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A novel method for catalytic electron transfer initiated cyclization reaction for the formation of cyclic acyl aminals through a unique method of carbon-carbon σ-bond activation has been developed. This new cyclization strategy employs a potent electrophile, generated by a photoinitiated single electron oxidation of a homobenzylic amide or t-buty] carbamate, which reacts with an appended nucleophile allowing for the formation of cyclic acyl aminals.

The Lewis acid-surfactant-combined catalyst (LASC) was employed in a novel method for effecting intramolecular Prins cyclization reactions in water. Acetals of 1,2 and 1,3 di- and tri- substituted alcohols with a tethered allyl silane have been converted to 2,6-syn-tetrahydropyrans. The LASCs are generated in situ by the addition of cerium nitrate to a solution of sodium dodecylsulfate and acetal in water. A heterogeneous reaction environment is created in which the acetal is trapped within the hydrophobic core of the immediately generated micelle. Intermolecular Prins cyclization is catalyzed upon interaction of the acetal with Lewis acidic cerium cations located at the surface of the micelle. LASC mediated intramolecular Prins cyclization reactions are efficient, high yielding, and an environmentally benign method of generating 2,6-cis-tetrahydropyrans.
A highly convergent route towards the total synthesis of the marine macrolide (+)-dactylolide is currently being pursued. The route involves the condensation of two highly functionalized segments of the molecule, an $\alpha,\beta$-unsaturated aldehyde and a 1,3-$\text{syn}$-diol, to form a cyclic $\alpha,\beta$-unsaturated acetal. Both enantiopure segments arise from vinylogous aldol reactions, providing the three necessary stereocenters. The key synthetic transformation involves intramolecular Prins cyclization of a cyclic $\alpha,\beta$-unsaturated acetal with a pendent allylsilane to provide the 2,6-$\text{cis}$-disubstituted-4-methylenetetrahydropyran core of the molecule efficiently and stereoselectively. Other key transformations include a completely $\text{trans}$ selective selenoxide-selenate [2,3] sigmatropic rearrangement and the selective oxidation of a primary allylic alcohol in the presence of a secondary alcohol with Dess-Martin periodinane.
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PREFACE

Mom, Dad, Michael and Ryan:

THANKS! Those six letters can never fully express my love and appreciation for you guys. Thankyou for standing by me, for laughing and crying with me, for sharing in the joy and the sweat, for picking me up in the toughest of times and riding high with me during the great times. Thankyou for every sacrifice you made for me, for your unconditional love and for every opportunity you have provided me. This is for you.

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Thank you for taking a chance on me. Thanks for your patience, for your tenacity, and for bringing out the best in me, for your genuine concern and drive to finish. It was a long, tough haul, but we made it. That’s one molecule down and one thousand more to go. Your Noble Prize awaits !!!

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Jay, Butch, Lijun, and Chris…There is light at the end of the tunnel. Thanks for your support, for you helpful suggestions and for sharing in this experience with me. You are all unbelievably talented and will no doubt go extremely far. Keep up the good work.
1. Mechanistic and stereochemical studies of photoinduced electron transfer initiated cyclization reactions: the role of nitrogen

1.1. Introduction to electron transfer

I. General

Photochemistry has become a widely accepted, fundamental branch of organic chemistry, playing an integral role in many syntheses. Photochemical transformations often provide routes to synthetic targets that cannot be attained by conventional transformations. Photoinduced electron transfer (PET) is the branch of photochemistry that exploits the ability of certain photoexcited molecules to act as strong oxidizing or reducing species, and induce a permanent chemical change in a ground state molecule through an electron transfer mechanism. After being oxidized or reduced by a photosensitizer, an organic substrate is transformed into a reactive intermediate that is capable of undergoing a variety of reactions. PET reactions provide a novel route to approaching difficult synthetic targets that could not be realized by conventional means.

Photoinduced electron transfer processes have widespread application in semiconductor photocatalysis, imaging systems, such as silver halide photography, spectral sensitization and xerography. Nature frequently invokes electron transfer in a variety of enzymatic processes such as oxidative phosphorylation, the DNA-photolyase reaction and photosynthesis. Despite the numerous applications and biological examples, the use of electron transfer reactions in preparative organic synthesis is limited to include a few examples such as the Birch reduction, acyloin condensation, Ullmann coupling, formation of Grignard reagents, protecting group removal, and $S_{RN1}$ reactions.
The perceived complexities of electron transfer processes are often responsible for their minimal utilization in reaction design. The reluctance to invoke these processes could be attributed to the lack of applicable data for predicting reaction outcomes as well as the inability to control various side reactions associated with the odd electron species generated. Over the past years an increased understanding of the kinetics, thermodynamics and primary reaction pathways of radical ions has renewed interest in their application toward reaction design. The ability to exploit the full potential of photoinduced electron transfer in reaction design requires an understanding of the principles of photochemistry and underlying theory of electron transfer.

II. Photochemical Principles

The absorption of light provides the impetus for all photochemical reactions. Core electrons and electrons in lower energy orbitals are normally not perturbed by the absorption of light. However, electrons in high lying molecular orbitals are susceptible to photoexcitation in the ultraviolet and visible regions of the electromagnetic spectrum (100-700 nm). The absorption of light generates an excited state species that is generally more reactive than its ground state analog. Most commonly one electron from the highest occupied orbital (HOMO) is promoted into the lowest unoccupied molecular orbital (LUMO) (Figure 1.1).13
Molecules cannot remain in the excited state for an extended length of time and therefore must lose their extra energy in some manner. Excited species can react in a variety of different ways, as shown in Figure 1.2.

**Figure 1.2: Photochemical pathways**

Photoexcited molecules are able to induce transitory or permanent changes in neighboring molecules through an electron transfer pathway. Electronic transitions create vacancies in low-lying bonding or non-bonding orbitals, called *holes*, which serve as much better electron acceptors than unoccupied orbitals of higher energy. Energy is released upon the
transfer of one electron from an orbital of infinite separation from the nucleus of the donor into a low-lying, vacant orbital nearer to the nucleus of the acceptor. The absorbed light can be converted to chemical energy by the transfer of an electron either to or from the excited state species in an energetically favorable, exothermic process.

The energy change associated with the excitation of a bound electron from its orbital into an orbital at infinite distance, or the difference in orbital energies between the low-lying bonding and higher nonbonding orbitals, is referred to as ionization potential (IP) (Figure 1.3). The reverse process, the amount of energy required to bring an electron from an infinite distance into a low-lying vacant orbital, is referred to as electron affinity (EA). IP’s and EA’s are quantities used to describe gas phase molecules, which are not directly applicable in describing molecules in solution.

**Figure 1.3: IP and EA of both the ground and excited state species**

The solvation of ions is an important factor in solution phase chemistry, resulting in the need for the solution phase analogs of IP and EA, oxidation and reduction potentials. Oxidation
potential is the potential at which an electron is removed from a molecule, and reduction potential is the potential at which an electron is added to a molecule. Variations in oxidation and reduction potentials parallel those in ionization potentials and electron affinities. Plots of redox potentials versus ionization potentials and electron affinities for structurally related compounds often show linear correlations.\textsuperscript{15} A ground state example of the redox process is shown in Figure 1.4, where electron transfer occurs between a donor and acceptor molecule. In the ground state the free energy change for the electron transfer process is the difference in redox potentials of the donor and acceptor. Because of the large HOMO-LUMO gap in the ground state of organic molecules, electron transfer would be a largely endothermic process.

\textbf{Figure 1.4:} Ground state redox reactions

\[ 
\begin{array}{cccc}
D & + & A & \rightarrow & D^+ & + & A^- \\
& & & & & & \\
& & & & & & \\
\end{array}
\]

In addition to a donor (D), and an acceptor (A), PET reactions require an electronic excitation source (light). In PET the electronically excited species serves as the oxidizing or reducing species, as shown in Figure 1.5. Here, the free energy change associated with electron transfer, which includes the redox potentials of the donor and acceptor, is made more negative by an additional term corresponding to the excitation energy. Electronic excitation exploits the large HOMO-LUMO gap, making electron transfer an energetically more favorable process.
The Rehm-Weller equation\textsuperscript{16} provides a useful expression for calculating the free energy change associated with PET reactions. For most PET reactions the number of electrons transferred, represented by $n$, is usually one and the charge associated with the transfer of one mole of electrons, the unit of Faraday, is represented by $F$. For most electron transfer processes this quantity, $nF$, is approximately equal to one and can be disregarded in the calculations. The oxidation potential of the donor (OP\textsubscript{D}), the reduction potential of the acceptor (OP\textsubscript{R}), and the equilibrium excitation energy ($\Delta G_{00}$), based on the wavelength of excitation, factor into the thermodynamic condition for spontaneous electron transfer. The work term, $w_p$, describes the coulombic attraction between ions generated by electron transfer. This term is not applicable to cases where electron transfer occurs between a charged and neutral species, due to the lack of electrostatic attraction between the species, and can therefore be disregarded.

$$\Delta G_{ET} = nF[\text{OP}_D - \text{OP}_R - \Delta G_{00} - w_p] \quad \text{Rehm-Weller Equation}$$
III. The Radical Cation

The most commonly observed primary reaction pathways for radical cations are: 1. A-B bond cleavage at the periphery of the electrophore (A-B = C-H, C-C, C-X, A-H, X-Y), 2. reactions initiated by attack of nucleophiles, and 3. radical based processes such as ET, dimerization, reactions with radicals, and hydrogen transfer (Figure 1.6). Over the past decade a broad body of knowledge concerning the primary reactions of radical cations has accumulated. For radical cations generated in solution a highly selective, predictable mode of fragmentation usually operates to give a neutral radical and a cation. This unimolecular bond dissociation is referred to as mesolytic cleavage. Fragmentation in solution is quite efficient, but the synthetic utility has been limited mostly to C-H, O-M, S-R, Si-Si, C-Si, C-Ge, C-N and C-Sn bonds.

Figure 1.6: Primary reaction pathways for radical cations

PET reactions exploit the ability of electronically excited molecules to function as strong oxidants and have proven to be an excellent method for generating radical cations in solution. In radical cations strong bonds, such as C-C, can be selectively cleaved to generate radicals and cations from unconventional precursors under mild reaction conditions. The majority of examples of C-C fragmentation stem from PET reactions of strained carbocyclic compounds, where strain release provides the driving force for bond scission. Examples of unstrained mesolytic C-C bond cleavage occur mostly in aromatic substrates with aliphatic side chains. The addition of alkyl, aryl, hydroxyl, siloxy and alkoxy substituents was found to lower the barrier to
mesolytic C-C bond cleavage of the radical cation due to increased stabilization of the resulting cationic fragment through electron donation. However, deprotonation is a competing process that reduces synthetic utility.

**IV. C-C Bond Fragmentation**

During measurements of standard oxidation potentials of a series of alkylbenzenes, Kochi and coworker’s were able to demonstrate that the lifetimes of the radical cations in acetonitrile were less than 100 µs. One important trend noticed during this study was that cyclic voltamograms (CV) of tert-butyl substituted benzenes were found to be reversible. The reversibility of the CV’s was associated with the absence of benzyl protons in the tert-butyl group, allowing for the extended lifetime of the radical cation. The shortened lifetime of alkylbenzenes having labile benzyl protons indicated that C-H bond activation was favored over C-C bond activation.

Arnold and coworker’s work with the irradiation of an acetonitrile-methanol (3:1) solution of 2,2-diphenylethyl methylether and 1,4-dicyanobenzene to yield exclusively diphenyl methane and the dimethyl acetal of formaldehyde provided the first example of a PET reaction involving a homobenzylic ether (Figure 1.7). This study revealed that with the appropriate substitution in the alkyl chain of alkylarenes, C-C bond activation effectively competed with C-H bond activation. It also provided a simple system for the study of the theory and application of C-C bond cleavages of radical cations in solution.
Arnold\textsuperscript{25} proposed a stepwise mechanism for the radical cation cleavage reaction (Figure 1.8). The first step in the mechanism is excitation of the sensitizer, 1,4-dicyanobenzene. Substitution of the singlet excited state energy and reduction potential into the Rehm-Weller equation\textsuperscript{16} showed that photoexcited 1,4-dicyanobenzene was capable of oxidizing any substituent with an oxidation potential of less than 2.4 V at the diffusion controlled rate of 1.8 x 10\textsuperscript{10} M\textsuperscript{-1}s\textsuperscript{-1}. Given that the oxidation potentials of the 2-phenylethyl ether systems chosen were below the limit (2.01-2.29 V) and the electron transfer process was energetically favorable by –3 kcal/mol it follows that formation of the radical cation would occur. The third step accounts for the competing process of return electron transfer from the sensitizer to the substrate. Return electron transfer is an exothermic process that usually occurs on the microsecond timescale. It is most often observed when the tight ion pair that results from the electrostatic attraction of the radical anion for the radical cation is unable to separate. Arnold found that this process was slowed in cases were the free energy change for return electron transfer was very exergonic. This large energy gap slowed the process of back electron transfer so that the rate fell into the Marcus\textsuperscript{26} inverted region. Thus, the rate of return electron transfer became slower than the rate of solvent separation of the radical ion pairs.
Figure 1.8: Mechanism for mesolytic C-C bond cleavage

1. Sensitizer (A) $\xrightarrow{hv}$ A$^*$
2. Ph$_2$CH-R + A$^*$ $\rightarrow$ Ph$_2$CH-R$^+$ + A$^*$
3. Ph$_2$CH-R$^+$ $\rightarrow$ Ph$_2$CH-R + A
4. Ph$_2$CH-R$^+$ $\rightarrow$ Ph$_2$CH + R$^+$
5. R$^+$ + CH$_3$OH $\rightarrow$ R-CH$_2$O$^-$ + H$^+$
6. Ph$_2$CH$^+$ + A$^*$ $\rightarrow$ Ph$_2$CH + A
7. Ph$_2$CH$^+$ + CH$_3$OH $\rightarrow$ Ph$_2$CH$_2$ + CH$_3$O$^-$

The fourth step in the mechanism represents C-C bond cleavage of the radical cation. Through subsequent work on a variety of aromatic substrates it was found that C-C bond cleavage depends upon the bond dissociation energy (BDE) of the C-C bond in the radical cation (Figure 1.9). An activation barrier of 10-15 kcal/mol was estimated for the C-C bond cleavage of the radical cation.$^{25}$

Figure 1.9: PET reactions of 2-phenyl ether systems, Snes. = 1,4-dicyanobenzene
In order to decrease the BDE of the radical cation enough to force C-C bond cleavage to be the major reaction pathway, either the BDE of the C-C bond must be decreased, or the oxidation potential of the fragment that becomes the cation must be decreased through appropriate substitution. Gas phase BDEs are most often derived from experimental data by the use of thermodynamic cycles as shown in Equations 1-4.\(^{27}\)

\[
\text{BDE} = \Delta H_f^\circ (R^+) + \Delta H_f^\circ (R') - \Delta H_f^\circ (R-R^+) \quad (1)
\]

\[
\text{BDE} = (\Delta H_f^\circ (R') + IP(R')) - \Delta H_f^\circ (R') - (\Delta H_f^\circ (R-R) + IP(R-R)) \quad (2)
\]

\[
D^\circ = 2\Delta H_f^\circ (R') - \Delta H_f^\circ (R-R) \quad (3)
\]

\[
\text{BDE} = D^\circ + IP(R') - IP(R-R) \quad (4)
\]

Substituting oxidation potentials for ionization potentials allows for the determination of solution phase BDEs. Through modulated photolysis/phase sensitive voltametry\(^{14}\) the oxidation and reduction potentials of transient free radicals can be determined, and applied to Equation 5 to provide a more accurate description of the behavior of free radicals in solution and BDE’s of radical cations. In Equation 5, \(\text{BDE}_S\) represents the bond dissociation energy of the ground state molecule, \(\text{OP}_S\) represents the oxidation potential of the substrate, and \(\text{OP}_E\) represents the oxidation potential of the electrophilic fragment. Figure 1.10 uses a simple schematic, where a monoalkylarene serves as the substrate, to illustrate the BDE of the radical cation.

\[
\text{BDE}_{RC} = \text{BDE}_S - \text{OP}_S + \text{OP}_E \quad (5)
\]
Arnold found that a significant decrease in the BDE of the radical cation could be achieved by substitution of an \(\alpha\)-oxymethyl for one benzyl group. Upon bond dissociation of a homobenzylic ether, a \(\pi\)-stabilized radical and more stabilized \(\alpha\)-oxycarbocation was formed. Arnold postulated that the regioselectivity of the reaction was dependent upon the redox properties of the two radicals formed upon homolytic bond cleavage. Bond cleavage occurred in such a way as to give the carbocation of the radical fragment that had the lower oxidation potential. In cases involving radical cations of ethers, the fragment containing the \(\alpha\)-oxygen had a lower oxidation potential than the benzylic radical.\(^{19}\) Thus, the ether serves to stabilize the formed carbocation as well as weaken the benzylic C-C bond.

Arnold’s findings were supported by the work of Camaioni\(^{26}\) with \(\alpha\)-Me and -OH substituted bibenzylic systems. Camaioni was able to show through the use of semiempirical calculations of bond dissociation energies (BDE) of bibenzyl radical cations with Me or OH substituents on the ethylene bridge, that mesolytic C-C bond cleavage was the primary reaction pathway. The substantially reduced C-C BDE in the substrates tested was attributed to the ability of the electron donating groups to stabilize the cleavage products. Kinetic studies of side chain
fragmentation reactions of arylalkanol radical cations and the effects of α- and β-OR groups by Baciocchi\textsuperscript{28} further supported Arnold’s findings. Baciocchi showed that in homobenzylic ethers the dominant reactive pathway upon photoinitiated oxidation was mesolytic cleavage of the benzyl C-C bond, as shown in Figure 1.11.

**Figure 1.11:** Radical cation bond dissociations studied by Camaioni

\[
\begin{align*}
X-C & \rightarrow X-C + H^+ \\
X-C-OH & \rightarrow X-C + OH^- \\
X-C & \rightarrow X-C + H^+
\end{align*}
\]

A kinetic preference for cleavage of the C-C bond parallel to the π system of the arene, allowing for orbital overlap and stabilization, was also demonstrated.\textsuperscript{25} In order for the alkoxy group to provide maximum stabilization of the incipient carbocation, one of the lone pairs of electrons on the oxygen atom must overlap with the C-C anti-bonding (σ\textsuperscript{*}) orbital to stabilize the transition state for C-C bond cleavage, as shown in Figure 1.12.

**Figure 1.12:** Kinetically preferred conformation for C-C bond cleavage

Maximum stabilization, calculated using semiempirical methods, was found to occur when the dihedral angle between the non-bonding pair of electrons of the oxygen and the adjacent C-C anti-bonding (σ\textsuperscript{*}) orbital was 0°. When the dihedral angle was 90°, stabilization was found to be at a minimum. This leads to the hypothesis that if a preferred conformation of
the ether does not have the alkoxy group oriented in such a way that a lone pair of electrons on the oxygen can overlap with the adjacent C-C anti-bonding ($\sigma^*$) orbital, cleavage may be inhibited. Maximum overlap between the $\pi$ system and the C-C bond being broken is also required. This was confirmed through Arnold’s study of methyl 2-phenylcyclopentyl ether radical cations (Figure 1.13). PET of *trans*-methyl 2-phenylcyclopentyl ether led to mesolytic cleavage of the benzyl, whereas the *cis* compound underwent isomerization under identical conditions.

**Figure 1.13: Kinetic preference for C-C bond cleavage**

The fifth step in Arnold’s proposed mechanism for mesolytic C-C bond cleavage involves nucleophilic attack on the carbocation by methanol to form the methyl ether. An example of a stereospecific nucleophilic attack in a PET reaction comes from the work of Dinnocenzo. PET reactions of 1,1-diphenyl-2-methylcyclopropane and 1,1-diphenyl-2,2-dimethylcyclopropane were shown to undergo ring opening by a three-electron $S_{N}2$ substitution at C-2 (Figure 1.14). The inversion of configuration was rationalized to be the result of backside nucleophilic attack onto the ring-closed radical cation. The bimolecular rate constants were measured and found to be between $10^6$ and $10^8$ M$^{-1}$s$^{-1}$, which point to rather rapid, nucleophile induced C-C bond cleavage. These cyclizations are rare examples of highly selective tertiary and neopentyl nucleophilic substitutions that are controlled by electronic factors rather than steric factors.
Figure 1.14: Stereospecific nucleophilic attack onto a radical cation

\[
\text{Ph} \quad \text{R} \quad \text{CH}_3 \quad \text{Ph} \quad \text{H} \quad \text{Ph} \quad \text{R} \quad \text{CH}_3
\]

\[\text{1-CN, h} \quad \text{v} \quad \text{CH}_3\text{OH}\]

\[R = \text{CH}_3, \text{H}\]

V. Electron Transfer Initiated Cyclizations (ETIC)

The extensive studies of PET reactions of alkyl arenes, C-C bond cleavage and mechanistic studies of radical cations, and more specifically homobenzylic ethers, have prompted the development of a new electron transfer initiated cyclization method through carbon-carbon σ-bond activation of homobenzylic ethers (Figure 1.15).

