# STEREOCHEMICAL AND REACTIVITY STUDIES OF TANDEM ETIC/ENOL ETHER CLEAVAGE REACTIONS

by

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**STEREOCHEMICAL ANC REACTIVITY STUDIES OF TANDEM ETIC/ENOL ETHER CLEAVAGE REACTIONS**

Jennifer Smotryski, M.S.

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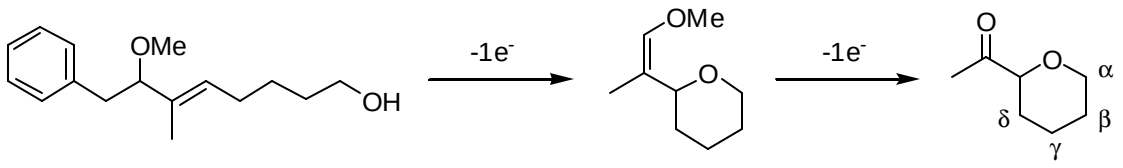
The electron transfer initiated cyclization (ETIC)/enol ether cleavage reaction has been developed in the Floreancig group as a mild and selective method for the formation of substituted tetrahydropyran rings systems, which are common in natural products. Reactions untilizing the initial substrate result in a methyl ketone substituted tetrahydropyran ring, however the addition of a side chain along the alkyl backbone of the substrate can lead to di-substituted tetrahydropyran rings. Products with side chains in the alpha and gamma positions containing aliphatic, alkoxy and siloxy groups have been synthesized. The *cis/trans* stereochemistry of the two side chains has been predicted based on transition state models and has been verified by NMR experimentation.



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# 1.0 THE ETIC/ENOL ETHER CLEAVAGE REACTION

## 1.1 INTRODUCTION

New synthetic transformations are constantly being designed to improve current methods of forming structural motifs commonly found in natural products. Of particular interest are reactions utilizing readily available substrates and displaying compatibility with sensitive functional groups. The activation of carbon-carbon bonds to form radical cations can be achieved chemoselectivity under mild conditions.[1] Radical cations are known to cleave mesolytically to form highly reactive radical and cationic fragments, making them an interesting target for further study.[2] The chemoselectivity allows for the oxidation of the carbon-carbon bonds in order to further functionalize these intermediates while avoiding potential modifications to senstivite groups within the molecule ensures compatibility with a range of functionalized substrates.

Another area of interest is the design of tandem reactions that achieve multiple transformations in a one-pot protocol. The ubiquitous nature of the carbon-carbon bond and selectivity of its activation imply the ability to design such a reaction. With the proper substrate design and reaction conditions, multiple carbon-carbon bond activations resulting in a series of transformations can be achieved.

### 1.1.1 Photoinitiated Electron Transfer

The activation of carbon-carbon bonds to form radical cation intermediates can be achieved either electrochemically, chemically (by use of chemical oxidants), or by photoinitiated electron transfer. The elaborate equipment often required for electrochemical oxidations[3] and the lack of a strong driving force for chemical oxidants limit the utility of these methods. Photoinduced electron transfer (PET) is an attractive method for removal of a single electron from a system due to the mild conditions used.[1]

PET involves electronic excitation of a donor (D) or acceptor (A) molecule which is then quenched by electron transfer.[4, 5] Excitation results in a dramatic change in redox properties of a molecule. An excited acceptor molecule becomes a stronger oxidizing agent for a more facile removal of an electron from the donor molecule. An excited donor molecule becomes a stronger reducing agent (Figure 1).[4]

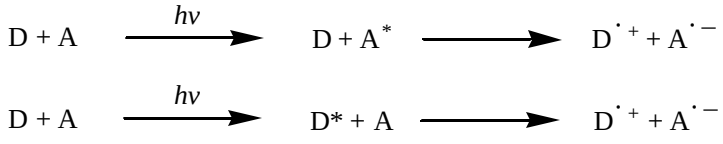



**Figure 1.** Modes of Photoinitiated Electron Transfer

The risk of potential return electron transfer to re-form the starting materials can be diminished by proper choice of solvent and through the use of co-sensitizers. Polar solvents promote the formation of free radical ions as opposed to radical ion pairs which are more likely to recombine to the ground state starting materials.[4] Sensitizers (S) are used to facilitate electron transfer when the substrates present have poor photochemical properties (Figure 2).[6]

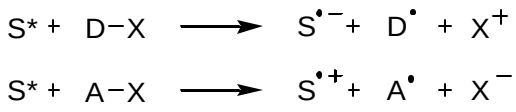


**Figure 2.** Use of Sensitizers in PET

### 1.1.2 Radical Cation Cleavage

Radical cations are known to cleave mesolytically to form a radical fragment and a cationic species (Figure 3).[2]

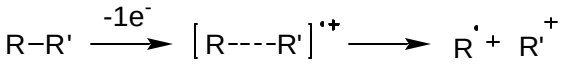


**Figure 3.** Generation and Mesolytic Fragmentation of a Radical Cation

Bond cleavage in unsymmetric systems can lead to mixtures of cationic and radical fragments (Figure 4).[7] An understanding of the thermodynamic aspects of this cleavage enables predictable bond fragmentation.

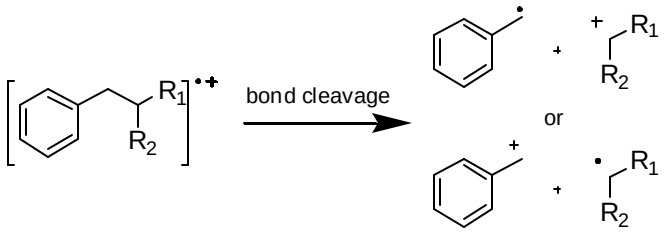



**Figure 4.** Multiple Products of Radical Cation Cleavage

The tendency of bond fragmentation in a radical cation can be approximated with respect to thermodynamics by the following equation:[8]

$$BDE_{(RC)} = BDE_S - E_{pa}(S) + E_{pa}(E)$$

Where $BDE_{(RC)}$ represents the bond dissociation energy of the radical cation bond, $BDE_S$ represents the bond dissociation energy for the bond in the neutral substrate, and $E_{(pa)}(S)$ and $E_{(pa)}(E)$ represent the oxidation potentials of the substrate and the electrophilic radical fragment formed, respectively.

Equation 1 predicts that lowering $E_{(pa)}(E)$ increases $BDE_{(RC)}$, enhancing bond fragmentation. Introducing an electron donating substituent on the arene lowers $E_{(pa)}(E)$. For example, the oxidation potential of *p*-methoxytoluene was found to be approximately 0.5 V lower than that of toluene.[9] Therefore a *p*-methoxybenzyl substituted substrate should be more reactive toward fragmentation than the simple benzyl.

Arnold and co-workers have studied the activation and cleavage of alkylarenes.[7] They were able to achieve selective cleavage to a benzyl radical and alkyl cation by incorporating an a-alkoxy group into the alkyl chain (Figure 5). Equation 1 also predicts that the carbocation of the radical with the lower oxidation potential is selectively formed upon radical cation cleavage. The oxidation potential of the a-alkoxy radical is approximately 0.6 V lower than that of the benzyl radical, ensuring formation of the alkoxy carbocation.[10] Substitution of the alkyl backbone of the substrate also results in a decrease in bond dissociation energy, increasing the ability of the substrate to undergo fragmentation.[2]

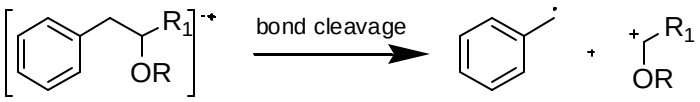
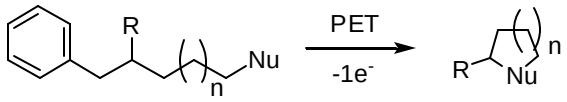



**Figure 5.** Selective Bond Cleavage

### 1.1.3 The ETIC Reaction

Our group has developed an electron transfer initiated cyclization (ETIC) reaction utilizing selective activation of carbon-carbon s-bonds (Figure 6).[11] Activation of a benzylic carbon-carbon bond yields a radical cation intermediate which can undergo cleavage followed by intramolecular nucleophilic attack of the resulting radical cation to form the cyclized product. This method generates highly reactive intermediates in a mild and selective manner, making it an ideal approach for synthesis of highly functionalized molecules.




R = electron donating group

**Figure 6.** General ETIC Reaction

The electron transfer initiated cyclization (ETIC) can be initiated by ground state activation using chemical oxidants such as ceric ammonium nitrate (CAN) or via photoinitiatied single electron transfer. [1, 5]

Under PET conditions, the reaction is initiated by electronic excitation of the sensitizer, N-methylquinolinium hexafluorophosphate ($NMQPF_6$), via irradiation with a Pyrex filtered, medium pressure mercury lamp. An electron is then transferred from the co-sensitizer (toluene) to the NMQ cation, forming the NMQ radical and a toluene radical cation. The toluene radical cation then abstracts an electron from the donor molecule, the substrate, regenerating toluene and forming the radical cation of the substrate. The NMQ radical is oxidized by oxygen from air

bubbling through the reaction to regenerate the NMQ cation, restarting the photoinitiation cycle (Figure 7).

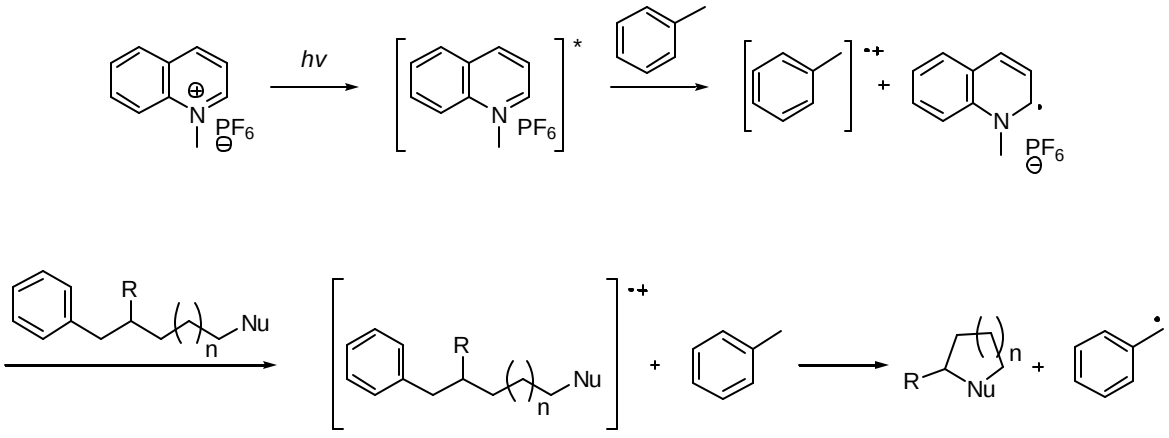



**Figure 7.** Electron Transfer Initiated Cyclization

Cyclization then takes place dissociatively to form the final product and benzyl radical (Figure 8). The substrate radical cation can fragment to form the benzyl radical and the oxocarbenium ion, followed by nucleophilic ring closure. Alternatively, ring closure can take place first, promoting cleavage of the benzylic bond.

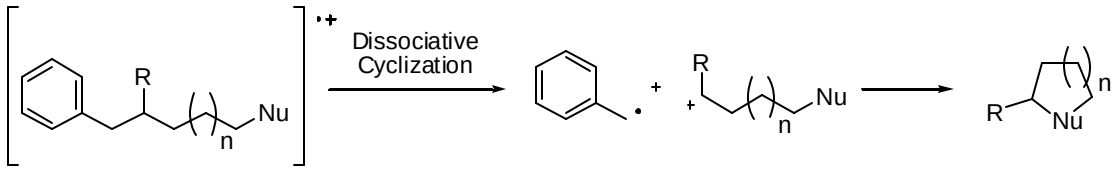



**Figure 8.** Dissociative Cyclization Pathway

### 1.1.4 Enol Ether Reactivity

Enol ethers are electron rich olefins with high electron density surrounding the ß carbon (Figure 9).

**Figure 9.** Resonance Forms of Enol Ethers

Electrophilic attack at the ß carbon is a major class of reactions for these species. They are also capable of undergoing [2 + 1], [2 + 2], and [2 + 4] cycloadditions with electrophilic p systems, generally through a dipolar addition.[12]

Oxidation of an enol ether by single electron transfer (SET) results in a radical cation, reversing the polarity (Figure 10). The high electrophilicity of the radical makes this species subject to nucleophilic attack.

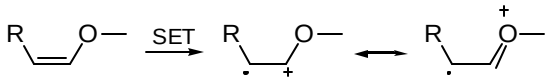



**Figure 10.** Oxidation of an Enol Ether to a Radical Cation

### 1.1.5 Oxidation of Enol Ethers

Moeller and co-workers have established a method of electrochemically oxidizing enol ethers.[13] The oxidations are achieved with a constant current system using $LiClO_4$ as an electrolyte solution, and 2,6-lutidine as a proton scavenger in methanol solvent. A co-solvent is used for systems with lower reactivity. The co-solvent acts to reduce the amount of methanol

around the electrode, slowing the rate of solvent trapping of the radical cation. The chemoselectivity and neutral reaction conditions of these transformations make them desirable in organic synthesis.

Photoinitiated electron transfer can also be used to achieve enol ether oxidation, as seen in the electron transfer initiated cyclization reaction. These conditions are mild enough to be compatible with highly functionalized molecules and do not require the specialized equipment utilized in electrochemistry.

