for 10 minutes before it was quenched with 3 drops of H_2O. After concentration, it was purified by flash chromatography (30% EtOAc in hexane) to give **2.89** (35 mg, 87%).

To **2.89** (15 mg, 0.054 mmol) in 0.9 mL THF and 3 mL HMPA was added TBAF (1 M in THF, 271 μL), and the mixture was heated to 80 °C for 1.5 h.[8] Then the reaction was diluted with

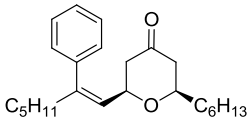
EtOAc, and washed with H_2O. The organic layer was concentrated and the residue was purified by flash chromatography (10% hexane in Et_2O) to give the desired product (7 mg, 91%). ^1H NMR (300 MHz, $CDCl_3$) δ 5.60 (dq, *J* = 1.1, 11.0 Hz, 1H), 5.43 (qdd, *J* = 1.6, 7.8, 11.1 Hz, 1H), 4.17-4.11 (m, 1H), 4.06 (ddd, *J* = 1.7, 4.9, 11.8 Hz, 1H), 3.84 (tt, *J* = 4.7, 11.0 Hz, 1H), 3.48 (dt, *J* = 2.1, 12.3 Hz, 1H), 1.97-1.87 (m, 2H), 1.69 (dd, *J* = 1.7, 6.8 Hz, 3H), 1.56-1.47 (m, 1H), 1.41-1.29 (m, 1H); ^{13}C (125 MHz, $CDCl_3$) δ 131.0, 127.0, 72.4, 68.3, 66.0, 41.7, 35.7, 13.7; IR (neat) 3383, 2922, 2852, 1073 cm^{-1}; HRMS(EI) calcd for $C_8H_{14}O_2$ (M^+) 142.0994, found 142.0989.



2-(4-(*tert*-Butyldimethylsilyloxy)-2-oxobutyl)dihydro-2*H*-pyran-4(3*H*)-one (2.91)

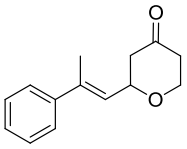
To the mixture of **2.70** and **2.71** (9 mg) in 0.2 mL THF under a N_2 atmosphere, 0.06 mL of TBAF in THF (1 M, 0.06 mmol) was added. The resulting mixture was stirred for 15 minutes before $KHCO_3$ (15 mg, 0.15 mmol), KF (9.0 mg, 0.15 mmol), 0.3 mL MeOH and H_2O_2 (30-32 wt. % in H_2O, 0.15 mL) were added.[9] After 31 h, the mixture was quenched with saturated $Na_2S_2O_3$ (aq), and extracted with EtOAc. After concentration, the alcohol was obtained and used as such. To the alcohol in 1 mL CH_2Cl_2 was added imidazole (3 mg, 0.04 mmol) and TBSCl (5.4 mg, 0.040 mmol). After 30 minutes, the mixture was concentrated and the residue was purified by flash chromatography (20% EtOAc in CH_2Cl_2) to give the desired product (7.9 mg, 75% over three steps). ^1H NMR (300 MHz, $CDCl_3$) δ 4.26 (dd, *J* = 7.4, 11.5 Hz, 1H), 4.16-4.07 (m, 1H), 3.90 (t, *J* = 6.2 Hz, 2H), 3.70 (dt, *J* = 2.9, 12.0 Hz, 1H), 2.89 (dd, *J* = 7.4, 16.5 Hz, 1H), 2.68-2.52 (m, 4H), 2.48 (td, *J* = 2.3, 14.6 Hz, 1H), 2.37-2.26 (m, 2H), 0.88 (s, 9H), 0.06 (s, 6H); ^{13}C (125 MHz, $CDCl_3$) δ 206.8, 206.1, 73.9, 66.7, 58.8, 49.8, 48.0, 46.8, 42.1, 29.9, 26.1, -5.2; IR

(neat) 2955, 2929, 2857, 1717, 1472, 1375, 1254, 1089, 836 cm^{-1}; HRMS(EI) calcd for $C_{11}H_{19}O_4Si$ (M^+-C_4H_9) 243.1053, found 243.1056.



(2*R*,6*R*)-2-Hexyl-6-((*Z*)-2-phenylhept-1-enyl)dihydro-2*H*-pyran-4(3*H*)-one (2.92)

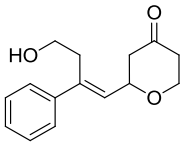
To the vinyl silane **2.69** (18 mg, 0.040 mmol) in 0.4 mL THF under a N_2 atmosphere, 0.09 mL of TBAF in THF (1 M, 0.09 mmol) was added. The resulting mixture was stirred for 15 minutes before PhI (6 μL, 0.05 mmol) and $Pd_2(dba)_3$ were added.[10] After another 30 minutes, the mixture was filtered through a short silica gel pad with CH_2Cl_2 and Et_2O. After concentration, it was purified by flash chromatography (8% Et_2O in hexane) to give the desired product (12 mg, 82%). ^1H NMR (600 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 7.1, 7.4 Hz, 2H), 7.29 (d, *J* = 7.3 Hz, 1H), 7.18 (d, *J* = 6.9 Hz, 2H), 5.50 (d, *J* = 8.8 Hz, 1H), 3.94 (ddd, *J* = 2.5, 8.9, 11.3 Hz, 1H), 3.44-3.40 (m, 1H), 2.42-2.33 (m, 3H), 2.31-2.28 (m, 2H), 2.21 (dd, *J* = 11.5, 14.3 Hz, 1H), 1.71-1.67 (m, 1H), 1.50-1.45 (m, 2H), 1.36-1.27 (m, 13H), 0.90 (t, *J* = 6.6 Hz, 3H), 0.85 (t, *J* = 6.8 Hz, 3H); ^{13}C (151 MHz, $CDCl_3$) δ 207.3, 146.9, 140.2, 128.2, 127.9, 127.3, 125.5, 76.5, 74.5, 48.1, 47.8, 39.0, 36.5, 31.8, 31.5, 29.1, 27.4, 25.4, 22.6, 22.5, 14.1, 14.0; IR (neat) 2954, 2926, 2856, 1719, 1045 cm^{-1}; HRMS(ESI) calcd for $C_{24}H_{36}O_2K$ $(M+K)^+$ 395.2352, found 395.2388.



(*E*)-2-(2-Phenylprop-1-enyl)dihydro-2*H*-pyran-4(3*H*)-one (2.93)

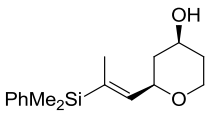
To the vinyl silane **2.75** (15 mg, 0.050 mmol) in 0.4 mL THF under a N_2 atmosphere, 0.11 mL of TBAF in THF (1 M, 0.11 mmol) was added. The resulting mixture was stirred for 10 minutes before PhI (7 μL, 0.06 mmol) and $Pd_2(dba)_3$ were added. After another 20 minutes, the mixture was filtered through a short silica gel pad with CH_2Cl_2 and Et_2O. After

concentration, it was purified by flash chromatography (15% EtOAc in hexane) to give the desired product (9.7 mg, 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.6 Hz, 2H), 7.34 (t, *J* = 7.2 Hz, 2H), 7.29 (t, *J* = 7.2 Hz, 1H), 5.81 (dd, *J* = 0.9, 7.7 Hz, 1H), 4.54 (dt, *J* = 5.4, 8.2 Hz, 1H), 4.37 (ddd, *J* = 0.9, 7.2, 11.4 Hz, 1H), 3.81 (dt, *J* = 2.8, 11.8 Hz, 1H), 2.67 (ddd, *J* = 7.3, 12.2, 14.6 Hz, 1H), 2.52-2.50 (m, 2H), 2.41-2.38 (m, 1H), 2.11 (d, *J* = 0.7 Hz, 3H); ^{13}C (151 MHz, $CDCl_3$) δ 206.7, 142.6, 139.3, 128.5, 127.9, 126.7, 126.1, 75.7, 66.7, 48.4, 42.5, 16.8; IR (neat) 2964, 2920, 2852, 1717, 1367, 1249, 1153, 1080, 757 cm^{-1}; HRMS(EI) calcd for $C_{14}H_{16}O_2$ (M^+) 216.1150, found 216.1144.



(*E*)-2-(4-Hydroxy-2-phenylbut-1-enyl)dihydro-2*H*-pyran-4(3*H*)-one (2.94)

To the mixture of **2.70** and **2.71** (15 mg) in 0.55 mL THF under a N_2 atmosphere, 0.1 mL of TBAF in THF (1 M, 0.1 mmol) was added. The resulting mixture was stirred for 25 minutes before PhI (12 μL, 0.1 mmol) and $Pd_2(dba)_3$ were added. After 5 h, the reaction was quenched by H_2O, and the crude mixture was extracted with EtOAc. After concentration, it was purified by flash chromatography (70% EtOAc in hexane) to give the desired product (10 mg, 69% over two steps). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39-7.32 (m, 5H), 5.83 (d, *J* = 7.8 Hz, 1H), 4.55 (q, *J* = 7.4 Hz, 1H), 4.36 (dd, *J* = 7.3, 11.4 Hz, 1H), 3.84 (dt, *J* = 2.8, 11.9 Hz, 1H), 3.70-3.65 (m, 1H), 3.62-3.56 (m, 1H), 2.89-2.81 (m, 2H), 2.67 (ddd, *J* = 7.3, 12.2, 14.7 Hz, 1H), 2.57-2.56 (m, 2H), 2.42-2.40 (m, 1H), 2.07 (t, *J* = 5.4 Hz, 1H); ^{13}C (151 MHz, $CDCl_3$) δ 206.2, 142.6, 141.1, 129.4, 128.8, 128.2, 126.9, 74.8, 66.6, 60.6, 48.5, 42.3, 34.3; IR (neat) 3359, 2922, 2854, 1714, 1650, 1367, 1246, 1041, 761 cm^{-1}; HRMS(EI) calcd for $C_{15}H_{18}O_3$ (M^+) 246.1256, found 246.1249.

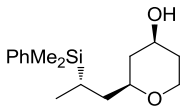


(2*R*,4*S*)-2-((*E*)-2-(Dimethyl(phenyl)silyl)prop-1-enyl)tetrahydro-2*H*-pyran-4-ol (2.101)

To a solution of **2.85** (40 mg, 0.15 mmol) in MeOH (1.4 mL) at –10 °C was added $NaBH_4$ (4 mg, 0.1 mmol) in one portion. After stirring at that temperature for 10 minutes, the reaction was quenched with H_2O. After concentration, it was purified by flash chromatography (30% EtOAc in hexane) to give the desired alcohol (35 mg, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51-7.48(m, 2H), 7.37-7.34 (m, 3H), 5.81 (qd, *J* = 1.5, 7.2 Hz, 1H), 4.21 (ddd, *J* = 1.8, 7.3, 11.1 Hz, 1H), 4.06 (dd, *J* = 1.6, 5.0, 11.8 Hz, 1H), 3.84 (tt, *J* = 4.7, 11.0 Hz, 1H), 3.48 (dt, *J* = 2.1, 12.4 Hz, 1H), 1.99-1.87 (m, 2H), 1.71 (d, 1.7 Hz, 3H), 1.66-1.50 (m, 2H), 0.36 (s, 6H); ^{13}C (125 MHz, $CDCl_3$) δ 140.6, 138.0, 137.4, 134.2, 129.2, 128.0, 73.5, 68.2, 66.0, 41.1, 35.7, 15.5, -3.4, -3.5; IR (neat) 3371, 2950, 2850, 1427, 1361, 1247, 1110, 1077, 832, 813 cm^{-1}; HRMS(EI) calcd for $C_{16}H_{24}O_2Si$ (M^+) 276.1546, found 276.1537.

General procedure for Crabtree's catalyst catalyzed hydrogenation of vinyl silane:[11]

A mixture of vinyl silane (1 eq) and Crabtree's catalyst (0.02 eq) in CH_2Cl_2 (0.02-0.04 M final substrate concentration) was evacuated and back-filled with H_2 three times. The mixture was stirred under H_2 atmosphere for 10 minutes, before another portion of Crabtree's catalyst (0.02 eq) was added, and the mixture was evacuated and back-filled with H_2 three times. More Crabtree's catalyst was added every 10 minutes until the reaction was complete monitored by TLC. The mixture was concentrated and the residue was purified by flash chromatography to give the desired product.



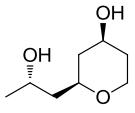
(2*R*,4*S*)-2-((*S*)-2-(Dimethyl(phenyl)silyl)propyl)tetrahydro-2*H*-pyran-4-ol (2.102)

The general procedure of Crabtree' catalyst catalyzed hydrogenation reaction was followed: A mixture of **2.101** (30 mg, 0.11 mmol) and Crabtree's catalyst (1.7 mg, 0.002 mmol) in CH_2Cl_2 (3 mL) was evacuated and back-filled with H_2 three times. The mixture was stirred under H_2 atmosphere for 5 h, before another portion of Crabtree's catalyst (1.7 mg, 0.0021 mmol) was added, and the mixture was evacuated and back-filled with H_2 three times. After 1 h, more Crabtree's catalyst (1.7 mg, 0.0021 mmol) was added, and 1.5 h later, the mixture was concentrated and the residue was purified by flash chromatography (25% EtOAc in hexane) to give the desired product (27 mg, 89%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52-7.50 (m, 2H), 7.36-7.35 (m, 3H), 4.01 (dd, *J* = 4.4, 11.8 Hz, 1H), 3.76-3.70 (m, 1H), 3.36-3.30 (m, 2H), 1.88-1.82 (m, 2H), 1.69 (ddd, *J* = 2.7, 9.5, 13.0 Hz, 1H), 1.51-1.44 (m, 2H), 1.22-1.15 (m, 2H), 0.92 (d, *J* = 7.1 Hz, 3H), 0.27 (s, 3H), 0.26 (s, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 138.5, 134.2, 129.0, 127.9, 73.5, 68.6, 66.1, 42.6, 38.1, 36.0, 14.8, 13.9, -4.7, -4.9; IR (neat) 3364, 2943, 2847, 1247, 1081, 1027, 813 cm^{-1}; HRMS(EI) calcd for $C_{15}H_{23}O_2Si$ (M^+-CH_3) 263.1467, found 263.1461.

General procedure for Fleming oxidation reactions:[12]

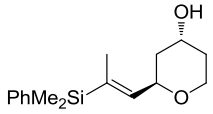
Potassium bromide (1.2 eq) and anhydrous sodium acetate (3.1 eq) were added to a stirred solution of the dimethylphenylsilane (1 eq) in glacial acetic acid (~0.17 M substrate concentration). Then peracetic acid (10 eq, 32 wt. % in dilute acetic acid) was added dropwise to the mixture at 0 °C. More sodium acetate (9.3 eq) and peracetic acid (30 eq) were added to the mixture and the mixture was stirred at room temperature for specified time. After the addition of ether and powdered $Na_2S_2O_3$ to the mixture, it was stirred vigorously for 30 minutes, filtered

through Celit with Et_2O, and the filtrate was washed with aqueous $NaHCO_3$. After concentration, the residue was purified by flash chromatography to give the desired alcohol.



(2*S*,4*S*)-2-((*S*)-2-Hydroxypropyl)tetrahydro-2*H*-pyran-4-ol (2.103)

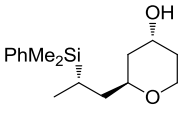
The general procedure of Fleming oxidation reaction was followed: KBr (4 mg, 0.03 mmol) and NaOAc (6.5 mg, 0.079 mmol) were added to a stirred solution of the **2.102** (7 mg, 0.02 mmol) in glacial acetic acid (120 μL). Then peracetic acid (32 μL) was added dropwise to the mixture at 0 °C. 1.5 h later, ether and powdered $Na_2S_2O_3$ were added to the mixture. The mixture was stirred vigorously for 30 minutes, filtered through Celit with Et_2O, and the filtrate was washed with aqueous $NaHCO_3$. After concentration, the residue was purified by flash chromatography (90% EtOAc in hexane) to give the desired product (3.2 mg, 80%, dr = 9:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.07-3.99 (m, 2H), 3.80 (tt, *J* = 4.7, 10.7 Hz, 1H), 3.75 (s, 1H), 3.57-3.53 (m, 1H), 3.44 (dt, *J* = 1.4, 12.1 Hz, 1H), 1.95-1.90 (m, 2H), 1.67 (dt, *J* = 4.7, 9.9 Hz, 2H), 1.55-1.49 (m, 1H), 1.32-1.28 (m, 1H), 1.18 (d, *J* = 6.1 Hz, 3H); ^{13}C (151 MHz, $CDCl_3$) δ 77.7, 68.3, 67.9, 66.2, 44.6, 42.1, 35.6, 23.6; IR (neat) 3417, 2956, 2848, 1643 cm^{-1}; HRMS(EI) calcd for $C_8H_{14}O_2$ (M^+-H_2O) 142.0994, found 142.0989.



(2*R*,4*R*)-2-((*E*)-2-(Dimethyl(phenyl)silyl)prop-1-en-1-yl)tetrahydro-2*H*-pyran-4-ol (2.104)

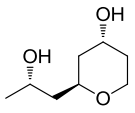
To a solution of **2.85** (33 mg, 0.12 mmol) in THF (6 mL) at –90 °C was added L-Selectride (180 μL, 0.180 mmol, 1 M in THF) dropwise over 5 minutes. After stirring at that temperature for 45 minutes, the reaction was quenched with saturated potassium sodium tartrate (aq). The mixture was diluted with Et_2O, and stirred at room temperature for 1 h. Then the mixture was extracted with EtOAc. After concentration, it was purified by flash chromatography (20% EtOAc in

hexane) to give the desired alcohol (25 mg, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50-7.48 (m, 2H), 7.35-7.34 (m, 3H), 5.78 (dd, *J* = 1.5, 7.3 Hz, 1H), 4.72-4.68 (m, 1H), 4.29-4.23 (m, 1H), 3.96 (dt, *J* = 2.1, 12.3 Hz, 1H), 3.82 (dd, *J* = 3.9, 11.5 Hz, 1H), 1.94-1.87 (m, 1H), 1.74 (d, *J* = 1.4 Hz, 3H), 1.70-1.66 (m, 2H), 0.99-0.91 (m, 1H), 0.35 (s, 6H); ^{13}C (125 MHz, $CDCl_3$) δ 141.2, 138.1, 137.4, 134.2, 129.2, 128.0, 69.0, 64.3, 62.3, 38.6, 33.1, 15.6, -3.3, -3.5; IR (neat) 3416, 2952, 2920, 2867, 1427, 1248, 1110, 1059, 832, 813 cm^{-1}; HRMS(EI) calcd for $C_{16}H_{24}O_2Si$ (M^+) 276.1546, found 276.1555.



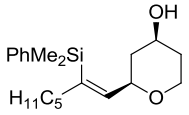
(2*R*,4*R*)-2-((*S*)-2-(Dimethyl(phenyl)silyl)propyl)tetrahydro-2*H*-pyran-4-ol (2.105)

The general Crabtree' catalyst mediated hydrogenation reaction procedure was followed with a mixture of **2.104** (21 mg, 0.076 mmol) and Crabtree's catalyst (1.4 mg, 0.0017 mmol) in CH_2Cl_2 (1.7 mL). The mixture was stirred under H_2 for 1 h and another portion of Crabtree's catalyst (1.4 mg, 0.0017 mmol) was added. After 30 minutes the mixture was concentrated and the residue was purified by flash chromatography (30% EtOAc in hexane) to give the desired product (19 mg, 90%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52-7.51(m, 2H), 7.36-7.35 (m, 3H), 4.20 (t, *J* = 3.0 Hz, 1H), 3.84-3.70 (m, 3H), 1.82 (ddt, *J* = 2.7, 5.6, 14.2 Hz, 1H), 1.62 (ddd, *J* = 3.5, 9.7, 13.4 Hz, 1H), 1.52-1.44 (m, 3H), 1.22 (m, 1H), 1.09 (ddd, *J* = 3.2, 11.8, 14.1 Hz, 1H), 0.95 (d, *J* = 7.3 Hz, 3H), 0.27 (s, 3H), 0.26 (s, 3H); ^{13}C (125 MHz, $CDCl_3$) δ 138.7, 134.3, 129.0, 127.9, 68.7, 64.5, 62.5, 39.9, 38.0, 33.4, 14.7, 13.9, -4.7, -4.8; IR (neat) 3419, 2921, 2863, 1248, 1110, 1069, 814 cm^{-1}; HRMS(EI) calcd for $C_{15}H_{23}O_2Si$ (M^+-CH_3) 263.1467, found 263.1459.