Figure 1.15: Electron transfer initiated cyclization

\[
\text{Ph} \quad \text{OC}_8\text{H}_{17} \quad \text{OH} \quad -1 \text{ e}^- \quad \text{[Ph} \quad \text{OC}_8\text{H}_{17} \quad \text{OH}]^+ \quad \text{C}_8\text{H}_{17}\text{O}
\]

This new method utilizes attack of an appended nucleophile on a homobenzylic ether following single electron oxidation to generate cyclic acetals. As demonstrated by Arnold and Camaioni the benzylic bond of homobenzylic ethers is significantly weakened upon single electron oxidation and allows for nucleophilic displacement of a benzyl radical. This method of C-C σ-bond activation was chosen for five main reasons: (1) substrate synthesis is facilitated by the generally inert benzyl group, (2) the mild reaction conditions allow for the inclusion of acid and base sensitive functionality in the cyclization substrate, (3) the oxidation potential of the substrate, and chemoselectivity of the oxidation can be altered in a rational manner through the introduction of substituents on the arene, (4) the reactivity of the system can be tuned by the introduction of substituents at the benzylic position, and (5) the highly electrophilic nature of the radical cations should allow a wide variety of nucleophiles to be employed in the reaction.
Initial attempts at cyclization of a homobenzyl ether using a variation of Arnold’s conditions\textsuperscript{28} resulted in little or no product formation. The inefficiency of cyclization was postulated to result from rapid regeneration of starting materials through return electron transfer in the tight ion pair formed by the radical anion of dicyanobenzene and the radical cation of the homobenzyl ether.

A study of nucleophile-assisted cleavage of benzyltrialkylsilane cation radicals by Dinnocenzo\textsuperscript{31} showed that the rate of return electron transfer could be slowed through the use of a cationic sensitizer and a neutral cosensitizer. Employing \textit{N}-methylquinolinium hexafluorophosphate (NMQPF\textsubscript{6}) as the cationic sensitizer in a photoinitiated electron transfer cyclization, coupled with the use of the aromatic cosolvent \textit{tert}-butylbenzene, dramatically increases the efficiency of the electron transfer initiated cyclization reaction. In these cyclizations, the photoexcited sensitizer NMQPF\textsubscript{6} serves as a single electron oxidant that oxidizes the aromatic cosolvent \textit{tert}-butylbenzene to its radical cation. Facile electron transfer between the radical cation of \textit{tert}-butylbenzene and the homobenzylic ether ensues to form the radical cation of the homobenzylic ether. Upon radical cation formation of the homobenzylic ether, the benzylic bond is so significantly weakened that it allows for attack by the appended nucleophile and displacement of a benzyl radical to form the desired cyclic acetal (Figure 1.16).
Because electron transfer depends on the proximity of the molecules involved, the aromatic cosolvent tert-butylbenzene is employed to facilitate the diffusion controlled electron transfer process. Electron transfer between a homobenzylic ether and the radical cation of tert-butylbenzene (generated by electron transfer to the photoexcited cationic sensitizer NMQPF₆) is postulated to be an isoenergetic process, because electron transfer is occurring between two monoalkylarenes having essentially the same oxidation potential. Therefore, the effective concentration of radical cations in solution was effectively increased through the use of the aromatic cosolvent.

Under these new cation sensitized electron transfer conditions cyclic acetals ranging in ring size from 5 to 8 carbons could be generated efficiently and in high yield. The proposed mechanism inferred from the product distribution is shown in Figure 1.17. The two possible reactive pathways involve either an associative (S_N2) type pathway leading to stereochemical inversion at the electrophilic center yielding cyclic acetal 2, or through a dissociative, stereorandom S_N1-type pathway, yielding cyclic acetal 3. The majority of products isolated...
appear to have resulted from a dissociative pathway. However, partitioning between the two pathways could be controlled through substrate structure, thus leading to a unique strategy for controlling anomeric stereochemistry.\textsuperscript{29}

\textbf{VI. Project Goal}

The new ETIC method developed in this group allows for the efficient generation of a variety of cyclic acetals that can be further manipulated and serve as advanced synthetic intermediates. It is known that alkyl, aryl, hydroxyl, siloxy and alkoxy substituents\textsuperscript{20} serve as stabilizing groups and can facilitate C-C bond cleavage upon single electron oxidation of a monoalkylarene, but little is known about the incorporation of nitrogen as a stabilizing group in the homobenzylic position in reactions involving radical cations. The same highlighted reasons for the choice of homobenzylic ethers for cyclization substrates apply toward the use of homobenzylic amides and carbamates in ETIC reactions. Cyclizations involving these moieties could produce mixed acylaminals (Figure 1.18).
Figure 1.18: ETIC involving homobenzylic amides or carbamates

Developing a mild cyclization method is of interest because it would allow for the facile generation of iminosugars and glyconic-δ-lactams, both of which represent classes of compounds that have exhibited biological and enzyme inhibitory activity (Figure 1.19). The mild ETIC reaction conditions would allow for the incorporation of acid sensitive functional groups in the substrate that would not be tolerated under conventional cyclization conditions. Therefore, studies into the synthetic and stereochemical aspects of photoinitiated single electron transfer initiated cyclization reactions of homobenzylic amides and carbamates, as well as homobenzylic ethers containing nitrogen nucleophiles, have been undertaken and are detailed herein.

Figure 1.19: Synthetic targets

- Siastatin B
- 3-Episiastatin B
- Glucono-delta-lactam: $R_1=R_3=H$, $R_2=R_4=OH$
- Manno-delta-lactam: $R_1=R_4=H$, $R_2=R_3=OH$
- Galactono-delta-lactam: $R_1=R_3=OH$, $R_2=R_4=H$
1.2. Results

The pioneering work\textsuperscript{30} on homobenzylic ethers following single electron oxidation showed that ETIC reactions were a viable synthetic method for carbon-carbon bond activation. The goal of the present work was to extend this method and to test the applicability of nitrogen in ETIC substrates. Incorporation of nitrogen in an ETIC reaction requires that it be protected as an amide, carbamate, or sulfonamide, rather than a free amine, which could be easily oxidized under the reaction conditions. If incorporated into an ETIC substrate as an amide or carbamate, nitrogen could function as a stabilizing group in the homobenzylic position. Also, the role of nitrogen containing groups as nucleophiles could be examined. We therefore set out synthesize and test nitrogen containing substrates for ETIC reactions, while simultaneously optimizing cyclization conditions and examining the stereochemical aspects of the reaction.

The first two substrates synthesized and tested under ETIC conditions are shown in Scheme 1.1. Starting from epoxypropylbenzene (4), amide 5 was obtained in 5 steps. Opening of the epoxide with allylmagnesium bromide at 0 \degree C led to the corresponding alcohol in 95\% yield. The alcohol was converted to the mesylate and then displaced with sodium azide in DMF at room temperature using tetrabutylammonium iodide as a phase transfer agent. The azide was reduced to the amine via the Staudinger\textsuperscript{34} reaction. The amine was then acylated with hexanoyl chloride in the presence of triethylamine to give a 41\% yield of amide 5. Subsequent hydroboration of amide 5 with 9-BBN and quenching with basic hydrogen peroxide yielded the cyclization substrate, amide 6, in 44\% yield.

Amide 6 was subjected to ETIC cyclization conditions using a slight excess (1.2 equivalents) of the sensitizer NMQPF\textsubscript{6}, the aromatic cosolvent tert-butylbenzene, the insoluble
base NaOAc, dichloroethane as the solvent, and Pyrex-filtered irradiation from a medium pressure mercury lamp. The desired cyclic acylaminal (7) was obtained in 86% isolated yield after five hours of irradiation. This result indicated that amides, which could be easily synthesized from the corresponding alcohol, served as excellent stabilizing groups in the homobenzylic position.

Tertiary amide 8 was formed in 82% by reaction of amide 5 with methyl iodide and sodium hydride at 0 °C in DMF. Hydroboration with 9-BBN followed by quenching with basic hydrogen peroxide provided the desired cyclization substrate, tertiary amide 9, in 92% yield. Amide 9 was subjected to the standard ETIC reaction conditions, 1.2 equivalents of NMQPF₆, tert-butylbenzene, NaOAc, and dichloroethane and the desired cyclic acylaminal 10 was obtained in an isolated yield of 56%.

Reaction times of four and six hours were required for ETIC reactions of both amide 6 and amide 9. Purification of cyclic acylaminals 7 and 10 was difficult and required flash chromatography on SiO₂ followed by preparatory thin layer chromatography. A change in color of the reaction mixture from colorless to dark red was observed for both cyclization reactions. Nonetheless, the cyclized products of both the secondary and tertiary amide were obtained and provided evidence that ETIC reactions involving homobenzylic amides are indeed a synthetically viable method for the generation of cyclic acyl aminals through nucleophilic attack on acyl imminium ions generated under mild reaction conditions.
Scheme 1.1: Synthesis of initial cyclization substrates

With two examples of successful ETIC reactions, the next step was to use stereochemistry as a mechanistic probe. This was done through the incorporation of a methyl group in the bishomobenzylic position as shown in Scheme 1.2. The hydroxyl group of 4-pentyln-1-ol was protected with tert-butyldimethylsilyl chloride and imidazole in DMF to provide 11 as the starting material for the synthesis of cyclization substrates 14 and 17. Olefin 12 was formed by carboalumination with trimethylaluminum and Cp₂ZrCl₂ followed by palladium catalyzed coupling with benzyl chloride. This reaction proved problematic in that initial attempts were low yielding and long reaction times were required. As much as a four-fold excess of trimethylaluminum was required, and made purification laborious. The moderate 76% yield was partially attributed to the inability to separate the desired olefin from the aluminum salts generated upon quenching. Performing the carboalumination reaction at -23 °C with one equivalent of water and one equivalent of trimethyl aluminum, based on Wipf’s procedure, successfully decreased reaction time from two days to two hours, and facilitated product purification.

Olefin 12 was hydroborated with BH₃·THF and quenched with basic hydrogen peroxide to provide an 81% yield of alcohol 13. The alcohol was converted to the mesylate with mesyl chloride and triethylamine in CH₂Cl₂, and then displaced with sodium azide at 55 °C in DMF.
The azide was reduced to the amine via the Staudinger\textsuperscript{34} reaction and then acylated with hexanoyl chloride in the presence of triethylamine to give the desired amide in 61% yield. The TBS ether was deprotected with TBAF to provide amide \textbf{14} in 96% yield. Amide \textbf{14} was subjected to standard ETIC reaction conditions to form a 2.4:1 mixture of diastereomers of cyclic acylaminal \textbf{15} in 76% yield. The mixture of diastereomers was purified by flash chromatography and the diastereomers were ultimately separated by preparative thin layer chromatography.

\textbf{Scheme 1.2:} Stereoselective synthesis of cyclization substrates

\begin{align*}
\textbf{11} & \xrightarrow{\text{a}} \textbf{12} & \xrightarrow{\text{b}} \textbf{13} & \xrightarrow{\text{c-g}} \textbf{14} \\
\textbf{16} & \xrightarrow{\text{h}} \textbf{15} & \textbf{18} & \xrightarrow{\text{h or j}} \textbf{17}
\end{align*}

\textbf{Reagents:} a) (1) 2.0 M Me$_3$Al-hexanes, Cp$_2$ZrCl$_2$, H$_2$O, CH$_2$Cl$_2$, (2) Pd(PPh$_3$)$_4$, BnCl, THF, 76% b) 1.0 M BH$_3$-THF, NaOH, H$_2$O$_2$, 81% c) Ms-Cl, Et$_3$N, CH$_2$Cl$_2$, d) Na$_2$SO$_3$, DMF, e) (Ph)$_3$P, H$_2$O, THF, f) C$_5$H$_{11}$COCl, Et$_3$N, THF, 61% g) TBAF, THF, 96% h) hv, NMQ, iBB, NaOAC, DCE, i) MeI, NaH, DMF, 36% j) hv, NMQ, NaHCO$_3$, CH$_3$CN, \textbf{18}: h: 43%, j: 67%

The stereochemical relationships between the amide and methyl ring substituent for acylaminal \textbf{15} were determined by comparison of coupling constants of the anomeric hydrogens (Figure 1.20). With a \textit{syn} relationship between the amide and methyl substituent, the anomeric hydrogen appeared in the $^1$H NMR spectrum as a doublets of doublets, showing a small coupling to the methyne hydrogen (3.1 Hz) and a large coupling to the amide hydrogen ($J = 6.0$ Hz). Upon addition of D$_2$O to the $^1$H NMR sample and exchange of the amide proton for a deuterium the signal corresponding to the anomeric hydrogen changed to a doublet with a small coupling to the
methine hydrogen \((J = 2.4 \text{ Hz})\) and the signal corresponding to the amide hydrogen was no longer apparent. In 15b the \textit{anti} relationship between the amide and methyl substituent resulted in the appearance of the anomeric hydrogen as a doublet of doublets, showing a large coupling to both the methine hydrogen and the amide hydrogen \((J = 9.5 \text{ Hz})\). Upon deuterium exchange the signal corresponding to the anomeric hydrogen changed to a doublet with a large coupling to the methine hydrogen (9.3 Hz) and the signal corresponding to the amide hydrogen was no longer apparent.

**Figure 1.20:** Relative stereochemical relationship of amide 15

![Diagram](image)

Amide 17 was synthesized to test the ability of tertiary amides to control the diastereoselectivity of ETIC reactions. Amide 16 was obtained in 36% yield by reaction of the TBS protected form of amide 14 with sodium hydride and methyl iodide in DMF as shown in Scheme 2. Deprotection of the TBS ether with TBAF provided amide 17 in 78% yield. When tertiary amide 17 was subjected to standard ETIC reaction conditions a single diastereomer of cyclic acylaminal 18 was isolated in 43% yield. A 67% yield was obtained when the cyclization was performed using the more polar solvent, acetonitrile, and NaHCO₃ as the base.

\(^1\text{H NMR} \) analysis of acylaminal 18 showed two doublets at 5.36 ppm \((J = 9.8 \text{ Hz})\) and 4.45 ppm \((J = 9.4 \text{ Hz})\), each corresponding to the anomeric hydrogen. The anomeric hydrogen exhibited a large coupling to the methyne hydrogen, indicating that the relative stereochemistry
was that of an \textit{anti} relationship between the amide and methyl substituent of the ring. The existence of two separate signals corresponding to the same anomeric hydrogen was caused by restricted rotation around the amide bond. A variable temperature $^1$H NMR study done in DMSO at 10 degree intervals from 298K to 378K showed the collapse of these two signals into a single signal above 358K.

Several attempts to synthesize the \textit{anti} diastereomer of amide 17 to test the stereoselectivity of the cyclization reaction were unsuccessful. Mitsonobu reactions on alcohol 13 led only to elimination back to an inseparable mixture of alkene 12 and the conjugated styrene adduct. Attempted hydroboration-amination$^{37}$ of alkene 12 was also unsuccessful. Because of the hindered nature of the tri-substituted olefin, only the alkyl borane was isolated out of the reaction mixture.

The mixture of diastereomers of amide 17a, shown also in Table 3, was synthesized in six steps starting from alcohol 13 (Scheme 1.3). Alcohol 13 was oxidized to ketone 19 in 74\% yield via the Swern$^{38}$ oxidation. Reaction of the ketone with hydroxylamine hydrochloride in ethanol buffered with NaOAc provided oxime 20 in 88\% yield. The oxime was reduced to the amine in the presence of nickel chloride and lithium aluminum hydride$^{39}$ at room temperature in ether. The resulting amine was acylated with hexanoyl chloride in the presence of triethylamine to yield 63\% of the corresponding amide. The amide was alkylated with methyl iodide and sodium hydride in DMF. The TBS protecting group was removed with TBAF to give amide 17a in 91\% yield. Subjecting amide 17a to catalytic aerobic ETIC reaction conditions provided the desired product in 56\% yield, having an \textit{anti} relationship between the amide and the methyl group. Catalytic aerobic ETIC reaction conditions will be discussed in detail later in the manuscript (Figure 1.24).
Scheme 1.3: Synthesis of a diastereomeric mixture of amides

Having gleaned the desired stereochemical information from the cyclization reactions of 14 and 17 and 17a, the next logical step was to increase the level of complexity of the functional groups on the tether of the substrate. The lack of information pertaining to the effects of placing electron withdrawing groups adjacent to the reactive center, coupled with the end goals in the development of this cyclization method for application in the total synthesis of glycosidase inhibitors and aminosugars, which are poly-oxygenated species, led to the synthesis of substrates with an oxygen containing functional group adjacent to the reactive center. Having a methoxy group in the bishomobenzylic position provides a handle for the examination of the stereochemical outcome of cyclization as well the desired increased functionality in the form of an easily synthetically installed, relatively non-reactive functional group (Scheme 1.4).

Scheme 1.4: Stereoselective synthesis of methyl ether substrates

Amide 24 was obtained in eight steps starting from L-phenylalanine. The 3:1 mixture of the diastereomeric β-amino alcohols 22a and 22b was prepared according to the Reetz procedure. This involved benzylaion of phenylalanine by refluxing with benzyl bromide,
potassium carbonate and sodium hydroxide. The benzyl ester was reduced to the alcohol with lithium aluminum hydride. Swern oxidation led to the aldehyde, and addition to the carbonyl with allyl magnesium bromide provided 22a and 22b. The alcohols were separated by flash chromatography, but could never be completely purified. Overall yield for the four steps was 56%.

Each of the diastereomers was carried separately through the synthetic sequence shown in Scheme 4. Formation of the methyl ether with sodium hydride and methyl iodide in DMF followed by hydroboration with BH$_3$·THF and quenching with basic hydrogen peroxide afforded a 73% yield of alcohol 23. Debenzylation proved to be the most problematic step in the sequence, never yielding more than 50%. Initial attempts using ammonium formate and Pd/C in refluxing methanol followed by acylation with hexanoyl chloride were very low yielding and resulted in a mixture of products including the monobenzylamine, the formamide, and the O-acylated amide. Debenzylation using 1,4-cyclohexadiene and Pd/C was also low yielding and required lengthy reaction times. Protection of the alcohol with pivaloyl chloride prior to debenzylation with ammonium formate and Pd/C in refluxing methanol proved to be the optimum conditions for debenzylation. The pivalate was easily removed with sodium methoxide in methanol to yield the desired cyclization substrate 24 in 49% yield.

**Figure 1.21:** ETIC reaction of amide 24

Amide 24 was subjected to a variety of ETIC reaction conditions as shown in Table 1.1. Solvent and base were varied, while the use of *tert*-butylbenzene as the aromatic cosolvent and an excess of the sensitizer NMQPF$_6$ remained constant. The mixture of cyclic acylaminals 25a
and 25b, shown in Figure 1.21, was purified by flash chromatography and then the diastereomers were separated by thin layer preparative chromatography. Using insoluble bases such as NaOAc and NaHCO₃ in the reaction mixture resulted in a lower than expected yield and isolation of a mixture of diastereomers 25a and 25b. Switching to the soluble base 2,6-dichloropyridine in DCE resulted in a four-fold increase in yield, and the isolation of a single diastereomer. Purification of both the starting material and the cyclization product were difficult, as was visualization of the reaction by TLC. Therefore, the discrepancy in diastereomeric ratios isolated from the reactions could again be attributed to these difficulties rather than any stereoelectronic factors.

**Table 1.1**: Variations of ETIC reaction conditions

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Base</th>
<th>Percent Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₂H₄Cl₂</td>
<td>NaOAc</td>
<td>6</td>
</tr>
<tr>
<td>C₂H₄Cl₂</td>
<td>2,6-dichloropyridine</td>
<td>21</td>
</tr>
<tr>
<td>CH₃CN</td>
<td>2,6-dichloropyridine</td>
<td>38</td>
</tr>
<tr>
<td>CH₃CN</td>
<td>NaHCO₃</td>
<td>5</td>
</tr>
</tbody>
</table>

As was seen with the ETIC reactions of amide 17, alkylation to form the tertiary amide results in isolation of a single diastereomer. Tertiary amide 26 was synthesized to demonstrate both stereoselectivity and tolerance of increased functionality in ETIC reactions. Methylating the amide of the pivalate ester with sodium hydride and methyl iodide prior to pivalate deprotection with sodium in methanol gave the desired starting material for cyclization, amide 26, in 96% yield. Subjecting amide 26 to the conditions shown to give the highest cyclization yields for amide 24 (excess NMQPF₆, 2,6-dichloropyridine and acetonitrile) failed to yield the desired cyclized product (Figure 1.22). Rather, amide 27 proved to be the only isolable product in 10% yield, resulting from nucleophilic attack of water on the acylimminium ion.
Because the reaction substrates were difficult to purify and visualize, having the alcohol protected during the debenzylation process facilitated substrate synthesis, and early work done in the Floreancig group with homobenzylic ethers showed that THP ethers could serve as nucleophiles in ETIC reactions, amide 28 (Figure 1.23) was synthesized and subjected to ETIC reaction conditions. The synthesis entailed protection of the diastereomer of alcohol 18 as the THP ether rather than the pivalate prior to debenzylation. This facilitated not only substrate purification, but also allowed for cleaner ETIC reactions and ease of reaction monitoring by TLC. An 18% isolated yield, as a 1:1 mixture of diastereomers was obtained when the reaction was only taken to 70% conversion.