### 1.1.6 Reactions of Enol Ether Radical Cations

Enol ether radical cations are highly reactive species capable of addition by a wide variety of nucleophiles. The addition of two oxygen atoms across an enol ether radical cation results in a dioxetane intermediate which can decompose by method A or B to form a ketone and an ester (Figure 11).[14] Method A takes place via attack of molecular (triplet state) oxygen on the enol ether radical cation to give the radical cation dioxetane intermediate, followed by electron transfer to another molecule of the enol ether substrate to yield the neutral dioxetane intermediate, which can cleave to give the final products, and another enol ether radical cation. Method B takes place by addition of the superoxide anion into the enol ether radical cation, affording the neutral dioxetane intermediate which cleaves to give the ketone and ester.[15]

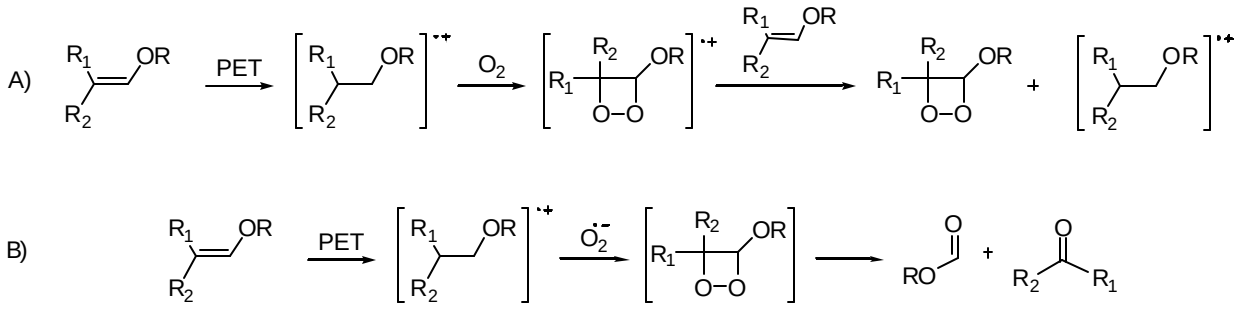



**Figure 11.** Reaction of Oxygen with an Enol Ether Radical Cation

Moeller's initial work focused on the coupling of enol ether radical cations with electron rich olefins to form carbon-carbon bonds and ring structures while retaining the functionality used to initiate the reaction (Figure 12).[16]

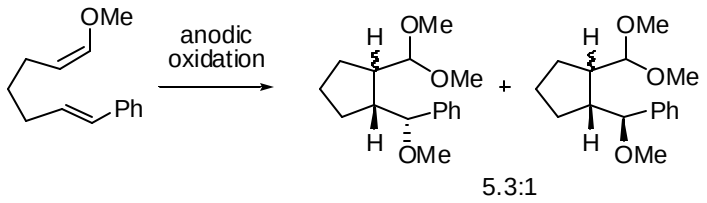



**Figure 12.** Moeller's Anodic Coupling of Electron Rich Olefins

His work was later extended to the coupling of the enol ether radical cations with alkyl olefins, styrenes, allylsilanes, vinylsilanes, electron rich aromatic rings, enol ethers and alcohols.[17] These coupling reactions have been used to form 5-, 6- and 7-membered rings,[18] tetrahydropyran and tetrahydrofuran systems,[3] quaternary centers and bicyclic as well as tricyclic ring skeletons (Figure 13).[19]

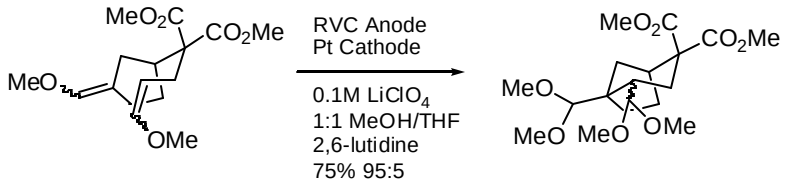



**Figure 13.** Formation of a Tricyclic System with a Quaternary Center

The high level of chemoselectivity in these reactions is due to the low oxidation potential of enol ethers compared to other functional groups. The stereochemistry of the products is generally obtained through kinetic control based on steric factors in the transition state (Figure 14).[19]

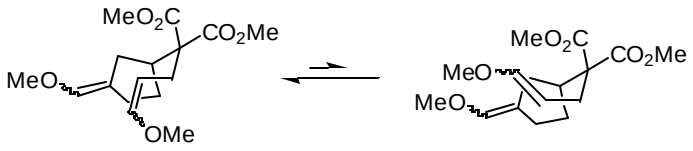



**Figure 14.** Transition States for Enol Ether Coupling

More recent work has been done by Chiba and co-workers on cross metathesis reactions of oxidized enol ethers.[16, 20, 21] Under electrochemical conditions (carbon felt anode, carbon felt counter electrode, lithium perchlorate/nitromethane electrolyte solution, constant current) a single electron transfer from the enol ether occurs resulting in a radical cation which then undergoes cross-metathesis with another enol ether. The mechanism of the transformation is similar to a transition-metal-catalyzed cross metathesis. A [2 + 2] cycloaddition takes place to form a four-membered radical cation cyclic intermediate then undergoes a retro [2 + 2] to form the newly substituted enol ether radical cation and an olefin (Figure 15). The radical cation can then accept an electron and be reduced to the olefin or react again with another olefin substrate.

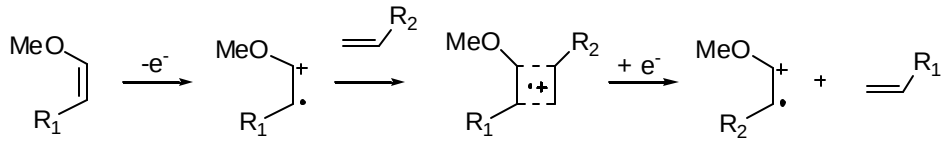



**Figure 15.** Cross Metathesis with an Enol Ether Radical Cation

## 1.2 THE ETIC/ENOL ETHER CLEAVAGE TANDEM REACTION

### 1.2.1 General

Tandem reactions are desirable in synthesis due to their potential for increasing the complexity of a molecule in a single step while reducing waste and eliminating the need for isolation and purification of intermediates.[22] With the proper substrate design, the product of an ETIC reaction can, under the same reaction conditions, serve as the substrate for another photoinitiated reaction. Moeller's work highlighting the oxidation of enol ethers suggested the ability to achieve a tandem reaction with an enol ether product of an ETIC reaction.[13] Due to the molecular oxygen that is already present in the reaction mixture, reaction of the enol ether radical cation with oxygen to afford a ketone was envisioned (Figure 16).

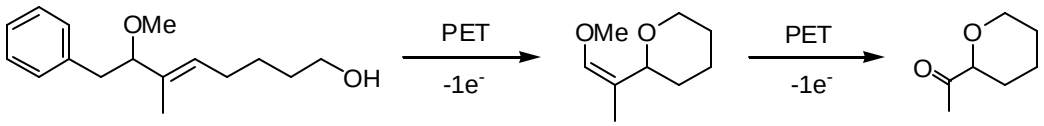



**Figure 16.** Tandem ETIC/Enol Ether Cleavage Reaction

Introducing unsaturation into the ETIC substrate allows for conjugate attack by the nucleophile resulting in an enol ether substituted ring product (Figure 17). This is due to the resonance of electrophilicity from the oxocarbenium ion through the conjugated p system to the ß-carbon.[23] It has also been shown that introducing an alkene at the homobenzylic position has a weakening effect on the benzylic bond, promoting bond dissociation.[24]

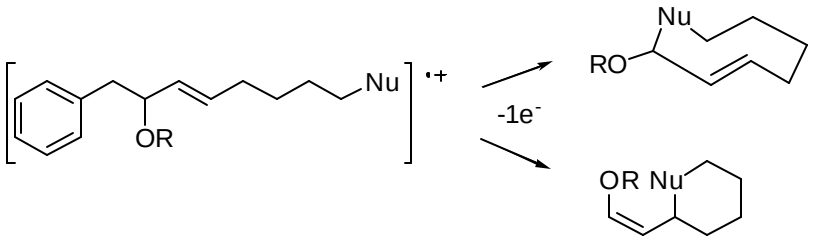



**Figure 17.** Modes of Nucleophilic Attack

The newly formed enol ether then reacts with oxygen as discussed above, to form a dioxetane intermediate which cleaves to give the final product (Figure 18).

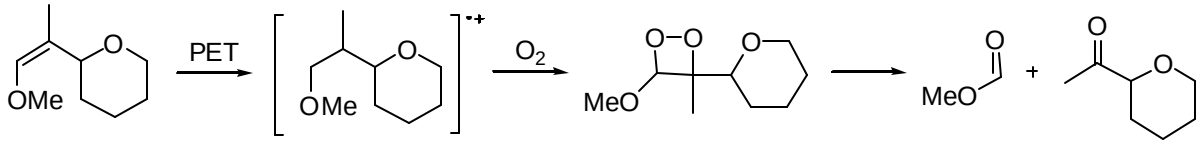



**Figure 18.** Enol Ether Cleavage Reaction

### 1.2.2 Applications in Synthesis

Disubstituted pyran rings are found in several natural products of interest.[25] One example is rhopaloic acid F (Figure 19), which has promising biological activities but limited natural availability.[26, 27] This natural product is of the first reported to inhibit protease activity of hRCE1

human RAS converting enzyme. The RAS membrane functions to control cell differentiation and proliferation. Mutated RAS genes are found in 30% of human cancers.[27]

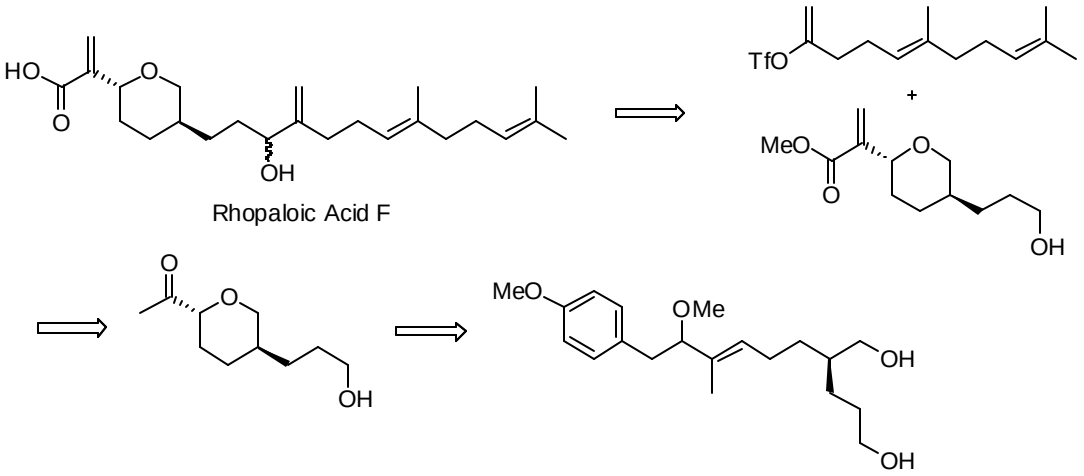



**Figure 19.** Retrosynthesis of Rhopaloic Acid F

The development of a new method to construct these motifs that would be compatible in the presence of diverse functional groups commonly found in complex natural products would be a useful advance. It was envisioned that the ETIC/enol ether tandem reaction could be used to form the pyran ring in rhopaloic acid F. Introducing substituents at various positions along the alkyl chain tethering the nucleophile creates a handle for further functionalization of the side chains toward the synthesis of various natural products (Figure 20).

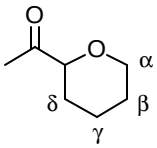



**Figure 20.** Substitution Positions along the Tetrahydropyran Ring.

## 1.3 PREVIOUS WORK

Previous work on the tandem ETIC/enol ether cleavage reaction was focused on substrate reactivity and reaction conditions. Initial work by Hua Liu utilized a *p*-methoxybenzyl group as the arene electroauxillary and free alcohols as the nucleophile (Figure 21). Some substrates were designed with substituents along the alkyl chain tethering the nucleophile. Reactions with these substrates were run on small scales and 30-40% yields were obtained based on impure samples.

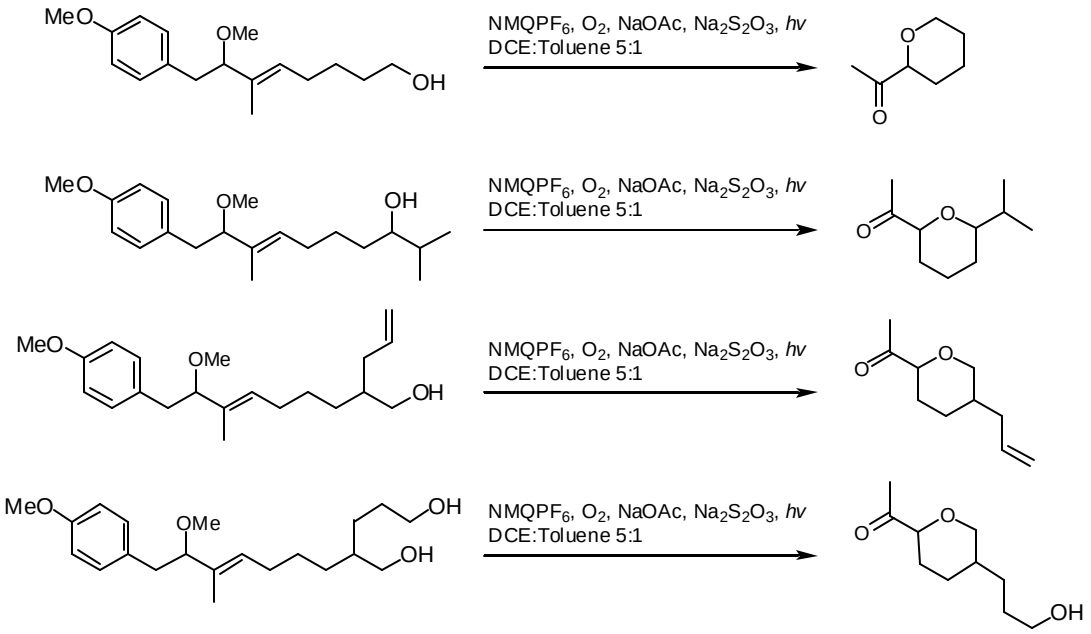



**Figure 21.** Initial ETIC/Enol Ether Cleavage Reaction Substrates

Later work by Conor McCutcheon was based on determining the reactivity of these systems by varying reaction conditions and the arene electroauxillary. The best results were obtained using dichloroethane as solvent, approximately 10 mol% of the $NMQPF_6$ catalyst and 0.02 molar concentration of the substrate. No substantial differences in yield were observed when using 200, 100, and 50 weight percent of NaOAc and $Na_2S_2O_3$ and reactions went to

completion in approximately 4-5 hours. Longer reaction times did not result in higher yields. Non-functionalized benzyl arenes were used to determine the necessity of the *p*-methoxy substituent for reactivity. *P*-methoxybenzyl substrates generally afforded 10-20% higher yields of the desired products than benzyl substrates, presumably due to the electron donating nature of the *p*-methoxybenzene susbtituent, which decreases its oxidation potential enhancing the chemoselectivity and reactivity.[8]

## 1.4 GOALS OF THE PROJECT

While the ß-substituted tetrahydropyran ring is the basis for rhopaloic acid F, many natural products contain tetrahydropyran rings with other substitution patterns. With this in mind, substrates were designed to yield tetrahydropyran rings substituted at the a- and ?- positions along the ring (Figure 22). A new synthetic route was also used to obtain these substrates.