(2*S*,4*R*)-2-((*S*)-2-Hydroxypropyl)tetrahydro-2*H*-pyran-4-ol (2.106)

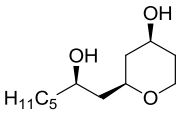
The general Fleming oxidation reaction procedure was followed with **2.105** (14 mg, 0.050 mmol), KBr (8 mg, 0.07 mmol), NaOAc (13 mg, 0.16 mmol), glacial acetic acid (200 μL), and peracetic acid (64 μL). The reaction was stirred at room temperature for 0.5 h and purified by flash chromatography (10% hexane in EtOAc) to give the desired product (6.3 mg, 79%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.24 (br, 1H), 4.06-4.01 (m, 2H), 3.92 (t, *J* = 12.7 Hz, 1H), 3.82 (dd, *J* = 5.3, 11.4 Hz, 1H), 3.79 (br, 1H), 1.88 (ddt, *J* = 3.2, 5.2, 15.6 Hz, 1H), 1.60-1.56 (m, 3H), 1.49-1.46 (m, 2H), 1.17 (d, *J* = 6.2 Hz, 3H); ^{13}C (151 MHz, $CDCl_3$) δ 73.2, 68.3, 63.6, 62.2, 44.4, 39.2, 32.8, 23.4; IR (neat) 3384, 2924, 1650, 1423, 1113, 1058 cm^{-1}; HRMS(EI) calcd for $C_8H_{14}O_2$ (M^+-H_2O) 142.0994, found 142.0987.



(2*R*,4*S*)-2-((*Z*)-2-(Dimethyl(phenyl)silyl)hept-1-enyl)tetrahydro-2*H*-pyran-4-ol (2.107)

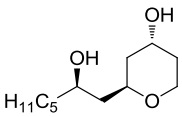
To a solution of **2.68** (28 mg, 0.080 mmol) in MeOH (0.9 mL) at –10 °C was added $NaBH_4$ (2 mg, 0.05 mmol) in one portion. After stirring at that temperature for 15 minutes, the reaction was quenched with H_2O. After concentration, it was purified by flash chromatography (15% EtOAc in hexane) to give the desired alcohol (24 mg, 85%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.55-7.53(m, 2H), 7.36-7.35 (m, 3H), 5.99 (d, *J* = 8.8 Hz, 1H), 3.87 (ddd, *J* = 1.1, 4.7, 11.7 Hz, 1H), 3.68 (dt, *J* = 1.8, 10.8 Hz, 1H), 3.43-3.39 (m, 1H), 3.02 (dt, *J* = 1.9, 12.3 Hz, 1H), 2.14 (t, *J* = 7.7 Hz, 2H), 1.73 (qd, *J* = 1.9, 12.4 Hz, 1H), 1.60 (pd, *J* = 2.3, 12.4 Hz, 1H), 1.37-1.31 (m, 4H), 1.30-1.24 (m, 4H), 0.87 (t, *J* = 6.7 Hz, 3H), 0.43 (s, 3H), 0.38 (s, 3H); ^{13}C (151 MHz, $CDCl_3$) δ 142.5, 142.4, 139.7, 134.0, 129.1, 128.0, 75.6, 68.1, 65.6, 41.5, 38.2, 35.4, 31.9, 30.2, 22.7, 14.3, -0.6, -0.9; IR

(neat) 3379, 2955, 2926, 2854, 1427, 1364, 1250, 1110, 1076, 833, 815 cm^{-1}; HRMS(EI) calcd for $C_{20}H_{32}O_2Si$ (M^+) 332.2172, found 332.2170.



(2*S*,4*S*)-2-((*R*)-2-Hydroxyheptyl)tetrahydro-2*H*-pyran-4-ol (2.109)

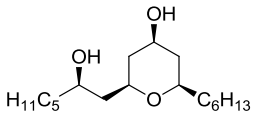
The general Crabtree' catalyst mediated hydrogenation reaction procedure was followed with a mixture of **2.107** (10 mg, 0.030 mmol) and Crabtree's catalyst (0.5 mg, 0.0006 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred under H_2 for 10 minutes and another portion of Crabtree's catalyst (0.5 mg, 0.0006 mmol) was added. The mixture was stirred under H_2 for another 15 minutes and the other portion of Crabtree's catalyst (0.5 mg, 0.0006 mmol) was added. After 10 minutes the mixture was concentrated and the residue was purified by flash chromatography (20% EtOAc in hexane) to give **2.108**. The general Fleming oxidation reaction procedure was followed with **2.108** from last step, KBr (3.4 mg, 0.029 mmol), NaOAc (6 mg, 0.07 mmol), glacial acetic acid (110 μL), and peracetic acid (30 μL). The reaction was stirred at room temperature for 1 h and purified by flash chromatography (25% hexane in EtOAc) to give the desired product (4 mg, 65% over two steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.03 (dd, *J* = 3.9, 11.8 Hz, 1H), 3.88 (br, 1H), 3.82 (tt, *J* = 4.7, 10.9 Hz, 1H), 3.65-3.61 (m, 1H), 3.41 (dt, *J* = 1.6, 12.4 Hz, 1H), 2.50 (br, 1H), 1.91-1.88 (m, 2H), 1.69 (ddd, *J* = 2.5, 8.1, 14.6 Hz, 1H), 1.56-1.36 (m, 6H), 1.35-1.28 (m, 5H), 0.90 (t, *J* = 6.6 Hz, 3H); ^{13}C (125 MHz, $CDCl_3$) δ 73.8, 68.7, 68.1, 66.0, 42.3, 41.4, 37.5, 35.6, 31.9, 25.5, 22.7, 14.1; IR (neat) 3385, 2923, 1651, 1427, 1110, 1059 cm^{-1}; HRMS(EI) calcd for $C_{12}H_{24}O_3Na$ $(M+Na)^+$ 239.1623, found 239.1618.



(2*S*,4*R*)-2-((*R*)-2-Hydroxyheptyl)tetrahydro-2*H*-pyran-4-ol (2.112)

To a solution of **2.68** (79 mg, 0.24 mmol) in THF (12 mL) at -90 °C was added

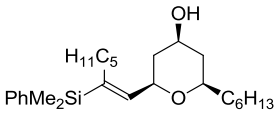
L-selectride (260 μL, 0.360 mmol, 1 M in THF) dropwise over 5 minutes. After stirring at that temperature for 40 minutes, the reaction was quenched with saturated potassium sodium tartrate (aq). The mixture was diluted with Et_2O, and stirred at room temperature for 0.5 h. Then the mixture was extracted with EtOAc. After concentration, it was purified by flash chromatography (20% EtOAc in hexane) to give **2.110** (73 mg, 92%). The general Crabtree' catalyst mediated hydrogenation reaction procedure was followed with a mixture of **2.110** (10 mg, 0.03 mmol) and Crabtree's catalyst (0.5 mg, 0.0006 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred under H_2 for 10 minutes and another portion of Crabtree's catalyst (0.5 mg, 0.0006 mmol) was added. The mixture was stirred under H_2 for another 10 minutes and the other portion of Crabtree's catalyst (0.5 mg, 0.0006 mmol) was added. After 10 minutes the mixture was concentrated and the residue was purified by flash chromatography (20% EtOAc in hexane) to give **2.111**. The general Fleming oxidation reaction procedure was followed with **2.111** from last step, KBr (4.3 mg, 0.036 mmol), NaOAc (9.7 mg, 0.12 mmol), glacial acetic acid (140 μL), and peracetic acid (40 μL). The reaction was stirred at room temperature for 30 minutes and purified by flash chromatography (25% hexane in EtOAc) to give the desired product (5.6 mg, 86% over two steps). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.27-4.25 (m, 1H), 4.10 (tdd, J = 2.5, 8.2, 11.0 Hz, 1H), 3.91-3.85 (m, 2H), 3.80 (dd, J = 5.0, 11.5 Hz, 1H), 2.78 (br,1H), 1.86 (ddt, J = 2.6, 5.2, 14.1 Hz, 1H), 1.70 (ddd, J = 2.5, 11.7, 14.0 Hz, 1H), 1.66-1.63 (m, 1H), 1.61-1.59 (m, 1H), 1.58-1.49 (m, 3H), 1.43-1.39 (m, 2H), 1.35-1.28 (m, 5H), 0.89 (t, J = 6.4 Hz, 3H); ^{13}C (125 MHz, $CDCl_3$) δ 69.6, 69.1, 64.1, 62.6, 42.1, 38.8, 37.6, 33.1, 32.1, 25.8, 22.9, 14.3; IR (neat) 3383, 2927, 1649, 1430, 1111, 1061 cm^{-1}; HRMS(ESI) calcd for $C_{12}H_{24}O_3Na$ $(M+Na)^+$ 239.1623, found 239.1611.



(2*R*,4*S*,6*S*)-2-Hexyl-6-((*R*)-2-hydroxyheptyl)tetrahydro-2*H*-pyran-4-ol (2.124)

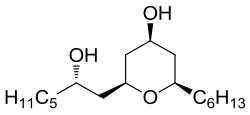
To a solution of **2.115** (40 mg, 0.14 mmol) in MeOH (1.5 mL) at –10 °C was added $NaBH_4$ (2.8 mg, 0.074 mmol) in one portion. After stirring at that temperature for 15 minutes, the reaction was quenched with H_2O. After concentration, it was purified by flash chromatography (15% EtOAc in hexane) to give the **2.117** (34 mg, 85%). To **2.117** (from last step) and dimethylphenylsilane (6 μL, 0.04 mmol) in acetone (0.25 mL) was added $[Cp^*Ru(MeCN)_3]PF_6$ (0.5 mg, 0.001 mmol) at 0 °C. After 10 minutes at 0 °C, the mixture was concentrated and purified by flash chromatography to give **2.119** (14 mg, 91%). The general Crabtree' catalyst mediated hydrogenation reaction procedure was followed with a mixture of **2.119** (14 mg) and Crabtree's catalyst (0.5 mg, 0.0006 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred under H_2 for 10 minutes and another portion of Crabtree's catalyst (0.5 mg, 0.0006 mmol) was added. After 10 minutes the mixture was concentrated and the residue was purified by flash chromatography (15% EtOAc in hexane) to give (2*R*,4*S*,6*R*)-2-((*R*)-2-(dimethyl(phenyl)silyl)-heptyl)-6-hexyltetrahydro-2*H*-pyran-4-ol. The general Fleming oxidation reaction procedure was followed with (2*R*,4*S*,6*R*)-2-((*R*)-2-(dimethyl(phenyl)silyl)heptyl)-6-hexyltetrahydro-2*H*-pyran-4-ol (from last step), KBr (5 mg, 0.04 mmol), NaOAc (16 mg, 0.20 mmol), glacial acetic acid (150 μL), and peracetic acid (80 μL). The reaction was stirred at room temperature for 1.5 h and purified by flash chromatography (30% hexane in EtOAc) to give the desired product (2.5 mg, 53% over two steps). ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.92-3.86 (m, 1H), 3.83 (ddd, *J* = 4.6, 10.8, 15.6 Hz, 1H), 3.68-3.64 (m, 1H), 3.32-3.29 (m, 1H), 2.89 (br, 1H), 1.97-1.94 (m, 1H), 1.88-1.85 (m, 1H), 1.73-1.64 (m, 2H), 1.57-1.11 (m, 20H), 0.91-0.87 (m, 6H); ^{13}C (151 MHz, $CDCl_3$) δ 76.0, 73.4, 68.9, 68.2, 41.6, 41.2, 40.9, 37.3, 36.0, 31.9, 31.8, 29.2, 25.6, 25.5, 22.7, 22.6, 14.1,

14.0; IR (neat) 3379, 2924, 2853, 1716, 1457 cm^{-1}; HRMS(EI) calcd for $C_{18}H_{36}O_3$ (M^+) 300.2664, found 300.2650.



(2*R*,4*S*,6*R*)-2-((*E*)-2-(Dimethyl(phenyl)silyl)hept-1-enyl)-6-hexyl-tetrahydro-2*H*-pyran-4-ol (2.121)

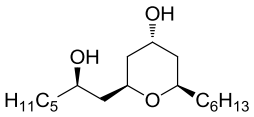
To a stirred solution of **2.117** (32 mg, 0.11 mmol) in 0.1 mL THF was added dimethylphenylsilane (20 µL, 0.13 mmol) and a solution of H_2PtCl_6•$6H_2O$ (0.001 M in THF, 114 µL). The mixture was heated at 50 °C for 5 h, cooled and filtered through Celite with Et_2O. The solvent was removed under vacuum and purified by flash chromatography (12% EtOAc in hexane) to give the desired product (31 mg, 65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52-7.49 (m, 2H), 7.35-7.32 (m, 3H), 5.82 (d, *J* = 7.8 Hz, 1H), 4.17 (ddd, *J* = 1.8, 8.9, 13.0 Hz, 1H), 3.85 (tdd, *J* = 4.6, 10.8, 15.6 Hz, 1H), 3.35-3.29 (m, 1H), 2.11 (t, *J* = 7.2 Hz, 2H), 2.00-1.89 (m, 2H), 1.70-1.60 (m, 1H), 1.48-1.33 (m, 4H), 1.33-1.29 (m, 7H), 1.22-1.11 (m, 6H), 0.89 (t, *J* = 7.1 Hz, 3H), 0.81 (t, *J* = 5.9 Hz, 3H), 0.37 (s, 3H), 0.36 (s, 3H); ^{13}C (151 MHz, $CDCl_3$) δ 142.6, 141.1, 138.8, 134.2, 129.1, 127.9, 76.0, 72.6, 68.5, 41.7, 41.2, 36.3, 32.4, 32.0, 30.8, 30.3, 29.5, 25.8, 22.8, 22.6, 14.3, 14.2, –2.4, –2.7; IR (neat) 3363, 2954, 2928, 2857, 1459, 1427, 1363, 1249, 1111, 1063, 831, 814 cm^{-1}; HRMS(ESI) calcd for $C_{26}H_{44}O_2SiNa$ $(M+Na)^+$ 439.3008, found 439.3014.



(2*R*,4*S*,6*S*)-2-Hexyl-6-((*R*)-2-hydroxyheptyl)tetrahydro-2*H*-pyran-4-ol (2.125)

The general Crabtree's catalyst mediated hydrogenation reaction procedure was followed with a mixture of **2.121** (10 mg, 0.024 mmol) and Crabtree's catalyst (0.5 mg, 0.0006 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred under H_2 atmosphere for 10 minutes and another portion of

Crabtree's catalyst (0.5 mg, 0.0006 mmol) was added. After 10 minutes, the mixture was concentrated and the residue was purified by flash chromatography (18% EtOAc in hexane) to give the desired product. The general Fleming oxidation reaction procedure was followed with the silane, KBr (3 mg, 0.02 mmol), NaOAc (20 mg, 0.24 mmol), glacial acetic acid (110 μL) and peracetic acid (120 μL). The reaction was stirred at room temperature for 5 h and purified by flash chromatography (30% EtOAc in hexane) to give the desired product (4.8 mg, 67% over two steps). ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.88 (br, 1H), 3.86-3.77 (m, 2H), 3.61-3.57 (m, 1H), 3.39-3.35 (m, 1H), 1.97-1.91 (m, 2H), 1.67-1.57 (m, 2H), 1.52-1.36 (m, 6H), 1.35-1.27 (m, 10H), 1.24-1.15 (m, 4H), 0.90 (t, J = 6.8 Hz, 3H), 0.88 (t, J = 7.1 Hz, 3H); ^{13}C (151 MHz, $CDCl_3$) δ 77.3, 76.3, 72.5, 68.0, 42.6, 41.9, 41.2, 37.8, 36.1, 32.2, 31.9, 29.5, 25.8, 25.4, 22.9, 22.8, 14.3; IR (neat) 3379, 2924, 2853, 1716, 1457, 1374, 1034 cm^{-1}; HRMS(EI) calcd for $C_{18}H_{36}O_3$ (M^+) 300.2664, found 300.2660.



(2*R*,4*R*,6*S*)-2-Hexyl-6-((*R*)-2-hydroxyheptyl)tetrahydro-2*H*-pyran-4-ol (2.126)

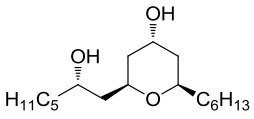
To a solution of **2.115** (102 mg, 0.37 mmol) in THF (15 mL) at –90 °C was added L-Selectride (550 μL, 0.550 mmol, 1 M in THF) dropwise over 5 minutes. After stirring at –90 °C for 20 minutes, the reaction was quenched with saturated potassium sodium tartrate (aq). The mixture was diluted with Et_2O, and stirred at room temperature for 1 h. The mixture was extracted with Et_2O, concentrated, and purified by flash chromatography (20% EtOAc in hexane) to give the desired alcohol (67 mg, 65%). To the alcohol (15 mg, 0.050 mmol) and dimethylphenylsilane (9.2 μL, 0.060 mmol) in acetone (0.4 mL) was added $[Cp^*Ru(MeCN)_3]PF_6$ (0.5 mg, 0.001 mmol) at 0 °C. After 30 minutes at 0 °C, the mixture was concentrated and purified by flash chromatography to give **2.122** (20 mg, 92%). To **2.122** (34 mg, 0.080 mmol) in DMF (0.15 mL)

was added imidazole (23 mg, 0.34 mmol), TBSCl (32 mg, 0.21 mmol) and DMAP (10 mg, 0.08 mmol) successively at room temperature. After stirring for 24 h, it was quenched with H_2O, and the mixture was extracted with Et_2O. After concentration, it was purified by flash chromatography (5% Et_2O in hexane) to give the *tert*-butyl(((2*R*,4*R*,6*R*)-2-((*Z*)-2-(dimethyl(phenyl)silyl)hept-1-en-1-yl)-6-hexyltetrahydro-2*H*-pyran-4-yl)oxy)dimethylsilane (42 mg, 97%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56-7.55 (m, 2H), 7.32-7.31 (m, 3H), 6.00 (d, *J* = 9.5 Hz, 1H), 4.37 (td, *J* = 7.0, 9.3 Hz, 1H), 4.12 (t, *J* = 2.6 Hz, 1H), 3.37 (p, *J* = 5.6 Hz, 1H), 2.13-2.04 (m, 2H), 1.49 (dd, *J* = 2.6, 7.3 Hz, 2H), 1.43-1.19 (m, 18H), 0.90 (t, *J* = 7.2 Hz, 3H), 0.85-0.83 (m, 12H), 0.43 (s, 3H), 0.40 (s, 3H), 0.00 (s, 3H), -0.01 (s, 3H); ^{13}C (151 MHz, $CDCl_3$) δ 143.8, 141.9, 140.0, 134.1, 128.9, 127.8, 71.4, 71.2, 65.4, 39.8, 39.1, 38.6, 36.5, 32.1, 31.9, 30.1, 29.6, 26.1, 25.8, 22.9, 22.7, 18.2, 14.4, 14.3, –0.2, –0.5, –4.6, –4.8; IR (neat) 2925, 2848, 1716, 1457, 1374, 1014 cm^{-1}; HRMS(ESI) calcd for $C_{32}H_{58}O_2Si_2Na$ $(M+Na)^+$ 553.3873, found 553.3837.

The general Crabtree's catalyst catalyzed hydrogenation reaction procedure was followed with a mixture of the vinylsilane (10 mg, 0.020 mmol) and Crabtree's catalyst (0.5 mg, 0.0006 mmol) in CH_2Cl_2 (1.0 mL). The mixture was stirred under H_2 for 10 minutes, and another portion of Crabtree's catalyst (0.5 mg, 0.0006 mmol) was added. After 10 minutes the mixture was concentrated and the residue was purified by flash chromatography (2% Et_2O in hexane) to give the desired product. The general Fleming oxidation reaction procedure was followed with the silane, KBr (3 mg, 0.02 mmol), NaOAc (21 mg, 0.24 mmol), glacial acetic acid (120 μL), and peracetic acid (200 μL). The reaction was stirred at room temperature for 18 h and purified by flash chromatography (10% Et_2O in hexane) to give the desired product (4.8 mg, 56% over two steps). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.19-4.18 (m, 1H), 4.16-4.12 (m, 1H), 3.89-3.86 (m, 1H),

3.80-3.75 (m, 1H), 3.35 (d, J = 4.5 Hz, 1H), 1.64-1.61 (m, 2H), 1.55-1.50 (m, 2H), 1.48-1.41 (m, 4H), 1.40-1.36 (m, 2H), 1.34-1.27 (m, 14H), 0.90-0.87 (m, 15H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C (151 MHz, $CDCl_3$) δ 72.3, 70.1, 69.4, 65.3, 41.4, 39.5, 39.1, 37.4, 36.4, 32.2, 32.0, 29.5, 26.0, 25.8, 25.7, 22.9, 22.8, 18.3, 14.3, 14.2, –4.6, –4.7; IR (neat) 3381, 2921, 2854, 1715, 1459, 1374, 1030 cm^{-1}; HRMS(EI) calcd for $C_{23}H_{47}O_3Si$ (M^+-CH_3) 399.3294, found 399.3280.

To the silyl ether (1.5 mg, 0.0050 mmol) in 0.5 mL THF was added Bu_4NF (17 μL, 1 M in THF). The reaction was stirred at rt for 5 h, then was concentrated and purified by flash chromatography (50% EtOAc in hexane) to give **2.126** (1.0 mg, 92%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.28 (br, 1H), 4.15-4.12 (m, 1H), 3.90-3.85 (m, 1H), 3.79-3.75 (m, 1H), 3.12 (d, J = 4.9 Hz, 1H),1.69-1.62 (m, 4H), 1.61-1.58 (m, 1H), 1.54-1.36 (m, 8H), 1.36-1.27 (m, 11H), 0.90 (t, J = 6.7 Hz, 3H), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C (151 MHz, $CDCl_3$) δ 72.1, 69.9, 69.4, 65.0, 41.7, 38.8, 38.5, 37.5, 36.4, 32.2, 32.0, 29.5, 25.9, 25.7, 22.9, 22.8, 14.3, 14.2; IR (neat) 3379, 2925, 2853, 1717, 1460, 1374, 1032 cm^{-1}; HRMS(ESI) calcd for $C_{23}H_{47}O_3SiNa$ $(M+Na)^+$ 323.2562, found 323.2541.