From the results of the ETIC reactions with α-amido ethers 24, 26, and 28, the need for a change in the form of the homobenzylic nitrogen stabilizing group was apparent. One slight modification to the system that also alleviated the problematic debenzylation step in the synthesis of the substrates, was switching from the homobenzylic amide to the t-butyl carbamate.
Starting from L-phenylalanine, a 6:1 diastereomeric mixture of alcohols \(30a\) and \(30b\) was prepared in 54% yield by reduction with lithium aluminum hydride, protection with “Boc” anhydride, Swern oxidation and addition of allyl magnesium bromide into the aldehyde (Scheme 1.5). Diastereomers \(30a\) and \(30b\) could be separated by flash chromatography, and \(30a\) was carried through the synthesis. The hydroxyl of \(30a\) was protected as the methyl ether with sodium hydride and methyl iodide in DMF. Subsequent hydroboration with BH\(_3\)-THF and quenching with basic hydrogen peroxide provided the desired alcohol in 65% yield. The alcohol was protected as THP ether with dihydropyran and \(p\)-toluenesulfonic acid to give carbamate \(31\) in 91% yield. Under ETIC reaction conditions (1.2 equivalents of NMQPF\(_6\), NaOAc, toluene, and dichloethane) a 2:1 ratio of the desired cyclized products \(32a\) and \(32b\) was obtained in 35% isolated yield (53% at 70% conversion). The aromatic cosolvent toluene was conveniently substituted for tert-butylbenzene due to similar oxidation potential, increased volatility and increased cost effectiveness. This reaction was a vast improvement from the ETIC reaction with the homobenzylic amides in terms of increased yields, and facile visualization and purification of products.

An admirable improvement in yield was also observed upon switching from an amide to a carbamate stabilizing group in the homobenzylic position. However, the reaction still could not be performed at the desired efficiency. Difficult purification, due to the number of the aromatic side products formed from the excess NMQPF\(_6\), which co-eluted with the desired products, and
long reaction times played a significant role in decreasing both reaction efficiency and yield. Throughout the course of the reactions a color change from colorless to deep, dark red was observed, presumably resulting from the oxidative decomposition of quinoline derived products. Reactions often did not proceed to complete conversion due to the formation of covalent adducts between the N-methylquinolyl radical (NMQ*) produced from the initial electron transfer and the benzyl radical produced in the displacement reaction. Once formed, these adducts can be oxidized in preference to the cyclization substrate, feed into the electron transfer cascade and produce a variety of aromatic waste products while consuming the photosensitizer. Deposition of the solid base onto the walls of the reaction flask was also observed, requiring the flask to be rotated periodically throughout the course of the reaction so as not to allow the deposition to impede the amount of light entering into the reaction. Nevertheless, the majority of problems with the reaction associated with the use of excess amounts of NMQPF₆ and the production of large quantities of aromatic waste products could presumably be eliminated through the use of a catalytic amount NMQPF₆.

Dinnocenzo³¹ reported that in transient absorption spectroscopic studies of NMQ-sensitized arene oxidations reactions the reduced form of NMQ reacts with dissolved oxygen at or close to the diffusion-controlled limit, whereas radical cations did not. Thus, NMQ⁻ could be oxidized to NMQ⁺ through a single electron transfer reaction involving O₂ as the terminal oxidant, regenerating the photosensitizer without affecting the electron transfer cascade or impeding the desired cyclization reaction. This information was used to develop a catalytic photosensitized electron transfer cyclization reaction under aerobic conditions (Figure 1.24).
Figure 1.24: A catalytic aerobic ETIC reaction

This new strategy was tested by subjecting amide \textit{28a} to the ETIC reaction conditions while simultaneously bubbling air through the reaction mixture and using only 0.5 equivalents of NMQPF$_6$ (Figure 1.25).

Figure 1.25: ETIC reaction under new aerobic conditions

The first aerobic cyclization was done using benzene as the aromatic cosolvent (Table 1.2). The additional products isolated from the reaction mixture resulted from decomposition of the starting material. Changing the aromatic cosolvent to toluene, as well as switching to the soluble base 2,6-dichloropyridine, failed to increase reaction yield.

Table 1.2: Altering aromatic cosolvents

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Base</th>
<th>Cosensitizer</th>
<th>Percent Yield (Stoichiometric NMQ)</th>
<th>Percent Yield (Catalytic NMQ)</th>
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<tr>
<td>C$_2$H$_4$Cl$_2$</td>
<td>NaOAc</td>
<td>Benzene</td>
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<tr>
<td>C$_2$H$_4$Cl$_2$</td>
<td>2,6-Dichloropyridine</td>
<td>Toluene</td>
<td>33</td>
<td>33</td>
</tr>
</tbody>
</table>

Even though the yield of the reaction was not dramatically increased, the catalytic aerobic conditions alleviated the majority of the difficulties previously associated with the cyclization reaction. Reaction times were decreased from 5 hours to 2 hours, and purification was facilitated due to the lack of aromatic side products. Deposition on the walls of the reaction flask and the
characteristic deep red color were no longer observed. More importantly, decomposition products 33 and 34 could be isolated, providing an explanation for the low yields and lack of mass balance observed in previous cyclization attempts.

Under the aerobic cyclization reaction conditions undesired reactive oxygen species are generated from molecular oxygen and benzyl peroxy radical. These unwanted reactive oxygen species decrease reaction yields, despite complete consumption of starting materials, especially on large scale. This was observed in reactions of homobenzylic ethers, where oxidative decomposition reactions resulting from the accumulation of reactive oxygen species was believed to be the cause of the drastic reduction in yield from 86% to 15%, when reactions were performed on a larger than a 1.0 g scale. One way of suppressing unwanted oxidative decomposition reactions associated with the accumulation of superoxide and benzyl peroxy radicals without inhibiting the cyclization was through the use of the mild reducing agent Na$_2$S$_2$O$_3$. Soluble reducing agents such as DMSO were found to completely inhibit the cyclization reaction, whereas solid Na$_2$S$_2$O$_3$ did not impede the electron transfer process, but rather reduced the superoxide and any unwanted reactive oxygen species. Having a reducing agent with low solubility in organic solvents was advantageous, in that electron transfer was not quenched, but rather the limited solubility allowed for enhanced reaction efficiency through the reduction of the unwanted reactive oxygen species. As shown in Figure 1.26, the products of the peroxide and superoxide reductions by Na$_2$S$_2$O$_3$ are water and benzaldehyde, neither of which was found to impede the cyclization reaction.
Figure 1.26: Catalytic aerobic ETIC reaction with Na$_2$S$_2$O$_3$

Under catalytic aerobic cyclization conditions (0.025 equivalents of NMQPF$_6$, toluene, NaOAc, dichloroethane and the gentle bubbling of air through the reaction mixture) both the reaction efficiency and ease of product isolation of amide 28a increased. Therefore, it was desirable to test the scope and generality of these conditions. The substrates tested under these new conditions are shown in Tables 1.3 and 1.4. All of the substrates previously cyclized under standard stoichiometric ETIC reaction conditions were subjected to the new catalytic conditions.
Table 1.3: Substrates tested under catalytic aerobic ETIC conditions

<table>
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<tr>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
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</tbody>
</table>

For amides 7, 14 and 17, the yield under catalytic conditions was within the same range as those observed under stoichiometric conditions. The difference, though, was in the ease of purification of the catalytic cyclization, and the 50 percent decrease in reaction time under catalytic conditions. Switching from the hydroxyl to the THP ether in 14a facilitated purification of the starting material, but resulted in a slight decrease in yield of the cyclized product. Cyclization with the THP ether of a tertiary amide, 17b, was unsuccessful. This was attributed to the combination of the decrease in nucleophilicity of the THP ether relative to the hydroxyl, and the decreased oxidation potential of the tertiary amide. Subjecting carbamate 31 to the catalytic
cyclization conditions resulted in a 10% increase in yield and decreased the reaction time from 4 to 2 hours. Cyclization with the tertiary carbamate, 35, resulted in complete decomposition.

A variety of substrates were synthesized to test what other nitrogen containing functional groups could be used as stabilizing groups in the homobenzylic position. The use of trifluoracetamides and oxazolidinones was thought to be a way of increasing the oxidation potential at the homobenzylic position without drastically altering the cyclization substrates.

Trifluoroacetamide 37 was synthesized as shown in Scheme 1.6. The Boc group of carbamate 30b was removed in trifluoroacetic acid. The free amine was protected as the trifluoroacetamide by reaction with trifluoroacetic anhydride in the presence of pyridine to give 36 in 45% yield. Subsequent hydroboration with BH₃·THF and quenching with basic hydrogen peroxide provided trifluoroacetamide 37 in 65% yield. No desired cyclized product was obtained when trifluoroacetamide 37 was subjected to catalytic aerobic ETIC reaction conditions for 3.5 h, and 80% of the starting material was recovered.

**Scheme 1.6: Synthesis of trifluoroacetamide 37**

![Scheme 1.6: Synthesis of trifluoroacetamide 37](image)

**Reagents:** a) TFA, b) (CF₃CO)₂O, pyr., CH₂Cl₂, 45%c) 1.0M BH₃-THF, NaOH, H₂O₂, THF, 65%

Oxazolidinone 39 was synthesized in four steps from carbamate 30b, as shown in Scheme 1.7. The Boc group of carbamate 30b was removed with trifluoroacetic acid, and oxazolidinone 38 was formed by reaction of the free amine with carbonyl diimidazole. The alkene was then hydroborated with BH₃·THF and quenched with basic hydrogen peroxide to provide the corresponding alcohol. The alcohol was protected as the THP ether with dihydropyran and p-toluenesulfonic acid to provide oxazolidinone 39 in 25% yield.
Oxazolidinone 39 was subjected to the catalytic aerobic cyclization conditions. However, after 12 hours no product formation was observed and 33% of the starting material was recovered.

**Scheme 1.7: Oxazolidinone synthesis**

Reagents: a) TFA, b) CDI, DMAP, THF, c) 1.0M BH₃·THF, NaOH, H₂O₂, THF, d) DHP, pTSOH, CH₂Cl₂, 25%

Because excellent stereocontrol had been exhibited in the reactions of tertiary amides 17 and 17a cyclization reactions involving an oxazoline were attempted. The synthesis of oxazoline 41 is shown in Scheme 1.8.

**Scheme 1.8: Oxazoline synthesis**

Reagents: a) 2,2-dimethoxypropane, PPTS, Tol., 32% b) 1.0M BH₃·THF, NaOH, H₂O₂, 71% c) DHP, PPTS, CH₂Cl₂, 90%

Carbamate 30b was reacted with 2,2-dimethoxypropane in refluxing toluene to give oxazoline 40 in 32% yield. Subsequent hydroboration with BH₃·THF and quenching with basic hydrogen peroxide provided the corresponding alcohol in 71% yield. The alcohol was protected as the THP ether with dihydropyran and p-toluenesulfonic acid to provide oxazoline 41 in 90% yield. Cyclization of oxazoline 41 under catalytic conditions resulted in the isolation of a single diastereomer, the cis-6,5-ring fusion with retention of configuration at the nitrogen center, in 85% isolated yield.

The cyclization was then repeated with a mixture of diastereomers, 41a, to test the stereoselectivity and proposed dissociative mechanism. The diastereomeric mixture was prepared
in the same manner as shown in Scheme 8, with the exception that a mixture of 30a and 30b was employed as the starting material. The cyclization provided a single diastereomer in 88% isolated yield.

Table 1.4 provides a summary of the cyclization substrates tested under catalytic aerobic ETIC reaction conditions to examine the scope and generality of nitrogen containing stabilizing groups that could be used in the homobenzylic position.

**Table 1.4: Additional homobenzylic stabilizing groups**

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
<th>D.R</th>
</tr>
</thead>
<tbody>
<tr>
<td>37</td>
<td>OMe</td>
<td>82</td>
<td>99:1</td>
</tr>
<tr>
<td>41</td>
<td>OTHP</td>
<td>82</td>
<td>99:1</td>
</tr>
<tr>
<td>41a</td>
<td>OTHP</td>
<td>88</td>
<td>99:1</td>
</tr>
<tr>
<td>39</td>
<td>OTHP</td>
<td>No Reaction</td>
<td></td>
</tr>
</tbody>
</table>

After successfully demonstrating the utility of several amides and t-butylcarbamates as stabilizing groups in the homobenzylic position we wanted to explore the range of nitrogen nucleophiles that could be employed in ETIC reactions. In order to do this, a reversion back to the use of homobenzylic ethers as the cyclization substrate was the initial step. A wide variety of successful ETIC reactions of homobenzylic ethers using appended oxygen nucleophiles had been demonstrated, and preliminary results of ETIC reactions of homobenzylic ethers with an appended acetamide were promising. Therefore, it was of interest to expand upon these results.
Alcohol 43 served as the starting material for the synthesis of all of the substrates shown in Scheme 1.9. The alcohol was converted to the mesylate with mesyl chloride and triethylamine. The mesylate was then displaced with sodium azide in DMF to provide azide 44 in 87% yield. Azide 44 was the first substrate containing a potential nitrogen nucleophile subjected to catalytic aerobic ETIC reaction conditions. No reaction was observed after three hours, and the starting material was re-isolated.

Scheme 1.9: Substrates containing appended nitrogen nucleophiles

Ethyl carbamate 46 and tert-butyl carbamate 47, were both formed from amine 45, which was obtained by reduction of azide 44 via the Staudinger reaction. Ethyl carbamate 46 was formed in 56% yield by reaction of amine 45 with potassium carbonate and ethyl chloroformate. Carbamate 47 was formed in 81% yield by reaction of amine 45 with Boc anhydride and triethylamine in a 1:1 mixture of dioxane and water. Neither carbamate 46 nor carbamate 47 provided the desired cyclization products when subjected to catalytic aerobic ETIC reaction conditions. In both cases, one major product was isolated from the reaction mixture, but the identities of those products have yet to be determined. For both carbamates it was believed that
oxidation of the carbamate followed by fragmentation was the operative reaction pathway. Subjecting the tert-butyl carbamate to the catalytic ETIC conditions with one equivalent of methanol tested this hypothesis (Figure 1.27). If preferential oxidation of the carbamate were occurring, the hemiaminal resulting from nucleophilic attack of the methanol would have been isolated. This however, did not occur and hemiacetal 50 was isolated from the reaction mixture.

Figure 1.27: Attempted trapping of carbamate radical cation

Acetamide 48 was prepared in 69% yield by acylation of amine 45 with acetic anhydride in the presence of a catalytic amount of DMAP. No desired cyclization products were observed when this substrate was subjected to catalytic aerobic ETIC conditions, only 20% of the starting material was recovered, and no identifiable decomposition products were isolated.

Sulfonamide 49 was formed in 34% yield by reaction of amine 45 with 4-nitrobenzylsulfonyl chloride and triethylamine. Sulfonamide 49 proved to be an excellent substrate for cyclization. No decomposition of the starting material was observed, and the cyclized product was obtained in 68% yield. Use of the nitrophenyl sulfonamide as a nucleophile proved advantageous because of the ease of removal following cyclization to allow for further synthetic manipulation.41

Sulfonamide 50 was prepared as shown in Scheme 1.10. The alcohol of amide 6 was converted to the mesylate with mesyl chloride and triethylamine. The mesylate was displaced with sodium azide in DMF at 55 °C. The azide was reduced to the corresponding amine via the Staudinger reaction, and the amine was sulfonylated with 4-nitrobenzenesulfonyl chloride and triethylamine in CH₂Cl₂ to afford sulfonamide 50 in 34% yield over four steps. Catalytic aerobic ETIC reaction of sulfonamide 50 afforded (N, N) acyl aminal 51 was in 64% yield.
Scheme 1.10: Sulfonamide synthesis

![Scheme 1.10: Sulfonamide synthesis](image)

Reagents: a) MsCl, Et₃N, CH₂Cl₂, b) NaN₃, DMF, 55 C, c) Ph₃P, THF, H₂O, d) p-NO₂C₆H₄SO₂Cl, Et₃N, CH₂Cl₂ (four steps) 34%

Table 1.5 summarizes the variety of homobenzyllic ethers with appended nitrogen nucleophiles tested under catalytic aerobic ETIC conditions.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>44</td>
<td>No Reaction</td>
<td></td>
</tr>
<tr>
<td>46</td>
<td>Decomposition</td>
<td></td>
</tr>
<tr>
<td>47</td>
<td>Decomposition</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>Decomposition</td>
<td>20% Recvd. SM</td>
</tr>
<tr>
<td>49</td>
<td>Decomposition</td>
<td>68</td>
</tr>
<tr>
<td>50</td>
<td>Decomposition</td>
<td>64</td>
</tr>
</tbody>
</table>

In addition to probing the mechanism of the ETIC reaction, the chemoselectivity of the single electron oxidation was examined through the incorporation of a trifluoromethyl group on
the arene. Incorporation of this group was predicted to increase the oxidation potential of the arene by 0.3V,\textsuperscript{42} effectively prohibiting its oxidation under the reaction conditions.

3-(Trifluoromethyl)phenylalanine (55)\textsuperscript{43} served as the starting material for the synthesis of both trifluoromethyl-substituted arenes, 57 and 58, as shown in Scheme 1.11. Ketimine 52\textsuperscript{44} was easily obtained by condensation of benzophenone imine and glycine methyl ester hydrochloride in CH\textsubscript{2}Cl\textsubscript{2}. Alkylation of ketimine 52 with the commercially available 3-(trifluoromethyl)benzyl chloride (53) in the presence of sodium hydride in DMF provided ketimine 54 in excellent yield. Hydrolysis of 54 with 6N HCl, followed by saponification of the hydrochloride salt with 15% NaOH in MeOH provided the desired starting material 55 in 92% yield.

**Scheme 1.11: Synthesis of 3-(trifluoromethyl)phenylalanine**

\[ \text{Ph} - \text{N} - \text{O} - \text{Me} \text{ Ph} \xrightarrow{a} F_3\text{C} - \text{Cl} \xrightarrow{b} F_3\text{C} - \text{N} - \text{Ph} \xrightarrow{OH} F_3\text{C} - \text{NH} - \text{OH} \]

*Reagents:* a) NaH, DMF, 95% b) 1. 6N HCl, 15% NaOH, MeOH, 92%

3-(Trifluoromethyl)phenylalanine (55) was reduced to the amino alcohol with LAH in THF, then reacted with di-\textit{tert}-butyldicarbonate in one pot to provide the Boc-protected amino alcohol (Scheme 1.12). The alcohol was oxidized to the aldehyde with Dess-Martin periodinane, which was subsequently reacted with allylmagnesium bromide to provide alcohol 56. The trifluoromethyl arene 57 was obtained in a 2% overall yield from alcohol 56 through methyl ether formation with methyl iodide and sodium hydride in DMF followed by hydroboration with BH\textsubscript{3}•THF. Trifluoromethyl-substituted arene 58 was obtained in a 6% yield from alcohol 56 by oxazoline formation with dimethoxypropane and PPTS in refluxing toluene followed by hydroboration with BH\textsubscript{3}•THF.
Both trifluoromethyl-susbsituted arenes 57 and 58 were subjected to catalytic aerobic ETIC reaction conditions. As shown in Figure 1.28, ETIC reaction of 57 lead only to decomposition of the starting material, while ETIC reaction of 58 provided the desired cis-6,5-ring fused product 42 as a single diastereomer in 74% yield.
1.3. Discussion of electron transfer initiated cyclization reactions

I. Reaction Stereochemistry

The incorporation of a methyl group, or methoxy group adjacent to the reactive center provided a means of exploring the stereochemical outcome of ETIC reactions of homobenzylic amides and carbamates through the analysis of coupling constants. Subjecting secondary amides to ETIC reaction conditions resulted in the isolation of a mixture of diastereomers. However, ETIC reactions of tertiary amides and tertiary carbamates were stereoselective processes.

When tertiary amide 17 was subjected to standard ETIC conditions the single diastereomer 18 was isolated. The relative stereochemistry of cyclic acylaminal 18 can be explained by examination of the transition state. If the transformation proceeds through an early transition state, allylic strain would be the dominant controlling factor, and the anti relationship between the methyl and amide would result from a desire to minimize steric interactions. Figure 1.29 illustrates the four possible chair-like early transition states that can be assumed: (A) illustrates the 1,3 allylic strain between the amide methyl and the backbone methyl, (B) depicts the preferred transition state and (C) and (D) show steric clashes between the carbonyl and methylene of the ring and the methyl of the iminium ion and methylene group, respectively. If a late transition state (E) is the operative mode, developing unfavorable diaxal interactions of the amide methyl with the hydrogens of the ring force the equatorial preference.
Figure 1.29: Stereocontrol in tertiary amide cyclizations

Subjecting the mixture of diastereomers, amide 17 to standard ETIC reaction conditions also resulted in the isolation of cyclic acylaminal 18. This result provided additional evidence for a dissociative mechanism, which will be discussed in a later portion of the document.