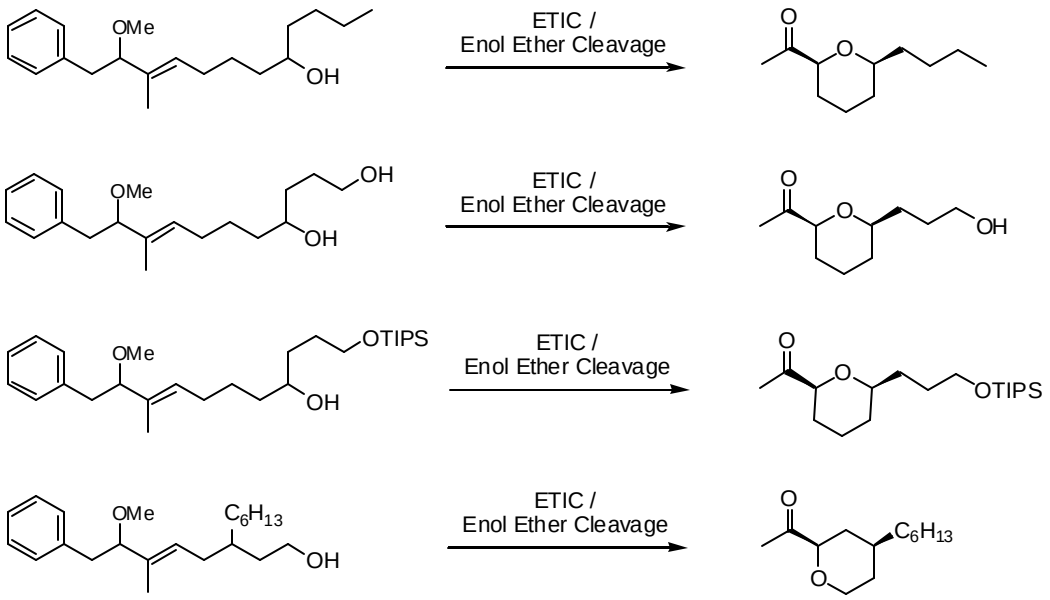



**Figure 22.** Alpha and Gamma Substitution of ETIC/Enol Ether Cleavage Substrates

It is also of importance to determine the stereochemical outcome of these reactions. By utilizing NMR spectroscopy, the relative *cis/trans* stereochemistry of the ring substituents can be determined. A prediction of the relative stereochemistry of the product ring substituents was made based on a transition state model for the cyclization. This model predicts the orientation of the ring substituents based on steric interactions concerning the substituted olefin during cyclization (Figure 23).

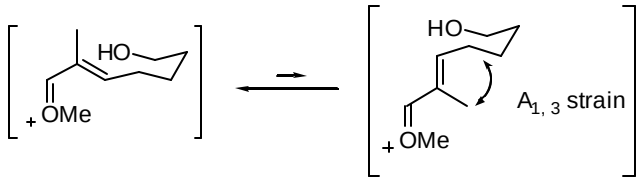



**Figure 23.** Transition State Model for Cyclization

Orientation of the olefin in a pseudo-axial conformation can lead to the development of $A_{1,3}$ strain in the transition state. These interactions are minimized when the olefin is positioned in an pseudo-equatorial conformation, making this the preferred orientation for cyclization. Substituents introduced along the alkyl chain of the molecule are also expected to be in the lower energy pseudo-equatorial orientation. With both groups in equatorial conformations during cyclization, the relative *cis*- or *trans*-stereochemistry of the final product can easily be determined (Figure 24).

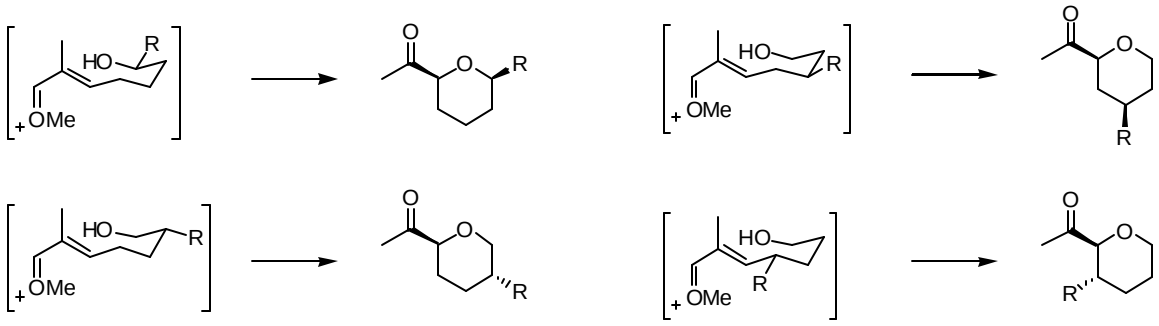



**Figure 24.** Prediction of Relative Stereochemistry of Ring Substituents

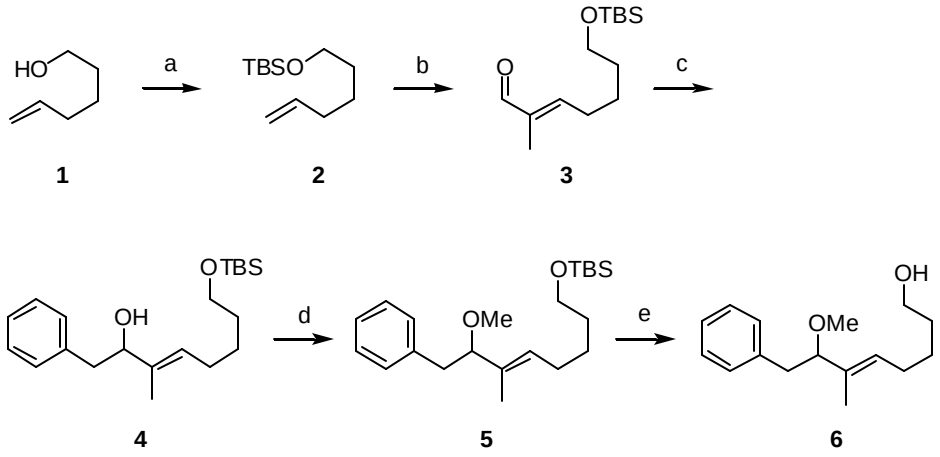
# 2.0 RESULTS AND DISCUSSION

## 2.1 SUBSTRATE SYNTHESIS

### 2.1.1 General

The synthesis of the initial ETIC/enol ether cleavage substrate is shown in Scheme 1. Protection of the commercially available 5-hexen-1-ol as its TBS ether provided compound **2** in 90% yield. The terminal olefin then underwent cross metathesis with methacrolein using Grubbs' second generation catalyst to give a 99% yield of aldehyde **3**. The aldehyde was converted to alcohol **4** in 79% yield via Grignard reaction with BnMgCl. Methylation of the free alcohol with NaH and MeI afforded methyl ether **5** in 94% yield. Subsequent TBAF deprotection gave an 85% yield of the final product **6**.

**Scheme 1**




a)TBSCl, imidazole, DMF, 90%; b) $CHOC(CH_3)CH_2$, Grubbs' II catalyst, $CH_2Cl_2$, 45°C, 99%; c)BnMgCl, $Et_2O$, -78°C to 0°C, 79%; d) NaH, MeI, THF, 0°C, 94%; e) TBAF, THF, 85%

Substrate **6** was then subjected to the ETIC/enol ether cleavage reaction conditions. *N*-methylquinolinium hexafluorophosphate ($NMQPF_6$) was used as a sensitizer with toluene as an aromatic co-sensitizer. Also present in the reaction mixture were $Na_2S_2O_3$ as a peroxide reducing agent, NaOAc as an insoluble base and 1,2 dichloroethane (DCE) as a solvent. Air was bubbled through the reaction mixture to act as the terminal oxidant. Stirring the reaction mixture with air for four hours while under irradiation from a Pyrex filtered, medium pressure mercury lamp afforded compound **7** in 16% yield (16% determined by isolation and by GC analysis) (Figure 25).

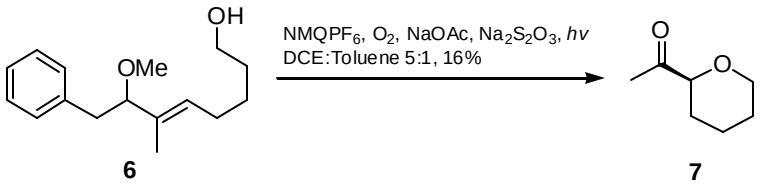



**Figure 25.** ETIC/Enol Ether Cleavage Reaction on an Unfunctionalized Substrate

GC yields were used to determine if volatility of the product and subsequent product loss during isolation was responsible for the low yields obtained. Three GC experiments were carried out using 0.5, 1.0 and 2.5 mmols of the pure product and each was combined with 1.0 mmol of the internal standard, *p*-cymene. The ratios of the peak areas of the internal standard and the product were obtained and plotted against the mmols of product used in each experiment (Figure 26). The resulting plot provided the inset equation where y represents the internal standard/product peak area ratio and x represents the amount of product present in mmols.

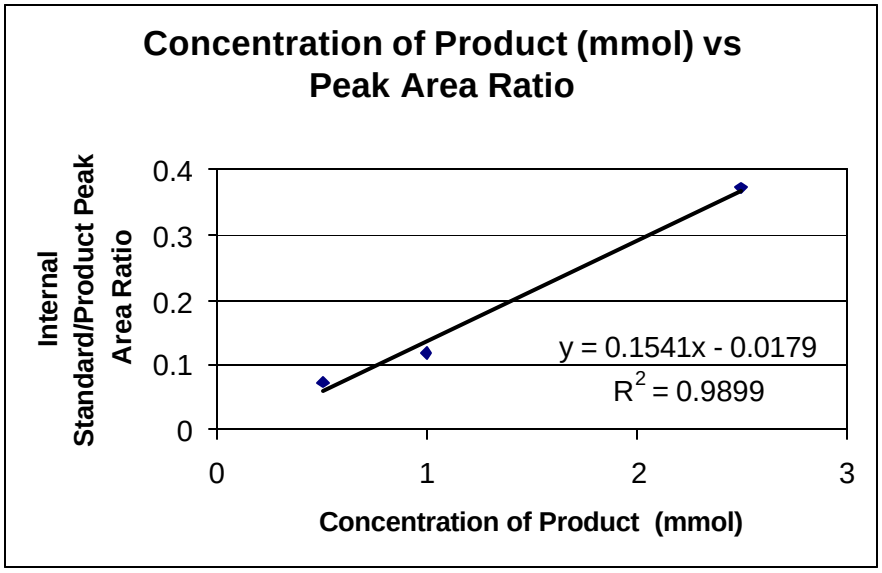



**Figure 26.** GC Yield Data

Upon completion of the ETIC/enol ether cleavage reaction, 1 mmol of *p*-cymene was added to an aliquot of the crude reaction mixture, which was then injected into the GC. The resulting peak area ratio was used with equation 1 to determine the amount of product present.

Due to the high correlation between GC and isolation yields, volatility of the product was ruled out as an explanation for the low yield of the reaction. Monitoring by TLC showed that the reaction ran to completion with minimal side products, that were not able to be identified.

The low yield of the reaction is presumed to be due to the lower reactivity of the benzyl group compared to *p*-methoxybenzyl toward radical formation and cleavage. As discussed above, the *p*-methoxybenzyl group substrates resulted in yields in the 30%-40% range.

### 2.1.2 a-Substituted Substrates

a-Substituted substrates were easily achieved by oxidation of alcohol **6** followed by Grignard addition (Figure 27). Parikh-Doering oxidation of substrate **6** resulted in a 90% yield aldehyde **8** which was converted to a secondary alcohol using various Grignard reagents.

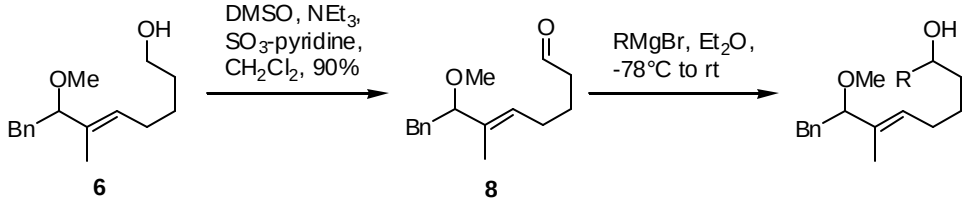



**Figure 27.** Incorporation of a-Substituents

In an attempt to determine if alcohols hindered at the alpha position would be successful substrates for our cyclization reactions, we chose to install a *sec*-butyl group on substrate **8** via Grignard addition. This reaction resulted in a reduction to the alcohol **6** by delivery of a hydride from the butyl moiety through a six-membered ring transition state (Figure 28).[28]

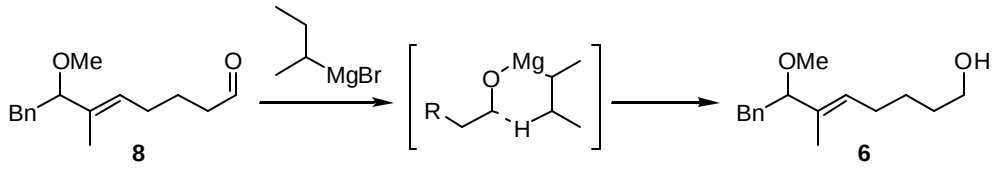



**Figure 28.** Reduction of Aldehyde **8** with *sec*-Butylmagnesium Bromide

The addition of straight-chain alkyl substituents was successful in achieving the a-substitued alcohol. *n*-Butyl and allyl substrates **9** and **10** were formed in 49% and 90% yield, respectively (Figure 29).