(2*R*,4*R*,6*S*)-2-Hexyl-6-((*S*)-2-hydroxyheptyl)tetrahydro-2*H*-pyran-4-ol (2.127)

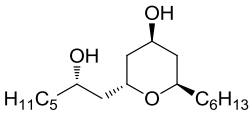
To a stirred solution of **2.118** (46 mg, 0.16 mmol) in 0.15 mL THF was added dimethylphenylsilane (30 μL, 0.19 mmol) and a solution of H_2PtCl_6•$6H_2O$ (0.001 M in THF, 164 μL). The mixture was heated at 50 °C for 6 h, cooled and filtered through Celite with Et_2O. The solvent was removed under vacuum and purified by flash chromatography (5% to 10% EtOAc in hexane) to give **2.123** (46 mg, 67%). To **2.123** (45 mg, 0.11 mmol) in DMF (0.2 mL) was added imidazole (30 mg, 0.43 mmol), TBSCl (41 mg, 0.27 mmol) and DMAP (10 mg, 0.080 mmol)

successively at room temperature. After stirring for 23 h, it was quenched with H_2O, and the mixture was extracted with Et_2O. After concentration, it was purified by flash chromatography (2% Et_2O in hexane) to give the desired product (55 mg, 96%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51-7.50 (m, 2H), 7.34-7.33 (m, 3H), 5.81 (d, *J* = 7.9 Hz, 1H), 4.71 (dt, *J* = 4.2, 8.7 Hz, 1H), 4.19 (br, 1H), 3.82-3.78 (m, 1H), 2.15-2.06 (m, 2H), 1.60-1.57 (m, 1H), 1.53-1.51 (m, 2H), 1.40-1.34 (m, 3H), 1.32-1.29 (m, 8H), 1.24-1.18 (m, 6H), 0.91 (s, 9H), 0.89 (t, *J* = 6.6 Hz, 3H), 0.81 (t, *J* = 6.5 Hz, 3H), 0.36 (s, 3H), 0.35 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C (151 MHz, $CDCl_3$) δ 142.5, 141.2, 139.1, 134.2, 129.0, 127.8, 71.9, 69.3, 65.4, 40.0, 39.2, 36.5, 32.5, 32.0, 30.8, 30.4, 29.5, 26.0, 25.7, 22.9, 22.7, 18.2, 14.3, 14.2, –2.3, –2.6, –4.6, –4.7; IR (neat) 2953, 2928, 2857, 1251, 1095, 1055, 832, 814, 772 cm^{-1}; HRMS(EI) calcd for $C_{32}H_{58}O_2Si_2$ (M^+) 530.3975, found 530.3970.

The general Crabtree's catalyst mediated hydrogenation reaction procedure was followed with a mixture of the silane (12 mg, 0.020 mmol) and Crabtree's catalyst (0.5 mg, 0.0006 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred under H_2 for 10 minutes and another portion of Crabtree's catalyst (0.5 mg, 0.0006 mmol) was added. After 10 minutes the mixture was concentrated and the residue was purified by flash chromatography (3% Et_2O in hexane) to give the desired product. The general Fleming oxidation reaction procedure was followed with the silane, KBr (3.2 mg, 0.030 mmol), NaOAc (23 mg, 0.28 mmol), glacial acetic acid (130 μL) and peracetic acid (180 μL). The reaction was stirred at room temperature for 8 h and purified by flash chromatography (4% EtOAc in hexane) to give the desired product (6.6 mg, 71% over two steps). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.22 (br, 1H), 4.15-4.14 (m, 1H), 4.05 (tt, *J* = 2.8, 10.0 Hz, 1H), 3.90-3.86 (m, 1H), 3.84-3.80 (m, 1H), 1.55-1.44 (m, 8H), 1.43-1.28 (m, 16H), 0.90 (s, 9H), 0.89-0.86 (m, 6H), 0.05 (s, 6H); ^{13}C (151 MHz, $CDCl_3$) δ 73.9, 72.8, 72.2, 65.0, 42.6, 40.2, 39.4,

37.9, 36.3, 32.3, 31.9, 29.6, 26.0, 25.8, 25.4, 22.9, 22.8, 18.3, 14.3, –4.7; IR (neat) 3505, 2928, 2856, 1726, 1463, 1254, 1076, 837 cm^{-1}; HRMS(ESI) calcd for $C_{24}H_{50}O_3SiNa$ $(M+Na)^+$ 437.3427, found 437.3465.

To the alcohol (1.5 mg, 0.0050 mmol) in THF (0.5 mL) was added Bu_4NF (17 μL, 1 M in THF). The reaction was stirred at room temperature for 5 h, then was concentrated and purified by flash chromatography (40% EtOAc in hexane) to give the desired product (1.0 mg, 92%). ^1H NMR (600 MHz, $CDCl_3$) δ 4.26-4.22 (m, 1H), 4.08-4.04 (m, 2H), 3.89-3.85 (m, 1H), 3.84-3.81 (m, 1H), 1.67-1.61 (m, 2H), 1.55-1.47 (m, 6H), 1.44-1.36 (m, 5H), 1.35-1.29 (m, 11H), 0.90 (t, *J* = 6.8 Hz, 3H), 0.88 (t, *J* = 7.1 Hz, 3H); ^{13}C (151 MHz, $CDCl_3$) δ 73.7, 72.7, 72.1, 64.7, 42.6, 39.4, 38.8, 37.8, 36.3, 32.2, 31.9, 29.5, 25.8, 25.4, 22.9, 22.8, 14.3; IR (neat) 3376, 2924, 2850, 1465, 1379, 1021 cm^{-1}; HRMS(ESI) calcd for $C_{18}H_{36}O_3Na$ $(M+Na)^+$ 323.2562, found 323.2548.



(2*R*,4*S*,6*R*)-2-Hexyl-6-((*S*)-2-hydroxyheptyl)tetrahydro-2*H*-pyran-4-ol (2.135)

To a freshly prepared SmI_2 solution[8] (8.0 mL, 0.06 M in THF, 0.48 mmol) was added a solution of **2.116** (65 mg, 0.23 mmol) and ^iPrOH (20 μL, 0.23 mmol) in THF (1 mL) dropwise. The reaction was stirred under argon for 6 h, and then was quenched with aq. $NaHCO_3$ at 0 °C. The crude mixture was extracted with EtOAc and the combined organic layer was dried over $MgSO_4$, concentrated, and purified by flash chromatography (15% EtOAc in hexane) to give **2.128** (55 mg, 85%). ^1H NMR (600 MHz, $CDCl_3$) δ 4.84-4.82 (m, 1H), 4.14 (m, 1H), 3.89-3.86 (m, 1H), 2.21 (dt, *J* = 2.1, 7.1 Hz, 2H), 2.02 (td, *J* = 2.1, 12.1 Hz, 1H), 1.97 (td, *J* = 2.3, 12.2 Hz, 1H), 1.65-1.60 (m, 1H), 1.54-1.49 (m, 3H), 1.48-1.14 (m, 14H), 0.92-0.88 (m, 6H); ^{13}C (75 MHz, $CDCl_3$) δ 87.6, 77.4, 70.5, 65.6, 64.8, 41.7, 40.3, 36.1, 32.0, 31.3, 29.4, 28.6, 25.5, 22.8, 22.4,

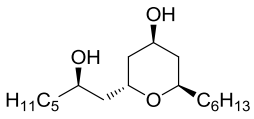
18.9, 14.3, 14.2; IR (neat) 3583, 3417, 2927, 2857, 1459, 1337, 1064 cm^{-1}; HRMS(ESI) calcd for $C_{18}H_{36}O_3K$ $(M+K)^+$ 319.2039, found 319.2029.

To the alcohol (18 mg, 0.06 mmol) and dimethylphenylsilane (12 μL, 0.080 mmol) in acetone (0.4 mL) was added $[Cp^*Ru(MeCN)_3]PF_6$ (0.5 mg, 0.001 mmol) at 0 °C. After 2 h at 0 °C, the mixture was concentrated and purified by flash chromatography to give **2.131** (23 mg, 86%). To **2.131** (16 mg, 0.04 mmol) in DMF (0.25 mL) was added imidazole (11 mg, 0.16 mmol), TBSCl (15 mg, 0.1 mmol) and DMAP (10 mg, 0.08 mmol) successively at room temperature. After stirring for 8 h, the reaction was quenched with H_2O, and the mixture was extracted with Et_2O. After concentration, the mixture was purified by flash chromatography (3% Et_2O in hexane) to give the *tert*-butyl(((2*S*,4*S*,6*R*)-2-((*Z*)-2-(dimethyl(phenyl)silyl)hept-1-en-1-yl)-6-hexyltetra-hydro-2*H*-pyran-4-yl)oxy)dimethylsilane (17 mg, 84%). ^1H NMR (600 MHz, $CDCl_3$) δ 7.53-7.51 (m, 2H), 7.33-7.32 (m, 3H), 6.30 (d, *J* = 9.4 Hz, 1H), 4.55 (p, *J* = 4.6 Hz, 1H), 4.05-4.02 (m, 1H), 3.70-3.67 (m, 1H), 2.11 (t, *J* = 7.6 Hz, 2H), 1.79 (td, *J* = 3.0, 12.4 Hz, 1H), 1.53-1.46 (m, 2H), 1.36-1.22 (m, 17H), 0.90-0.85 (m, 15H), 0.44 (s, 3H), 0.42 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C (151 MHz, $CDCl_3$) δ 142.4, 141.7, 139.4, 134.0, 129.1, 128.0, 70.5, 69.2, 65.4, 40.0, 39.5, 38.7, 35.6, 32.1, 31.8, 30.3, 29.5, 26.2, 26.1, 22.9, 22.7, 18.4, 14.3, 14.2, –0.4, –0.5, –4.4, –4.5; IR (neat) 2927, 2846, 1715, 1459, 1373, 1011 cm^{-1}; HRMS(ESI) calcd for $C_{32}H_{58}O_2Si_2Na$ $(M+Na)^+$ 553.3873, found 553.3822.

The general Crabtree' catalyst mediated hydrogenation reaction procedure was followed with a mixture of the vinylsilane (7.5 mg, 0.010 mmol) and Crabtree's catalyst (0.5 mg, 0.0006 mmol) in CH_2Cl_2 (0.8 mL). The mixture was stirred under H_2 for 15 minutes and another portion of Crabtree's catalyst (0.5 mg, 0.0006 mmol) was added. After 15 minutes the mixture was concentrated and the residue was purified by flash chromatography (4% Et_2O in hexane) to give

the desired product. The general Fleming oxidation reaction procedure was followed with the silane, KBr (3 mg, 0.03 mmol), NaOAc (14 mg, 0.17 mmol), glacial acetic acid (100 μL), and peracetic acid (130 μL). The reaction was stirred at room temperature for 5 h and purified by flash chromatography (10% EtOAc in hexane) to give the (*S*)-1-((2*R*,4*S*,6*R*)-4-((*tert*-butyldimethylsilyl)oxy)-6-hexyltetrahydro-2*H*-pyran-2-yl)heptan-2-ol (3.7 mg, 65% over two steps). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.35-4.31 (m, 1H), 4.01 (tt, *J* = 4.9, 9.7 Hz, 1H), 3.79 (br, 1H), 3.64 (tt, *J* = 4.9, 9.5 Hz, 1H), 2.48 (br, 1H), 1.91 (ddd, *J* = 3.5, 12.3, 16.4 Hz, 1H), 1.81 (td, *J* = 4.1, 15.7 Hz, 1H), 1.78-1.68 (m, 1H), 1.67-1.60 (m, 2H), 1.54-1.38 (m, 6H), 1.37-1.26 (m, 13H), 0.92-0.88 (m, 15H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C (151 MHz, $CDCl_3$) δ 70.6, 69.2, 67.1, 65.4, 39.7, 39.4, 39.2, 37.5, 35.5, 32.1, 32.0, 29.6, 26.3, 26.0, 25.8, 22.9, 18.3, 14.3, 14.2, –4.4, –4.5; IR (neat) 3510, 2918, 2859, 1726, 1466, 1251, 1079, 837 cm^{-1}; HRMS(ESI) calcd for $C_{24}H_{50}O_3SiNa$ $(M+Na)^+$ 437.3427, found 437.3432.

To the alcohol (3 mg, 0.01 mmol) in THF (0.6 mL) was added Bu_4NF (30 μL, 1 M in THF). The reaction was stirred at room temperature for 24 h, then was concentrated and purified by flash chromatography (30% hexane in EtOAc) to give **2.135** (2.1 mg, 97%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.40-4.37 (m, 1H), 4.02 (tt, *J* = 5.3, 9.7 Hz, 1H), 3.77 (br, 1H), 3.60-3.56 (m, 1H), 2.17 (br, 1H), 2.00 (ddd, *J* = 2.9, 11.0, 14.2 Hz, 1H), 1.96-1.94 (m, 1H), 1.83-1.81 (m, 1H), 1.68-1.62 (m, 2H), 1.55-1.50 (m, 1H), 1.45-1.39 (m, 5H), 1.36-1.28 (m, 13H), 0.90 (t, *J* = 6.8 Hz, 3H), 0.89 (t, *J* = 7.1 Hz, 3H); ^{13}C (151 MHz, $CDCl_3$) δ 69.4, 68.9, 68.7, 65.0, 40.9, 39.0, 38.4, 37.7, 36.1, 32.1, 32.0, 29.6, 26.0, 25.8, 22.9, 14.3, 14.2; IR (neat) 3375, 2927, 2851, 1465, 1381, 1026 cm^{-1}; HRMS(ESI) calcd for $C_{18}H_{36}O_3Na$ $(M+Na)^+$ 323.2562, found 323.2574.



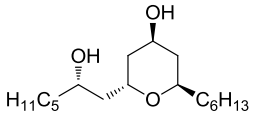
(2*R*,4*S*,6*R*)-2-Hexyl-6-((*R*)-2-hydroxyheptyl)tetrahydro-2*H*-pyran-4-ol (2.136)

To a stirred solution of **2.128** (54 mg, 0.19 mmol) in THF (0.18 mL) was added dimethylphenylsilane (35 μL, 0.22 mmol) and a solution of H_2PtCl_6•$6H_2O$ (0.001 M in THF, 193 μL). The mixture was heated at 50 °C for 3.5 h, cooled and filtered through Celite with Et_2O. The solvent was removed under vacuum and purified by flash chromatography (15% EtOAc in hexane) to give **2.132** (65 mg, 62%). To **2.132** (22 mg, 0.05 mmol) in CH_2Cl_2 (2 mL) was added imidazole (6 mg, 0.09 mmol), TBSCl (10 mg, 0.068 mmol) and DMAP (5 mg, 0.04 mmol) successively at room temperature. After stirring for 8 h, the mixture was concentrated and purified by flash chromatography (4% Et_2O in hexane) to give the *tert*-Butyl((2*S*,4*S*,6*R*)-2-((*E*)-2-(dimethyl(phenyl)silyl)hept-1-enyl)-6-hexyltetrahydro-2*H*-pyran-4-yloxy)dimethylsilane (28 mg, 99%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51-7.50 (m, 2H), 7.35-7.34 (m, 3H), 5.95 (d, *J* = 7.5 Hz, 1H), 4.85 (td, *J* = 4.3, 8.0 Hz, 1H), 3.96 (ddd, *J* = 3.7, 7.4, 12.6 Hz, 1H), 3.65-3.61 (m, 1H), 2.27-2.22 (m, 1H), 2.16-2.11 (m, 1H), 1.82-1.80 (m, 1H), 1.72 (td, *J* = 4.0, 12.8 Hz, 1H), 1.69-1.64 (m, 2H), 1.51-1.35 (m, 3H), 1.34-1.27 (m, 8H), 1.24-1.17 (m, 5H), 0.90-0.88 (m, 12H), 0.82 (t, *J* = 6.2 Hz, 3H), 0.38 (s, 6H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C (151 MHz, $CDCl_3$) δ 144.0, 140.4, 138.9, 134.2, 129.1, 127.9, 70.5, 67.5, 65.7, 40.5, 40.3, 35.8, 32.5, 32.1, 30.5, 29.9, 29.5, 26.1, 26.0, 22.9, 22.7, 18.4, 14.3, 14.2, –2.3, –2.4, –4.4, –4.5; IR (neat) 2955, 2929, 2856, 1250, 1096, 1048 cm^{-1}; HRMS(ESI) calcd for $C_{32}H_{58}O_2Si_2Na$ $(M+Na)^+$ 553.3873, found 553.3916.

The general Crabtree's catalyst mediated hydrogenation reaction procedure was followed with a mixture of the silane (9 mg, 0.02 mmol) and Crabtree's catalyst (0.5 mg, 0.0006 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred under H_2 for 15 minutes, then another portion of Crabtree's catalyst (0.5 mg, 0.0006 mmol) was added. After 20 minutes the mixture was

concentrated and the residue was purified by flash chromatography (5% Et_2O in hexane) to give the desired product. The general Fleming oxidation reaction procedure was followed with the silane, KBr (2.4 mg, 0.020 mmol), NaOAc (13 mg, 0.16 mmol), glacial acetic acid (100 μL), and peracetic acid (120 μL). The reaction was stirred at room temperature for 3.5 h and purified by flash chromatography (10% EtOAc in hexane) to give the desired product (4.2 mg, 60% over two steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.24-4.22 (m, 1H), 4.02-3.97 (m, 1H), 3.84-3.80 (m, 1H), 3.79-3.75 (m, 1H), 3.72 (s, 1H), 1.86-1.76 (m, 3H), 1.63-1.61 (m, 2H), 1.50-1.34 (m, 8H), 1.31-1.28 (m, 11H), 0.91-0.87 (m, 15H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C (125 MHz, $CDCl_3$) δ 72.9, 71.3, 70.9, 65.1, 40.2, 39.7, 39.2, 37.7, 35.3, 32.2, 31.9, 29.6, 26.1, 26.0, 25.4, 22.9, 22.8, 18.3, 14.3, –4.4, –4.5; IR (neat) 3515, 2916, 2855, 1726, 1460, 1249, 1081, 837 cm^{-1}; HRMS(ESI) calcd for $C_{24}H_{50}O_3SiNa$ $(M+Na)^+$ 437.3427, found 437.3428.

To the alcohol (3.5 mg, 0.0080 mmol) in THF (0.6 mL) was added Bu_4NF (30 μL, 1 M in THF). The reaction was stirred at room temperature for 8 h, then was concentrated and purified by flash chromatography (45% hexane in EtOAc) to give **2.136** (2.5 mg, 97%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.32-4.30 (m, 1H), 4.02 (ddd, *J* = 4.0, 9.0, 13.5 Hz, 1H), 3.86-3.80 (m, 1H), 3.78-3.74 (m, 1H), 3.48 (br, 1H), 1.99-1.97 (m, 1H), 1.91 (td, *J* = 9.9, 14.6 Hz, 1H), 1.81-1.78 (m, 1H), 1.68-1.64 (m, 2H), 1.50-1.37 (m, 7H), 1.34-1.27 (m, 12H), 0.90 (t, *J* = 6.8 Hz, 3H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C (151 MHz, $CDCl_3$) δ 73.1, 72.9, 69.9, 64.7, 40.4, 39.6, 38.5, 37.6, 36.0, 32.1, 31.9, 29.6, 25.8, 25.4, 22.9, 22.8, 14.3; IR (neat) 3378, 2921, 2852, 1464, 1380, 1069 cm^{-1}; HRMS(ESI) calcd for $C_{18}H_{36}O_3Na$ $(M+Na)^+$ 323.2562, found 323.2582.



(2*R*,4*R*,6*R*)-2-Hexyl-6-((*S*)-2-hydroxyheptyl)tetrahydro-2*H*-pyran-4-ol (2.137)

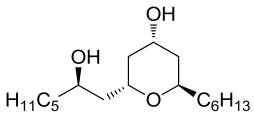
To a solution of **2.116** (47 mg, 0.17 mmol) in THF (7 mL) at –90 °C was added L-Selectride (252 µL, 0.252 mmol, 1 M in THF) dropwise over 10 minutes. After stirring at that temperature for 15 minutes, the reaction was quenched with saturated potassium sodium tartrate (aq). The mixture was diluted with Et_2O, and stirred at room temperature for 1 h. Then the mixture was extracted with Et_2O. After concentration, it was purified by flash chromatography (15% EtOAc in hexane) to give **2.129** (42 mg, 89%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.71 (dd, *J* = 2.0, 5.3 Hz, 1H), 4.20-4.16 (m, 1H), 4.13 (qd, *J* = 3.4, 12.4 Hz, 1H), 3.11 (d, *J* = 9.1 Hz, 1H), 2.25 (dt, *J* = 2.0, 7.1 Hz, 2H), 2.03 (ddd, *J* = 3.6, 5.6, 14.0 Hz, 1H), 1.90-1.88 (m, 1H), 1.81-1.78 (m, 1H), 1.54-1.49 (m, 4H), 1.43-1.29 (m, 13H), 0.91 (t, *J* = 7.2 Hz, 3H), 0.89 (t, *J* = 7.1 Hz, 3H); ^{13}C (125 MHz, $CDCl_3$) δ 88.5, 80.0, 66.5, 65.5, 61.9, 38.9, 37.0, 35.8, 32.0, 31.3, 29.4, 28.4, 25.5, 22.9, 22.4, 18.9, 14.3, 14.2; IR (neat) 3356, 2926, 2856, 1457, 1366, 1334, 1045 cm^{-1}; HRMS(EI) calcd for $C_{18}H_{30}O$ (M^+) 262.2297, found 262.2289.