II. Optimization

Initial ETIC reactions of homobenzylic amides and carbamates were successful and the desired cyclic acylaminals were obtained in high yields. However, these yields varied due to difficulty in purifying the desired product. Earlier work done with the cyclization reactions of homobenzylic ethers\textsuperscript{31} demonstrated that using less than a stoichiometric amount of sensitizer resulted in recovery of starting materials, and excess was required for complete conversion. The use of 1.2 equivalents of NMQPF\textsubscript{6} created aromatic by-products from radical-radical coupling reactions. Mesolytic cleavage of the benzylic bond of the radical cation generates a benzyl radical as a reactive intermediate, which can participate in unwanted side reactions. Purification by flash chromatography followed by preparatory thin layer chromatography was necessary. In
addition to the purification difficulties, long reaction times, on the order of 4 to 6 hours, were required. During the course of the reaction, deposition of the solid NaOAc on the walls of the reaction flask, as well as a color change from colorless to a deep, dark red were observed. Both the color change and the deposition were thought to impede the course of the reaction.

In an attempt to optimize the reaction conditions, a catalytic photosensitized electron transfer cyclization reaction under aerobic conditions was developed. The gentle bubbling of air through the reaction mixture during irradiation regenerated the photosensitizer NMQPF₆. This allowed for the use of 0.25 mole percent of NMQPF₆, which alleviated the purification difficulties associated with the use of excess photosensitizer. This also allowed for the isolation of decomposition products, and reduced reaction times from 5 to 2 hours. Any unwanted reactive oxygen species generated during the catalytic cycle could be reduced by the addition of solid sodium thiosulfate into the reaction mixture.

III. Mechanistic Insights

The isolation of a mixture of diastereomers resulting from ETIC reactions of secondary amides and carbamates indicated that the reaction proceeds by a largely dissociative, rather than associative pathway involving discrete acyminium ion formation as a result of mesolytic cleavage of the benzylic C-C bond. Had the product isolated from these reactions been a single diastereomer with inversion of configuration at the reactive center, an associative mechanism would have been assumed.

Figure 1.30 illustrates the proposed mechanism. Upon single electron oxidation of the homobenzylic amide 14 the radical cation is formed. The benzylic bond of the radical cation then
fragments to give a stabilized benzyl radical and an acyliminium ion. The cation is then attacked by the appended hydroxyl group, and upon proton transfer the desired product is formed. Because the intermediate is a sp² hybridized carbon, attack from either face is possible, resulting in a mixture of diastereomers. Subjecting a 2:1 mixture of diastereomers of 15 to ETIC reaction conditions for 4 hours resulted in recovery of the same 2:1 mixture. To discount the possibility that the 2:1 mixture was an equilibrium mixture, the syn diastereomer (15b) was subjected to the aerobic catalytic ETIC reaction conditions. Over prolonged reaction times approximately 10% epimerization was observed. However, this rate of epimerization is not sufficient to account for the observed product ratios.

**Figure 1.30: Proposed dissociative mechanism**

Further evidence for a dissociative mechanism was provided by subjecting mixtures of diastereomers of tertiary amides as well as acyloxazolines to ETIC reaction conditions. In both cases the single diastereomer that was isolated, was the same as that which was isolated from ETIC reactions of single diastereomers of tertiary amides or oxazolines.

Changing from a methyl adjacent to the reactive center to a methoxy group had a definite impact on the ETIC reaction. As is evident by examination of ETIC reactions of amides 24 and 26, oxygen containing functional groups placed adjacent to the reactive center result in decreased yields. Comparison of the ETIC reaction of amide 14 to that of amide 24 shows a 50% decrease in yield upon incorporation of the methoxy group, as shown in Figure 1.31.
In addition to the benzylic bond, the C-C bond between the amide and methyl ether of the radical cations of amides 24, and 26 could be cleaved. Having a stabilizing group such as the methyl ether adjacent to the reactive center lowers both the bond dissociation energy of the substrate, as well as the oxidation potential of the electrophilic fragment. Upon formation of the radical cation two mesolytic bond cleavages are possible, the benzylic C-C bond or the C-C bond between the amide and methyl ether. Both bond cleavages result in a cation stabilized by the amide to form the acyl imminium ion (Figure 1.32).

These two possible bond dissociations played an even larger role in the cyclization reaction of tertiary amide 26, where no cyclization was observed and the only product isolated was amide 27 resulting from cleavage of the bis-homobenzylic bond. According to
electrochemical oxidation potentials, the tertiary amide is more readily oxidized than the secondary amide by as much as 0.80 V.\textsuperscript{41} Figure 1.33 shows a suggested a mechanism for the formation of amide 27. After mesolytic cleavage of the bis-homobenzylic bond, the imminium ion is attacked by adventitious water present in the system. Proton transfer from the water to the nitrogen of the hemiaminal followed by formation of the carbonyl displaces amide 27.

**Figure 1.33: Mechanism for formation of amide 27**

![Mechanism diagram](attachment:image)

Even though the electrochemical oxidation potentials\textsuperscript{42} of carbamates are known to be lower than those of amides, higher yields and cleaner reactions were observed with homobenzylic tert-butyl carbamates having an oxygen containing functional group adjacent to the reactive center than with the corresponding homobenzylic amides. The mechanism is not fully understood, given that there are two easily oxidizable substituents within the substrate. Theoretically, the nitrogen of the carbamate can be oxidized in preference to the arene to form radical cation A (Figure 1.34). Alternatively, the steric bulk of the tert-butylcarbamate might limit oxidation of the nitrogen, allowing for preferential oxidation of the arene, radical cation B. In either case, mesolytic cleavage of the benzylic C-C bond to form the acyliminium ion is possible.
Figure 1.34: Possible radical cations

Homobenzylic Boc protected oxazolines proved to be outstanding ETIC substrates. Superb stereocontrol was exhibited and excellent yields were observed despite the lower oxidation potential of the tertiary carbamate. The increased yields, relative to the acyclic cyclization substrate 31, can be explained through molecular orbital analysis of the radical cation. Proper orbital alignment of the SOMO of the carbamate radical cation and the benzylic C-C bond is required for mesolytic benzylic bond cleavage. If proper orbital overlap of the lone pair of the ether oxygen with the $\sigma^*$ of the homobenzylic C-C bond can be achieved, the alternative reactive pathway involving mesolytic cleavage of the homobenzylic C-C bond becomes an operative reactive pathway.

Figure 1.35 shows that the dihedral angle between the lone pair of the ether oxygen in the oxazoline cyclization substrate 41 and the $\sigma^*$ orbital of the homobenzylic bond cannot attain proper alignment for bond cleavage. Alternatively, in the acyclic substrate 31 the proper orbital overlap can be achieved allowing for the undesired bond cleavage and decreasing reaction yield.

Figure 1.35: Ideal geometries for $\beta$-alkoxy carbamate radical cation C-C bond fragmentation

Additional support for the reaction proceeding through amide or carbamate oxidation was provided by ETIC reactions of trifluoromethyl-substituted arenes 57 and 58. Incorporation of the
trifluoromethyl group is expected to increase the oxidation potential of the arene by $0.3\text{V}^{45}$ thereby inhibiting the reaction if oxidation of the arene is the relevant reaction pathway. Cyclization of 58 provided the desired bicyclo [4.3.0] fused product 42 in good yield, whereas subjecting trifluoromethyl-substituted arene 57 to ETIC reaction conditions resulted in complete decomposition of the starting material.

The scope and generality of the ETIC reaction of substrates having an oxygen containing functional group adjacent to the reactive center was further tested by varying the stabilizing group in the homobenzylic position. ETIC reactions with homobenzylic trifluoroacetamides and oxizolidinones were unsuccessful. Neither group was able to stabilize the cation formed from mesolytic cleavage of the benzylic bond. Due to the electron withdrawing nature of both the trifluoromethyl group and the oxizolidinone, the nitrogen was unable to form the acyliminium ion necessary for cyclization.
1.4. Conclusion

A new photoinitiated single electron transfer cyclization reaction has been developed. Amides and carbamates can be used as stabilizing groups in the homobenzylic position of alkyl arenes with appended nucleophiles. Upon single electron oxidation of the alkyl arene a radical cation is formed in which the benzyl C-C bond can selectively undergo mesolytic cleavage leading to a benzyl radical and a cationic fragment. The cationic fragment is then subject to nucleophilic attack by the appended nucleophile to form the desired heterocycle.

Through the course of development of this cyclization method it was discovered that both amides and t-butyl carbamates act as stabilizing groups in the homobenzylic position. Placing oxygen containing functional groups in the bis-homobenzylic position decreases reaction yields and allows for the operation of alternative reactive pathways. However, the use of homobenzylic t-butyl carbamates in substrates bearing oxygen containing functional groups in the bis-homobenzylic position leads to more efficient cyclization reactions.

A catalytic variant of the single electron transfer cyclization reaction has been developed. Regeneration of the photoactivated sensitizer N-methylquinolinium hexafluorophosphate can be achieved under aerobic conditions. The addition of the mild, partially soluble reducing agent sodium thiosulfate into the reaction mixture suppresses decomposition attributed to the formation of unwanted reactive oxygen species. Switching from the stoichiometric to the catalytic variant of the cyclization reaction facilitates purification and reaction efficiency.

Mechanistically, the electron transfer initiated cyclization reactions appear to be following a dissociative route. The use secondary amides and carbamates in the homobenzylic
position leads to diastereomeric mixtures of products. Tertiary, homobenzylic amides and oxazolines provide superb, complementary stereocontrol.

Nitrogen can be used as a nucleophile in electron transfer initiated cyclization reactions. Homobenzylic ethers as well as homobenzylic carbamates containing appended sulfonamide nucleophiles have been subjected to the catalytic ETIC reaction conditions, and the resulting \((N, N)\) and \((N, O)\) acylaminals have been isolated in good yields.
1.5. Experimental

**General Procedures.** All reactions were performed in oven or flame-dried glassware under a positive pressure of N₂ with magnetic stirring unless otherwise noted.

**Instrumentation.** Proton ($^1$H NMR) and carbon ($^{13}$C NMR) nuclear magnetic resonance spectra were recorded on Bruker Avance 300 spectrometers at 300 MHz and 75 MHz, respectively. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. The solvent peak or the internal standard tetramethylsilane were used as reference values. For $^1$H NMR: CDCl₃ = 7.27 ppm, TMS = 0.00 ppm. For $^{13}$C NMR: CDCl₃ = 77.23, TMS = 0.00. For the proton data: s = singlet; d = doublet; t = triplet; q = quartet; dd = doublet of doublets; dt = doublet of triplets; b = 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 CH₂Cl₂ and then evaporating the CH₂Cl₂.

**Materials.** Analytical TLC was performed on E. Merck pre-coated (25 mm) silica gel 60F-254 plates. Visualization was done under UV (254 nm). Flash chromatography was done using ICN SiliTech 32-63 60 Å silica gel. Reagent grade ethyl acetate and hexanes (commercial mixture) were purchased from EM Science and used as is for chromatography. Reagent grade methylene chloride (CH₂Cl₂), dichloroethane (C₂H₄Cl₂), acetonitrile (CH₃CN), benzene and toluene were distilled from CaH₂. Diethyl ether (Et₂O) and tetrahydrofuran (THF) were distilled from sodium
benzophenone ketyl prior to use. Anhydrous N,N-dimethylformamide (DMF), methanol, dimethyl sulfoxide (DMSO) and tert-butylbenzene were purchased from Aldrich and used as is.

Compounds originating from phenylalanine were found to have racemized during the synthesis.

**Hexanoic acid (1-benzylpent-4-enyl)amide (5)**

To 1-Phenylhex-5-en-2-ol (2.51 g, 14.22 mmol) in CH₂Cl₂ (35 mL) at 0 °C were added methanesulfonyl chloride (2.44 g, 21.3 mmol) and triethylamine (5.76 g, 56.8 mmol). The reaction mixture was stirred for 3 h at room temperature then was quenched with water. The reaction mixture was extracted with CH₂Cl₂, then the organic layer was washed with water and saturated NaCl, dried (Na₂SO₄) and concentrated. The resulting residue was dissolved in DMF (35 ml) at 23 °C under N₂. Sodium azide (9.24 g, 14.2 mmol) and tetrabutyl ammonium iodide (50 mg) were added. The reaction mixture was stirred for 18 h, then was quenched with water, and extracted into hexanes. The organic layer was washed with saturated NaCl, dried (Na₂SO₄), and concentrated. The resulting residue was then dissolved in THF (15 mL) at 23 °C under N₂ and triphenylphosphine (1.73 g, 6.59 mmol) was added. The reaction mixture was allowed to stir for 18 h then was quenched with water (2 mL). The reaction mixture was then allowed to stir for an additional 18 h. The temperature was decreased to 0 °C and hexanoyl chloride (1.63 g, 8.25 mmol) and triethylamine (1.11 g, 10.9 mmol) were added. After 1 h the reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with saturated NaCl (2x 10 mL), dried (Na₂SO₄) and concentrated. The crude product was purified by flash chromatography (20% EtOAc in hexanes) to afford the desired product (0.612 g, 40.7%): ¹H NMR (300 MHz, CDCl₃) δ 7.32-7.16 (m, 5H), 5.78 (m, 1H), 5.19 (b s, 1H), 4.98 (d, J = 14.0, 2H), 4.95 (d, J = 8.5, 2H) 4.23 (m, 1H), 2.76 (t J = 5.15 , 2H), 2.14-
2.07 (m, 6H), 1.62-1.21 (m, 6H), 0.88 (t, J = 6.7 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 173.1 137.94, 129.5, 128.6, 114.8, 49.7, 40.9, 36.7, 33.3, 31.3, 30.3, 22.4, 14.1; IR (neat) 3290, 3066, 3027, 2933, 2855, 1643, 1544, 1453, 894, 748 cm$^{-1}$; HRMS (EI) calcd for C$_{18}$H$_{27}$NO 273.2093, found 273.2100.

**Hexanoic acid (1-benzyl-5-hydroxypentyl)amide (6)**

![Chemical structure](image)

To hexanoic acid (1-benzylpent-4-enyl)amide (0.212 g, 0.777 mmol) in THF (10 mL) at 23 ºC was added 9-BBN (0.5 M in THF, 3.11 ml, 1.55 mmol). The reaction was stirred for 3.5 h, then quenched at 0 ºC with water (2 mL) followed by 20% aqueous NaOH (1 mL), 30% aqueous hydrogen peroxide solution (1 mL) and saturated Na$_2$SO$_3$ (2 mL). The reaction mixture was stirred for an addition hour, then was extracted with ethyl acetate, washed with saturated NaCl (2x 10 mL), dried (Na$_2$SO$_4$) and concentrated. The resulting residue was purified by column chromatography (50% EtOAc in hexanes) to afford the desired product (0.099 g, 43.7%): $^1$H NMR (300 MHz, CDCl$_3$) δ 7.32-7.16 (m, 5H), 5.23 (bd, J = 3.2 Hz 1H), 4.23 (m, 1H) 3.62 (t, J = 5.7 Hz, 2H) 2.79 (d, J = 7.6 Hz, 2H), 2.11 (m. 2H), 1.58-1.21 (m, 12H), 0.87 (t, J = 6.7 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 173.1, 138.1, 129.5, 128.4, 126.5, 62.4, 49.9, 41.1, 37.0, 33.9, 32.4, 31.4, 25.6, 22.5, 22.3, 14.0; IR (neat) 3281, 2933, 2860, 1638, 1552, 1445, 1053, 748, 701 cm$^{-1}$; HRMS (EI) calcd for C$_{18}$H$_{29}$NO$_2$ 291.2198, found 292.2270.

**Hexanoic acid (tetrahydropyran-2-yl)amide (7)**

![Chemical structure](image)

This procedure is representative of a standard ETIC reaction. To hexanoic acid (1-benzyl-5-hydroxypentyl)amide (0.050 g, 0.172 mmol) in dichloroethane (5 mL)
and toluene (1 mL) in a borosilicate flask at 20 °C were added N- methylquinolinium hexafluorophosphate (0.059 g, 0.206 mmol), and sodium acetate (0.100 g, 1.21 mmol). The mixture was stirred at room temperature while irradiating for 5 h at 320nm with a medium pressure mercury lamp. The distance between the reaction flask and lamp was 4 cm. The lamp was cooled by a cold water circulation through a pyrex jacket surrounding the lamp. The pyrex cold jacket also served as a filter to remove all wavelengths below 290 nm emitted by the lamp. Upon completion, the reaction mixture was filtered, concentrated, and purified by flash chromatography (50% EtOAc in hexanes) to provide the desired product (0.029 g, 86%): \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 6.05 \text{ (d, J = 7.9 Hz, 1H)}, 5.09 \text{ (dt, J = 8.3, 2.3 Hz, 1H)}, 3.96 \text{ (m, 1H)}, 3.58 \text{ (m, 1H)}, 2.16 \text{ (m, 1H)} 1.64 – 1.26 \text{ (m, 10H)}, 0.87 \text{ (t, J = 6.7 Hz)}; ^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta 172.9, 77.8, 36.9, 31.7, 31.5, 25.3, 25.2, 23.0, 22.5, 22.3, 14.0; IR (neat) 3286, 2950, 2855, 1660, 1544, 1453, 1208, 1083, 1032, 903 cm\(^{-1}\); HRMS (EI) cald for C\(_{11}\)H\(_{21}\)NO\(_2\) 199.1572, found 199.158809.

This procedure is representative of an ETIC reaction done under catalytic aerobic conditions. To hexanoic acid (1-benzyl-5-hydroxypentyl)amide (0.089 g, 0.306 mmol) in dichloroethane (10 mL) and toluene (2 mL) in a borosilicate flask at 20 °C were added N- methylquinolinium hexafluorophosphate (0.002 g, 0.007 mmol), sodium acetate (0.178 g, 2.17 mmol), and sodium thiosulfate (0.178 g, 1.13 mmol). The mixture was stirred at room temperature while bubbling air gently and irradiating for 3 h at a distance of 4 cm from a medium pressure mercury lamp. The lamp was cooled by a cold water circulation through a pyrex jacket surrounding the lamp. The pyrex cold jacket also served as a filter to remove all wavelengths below 290 nm emitted by the
lamp. The reaction mixture was filtered, concentrated, and purified by flash chromatography (50% EtOAc in hexanes) to provide the desired product (0.045 g, 75%)

**Hexanoic acid (1-benzylpent-4-enyl)methylamide (8)**

To a suspension of sodium hydride (60% dispersion in mineral oil, 0.234 g, 5.85 mmol) in DMF (20 mL) at 0 °C was added hexanoic acid (1-benzylpent-4-enyl)methylamide (0.400 g, 1.46 mmol). The reaction mixture was stirred for 30 minutes then methyl iodide (2.07 g, 14.6 mmol) was added. The reaction mixture stirred for 12 h then was quenched with water (2 mL), extracted with EtOAc (3 x 15 mL), washed with water and saturated NaCl, dried (Na₂SO₄) and concentrated. The resulting residue was purified by flash chromatography (50% EtOAc in hexanes) to provide the desired product (0.345 g, 82%): ¹H NMR (300 MHz, CDCl₃) δ 7.29-7.08 (m, 5H), 5.89 (m, 1H), 4.99 (m, 1H), 3.91 (m, 1H), 2.85 (s, 3H), 2.74 (m, 5H), 2.17 (dt, J = 4.9, 2.4, 1H), 2.01 (m, 2H), 1.73-1.06 (m, 10H), 0.86 (m, 3H).

**Hexanoic acid (1-benzyl-5-hydroxypentyl)methylamide (9)**

To hexanoic acid (1-benzylpent-4-enyl)methylamide (0.345 g, 1.20 mmol) in THF (20 mL) at 23 °C was added 9-BBN (0.5 M in THF, 4.80 ml, 2.40 mmol). The reaction was stirred for 3 h, then quenched at 0 °C with water (2 mL) followed by 20% aqueous NaOH (1 mL), 30% aqueous hydrogen peroxide solution (1 mL) and saturated Na₂SO₃ (2 mL). The reaction mixture was stirred for an addition hour, then was extracted with ethyl acetate, washed with saturated NaCl, dried (Na₂SO₄) and concentrated. The resulting residue was purified by column chromatography (50% EtOAc in hexanes) to afford the desired
product (0.339 g, 92%): $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.29-7.08 (m, 5H), 5.02 (bs, 1H), 3.92 (m, 1H), 3.62 (m, 2H), 2.85 (m, 5H), 2.17 (m, 2H), 2.03 (m, 1H), 1.63-1.18 (m, 12H), 0.86 (m, 3H).