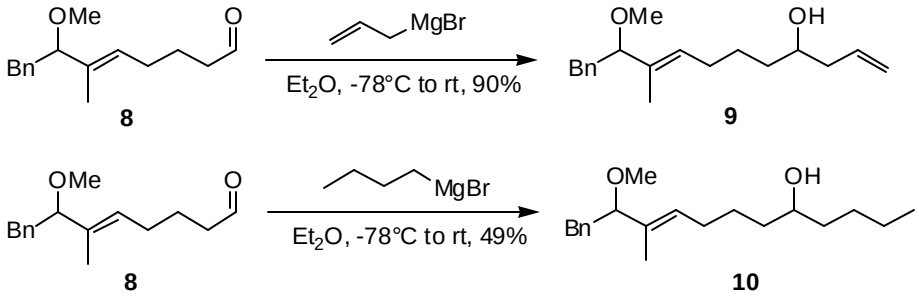



**Figure 29.** Incorporation of Straight-Chain Alkyl Substituents

Subjecting alcohol **10** to the ETIC/enol ether cleavage conditions resulted in a 16% yield of the desired product **11** (Figure 30). The high correlation between this and the yield of the unfunctionalized substrate (also 16%) implies that steric hindrance due to the secondary alcohol is not a factor in the decreased yield.

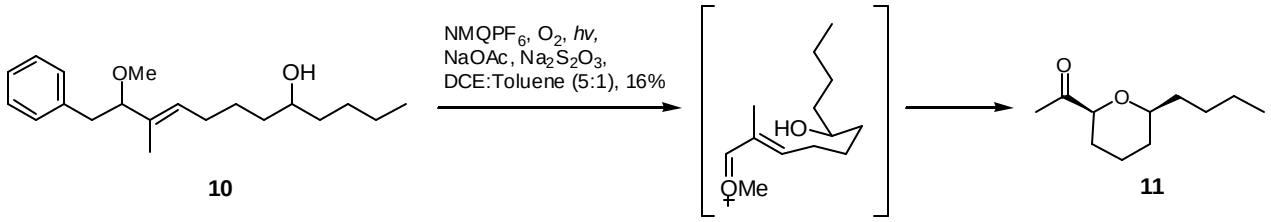
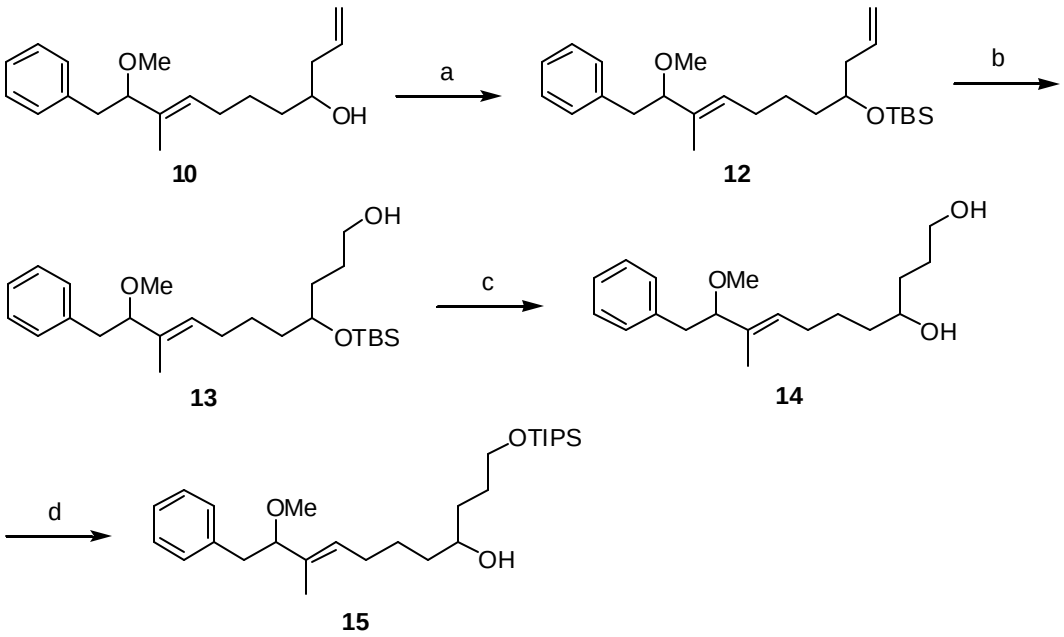



**Figure 30.** ETIC/Enol Ether Cleavage Reaction of *n*-Butyl Substrate

To increase the range of substituents used, hydroboration-oxidation using disiamyl borane was used to transform allyl compound **12** to alcohol **13** in 50% yield. Diol **13** was obtained in 60% yield by TBAF deprotection of **12** (Scheme 2). Selective protection of the primary alcohol with triisopropylsilyl chloride afforded substrate **14** in 28% yield.

**Scheme 2**




a) TBSCl, imidazole, DMF, 71%; b) i) $BH_3$-THF, 2-Methyl-2-butene, 0°C, ii) olefin in THF, 0°C, iii) Ethanol, 10% NaOH, 30% $H_2O_2$, 50°C, 50%; c) TBAF, THF, 60%; d) TIPSCl, imidazole, DMF, 28%

The ETIC/enol ether cleavage reaction of **15** also proceeded with a 16% yield to give the desired product **16** as a single diastereomer (Figure 31). The *cis*-relationship of the ring substituents was confirmed through analysis of decoupled, NOESY and COSY $^{1}$H NMR spectra. Peak assignments were made through the use of decoupled and COSY spectra (Figure 32). A NOESY crosspeak between protons a and b confirmed their *cis* relationship. Due to the small amount of material obtained and the number of overlapping peaks, coupling constants could not be determined with certainty.

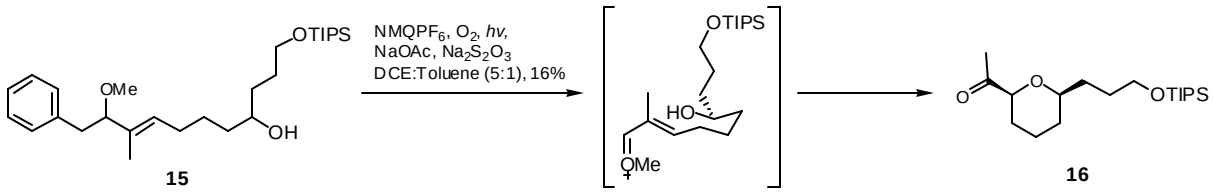



**Figure 31.** ETIC/Enol Ether Reaction of TIPS Protected Substrate

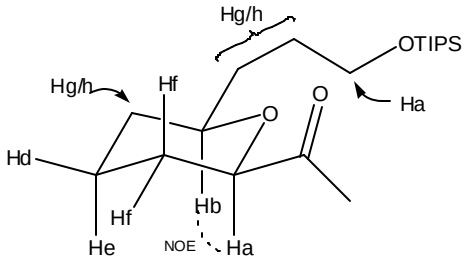



**Figure 32.** Proton Assignments for ETIC/Enol Ether Cleavage Product

Diol **14** was also subjected to ETIC/enol ether cleavage reaction conditions (Figure 33). The crude reaction mixture was subjected to TBDPS protection conditions (TBDPSCl, imidazole) and stirred overnight. The desired product **17** was obtained, however, the presence of

inseparable and unidentifiable aromatic impurities prevented an accurate determination of the yield.

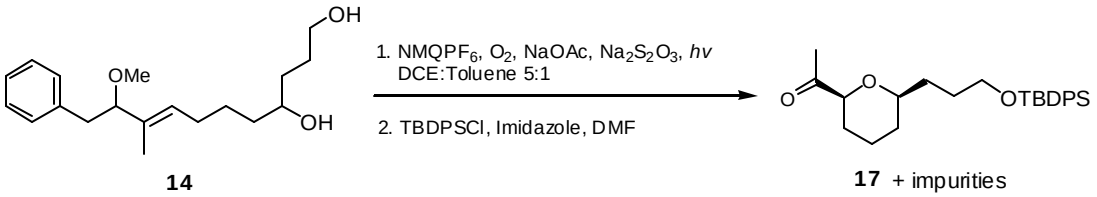
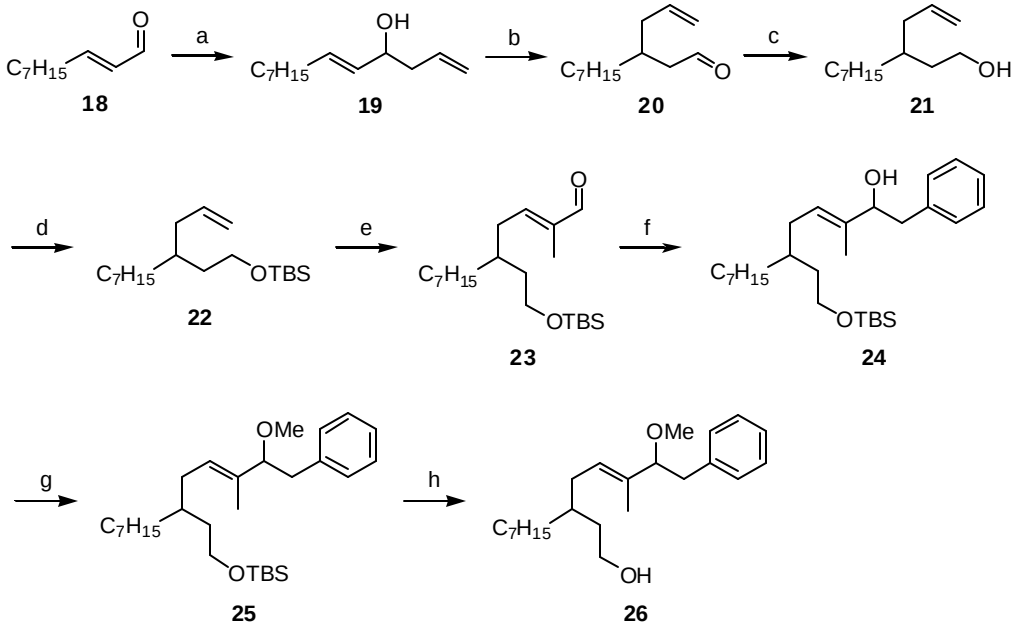



**Figure 33.** ETIC/Enol Ether Reaction with Subsequent TBDPS Protection

### 2.1.3 ?-Substituted Substrate

The second substitution pattern studied was ?-substitution (Scheme 3). Allylation of *trans*-2-decenal (**18**) proceeds with a 94% yield to give alcohol **19**. Anionic oxy-Cope rearrangement afforded a 50% yield of the ? substituted aldehyde **20**. Reduction of **20** with $LiAlH_4$ to the alcohol **21** followed by TBS protection provided a 73% yield of olefin **22** which subsequently underwent cross metathesis with methacrolein using Grubbs' second generation catalyst to give aldehyde **23** in 76% yield. The aldehyde was benzylated via Grignard addition to give a 56% yield of secondary alcohol **24**. Methylation of the alcohol to compound **25** followed by deprotection of the TBS group gave a 55% yield of final substrate **26** over two steps.

**Scheme 3**




a) $CH_2CHCH_2MgBr$, $Et_2O$, -78°C to 0°C, 94%; b) KH, 18-C-6, THF, 0°C to rt, 50%; c) $LiAlH_4$, THF, -78°C; d) TBSCl, imidazole, DMF, 73% over two steps; e) methacrolein, Grubb's II catalyst, $CH_2Cl_2$, 40°C, 76%; f) BnMgCl, $Et_2O$, -78°C to 0°C, 56%; g) NaH, MeI, THF 0°C to rt; h) TBAF, THF, 55% over two steps

The reaction of substrate **26** under ETIC/enol ether cleavage conditions resulted in a 32% yield of the desired *cis* product **27** (figure 34).

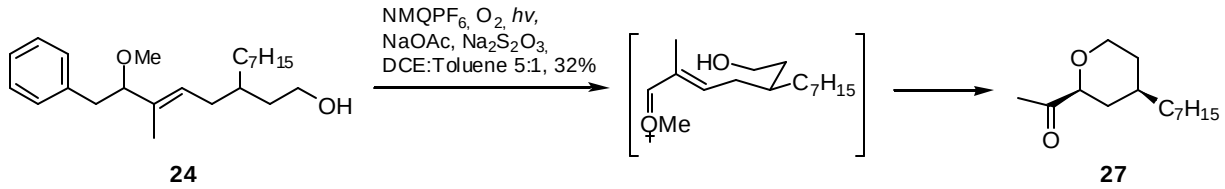



**Figure 34.** ETIC/Enol Ether Cleavage Reaction of ?-Substituted Substrate

The *cis*-relationship of the tetrahydropyran ring substituents was confirmed through analysis of NOESY and COSY spectra. Peak assignments were made utilizing 1H COSY and decoupled spectra (Figure 35). The coupling constants between protons b, e and $f_1$ established an axial-equatorial relationship between protons b and $f_1$ ($J_{HbHe}$= 11.8) and an axial-axial

relationship between protons b and e ($J_{HbHf1}$ = 2.2). NOESY crosspeaks between protons e and b as well as e and f2 indicate that protons b and f2 are in close spatial proximity to e, indicating a *cis* relationship. Further evidence for the *cis* relationship is the NOESY correlation between proton c and f2. Proton c is assigned the axial position due to the higher coupling constant with protons h ($J_{HcHh}$ = 12.3 while $J_{HaHh}$ = 2.1).