To **2.129** (10 mg, 0.038 mmol) and dimethylphenylsilane (8 µL, 0.04 mmol) in acetone (0.2 mL) was added [Cp*Ru(MeCN)$_3$]PF_6 (0.5 mg, 0.001 mmol) at 0 °C. After 1 h at 0 °C, the mixture was concentrated and purified by flash chromatography to give **2.133** (15 mg, 99%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.54-7.52 (m, 2H), 7.37-7.36 (m, 3H), 6.00 (d, *J* = 8.9 Hz, 1H), 4.01-3.98 (m, 1H), 3.92 (q, *J* = 5.9 Hz, 1H), 3.53 (ddd, *J* = 4.6, 10.7, 15.3 Hz, 1H), 2.14 (t, *J* = 7.7 Hz, 2H), 1.73-1.70 (m, 1H), 1.48-1.44 (m, 2H), 1.43-1.35 (m, 2H), 1.30-1.24 (m, 12H), 1.16-1.14 (m, 2H), 1.12-1.06 (m, 1H), 0.90 (t, *J* = 7.1 Hz, 3H), 0.88 (t, *J* = 7.1 Hz, 3H), 0.42 (s, 3H), 0.39 (s, 3H); ^{13}C (151 MHz, $CDCl_3$) δ 143.5, 140.5, 140.0, 133.9, 129.2, 128.1, 73.4, 68.7, 64.4, 41.5, 38.3, 37.7, 32.0, 31.9, 31.7, 30.2, 29.4, 26.6, 22.9, 22.7, 14.4, 14.3, –0.6, –1.1; IR (neat) 3382, 2926,

2854, 1650, 1540, 1457, 1366, 1252, 1110 cm^{-1}; HRMS(EI) calcd for $C_{26}H_{44}O_2Si$ (M^+) 416.3111, found 416.3107.

To **2.133** (30 mg, 0.072 mmol) in CH_2Cl_2 (1.5 mL) was added imidazole (7 mg, 0.1 mmol), TBSCl (13 mg, 0.086 mmol) and DMAP (3 mg, 0.02 mmol) successively at room temperature. After stirring for 3 h, the mixture was concentrated and purified by flash chromatography (4% Et_2O in hexane) to give the desired product (36 mg, 94%). The general Crabtree's catalyst mediated hydrogenation reaction procedure was followed with the vinylsilane (10 mg, 0.020 mmol) and Crabtree's catalyst (0.5 mg, 0.0006 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred under H_2 for 10 minutes and another portion of Crabtree's catalyst (0.5 mg, 0.0006 mmol) was added. After 10 minutes the mixture was concentrated and the residue was purified by flash chromatography (5% EtOAc in hexane) to give the desired product. The general Fleming oxidation reaction procedure was followed with the silane, KBr (3.2 mg, 0.027 mmol), NaOAc (8.2 mg, 0.10 mmol), glacial acetic acid (120 μL), and peracetic acid (45 μL). The reaction was stirred at room temperature for 2 h and purified by flash chromatography (25% Et_2O in hexane) to give the (*S*)-1-((2*R*,4*R*,6*R*)-4-(*tert*-Butyldimethylsilyloxy)-6-hexyltetrahydro-2*H*-pyran-2-yl)heptan-2-ol (5.6 mg, 74% over two steps). ^1H NMR (600 MHz, $CDCl_3$) δ, 4.02-3.94 (m, 3H), 3.88-3.83 (m, 1H), 2.68 (d, *J* = 4.2 Hz, 1H), 1.86 (ddd, *J* = 2.4, 8.8, 14.6 Hz, 1H), 1.77-1.75 (m, 1H), 1.73-1.66 (m, 2H), 1.64-1.60 (m, 1H), 1.53-1.48 (m, 2H), 1.43-1.36 (m, 4H), 1.36-1.29 (m, 13H), 0.90-0.85 (m, 15H), 0.06 (s, 6H); ^{13}C (151 MHz, $CDCl_3$) δ 71.8, 69.1, 66.9, 65.3, 41.8, 41.0, 38.9, 37.7, 32.3, 32.2, 32.0, 29.4, 26.4, 26.1, 25.7, 22.9, 22.8, 18.3, 14.3, 14.2, –4.4, –4.5; IR (neat) 3508, 2929, 2856, 1463, 1253, 1105, 1045, 835 cm^{-1}; HRMS(ESI) calcd for $C_{24}H_{50}O_3SiNa$ $(M+Na)^+$ 437.3427, found 437.3422.

To the alcohol (1.7 mg, 0.0039 mmol) in THF (0.4 mL) was added Bu_4NF (20 μL, 1 M in THF). The reaction was stirred at room temperature for 5 h then was concentrated and purified by flash chromatography (30% hexane in EtOAc) to give **2.137** (1.2 mg, 97%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.06-4.00 (m, 2H), 3.93 (tdd, *J* = 2.6, 8.1, 10.7 Hz, 1H), 3.86 (br, 1H), 2.66 (s, 1H), 1.90-1.83 (m, 2H), 1.77-1.73 (m, 2H), 1.63-1.58 (m, 2H), 1.53-1.46 (m, 1H), 1.43-1.29 (m, 17H), 0.90 (t, *J* = 6.8 Hz, 3H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C (151 MHz, $CDCl_3$) δ 72.9, 69.1, 66.5, 64.8, 42.2, 41.2, 38.4, 37.8, 32.1, 32.0, 31.8, 29.3, 26.4, 25.7, 22.9, 22.8, 14.3, 14.2; IR (neat) 3383, 2927, 2850, 1462, 1381, 1076 cm^{-1}; HRMS(ESI) calcd for $C_{18}H_{36}O_3Na$ $(M+Na)^+$ 323.2562, found 323.2567.



(2*R*,4*R*,6*R*)-2-Hexyl-6-((*R*)-2-hydroxyheptyl)tetrahydro-2*H*-pyran-4-ol (2.138)

To a stirred solution of **2.129** (37 mg, 0.13 mmol) in 0.12 mL THF was added dimethylphenylsilane (25 μL, 0.15 mmol) and a solution of H_2PtCl_6•$6H_2O$ (0.001 M in THF, 130 μL). The mixture was heated at 50 °C for 5 h, cooled and filtered through Celite with Et_2O. The solvent was removed under vacuum and purified by flash chromatography (15% EtOAc in hexane) to give **2.134** (35 mg, 64%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51-7.49 (m, 2H), 7.35-7.32 (m, 3H), 5.86 (d, *J* = 7.8 Hz, 1H), 4.49 (ddd, *J* = 2.7, 8.0, 10.5 Hz, 1H), 4.08-4.03 (m, 2H), 2.11 (t, *J* = 7.2 Hz, 2H), 1.95-1.91 (m, 1H), 1.87-1.84 (m, 1H), 1.78-1.70 (m, 1H), 1.63 (ddd, *J* = 5.6, 10.6, 12.6 Hz, 1H), 1.46-1.39 (m, 2H), 1.37-1.27 (m, 9H), 1.25-1.18 (m, 5H), 0.89 (t, *J* = 6.7 Hz, 3H), 0.82 (t, *J* = 6.7 Hz, 3H), 0.38 (s, 3H), 0.37 (s, 3H); ^{13}C (151 MHz, $CDCl_3$) δ 142.3, 141.5, 138.7, 134.2, 129.1, 127.9, 73.0, 65.5, 64.7, 41.4, 38.1, 32.4, 32.1, 32.0, 30.5, 30.3, 29.5, 26.5,

22.9, 22.6, 14.3, 14.2, –2.4, –2.7; IR (neat) 3375, 2928, 2856, 1456, 1427, 1372, 1249, 1111, 1054, 814 cm^{-1}; HRMS(EI) calcd for $C_{26}H_{44}O_2Si$ (M^+) 416.3111, found 416.3118.

To **2.134** (27 mg, 0.065 mmol) in CH_2Cl_2 (2 mL) were added imidazole (7 mg, 0.1 mmol), TBSCl (12 mg, 0.080 mmol) and DMAP (5 mg, 0.04 mmol) successively at room temperature. After stirring for 8 h, the mixture was concentrated and purified by flash chromatography (3% Et_2O in hexane) to give the *tert*-butyl((2*S*,4*R*,6*R*)-2-((*E*)-2-(dimethyl(phenyl)silyl)hept-1-enyl)-6-hexyltetrahydro-2*H*-pyran-4-yloxy)dimethylsilane (34 mg, 99%). ^1H NMR (600 MHz, $CDCl_3$) δ 7.52-7.50 (m, 2H), 7.34-7.33 (m, 3H), 5.93 (d, *J* = 7.9 Hz, 1H), 4.49 (td, *J* = 2.9, 8.7 Hz, 1H), 4.02 (ddd, *J* = 4.5, 9.4, 13.9 Hz, 1H), 2.15-2.08 (m, 2H), 1.81-1.79 (m, 1H), 1.75-1.69 (m, 2H), 1.64 (ddd, *J* = 5.2, 9.6, 14.7 Hz, 1H), 1.44-1.39 (m, 3H), 1.34-1.25 (m, 8H), 1.23-1.17 (m, 5H), 0.90-0.88 (m, 12H), 0.82 (t, *J* = 6.7 Hz, 3H), 0.37 (s, 3H), 0.36 (s, 3H), 0.07 (s, 6H); ^{13}C (151 MHz, $CDCl_3$) δ 141.9, 139.9, 134.3, 129.0, 127.9, 72.4, 65.8, 65.3, 41.3, 38.7, 32.4, 32.3, 32.0, 30.5, 30.4, 29.5, 26.5, 26.1, 22.9, 22.6, 18.4, 14.3, 14.2, –2.4, –2.6, –4.4; IR (neat) 2959, 2927, 2856, 1248, 1087, 1043 cm^{-1}; HRMS(ESI) calcd for $C_{32}H_{58}O_2Si_2Na$ $(M+Na)^+$ 553.3873, found 553.3880.

The general Crabtree's catalyst mediated hydrogenation reaction procedure was followed with the vinylsilane (12 mg, 0.022 mmol) and Crabtree's catalyst (0.5 mg, 0.0006 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred under H_2 for 15 minutes, and another portion of Crabtree's catalyst (0.5 mg, 0.0006 mmol) was added. After 15 minutes more Crabtree's catalyst (0.5 mg, 0.0006 mmol) was added. This was repeated three more times, then after 1.5 h at room temperature the mixture was concentrated and the residue was purified by flash chromatography (3% Et_2O in hexane) to give the desired product. The general Fleming oxidation reaction procedure was followed with the silane, KBr (3.2 mg, 0.027 mmol), NaOAc (23 mg, 0.28 mmol), glacial acetic

acid (130 μL), and peracetic acid (180 μL). The reaction was stirred at room temperature for 6 h and purified by flash chromatography (5% EtOAc in hexane) to give the desired product (5.8 mg, 62% over two steps). ^{1}H NMR (600 MHz, $CDCl_3$) δ, 4.03 (qd, *J* = 4.7, 8.8 Hz, 1H), 3.98 (ddd, *J* = 4.4, 9.2, 13.7 Hz, 1H), 3.86 (td, *J* = 2.6, 9.9 Hz, 1H), 3.85 (s, 1H), 3.79-3.76 (m, 1H), 1.82-1.79 (m, 1H), 1.77-1.72 (m, 2H), 1.67-1.60 (m, 2H), 1.52-1.47 (m, 2H), 1.39-1.36 (m, 4H), 1.35-1.29 (m, 13H), 0.90-0.88 (m, 15H), 0.06 (s, 6H); ^{13}C (151 MHz, $CDCl_3$) δ 72.6, 71.8, 70.9, 64.7, 42.1, 41.4, 38.5, 37.5, 32.1, 32.0, 31.7, 29.2, 25.9, 25.8, 25.2, 22.7, 22.6, 18.1, 14.1, –4.6; IR (neat) 3505, 2928, 2856, 1726, 1463, 1254, 1117, 1076, 837 cm^{-1}; HRMS(ESI) calcd for $C_{24}H_{50}O_3SiNa$ $(M+Na)^+$ 437.3427, found 437.3425.

To the alcohol (2.7 mg, 0.0065 mmol) in THF (0.7 mL) was added Bu_4NF (30 μL, 1 M in THF). The reaction was stirred at room temperature for 8 h, then was concentrated and purified by flash chromatography (30% hexane in EtOAc) to give **2.138** (1.8 mg, 92%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.09-4.06 (m, 1H), 4.00 (ddd, *J* = 4.7, 10.6, 15.2 Hz, 1H), 3.84-3.78 (m, 2H), 3.77 (s, 1H), 1.94 (td, *J* = 2.2, 12.4 Hz, 1H), 1.85 (td, *J* = 2.3, 12.7 Hz, 1H), 1.80-1.75 (m, 1H), 1.69-1.60 (m, 3H), 1.51-1.47 (m, 1H), 1.43-1.36 (m, 5H), 1.34-1.28 (m, 12H), 0.90 (t, *J* = 6.7 Hz, 3H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C (151 MHz, $CDCl_3$) δ 73.0, 72.2, 70.1, 64.2, 42.6, 41.7, 38.0, 37.5, 32.0, 31.7, 31.4, 29.1, 26.0, 25.2, 22.7, 22.6, 14.1; IR (neat) 3381, 2925, 2852, 1461, 1380, 1074 cm^{-1}; HRMS(ESI) calcd for $C_{18}H_{36}O_3Na$ $(M+Na)^+$ 323.2562, found 323.2535.

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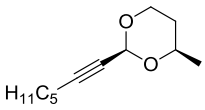
APPENDIX C

STEREOSELECTIVE SYNTHESIS OF TERTIARY ETHERS THROUGH GEOMETRIC CONTROL OF HIGHLY SUBSTITUTED OXOCARBENIUM IONS

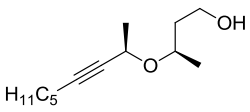
General Experimental Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on a Bruker Avance 300 spectrometer at 300 MHz and 75 MHz, a Bruker Avance 400 spectrometer at 400 MHz and 100 MHz, a Bruker Avance 500 spectrometer at 500 MHz and 125 MHz, a Bruker Avance 600 spectrometer at 600 MHz and 151 MHz if specified. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. The solvent peak was used as a reference value, for ^{1}H NMR: $CDCl_3$ = 7.26 ppm, for ^{13}C NMR: $CDCl_3$ = 77.23. Data are reported as follows: (s = singlet; d = doublet; t = triplet; q = quartet; dd = doublet of doublets; dt = doublet of triplets; br = broad). High resolution and low resolution mass spectra were recorded on a VG 7070 spectrometer. Infrared (IR) spectra were collected on a Mattson Cygnus 100 spectrometer. Samples for IR were prepared as a thin film on a NaCl plate by dissolving the compound in CH_2Cl_2 and then evaporating the CH_2Cl_2. Analytical TLC was performed on E. Merck pre-coated (25 mm) silica gel 60F-254 plates. Visualization was done under UV light (254 nm). Flash chromatography was done using ICN SiliTech 32-63 60 Å silica gel. Methylene chloride was distilled under N_2 from CaH_2, and 1,2–dichloroethane was dried

over 4Å molecular sieves. Reagent grade ethyl acetate, diethyl ether, pentane and hexanes were purchased from EM Science and used as purchased for chromatography. Tetrahydrofuran and diethyl ether were dried by passage through an activated alumina column under positive N_2 pressure. Anhydrous (*N*,*N*)-dimthylformamide (DMF), methanol (MeOH), dimethyl sulfoxide (DMSO), acetone were purchased from Aldrich and used as it is. Activated 4 Å molecular sieves were obtained through drying in oven at 150 °C overnight. All reactions were performed in oven or flame-dried glassware under a positive pressure of N_2 with magnetic stirring unless otherwise noted.



(2*S*,4*R*)-2-(Hept-1-yn-1-yl)-4-methyl-1,3-dioxane (3.10)

The mixture of oct-2-ynal (3.43 g, 27.6 mmol), 1,3-butanediol (2.50 mL, 27.6 mmol) and PPTs (30 mg, 0.12 mmol) in 30 mL benzene was heated at reflux with azeotropic removal of water overnight. Then the reaction mixture was concentrated and purified by flash chromatography (5% EtOAc in pentane) to give the desired product (3.3 g, 61%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.21 (s, 1H), 4.11 (dd, *J* = 4.9, 11.6 Hz, 1H), 3.85-3.72 (m, 2H), 2.22 (dt, *J* = 1.3, 7.1 Hz, 2H), 1.80-1.63 (m, 1H), 1.56-1.29 (m, 7H), 1.26 (d, *J* = 6.2 Hz, 3H), 0.86 (t, *J* = 6.9 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 91.8, 86.4, 75.8, 73.7, 67.1, 32.8, 31.2, 28.0, 22.3, 21.8, 18.7, 14.0; IR (neat) 2933, 2859, 2253, 1462, 1430, 1399, 1375, 1356, 1222, 1248, 1166, 1145, 1103, 1053, 1021, 994, 964, 951, 933 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{20}O_2$ (M^+) 196.1463, found 196.1458.



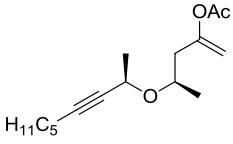
(*R*)-3-((*R*)-Non-3-yn-2-yloxy)butan-1-ol (3.11)

To **3.10** (196 mg, 1.00 mmol) in 20 mL toluene at 0 ℃ was added $AlMe_3$

(2 M in toluene, 6 mL) dropwise.[1] After stirring at rt for 30 minutes, the mixture was poured into 40 mL 2 N NaOH (aq), and the organic layer was separated. After concentration, the resulting residue was purified by flash chromatography (20% EtOAc in pentane) to give the desired product (160 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.24 (tq, *J* = 1.9, 6.5 Hz, 1H), 3.89 (qd, *J* = 6.4, 12.8 Hz, 1H), 3.79-3.71 (m, 2H), 2.44 (br, 1H), 2.18 (dt, *J* = 1.9, 7.1 Hz, 2H), 1.77-1.65 (m, 2H), 1.53-1.46 (m, 2H), 1.38 (d, *J* = 6.5 Hz, 3H), 1.36-1.29 (m, 4H), 1.27 (d, *J* = 6.3 Hz, 3H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 85.1, 81.1, 73.8, 64.6, 60.5, 38.5, 31.2, 28.5, 23.2, 22.3, 21.0, 18.8, 14.1; IR (neat) 3405, 2960, 2933, 2863, 1458, 1372, 1328, 1166, 1136, 1080, 1058 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{24}O_2$ (M^+) 212.1776, found 212.1769.

General procedure for the enol acetate preparation:[2]

A mixture of Na_2CO_3 (15%), [(*p*-cymene)$RuCl_2$]$_2$ (0.04 eq), tri(2-furyl)phosphine (0.08 eq), acetic acid (2.0 eq), and 1-decyne (0.5 eq) in toluene was heated to 80 °C and stirred for 1 h. Another portion of acetic acid (2.0 eq) and the alkyne substrate (1.0 eq) were dissolved in toluene and added to the mixture (~0.15 M final substrate concentration). The reaction was stirred at 80 °C overnight. Then crude mixture was concentrated on a rotary evaporator and purified by flash chromatography to give the desired enol acetate product.



(*R*)-4-((*R*)-Non-3-yn-2-yloxy)pent-1-en-2-yl acetate (3.12)

To a solution of **3.11** (680 mg, 3.20 mmol), Et_3N (1.43 mL, 10.2 mmol) and DMSO (26.8 mmol, 1.90 mL) in 12 mL CH_2Cl_2 at 0 ℃ was added Py•SO_3 (816 mg, 5.13 mmol) in one portion. The mixture was allowed to warm to rt for 5 h before it was quenched by H_2O. The aqueous layer was extracted with Et_2O and the combined organic layers were dried over

$MgSO_4$. After filtration and concentration, the residue was purifier by flash chromatography (7% EtOAc in pentane) to give (*R*)-3-((*R*)-non-3-yn-2-yloxy)butanal (620 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1H), 4.25-4.15 (m, 2H), 2.63 (ddd, *J* = 2.3, 6.6, 16.3, Hz, 1H), 2.46 (dd, *J* = 2.0, 5.4, 16.3 Hz, 1H), 2.16 (dt, *J* = 1.9, 7.1 Hz, 2H), 1.47 (p, *J* = 7.1 Hz, 2H), 1.37-1.22 (m, 10H), 0.86 (t, *J* = 7.0 Hz, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 201.5, 85.4, 80.6, 69.4, 64.4, 50.3, 31.2, 28.5, 23.0, 22.3, 21.6, 18.7, 14.1; IR (neat) 2959, 2933, 2862, 1727, 1458, 1373, 1328, 1168, 1102, 1081 cm^{-1}.