**Hexanoic acid methyl(tetrahydropyran-2-yl)amide (10)**

![Chemical Structure](image)

To Hexanoic acid (1-benzyl-5-hydroxypentyl)methylamide (0.100 g, 0.327 mmol) in dichloroethane (7 mL) and tert-butylbenzene (1 mL) in a borosilicate flask at 20 °C were added N- methylquinolinium hexafluorophosphate (0.114 g, 0.393 mmol) and sodium acetate (0.227 g, 2.67 mmol). The mixture was stirred for 6 h at 20 °C while irradiating. The reaction mixture was filtered, concentrated, and purified by flash chromatography (50% Acetone in hexanes) to provide the desired product (0.039 g, 55%): $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.64 (dd, $J$ = 5.6, 3.27 1H), 4.82 (dd $J$ = 8.5, 1.8 1H), 4.02 (bt, $J$ = 12.9 2H), 3.58 (m, 1H), 2.91 (s, 3H), 2.88 (s, 3H), 2.41 – 2.25 (m, 4H), 1.99 – 1.24 (m, 12H), 0.88 (t, $J$ = 5.5, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 173.3, 85.42, 81.16, 68.35, 34.14, 33.49, 31.67, 29.69, 29.17, 28.58, 27.34, 25.34, 25.18, 25.08, 24.52, 23.54, 23.43, 23.12, 22.56, 14.03; IR (neat) 2933, 2855, 1660, 1462, 1410, 1372, 1316, 1079, 1036, 911 cm$^{-1}$; HRMS (EI) cald for C$_{12}$H$_{23}$NO$_2$ 213.1728, found 213.1732.

**tert-Butyldimethylpent-4-ynoxy-silane (11)**

![Chemical Structure](image)

To 4-pentyn-1-ol (1.99 g, 23.7 mmol) in DMF (20 mL) at 0 °C were added imidazole (2.42 g, 35.6 mmol) and tert-butyldimethylsilyl chloride (3.94 g, 26.1 mmol). The
reaction was stirred at 20 ºC for 18 h, and then quenched with saturated NH₄Cl, extracted with hexanes, washed with saturated NaCl, dried (Na₂SO₄) and concentrated. The resulting residue was purified by column chromatography (10% EtOAc in hexanes) to afford the desired product (4.49 g, 95%): ¹H NMR (300 MHz, CDCl₃) δ 3.73 (t, J = 6.0 2H), 2.30 (dt, J = 2.7, 4.5 2H) 1.96 (t, J = 2.7 1H), 1.78 (m, 2H), 0.93 (s, 9H), 0.08 (s, 6H).

**tert-Butyldimethyl-(4-methyl-6-phenylhex-4-enyloxy)silane (12)**

To a room temperature suspension of bis(cyclopentadienyl)zirconium dichloride (5.00 g, 17.24 mmol) in CH₂Cl₂ (100 mL) was added trimethylaluminum (2.0 M in hexanes, 22.68 mL, 45.36 mmol). The reaction mixture was stirred for 30 min. before tert-Butyl-dimethyl-pent-4-ynyloxy-silane (3.42 g, 17.24 mmol) was added. The reaction mixture was stirred for 18 h then a solution of benzyl chloride (2.23 g, 17.24 mmol) and palladium tetrakis-triphenylphosphine (0.597 g, 0.517 mmol) in THF (20 mL) was added. The reaction mixture was stirred for 12 h then quenched at -78 ºC with ethanol (3 mL) and stirred for 2 h with saturated sodium potassium tartrate (15 mL). The mixture was extracted with ether and the organic layer was washed with water and saturated NaCl, dried (Na₂SO₄) and concentrated. The resulting residue was purified by column chromatography (5% EtOAc in hexanes) to afford tert-Butyl-dimethyl-(4-methyl-6-phenyl-hex-4-enyloxy)-silane (5.98 g, 76%): ¹H NMR (300 MHz, CDCl₃) δ 7.33-7.18 (m, 5H), 5.38 (t, J = 1.2, 1H), 3.63 (t, J = 6.6, 2H), 3.40 (d, J = 7.3, 2H), 2.11 (t, J = 7.2, 2H), 1.75 (s, 3H), 1.69 (m, 2H), 0.92 (s, 9H), 0.06 (s, 6H).
**6-(*tert*-Butyldimethylsilanyloxy)-(*3S*)-methyl-1-phenylhexan-(*2R*)-ol (13)**

![Chemical Structure]

To *tert*-Butyldimethyl-(4-methyl-6-phenylhex-4-enyloxy)silane (0.200 g, 0.656 mmol) in THF (10 mL) at 0 °C was added diborane (1.0 M in THF, 1.97 mL, 1.97 mmol). The reaction was allowed to stir for 3 h, then quenched at 0 °C with water (2 ml) followed by 20% aqueous NaOH (1 ml), 30% aqueous hydrogen peroxide solution (1 ml) and saturated Na₂SO₃ (2 ml). The reaction mixture was stirred for an additional hour, then was extracted with ethyl acetate, washed with saturated NaCl (2x 10 mL), dried (Na₂SO₄) and concentrated. The resulting residue was purified by column chromatography (20% EtOAc in hexanes) to afford 6-(*tert*-butyldimethylsilanyloxy)-(*3S*)-methyl-1-phenyl-hexan-2R-ol (0.171 g, 81%): ¹H NMR (300 MHz, CDCl₃) δ 7.33-7.22 (m, 5H), 3.63 (m, 3H), 2.89 (dd, *J* = 10.5, 3.1, 1H), 2.58 (dd, *J* = 9.7, 3.8, 1H), 1.67-1.50 (m, 3H), 1.26 (m, 2H), 1.02 (d, *J* = 6.7, 3H), 0.91 (s, 9H), 0.06 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 139.3, 129.4, 128.6, 126.4, 76.7, 63.6, 40.1, 38.2, 30.5, 28.3, 26.1, 18.4, 15.5, -5.13; HRMS EI calcd for C₁₅H₂₅O₂Si (M-40) 265.1623, found 265.1628.

**Hexanoic acid [1-benzyl-5-(*tert*-butyldimethylsilanyloxy)-(*2S*)-methylpentyl]amide**

To 6-(*tert*-butyldimethylsilanyloxy)-(*3S*)-methyl-1-phenylhexan-(*2R*)-ol (0.620 g, 1.92 mmol) in CH₂Cl₂ (10 mL) at 0 °C were added methanesulfonyl chloride (0.330 g, 2.88 mmol) and triethyl amine (0.778 g, 7.69 mmol). The reaction mixture was stirred for 3 h at room temperature, and was then quenched with water. The reaction mixture was extracted with CH₂Cl₂, and then the organic layer was washed with water and saturated NaCl,
dried (Na₂SO₄) and concentrated. The resulting residue was dissolved in DMF (10 mL), sodium azide (9.24 g, 14.2 mmol) was added and the reaction mixture was stirred at 55 °C for 12 h. The reaction mixture was quenched with water and extracted with hexanes. The organic layer was washed with saturated NaCl, dried (Na₂SO₄), and concentrated. The resulting residue was then dissolved in THF (10 mL) at 23 °C under N₂ and triphenylphosphine (0.299 g, 1.14 mmol) was added. The reaction mixture was allowed to stir for 18 h then was quenched with water (1 mL). The reaction mixture was then allowed to stir for an additional 18 h. The temperature was decreased to 0 °C and hexanoyl chloride (0.192 g, 1.42 mmol) and triethylamine (0.192 g, 1.90 mmol) were added. After 1 hour the reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with saturated NaCl (2x 10 mL), dried (Na₂SO₄) and concentrated. The crude product was purified by flash chromatography (20% EtOAc in hexanes) to afford the desired product (0.399 g, 61%): ¹H NMR (300 MHz, CDCl₃) δ 7.30-7.17 (m, 5H), 5.19 (d, J = 9.4, 1H), 4.26 (m, 1H), 3.56 (m, 2H), 2.75 (m, 2H), 2.35 (t, J = 7.5, 2H), 2.07 (m, 2H), 1.53-1.18 (m, 9H), 0.88 (m, 12H), 0.05 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 172.7, 138.5, 129.1, 128.4, 126.4, 63.3, 53.3, 38.5, 37.1, 35.1, 31.4, 30.5, 29.8, 26.0, 25.5, 22.4, 14.6, 14.0, -5.17; IR (neat) 3437, 2958, 2934, 2859, 2253, 1663, 1508, 1465, 1386, 1259, 1097, 906 cm⁻¹; HRMS (EI), (M-57) calcd for C₂₁H₃₆NO₂Si 362.2515, found 362.2520.

**Hexanoic acid (1-benzyl-5-hydroxy-(2S)-methylpentyl)amide (14)**

\[
\text{BnOH} \quad \text{HN} \quad \text{C₅H₁₁} \quad \text{O} \quad 14
\]

To hexanoic acid [1-benzyl-5-(tert-butyldimethylsilanyloxy)-(2S)-methylpentyl]amide (0.244 g, 0.581 mmol) at 23 °C in THF (10 mL) was added tetrabutylammonium fluoride hydrate (0.228 g, 0.872 mmol). The reaction mixture was stirred
for 12 h, and then quenched with saturated NH₄Cl (2 mL), extracted with ethyl acetate, dried (Na₂SO₄) and concentrated. The resulting residue was purified by column chromatography (50% EtOAc in hexanes) to afford the desired product (0.170 g, 96%): \(^1\)H NMR (300 MHz, CDCl₃) \(\delta\) 7.27-7.14 (m, 5H), 5.55 (d, \(J = 9.4\), 1H), 4.31 (m, 1H), 3.72 (m, 3H), 3.54 (m, 2H), 2.72 (m, 2H), 2.06 (m, 2H), 1.83 (m, 3H), 1.57-1.44 (m, 6H), 1.23-1.15 (m, 4H), 0.92 (d, \(J = 6.8\), 3H), 0.83 (t, \(J = 7.3\), 3H); \(^{13}\)C NMR (75 MHz, CDCl₃) \(\delta\) 173.1, 138.4, 129.1, 129.0, 128.4, 126.4, 62.8, 52.7, 38.7, 37.0, 35.5, 31.3, 30.4, 29.9, 25.5, 22.4, 14.5, 13.9; IR (neat) 3286, 3070, 2933, 2873, 1638, 1544, 1453, 1062, 735, 696 cm\(^{-1}\); HRMS (EI) calcd for C\(_{12}\)H\(_{24}\)NO\(_2\) (M-91) 214.1807, found 214.1812.

**Hexanoic acid [1-benzyl-2-methyl-5-(tetrahydropyran-2-yloxy)pentyl]amide (14a)**

To hexanoic acid (1-benzyl-5-hydroxy-(2S)-methylpentyl)amide (0.178 g, 0.583 mmol) at 0 °C in CH₂Cl₂ (10 mL) was added dihydropyran (0.0732 g, 0.871 mmol) and \(p\)-toluenesulfonic acid (0.133 g, 0.699 mmol). The reaction mixture was stirred for 12 h, then diluted with ether (15 mL), washed with NaHCO₃ (2 x 15 mL) and saturated NaCl (2 x 15 mL), dried (Na₂SO₄) and concentrated. The resulting residue was purified by flash chromatography (30% EtOAc in hexanes) to provide the desired product (0.137 g, 60%): \(^1\)H NMR (30 MHz, CDCl₃) \(\delta\) 7.24-7.16 (m, 5H), 5.62 (d, \(J = 9.2\), 1H), 4.52 (bs, 1H), 4.25 (bs, 1H), 3.82 (m, 1H), 3.68 (m, 1H), 3.47 (m, 1H), 3.32 (m, 1H), 2.75 (m, 2H), 2.06 (m, 2H), 1.51 (m, 12H), 1.19 (m, 4H), 0.93 (d, \(J = 6.8\), 3H), 0.84 (t, \(J = 6.9\), 3H); \(^{13}\)C NMR (75 MHz, CDCl₃) \(\delta\) 172.4, 128.8, 128.0, 125.9, 98.62, 98.56, 67.34, 62.07, 60.13, 54.00, 52.99, 38.22, 36.62, 35.06, 31.08, 30.51, 29.95, 27.11, 25.30, 25.24, 22.16, 20.78, 19.44, 15.83, 14.27, 13.95, 13.70; IR
Hexanoic acid ((3S)-methyl-tetrahydropyran-2-yl)amide (15a,b)

Hexanoic acid (1-benzyl-5-hydroxy-(2S)-methylpentyl)amide (0.016g, 0.053 mmol) was subjected to both standard ETIC reaction conditions. The reaction mixture was filtered, concentrated, and purified by flash chromatography (50% EtOAc in hexanes) to provide the desired product as a separable mixture of diastereomers (0.008 g, 75%): Hexanoic acid ((3S)-methyltetrahydropyran-2S-yl)amide (15a) $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.96 (bd, $J = 7.65$, 1H), 5.31 (dd, $J = 3.1$, 6.0, 1H), 3.85 (m, 1H), 3.67 (m, 1H), 2.21 (t, $J = 7.4$, 2H), 1.98-1.31 (m, 13H), 0.97 (d, $J = 6.9$, 3H), 0.90 (t, $J = 1.7$, 3H); $^1$H NMR (330MHz, CDCl$_3$, D$_2$O) $\delta$ 5.31 (d, $J = 2.4$, 1H), 3.85 (m, 1H), 3.67 (m, 1H), 2.21 (t, $J = 7.4$, 2H), 1.98-1.31 (m, 13H), 0.97 (d, $J = 6.9$, 3H), 0.90 (t, $J = 1.7$, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 173.0, 79.1, 65.7, 37.1, 36.39, 31.92, 31.61, 29.0, 25.4, 22.5, 21.8, 14.1, 13.1; IR (neat) 3440, 2954, 2851, 1655, 1466, 1075, 997, 731 cm$^{-1}$; HRMS (EI) calcd for C$_{12}$H$_{23}$NO$_2$ 213.1728, found 213.1731. Hexanoic acid ((3S)-methyltetrahydropyran-2R-yl)amide (15b) $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.75 (bs, 1H), 4.79 (t, $J = 9.5$, 1H), 3.00 (m, 1H), 3.57 (m, 1H), 2.20 (t, $J = 7.15$, 2H), 1.90 (m, 1H), 1.63-1.26 (m, 12H), 0.89 (m, 6H); $^1$H NMR (330MHz, CDCl$_3$, D$_2$O) $\delta$ 4.79 (d, $J = 9.3$, 1H), 3.00 (m, 1H), 3.57 (m, 1H), 2.20 (t, $J = 7.15$, 2H), 1.90 (m, 1H), 1.63-1.26 (m, 12H), 0.89 (m, 6H); $^{13}$C NMR (75MHz, CDCl$_3$) $\delta$ 173.3, 82.9, 67.8, 37.1, 36.4, 32.1, 31.6, 26.0, 25.4, 22.5, 17.4, 14.1.
Hexanoic acid (1-benzyl-5-hydroxypentyl)amide (0.064 g, 0.212 mmol) was subjected to catalytic aerobic cyclization conditions. The reaction mixture was filtered, concentrated, and purified by flash chromatography (70% EtOAc in hexanes) to provide the desired product (0.032 g, 72%)

6-(tert-Butyldimethylsilyloxy)-3S-methyl-1-phenylhexan-2-one (19)

To a solution of DMSO (0.242 g, 3.10 mmol) and oxalyl chloride (0.243 g, 1.86 mmol) in CH₂Cl₂ at –78 °C was added 6-(tert-butyldimethylsilyloxy)-(3R)-methyl-1-phenylhexan-(2R)-ol (0.200 g, 0.620 mmol). The reaction mixture was stirred at –78 °C for 30 min. before triethylamine (0.313 g, 3.10 mmol) was added. The reaction mixture was warmed to room temperature, quenched with water, washed with saturated NaCl (2 x 15 mL), dried (MgSO₄) and concentrated. The resulting residue was purified by flash chromatography (10% EtOAc in hexanes) to yield the desired product (0.147 g, 74%): ¹H NMR (300 Mhz, CDCl₃) δ 7.29–7.20 (m, 5H), 3.72 (s, 2H), 3.53 (t, J = 5.9, 2H), 2.67 (m, 1H), 1.69 (m, 1H), 1.40 (m, 3H), 1.07 (d, J = 6.9, 3H), 0.08 (s, 9H), 0.01 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 211.9, 134.4, 129.7, 128.8, 127.1, 63.0, 48.5, 45.4, 30.4, 29.3, 26.1, 18.5, 16.6, 0.21, -5.08; IR (neat) 2930, 1716, 1459, 1246, 1101, 832, 770, 696 cm⁻¹; HRMS (EI) calcd for C₁₉H₃₂O₂Si 320.2171, found 320.2156.
6-(tert-Butyldimethylsilyloxy)-3S-methyl-1-phenylhexan-2-one oxime (20)

To 6-(tert-butyldimethylsilyloxy)-(3S)-methyl-1-phenylhexan-2-one (0.147 g, 0.458 mmol) in EtOH (5 mL) at 23 °C were added ammonium hydroxide hydrochloride (0.063 g, 0.917 mmol) and sodium acetate (0.150 g, 1.83 mmol). A white precipitate was immediately observed. The reaction mixture was stirred for 1 h, then quenched with water, extracted with CH₂Cl₂, dried (Na₂SO₄) and concentrated. The resulting residue was purified by flash chromatography (20% EtOAc in hexanes) to yield the desired product (0.134 g, 88%): ¹H NMR (300 MHz, CDCl₃) δ 7.27-7.21 (m, 5H), 3.72 (s, 2H), 3.51 (m, 2H), 3.27 (m, 1H), 2.37 (m, 1H), 1.43-1.39 (m, 3H), 1.02 (dd, J = 6.9, 7.5, 3H), 0.88 (s, 9H), 0.01 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 129.4, 129.1, 128.6, 128.5, 126.7, 126.4, 106.5, 63.1, 38.3, 37.4, 32.3, 32.0, 31.0, 30.6, 30.5, 30.0, 26.1, 18.5, 17.5, 0.21, -5.08; IR (neat) 3260, 3075, 2924, 1462, 1247, 1096, 946, 838, 778, 696 cm⁻¹; HRMS (EI) calcd for C₁₉H₃₃NO₂Si 335.2280, found 335.2283.

Hexanoic acid [1-benzyl-5-(tert-butyldimethylsilyloxy)-(2S)-methylpentyl]amide

To a suspension of nickel chloride (0.311 g, 2.39 mmol) in ether (10 mL) at 23 °C was added lithium aluminum hydride (0.091 g, 2.39 mmol). A black precipitate formed immediately and the reaction mixture was stirred for 5 minutes before 6-(tert-butyldimethylsilyloxy)-3R-methyl-1-phenylhexan-2-one oxime (0.134 g, 0.399 mmol) was added. The reaction mixture was stirred for 10 minutes, then quenched with water (3 mL), filtered over celite, washed with CH₂Cl₂ (2 x 15 mL) and methanol (2 x 15 mL). The filtrate was made basic by the addition of 15 % NaOH, then extracted in CH₂Cl₂ and washed with saturated NaCl (2 x 15 ml), dried (Na₂SO₄) and concentrated. The resulting residue was dissolved in THF
(10 mL) and at 0 °C under N2 hexanoyl chloride (0.085 g, 0.599 mmol) and triethylamine (0.278 g, 1.99 mmol) were added. The reaction mixture was stirred for 1 h, then quenched with water, washed with NaCl, dried (Na2SO4) and concentrated. The resulting residue was purified by flash chromatography (30% EtOAc in hexanes) to yield the desired product (0.105 g, 63%): 

\[
{^1}H \text{ NMR } (300 \text{ MHz}, \text{CDCl}_3) \delta 7.27-7.19 (m, 5H), 5.13 (d, J = 9.2, 1H), 4.24 (m, 1H), 3.58 (m, 2H), 2.91-2.72 (m, 2H), 2.35 (t, J = 7.5, 2H), 2.06 (m, 2H), 1.69-1.20 (m, 10H), 0.90 (m, 12H), 0.03 (s, 6H); {^{13}}C \text{ NMR } (75 \text{ MHz}, \text{CDCl}_3) \delta 172.7, 138.6, 129.3, 129.2, 128.6, 126.5, 63.5, 63.4, 54.4, 53.4, 37.4, 37.2, 35.8, 35.2, 31.5, 31.4, 30.8, 30.6, 29.9, 28.4, 26.1, 25.6, 24.6, 22.6, 22.5, 16.4, 14.7, 14.1, 0.21, -5.02; \text{IR (neat) } 3290, 2954, 2855, 1724, 1643, 1544, 1380, 1251, 1088, 843, 774, 701; \text{HRMS calcd for C}_{25}H_{46}NO_2Si 420.3297, found 420.3302.
\]

**Hexanoic acid [1-benzyl-5-(tert-butyldimethylsilanyloxy)-(2)-methylpentyl]-methylamide**

To a suspension of sodium hydride (60% dispersion in mineral oil, 0.234 g, 5.85 mmol) in DMF (20 mL) at 0 °C was added hexanoic acid [1-benzyl-5-(tert-butyldimethylsilanyloxy)-(2S)-methylpentyl]amide (0.338 g, 1.23 mmol). The reaction mixture was stirred for 30 minutes then methyl iodide (1.75 g, 12.4 mmol) was added. The reaction mixture stirred for 12 h then was quenched with water (2 mL), extracted in EtOAc, washed with water and saturated NaCl, dried (Na2SO4) and concentrated. The resulting residue was purified by flash chromatography (50% EtOAc in hexanes) to provide the desired product (0.193 g, 36%): 

\[
{^1}H \text{ NMR } (30 \text{ MHz}, \text{CDCl}_3) \delta 7.27-7.06 (m, 5H), 3.68 (m, 2H), 3.55 (m, 1H),
\]
3.03 (m, 1H), 2.84 (s, 3H), 2.66 (m, 2H), 2.08 (m, 1H), 1.78-0.69 (m, 25H), 0.06 (s, 6H); HRMS (EI) (M- 57) calcd for C\textsubscript{22}H\textsubscript{38}NO\textsubscript{2}Si 376.2671, found 376.2670.