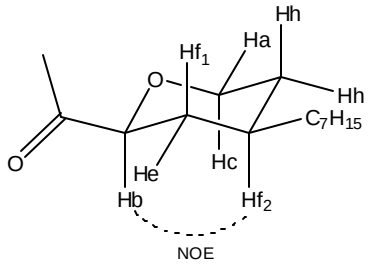



**Figure 35.** Proton Assignments for ETIC/Enol Ether Cleavage Product

The higher yield of the ?-substituted product in comparison the a-potentially be due to lack of steric hindrance of the alcohol for addition into the enol ether. The primary alcohol of the ?-substituted substrate is less hindered toward the reaction than the secondary alcohol due to the absence of a-substitution (Figure 36).


**Figure 36.** Comparison of Steric Hindrance in the Transition State of a - and ?-substituted Substrates

## 2.2 CONCLUSION

The tandem ETIC/enol ether cleavage reaction highlights the use of selective activation of a typically non-reactive carbon-carbon s-bond to form highly reactive intermediates. The mild and selective nature of the photoinitiated electron transfer (PET) conditions used for activation make the reaction desirable for use in natural product synthesis. The tandem nature of the reaction eliminates the need for isolation and purification of reactive intermediates, reducing product loss and the amount of waste produced.

Substrates were designed to determine a method for predicting the stereochemistry of the final product as well as to test the functional group compatibility of the reaction. A new route was used to obtain these substrates in moderate to good overall yield. It was determined that the stereochemistry of the final product could be predicted by analyzing steric factors in the six-membered ring transition state model. The ETIC/enol ether cleavage reaction was compatible with simple alkyl side chains as well as alcohols and TIPS protected silyl ethers. Upon comparison with results from previous ETIC/enol ether cleavage reactions, it was determined that *p*-methoxy substitution on the arene is not necessary for reactivity, however it leads to increased yields of the final product (16%-32% yield for benzyl substrates compared to previously determined 30%-40% for *p*-methoxybenzyl).

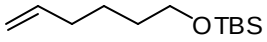
# 3.0 EXPERIMENTAL

All reactions were performed in flame or oven dried glassware under an atmosphere of nitrogen with magnetic stirring.

Proton ($^1$H NMR) and carbon ($^{13}$C NMR) nuclear magnetic resonance spectra were obtained on Bruker Avance 300 and 75 MHz spectrometers. Chemical shifts are given in parts per million (ppm) on the delta (d) scale. The solvent peak was used as a reference value. For $^1$H NMR: $CDCl_3$ = 7.27 ppm, for $^{13}$C NMR: $CDCl_3$ = 77.0 ppm. For proton data: s = singlet; d = doublet; t = triplet; q = quartet; dd = doublet of doublets; dt = doublet of triplets; dq = doublet of quartets; br = broad; m = multiplet. High resolution and low resolution mass spectra were obtained on a VG 7070 spectrometer. Infrared (IR) spectra were collected on an Avatar 360 FTIR spectrometer. Analytical thin layer chromatography (TLC) was performed on E. Merck pre-coated (25 nm) silica gel 60F-254 plates. Flash column chromatography was performed using ICN Silitech 32-63 60Å silica gel.

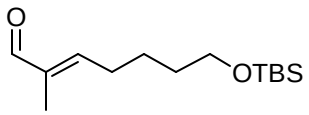
Reagent grade ethyl acetate and hexanes were purchased from Mallinckrodt chemicals and used for column chromatography. Reagent grade methylene chloride ($CH_2Cl_2$), triethylamine ($NEt_3$) and dichloroethane (DCE) were distilled from $CaH_2$. Tetrahydrofuran (THF), toluene, and diethyl ether ($Et_2O$) were dried by passing through an aluminum drying column. Anhydrous N,N-dimethylformamide (DMF), ethanol (EtOH), methanol (MeOH) and dimethyl sulfoxide (DMSO) were purchased from Aldrich and used as is.

***tert*-Butyl(hex-5-enyloxy)dimethylsilane 2**




To hex-5-en-1-ol (0.300 g, 3.00 mmol) in DMF (6 mL) at room temperature was added imidazole (0.450 g, 6.60 mmol) followed by TBSCl (0.500 g, 3.30 mmol). The reaction mixture was then stirred 24 hours. The reaction was diluted with ether and washed with water. The aqueous layer was then extracted with ether. The combined organic layers were dried over $Na_2SO_4$ and concentrated. The resulting residue was then purified via flash column chromatography (25% EtOAc in Hexanes) to provide the desired product (0.576 g, 90%): $^1$H NMR (300 MHz, $CDCl_3$) d 5.86-5.77 (m, 1H), 5.03 (d, *J* = 17.1 Hz, 1H), 4.94 (d, *J* = 10.2 Hz, 1H), 3.61 (t, *J* = 6.2 Hz, 2H), 2.06 (q, *J* = 6.9 Hz, 2H), 1.55-1.42 (m, 4H), 0.90 (s, 9H) 0.05 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) d 138.7, 114.4, 62.9, 33.6, 32.3, 25.9, 25.2, 18.3, -5.4; IR (neat) 3078, 2900, 1641, 1254, 1097 $cm^{-1}$; HRMS (EI) calcd for $C_{12}H_{26}OSi$ 214.1753, found 199.1516 (N – $CH_3$).

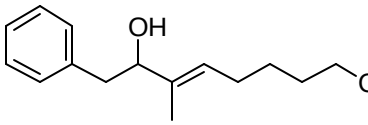
**7-(*tert*-Butyldimethylsilanyloxy)-2-methylhept-2-enal 3**




To *tert*-butyl(hex-5-enyloxy)dimethylsilane (0.400 g, 1.86 mmol) and methacrolein (1.45 g, 18.6 mmol) in $CH_2Cl_2$ was added Grubb's 2$^{nd}$ generation catalyst ( 0.158 g, 0.186 mmol). The reaction was refluxed at 40 °C for 7 hours and quenched by the addition of ethyl vinyl ether (3 mL). The reaction mixture was stirred for 30 minutes then cooled to room temperature and concentrated. The resulting residue was purified via flash column chromatography (3% EtOAc in Hexanes) to give the desired product ( 0.476 g, 99%): $^1$H NMR (300 MHz, $CDCl_3$) d 9.40 (s, 1H), 6.50 (t, *J* = 6.3 Hz, 1H), 3.64 (t, *J* = 1.0 Hz, 2H), 2.38 (d, *J* = 6.3 Hz, 2H), 1.68 (s, 3H), 1.55-1.51 (m, 4H), 0.90 (s, 9H), 0.05 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) d 195.1, 154.6, 139.3, 62.5, 32.3, 28.6, 25.8, 24.7, 18.2, 9.1, -5.4; IR

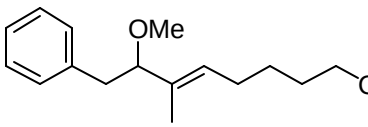
(neat) 3357, 2900, 1685, 1646, 1253, 1097 $cm^{-1}$; HRMS (EI) calcd for $C_{14}H_{28}O_2Si$ 256.1859, found 241.1623 (N - $CH_3$)

**8-(*tert*-Butyldimethylsilanyloxy)-3-methyl-1-phenyloct-3-en-2-ol 4**




To 7-(*tert*-Butyldimethylsilanyloxy)-2-methylhept-2-enal (0.425 g, 1.63 mmol) in $Et_2O$ (10 mL) at -78 °C was added benzylmagnesium bromide (1.97 g, 2.61 mL) dropwise. The reaction mixture was stirred 30 minutes then warmed to 0 °C for 2.5 hours. The mixture was quenched with $NH_4Cl_{(aq)}$ and stirred while warmed to room temperature. The organic layer was washed with water and brine. The aqueous layer was then extracted with ether. The combined organic layers were dried over $Na_2SO_4$ and concentrated. The resulting residue was purified via flash column chromatography (15% EtOAc in Hexanes) to provide the desired product ( 0.4012 g, 71%): $^1$H NMR (300 MHz, $CDCl_3$) d 7.33-7.7.21 (m, 5H), 5.37 (t, *J* = 7.2 Hz, 1H), 4.22 (dd, *J* = 5.6, 7.8 Hz, 1H), 3.59 (t, *J* = 6.2 Hz, 2H), 2.84 (dd, *J* = 7.9, 12.4 Hz, 2H), 1.54 (s, 3H), 1.50-1.33 (m, 6H), 0.90 (s, 9H), 0.05 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) d 138.6, 136.3, 129.3, 128.3, 126.9, 126.3, 63.0, 42.1, 32.4, 27.2, 25.9, 25.6, 18.3, 11.8, -5.3; IR (neat) 3415, 3085, 3063, 2900, 1603, 1254, 1093, 731, 699 $cm^{-1}$; HRMS (EI) calcd for $C_{21}H_{36}O_2Si$ 348.2485, found 348.2470.

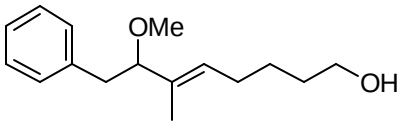
***tert*-Butyl(7-methoxy-6-methyl-8-phenyloct-5-enyloxy)dimethylsilane 5**




To 8-(*tert*-Butyldimethylsilanyloxy)-3-methyl-1-phenyloct-3-en-2-ol (0.312 g, 0.896 mmol) in THF (8 mL) at 0 °C was added NaH (0.143 g, 3.58 mmol) in small portions. The reaction mixture was stirred for 30 minutes and methyl iodide (0.509 g, 3.58 mmol) was added dropwise. The reaction was warmed

to room temperature and stirred for 4 hours, then quenched by the addition of $NH_4Cl_{(aq)}$. The organic layer was washed with water and brine. The aqueous layer was washed with EtOAc. The combined organic layers were then dried over $Na_2SO_4$ and concentrated. The resulting residue was purified via flash column chromatography (10% EtOAc in Hexanes) to give the desired product (0.3059 g, 94%): $^1$H NMR (300 MHz, $CDCl_3$) d 7.53-7.18 (m, 5H), 5.22 (t, *J* = 6.3 Hz, 1H), 3.66 (t, *J* = 6.9 Hz, 1H), 3.56 (t, *J* = 7.5 Hz, 2H), 3.15 (s, 3H), 2.92 (dd, *J* = 13.8, 7.1 Hz, 1H), 2.73 (dd, *J* = 13.8, 7.1 Hz, 1H), 2.00 (qd, *J* = 7.2, 3.1 Hz, 2H), 1.59 (s, 3H), 1.45-1.29 (m, 4H), 0.90 (s, 9H), 0.05 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) d 139.1, 133.3, 129.6, 129.2, 128.0, 125.9, 88.6, 63.0, 55.8, 40.5, 32.3, 27.2, 25.9, 25.6, 18.3, 10.6, -5.3; IR (neat) 3085, 3063, 2900, 1604, 1254, 1097, 742, 698 $cm^{-1}$, HRMS (EI) calcd for $C_{22}H_{38}O_2Si$ 362.2641, found 362.2648.

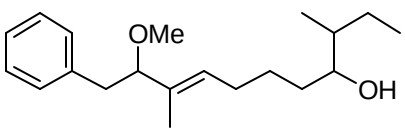
**7-Methoxy-6-methyl-8-phenyloct-5-en-1-ol 6**




To *tert*-Butyl(7-methoxy-6-methyl-8-phenyloct-5-enyloxy)dimethylsilane (2.84 g, 5.64 mmol) in THF (100 mL) was added 1M TBAF (8.46 mmol) dropwise. The reaction mixture was stirred 4 hours and quenched with water. The organic layers were washed with water and brine. The aqueous layer was washed with EtOAc. The combined organic layers were then dried over $Na_2SO_4$ and concentrated. The resulting residue was purified via flash column chromatography (20% EtOAc in Hexanes) to afford the desired product (1.19 g, 85%): $^1$H NMR (300 MHz, $CDCl_3$) d 7.35-7.24 (m, 5H), 5.19 (t, *J* = 6.6 Hz, 1H), 3.68 (t, *J* = 6.9 Hz, 1H), 3.57 (t, *J* = 6.2 Hz, 2H), 3.16 (s, 3H), 2.92 (dd, *J* = 13.8, 7.1 Hz, 1H), 2.73 (dd, *J* = 13.8, 7.1 Hz, 1H), 2.03 (q, *J* = 6.8 Hz, 3H), 1.59 (s, 3H), 1.49-1.43 (m, 4H); $^{13}$C NMR (75 MHz, $CDCl_3$) d 139.0, 133.5, 129.4, 129.2, 128.0, 125.9, 88.5, 62.8, 55.8, 40.4, 32.1, 27.1, 25.4, 10.6, IR (neat) 3383,

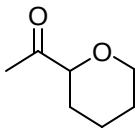
3086, 3062, 2932, 1603, 1095, 745, 699 $cm^{-1}$; HRMS (EI) calcd for $C_{16}H_{24}O_2$ 248.1776, found 248.1764.