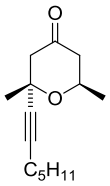
To a solution of (*R*)-3-((*R*)-non-3-yn-2-yloxy)butanal (446 mg, 2.12 mmol) and $(MeO)_2P(O)C(N_2)C(O)CH_3$[3] (570 mg, 3.00 mmol) in 10 mL dry MeOH was added K_2CO_3 (586 mg, 4.24 mmol) in one portion at 0 ℃. After stirring at the same temperature for 30 minutes, the reaction was quenched with saturated NH_4Cl (aq), and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, filtrated and concentrated. The resulting residue was purified by flash chromatography (5% EtOAc in pentane) to give (*R*)-2-((*R*)-pent-4-yn-2-yloxy)non-3-yne (100 mg, 23%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.32 (tq, *J* = 1.9, 6.5 Hz, 1H), 3.94 (qd, *J* = 6.3, 11.2 Hz, 1H), 2.43 (ddd, *J* = 2.7, 4.8, 16.7 Hz, 1H), 2.32 (ddd, *J* = 2.7, 6.9, 16.7 Hz, 1H), 2.20 (dt, *J* = 1.9, 7.1 Hz, 2H), 1.99 (t, *J* = 2.7 Hz, 1H), 1.52 (p, *J* = 7.0 Hz, 2H), 1.40 (d, *J* = 6.6 Hz, 3H), 1.39-1.33 (m, 4H), 1.32 (d, *J* = 6.2 Hz, 3H), 0.91 (t, *J* = 7.1 Hz, 3H).

The general procedure for the preparation of enol acetate was followed: A 50 mL RBF was charged with Na_2CO_3 (8.0 mg, 0.075 mmol), dichloro(p-cymene)ruthenium(II) dimer (12 mg, 0.019 mmol), tri(2-furyl)phosphine (9.0 mg, 0.039 mmol). Then 4.0 mL toluene was added into the flask, followed by acetic acid (42 uL, 0.73 mmol) and 1-decyne (18 uL, 0.10 mmol). The mixture was then heated to 80 °C and stirred for 1 h. Then (*R*)-2-((*R*)-pent-4-yn-2-yloxy)non-3-

yne (100 mg, 0.485 mmol) in 2.0 mL toluene was added into the reaction through syringe. The reaction was stirred at the same temperature overnight. Then crude mixture was loaded onto a short plug of silica gel and washed off with Et_2O. The residue was concentrated on a rotary evaporator and purified by chromatography (6% Et_2O in hexane) to give the desired product (84 mg, 65%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.80 (s, 2H), 4.23 (tq, *J* = 1.8, 6.5 Hz, 1H), 3.88 (qd, *J* = 6.3, 12.4 Hz, 1H), 2.48 (dd, *J* = 6.1, 14.8 Hz, 1H), 2.30 (dd, *J* = 6.1, 14.8 Hz, 1H), 2.20 (dt, *J* = 1.7, 7.1 Hz, 2H), 2.16 (s, 3H), 1.51 (q, *J* = 7.1 Hz, 2H), 1.41-1.29 (m, 7H), 1.26 (d, *J* = 6.2 Hz, 3H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C (151 MHz, $CDCl_3$) δ 169.1, 153.4, 103.7, 84.8, 80.8, 71.3, 64.0, 40.3, 31.0, 28.4, 22.9, 22.2, 21.2, 21.0, 18.7, 14.0; IR (neat) 2958, 2932, 2861, 1758, 1665, 1369, 1327, 1218, 1190, 1129, 1082, 1019 cm^{-1}; HRMS(EI) calcd for $C_{16}H_{26}O_3$ (M^+) 266.1882, found 266.1880.

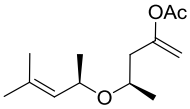
General procedure for the cyclization reaction:

Substrate (1 eq), 2,6-dichloropyridine (2 eq) and 4 Å molecular sieves (2 mass eq) were dissolved in anhydrous 1,2-dichloroethane to give a ~0.1 M solution. The mixture was stirred at room temperature for 15 minutes, followed by addition of $LiClO_4$ (0.3 eq). After 5 minutes, DDQ (2 eq) was added. The reaction was monitored by TLC at room temperature unless specified and, upon starting material consumption, was quenched by 5% aqueous $NaHCO_3$. The mixture was extracted with CH_2Cl_2 three times, and combined organic layers were dried over $MgSO_4$. The filtrate was concentrated and purified by flash chromatography to give the desired product.



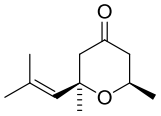
(2*S*,6*R*)-2-(Hept-1-ynyl)-2,6-dimethyldihydro-2*H*-pyran-4(3*H*)-one (3.14)

The general procedure of cyclization reaction was followed: **3.12** (23 mg, 0.086 mmol), 2,6-dichloropyridine (26 mg, 0.18 mmol) and 4 Å molecular sieves (45 mg) were dissolved in 0.9 mL anhydrous 1,2-dichloroethane, followed by DDQ (79 mg, 0.35 mmol). The reaction was stirred at room temperature for 18 h and then quenched by 5% aqueous $NaHCO_3$. The crude mixture was extracted with CH_2Cl_2 (3x). After concentration, it was purified by flash chromatography (5% EtOAc in hexane) to give the desired product (14 mg, 72%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.33 (ddq, *J* = 2.8, 6.2, 12.3 Hz, 1H), 2.51 (dd, *J* = 1.7, 13.7 Hz, 1H), 2.44 (d, *J* = 13.7 Hz, 1H), 2.38-2.35 (m, 1H), 2.18-2.13 (m, 3H), 1.60 (s, 3H), 1.50-1.45 (m, 2H), 1.34 (d, *J* = 6.2 Hz, 3H), 1.33-1.30 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H); ^{13}C (151 MHz, $CDCl_3$) δ 205.9, 88.7, 79.2, 72.1, 68.9, 53.9, 48.7, 31.0, 30.3, 28.2, 22.1, 22.0, 18.5, 14.0 ; IR (neat) 2959, 2931, 2859, 1726, 1300, 1257, 1195, 1176, 1156, 1092 cm^{-1}; HRMS(EI) calcd for $C_{14}H_{22}O_2$ (M^+) 222.1620, found 222.1614.



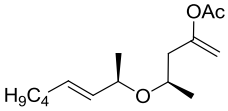
(*R*)-4-(((*R*)-4-Methylpent-3-en-2-yl)oxy)pent-1-en-2-yl acetate (3.15)

Substrate **3.15** was prepared following the same synthetic route to substrate **3.12**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.08 (pd, *J* = 1.3, 7.7 Hz, 1H), 4.80 (s, 2H), 4.25 (qd, *J* = 6.3, 9.0 Hz, 1H), 3.59 (qd, *J* = 6.3, 12.6 Hz, 1H), 2.49 (dd, *J* = 6.1, 14.6 Hz, 1H), 2.28 (dd, *J* = 6.4, 14.6 Hz, 1H), 2.14 (s, 3H), 1.73 (d, *J* = 1.0 Hz, 3H), 1.67 (d, *J* = 1.1 Hz, 3H), 1.16 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 153.9, 133.8, 128.5, 103.8, 70.3, 69.7, 41.0, 26.0, 21.8, 21.4, 21.3, 18.3; IR (neat) 2970, 2965, 2850, 1758, 1564, 1370, 1190, 1021 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{22}O_3$ (M^+) 226.1569, found 226.1566.



(2*R*,6*R*)-2,6-Dimethyl-2-(2-methylprop-1-en-1-yl)dihydro-2*H*-pyran-4(3*H*)-one (3.43)

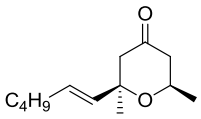
The general cyclization reaction procedure was followed with **3.15** (50 mg, 0.22 mmol), 2,6-dichloropyridine (49 mg, 0.33 mmol), 4 Å molecular sieves (100 mg), nitromethane (2.2 mL), $LiClO_4$ (7 mg, 0.07 mmol), and DDQ (125 mg, 0.551 mmol). The reaction was stirred at room temperature for 10 h and then quenched by Et_3N. The crude was purified by flash chromatography (10% to 15% Et_2O in pentane) to give the desired product (21 mg, 52%, dr = 3:1). Data for the *cis*-**3.43**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.29 (d, *J* = 1.0 Hz, 1H), 4.08-4.02 (m, 1H), 2.61 (d, *J* = 13.9 Hz, 1H), 2.37-2.35 (m, 2H), 2.28-2.22 (m, 1H), 1.88 (s, 3H), 1.74 (s, 3H), 1.35 (d, *J* = 6.0 Hz, 3H), 1.32 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 208.3, 135.8, 130.4, 78.0, 67.1, 52.8, 49.7, 27.5, 24.2, 22.7, 19.4; Data for the *trans*-**3.43**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.00 (s, 1H), 3.94-3.89 (m, 1H), 2.35-2.32 (m, 3H), 2.20-2.16 (m, 1H), 1.80 (s, 3H), 1.69 (s, 3H), 1.46 (s, 3H), 1.30 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 208.3, 138.3, 125.3, 78.0, 67.6, 55.2, 49.3, 29.7, 26.9, 22.6, 18.4; Data for the mixture of isomers: IR (neat) 2960, 2928, 2870, 1725, 1379, 1278, 1176, 1085, 975 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{18}O_2$ (M^+) 182.1307, found 182.1302.



(*R*)-4-((*R*,*E*)-Oct-3-en-2-yloxy)pent-1-en-2-yl acetate (3.16)

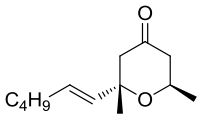
Substrate **3.16** was prepared following the same synthetic route to substrate **3.12**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.56 (td, *J* = 6.7, 15.3 Hz, 1H), 5.34 (tdd, *J* = 1.4, 7.8, 15.4 Hz, 1H), 4.79 (s, 2H), 3.88 (p, *J* = 6.4 Hz, 1H), 3.64 (qd, *J* = 6.3, 12.5 Hz, 1H), 2.49 (dd, *J* = 6.1, 14.7 Hz, 1H), 2.28 (dd, *J* = 6.4, 14.7 Hz, 1H), 2.15 (s, 3H), 2.04 (q, *J* = 6.8 Hz, 2H), 1.40-1.29 (m, 4H), 1.19 (d, *J* = 6.4 Hz, 3H), 1.15 (d, *J* = 6.3 Hz, 3H), 0.91 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR

(125 MHz, $CDCl_3$) δ 169.3, 153.9, 132.9, 132.6, 103.8, 75.1, 69.8, 40.7, 32.0, 31.6, 22.4, 22.2, 21.4, 21.3, 14.1; IR (neat) 2966, 2915, 2872, 1759, 1666, 1370, 1212, 1120, 1109, 1018, 971 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{26}O_3$ (M^+) 254.1882, found 254.1879.



(2*R*,6*R*)-2-((*E*)-Hex-1-en-1-yl)-2,6-dimethyldihydro-2*H*-pyran-4(3*H*)-one (*cis*-3.45)

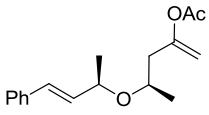
The general cyclization reaction procedure was followed with **3.16** (44 mg, 0.17 mmol), 2,6-dichloropyridine (38 mg, 0.26 mmol), 4 Å molecular sieves (90 mg), nitromethane (1.7 mL), $LiClO_4$ (5.5 mg, 0.052 mmol), and DDQ (98 mg, 0.43 mmol). The reaction was stirred at room temperature for 5.5 h and then quenched by Et_3N. The crude mixture was purified by flash chromatography (9%-20% Et_2O in hexane) to give the desired product (31 mg, 85%, dr = 3:1). ^1H NMR (600 MHz, $CDCl_3$) δ 5.67 (td, *J* = 6.5, 15.5 Hz, 1H), 5.59 (d, *J* = 15.7 Hz, 1H), 4.09-4.04 (m, 1H), 2.48 (d, *J* = 13.6 Hz, 1H), 2.34 (td, *J* = 2.2, 14.0 Hz, 1H), 2.30 (dd, *J* = 1.9, 13.6 Hz, 1H), 2.22 (dd, *J* = 11.8, 14.3 Hz, 1H), 2.04 (q, *J* = 6.7 Hz, 2H), 1.37-1.34 (m, 3H), 1.32 (d, *J* = 6.1 Hz, 3H), 1.30-1.29 (m, 1H), 1.26 (s, 3H), 0.89 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 208.2, 135.7, 129.2, 76.8, 67.2, 52.0, 49.4, 32.1, 31.4, 23.2, 22.7, 22.5, 14.2; IR (neat) 2962, 2928, 2872, 1724, 1379, 1278, 1176, 1085, 975 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{22}O_2$ (M^+) 210.1620, found 210.1617.



(2*S*,6*R*)-2-((*E*)-Hex-1-en-1-yl)-2,6-dimethyldihydro-2*H*-pyran-4(3*H*)-one (*trans*-3.45)

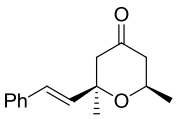
^1H NMR (600 MHz, $CDCl_3$) δ 5.50 (td, *J* = 6.7, 16.0 Hz, 1H), 5.33 (d, *J* = 16.1 Hz, 1H), 3.97-3.91 (m, 1H), 2.67 (dd, *J* = 1.8, 14.5 Hz, 1H), 2.38 (d, *J* = 14.4 Hz, 1H), 2.27 (td, *J* = 2.2, 14.4

Hz, 1H), 2.13 (dd, *J* = 11.2, 14.3 Hz, 1H), 2.01 (q, *J* = 7.0 Hz, 2H), 1.37 (s, 3H), 1.34-1.30 (m, 3H), 1.28 (d, *J* = 6.1 Hz, 3H), 1.27-1.26 (m, 1H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 208.0, 133.9, 133.4, 77.1, 67.4, 49.8, 49.0, 32.4, 31.4, 30.7, 22.4, 14.1; IR (neat) 2961, 2929, 2871, 1725, 1379, 1278, 1176, 1085, 977 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{22}O_2$ (M^+) 210.1620, found 210.1610.



(*R*)-4-(((*R*,*E*)-4-Phenylbut-3-en-2-yl)oxy)pent-1-en-2-yl acetate (3.17)

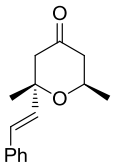
Substrate **3.17** was prepared following the same synthetic route to substrate **3.12**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.28 (m, 4H), 7.26-7.22 (m, 1H), 6.51 (d, *J* = 16.0 Hz, 1H), 6.12 (dd, *J* = 7.7, 16.0 Hz, 1H), 4.82 (s, 2H), 4.13 (p, *J* = 6.5 Hz, 1H), 3.71 (qd, *J* = 6.3, 12.5 Hz, 1H), 2.55 (dd, *J* = 6.1, 14.6 Hz, 1H), 2.31 (dd, *J* = 6.1, 14.5 Hz, 1H), 2.13 (s, 3H), 1.31 (d, *J* = 6.4 Hz, 3H), 1.19 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 153.7, 136.8, 132.5, 130.7, 128.7, 127.8, 126.6, 103.8, 75.0, 70.2, 40.6, 22.1, 21.3, 21.2; IR (neat) 2974, 2929, 1756, 1666, 1494, 1447, 1370, 1192, 1130, 1067, 1021, 968, 875, 750, 694 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{22}O_3Na$ $(M+Na)^+$ 297.1467, found 297.1486.



(2*R*,6*R*)-2,6-Dimethyl-2-((*E*)-styryl)dihydro-2*H*-pyran-4(3*H*)-one (*cis*-3.46)

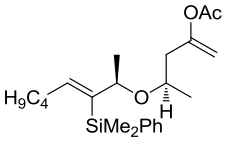
The general cyclization reaction procedure was followed with **3.17** (30 mg, 0.11 mmol), 2,6-dichloropyridine (24 mg, 0.16 mmol), 4 Å molecular sieves (60 mg), nitroethane (1.1 mL), $LiClO_4$ (3.5 mg, 0.033 mmol), and DDQ (38 mg, 0.16 mmol). The reaction was stirred at –60 °C for 4 h and then quenched by Et_3N. The crude mixture was purified by flash chromatography (15% Et_2O in hexane to 10% EtOAc in hexane) to give the desired product (21 mg, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.40 (m, 2H), 7.35-7.30 (m, 2H), 7.25-7.22 (m,

1H), 6.65 (d, *J* = 16.1 Hz, 1H), 6.32 (d, *J* = 16.1 Hz, 1H), 4.20-4.10 (m, 1H), 2.59 (d, *J* = 13.7 Hz, 1H), 2.46-2.36 (m, 2H), 2.28 (dd, *J* = 11.0, 13.9 Hz, 1H), 1.40-1.38 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.6, 136.7, 135.2, 128.8, 127.9, 127.8, 126.8, 76.8, 67.4, 51.9, 49.4, 23.5, 22.7; IR (neat) 2974, 1720, 1494, 1415, 1380, 1302, 1175, 1083, 1018, 970, 749, 694 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{18}O_2Na$ $(M+Na)^+$ 253.1204, found 253.1229.



(2*S*,6*R*)-2,6-Dimethyl-2-((*E*)-styryl)dihydro-2*H*-pyran-4(3*H*)-one (*trans*-3.46)

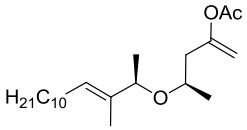
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.28 (m, 4H), 7.27-7.25 (m, 1H), 6.44 (d, *J* = 16.6 Hz, 1H), 6.12 (d, *J* = 16.6 Hz, 1H), 4.05-3.95 (m, 1H), 2.84 (dd, *J* = 1.6, 14.5 Hz, 1H), 2.51 (d, *J* = 14.6 Hz, 1H), 2.34-2.28 (m, 1H), 2.20 (dd, *J* = 11.0, 14.4 Hz, 1H), 1.49 (s, 3H), 1.31 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.5, 136.2, 133.1, 132.1, 128.8, 128.3, 126.7, 77.4, 67.9, 49.8, 49.0, 30.6, 22.4; IR (neat) 2974, 1720, 1494, 1413, 1380, 1301, 1175, 1082, 1018, 970, 749, 696 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{18}O_2Na$ $(M+Na)^+$ 253.1204, found 253.1228.



(*R*)-4-(((*R*,*Z*)-3-(Dimethyl(phenyl)silyl)oct-3-en-2-yl)oxy)pent-1-en-2-yl acetate (3.18)

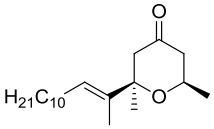
Substrate **3.18** was prepared following the similar synthetic route to substrate **3.12**. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47-7.45 (m, 2H), 7.28-7.27 (m, 3H), 6.26 (t, *J* = 7.4 Hz, 1H), 4.73-4.72 (m, 2H), 4.00 (q, *J* = 6.4 Hz, 1H), 3.56 (qd, *J* = 6.3, 12.6 Hz, 1H), 2.45 (dd, *J* = 5.3, 14.5 Hz, 1H), 2.21 (dd, *J* = 6.8, 14.5 Hz, 1H), 2.05 (s, 3H), 1.91-1.85 (m, 2H), 1.44 (d, *J* = 6.4 Hz, 3H), 1.11 (d, *J* = 6.2 Hz, 3H), 1.10-1.02 (m, 4H), 0.69 (t, *J* = 7.1 Hz, 3H), 0.36 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.3, 153.9, 145.2, 140.1, 139.5, 133.9, 128.9, 127.9, 103.9, 79.0, 70.0, 40.5,

32.0, 31.9, 23.8, 22.5, 21.3, 21.0, 14.1, 0.1, -0.3; IR (neat) 2975, 2928, 1756, 1667, 1490, 1371, 1190, 1067, 1022, 969, 876, cm^{-1}; HRMS (EI) calcd for $C_{23}H_{36}O_3Si$ (M^+) 388.2434, found 388.2441.



(*R*)-4-(((*R*,*E*)-3-Methyltetradec-3-en-2-yl)oxy)pent-1-en-2-yl acetate (3.19)[4]

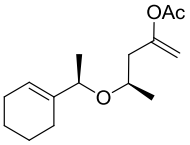
Substrate **3.19** was prepared following the same synthetic route to substrate **3.12**. ^1H NMR (500 MHz, $CDCl_3$) δ 5.32 (t, *J* = 6.5 Hz, 1H), 4.79 (d, *J* = 1.3 Hz, 1H), 4.78 (s, 1H), 3.85 (q, *J* = 6.4 Hz, 1H), 3.54 (qd, *J* = 6.3, 12.5 Hz, 1H), 2.48 (dd, *J* = 5.6, 14.6 Hz, 1H), 2.26 (dd, *J* = 6.6, 14.6 Hz, 1H), 2.14 (s, 3H), 2.08-1.95 (m, 2H), 1.56 (s, 3H), 1.41-1.27 (m, 16H), 1.18 (d, 6.5 Hz, 3H), 1.13 (d, *J* = 6.3 Hz, 3H), 0.89 (t, 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3, 154.0, 136.5, 127.9, 103.8, 79.6, 69.5, 40.4, 32.1, 29.9, 29.8, 29.8, 29.7, 29.6, 29.5, 27.8, 22.9, 21.4, 21.2, 20.5, 14.3, 10.8; IR (neat) 2925, 2855, 1760, 1666, 1369, 1192, 1080, 1020 cm^{-1}; HRMS (EI) calcd for $C_{22}H_{40}O_3$ (M^+) 352.2977, found 352.2987.