This procedure was repeated using a mixture of both hexanoic acid [1S-benzyl-5-\((\text{tert}-\text{butyldimethylsilyl})\text{oxy}\)-2S-methylpentyl]amide and hexanoic acid [1R-benzyl-5-\((\text{tert}-\text{butyldimethylsilyl})\text{oxy}\)-2S-methylpentyl]amide to yield the desired mixture of diastereomers.

\(\text{\(^1H\) NMR (300 MHz, CDCl\textsubscript{3}) \delta 7.26-7.23 (m, 5H), 3.62 (m, 2H), 3.01 (m, 1H), 2.97 (m, 1H), 2.83 (s, 3H), 2.61 (m, 4H), 2.25 (m, 1H), 2.01 (m, 2H), 1.70-0.67 (m, 22H), 0.03 (m, 6H); \text{\(^{13}C\) NMR (75 MHz, CDCl\textsubscript{3}) \delta 172.7, 139.1, 129.2, 129.1, 128.9, 128.7, 128.3, 126.7, 126.2, 65.2, 64.6, 63.5, 63.4, 36.1, 35.6, 35.4, 32.6, 31.7, 30.7, 30.3, 30.1, 29.9, 27.7, 26.1, 24.8, 24.6, 22.6, 22.5, 17.5, 16.7, 14.1, 0.21, -5.03.}\)

**Hexanoic acid (1-benzyl-5-hydroxy-(2S)-methylpentyl)methylamide (17)**

To hexanoic acid [1-benzyl-5-\((\text{tert}-\text{butyldimethylsilyl})\text{oxy}\)-(2S)-methylpentyl]methylamide (0.193 g, 0.671 mmol) at 23 ºC in THF (10 mL) was added tetrabutylammonium fluoride hydrate (0.263 g, 1.00 mmol). The reaction mixture was stirred for 12 h, then quenched with saturated NH\textsubscript{4}Cl (2 mL), extracted in ethyl acetate, dried (Na\textsubscript{2}SO\textsubscript{4}) and concentrated. The resulting residue was purified by column chromatography (50% EtOAc in hexanes) to afford the desired product (0.110 g, 78%): \(^1H\) NMR (300 MHz, CDCl\textsubscript{3}) \(\delta 7.27-7.06 (m, 5H), 3.74 (t, J = 6.2, 1H), 3.67 (t, J = 4.9, 1H), 3.55 (dt, J = 2.3, 8.2, 1H), 3.12 (dd, J = 4.8, 9.9, 1H), 3.03 (dd, J = 2.9, 11.1, 1H), 2.84 (s, 3H), 2.67 (s, 3H), 2.06 (m, 1H), 1.83-0.78 (m, 13H).
This procedure was repeated using a mixture of both hexanoic acid [1S-benzyl-5-\((\text{tert}\text{-}\text{butyldimethylsilanyloxy})\text{-}2\text{S}\text{-}\text{methylpentyl}\)]-methylamide and hexanoic acid [1R-benzyl-5-\((\text{tert}\text{-}\text{butyldimethylsilanyloxy})\text{-}2\text{S}\text{-}\text{methylpentyl}\)]methylamide to yield the desired mixture of diastereomers. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.27-7.05 (m, 5H), 3.72-3.49 (m, 3H), 3.12-2.99 (m, 2H), 2.83 (s, 3H), 2.64 (m, 5H), 2.10-2.00 (m, 3H), 1.77-0.79 (m, 16H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 174.2, 138.8, 129.0, 128.7, 128.6, 128.2, 126.6, 126.1, 65.2, 64.5, 62.8, 62.7, 60.5, 59.0, 36.3, 35.5, 33.8, 32.4, 31.5, 30.0, 29.8, 29.7, 29.2, 28.9, 25.8, 24.7, 24.5, 24.1, 22.4, 19.8, 16.3, 14.0, 13.7.

**Hexanoic acid methyl-((3S)-methyltetrahydropyran-2R-yl)amide (18)**

Hexanoic acid (1-benzyl-5-hydroxy-(2S)-methylpentyl)methylamide (0.036 g, 0.113 mmol) was subjected to standard ETIC reaction conditions. The reaction mixture was filtered, concentrated, and purified by flash chromatography (50% EtOAc in hexanes) to provide the desired product (0.011 g, 43%): $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.36 (d, $J$ = 9.8, 1H), 4.45 (d, $J$ = 9.4, 1H), 4.02 (m, 2H), 3.54 (m, 2H), 2.91 (d, $J$ = 11.8, 3H), 2.31 (m, 3H), 1.99-1.25 (m, 6H), 0.90 (m, 3H), 0.80 (m, 3H); $^1$H NMR (300 MHz, DMSO, 378K) $\delta$ 4.85 (bs, 1H), 4.02 (m, 2H), 3.54 (m, 2H), 2.91 (d, $J$ = 11.8, 3H), 2.31 (m, 3H), 1.99-1.25 (m, 6H), 0.90 (m, 3H), 0.80 (m, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 174.3, 90.9, 86.0, 68.5, 34.3, 33.7, 33.3, 32.5, 32.2, 31.9, 26.4, 26.1, 25.4, 22.7, 17.0, 16.7, 14.1; IR (neat) 2952, 2853, 1654, 1456, 1073, 1005; HRMS (EI) calcd for C$_{13}$H$_{25}$NO$_2$ 227.1885, found 227.1891.
To hexanoic acid (1-benzyl-5-hydroxy-(2S)-methylpentyl)methylamide (0.036 g, 0.113 mmol) in acetonitrile (5 mL) and tert-butylbenzene (1 mL) in a borosilicate flask at 23 °C were added N-methylquinolinium hexafluorophosphate (0.039 g, 0.136 mmol) and sodium bicarbonate (0.078 g, 0.929 mmol). The mixture was stirred for 3 h at 23 °C while irradiating. The reaction mixture was filtered, concentrated, and purified by flash chromatography (50% EtOAc in hexanes) to provide the desired product (0.011 g, 43%).

Hexanoic acid (1-benzyl-5-hydroxy-(2S)-methylpentyl)methylamide (0.064 g, 0.212 mmol) was subjected to catalytic aerobic ETIC reaction conditions. The reaction mixture was filtered, concentrated, and purified by flash chromatography (90% EtOAc in hexanes) to provide the desired product as separable mixture of diastereomers (0.032 g, 72%).

2-Dibenzylamino-1-phenylhex-5-en-3-ol (22)

To a solution of potassium carbonate (18.28 g, 132.2 mmol) and sodium hydroxide (5.281 g, 132.2 mmol) in water (100 mL) at 23 °C was added L-phenylalanine (10.00 g, 66.13 mmol). Benzyl bromide (33.92 g, 198.3 mmol) was added drop wise to the reaction mixture over a period of one hour while refluxing. The reaction mixture was refluxed for 1 h, cooled and the organic layer was separated, washed with saturated NaCl and dried (MgSO₄) and concentrated. The resulting residue was dissolved in ether (10 mL) and added drop wise to a suspension of LiAlH₄ (95% dispersion in mineral oil, 0.6822 g, 17.08 mmol) at 0°C under N₂ in ether (60 mL). The reaction mixture was stirred at 23 °C for 2 h, then quenched with water (1 mL), 15% NaOH (3mL), water (3 mL) and filtered. The filtrate was
washed with saturated NaCl, dried (MgSO₄), concentrated, and placed under vacuum at 40 °C for 16 h. The resulting residue was added to solution of DMSO (2.444 g, 31.31 mmol) and oxalyl chloride (2.0M solution in CH₂Cl₂, 7.826 ml, 15.65 mmol) at −78 °C in CH₂Cl₂. The reaction mixture was allowed to stir for 30 minutes before. The reaction mixture was stirred for 2 h at −78 °C, then quenched with triethyl amine (7.199 g, 71.15 mmol), warmed to 23 °C, quenched with water (2 mL), extracted in CH₂Cl₂, washed with water, saturated NaCl, dried (MgSO₄), and concentrated. The resulting residue was dissolved in ether (50 mL) and added to a solution of allyl magnesium bromide (1.0M in ether, 42.69 mL, 42.69 mmol) at −78 °C under N₂. The reaction mixture was stirred for 1.5 h, then quenched with saturated NH₄Cl, extracted with EtOAc, washed with water (2 × 15 mL), saturated NaCl, dried (MgSO₄) and concentrated. The resulting residue was purified by flash chromatography (5% EtOAc in hexanes). The mixture of diastereomers was separated during the purification process. 2-Dibenzylamino-1-phenylhex-5-en-(3S)-ol (22a): ¹H NMR (300 MHz, CDCl₃) δ 7.35-7.20 (m, 15H), 5.69 (m, 1H), 5.08 (m, 2H), 3.87 (m, 1H), 3.76 (m, 4H), 3.01 (m, 3H), 2.48 (m, 1H), 2.14 (m, 1H), 1.86 (bs, 1H); ¹³C NMR (75 MHz, CDCl₃) 141.1, 139.9, 135.4, 129.6, 128.6, 128.5, 127.1, 126.0, 118.2, 70.9, 63.2, 55.0, 40.0, 32.3. 2-Dibenzylamino-1-phenylhex-5-en-(3R)-ol (22b): ¹H NMR (300 MHz, CDCl₃) δ 7.34-7.22 (m, 5H), 5.77 (m, 1H) 4.96 (m, 2H), 4.36 (m, 1H), 3.97 (d, J = 13.2, 2H), 3.68 (dt, J = 5.3, 3.07 1H), 3.43 (d, J = 13.3, 2H), 3.15-2.73 (m, 3H), 2.23 (m, 1H), 1.94 (m, 1H).

**Dibenzyl-(1-benzyl-2-methoxypent-4-enyl)amine**

![Structure of Dibenzyl-(1-benzyl-2-methoxypent-4-enyl)amine](image)

To a suspension of NaH (60% dispersion in mineral oil, 0.251 g, 6.29 mmol) in DMF
(30 mL) at 0 °C was added 2-Dibenzylamino-1-phenylhex-5-en-3(3S)-ol (0.668 g, 1.79 mmol). The reaction mixture was stirred for 30 minutes then methyl iodide (1.27 g, 8.99 mmol) was added. The reaction mixture was quenched after 1.5 h with ice chips, extracted with hexanes, washed with saturated NaCl, dried (MgSO₄) and concentrated. The resulting residue was purified by flash chromatography (5% EtOAc in hexanes) to provide the desired product, dibenzyl-(1-benzyl-2S-methoxypent-4-enyl)amine (0.652 g, 94%): ¹H NMR (300 MHz, CDCl₃) δ 7.44-7.16 (m, 15H), 5.38 (m, 1H), 4.82 (m, 2H), 4.23 (d, J = 13.5, 2H), 3.58 (d, J = 13.6, 2H), 3.32 (s, 3H), 3.12-2.90 (m, 3H), 2.47 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 141.0, 140.8, 136.1, 129.4, 129.4, 128.5, 128.4, 128.3, 126.9, 125.9, 116.2, 82.6, 61.4, 58.4, 55.7, 35.5, 30.1; IR (neat) 3058, 3027, 2920, 2817, 1952, 1879, 1806, 1643, 1595, 1496, 1449, 1372, 1096, 903, 744, 701; HRMS (EI) cacld for 384.2327, found 384.2333. Dibenzyl-(1-benzyl-2R-methoxypent-4-enyl)amine: ¹H NMR (300 MHz, CDCl₃) δ 7.32-7.09 (m, 15H), 5.58 (m, 1H), 4.91 (m, 2H), 3.82 (d, J = 14.0, 2H), 3.54 (bd, J = 13.9, 3H), 3.37 (s, 3H), 2.97 (m, 3H), 2.41 (m, 1H), 2.20 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 140.3, 134.9, 129.8, 128.9, 128.1, 126.7, 125.8, 117.5, 80.7, 61.0, 57.0, 54.4, 36.4, 32.0.

**5S-Dibenzylamino-4-methoxy-6-phenylhexan-1-ol (23)**

To Dibenzyl-(1-benzyl-2S-methoxypent-4-enyl)amine (0.652 g, 1.69 mmol) in THF (20 mL) at 0 °C was added BH₃ (1.0 M in THF, 5.07 mL, 5.07 mmol). The reaction was allowed to stir for 1 h, then quenched at 0 °C with water (2 mL) followed by 20% aqueous NaOH (1 mL), 30% aqueous hydrogen peroxide solution (1 mL) and saturated Na₂SO₃ (2 mL). The reaction mixture was stirred for an addition hour, then was extracted with ethyl
acetate, washed with saturated NaCl, dried (MgSO₄) and concentrated. The resulting residue was purified by column chromatography (30% EtOAc in hexanes) to afford the desired product, 5S-Dibenzylamino-4S-methoxy-6-phenyl-hexan-1-ol (0.500 g, 73%): ¹H NMR (300 MHz, CDCl₃) δ 7.41-7.18 (m, 15H), 4.18 (d, J = 13.38, 2H), 3.55 (d, J = 13.34, 2H), 3.40 (m, 3H), 3.28 (s, 3H), 3.12 (m, 2H), 2.99 (m, 2H), 1.82 (m, 1H), 1.64 (m, 1H), 1.14 (m, 1H), 0.99 (m, 1H), 0.72 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 141.1, 129.5, 129.4, 128.5, 128.4, 126.9, 125.9, 82.3, 63.2, 60.5, 57.8, 55.7, 30.2, 29.0, 25.6; IR (neat) 3359, 3058, 3023, 2933, 2821, 1961, 1879, 1806, 1604, 1501, 1458, 1367, 1096, 744, 705; HRMS (EI) cacléd for 402.2433, found 402.2422.

5S-Dibenzylamino-4R-methoxy-6-phenylhexan-1-ol: ¹H NMR (300 MHz, CDCl₃) δ 7.34-7.20 (m, 15H), 3.81 (d, J = 13.9, 2H), 3.66 (d, J = 14.0, 2H), 3.53 (m, 3H), 3.36 (s, 3H), 3.05-2.90 (m, 3H), 1.70 (m, 1H), 1.56 (m, 3H), 1.32 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 141.6, 140.2, 129.6, 128.8, 128.1, 126.7, 125.7, 81.4, 62.9, 61.1, 56.9, 54.5, 32.2, 28.5, 27.4.

Hexanoic acid (1-benzyl-5-hydroxy-2-methoxypentyl)amide (24)

To 5S-dibenzyramino-4S-methoxy-6-phenyl-hexan-1-ol (0.553 g, 1.37 mmol) in CH₂Cl₂ at 0 ºC was added treithylamine (0.624 g, 6.17 mmol), pivaloyl chloride (0.331 g, 2.74 mmol), and DMAP (cat.). The reaction mixture was allowed to stir for 12 h, then was quenched with water, washed with saturated NaHCO₃, dried (MgSO₄) and concentrated. The resulting residue was dissolved in EtOH (20 mL) at 23 ºC under N₂ and palladium (10% on carbon, 0.400g) and 1,4 cyclohexadiene (0.328 g, 4.10 mmol) were added. The reaction mixture stirred at 40 ºC for 12 h, filtered over celite, washed with EtOH, and concentrated. The resulting residue was dissolved in THF (10 mL) and triethylamine (0.083 g, 0.820 mmol) and hexanoyl
chloride (0.055 g, 0.615 mmol) were added at 0 °C under N₂. The reaction mixture was stirred for 1.5 h, then quenched with water, washed with saturated NaCl (2 x 15 mL), dried (MgSO₄) and concentrated. The resulting residue was dissolved in MeOH (5 mL) and Na (small piece) was added at 0 °C under N₂. The reaction mixture was stirred at 40 °C for 12 h, the quenched with water, concentrated, redissolved in EtOAc (25 mL), washed with NaCl, dried (MgSO₄), and concentrated. The resulting residue was purified by flash chromatography (50% acetone in hexanes) to yield the desired product (0.088 g, 49%): ¹H NMR (300 MHz, CDCl₃) δ 7.31–7.21 (m, 5H), 5.73 (d, J = 9.26, 1H), 4.35 (m, 1H), 3.57 (m, 2H), 3.42 (s, 3H), 3.08 (t, J = 5.9, 1H), 2.87 (dd, J = 4.9, 2.2, 2H), 2.14 (m, 2H), 1.91 (bs, 1H), 1.58–1.18 (m, 10H), 0.87 (t, J = 7.1, 3H); ¹³C NMR (75 MHz, CDCl₃) 172.6, 138.3, 129.2, 128.5, 126.4, 80.2, 62.5, 57.8, 51.8, 38.4, 36.8, 31.3, 28.7, 26.2, 25.4, 22.4, 13.9; IR (neat) 3433, 3156, 2930, 2867, 1659, 1504, 1465, 1378, 1093, 906, 649.

Hexanoic acid (1-benzyl-5-hydroxy-2R-methoxypentyl)amide: ¹H NMR (300 MHz, CDCl₃) δ 7.32–7.19 (m, 5H), 5.57 (d, J = 8.9, 1H), 4.44 (m, 1H), 3.66 (m, 1H), 3.42 (s, 3H), 3.32 (m, 1H), 2.94 (dd, J = 5.0, 9.2, 1H), 2.80 (dd, J = 4.8, 9.4, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 173.0, 138.2, 129.2, 128.7, 126.6, 82.3, 62.7, 58.0, 51.5, 37.0, 35.4, 31.4, 28.7, 26.4, 25.5, 22.5, 14.1.

Hexanoic acid [1-benzyl-2-methoxy-5-(tetrahydropyran-2-yloxy)pentyl]amide (28)

To hexanoic acid (1-benzyl-5-hydroxy-2S-methoxypentyl)amide (0.087 g, 0.273 mmol) in CH₂Cl₂ at 0 °C was added dihydropyran (0.115 g, 1.36 mmol) and pyridinium p-toluene sulfonic acid (cat.). The reaction mixture was stirred for 12 h, then diluted with ether (15 mL), washed with saturated NaHCO₃, dried (MgSO₄) and concentrated. The resulting residue was purified by flash chromatography (50% EtOAc in
hexanes) to afford the desired product, hexanoic acid [1-benzyl-2S-methoxy-5-(tetrahydro-
pyran-2-yloxy)-pentyl]-amide (0.062 g, 56%): $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.32-7.18 (m, 5H),
5.78 (d, $J = 9.2$, 1H), 4.51 (m, 1H), 4.31 (m, 1H), 3.28 (m, 1H), 3.67 (m, 1H), 3.44 (m, 1H), 3.42
(s, 3H), 3.30 (m, 1H), 3.12 (m, 1H), 2.87 (m, 2H), 2.14 (t, $J = 2.1$, 2 H), 1.66-1.48 (m, 16H), 0.89
(t, $J = 6.8$, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 172.9, 138.6, 129.4, 128.6, 126.5, 98.9, 79.9, 67.4,
62.4, 58.2, 52.2, 38.6, 37.0, 31.5, 30.8, 27.2, 25.8, 25.7, 22.5, 19.8, 14.1; HRMS (EI) calcd for
C$_{19}$H$_{31}$NO$_3$ 321.2303, found 321.3214.

**Hexanoic acid (3-methoxytetrahydropyran-2-yl)amide (25)**

Hexanoic acid (1-benzyl-5-hydroxy-2S-methoxypentyl)amide (0.045 g, 0.139 mmol) was subjected to standard ETIC reaction conditions. The reaction mixture was filtered, concentrated, and purified by flash chromatography (50% acetone in hexanes) to provide the desired product as a separable mixture of diastereomers (0.001 g, 4%): **Hexanoic acid (3S-methoxytetrahydropyran-2R-yl)amide (25a)** $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.88 (bd, $J = 7.4$, 1H), 4.96 (dd, $J = 8.5$, 8.55, 1H), 3.88 (m, 1H), 3.55 (dt, $J = 2.7$, 8.8, 1H), 3.36 (s, 3H), 3.02 (m, 1H), 2.23 (t, $J = 7.4$, 2H), 1.69-1.26 (m, 10H), 0.88 (m, 3H);
$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 173.3, 82.9, 67.8, 37.1, 36.4, 32.1, 31.6, 29.9, 26.0, 25.4, 22.6,
17.4, 14.1; IR (neat) 3431, 2952, 2930, 2848, 1683, 1504, 1463, 1382, 1211, 1092, 1070, 1044,
907; HRMS (EI), (M-32) calcd for C$_{11}$H$_{19}$NO$_2$ 197.1415, found 197.1420. **Hexanoic acid (3S-
methoxytetrahydropyran-2S-yl)amide (25b)**: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 6.54 (d, $J = 7.9$,
1H), 5.19 (dd, $J = 1.5$, 7.8, 1H), 3.94 (m, 1H), 3.62 (dt, $J = 2.2$, 9.4, 2H), 3.40 (s, 3H), 3.28 (m,
1H), 2.21 (t, J = 7.8, 2H), 1.64-1.25 (m, 10H), 0.91 (t, J = 6.5, 3H); ¹³C NMR (CDCl₃) δ 173.2, 75.2, 66.8, 56.7, 36.9, 31.6, 29.9, 25.3, 25.0, 22.6, 19.9, 14.1.