**(E)-10-Methoxy-3,9-dimethyl-11-phenylundec-8-en-4-ol**




To (E)-7-Methoxy-6-methyl-8-phenyloct-5-enal ( 0.262 g, 1.05 mmol) in dry ether (6.5 ml) at -78 °C was added *sec*-butylmagnesium bromide dropwise. The reaction mixture was stirred at -78 °C for 30 min then warmed to 0 °C and stirred for 2 h and 45 min. The reaction was quenched with $NH_4Cl_{(aq)}$ and warmed to room temperature. The organic layers were washed with water and brine. The combined aqueous layer was washed with EtOAc. The combined organic layers were dried over $Na_2SO_4$ and concentrated. NMR analysis of the crude residue showed the reduced product, 7-Methoxy-6-methyl-8-phenyloct-5-en-1-ol **6.**

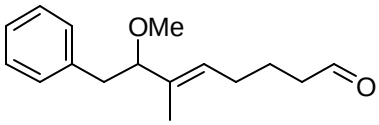
**1-(Tetrahydro-2H-pyran-2-yl)ethanone 7**




7-Methoxy-6-methyl-8-phenyloct-5-en-1-ol (0.200 g, 0.806 mmol), NMQ·$PF_6$ (0.020 g, 0.069 mmol), NaOAc (0.564 g, 6.85 mmol) and $Na_2S_2O_3$ (0.552 g, 3.63 mmol) were combined in DCE (17 mL) and toluene (3 mL). The reaction mixture was stirred with air bubbling through and irradiation with a medium pressure, Pyrex filtered mercury lamp for 4.5 hours. The reaction mixture was filtered through silica gel and concentrated under reduced pressure to remove the majority of the solvent, and was then blown dry with compressed air at 0 °C. The resulting residue was purified via flash column chromatography (5% ether in pentane) to give the desired product (0.0165 g, 16%): $^1$H NMR

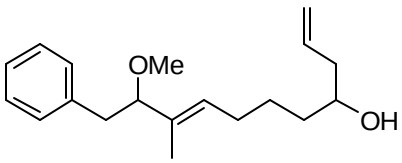
(300 MHz, $CDCl_3$) d 4.09-4.04 (m, *J* = 11.2 Hz, 1H), 3.78 (dd, *J* = 13.5, 2.4 Hz, 1H), 3.48 (td, *J* = 11.5, 3.3 Hz, 1H), 2.18 (s, 3H), 1.93-1.87 (m, 2H), 1.57 (s, 4H)

**(E)-7-Methoxy-6-methyl-8-phenyloct-5-enal 8**




To 7-Methoxy-6-methyl-8-phenyloct-5-en-1-ol (0.697 g, 2.81 mmol) in $CH_2Cl_2$ (4 mL) was added $NEt_3$ (1.17 mL, 8.42 mmol), DMSO (4.4 mL) and $SO_3$·pyridine complex (0.722 g, 4.85 mmol). The reaction mixture was stirred 3 hours at room temperature and quenched with the addition of water. The aqueous layer was washed with $CH_2Cl_2$. The combined organic layers were washed with water, brine, and 10% HCl solution, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give the desired product (0.683 g, 98%): $^1$H NMR (300 MHz, $CDCl_3$) d 9.67 (s, 1H), 7.28-7.17 (m, 5H), 5.13 (t, *J* = 7.0 Hz, 1H), 3.69 (t, *J* = 7.1 Hz, 1H), 3.16 (s, 3H), 2.95 (dd, *J* = 13.8, 7.1 Hz, 1H), 2.72 (dd, *J* = 13.8, 7.1 Hz, 1H), 2.18, (t, *J* = 6.9 Hz, 2H), 2.03 (q, *J* = 7.1 Hz, 2H), 1.59-1.47 (m, 5H) ; $^{13}$C NMR (75 MHz, $CDCl_3$) d 202.5, 138.9, 134.6, 129.2, 128.2, 126.0, 88.5, 55.9, 42.9, 40.3, 26.6, 21.6, 10.7, IR (neat) 3064, 3028, 2930, 1723, 1642, 1095, 737, 700 $cm^{-1}$; HRMS (EI) calcd for $C_{16}H_{22}O_2$ 246.1620, found 215.1442 (N – $OCH_3$).

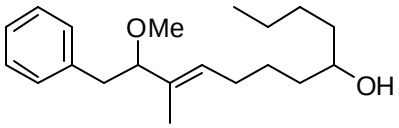
**(E)-10-Methoxy-9-methyl-11-phenylundeca-1,8-dien-4-ol 9**




To (E)-7-methoxy-6-methyl-8-phenyloct-5-enal (0.827 g, 3.36 mmol) in dry ether (22 mL) was added 1M allylmagnesium bromide (8.40 mmol) dropwise at -78 °C. The reaction mixture was warmed to 0 °C and stirred 2 hours. The reaction was quenched with the addition of $NH_4Cl_{(aq)}$. The aqueous layer was washed with ether and the combined organic layers were

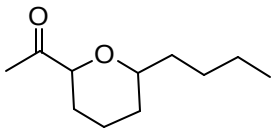
washed with water and brine, dried over $Na_2SO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (10% EtOAc in hexanes) to afford the desired product (0.880 g, 91%): $^1$H NMR (300 MHz, $CDCl_3$) d 7.29-7.16 (m, 5H), 5.81-5.72 (m, 1H), 5.23-5.10 (m, 3H), 3.68 (t, *J* = 6.9 Hz, 1H), 3.70-3.66 (m, 1H), 3.17 (s, 3H), 2.91 (dd, *J* = 13.7, 6.9 Hz, 1H), 2.72 (dd, *J* = 13.7, 6.9 Hz, 1H), 2.33-2.28 (m, 1H) 2.25-2.08 (m, 2H), 2.02-2.00 (m, 2H), 1.59 (s, 3H), 1.40-1.32 (m, 4H); $^{13}$C NMR (75 MHz, $CDCl_3$) d 139.1, 134.8, 133.5, 129.3, 129.3, 129.2, 128.0, 125.9, 118.1, 88.5, 70.5, 55.8, 41.9, 40.4, 36.2, 27.3, 25.3, 10.6; IR (neat) 3423, 2930, 1640, 1248, 1094, 742, 698 cm$^{-1}$; HRMS (EI) calcd for $C_{18}H_{28}O_2$ 288.2089, found 288.2082.

**(E)-11-Methoxy-10-methyl-12-phenyldodec-9-en-5-ol 10**



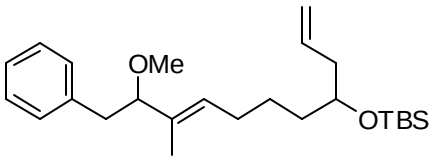

To (E)-7-methoxy-6-methyl-8-phenyloct-5-enal (0.283 g, 1.14 mmol) in dry ether (7 mL) at -78 °C was added 2M *n*-BuMgCl (2.28 mmol, 1.14 mL) dropwise. The reaction mixture was stirred for 30 minutes, then warmed to 0°C and stirred 5 hours. The reaction was quenched with $NH_4Cl_{(aq)}$. The aqueous layer was washed with EtOAc and the combined organic layers were washed with water and brine, dried over $Na_2SO_4$ and concentrated under reduced pressure. The resulting residue was purified via flash column chromatography (10% EtOAc in hexanes) to give the desired product (0.200 g, 58%): $^1$H NMR (300 MHz, $CDCl_3$) d 7.36-7.16 (m, 5H), 5.36-5.32 (m, 1H), 3.70 (t, *J* = 6.2 Hz, 1H), 3.57-3.51 (m, 1H), 3.16 (s, 3H), 2.91 (dd, *J* = 13.7, 6.9 Hz, 1H), 2.72 (dd, *J* = 13.7, 6.9 Hz, 1H), 2.05-2.01 (m, 2H), 1.60 (s, 3H), 1.40-1.26 (m, 12H), 0.94-0.89 (m, 3H).

**1-(6-Butyltetrahydro-2H-pyran-2-yl)ethanone 11**



(E)-11-methoxy-10-methyl-12-phenyldodec-9-en-5-ol (0.050 g, 0.164 mmol), NMQ·$PF_6$ (0.004 g, 0.014 mmol), NaOAc (0.115 g, 1.39 mmol) and $Na_2S_2O_3$ (0.112 g, 0.738 mmol) were combined in DCE (2.5 mL) and toluene (0.5 mL). The reaction mixture was stirred with air bubbling through and irradiation with a medium pressure, Pyrex filtered mercury lamp for 5 hours. The reaction mixture was filtered through silica gel and concentrated under reduced pressure to remove the majority of the solvent, and was then blown dry with compressed air at 0 °C. The resulting residue was analyzed by GC to determine the presence of the desired product (12%): $^1$H NMR (300 MHz, $CDCl_3$) d 3.77 (dd, *J* = 11.8, 2.5 Hz, 1H), 3.30-3.28 (m, 1H), 2.21 (s, 3H), 1.93-1.88 (m, 1H), 1.56-1.52 (m, 4H), 1.51-1.38 (m, 2H), 1.32-1.12 (m, 4H), 0.89 (t, *J* = 7.3 Hz, 3H).

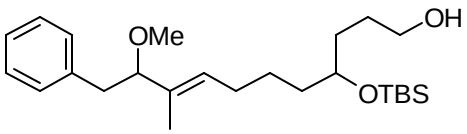
**((E)-10-Methoxy-9-methyl-11-phenylundeca-1,8-dien-4-yloxy)(*tert*-butyl)dimethylsilane 12**



To (E)-10-methoxy-9-methyl-11-phenylundeca-1,8-dien-4-ol (0.880 g, 3.05 mmol) in DMF (6.6 mL) was added imidazole (0.457 g, 6.72 mmol) followed by TBSCl (0.506 g, 3.35 mmol). The reaction mixture was stirred overnight (~15 hours) and diluted with ether and washed with water. The aqueous layer was washed with ether and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified via flash column chromatography (10% EtOAc in hexanes) to give the desired product ( 0.872 g, 71%): $^1$H NMR (300 MHz, $CDCl_3$) d 7.29-7.18 (m, 5H), 5.85-5.76 (m, 1H), 5.22 (t, *J* = 7.0 Hz, 1H), 5.06-5.01 (m, 3H), 3.68 (t, *J* = 6.69 Hz, 2H), 3.16 (s, 3H), 2,92 (dd, *J* = 13.6, 7.3 Hz, 1H), 2.76 (dd, *J* = 13.6, 7.3 Hz, 1H), 2.19 (t, *J* = 5.9 Hz, 2H), 2.04-1.97 (m, 2H), 1.62 (s,

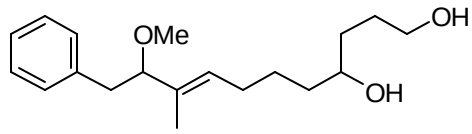
3H), 1.37-`.28 (m, 6H), 0.90 (s, 12H), 0.05 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) d 139.1, 135.4, 133.4, 129.5, 129.4, 129.2, 128.0, 125.9, 116.6, 88.6, 71.8, 55.8, 41.9, 40.6, 36.3, 27.5, 25.7, 25.1, 18.1, 10.7, -4.5; IR (neat) 3064, 3028, 2928, 1641, 1254, 1096, 743, 698 $cm^{-1}$; HRMS (EI) calcd for $C_{25}H_{42}O_2Si$ 402.2954, found 371.2756 (N-$CH_3$)

**((E)-10-Methoxy-9-methyl-11-phenylundeca-1,8-dien-4-yloxy)(*tert*-butyl)dimethylsilane 13**



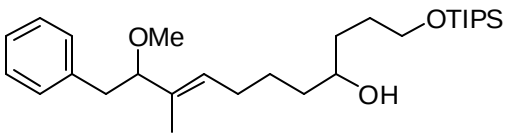

To neat 2-methyl-2-butene (0.081 mL, 0.768 mmol) at 0 °C was added 1M $BH_3$·THF (0.384 mmol) dropwise. Let stir at 0 °C 20 minutes then added ((E)-10-methoxy-9-methyl-11-phenylundeca-1,8-dien-4-yloxy)(*tert*-butyl)dimethylsilane (0.055 g, 0.192 mmol) in THF (0.14 mL). The reaction mixture was stirred at 0 °C for 24 hours. Added ethanol (0.18 mL), $NaOH_{(aq)}$ (0.02 mL) and 30% $H_2O_2$ (0.12 mL). The reaction mixture was heated to 50 °C and stirred 2 hours. The mixture was washed with EtOAc and the combined organic layers were washed with water and brine and dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The residue was purified via flash column chromatography (20% EtOAc in hexanes) to give the desired product (0.0407, 50%): $^1$H NMR (300 MHz, $CDCl_3$) 7.28-7.16 (m, 5H), 5.23-5.19 (m, 1H), 3.69-3.60 (m, 4H), 3.15 (s, 3H), 2.93 (dd, *J* = 13.5, 7.2 Hz, 1H), 2.75 (dd, *J* = 13.5, 7.2 Hz, 1H), 2.00-1.96 (m, 3H), 1.59 (s, 3H), 1.53-1.48 (m, 3H), 1.44-1.32 (m, 2H), 1.30-1.21 (m, 3H), 0.90 (s, 9H), 0.05 (s, 6H); d $^{13}$C NMR (75 MHz, $CDCl_3$) d 139.1, 133.5, 129.3, 128.0, 125.9, 88.5, 71.9, 55.8, 40.6, 36.1, 33.3, 28.1, 27.6, 25.9, 25.3, 18.1, 10.7, -4.5; IR (neat) 3396, 2928, 1666, 1462, 1255, 1097, 773, 698 $cm^{-1}$; HRMS (EI) calcd for $C_{25}H_{44}O_3$ 420.3060, found 389.2866 (N – $OCH_3$).

**(E)-10-Methoxy-9-methyl-11-phenylundec-8-ene-1,4-diol 14**




To ((E)-10-methoxy-9-methyl-11-phenylundeca-1,8-dien-4-yloxy)(*tert*-butyl)dimethylsilane (1.03 g, 2.44 mmol) in THF (40 mL) was added 1M TBAF (3.66 mmol) dropwise. The reaction was stirred at room temperature 4 hours and quenched by addition of water. The aqueous layer was washed with $CH_2Cl_2$ and the combined organic layers were washed with water and brine, dried over $Na_2SO_4$ and concentrated under reduced pressure. The resulting residue was purified via flash column chromatography (20-60% EtOAc in hexanes) to afford the desired product (0.450 g, 60%): $^1$H NMR (300 MHz, $CDCl_3$) d 7.28-7.16 (m, 5H), 5.20 (t, *J* = 6.0 Hz, 1H), 3.72-3.66 (m, 3H), 3.65-3.58 (m, 1H), 3.16 (s, 3H), 2.92 (dd, *J* = 13.7, 6.9 Hz, 1H), 2.73 (dd, *J* = 13.7, 6.9 Hz, 1H), 2.04-2.01 (m, 2H), 1.71-1.67 (m, 2H), 1.67-1.58 (m, 3H), 1.36-1.27 (m, 4H), 1.26-1.10 (m, 4H); $^{13}$C NMR (75 MHz, $CDCl_3$) d 139.1, 133.6, 129.2, 128.0, 125.9, 88.5, 71.7, 63.0, 55.8, 40.4, 37.0, 34.2, 29.1, 27.3, 25.4, 10.7; IR (neat) 3239, 2933, 1644, 1454, 1095 cm$^{-1}$; HRMS (EI) calcd for $C_{19}H_{30}O_3$ 306.2195, found 289.2165 (N – OH).