(2*R*,6*R*)-2,6-Dimethyl-2-((*E*)-tridec-2-en-2-yl)dihydro-2*H*-pyran-4(3*H*)-one (3.48)

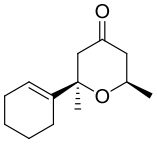
The general cyclization reaction procedure was followed with **3.19** (52 mg, 0.15 mmol), 2,6-dichloropyridine (44 mg, 0.30 mmol), 4 Å molecular sieves (100 mg), nitromethane (1.5 mL), $LiClO_4$ (4.7 mg, 0.044 mmol), and DDQ (110 mg, 0.485 mmol). The reaction was stirred at room temperature for 13 h and then quenched by Et_3N. The crude mixture was purified by flash chromatography (6% Et_2O in hexane) to give the desired product (38 mg, 84%, dr = 26:1). ^1H NMR (500 MHz, $CDCl_3$) δ 5.51 (dt, *J* = 1.1, 6.9 Hz, 1H), 4.11-4.04 (m, 1H), 2.53 (d, *J* = 13.5

Hz, 1H), 2.40-2.33 (m, 2H), 2.22 (dd, *J* = 11.1, 13.7 Hz, 1H), 2.03 (q, *J* = 7.1 Hz, 2H), 1.70 (d, *J* = 0.4 Hz, 3H), 1.38-1.35 (m, 2H), 1.33 (d, *J* = 6.0 Hz, 3H), 1.27-1.26 (m, 17H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 208.8, 139.1, 124.4, 79.2, 67.0, 50.9, 49.4, 32.1, 29.9, 29.8, 29.7, 29.7, 29.6, 28.1, 22.9, 22.7, 22.6, 14.3, 12.3; IR (neat) 2957, 2923, 2853, 1722, 1457, 1444, 1379, 1299, 1278, 1018 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{36}O_2$ (M^+) 308.2715, found 308.2729.



(*R*)-4-((*R*)-1-(Cyclohex-1-en-1-yl)ethoxy)pent-1-en-2-yl acetate (3.20)

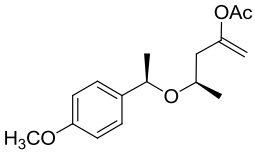
Substrate **3.20** was prepared following the same synthetic route to substrate **3.12**. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.59 (br, 1H), 4.79 (s, 2H), 3.84 (q, *J* = 6.4 Hz, 1H), 3.56 (qd, *J* = 6.2, 12.5 Hz, 1H), 2.50 (dd, *J* = 5.7, 14.5 Hz, 1H), 2.26 (dd, *J* = 6.5, 14.5 Hz, 1H), 2.15 (s, 3H), 2.06-2.00 (m, 2H), 1.97-1.92 (m, 2H), 1.69-1.62 (m, 2H), 1.58-1.50 (m, 2H), 1.19 (d, *J* = 6.5 Hz, 3H), 1.14 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.3, 154.0, 139.4, 124.1, 103.8, 78.5, 69.6, 40.4, 25.3, 23.0, 22.8, 21.4, 21.2, 20.3; IR (neat) 2975, 2930, 1758, 1666, 1439, 1370, 1290, 1218, 1193, 1139, 1070, 1019, 975, 921, 873 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{24}O_3Na$ $(M+Na)^+$ 275.1623, found 275.1596.



(2*R*,6*R*)-2-(Cyclohex-1-en-1-yl)-2,6-dimethyldihydro-2*H*-pyran-4(3*H*)-one (3.49)

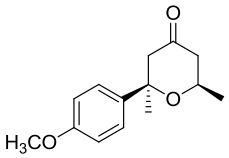
The general cyclization reaction procedure was followed with **3.20** (70 mg, 0.28 mmol), 2,6-dichloropyridine (82 mg, 0.55 mmol), 4 Å molecular sieves (140 mg), nitromethane (2.7 mL), $LiClO_4$ (9 mg, 0.08 mmol), and DDQ (220 mg, 0.969 mmol). The reaction was stirred at room temperature for 2.5 hours and then quenched by Et_3N. The crude mixture was purified by flash

chromatography (30% CH_2Cl_2 in hexane to 10% Et_2O in hexane) to give the desired product (50 mg, 86%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.79 (br, 1H), 4.09-4.04 (m, 1H), 2.50 (d, 13.6 Hz, 1H), 2.37-2.32 (m, 2H), 2.21 (dd, *J* = 11.8, 14.3 Hz, 1H), 2.11-2.02 (m, 4H), 1.66-1.54 (m, 4H), 1.31 (d, *J* = 6.0 Hz, 3H), 1.24 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 208.8, 141.9, 120.7, 78.8, 66.9, 50.7, 49.4, 25.2, 23.9, 23.1, 22.6, 22.5, 22.4; IR (neat) 2973, 2930, 2858, 2839, 1722, 1444, 1381, 1341, 1297, 1277, 1231, 1180, 1151, 1107, 1076, 1036, 1013, 966 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{20}O_2$ (M^+) 208.1463, found 208.1468.



(*R*)-4-((*R*)-1-(4-Methoxyphenyl)ethoxy)pent-1-en-2-yl acetate (3.21)

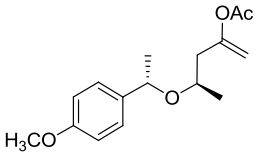
Substrate **3.21** was prepared following the same synthetic route to substrate **3.12**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.23 (m, 2H), 6.91-6.86 (m, 2H), 4.80 (s, 2H), 4.50 (q, *J* = 6.5 Hz, 1H), 3.82 (s, 3H), 3.56-3.43 (m, 1H), 2.56 (dd, *J* = 5.7, 14.6 Hz, 1H), 2.32 (dd, *J* = 6.4, 14.7 Hz, 1H), 2.11 (s, 3H), 1.39 (d, *J* = 6.5 Hz, 3H), 1.07 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 159.2, 153.8, 136.8, 127.7, 114.0, 103.9, 75.6, 70.2, 55.5, 40.5, 24.5, 21.4, 21.1; IR (neat) 2973, 1755, 1612, 1512, 1370, 1288, 1245, 1191, 1088, 1036, 833 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{22}O_4$ (M^+) 278.1518, found 278.1525.



(2*R*,6*R*)-2-(4-Methoxyphenyl)-2,6-dimethyldihydro-2*H*-pyran-4(3*H*)-one (3.50)

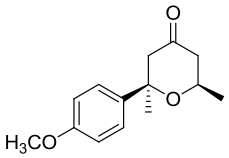
The general cyclization reaction procedure was followed with **3.21** (43 mg, 0.15 mmol), 2,6-dichloropyridine (46 mg, 0.31 mmol), 4 Å molecular sieves (90 mg), nitromethane (1.5 mL), $LiClO_4$ (5 mg, 0.05 mmol), and DDQ (70 mg, 0.31 mmol). The reaction was stirred at room temperature for 2 h and then quenched by Et_3N. The crude mixture was

purified by flash chromatography (40% CH_2Cl_2 in hexane to 10% EtOAc in hexane) to give the desired product (29 mg, 78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.9 Hz, 2H), 6.90 (d, *J* = 8.9 Hz, 2H), 4.27-4.17 (m, 1H), 3.81 (s, 3H), 2.72-2.61 (m, 2H), 2.46-2.40 (m, 1H), 2.29 (dd, *J* = 11.0, 14.1 Hz, 1H), 1.48 (s, 3H), 1.42 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 207.9, 158.8, 139.6, 125.5, 113.8, 77.9, 67.2, 55.5, 53.4, 49.4, 25.5, 22.8; IR (neat) 2972, 2931, 1713, 1608, 1515, 1450, 1412, 1384, 1310, 1280, 1252, 1182, 1111, 1029, 843 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{18}O_3$ (M^+) 234.1256, found 234.1245.



(*R*)-4-((*S*)-1-(4-Methoxyphenyl)ethoxy)pent-1-en-2-yl acetate (3.22)[5]

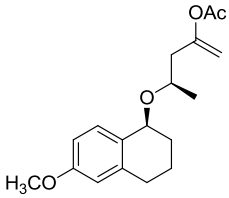
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25-7.23 (m, 2H), 6.88-6.86 (m, 2H), 4.75 (d, *J* = 1.3 Hz, 1H), 4.70 (s, 1H), 4.50 (q, *J* = 6.5 Hz, 1H), 3.81 (s, 3H), 3.49-3.43 (m, 1H), 2.41 (dd, *J* = 6.6, 14.7 Hz, 1H), 2.28 (dd, *J* = 6.3, 14.5 Hz, 1H), 1.95 (s, 3H), 1.39 (d, *J* = 6.5 Hz, 3H), 1.17 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 159.1, 153.5, 136.2, 127.8, 113.8, 103.6, 74.5, 69.2, 55.4, 41.9, 24.7, 21.2, 19.2; IR (neat) 2973, 1755, 1612, 1512, 1370, 1288, 1245, 1191, 1088, 1036, 833 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{22}O_4$ (M^+) 278.1518, found 278.1523.



(2*R*,6*R*)-2-(4-Methoxyphenyl)-2,6-dimethyldihydro-2*H*-pyran-4(3*H*)-one (3.50)

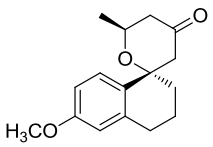
The general cyclization reaction procedure was followed with **3.22** (39 mg, 0.14 mmol), 2,6-dichloropyridine (42 mg, 0.28 mmol), 4 Å molecular sieves (80 mg), nitromethane (1.4 mL), $LiClO_4$ (4.5 mg, 0.042 mmol), and DDQ (63 mg, 0.28 mmol). The reaction was stirred at room temperature for 2 h and then quenched by Et_3N. The crude mixture

was purified by flash chromatography (40% CH_2Cl_2 in hexane to 10% EtOAc in hexane) to give the desired product (25 mg, 74%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.9 Hz, 2H), 6.90 (d, *J* = 8.9 Hz, 2H), 4.27-4.17 (m, 1H), 3.81 (s, 3H), 2.72-2.61 (m, 2H), 2.46-2.40 (m, 1H), 2.29 (dd, *J* = 11.0, 14.1 Hz, 1H), 1.48 (s, 3H), 1.42 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 207.9, 158.8, 139.6, 125.5, 113.8, 77.9, 67.2, 55.5, 53.4, 49.4, 25.5, 22.8; IR (neat) 2972, 2931, 1713, 1608, 1515, 1450, 1412, 1384, 1310, 1280, 1252, 1182, 1111, 1029, 843 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{18}O_3$ (M^+) 234.1256, found 234.1245.



(*R*)-4-(((*S*)-6-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)oxy)pent-1-en-2-yl acetate (3.23)

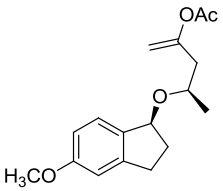
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.5 Hz, 1H), 6.73 (dd, *J* = 2.6, 8.5 Hz, 1H), 6.61 (d, *J* = 2.3 Hz, 1H), 4.84 (d, *J* = 1.2 Hz, 1H), 4.82 (s, 1H), 4.46 (t, *J* = 4.4 Hz, 1H), 3.83-3.78 (m, 1H), 3.78 (s, 3H), 2.81 (td, *J* = 5.3, 16.6 Hz, 1H), 2.71-2.66 (m, 1H), 2.59 (dd, *J* = 6.7, 14.6 Hz, 1H), 2.38 (dd, *J* = 6.1, 14.7 Hz, 1H), 2.12 (s, 3H), 2.06-1.96 (m, 2H), 1.86-1.80 (m, 1H), 1.74-1.68 (m, 1H), 1.26 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.4, 159.0, 153.8, 139.2, 131.0, 129.6, 113.5, 112.3, 104.0, 73.9, 70.7, 55.4, 41.8, 29.7, 29.3, 21.7, 21.4, 18.6; IR (neat) 2933, 1754, 1665, 1608, 1501, 1450, 1369, 1316, 1254, 1189, 1123, 1064, 1038, 1015, 985 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{24}O_4$ (M^+) 304.1675, found 304.1671.



(1*S*,6'*S*)-6-Methoxy-6'-methyl-3,4,5',6'-tetrahydro-2*H*-spiro[naphthalene-1,2'-pyran]-4'(3'*H*)-one (3.52)

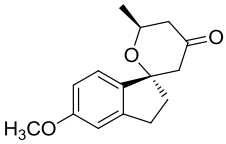
The general cyclization reaction procedure was followed with **3.23** (60 mg, 0.20 mmol), 2,6-dichloropyridine (44 mg, 0.30 mmol), 4 Å molecular sieves (120 mg), nitromethane (2 mL),

$LiClO_4$ (6.3 mg, 0.059 mmol), and DDQ (89 mg, 0.39 mmol). The reaction was stirred at 0 °C for 40 minutes and then quenched by Et_3N. The crude mixture was purified by flash chromatography (10% EtOAc in hexane) to give the desired product (42 mg, 82%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.7 Hz, 1H), 6.83 (dd, *J* = 2.7, 8.7 Hz, 1H), 6.59 (d, *J* = 2.6 Hz, 1H), 4.18-4.13 (m, 1H), 3.79 (s, 3H), 2.83-2.72 (m, 3H), 2.59 (dd, *J* = 1.9, 14.0 Hz, 1H), 2.45-2.42 (m, 1H), 2.37 (dd, *J* = 11.0, 13.8 Hz, 1H), 2.01-1.92 (m, 2H), 1.87-1.83 (m, 1H), 1.74-1.68 (m, 1H), 1.36 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 208.4, 159.0, 138.4, 132.6, 128.5, 113.4, 113.0, 77.4, 67.0, 55.5, 53.1, 49.6, 32.4, 29.9, 23.0, 20.0; IR (neat) 2930, 1754, 1714, 1674, 1605, 1500, 1450, 1345, 1250, 1179, 1017 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{20}O_3$ (M^+) 260.1412, found 260.1410.



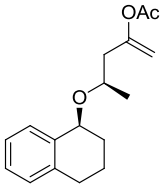
(*R*)-4-(((*S*)-5-Methoxy-2,3-dihydro-1H-inden-1-yl)oxy)pent-1-en-2-yl acetate (3.24)[6]

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.2 Hz, 1H), 6.77-6.75 (m, 2H), 4.94 (dd, *J* = 4.5, 6.1 Hz, 1H), 4.82 (s, 1H), 4.81 (s, 1H), 3.84-3.80 (m, 1H), 3.79 (s, 3H), 3.04 (ddd, *J* = 5.7, 8.2, 15.2 Hz, 1H), 2.76 (ddd, *J* = 5.9, 8.0, 14.5 Hz, 1H), 2.52 (dd, *J* = 7.0, 14.8 Hz, 1H), 2.39-2.34 (m, 2H), 2.12 (s, 3H), 2.07-2.01 (m, 1H), 1.26 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.4, 160.3, 153.7, 145.7, 135.8, 125.9, 112.8, 109.9, 103.9, 81.8, 71.7, 55.6, 41.6, 34.4, 30.5, 21.4, 21.3; IR (neat) 2934, 1755, 1666, 1609, 1492, 1454, 1370, 1329, 1255, 1191, 1140, 1099, 1026, 983, 872, 814 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{22}O_4Na$ $(M+Na)^+$ 313.1416, found 313.1421.



(1*S*,6'*S*)-5-Methoxy-6'-methyl-2,3,5',6'-tetrahydrospiro[indene-1,2'-pyran]-4'(3'*H*)-one (3.53)

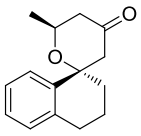
The general cyclization reaction procedure was followed with **3.24** (37 mg, 0.13 mmol), 2,6-dichloropyridine (28 mg, 0.19 mmol), 4 Å molecular sieves (74 mg), nitromethane (1.3 mL), $LiClO_4$ (4.1 mg, 0.039 mmol), and DDQ (57 mg, 0.25 mmol). The reaction was stirred at 0 °C for 30 minutes and then quenched by Et_3N. The crude mixture was purified by flash chromatography (10% EtOAc in hexane) to give the desired product (26 mg, 84%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.3 Hz, 1H), 6.84 (dd, *J* = 2.2, 8.3 Hz, 1H), 6.77 (s, 1H), 4.07-4.01 (m, 1H), 3.80 (s, 3H), 2.98 (td, *J* = 5.9, 16.1 Hz, 1H), 2.83 (td, *J* = 8.2, 16.2 Hz, 1H), 2.69 (d, *J* = 13.6 Hz, 1H), 2.43-2.37 (m, 3H), 2.16 (dd, *J* = 5.9, 7.9 Hz, 2H), 1.37 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 207.7, 160.7, 143.7, 138.1, 124.0, 113.8, 109.8, 87.5, 69.2, 55.7, 51.5, 49.7, 36.0, 29.8, 22.7; IR (neat) 2925, 1718, 1608, 1493, 1455, 1326, 1247, 1143, 1078, 1022 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{18}O_3$ (M^+) 246.1256, found 246.1250.



(*R*)-4-(((*S*)-1,2,3,4-Tetrahydronaphthalen-1-yl)oxy)pent-1-en-2-yl acetate (3.25)

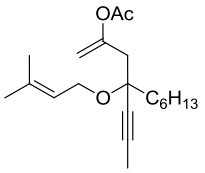
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39-7.38 (m, 1H), 7.18-7.16 (m, 2H), 7.09-7.08 (m, 1H), 4.84 (d, *J* = 1.3 Hz, 1H), 4.83 (s, 1H), 4.50 (t, *J* = 4.7 Hz, 1H), 3.83 (qd, *J* = 6.3, 12.6 Hz, 1H), 2.84 (td, *J* = 5.8, 16.7 Hz, 1H), 2.74-2.69 (m, 1H), 2.61 (dd, *J* = 6.6, 14.6 Hz, 1H), 2.39 (dd, *J* = 6.2, 14.7 Hz, 1H), 2.12 (s, 3H), 2.06-1.96 (m, 2H), 1.91-1.86 (m, 1H), 1.76-1.71 (m, 1H), 1.28 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.4, 153.7, 137.7, 137.2, 129.6, 129.1, 127.7, 125.9, 104.1, 74.4, 71.0, 41.8, 29.3, 29.2, 21.7, 21.4, 18.8; IR (neat) 2933, 1754,

1665, 1490, 1453, 1369, 1189, 1126, 1066, 1015, 985, 871, 763, 739 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{22}O_3Na$ $(M+Na)^+$ 297.1467, found 297.1461.



(1*S*,6'*S*)-6'-Methyl-3,4,5',6'-tetrahydro-2*H*-spiro[naphthalene-1,2'-pyran]-4'(3'*H*)-one (3.54)

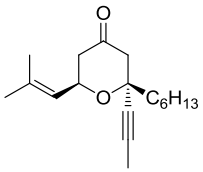
The general cyclization reaction procedure was followed with **3.25** (32 mg, 0.12 mmol), 2,6-dichloropyridine (26 mg, 0.17 mmol), 4 Å molecular sieves (65 mg), nitromethane (1.1 mL), $LiClO_4$ (3.8 mg, 0.036 mmol), and DDQ (79 mg, 0.35 mmol). The reaction was stirred at room temperature for 7 hours and then quenched by Et_3N. The crude mixture was purified by flash chromatography (7% EtOAc in hexane) to give the desired product (18 mg, 67%). ^1H NMR (600 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 0.8, 7.9 Hz, 1H), 7.28-7.26 (m, 1H), 7.20 (dt, *J* = 1.3, 7.6 Hz, 1H), 7.08 (d, *J* = 7.6 Hz, 1H), 4.22-4.16 (m, 1H), 22.85-2.76 (m, 2H), 2.73 (d, *J* = 14.0 Hz, 1H), 2.63 (dd, *J* = 1.9, 14.0 Hz, 1H), 2.47-2.44 (m, 1H), 2.39 (ddd, *J* = 0.5, 10.7, 13.9 Hz, 1H), 2.05 (ddd, *J* = 2.5, 6.1, 12.7 Hz, 1H), 1.99-1.94 (m, 1H), 1.89-1.84 (m, 1H), 1.77-1.69 (m, 1H), 1.38 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 208.2, 140.1, 136.7, 129.1, 127.8, 127.1, 126.9, 77.5, 67.1, 53.1, 49.6, 32.3, 29.5, 23.0, 20.0; IR (neat) 2933, 1717, 1450, 1314, 1274, 1172, 1022, 759 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{18}O_2$ (M^+) 230.1307, found 230.1306.