The cyclization reaction was repeated using the various conditions shown in Table 1.6.

**Table 1.6: ETIC conditions with varying base and solvent**

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Base</th>
<th>Time</th>
<th>Yield</th>
<th>D.R</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCE</td>
<td>2, 6-dichloropyridine</td>
<td>5 h</td>
<td>21</td>
<td>100:0</td>
</tr>
<tr>
<td>MeCN</td>
<td>2,6-dichloropyridine</td>
<td>5 h</td>
<td>38</td>
<td>3:1</td>
</tr>
<tr>
<td>MeCN</td>
<td>NaHCO₃</td>
<td>5 h</td>
<td>5</td>
<td>100:0</td>
</tr>
</tbody>
</table>

The cyclization reaction was repeated with hexanoic acid [1-benzyl-2-methoxy-5-(tetrahydropyran-2-yloxy)pentyl]amide (28) using the various reaction conditions shown in Table 1.7.

**Table 1.7: ETIC conditions with variation in aromatic cosolvent**

<table>
<thead>
<tr>
<th>SOLVENT</th>
<th>BASE</th>
<th>COSENSITIZER</th>
<th>TIME</th>
<th>YIELD</th>
<th>D.R</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCE</td>
<td>NaOAc</td>
<td>tert-Butylbenzene</td>
<td>2.5</td>
<td>18</td>
<td>1:1</td>
</tr>
<tr>
<td>DCE</td>
<td>NaOAc</td>
<td>Benzene</td>
<td>1.5</td>
<td>25</td>
<td>2:1</td>
</tr>
</tbody>
</table>

Hexanoic acid [1-benzyl-2-methoxy-5-(tetrahydropyran-2-yloxy)pentyl]amide (28) (0.040 g, 0.0.098 mmol) was subjected to catalytic aerobic ETIC reaction conditions. The reaction mixture was filtered, concentrated and purified by flash chromatography (70% EtOAc in hexanes) to afford the desired product as a mixture of diastereomers, hexanoic acid (3-methoxytetrahydropyran-2-yl)amide (0.007 g, 30%), as well as 4-(tetrahydropyran-2-yloxy)butyric acid methyl ester (33) (0.0037 g, 0.0183 mmol) ¹H NMR (300 MHz, CDCl₃) δ 4.57 (t, J = 2.7, 1H), 3.83-
3.72 (m, 2H), 3.67 (s, 3H), 3.51-3.39 (m, 2H), 2.42 (dt, J = 1.5, 7.5), 1.94 (m, 2H), 1.81-1.49 (m, 6H); $^{13}$C NMR (CDCl$_3$) $\delta$ 174.1, 129.6, 129.1, 128.5, 127.8, 98.8, 66.4, 62.2, 51.6, 44.5, 37.5, 31.3, 31.1, 30.7, 25.5, 25.2, 23.9, 22.5, 19.5, 14.0; IR 2990, 1794, 1651, 1469, 1382, 1097, 913; HRMS (EI) (M - 84) calcd for 117.0551, found 117.0553.

The cyclization reaction was repeated using the various conditions shown in Table 1.8.

**Table 1.8: Catalytic aerobic ETIC conditions**

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Base</th>
<th>Cosensitizer</th>
<th>Time</th>
<th>Yield</th>
<th>D.R</th>
</tr>
</thead>
<tbody>
<tr>
<td>*DCE</td>
<td>NaOAc</td>
<td>Benzene</td>
<td>3</td>
<td>6</td>
<td>100:0</td>
</tr>
<tr>
<td>DCE</td>
<td>2,6-dichloropyridine</td>
<td>Toluene</td>
<td>2</td>
<td>33</td>
<td>2.5:1</td>
</tr>
</tbody>
</table>

* Molecular sieves were added to the reaction mixture

(1-Benzyl-2-methoxypent-4-enyl)carbamic acid tert-butyl ester (30a)

![Structure of 30a]

To a suspension of lithium aluminum hydride (1.31 g, 36.3 mmol) refluxing in THF under N$_2$ L-phenylalanine (3.00 g, 18.1 mmol) was added in small portions. The reaction mixture was stirred for 12 h, then cooled to 0 ºC and quenched with water (1 mL), NaOH, 15%, 1.5 mL), water (5 mL), and di-tert-butyl-dicarbonate (in 20 mL of CH$_2$Cl$_2$, 3.95 g, 18.2 mmol) was added. The reaction was stirred at 60 ºC for 12 h, cooled and filtered through a pad of Na$_2$SO$_4$. The resulting residue was added to a solution of oxalyl chloride (2.0 M in CH$_2$Cl$_2$, 6.97 mL, 13.9 mmol) and DMSO (1.23 g, 15.9 mmol) in CH$_2$Cl$_2$ at -78 ºC under N$_2$. The reaction mixture was stirred for 1 h, then quenched with triethylamine (4.02 g, 39.8 mmol), warmed to room temperature, quenched with water, extracted with CH$_2$Cl$_2$, washed with saturated NaCl, dried (MgSO$_4$) and concentrated. The resulting residue was dissolved in THF
(30 mL) and vinyl magnesium bromide (1.0 M in THF, 23.8 mL, 23.8 mmol) was added at 0 ºC under N₂. The reaction was stirred for 12 h, then quenched with saturated NH₄Cl, acidified to pH 4.0, extracted with EtOAc, dried (Na₂SO₄) and concentrated. The resulting residue was added to a suspension of sodium hydride (60% dispersion in mineral oil, 0.065 g, 1.61 mmol) in DMF (10 mL) at 0 ºC under N₂. The reaction mixture was stirred for 30 minutes, and then methyl iodide (1.14 g, 8.06 mmol) was added. The reaction mixture was stirred for 3 h, then quenched with water, washed with saturated NaCl, dried (Na₂SO₄) and concentrated. The resulting residue was purified by flash chromatography (10% EtOAc in hexanes) to afford the desired product as a separable mixture of diastereomers (0.237 g, 54%).: ¹H NMR (300 MHz, CDCl₃) δ 7.26-7.20 (m, 5H), 5.66 (m, 1H), 5.30 (m, 2H), 4.89 (d J = 9.6, 1H), 3.93 (m, 1H), 3.36 (s, 3H), 3.07 (m, 1H), 2.82 (m, 2H), 2.33 (m, 1H), 2.14 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 155.4, 138.4, 133.9, 129.1, 128.2, 126.0, 117.5, 79.5, 78.7, 57.6, 53.3, 38.7, 34.7, 28.2; IR (neat) 3440, 3341, 3062, 2980, 2924, 1698, 1496, 1440, 1363, 1238, 1169, 1096.

(1-Benzyl-5-hydroxy-2-methoxypentyl)carbamic acid tert-butyl ester

To (1-benzyl-2-methoxypent-4-enyl)carbamic acid tert-butyl ester (0.437 g, 1.43 mmol) in THF (10 mL) at 0 ºC was added BH₃ (1.0 M in THF, 4.30 mL, 4.30 mmol). The reaction was allowed to stir for 1 h, then quenched at 0 ºC with water (2 mL) followed by 20% aqueous NaOH (1 mL), 30% aqueous hydrogen peroxide solution (1 mL) and saturated Na₂SO₃ (2 mL). The reaction mixture was stirred for an addition hour, then was extracted with ethyl acetate, washed with saturated NaCl (2x 10 mL), dried (MgSO₄) and concentrated. The resulting residue was purified by column chromatography (30% EtOAc in
hexanes) to afford the desired product (0.302 g, 65%): $^1$H NMR (300 MHz, CDCl$_3$) δ 7.33-7.15 (m, 5H), 4.83 (d, $J$ = 9.5, 1H), 3.93 (m, 1H), 3.57 (m, 2H), 3.55 (s, 3H), 3.02 (m, 1H), 2.80 (m, 2H), 1.79 (bs, 1H), 1.62-1.44 (m, 4H), 1.36 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 138.7, 129.4, 128.6, 126.4, 80.4, 79.4, 62.7, 57.9, 53.6, 38.8, 28.9, 28.5, 26.2; IR (neat) 3445, 3346, 2978, 2930, 2871, 1695, 1497, 1366, 1172, 1069; HRMS (EI) calcd for C$_{18}$H$_{30}$NO$_4$ 324.2174, found 324.2177.

[1-Benzyl-2-methoxy-5-(tetrahydropyran-2-yloxy)pentyl]carbamic acid tert-butyl ester (31)

To (1-benzyl-5-hydroxy-2-methoxypentyl)carbamic acid tert-butyl ester (0.200 g, 0.618 mmol) in CH$_2$Cl$_2$ at 0 °C was added dihydropyran (0.078 g, 0.927 mmol) and pyridinium p-toluene sulfonic acid (0.199 g, 0.742 mmol). The reaction mixture was stirred for 12 h, then diluted with ether (15 mL), washed with saturated NaHCO$_3$, dried (MgSO$_4$) and concentrated. The resulting residue was purified by flash chromatography (20% EtOAc in hexanes) to afford the desired product, [1-benzyl-2-methoxy-5-(tetrahydropyran-2-yloxy)-pentyl]carbamic acid tert-butyl ester, (0.228 g, 91%): $^1$H NMR (300 MHz, CDCl$_3$) δ 155.8, 139.2, 138.8, 129.4, 129.2, 129.1, 128.5, 128.4, 128.3, 126.3, 126.1, 99.0, 83.2, 82.4, 80.1, 79.3, 67.6, 67.4, 62.4, 58.5, 58.1, 53.8, 38.8, 35.4, 35.1, 30.8, 28.5, 27.0, 25.8, 25.7, 19.7.
(3-Methoxytetrahydropyran-2-yl)carbamic acid tert-butyl ester (32a,b)

\[ \text{[1-Benzyl-2-methoxy-5-(tetrahydropyran-2-yloxy)pentyl]carbamic acid tert-butyl ester} \]

0.055 g, 0.135 mmol) was subjected to standard ETIC reaction conditions. The reaction mixture was filtered, concentrated, and purified by flash chromatography (30% acetone in hexanes) to provide the desired product as a separable mixture of diastereomers (0.011 g, 53%): (3S-Methoxytetrahydropyran-2S-yl)carbamic acid tert-butyl ester (32a): \( ^1H \text{NMR} \ (300 \text{ MHz, CDCl}_3) \delta 5.70 \text{ (bs, 1H), 4.90 (bd, } J = 9.4, 1H), 3.93 \text{ (m, 1H), 3.53 (dt, } J = 2.3, 9.48, 1H), 3.38 \text{ (s, 3H), 3.31 (m, 1H), 2.11 (m, 1H), 1.80-1.25 (m, 12H); } ^{13}C \text{NMR} \ (75 \text{ MHz, CDCl}_3) \delta 155.3, 79.8, 75.5, 66.2, 56.7, 28.4, 25.5, 20.3; \text{ IR (neat) 3443, 3338, 2930, 1719, 1490, 1367, 1064, 984, 878 cm}^{-1} \). (3S-Methoxytetrahydropyran-2R-yl)carbamic acid tert-butyl ester (32b): \( ^1H \text{NMR} \ (300 \text{ MHz, CDCl}_3) \delta 5.11 \text{ (bs, 1H), 4.66 (t, } J = 8.4, 1H), 3.88 \text{ (m, 1H), 3.50 (dt, } J = 2.2, 9.2, 1H), 3.38 \text{ (s, 3H), 2.98 (m, 1H), 2.22 (m, 1H), 1.68-1.44 (m, 12H); } ^{13}C \text{NMR} \ (75 \text{ MHz, CDCl}_3) \delta 155.3, 83.0, 80.4, 66.5, 56.7, 29.9, 28.5, 24.8. \)

[1-Benzyl-2-methoxy-5-(tetrahydropyran-2-yloxy)pentyl]carbamic acid tert-butyl ester (31) (0.055 g, 0.135 mmol) was subjected to catalytic aerobic ETIC reaction conditions. The reaction mixture was filtered, concentrated and purified by flash chromatography (30% EtOAc in hexanes) to provide the desired product as a separable mixture of diastereomers.
5R- Allyl-4S-benzyl-2,2-dimethyloxazolidine-3-carboxylic acid tert-butyl ester (40)

To (1-benzyl-2R-hydroxypent-4-enyl)carbamic acid tert-butyl ester (1.25 g, 4.29 mmol) in toluene (15 mL) at 23 ºC was added 2,2-dimethoxypropane (5.36 g, 51.5 mmol) and pyridinium p-toluene sulfonic acid (cat.). The reaction mixture was stirred at 80 ºC for 3 h, then concentrated and purified by flash chromatography (5% EtOAc in hexanes) to afford the desired product (0.454 g, 32%): 1H NMR (300 MHz, CDCl3) δ 7.28-7.19 (m, 5H), 5.55 (M, 1H), 4.93 (m, 2H), 3.95 (m, 2H), 3.85 (m,1H), 3.24 (dd, J = 2.6, 10.5, 1H), 2.85 (m, 1H), 2.11 (m, 2H), 1.62-1.25 (m, 8H); 13C NMR (75 MHz, CDCl3) δ 152.5, 137.9, 133.9, 130.0, 129.6, 128.5, 126.6, 117.7, 94.8, 93.9, 80.2, 79.0, 62.8, 40.0, 39.6, 38.9, 37.7, 28.7, 27.8, 27.2; IR (neat), 3066, 2976, 2929, 1703, 1376, 1260, 1083, 916, 705 cm⁻¹; HRMS (EI) calcd for C17H24NO3 290.1756, found 290.1754.

4S-Benzyl-5R-(3-hydroxypropyl)-2,2-dimethyloxazolidine-3-carboxylic acid tert-butyl ester

To 5R-allyl-4S-benzyl-2,2-dimethyloxazolidine-3-carboxylic acid tert-butyl ester (0.432 g, 1.30 mmol) in THF (10 mL) at 0 ºC was added BH₃ (1.0 M in THF, 3.91 mL, 3.91 mmol). The reaction was allowed to stir for 1 h, then quenched at 0 ºC with water (2 mL) followed by 20% aqueous NaOH (1 mL), 30% aqueous hydrogen peroxide solution (1 mL) and saturated Na₂SO₃ (2 mL). The reaction mixture was stirred for an additional hour, then was extracted with ethyl acetate, washed with saturated NaCl (2x 10 mL), dried (MgSO₄) and concentrated. The resulting residue was purified by column chromatography (20% EtOAc in hexanes) to afford the desired product (0.325 g, 71%): 1H NMR (300 MHz, CDCl₃) δ 7.33-7.22
(m, 5H), 3.94 (m, 1H), 3.82 (m, 1H), 3.53 (m, 2H), 3.27 (dd, J = 2.5, 10.5, 1H), 2.83 (m, 1H), 1.78-1.29 (m, 19H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 152.5, 137.7, 129.8, 129.4, 128.5, 126.6, 80.0, 79.3, 78.3, 63.7, 63.3, 62.5, 39.8, 37.4, 31.7, 31.0, 28.9, 28.5, 27.5, 26.9; IR (neat) 3457, 3065, 1683, 1493, 1477, 1457, 1457, 1398, 1176, 1085, 728 cm$^{-1}$; HRMS (EI) calcd for C$_{20}$H$_{32}$NO$_4$ 350.2331, found 350.2336.

4-Benzyl-2,2-dimethyl-5-[3-(tetrahydropyran-2-yloxy)propyl]oxazolidine-3-carboxylic acid tert-butyl ester (41)

To (4S-Benzyl-5R-(3-hydroxypropyl)-2,2-dimethyloxazolidine-3-carboxylic acid tert-butyl ester (0.296 g, 0.845 mmol) in CH$_2$Cl$_2$ (15 mL) at 0 °C was added dihydropyran (0.106 g, 1.26 mmol) and pyridinium p-toluenesulfonic acid (cat.). The reaction mixture was stirred for 3 h, then concentrated. The resulting residue was purified by flash chromatography (5% EtOAc in hexanes) to afford the desired product (0.2329 g, 90%): $^1$H NMR (300 MHz, CDCl$_3$) δ 7.29-7.23 (m, 5H), 4.52 (m, 1H), 3.82 (m, 1H), 3.63 (m, 1H), 3.50 (m, 1H), 3.25 (m, 1H), 2.86 (m, 1H), 1.72-1.30 (m, 25H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 152.5, 138.1, 129.8, 129.4, 128.6, 128.4, 126.6, 98.7, 79.9, 66.9, 63.7, 62.3, 39.9, 30.7, 28.6, 27.3, 25.7, 25.5, 19.6; IR (neat) 3025, 2938, 2863, 1691, 1453, 1390, 1255, 1176, 1116, 1077, 1029, 910, 732 cm$^{-1}$; HRMS (EI) calcd for C$_{25}$H$_{40}$NO$_5$ 434.2906, found 434.2896.
This procedure was repeated with a mixture of (4S-Benzyl-5R-(3-hydroxypropyl)2,2-dimethyloxazolidine-3-carboxylic acid tert-butyl ester and (4S-Benzyl-5S-(3-hydroxypropyl)-2,2-dimethyloxazolidine-3-carboxylic acid tert-butyl ester (0.216 g, 61%). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.25-7.18 (m, 5H), 4.50 (m, 1H), 4.25 (m, 1H), 4.15 (m, 1H), 4.04 (m, 1H), 3.91 (m, 1H), 3.78 (m, 1H), 3.60 (m, 1H), 3.46 (m, 1H), 3.24 (m, 1H), 1.73-1.34 (m, 25H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 152.1, 151.8, 139.3, 138.0, 129.5, 129.4, 129.2, 128.5, 128.4, 128.3, 126.2, 126.0, 125.47, 98.8, 98.7, 92.8, 92.2, 80.0, 79.6, 77.5, 77.4, 67.1, 67.0, 62.3, 62.2, 62.1, 60.9, 60.7, 36.6, 36.0, 30.8, 30.79, 28.7, 28.5, 28.4, 28.1, 27.8, 27.6, 27.3, 26.8, 26.7, 26.4, 26.3, 25.8, 25.6, 25.0, 23.8, 21.6, 19.6, 19.5.

2,2-Dimethyl-tetrahydropyran[2,3-d]oxazole-3-carboxylic acid tert-butyl ester (42)

4S-Benzyl-2,2-dimethyl-5R-[3-(tetrahydropyran-2-yloxy)propyl]oxazolidine-3-carboxylic acid tert-butyl ester (0.100 g, 0.230 mmol) was subjected to catalytic aerobic ETIC reaction conditions. The reaction mixture was filtered, concentrated and purified by flash chromatography (10% EtOAc in hexanes) to provide the desired product as a single diastereomer (0.503 g, 85%). $^1$H NMR (300 MHz, CDCl$_3$, 323K) δ 5.15 (bs, 1H), 3.97 (m, 1H), 3.88 (m, 2H), 3.43 (dt, $J = 2.8$, 8.5, 2H), 2.13-2.08 (m, 2H), 1.95-1.38 (m, 17H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 151.9, 128.4, 100.2, 93.9, 83.2, 77.4, 71.2, 63.7, 31.5, 28.4, 24.8, 22.5, 19.7, 13.9; IR (neat) 2974, 2934, 2871, 1706, 1457, 1394, 1263, 1180, 1081, 1017 cm$^{-1}$; HRMS (EI) calcd for C$_{12}$H$_{20}$NO$_4$ 242.1392, found 242.1402.
This procedure was repeated with the mixture of 4S-Benzyl-2,2-dimethyl-5R-[3-(tetrahydropyran-2-yloxy)propyl]oxazolidine-3-carboxylic acid tert-butyl ester and 4S-Benzyl-2,2-dimethyl-5S-[3-(tetrahydropyran-2-yloxy)propyl]oxazolidine-3-carboxylic acid tert-butyl ester and the addition of 200 weight percent of Na₂S₂O₃ to yield a mixture of enantiomers of 2,2-dimethyl-tetrahydro-pyrano[2,3-d]oxazole-3-carboxylic acid tert-butyl ester (0.042 g, 88%).