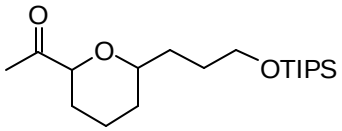
**10-Methoxy-9-methyl-11-phenyl-1-triisopropylsilanyloxyundec-8-en-4-ol 15**




To (E)-10-methoxy-9-methyl-11-phenylundec-8-ene-1,4-diol (0.0148 g, 0.0483 mmol) in DMF (0.5 mL) was added imidazole (0.009 g, 0.106 mmol) followed by TIPSCl (0.0102 g, 0.053 mmol). The reaction mixture was stirred at room temperature for 11 hours, diluted with ether and washed with water. The aqueous phase was washed with ether and the combined organic layers were dried over $Na_2SO_4$ and concentrated under reduced pressure. The resulting residue was purified via flash column chromatography (10% EtOAc in hexanes) to give the desired product (0.0064 g,

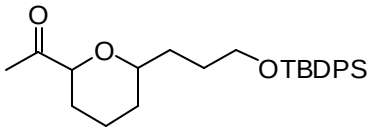
28%): $^{1}$H NMR (300 MHz, $CDCl_3$) d 7.28-7.16 (m, 5H), 5.21 (t, *J* = 6.3 Hz, 1H), 3.75 (t, *J* = 4.5 Hz, 2H), 3.67 (t, *J* = 6.6 Hz, 1H), 3.59-3.54 (m, 1H), 3.16 (s, 3H), 2.93 (dd, *J* = 13.5, 7.2 Hz, 1H), 2.73 (dd, *J* = 13.5, 7.2 Hz, 1H) 2.01 (br, 1H), 1.66-1.64 (m, 3H), 1.59 (s, 3H), 1.45-1.24 (m, 6H), 1.16-1.12 (m, 4H), 1.08 (s, 18H); $^{13}$C NMR (75 MHz, $CDCl_3$) d 139.1, 133.3, 129.5, 128.0, 125.9, 88.6, 71.3, 63.7, 55.8, 40.4, 36.8, 34.7, 29.3, 27.4, 25.5, 17.9, 11.9, 10.6, 10.5 ; IR (neat) 3430, 2944, 1603, 1463, 1265, 1097, 791, 736 $cm^{-1}$; HRMS (EI) calcd for $C_{28}H_{50}O_3$ 462.3529, found 445.3481 (N - OH).

**1-[6-(3-Triisopropylsilanyloxypropyl)-tetrahydropyran-2-yl]-ethanone 16**



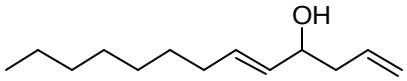

10-Methoxy-9-methyl-11-phenyl-1-triisopropylsilanyloxy-undec-8-en-4-ol (0.0290 g, 0.063 mmol), NMQ·$PF_6$ (0.002 g, 0.005 mmol), NaOAc (0.044 g, 0.532 mmol) and $Na_2S_2O_3$ (0.043 g, 0.282 mmol) were combined in DCE (3 mL) and toluene (0.6 mL). The reaction mixture was stirred with air bubbling through and irradiation with a medium pressure, Pyrex filtered mercury lamp for 4 hours. The reaction was filtered and concentrated. The resulting residue was purified via flash column chromatography (10% EtOAc in hexanes) to give the desired product (~0.004 g, 16%): $^{1}$H NMR (300 MHz, $CDCl_3$) d 3.77-3.71 (m, 3H), 3.39-3.34 (m, 1H), 2.21 (s, 3H), 1.95-1.91 (m, 2H), 1.89-1.82 (m, 2H), 1.78-1.55 (m, 6H), 1.31-1.18 (m, 3H), 1.18-1.00 (m, 18H); $^{13}$C NMR (75 MHz, $CDCl_3$) d 210.3, 83.4, 78.0, 63.6, 32.9, 31.3, 29.2, 27.9, 25.9, 23.5, 18.2, 12.2; IR (neat) 2943, 2865, 1720, 1463, 1101 $cm^{-1}$; HRMS (EI) calcd for $C_{19}H_{38}O_3Si$ 342.5887, found 299.2039 (N – $C_3H_7$).

**1-[6-(3-*tert*-Butyldiphenylsilanyloxypropyl)tetrahydropyran-2-yl]-ethanone 17**




(E)-10-methoxy-9-methyl-11-phenylundec-8-ene-1,4-diol (0.100 g, 0.326 mmol), NMQ·$PF_6$ (0.008 g, 0.028 mmol), NaOAc (0.230 g, 2.78 mmol) and $Na_2S_2O_3$ (0.225 g, 1.47 mmol) were combined in DCE (10 mL) and toluene (2 mL). The reaction mixture was stirred with air bubbling through and irradiation with a medium pressure, Pyrex filtered mercury lamp for 4 hours. The reaction was filtered and imidazole (0.048 g, 0.717 mmol) was added followed by TBDPSCl (0.099 g, 0.359 mmol). The reaction mixture was stirred for 3 hours and 15 mintues and quenched by addition of water. The aqueous layer was extracted with $CH_2Cl_2$. The combined organic layers were washed with water and brine, dried over $Na_2SO_4$ and concentrated under reduced pressure. The resulting residue was purified via flash column chromatography (5% EtOAc in hexanes) to give the desired product: $^1$H NMR (300 MHz, $CDCl_3$) 7.78-7.71 (m, 25H), 7.47-7.21 (m, 36H), 3.76-3.70 (m, 3H), 3.33-3.29 (m, 1H), 2.18 (s, 3H), 2.00-1.42 (m, 10H), 1.38-1.09 (m 81H).

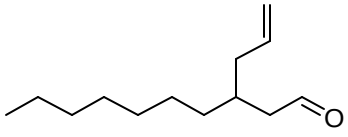
**(E)-Dodeca-1,5-dien-4-ol 19**




To *trans*-2-decenal (1.25 g, 8.10 mmol) in dry ether (50 mL) was added 1M allylmagnesium bromide (20.25 mmol) dropwise at 0 °C. The reaction mixture was stirred 4 hours and quenched by addition of $NH_4Cl_{(aq)}$. The aqueous layer was washed with ether and the combined organic layers were washed with water and brine, dried over $Na_2SO_4$ and concentrated under reduced pressure. The resulting residue was purified via flash column chromatography (15% EtOAc in hexanes) to give the desired product (1.498 g, 94%): $^1$H NMR (300 MHz, $CDCl_3$) d 5.99-5.79 (m, 1H), 5.79-5.63 (m, $J$ = 16.2, 6.6, 1.2 Hz, 1H) 5.50-5.446 (m, 1H), 5.16-5.10 (m, 2H), 4.11-4.02 (m, 1H), 2.31-2.26 (m, 2H), 2.02 (q, $J$ = 6.6 Hz, 2H), 1.75 (d,

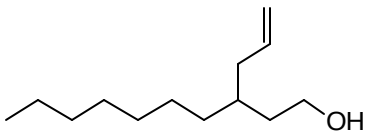
*J* = 3.5 Hz, 1H), 1.38-1.24 (m, 10H), 0.88 (t, *J* = 6.9 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) d 134.4, 132.3, 131.9, 117.9, 71.8, 42.0, 32.1, 31.8, 29.1, 22.6, 14.0; IR (neat) 3417, 1669, 1640, 1264 $cm^{-1}$; HRMS (EI) calcd for $C_{13}H_{24}O$ 196.1827, found 179.1798 (N – OH).

**3-Allylnonanal 20**



To KH (2.41 g, 18.4 mmol) in THF (100 mL) was added 18-crown-6 at 0 °C. The reaction mixture was stirred 20 minutes and (E)-dodeca-1,5-dien-4-ol (1.198 g, 6.11 mmol) was added in THF (12 mL) dropwise. The reaction was slowly warmed to room temperature while stirring 20 hours. The reaction was quenched by the addition of water, the aqueous layer was washed with EtOAc and the combined organic layers were washed with water and brine, dried over $Na_2SO_4$ and concentrated under reduced pressure. The resulting residue was purified via flash column chromatography (5% EtOAc in hexanes) to afford the desired product (0.600 g, 50%): $^1$H NMR (300 MHz, $CDCl_3$) d 9.71 (t, *J* = 2.1 Hz, 1H), 5.73-5.64 (m, 1H), 5.01-4.96 (m, 2H), 2.37-2.28 (m, 2H), 2.15-2.98 (m, 3H), 1.23 (s, 12H), 0.84 (t, *J* = 6.3 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) d 202.6, 136.0, 116.8, 47.9, 38.3, 33.9, 32.7, 31.7, 29.6, 29.1, 26.6, 22.5, 13.9; IR (neat) 3077, 2925, 2719, 1727, 1640 $cm^{-1}$; HRMS (EI) calcd for $C_{13}H_{24}O$ 196.1827, found 196.1821.

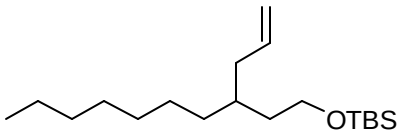
**3-Allylnonan-1-ol 21**



To 3-allylnonanal (0.469g, 2.39 mmol) in THF (150 mL) was added 1M $LiAlH_4$ (3.50 mmol) dropwise at -78 °C. The reaction was stirred at -78 °C for 2 hours then poured into a 3:1 mixture of $Et_2O$ in 1M HCl (100 mL total). The organic layer was washed with water, dried over $Na_2SO_4$ and concentrated under

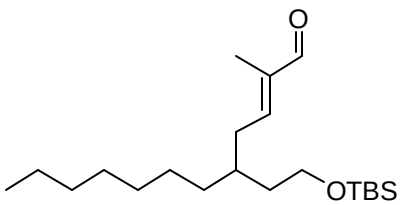
reduced pressure. The resulting residue was purified via flash column chromatography (10% EtOAc in hexanes) to give the desired product (0.219g, 46%) $^{1}$H NMR (300 MHz, $CDCl_3$) d 5.81-5.69 (m, 1H), 5.05-4.98 (m, 2H), 3.66 (t, *J* = 6.9 Hz, 2H), 2.07-2.03 (m, 2H), 1.53 (t, *J* = 4.5 Hz, 4H), 1.32-1.21 (m, 12H), 0.90 (t, *J* = 6.6 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) d 137.0, 115.9, 61.0, 38.1, 36.6, 34.2, 33.6, 31.8, 29.9, 29.3, 26.6, 22.6, 14.0; IR (neat) 3348, 2925, 1639, 1264, 1055 $cm^{-1}$; HRMS (EI) calcd for $C_{13}H_{26}O$ 198.1984, found 198.1988.

**(3-Allylnonyloxy)(*tert*-butyl)dimethylsilane 22**




To 3-allylnona-1-ol (0.457 g, 2.31 mmol) in DMF (4.5 mL) was added imidazole (0.346 g, 5.07 mmol) followed by TBSCl (0.383g, 2.54 mmol). The reaction mixture was stirred 17 hours, diluted with ether and washed with water. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified via flash column chromatography (10% EtOAc in hexanes) to afford the desired product (0.625 g, 87%): $^{1}$H NMR (300 MHz, $CDCl_3$) d 5.82-5.73 (m, 1H), 5.03-4.98 (m, 2H), 3.65 (t, *J* = 6.9 Hz, 2H), 2.05 (t, *J* = 6.3 Hz, 2H), 1.51 (t, *J* = 6.0 Hz, 3H) 1.27 (s, 12H), 0.97-0/81 (m, 12H), 0.10-0.02 (m, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) d 137.3, 115.7, 61.4, 38.2, 36.6, 34.2, 33.6, 31.9, 29.9, 26.7, 25.9, 25.7, 22.7, 14.1, -5.3; IR (neat) 3076, 2927, 1639, 1254, 1098 $cm^{-1}$; HRMS (EI) calcd for $C_{19}H_{40}OSi$ 312.2848, found 255.2153 (N – $C_4H_9$).

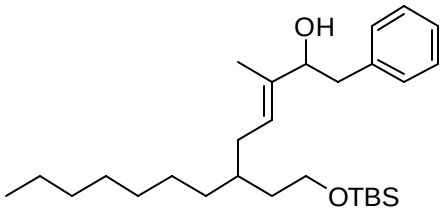
**5-[2-(*tert*-Butyldimethylsilanyloxy)-ethyl]-2-methyldodec-2-enal 23**




To (3-allylnonyloxy)(*tert*-butyl)dimethylsilane in $CH_2Cl_2$ (25 mL) was added methacrolein (1.75 g, 22.4 mmol) followed by Grubb's second generation catalyst (0.095 g, 0.112 mmol). The

reaction mixture was refluxed at 40 °C for 21 hours. Ethyl vinyl ether (3 mL) was added and the reaction mixture was stirred 30 minutes while cooling to room temperature. The resulting mixture was concentrated under reduced pressure and purified via flash column chromatography (3% EtOAc in hexanes) to give the desired product (0.600 g, 76%): $^{1}$H NMR (300 MHz, $CDCl_3$) d 9.47 (s, 1H), 6.53, (td, *J* = 7.2, 1.0 Hz, 1H), 3.65 (t, *J* = 12.5 Hz, 2H), 2.35 (t, *J* = 6.7 Hz, 2H), 1.75 (s, 3H), 0.89 (s, 15H), 0.05 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) d 195.2, 153.9, 140.0, 61.0, 36.8, 34.5, 33.8, 33.4, 31.8, 29.8, 29.3, 26.7, 25.9, 22.6, 18.3, 14.0, 9.4, -5.4; IR (neat) 2927, 1692, 1644, 1254, 1099 $cm^{-1}$; HRMS (EI) calcd for $C_{21}H_{42}O_2Si$ 354.2954, found 339.2727 (N – $CH_3$).