4-((3-Methylbut-2-en-1-yl)oxy)-4-(prop-1-yn-1-yl)dec-1-en-2-yl acetate (3.55)

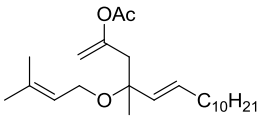
^1H NMR (600 MHz, $CDCl_3$) δ 5.33 (t, *J* = 6.7 Hz, 1H), 4.87 (s, 2H), 4.06 (p, *J* = 10.7 Hz, 2H), 2.67-2.62 (m, 2H), 2.12 (s, 3H), 1.88 (s, 3H), 1.74 (s, 3H), 1.72-1.69 (m, 2H), 1.70 (s, 3H), 1.48-1.29 (m, 8H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4,

152.4, 136.1, 121.9, 105.7, 82.8, 79.7, 75.3, 61.0, 42.4, 39.3, 32.1, 29.7, 26.1, 24.2, 22.9, 21.4, 18.3, 14.3, 3.8; IR (neat) 2926, 2858, 1758, 1663, 1442, 1369, 1196, 1056, 873 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{32}O_3Na$ $(M+Na)^+$ 343.2249, found 343.2216.



(2*R*,6*R*)-2-Hexyl-6-(2-methylprop-1-en-1-yl)-2-(prop-1-yn-1-yl)dihydro-2*H*-pyran-4(3*H*)-one (3.80)

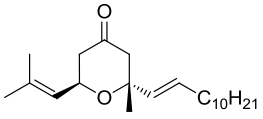
The general cyclization reaction procedure was followed with **3.55** (40 mg, 0.12 mmol), 2,6-dichloropyridine (37 mg, 0.25 mmol), 4 Å molecular sieves (80 mg), 1,2-dichloroethane (1.2 mL), $LiClO_4$ (4 mg, 0.04 mmol), and DDQ (62 mg, 0.27 mmol). The reaction was stirred at 0 °C for 2.3 hours and then quenched by Et_3N. The crude mixture was purified by flash chromatography (40% CH_2Cl_2 in hexane to 8% EtOAc in hexane) to give the desired product (27 mg, 79%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.24 (d, *J* = 6.8 Hz, 1H), 4.92 (ddd, *J* = 3.1, 7.9, 11.0 Hz, 1H), 2.49 (dd, *J* = 1.6, 13.7 Hz, 1H), 2.41 (d, *J* = 13.7 Hz, 1H), 2.35-2.32 (m, 1H), 2.28 (dd, *J* = 11.0, 14.2 Hz, 1H), 1.85 (s, 3H), 1.75 (s, 3H), 1.71 (d, *J* = 0.8 Hz, 3H), 1.58-1.29 (m, 10H), 0.88 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 206.5, 138.2, 124.6, 85.2, 77.7, 75.6, 69.8, 52.9, 47.8, 43.1, 32.0, 29.5, 25.9, 24.1, 22.8, 18.8, 14.3, 3.7; IR (neat) 2924, 2857, 1724, 1448, 1377, 1319, 1291, 1261, 1207, 1118, 1046 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{28}O_2Na$ $(M+Na)^+$ 299.1987, found 299.1979.



(*E*)-4-Methyl-4-((3-methylbut-2-en-1-yl)oxy)hexadeca-1,5-dien-2-yl acetate (3.56)

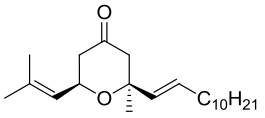
^{1}H NMR (600 MHz, $CDCl_3$) δ 5.57 (td, *J* = 6.7, 15.8 Hz, 1H), 5.43 (d, *J* = 15.8 Hz, 1H), 5.28 (t, *J* = 6.7 Hz, 1H), 4.82 (s, 1H), 4.80 (s, 1H), 3.81-3.79 (m, 2H), 2.54 (d, *J* = 14.5 Hz, 1H), 2.47 (d,

J = 14.5 Hz, 1H), 2.09 (s, 3H), 2.06 (q, J = 7.0 Hz, 2H), 1.72 (s, 3H), 1.63 (s, 3H), 1.39-1.36 (m, 2H), 1.32 (s, 3H), 1.3-1.24 (m, 14H), 0.89 (t, J = 6.8 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.3, 153.0, 135.6, 134.2, 131.7, 122.4, 105.5, 76.3, 59.3, 44.8, 32.8, 32.1, 29.9, 29.7, 29.6, 29.4, 26.1, 22.9, 22.5, 21.5, 18.2, 14.4; IR (neat) 2925, 2854, 1759, 1662, 1454, 1369, 1200, 1027, 978 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{42}O_3Na$ $(M+Na)^+$ 401.3032, found 401.3020.



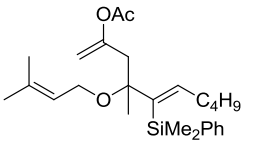
(2*R*,6*R*)-2-((*E*)-Dodec-1-en-1-yl)-2-methyl-6-(2-methylprop-1-en-1-yl)dihydro-2*H*-pyran-4(3*H*)-one (3.81)

The general cyclization reaction procedure was followed with **3.56** (45 mg, 0.12 mmol), 2,6-dichloropyridine (35 mg, 0.24 mmol), 4 Å molecular sieves (90 mg), 1,2-dichloroethane (1.2 mL), $LiClO_4$ (3.8 mg, 0.036 mmol), and DDQ (54 mg, 0.24 mmol). The reaction was stirred at 0 °C for 2 h and then quenched by Et_3N. The crude mixture was purified by flash chromatography (35% CH_2Cl_2 in hexane to 5% EtOAc in hexane) to give the desired products (38 mg, 95%, dr = 15.7:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.56 (td, J = 6.7, 16.1 Hz, 1H), 5.38 (d, J = 16.1 Hz, 1H), 5.25 (d, J = 8.1 Hz, 1H), 4.58-4.52 (m, 1H), 2.68 (d, J = 14.4 Hz, 1H), 2.41 (d, J = 14.4 Hz, 1H), 2.29-2.21 (m, 2H), 2.04 (q, J = 6.9 Hz, 2H), 1.75 (s, 3H), 1.65 (s, 3H), 1.39 (s, 3H), 1.36-1.34 (m, 2H),1.30-1.25 (m, 14H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.7, 137.5, 134.3, 133.2, 124.9, 77.2, 68.4, 50.0, 47.6, 32.7, 32.1, 30.7, 29.9, 29.8, 29.7, 29.6, 29.3, 29.2, 26.0, 22.9, 18.6, 14.3; IR (neat) 25, 2854, 1759, 1723, 1444, 1371, 1206, 1115, 1046, 981 cm^{-1}; HRMS (EI) calcd for $C_{22}H_{38}O_2$ (M^+) 334.2872, found 334.2879.



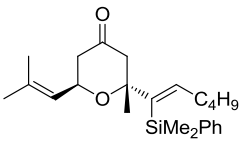
(2*S*,6*R*)-2-((*E*)-Dodec-1-en-1-yl)-2-methyl-6-(2-methylprop-1-en-1-yl)dihydro-2*H*-pyran-4(3*H*)-one (3.81-minor)

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.66 (td, *J* = 6.2, 15.6 Hz, 1H), 5.62 (d, *J* = 15.7 Hz, 1H), 5.28-5.26 (m, 1H), 4.66 (ddd, *J* = 3.3, 8.1, 11.2 Hz, 1H), 2.55 (d, *J* = 13.6 Hz, 1H), 2.38-2.28 (m, 3H), 2.03 (q, *J* = 6.4 Hz, 2H), 1.75 (s, 3H), 1.69 (s, 3H), 1.44 (s, 3H), 1.38-1.35 (m, 2H),1.29-1.26 (m, 14H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 208.0, 137.0, 135.8, 129.4, 125.1, 76.9, 68.3, 52.1, 48.0, 32.5, 32.1, 30.5, 29.9, 29.8, 29.6, 29.5, 29.3, 26.0, 23.1, 22.9, 18.6, 14.4; IR (neat) 2925, 2854, 1759, 1723, 1444, 1371, 1206, 1115, 1046, 981 cm^{-1}; HRMS (EI) calcd for $C_{22}H_{38}O_2$ (M^+) 334.2872, found 334.2885.



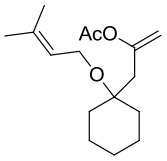
(*Z*)-5-(Dimethyl(phenyl)silyl)-4-methyl-4-((3-methylbut-2-en-1-yl)oxy)deca-1,5-dien-2-yl acetate (3.57)

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.55-7.53 (m, 2H), 7.32-7.31 (m, 3H), 6.17 (t, *J* = 7.5 Hz, 1H), 5.27 (t, *J* = 6.3 Hz, 1H), 4.83 (s, 1H), 4.81 (s, 1H), 3.92-3.78 (m, 2H), 2.87 (d, *J* = 14.8 Hz, 1H), 2.42 (d, *J* = 14.8 Hz, 1H), 2.09 (s, 3H), 1.94-1.90 (m, 2H), 1.71 (s, 3H), 1.60 (s, 3H), 1.45 (s, 3H), 1.22-1.07 (m, 4H), 0.73 (t, *J* = 7.2 Hz, 3H), 0.47 (s, 3H), 0.46 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.5, 153.5, 144.9, 142.1, 141.3, 134.4, 133.9, 128.6, 127.8, 122.6, 105.4, 81.0, 59.7, 44.2, 32.2, 31.9, 26.0, 23.8, 22.6, 21.5, 18.3, 14.1, 2.1, 1.6; IR (neat) 2959, 2927, 2858, 1758, 1453, 1428, 1370, 1250, 1199, 1108, 1089, 1036, 836, 818, 773, 731, 701, 660 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{40}O_3SiNa$ $(M+Na)^+$ 451.2644, found 451.2622.



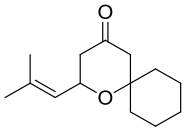
(2*R*,6*R*)-2-((*Z*)-1-(Dimethyl(phenyl)silyl)hex-1-en-1-yl)-2-methyl-6-(2-methylprop-1-en-1-yl)dihydro-2*H*-pyran-4(3*H*)-one (3.82)

The general cyclization reaction procedure was followed with **3.57** (14 mg, 0.031 mmol), 2,6-dichloropyridine (10 mg, 0.068 mmol), 4 Å molecular sieves (30 mg), 1,2-dichloroethane (0.04 mL), $LiClO_4$ (1 mg, 0.010 mmol), and DDQ (15 mg, 0.066 mmol). The reaction was stirred at 0 °C for 0.5 h and then quenched by Et_3N. The crude mixture was purified by flash chromatography (30% CH_2Cl_2 in hexane to 5% EtOAc in hexane) to give the desired products (9.4 mg, 76%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52-7.50 (m, 2H), 7.33-7.31 (m, 3H), 6.20 (t, *J* = 7.5 Hz, 1H), 5.29-5.28 (m, 1H), 4.57-4.54 (m, 1H), 3.04 (d, *J* = 14.2 Hz, 1H), 2.47 (d, *J* = 14.2 Hz, 1H), 2.24-2.22 (m, 2H), 1.98-1.83 (m, 2H), 1.73 (s, 3H), 1.54 (s, 3H), 1.53 (s, 3H), 1.17-1.05 (m, 4H), 0.72 (t, *J* = 7.2 Hz, 3H), 0.46 (s, 3H), 0.44 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 207.7, 147.6, 140.3, 140.2, 134.0, 133.9, 128.9, 127.9, 125.6, 82.5, 69.6, 51.6, 47.8, 32.6, 31.7, 31.6, 25.9, 22.5, 18.7, 14.1, 2.3, 1.3; IR (neat) 2925, 2855, 1723, 1428, 1293, 1249, 1108, 1045, 810, 775, 730, 700 cm^{-1}; HRMS (EI) calcd for $C_{24}H_{36}O_2Si$ (M^+) 384.2485, found 384.2489.



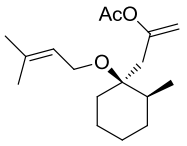
3-(1-((3-Methylbut-2-en-1-yl)oxy)cyclohexyl)prop-1-en-2-yl acetate (3.58)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.33-5.31 (m, 1H), 4.84 (d, *J* = 0.9 Hz, 1H), 4.80 (s, 1H), 3.85-3.84 (m, 2H), 2.43 (s, 2H), 2.12 (s, 3H), 1.82-1.79 (m, 2H), 1.73 (s, 3H), 1.66 (s, 3H), 1.61-1.20 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 153.1, 135.4, 122.2, 105.3, 75.0, 57.5, 34.7, 26.1, 25.9, 22.1, 21.4, 18.3; IR (neat) 2931, 2857, 1756, 1663, 1449, 1369, 1201, 1057, 1024, 961, 872 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{26}O_3Na$ $(M+Na)^+$ 289.1780, found 289.1786.



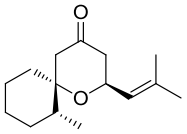
2-(2-Methylprop-1-en-1-yl)-1-oxaspiro[5.5]undecan-4-one (3.83)

The general cyclization reaction procedure was followed with **3.58** (45 mg, 0.17 mmol), 2,6-dichloropyridine (50 mg, 0.34 mmol), 4 Å molecular sieves (90 mg), 1,2-dichloroethane (1.7 mL), $LiClO_4$ (5.4 mg, 0.051 mmol), and DDQ (77 mg, 0.34 mmol). The reaction was stirred at room temperature for 20 minutes and then quenched by Et_3N. The crude mixture was purified by flash chromatography (15% Et_2O in hexane) to give the desired product (33 mg, 88%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.26 (d, J = 8.0 Hz, 1H), 4.56 (dt, J = 4.4, 9.2 Hz, 1H), 2.33-2.29 (m, 4H), 1.82-1.72 (m, 5H), 1.70 (s, 3H), 1.57-1.29 (m, 8H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 208.5, 137.0, 125.4, 76.6, 67.1, 52.4, 48.1, 39.8, 32.2, 26.1, 25.7, 22.0, 21.6, 18.6; IR (neat) 2931, 2858, 1719, 1449, 1375, 1307, 1262, 1235, 1204, 1156, 1121, 1048, 978 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{22}O_2$ (M^+) 222.1620, found 222.1613.



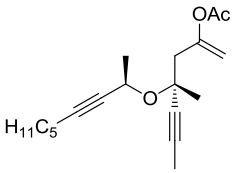
3-((1*S*,2*S*)-2-Methyl-1-((3-methylbut-2-en-1-yl)oxy)cyclohexyl)prop-1-en-2-yl acetate (3.59)[7-8]

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.30-5.25 (m, 1H), 4.84 (s, 2H), 3.85-3.83 (m, 2H), 2.61-2.49 (m, 2H), 2.14 (s, 3H), 1.85-1.77 (m, 1H), 1.73 (d, J = 0.8 Hz, 3H), 1.64 (s, 3H), 1.61-1.22 (m, 8H), 0.93 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.4, 153.8, 134.5, 122.7, 105.5, 77.4, 57.4, 39.3, 37.7, 31.5, 30.5, 26.0, 25.2, 22.3, 21.4, 18.4, 15.4; IR (neat) 2966, 2931, 2857, 1759, 1661, 1446, 1370, 1209, 1186, 1147, 1081, 1058, 1040, 1022, 875 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{28}O_3Na$ $(M+Na)^+$ 303.1936, found 303.1922.



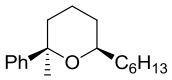
(2*S*,6*R*,7*R*)-7-Methyl-2-(2-methylprop-1-en-1-yl)-1-oxaspiro[5.5]undecan-4-one (3.84)

The general cyclization reaction procedure was followed with **3.59** (30 mg, 0.11 mmol), 2,6-dichloropyridine (32 mg, 0.22 mmol), 4 Å molecular sieves (60 mg), 1,2-dichloroethane (1.1 mL), $LiClO_4$ (4 mg, 0.03 mmol), and DDQ (49 mg, 0.21 mmol). The reaction was stirred at – 30 °C for 5 h and then quenched by Et_3N. The crude mixture was purified by flash chromatography (30% CH_2Cl_2 in hexane to 5% EtOAc in hexane) to give the desired product (21 mg, 81%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.24 (d, *J* = 7.8 Hz, 1H), 4.52-4.48 (m, 1H), 2.68 (d, *J* = 13.6 Hz, 1H), 2.26-2.19 (m, 2H), 2.02-1.95 (m, 2H), 1.75 (s, 3H), 1.67 (s, 3H), 1.61-1.52 (m, 1H), 1.45-1.38 (m, 4H), 1.31-1.22 (m, 2H), 1.14-1.08 (m, 1H), 0.98 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.7, 135.5, 125.8, 77.5, 67.0, 50.4, 48.0, 40.8, 32.9, 30.3, 26.1, 21.0, 18.5, 15.3; IR (neat) 2966, 2930, 2857, 1718, 1448, 1377, 1308, 1297, 1262, 1164, 1049, 975 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{24}O_2$ (M^+) 236.1776, found 236.1777.



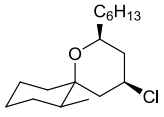
(*R*)-4-Methyl-4-((*R*)-non-3-yn-2-yloxy)hept-1-en-5-yn-2-yl acetate (3.60)

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.87 (s, 1H), 4.86 (d, *J* = 1.0 Hz, 1H), 4.61 (tq, *J* = 2.0, 6.6 Hz, 1H), 2.67 (d, *J* = 14.5 Hz, 1H), 2.54 (d, *J* = 14.5 Hz, 1H), 2.18 (dt, *J* = 1.9, 7.1 Hz, 2H), 2.13 (s, 3H), 1.87 (s, 3H), 1.56 (s, 3H), 1.52-1.48 (m, 2H), 1.37 (d, *J* = 6.6 Hz, 3H), 1.36-1.28 (m, 4H), 0.90 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.4, 152.4, 105.8, 84.4, 83.0, 82.2, 79.9, 77.5, 77.2, 77.0, 73.7, 60.7, 46.6, 31.2, 28.6, 27.7, 24.3, 22.4, 21.5, 19.0, 14.2, 3.9; IR (neat) 2964, 2929, 2853, 1756, 1659, 1443, 1371, 1203, 1183, 1148, 1085, 1052, 1043, 1026, 877 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{28}O_3$ (M^+) 304.2038, found 304.2029.



(2*R*,6*R*)-6-Hexyl-2-methyl-2-phenyltetrahydro-2*H*-pyran (3.87)

To a mixture of homoallylic alcohol **3.86** (157 mg, 1.00 mmol), acetophenone (118 μL, 1.00 mmol) and NaI (150 mg, 1.00 mmol) in 1.2 mL dry acetonitrile was added anhydrous TMSCl (124 μL, 1.00 mmol) dropwise and the resulting mixture stirred at room temperature.[9] After 4 h later, the reaction was quenched by the addition of H_2O, and the mixture was extracted with EtOAc. The organic layer was washed with $Na_2S_2O_3$ solution, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude mixture was purified by flash chromatography (20% CH_2Cl_2 in hexane) to give the desired product (51 mg, 13%). To the 4-iodotetrahydropyran (48 mg, 0.12 mmol) and AIBN (4.1 mg, 0.020 mmol) in 1.3 mL toluene was added $^nBu_3SnH$, and the mixture was heated to 80 °C for 1 h. After concentration, the crude mixture was purified by flash chromatography (hexane to 5% to 10% CH_2Cl_2 in hexane) to give the desired product (29 mg, 90%). ^1H NMR (600 MHz, $CDCl_3$) δ 7.50-7.49 (m, 2H), 7.33 (t, J = 7.9 Hz, 2H), 7.23-7.21 (m, 1H), 3.76-3.72 (m, 1H), 1.95-1.92 (m, 1H), 1.84-1.76 (m, 2H), 1.65-1.56 (m, 3H), 1.53-1.51 (m, 1H), 1.49 (s, 3H), 1.47-1.44 (m, 1H), 1.42-1.37 (m, 1H), 1.36-1.29 (m, 6H), 1.23-1.16 (m, 1H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 150.8, 128.2, 126.4, 124.4, 74.6, 70.3, 37.1, 36.4, 32.1, 31.8, 29.6, 25.8, 23.4, 22.9, 20.5, 14.4; IR (neat) 2930, 2856, 1493, 1446, 1371, 1257, 1204, 1071, 761 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{28}O$ (M^+) 260.2140, found 260.2128.



(2*S*,4*R*,6*S*,7*S*)-4-Chloro-2-hexyl-7-methyl-1-oxaspiro[5.5]undecane (3.89)

To $AlCl_3$ in 0.5 mL CH_2Cl_2 at 0 °C was added alcohol **3.88** (155 mg, 1.00 mmol) and heptanal (147 μL, 1.00 mmol) in 2 mL CH_2Cl_2.[10] After striring at room temperature for 2.5 h, the reaction was quenched with a buffer solution (PH = 7.5). The mixture was extracted with

Et_2O for two times, and the organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude mixture was purified by flash chromatography (5% CH_2Cl_2 in hexane) to give the desired product (60 mg, 21%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.27 (tt, *J* = 4.4, 12.1 Hz, 1H), 3.46-3.42 (m, 1H), 2.15-2.13 (m, 1H), 2.07 (pd, *J* = 1.9, 12.4 Hz, 1H), 1.89 (t, *J* = 12.4 Hz, 1H), 1.75 (ddd, *J* = 1.6, 4.4, 12.5 Hz, 1H), 1.66-1.63 (m, 1H), 1.53-1.44 (m, 3H), 1.41-1.33 (m, 6H), 1.32-1.24 (m, 8H), 1.02-0.97 (m, 1H), 0.91 (t, *J* = 6.4 Hz, 3H), 0.89 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 75.3, 68.7, 55.5, 43.4, 43.3, 40.8, 36.7, 32.1, 31.1, 30.6, 29.6, 26.2, 25.8, 22.9, 21.1, 15.2, 14.4; IR (neat) 2930, 2856, 1457, 1377, 1335, 1257, 1218, 1141, 1064, 998, 871, 798, 706 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{31}OCl$ (M^+) 286.2063, found 286.2060.