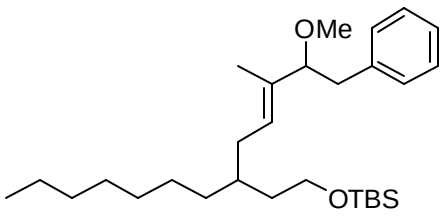
**6-[2-(*tert*-Butyldimethylsilanyloxy)-ethyl]-3-methyl-1-phenyltridec-3-en-2-ol 24**




To 5-[2-(*tert*-Butyldimethylsilanyloxy)-ethyl]-2-methyldodec-2-enal (0.600 g, 1.70 mmol) in ether (15 mL) at 0°C was added 20% benzylmagnesium chloride (0.770 g, 5.10 mmol) dropwise. The reaction was stirred 2.5 hours and quenched with the addition of $NH_4Cl_{(aq)}$. The aqueous layer was washed with ether and the combined organic layers were washed with water and brine, dried over $Na_2SO_4$ and concentrated under reduced pressure. The resulting residue was purified via flash column chromatography (10% EtOAc in hexanes) to give the desired product (0.425 g, 56%): $^{1}$H NMR (300 MHz, CDCl3) d 7.31-7.19 (m, 5H), 5.38-5.34 (m, 1H), 4.24 (t, *J* = 6.6 Hz, 1H), 3.60 (t, *J* = 6.6 Hz, 2H), 2.83 (d, *J* = 6.9 Hz, 2H), 1.98 (t, *J* = 6.6 Hz, 2H), 1.69-1.64 (m, 4H), 1.46-1.41 (m, 3H), 1.27-1.11 (m, 13H), 0.89 (s, 12H), 0.05 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) d 138.6, 136.9, 129.3, 128.3, 126.3, 125.5, 78.7, 61.4, 42.1, 36.6, 34.7, 33.6, 31.7, 29.9, 29.3, 26.7, 25.9, 22.6,

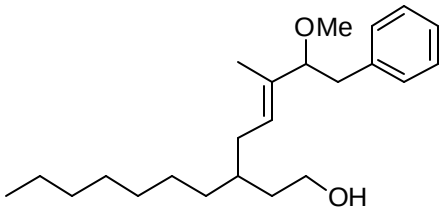
18.3, 14.1, 11.9, -5.3.; IR (neat) 3431, 3028, 2926, 1603, 1463, 1264, 1095, 775, 700 $cm^{-1}$; HRMS (EI) calcd for $C_{27}H_{50}O_2Si$ 446.3580, found 446.3560.

***tert*-Butyl-[3-(4-methoxy-3-methyl-5-phenylpent-2-enyl)-decyloxy]-dimethylsilane 25**



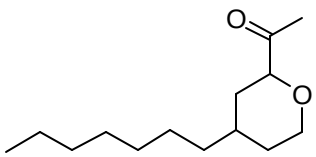

To 6-[2-(*tert*-Butyldimethylsilanyloxy)-ethyl]-3-methyl-1-phenyltridec-3-en-2-ol (0.425 g, 0.956 mmol) in THF (5 mL) at 0°C was added NaH (0.115 g, 2.87 mmol) in portions. The mixture was stirred 15 minutes and MeI (0.178 mL, 2.87 mmol) was added dropwise. The reaction was warmed to room temperature and stirred 26 hours. The reaction was quenched by the addition of water. The aqueous layer was washed with EtOAc and the combined organic layers were washed with water and brine, dried over $Na_2SO_4$ and concentrated under reduced pressure. The resulting residue was used without further purification. $^1$H NMR (300 MHz, CDCl3) d 7.29-7.17 (m, 5H), 5.24 (t, *J* = 7.2 Hz, 1H), 3.70 (t, *J* = 6.9 Hz, 1H), 3.68-3.57 (m, 2H), 3.21 (s, 3H), 2.93 (dd, *J* = 13.5, 6.3 Hz, 1H), 2.73 (dd, *J* = 13.5, 6.3 Hz, 1H), 1.99 (br q, *J* = 6.6 Hz, 2H), 1.61 (s, 3H), 1.46-1.15 (m, 14H), 0.90 (s, 9H), 0.05 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) d 139.1, 134.0, 129.2, 128.1, 125.9, 88.7, 61.4, 55.8, 40.5, 36.6, 34.6, 33.5, 31.9, 31.6, 29.9, 29.3, 26.7, 25.9, 22.7, 18.3, 14.1, 10.9, -5.3; IR (neat) 3027, 2924, 1604, 1454, 1255, 1098, 774, 698 $cm^{-1}$; HRMS (EI) calcd for $C_{29}H_{52}O_2Si$ 460.3737, found 403.3034 (N – $C_4H_9$).

**3-(4-Methoxy-3-methyl-5-phenylpent-2-enyl)-decan-1-ol 26**




To *tert*-Butyl-[3-(4-methoxy-3-methyl-5-phenylpent-2-enyl)-decyloxy]-dimethylsilane (0.440 g, 0.956 mmol) in THF (12 mL) was added 1M TBAF (2.86 mmol) dropwise. The reaction was stirred at room temperature for 3 hours and quenched by the addition of water. The aqueous layer was washed with EtOAc and the combined organic layers were washed with water and brine, dried over $Na_2SO_4$ and concentrated under reduced pressure. The resulting residue was purified via flash column chromatography (10% EtOAc in hexanes) to give the desired product (0.181 g, 55% over two steps): $^1$H NMR (300 MHz, $CDCl_3$) d 7.30-7.17 (m, 5H), 5.19 (q, *J* = 6.8 Hz, 1H), 3.78 (t, *J* = 7.2 Hz, 1H), 3.61-3.53 (m, 2H), 3.18 (s, 3H), 2.94 (ddd, *J* = 13.5, 7.7, 2.3 Hz, 1H), 2.73 (ddd, *J* = 13.5, 7.7, 2.3 Hz, 1H), 2.02-1.97 (m, 3H), 1.58 (s, 3H), 1.47-1.09 (m, 15H), 0.87 (t, *J* = 6.9 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) d 138.9, 134.2, 129.3, 128.0, 125.9, 88.7, 61.0, 55.8, 40.3, 36.6, 34.6, 33.5, 31.7, 29.9, 29.3, 26.7, 22.6, 14.0, 10.7; IR (neat) 3403, 2936, 1651, 1454, 1096, 740, 698 $cm^{-1}$; HRMS (EI) calcd for $C_{23}H_{38}O_2$ 346.2872, found 329.2843 (N – OH).

**1-(4-Heptyltetrahydro-2H-pyran-2-yl)ethanone 27**




3-(4-Methoxy-3-methyl-5-phenylpent-2-enyl)-decan-1-ol (0.100 g, 0.286 mmol), NMQ·$PF_6$ (0.007 g, 0.024 mmol), NaOAc (0.200 g, 2.43 mmol) and $Na_2S_2O_3$ (0.197 g, 1.28 mmol) were combined in DCE (14 mL) and toluene (2.5 mL). The reaction mixture was stirred with air bubbling through and irradiation with a medium pressure, Pyrex filtered mercury lamp for 5.5 hours. The reaction mixture was filtered through cotton and concentrated under reduced pressure. The resulting

residue was purified via flash column chromatography (5% EtOAc in hexanes) to give the desired product (0.021 g, 32%): $^{1}$H NMR (300 MHz, $CDCl_3$); 4.09 (dd, *J* = 11.4, 4.6 Hz, 1H), 3.75 (dd, *J* = 11.8, 2.2 Hz, 1H), 3.44 (dd, *J* = 12.4, 2.1 Hz, 1H), 2.19 (s, 3H), 1.96-1.91 (m, 1H), 1.62-1.58 (m, 1H), 1.58-1.53 (m, 3H), 1.39-1.09 (m, 13H), 1.01-0.88 (m, 2H), 0.88 (t, *J* = 3.5 Hz, 3H); d $^{13}$C NMR (75 MHz, $CDCl_3$) d 209.3, 82.9, 67.9, 53.4, 36.8, 34.7, 32.3, 31.8, 29.7, 29.2, 26.2, 25.7, 22.6, 14.1; IR (neat) 2923, 2854, 1720, 1455, 1377, 1257, 1098 $cm^{-1}$; HRMS (EI) calcd for $C_{14}H_{26}O_2$ 226.1933, found 226.1917.

## 4.0 REFERENCES


1. Kumar, V. S.; Floreancig, P. E. "Electron Transfer Initiated Cyclizations: Cyclic Acetal Synthesis through Carbon-Carbon s-Bond Activation" *J. Am. Chem. Soc.* **2001**, *123*, 3842-3843.

2. Freccero, M.; Pratt, A.; Albini, A.; Long, C. "A Kinetic Evaluation of Carbon-Hydrogen, Carbon-Carbon, and Carbon-Silicon Bond Activation in Benzylic Radical Cations" *J. Am. Chem. Soc.* **1998**, *120*, 284-297.

3. Moeller, K. D. "Synthetic Applications of Anodic Electrochemistry" *Tetrahedron* **2000**, *56*, 9527-9554.

4. Mattay, J. "Photoinduced Electron Transfer in Organic Synthesis" *Synthesis* **1989,** 223-252.

5. Fagnoni, F.; Mella, M.; Albini, A. "Radical Addition to Alkenes via Electron Transfer Photosensitization" *J. Am. Chem. Soc.* **1995**, *117*, 7877-7881.

6. Smith, M. B. *Organic Synthesis;* 2nd Edition; McGraw Hill, New York, NY, 2002, pp 988-990.

7. Popielarz, R.; Arnold, D. A. "Radical Ions in Photochemistry. Carbon-Carbon Bond Cleavage of Radical Cations in Solution: Theory and Application" *J. Am. Chem. Soc.* **1990**, *112*, 3068-3082.

8. Wang, L.; Seiders, J. R.; Floreancig, P. E. "Structure-Activity Relationships in Oxidative Carbon-Carbon Bond Forming Reactions: A Mild and Efficient Approach to Stereoselective Synthesis of 2,6-Disubstituted Tetrahydropyrones" *J. Am. Chem. Soc.* **2004**, *126*, 12596-12603.

9. *Encyclopedia of Electrochemistry of the Elements*; Bard, A. J.; Ed.; Marcel Dekker Inc: New York, 1984; Vol. 15, p. 48.

10. Wayner, D. D. M.; McPhee, D. J.; Griller, D. "Oxidation and Reduction Potentials of Transient Free Radicals" *J. Am. Chem. Soc.* **1998**, *110*, 132-137.

11. Seiders, J. R.; Wang, L.; Floreancig, P. E. "Tuning Reactivity and Chemoselectivity in Electron Transfer Initiated Cyclization Reactions: Applications to Carbon-Carbon Bond Formation" *J. Am. Chem. Soc.* **2003**, *125*, 2406-2407.

12. Effenberger, F. “The Chemistry of Enol Ethers” *Angew. Chem. Int. Ed.* **1969**, *8*(5), 295-312.

13. Sutterer, A.; Moeller, K. D. “Reversing the Polarity of Enol Ethers: An Anodic Route to Tetrahydrofuran and Tetrahydropyran Rings” *J. Am. Chem. Soc.* **2000**, *122*, 5636-5637.

14. Tokunaga, M.; Shirogane, Y.; Aoyama, H.; Obora, Y.; Tsuji, Y. *J. Organomet. Chem.* **2005**, *690*, 5378-5382.

15. Nelsen, S. F.; Akaba, R. “Oxygenation Reaction of Adamantylideneadamantane Cation Radical” *J. Am. Chem. Soc.* **1981**, *103*, 2096-2097.

16. Moeller, K. D.; Marzabadi, M. R.; New D. G.; Chiang, M. Y.; Keith, S. “Oxadative Organic Electrochemistry: A Novel Intramolecular Coupling of Electron-Rich Olefins” *J. Am. Chem. Soc.* **1990**, *112*, 6123-6124.

17. Frey, D. A.; Reddy, H. K.; Moeller, K. D. “Intramolecular Anodic Olefin Coupling Reactions: The Use of Allylsilane Coupling Partners with Allylic Alkoxy Groups” *J. Org. Chem.* **1999**, *64*, 2805-2813.

18. New. D. G.; Tesfai, Z.; Moeller, K. D. “Intramolecular Anodic Olefin Coupling Reactions and the Use of Electron-Rich Aryl Rings” *J. Org. Chem.* **1996**, *61*, 1578-1598.

19. Reddy, S. H. K.; Chiba, K.; Sun, Y.; Moeller, K. D. “Anodic Oxidations of Electron-Rich Olefins: Radical Cation Based Approaches to the Synthesis of Bridged Bicyclic Ring Skeletons” *Tetrahedron* **2001**, *57*, 5183-5197.

20. Chiba, K.; Miura, T.; Kim, S.; Kitano, Y.; Tada, M. “Electrocatalytic Intermolecular Olefin Cross-Coupling by Anodically Induced Formal [2 + 2] Cycloaddition between Enol Ethers and Alkenes” *J. Am. Chem. Soc.* **2001,** *123*, 11314-11315.

21. Miura, T.; Kim, S.; Yoshikazu, K.; Tada, M.; Chiba, K. “Electrochemical Enol Ether/Olefin Cross-Metathesis in a Lithium Perchlorate/Nirtomethane Electrolyte Solution” *Angew. Chem. Int. Ed.* **2006**, *45*, 1461-1463.

22. Tietze, L. F. “Domino Reactions in Organic Synthesis” *Chem. Rev.* **1996**, *96*, 115-136.

23. Denmark, S. E.; Heemstra, J. R.; Beutner, G. L. “Catalytic, Enantioselective, Vinylogous Aldol Reactions” *Angew. Chem. Int. Ed.* **2005**, *44*, 4682-4698.

24. Baciocchi, E.; Bietti, M.; Lanzalunga, O. “Mechanistic Aspects of ß-Bond-Cleavage Reactions of Aromatic Radical Cations” *Acc. Chem. Res.* **2000**, *33*, 243-251.

25. Elliot, M. C. J. Chem. Soc., Perkin Trans. 1 **1998**, 32, 4175.

26. Craig, K. S.; Williams, D. E.; Hollander, I.; Frommer, E.; Mallon, R.; Collins, K.; Wojciechowicz, D.; Tahir, A.; Van Soest, R.; Andersen, R. J. *Tetrahedron Lett.* **2002**, *43*, 4801-4804.

27. Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2004**, *21*, 1-49.

28. Smith, M. B. *Organic Synthesis: Second Edition*, McGraw-Hill, New York, NY, 2004, pp. 603-604.