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APPENDIX D

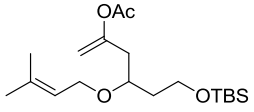
DDQ-CATALYZED REACTIONS USING MANGANESE DIOXIDE AS A TERMINAL OXIDANT

General Experimental Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on a Bruker Avance 300 spectrometer at 300 MHz and 75 MHz, a Bruker Avance 400 spectrometer at 400 MHz and 101 MHz, a Bruker Avance 500 spectrometer at 500 MHz and 125 MHz, a Bruker Avance 600 spectrometer at 600 MHz and 151 MHz if specified. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. The solvent peak was used as a reference value, for ^{1}H NMR: $CDCl_3$ = 7.26 ppm, for ^{13}C NMR: $CDCl_3$ = 77.23. Data are reported as follows: (s = singlet; d = doublet; t = triplet; q = quartet; dd = doublet of doublets; dt = doublet of triplets; br = broad). High resolution and low resolution mass spectra were recorded on a VG 7070 spectrometer. Infrared (IR) spectra were collected on a Mattson Cygnus 100 spectrometer. Samples for IR were prepared as a thin film on a NaCl plate by dissolving the compound in CH_2Cl_2 and then evaporating the CH_2Cl_2. Analytical TLC was performed on E. Merck pre-coated (25 mm) silica gel 60F-254 plates. Visualization was done under UV light (254 nm). Flash chromatography was done using ICN SiliTech 32-63 60 Å silica gel. Methylene chloride was distilled under N_2 from CaH_2, and 1,2–dichloroethane was dried

over 4Å molecular sieves. Reagent grade ethyl acetate, diethyl ether, pentane and hexanes were purchased from EM Science and used as purchased for chromatography. Tetrahydrofuran and diethyl ether were dried by passage through an activated alumina column under positive N_2 pressure. Anhydrous (*N*,*N*)-dimthylformamide (DMF), methanol (MeOH), dimethyl sulfoxide (DMSO), acetone were purchased from Aldrich and used as it is. Activated 4 Å molecular sieves were obtained through drying in oven at 150 °C overnight. All reactions were performed in oven or flame-dried glassware under a positive pressure of N_2 with magnetic stirring unless otherwise noted.

General procedure for the cyclization reactions:

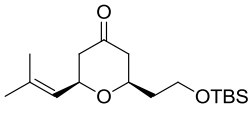
Substrate (1 eq), 2,6-dichloropyridine (2 eq), MnO_2 (6 eq) and 4 Å molecular sieves (2 mass eq) were suspended in anhydrous nitromethane to give a ~0.1 M solution (substrate concentration). The mixture was stirred at room temperature for 15 minutes, followed by the addition of DDQ (0.05 eq). The mixture was stirred at rt for 10 h and a second portion of DDQ (0.05 eq) was added. After an additional 14 h, the last portion of DDQ (0.05 eq) was added. The reaction was monitored by TLC and, upon starting material consumption, was quenched by Et_3N. The mixture was filtrated through a short pad of Celit with Et_2O. The filtration was concentrated and purified by flash chromatography to give the desired product.



6-((*tert*-Butyldimethylsilyl)oxy)-4-((3-methylbut-2-en-1-yl)oxy)hex-1-en-2-yl acetate (4.1)

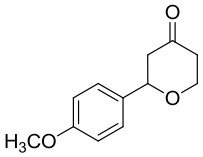
Substrate **4.1** was prepared following the same synthetic route to substrate **1.93**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.36-5.32 (m, 1H), 4.82 (s, 2H), 4.04 (dd, *J* = 7.0, 11.0 Hz, 1H), 3.96-3.92 (m,

1H), 3.77-3.62 (m, 3H), 2.50 (dd, J = 6.4, 10.9 Hz, 1H), 2.41 (dd, J = 5.8, 14.7 Hz, 1H), 2.14 (s, 3H), 1.74 (s, 3H), 1.73-1.70 (m, 2H), 1.68 (s, 3H), 0.90 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 169.3, 153.8, 136.9, 121.5, 103.8, 73.1, 66.2, 59.6, 38.8, 37.8, 26.1, 26.0, 21.3, 18.5, 18.2, -5.1, -5.2; IR (neat) 2927, 2859, 1759, 1651, 1254, 1200, 1094, 1020, 835, 773 cm^{-1}; HRMS(EI) calcd for $C_{19}H_{36}O_4Si$ (M^+) 356.2383, found 356.2376.



(2*R*,6*R*)-2-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-6-(2-methylprop-1-en-1-yl)dihydro-2*H*-pyran-4(3*H*)-one (4.3)

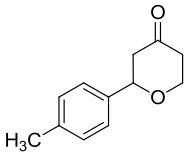
The general procedure of cyclization reaction was followed: **4.1** (42 mg, 0.12 mmol), 2,6-dichloropyridine (35 mg, 0.23 mmol), MnO_2 (61 mg, 0.70 mmol) and 4 Å molecular sieves (60 mg) were dissolved in 1.1 mL anhydrous nitromethane, followed by DDQ (3 x 1.4 mg, 15% eq). The reaction was stirred at room temperature for 48 h and then quenched by Et_3N. The mixture was filtrated through a short pad of Celit with Et_2O. The filtration was concentrated and purified by flash chromatography (30% CH_2Cl_2 in hexane to 5% EtOAc in hexane) to give the desired product (29 mg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.23-5.21 (m, 1H), 4.34-4.25 (m, 1H), 3.86-3.75 (m, 2H), 3.72-3.67 (m, 1H), 2.39-2.25 (m, 4H), 1.89-1.79 (m, 1H), 1.74 (s, 3H), 1.72-1.69 (m, 1H), 1.67 (s, 3H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C (100 MHz, $CDCl_3$) δ 207.6, 137.4, 124.7, 74.3, 73.8, 59.0, 48.2, 48.1, 39.5, 26.1, 25.9, 18.6, 18.4, -5.2, -5.3; IR (neat) 2953, 2927, 2859, 1724, 1469, 1385, 1361, 1325, 1253, 1146, 1098, 1025, 940, 901, 835, 777 cm^{-1}; HRMS(EI) calcd for $C_{17}H_{32}O_3Si$ (M^+) 312.2121, found 312.2124.



2-(4-Methoxyphenyl)dihydro-2*H*-pyran-4(3*H*)-one (4.5)

The general procedure of cyclization reaction was followed: **4.4**[1] (35 mg, 0.14

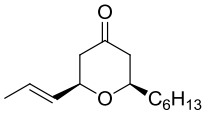
mmol), 2,6-dichloropyridine (41 mg, 0.28 mmol), MnO_2 (75 mg, 0.84 mmol) and 4 Å molecular sieves (40 mg) were dissolved in 1.4 mL anhydrous nitromethane, followed by DDQ (3 x 1.6 mg, 15% eq). The reaction was stirred at room temperature for 41 h and then quenched by Et_3N. The mixture was filtrated through a short pad of Celit with Et_2O. The filtration was concentrated and purified by flash chromatography (15% EtOAc in hexane) to give the desired product (22 mg, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.29 (m, 2H), 6.93-6.90 (m, 2H), 4.60 (dd, *J* = 3.9, 10.1 Hz, 1H), 4.41 (ddd, *J* = 1.5, 7.3, 11.5 Hz, 1H), 3.87-3.83 (m, 1H), 3.81 (s, 3H), 2.76-2.69 (m, 1H), 2.67-2.63 (m, 2H), 2.43 (dm, *J* = 14.6 Hz, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 206.8, 159.7, 132.9, 127.3, 114.2, 79.7, 66.9, 55.5, 50.1, 42.4. These data are consistent with reported literature values.[1]



2-*p*-Tolyldihydro-2*H*-pyran-4(3*H*)-one (4.7)

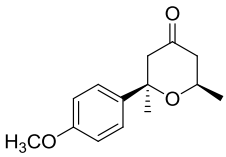
The general procedure of cyclization reaction was followed: **4.6**[1] (49 mg, 0.21 mmol), 2,6-dichloropyridine (46 mg, 0.31 mmol), MnO_2 (109 mg, 1.25 mmol) and 4 Å molecular sieves (80 mg) were dissolved in 2 mL anhydrous nitromethane, followed by DDQ (3 x 2.4 mg, 15% eq). The reaction was stirred at room temperature for 44 h and then quenched by Et_3N. The mixture was filtrated through a short pad of Celit with Et_2O. The filtration was concentrated and purified by flash chromatography (30% CH_2Cl_2 in hexane to 7% EtOAc in hexane) to give the desired product (33 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.1 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 4.64 (dd, *J* = 5.4, 8.7 Hz, 1H), 4.43 (ddd, *J* = 1.5, 7.4, 11.5 Hz, 1H), 3.89 (td, *J* = 2.9, 12.0 Hz, 1H), 2.73 (ddd, *J* = 7.4, 12.3, 14.6 Hz, 1H), 2.66-2.64 (m, 2H), 2.44 (dm, *J* = 14.4 Hz, 1H), 2.36 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 206.8, 138.2,

137.8, 129.6, 125.9, 80.0, 66.9, 50.2, 42.4, 21.4. These data are consistent with reported literature values.[1]



(2*R*,6*R*)-2-Hexyl-6-((*E*)-prop-1-en-1-yl)dihydro-2*H*-pyran-4(3*H*)-one (4.8)

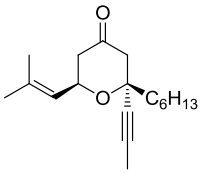
The general procedure of cyclization reaction was followed: **1.88** (26 mg, 0.097 mmol), 2,6-dichloropyridine (22 mg, 0.15 mmol), MnO_2 (51 mg, 0.58 mmol) and 4 Å molecular sieves (40 mg) were dissolved in 1.0 mL anhydrous nitromethane, followed by DDQ (3 x 1.1 mg, 15% eq). The reaction was stirred at room temperature for 40 h and then quenched by Et_3N. The mixture was filtrated through a short pad of Celit with Et_2O. The filtration was concentrated and purified by flash chromatography (30% CH_2Cl_2 in Hexane to 5% EtOAc in hexane) to give the desired product (20 mg, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.73 (ddq, *J* = 0.9, 12.5, 15.2 Hz, 1H), 5.53 (ddq, *J* = 1.5, 6.1, 15.2 Hz, 1H), 4.05-4.00 (m, 1H), 3.59 (ddt, *J* = 2.7, 7.0, 14.3 Hz, 1H), 2.38-2.32 (m, 3H), 2.28-2.18 (m, 1H), 1.71-1.64 (m, 3H), 1.55-1.26 (m, 10H), 0.87 (t, *J* = 6.6 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 207.4, 130.7, 128.4, 77.5, 77.2, 48.0, 47.9, 36.6, 31.9, 29.3, 25.4, 22.7, 17.9, 14.2. These data are consistent with reported literature values.[2]



(2*R*,6*R*)-2-(4-Methoxyphenyl)-2,6-dimethyl-tetrahydropyran-4-one (4.9)

The general procedure of cyclization reaction was followed: **3.21** (46 mg, 0.17 mmol), 2,6-dichloropyridine (49 mg, 0.33 mmol), MnO_2 (86 mg, 0.99 mmol) and 4 Å molecular sieves (80 mg) were dissolved in 1.6 mL anhydrous nitromethane, followed by DDQ (4 x 1.9 mg, 20% eq). The reaction was stirred at room temperature for 48 h and then quenched by Et_3N. The mixture was filtrated through a short pad of Celit with Et_2O.

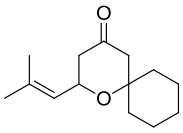
The filtration was concentrated and purified by flash chromatography (30% CH_2Cl_2 in hexane to 7% EtOAc in hexane) to give the desired product (29 mg, 75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.9 Hz, 2H), 6.90 (d, *J* = 8.9 Hz, 2H), 4.27-4.17 (m, 1H), 3.81 (s, 3H), 2.72-2.61 (m, 2H), 2.46-2.40 (m, 1H), 2.29 (dd, *J* = 11.0, 14.1 Hz, 1H), 1.48 (s, 3H), 1.42 (d, *J* = 6.0 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 207.9, 158.8, 139.6, 125.5, 113.8, 77.9, 67.2, 55.5, 53.4, 49.4, 25.5, 22.8. These data are consistent with reported literature values.[3]



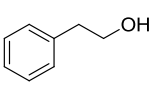
(2*R*,6*R*)-2-Hexyl-6-(2-methylprop-1-enyl)-2-(prop-1-ynyl)dihydro-2*H*-pyran-4(3*H*)-one (4.10)

The general procedure of cyclization reaction was followed: **3.55** (35 mg, 0.11 mmol), 2,6-dichloropyridine (24 mg, 0.16 mmol), MnO_2 (57 mg, 0.66 mmol) and 4 Å molecular sieves (70 mg) were dissolved in 1.1 mL anhydrous nitromethane, followed by DDQ (3 x 1.4 mg, 15% eq). The reaction was stirred at room temperature for 40 h and then quenched by Et_3N. The mixture was filtrated through a short pad of Celit with Et_2O. The filtration was concentrated and purified by flash chromatography (30% CH_2Cl_2 in hexane to 5% EtOAc in hexane) to give the desired product (21 mg, 70%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.24 (d, *J* = 6.8 Hz, 1H), 4.92 (ddd, *J* = 3.1, 7.9, 11.0 Hz, 1H), 2.49 (dd, *J* = 1.6, 13.7 Hz, 1H), 2.41 (d, *J* = 13.7 Hz, 1H), 2.36-2.31 (m, 1H), 2.28 (dd, *J* = 11.0, 14.2 Hz, 1H), 1.85 (s, 3H), 1.75 (s, 3H), 1.71 (d, *J* = 0.8 Hz, 3H), 1.57-1.28 (m, 10H), 0.88 (t, *J* = 6.6 Hz, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 206.5, 138.2, 124.6, 85.2, 77.7, 75.6, 69.8, 52.9, 47.8, 43.1, 32.0, 29.5, 25.9, 24.1, 22.8, 18.8, 14.3, 3.7. These data are consistent with reported literature values.[3]

2-(2-Methylprop-1-enyl)-1-oxaspiro[5.5]undecan-4-one (4.11)

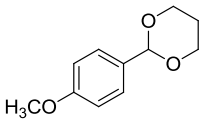


The general procedure of cyclization reaction was followed: **3.58** (38 mg, 0.14 mmol), 2,6-dichloropyridine (31 mg, 0.21 mmol), MnO_2 (74 mg, 0.85 mmol) and 4 Å molecular sieves (60 mg) were dissolved in 1.4 mL anhydrous nitromethane, followed by DDQ (3 x 1.7 mg, 15% eq). The reaction was stirred at room temperature for 30 h and then quenched by Et_3N. The mixture was filtrated through a short pad of Celit with Et_2O. The filtration was concentrated and purified by flash chromatography (30% CH_2Cl_2 in hexane to 15% Et_2O in hexane) to give the desired product (26 mg, 81%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.26 (d, *J* = 8.0 Hz, 1H), 4.56 (dt, *J* = 4.4, 9.2 Hz, 1H), 2.33-2.29 (m, 4H), 1.76-1.70 (m, 5H), 1.70 (s, 3H), 1.57-1.31 (m, 8H); ^{13}C (100 MHz, $CDCl_3$) δ 208.5, 137.0, 125.4, 76.6, 67.1, 52.4, 48.1, 39.8, 32.2, 26.1, 25.7, 22.0, 21.6, 18.6. These data are consistent with reported literature values.[3]



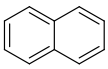
2-Phenylethanol (4.13)

To **4.12** (60 mg, 0.25 mmol) and MnO_2 (129 mg, 1.48 mmol) in anhydrous nitromethane (1.3 mL) was added MeOH (60 μL) and DDQ (2.8 mg, 0.012 mmol). The mixture was stirred at 60 °C for 10 h and a second portion of DDQ (2.8 mg, 0.012 mmol) was added. After an additional 18 h the last portion of DDQ (2.8 mg, 0.012 mmol) was added. After another 20 h, the reaction was quenched by Et_3N. The mixture was filtrated through a short pad of Celit with Et_2O. The filtration was concentrated and purified by flash chromatography (10% to 15% EtOAc in hexane) to give the desired alcohol (27 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.26 (m, 4H), 3.86-3.85 (m, 2H), 2.89 (t, *J* = 6.7 Hz, 2H), 2.07 (br, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 138.7, 129.2, 128.7, 126.6, 63.7, 39.3.



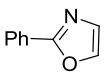
2-(4-Methoxyphenyl)-1,3-dioxane (4.15)

4.14 (45 mg, 0.23 mmol), MnO_2 (120 mg, 1.38 mmol), $NaHCO_3$ (39 mg, 0.46 mmol) and 4 Å molecular sieves (80 mg) were dissolved in 1.5 mL anhydrous nitromethane, followed by DDQ (3 x 2.6 mg, 15% eq). The reaction was stirred at room temperature for 40 h and then quenched by Et_3N. The mixture was filtrated through a short pad of Celit with Et_2O. The filtration was concentrated and purified by flash chromatography (10% EtOAc in hexane) to give the desired product (42 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.40 (m, 2H), 6.92-6.88 (m, 2H), 5.47 (s, 1H), 4.26 (ddd, *J* = 1.2, 4.9, 11.8 Hz, 2H), 4.18 (dt, *J* = 2.5, 12.3 Hz, 2H), 3.81 (s, 3H), 2.29-2.16 (m, 1H), 1.46-1.43 (m, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 160.1, 131.5, 127.5, 113.8, 101.7, 67.6, 55.5, 25.9. These data are consistent with reported literature values.[4]



Naphthalene (4.17)

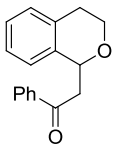
4.16 (46 mg, 0.35 mmol) and MnO_2 (185 mg, 2.13 mmol) were dissolved in 2.5 mL anhydrous nitromethane, followed by DDQ (2 x 4 mg, 10% eq). The reaction was stirred at room temperature for 24 h. The mixture was filtrated through a short pad of Celit with Et_2O. The filtration was concentrated and purified by flash chromatography (hexane) to give the desired product (43 mg, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00-7.97 (m, 4H), 7.63-7.61 (m, 4H); ^{13}C (100 MHz, $CDCl_3$) δ 133.7, 128.1, 126.0.



2-Phenyloxazole (4.19)

4.18 (60 mg, 0.41 mmol) and MnO_2 (213 mg, 2.45 mmol) were dissolved in 4.0 mL anhydrous benzene, followed by DDQ (4 x 4.7 mg, 20% eq). The reaction was stirred at 80 °C

for 48 h. The mixture was filtrated through a short pad of Celit with Et_2O. The filtration was concentrated and purified by flash chromatography (20% EtOAc in hexane) to give the desired product (51 mg, 86%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08-8.05 (m, 2H), 7.72 (s, 1H), 7.49-7.44 (m, 3H), 7.25 (s, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 138.8, 130.5, 129.0, 128.6, 127.7, 126.6. These data are consistent with reported literature values.[5]



2-(Isochroman-1-yl)-1-phenylethanone (4.22)

Isochroman (27 mg, 0.20 mmol), acetophenone (72 mg, 0.60 mmol) and MnO_2 (105 mg, 1.21 mmol) were dissolved in 0.25 mL anhydrous nitromethane, followed by DDQ (4 x 2.3 mg, 20% eq). The reaction was stirred at 100 °C for 48 h. The mixture was filtrated through a short pad of Celit with Et_2O. The filtration was concentrated and purified by flash chromatography (40% CH_2Cl_2 in hexane to 10% EtOAc in hexane) to give the desired product (21 mg, 42%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05-8.01 (m, 2H), 7.59 (tt, *J* = 1.4, 8.6 Hz, 1H), 7.51-7.45 (m, 2H), 7.23-7.10 (m, 4H), 5.52 (dd, *J* = 3.4, 8.5 Hz, 1H), 4.13 (ddd, *J* = 3.7, 5.4, 11.3 Hz, 1H), 3.82 (ddd, *J* = 3.8, 9.5, 13.4 Hz, 1H), 3.63 (dd, *J* = 8.7, 16.2 Hz, 1H), 3.33 (dd, *J* = 3.6, 16.2 Hz, 1H), 3.03 (ddd, *J* = 6.0, 10.0, 16.2 Hz, 1H), 2.73 (td, *J* = 3.2, 15.8 Hz, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 198.4, 137.8, 137.5, 134.3, 133.4, 129.3, 128.8, 128.6, 126.8, 126.5, 124.8, 72.9, 63.7, 45.7, 29.2. These data are consistent with reported literature values.[6]

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