4S-Benzyl-5S-[3-(tetrahydro-pyran-2-yloxy)propyl]oxazolidin-2-one (39)

To trifluoroacetic acid (10 mL) at 0 °C was added (1-benzyl-2S-hydroxypent-4-enyl)-carbamic acid tert-butyl ester (0.410 g, 1.40 mmol). The reaction mixture was stirred for 15 minutes, and then concentrated. The resulting residue was redissolved in CH₂Cl₂, washed with saturated NaHCO₃, dried (Na₂SO₄) and concentrated. The resulting residue was dissolved in THF (10 mL) and carbonyl diimidazole (0.342 g, 2.11 mmol) and DMAP (cat.) were added. The reaction mixture was stirred for 12 h, quenched with water, extracted with EtOAc, washed with saturated NaCl (2 x 15 ml), dried (Na₂SO₄) and concentrated. The resulting residue was dissolved in THF (10 mL) and BH₃ (1.0 M in THF, 3.91 mL, 3.91 mmol) was added at 0 °C under N₂. The reaction was allowed to stir for 1 h, then quenched at 0 °C with water (2 mL) followed by 20% aqueous NaOH (1 mL), 30% aqueous hydrogen peroxide solution (1 mL) and saturated Na₂SO₃ (2 mL). The reaction mixture was stirred for an addition hour, then was extracted with ethyl acetate, washed with saturated NaCl, dried (MgSO₄) and concentrated. The resulting residue was dissolved in CH₂Cl₂ (10 mL) and dihydropyran (0.0.091 g, 1.08mmol) and pyridinium p-toluene sulfonic acid (0.165 g, 0.869 mmol) were added at 0 °C under N₂. The reaction mixture was stirred for 3 h, then concentrated, redissolved in CH₂Cl₂, washed with saturated NaHCO₃, dried (MgSO₄) and concentrated. The
resulting residue was purified by flash chromatography (40% EtOAc in hexanes) to yield the desired product (0.058 g, 25%): $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.35-7.17 (m, 5H), 5.12 (bs, 1H), 4.72 (m, 1H), 4.59 (m, 1H), 4.00 (m, 1H), 3.87 (m, 2H), 3.48 (m, 2H), 2.93 (dd, $J = 3.4, 9.4, 1$H), 2.69 (dd, $J = 11.3, 13.0, 1$H), 1.95-1.27 (m, 11H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 158.7, 136.7, 129.1, 127.2, 99.2, 79.8, 66.8, 62.6, 56.9, 36.3, 26.3, 25.5, 19.8; IR (neat) 3281, 2972, 2864, 1754, 1445, 1384, 1126, 1070, 1023, 984, 731, 696 cm$^{-1}$.

To 4S-Benzyl-5S-[3-(tetrahydropyran-2-yloxy)propyl]oxazolidin-2-one (0.058 g, 0.182 mmol) in dichloroethane (5 mL) and toluene (1 mL) in a borosilicate flask at 20 ºC were added $N$-methylquinolinium hexafluorophosphate (0.003 g, 0.012 mmol) and sodium acetate (0.116 g, 1.41 mmol). The mixture was stirred at room temperature while bubbling air gently and irradiating for 12 hours. The reaction mixture was filtered, concentrated. No desired cyclization product was obtained, and the starting material (0.019g, 33%) was re-isolated by flash chromatography (40% EtOAc in hexanes).

**N-(1S-Benzyl-2R-methoxypent-4-enyl)-2,2,2-trifluoroacetamide (36)**

To trifluoroacetic acid (10 mL) at 0 ºC was added (1-benzyl-2R-methoxypent-4-enyl)-carbamic acid tert-butyl ester (0.158 g, 519 mmol). The reaction mixture was stirred for 15 minutes, and then concentrated. The resulting residue was redissolved in CH$_2$Cl$_2$, washed with saturated NaHCO$_3$, dried (Na$_2$SO$_4$) and concentrated. The resulting residue was dissolved in CH$_2$Cl$_2$ (10 mL) and trifluoroacetic anhydride (0.250 g, 1.19 mmol) and pyridine (0.129 g, 1.63 mmol) were added at 0 ºC under N$_2$. The reaction mixture was stirred for 3 h and
then concentrated. The resulting residue was purified by flash chromatography (30% EtOAc in hexanes) to yield the desired product (0.071 g, 45%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.28-7.15 (m, 5H), 6.38 (d, $J = 6.45$, 1H), 5.82 (m, 1H), 5.19 (m, 1H), 4.35 (m, 1H), 3.43 (s, 4H), 3.04 (dd, $J = 4.5$, 9.8, 1H), 2.73 (dd, $J = 3.9$, 10.0, 1H), 2.53 (m, 1H), 2.30 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 156.8, 137.2, 133.5, 129.2, 128.7, 127.0, 118.4, 81.3, 58.0, 53.3, 34.8, 34.5; IR (neat) 3303, 3062, 3027, 2933, 1686, 1445, 1195, 1096, 916, 756, 701 cm$^{-1}$; HRMS (EI) calcd for C$_{15}$H$_{18}$NO$_2$F$_3$ 301.1289, found 301.1277.

N-(1S-Benzyl-5-hydroxy-2R-methoxypentyl)-2,2,2-trifluoroacetamide (37)

To N-(1-Benzyl-2R-methoxy-pent-4-enyl)-2,2,2-trifluoroacetamide (0.071 g, .237 mmol) in THF (10 mL) was added BH$_3$ (1.0 M in THF, 3.91 mL, 3.91 mmol) at 0 °C under N$_2$. The reaction was allowed to stir for 2 h, then quenched at 0 °C with water (2 mL) followed by 20% aqueous NaOH (1 mL), 30% aqueous hydrogen peroxide solution (1 mL) and saturated Na$_2$SO$_3$ (2 mL). The reaction mixture was stirred for an addition hour, then was extracted with ethyl acetate, washed with saturated NaCl, dried (MgSO$_4$) and concentrated. The resulting residue was purified by flash chromatography (50% EtOAc in hexanes) to yield the desired product (0.049 g, 65%) $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.29-7.15 (m, 5H), 6.63 (d, $J = 8.4$, 1H), 4.37 (m, 1H), 3.64 (m, 2H), 3.41 (s, 3H), 3.33 (m, 1H), 2.97 (dd, $J = 4.9$, 9.2, 1H), 2.79 (dd, $J = 4.8$, 9.5, 1H), 2.04 (bs, 1H), 1.69 (m, 4H), $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 156.9, 137.2, 129.2, 128.7, 126.9, 121.6, 117.8, 81.9, 65.1, 60.7, 53.0, 35.3, 29.8, 28.2, 26.1, 21.1, 18.9, 14.2; IR (neat) 3307, 3092, 2937, 1707, 1561, 1453, 1372, 1182, 1083, 873, 744, 705 cm$^{-1}$; HRMS (EI) (M-18) calcd for C$_{15}$H$_{18}$NO$_2$F$_3$ 301.1289, found 301.1283.
To N-(1-benzyl-5-hydroxy-2R-methoxypentyl)-2,2,2-trifluoroacetamide (0.045 g, 0.140 mmol) in dichloroethane (5 mL) and toluene (1 mL) in a borosilicate flask at 20 °C were added N-methylquinolinium hexafluorophosphate (0.001 g, 0.003 mmol), sodium acetate (0.090 g, 1.09 mmol), and sodium thiosulfate (0.090 g, 0.569 mmol). The mixture was stirred at room temperature while bubbling air gently and irradiating for 3.5 h. The reaction mixture was filtered, concentrated. No desired cyclization product was obtained, and the starting material (0.035 g, 80%) was re-isolated by flash chromatography (50% EtOAc in hexanes).

4-Nitro-N-(5-octyloxy-6-phenylhexyl)benzenesulfonamide (49)

To 5-Octyloxy-6-phenylhexan-1-ol (0.200 g, 0.652 mmol) in CH₂Cl₂ (35 ml) at 0 °C were added methanesulfonyl chloride (0.111 g, 0.978 mmol) and triethyl amine (0.264 g, 2.61 mmol). The reaction mixture was stirred for 3 hrs. at room temperature then was quenched with water. The reaction mixture was extracted in CH₂Cl₂, and then the organic layer was washed with water and saturated NaCl, dried (Na₂SO₄) and concentrated. The resulting residue was dissolved in DMF (10 mL) at 23 °C under N₂ and sodium azide (0.051 g, 0.783 mmol) was added. The reaction mixture was stirred at 55 °C for 12 h then was quenched with water, extracted into hexanes, washed with saturated NaCl, dried (Na₂SO₄), and concentrated. The resulting residue was then dissolved in THF (15 mL) at 23 °C under N₂ and triphenylphosphine (0.132 g, 0.503 mmol) was added. The reaction mixture was allowed to stir for 18 h then was quenched with water (0.5 mL). The reaction mixture was then allowed to stir for an additional 8 h and concentrated. The resulting residue was dissolved in CH₂Cl₂ (10 mL) and at 0 °C triethylamine (0.132 g, 1.30 mmol) and 4-nitrobenzylsulfonyl
chloride (0.108 g, 0.491 mmol) were added. The reaction mixture was stirred at 23 °C for 12 h, then quenched with water (2 mL), washed with saturated NaCl, dried (MgSO₄) and concentrated. The resulting residue was purified by flash chromatography (20% EtOAc in hexanes) to yield the desired product (0.055 g, 34%): ¹H NMR (300 MHz, CDCl₃) δ 8.35 (d, J = 8.68, 2H), 8.04 (d, J = 8.61, 2H), 7.29-7.13 (m, 5H), 4.98 (t, J = 5.88, 1H), 3.36 (m, 4H), 2.98 (m, 2H), 2.84 (dd, J = 5.9, 7.7, 1H), 2.63 (dd, J = 6.5, 7.0, 1H), 1.48-1.13 (m, 18H), 0.87 (t, J = 6.87, 3H); ¹³C NMR δ 150.1, 146.1, 138.9, 129.5, 128.4, 126.2, 124.5, 80.7, 69.8, 43.3, 42.3, 40.7, 33.3, 31.9, 30.2, 29.7, 29.5, 29.4, 26.3, 22.8, 22.6, 14.2; IR (neat) 3208, 3092, 3023, 2924, 2855, 1600, 1522, 1458, 1333, 1088, 855, 739, 705 cm⁻¹; HRMS (CI), (M+1 = 491).

1-(4-Nitrobenzenesulfonyl)-2-octyloxypiperidine (49a)

4-Nitro-N-(5-octyloxy-6-phenylhexyl)benzenesulfonamide (0.055 g, 0.113 mmol) was subjected to catalytic aerobic ETIC reaction conditions. The reaction mixture was filtered, concentrated. The resulting residue was purified by flash chromatography (10% EtOAc in hexanes) to yield the desired product (0.031 g, 68%): ¹H NMR (300 MHz, CDCl₃) δ 8.35 (d, J = 8.8, 2H), 8.04 (d, J = 8.9, 2H), 5.22 (m, 1H), 3.61 (dd, J = 2.9, 10.0, 1H), 3.36 (m, 2H), 3.07 (t, J = 2.7, 10.1, 1H), 1.89 (m, 1H), 1.62-1.23 (m, 18H), 0.88, (t, J = 7.0, 3H); ¹³C NMR (75 MHz, CDCl₃) 130.1, 124.2, 84.6, 67.9, 63.2, 41.5, 33.1, 29.9, 29.6, 29.5, 26.4, 24.8, 22.7, 21.2, 18.1, 14.3, 14.1; IR (neat) 3561, 3101, 2924, 2855, 1604, 1535, 1466, 1350, 1165, 1105, 937, 847, 744; HRMS (EI) calcd for C₁₉H₂₉N₂O₅S 398.1875, found 398.1868.
To 4-Octyloxy-5-phenylpentan-1-ol (0.200 g, 0.652 mmol) in CH$_2$Cl$_2$ (10 mL) at 0 ºC were added methanesulfonyl chloride (0.112 g, 0.978 mmol) and triethylamine (0.264 g, 2.61 mmol). The reaction mixture was stirred for 3 h at room temperature then was quenched with water. The reaction mixture was extracted with CH$_2$Cl$_2$, and then the organic layer was washed with water and saturated NaCl, dried (Na$_2$SO$_4$) and concentrated. The resulting residue was dissolved in DMF (10 ml) at 23 ºC under N$_2$ and sodium azide (0.051 g, 0.784 mmol) was added. The reaction mixture was stirred for 18 h at 0 ºC, then was quenched with water, and extracted into hexanes. The organic layer was washed with saturated NaCl, dried (Na$_2$SO$_4$), and concentrated. The resulting residue was purified by column chromatography (10% EtOAc in hexanes) to yield the desired product (0.189 g, 87%): 1H NMR (300 MHz, CDCl$_3$) $\delta$ 7.32-7.18 (m, 5H), 3.42 (m, 3H), 3.26 (t, $J$ = 6.6, 2H), 2.88 (dd, $J$ = 6.1, 7.49, 1H), 2.70 (dd, $J$ = 6.4, 7.1, 1H), 1.62-1.27 (m, 16H), 0.90 (t, $J$ = 6.9, 3H); 13C NMR (75 MHz, CDCl$_3$) $\delta$ 139.3, 129.7, 128.4, 126.2, 80.8, 69.9, 51.6, 41.0, 33.8, 32.0, 30.4, 29.6, 29.5, 29.1, 26.4, 23.0, 22.9, 14.3.

To (5-Azido-2-octyloxy-pentyl)benzene (0.050 g, 0.151 mmol) in dichloroethane (5 mL) and toluene (1 mL) in a borosilicate flask at 20 ºC were added N- methylquinolininium hexafluorophosphate (0.001 g, 0.003 mmol), sodium acetate (0.100 g, 1.22 mmol), and sodium thiosulfate (0.100 g, 0.595 mmol). The mixture was stirred at room temperature while bubbling air gently and irradiating for 3 h. The reaction mixture was filtered, concentrated. No desired cyclization product was obtained, and the starting material was re-isolated by flash chromatography (10% EtOAc in hexanes).
N-(4-Octyloxy-5-phenylpentyl)acetamide (48)

To (5-azido-2-octyloxypentyl)benzene (0.818 g, 2.47 mmol) in THF (15 mL) at 23 ºC was triphenylphosphine (1.73 g, 6.59 mmol). The reaction mixture was allowed to stir for 18 h then was quenched with water (2 mL). The reaction mixture was then allowed to stir for an additional 18 h, and concentrated. The resulting residue was dissolved in CH$_2$Cl$_2$ (10 mL) and triethylamine (0.134 g, 1.31 mmol) and acetic anhydride (0.037 g, 0.360 mmol) were added at 0 ºC under N$_2$. The reaction mixture was stirred for 1.5 h, and then quenched with water, extracted into CH$_2$Cl$_2$, washed with saturated NaCl, dried (Na$_2$SO$_4$) and concentrated. The resulting residue was purified by flash chromatography (50% EtOAc in hexanes) to yield the desired product (0.75 g, 69%): $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.26-7.16 m, 5H), 5.84 (bs, 1H), 3.38 (m, 3H), 3.20 (m, 2H), 2.82 (dd, $J = 6.1, 7.49$, 1H), 2.68 (dd, $J = 6.4, 7.14$, 1H), 1.93 (s, 3H), 1.46-1.25 (m, 18H), 0.88 (t, $J = 6.78$, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 170.2, 139.1, 129.5, 128.2, 126.1, 80.8, 69.7, 40.8, 39.7, 33.7, 31.9, 30.2, 29.6, 29.5, 29.3, 26.3, 23.3, 23.0, 22.7, 14.2; IR (neat) 3286, 3083, 2929, 2855, 1651, 1552, 1449, 1363, 1290, 1101; HRMS (EI) calcd for C$_{22}$H$_{38}$NO$_2$ 348.2902, found 348.2900.

To N-(4-octyloxy-5-phenylpentyl)acetamide (0.075 g, 0.216 mmol) in dichloroethane (5 mL) and toluene (1 mL) in a borosilicate flask at 20 ºC were added N-methylquinolinium hexafluorophosphate (0.001 g, 0.003 mmol), sodium acetate (0.150 g, 1.83 mmol), and sodium thiosulfate (0.150 g, 0.893 mmol). The mixture was stirred at room temperature while bubbling air gently and irradiating for 19 h. The reaction mixture was filtered, concentrated. No desired cyclization product was obtained, and the starting material (0.015 g, 20%) was re-isolated by flash chromatography (50% EtOAc in hexanes).
(4-Octyloxy-5-phenylpentyl)carbamic acid ethyl ester (46)

To (5-azido-2-octyloxypentyl)benzene (0.539 g, 1.63 mmol) in THF (15 mL) at 23 °C was added triphenylphosphine (0.513 g, 1.95 mmol). The reaction mixture was allowed to stir for 18 h then was quenched with water (2 mL). The reaction mixture was then allowed to stir for an additional 18 h, and concentrated. The resulting residue was dissolved in acetone (10 mL) and potassium carbonate (0.676 g, 4.89 mmol) and ethyl chloroformate (0.353 g, 0.326 mmol) were added under N₂. The reaction mixture was refluxed for 1.5 h, filtered to remove the solid potassium carbonate, and concentrated. The resulting residue was purified by flash chromatography (20% EtOAc in hexanes) to yield the desired product (0.172 g, 56%): 

**¹H NMR (300 MHz, CDCl₃)** δ 7.33-7.25 (m, 5H), 4.76 (bs, 1H), 4.19 (q, J = 7.04, 2H), 3.46 (m, 3H), 3.22 (m, 2H), 2.93 (dd, J = 6.1, 7.45, 1H), 2.76 (dd, J = 6.3, 7.3, 1H), 1.54-1.28 (m, 18H), 0.96 (t, J = 6.9, 3H); 
**¹³C NMR (75 MHz, CDCl₃)** δ 139.3, 129.7, 129.6, 128.4, 128.3, 126.1, 80.8, 69.8, 60.8, 40.9, 33.8, 32.0, 30.3, 29.6, 29.4, 26.4, 22.8, 14.8, 14.3; 
**IR (neat)** 3337, 3027, 2916, 2955, 1698, 1531, 1449, 1376, 1341, 1247, 1096, 774, 744; 
**HRMS (EI)** calcd for C₂₃H₄₀NO₃ 378.3008, found 378.3009.

To (4-octyloxy-5-phenylpentyl)carbamic acid ethyl ester (0.080 g, 0.212 mmol) in dichloroethane (5 mL) and toluene (1 mL) in a borosilicate flask at 20 °C were added N-methylquinolinium hexafluorophosphate (0.002 g, 0.005 mmol), sodium acetate (0.160 g, 1.95 mmol), and sodium thiosulfate (0.160 g, 0.952 mmol). The mixture was stirred at room temperature while bubbling air gently and irradiating for 5 h. The reaction mixture was filtered, concentrated. No desired cyclization product was obtained, but one major product was obtained.
from the reaction mixture: $^1$H NMR (300 MHz, CDCl$_3$, 343 K), 6.74 (dt, $J = 1.9$, 6.7, 1H), 5.34 (bs, 1H), 4.90 (m, 1H), 4.08 (m, 3H), 3.81 (m, 1H), 3.52 (m, 2H), 3.40 (t, $J = 6.4$, 2H), 3.31 (t, $J = 6.41$, 2H), 3.06 (bs, 4H), 2.89 (dt, $J = 2.9$, 9.9, 1H), 2.50 (bs, 1H), 1.99 (m, 2H), 1.80-1.17 (m, 2H), 0.87 (t, $J = 6.93$, 3H); IR (neat) 3488, 2924, 2855, 1707, 1651, 1415, 1372, 1337, 1264, 1234, 1174, 1118, 1092, 1049, 989 cm$^{-1}$ HRMS (EI) calcd for C$_{16}$H$_{32}$NO$_3$ 286.2382, found 286.2371; HRMS (FAB) calcd for C$_{16}$H$_{31}$NO$_3$ 285.2303, found 285.2301.

(4-Octyloxy-5-phenylpentyl)carbamic acid tert-butyl ester (47)

To (5-azido-2-octyloxypentyl)benzene (0.139 g, 419 mmol) in THF (10 mL) at 23 ºC was added triphenyl phosphine (0.132 g, 0.503 mmol). The reaction mixture was allowed to stir for 18 h then was quenched with water (2 mL). The reaction mixture was then allowed to stir for an additional 18 h, and concentrated. The resulting residue was dissolved in a solution of dioxane (5 mL) and water (5mL) and triethylamine (0.0636 g, 0.629 mmol) and di-tert-butyldicarbonate (0.101 g, 0.462 mmol) were added at 0 ºC. The reaction mixture was stirred for 2 h, and then concentrated. The resulting residue was redissolved in EtOAc and washed with water and saturated NaCl, dried (Na$_2$SO$_4$) and concentrated. The resulting residue was purified by flash chromatography (30% EtOAc in hexanes) to yield the desired product (0.137 g, 81%): $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.30-7.18 (m, 5H), 4.51 (bs, 1H), 3.37(m, 3H), 3.10 (m, 2H), 2.85 (dd, $J = 6.1$, 7.5, 1H), 2.69 (dd, $J = 6.3$, 7.3, 1H), 1.53-1.26, (m, 27H), 0.88 (t, $J = 6.9$, 3H); $^{13}$C NMR (75MHz, CDCl$_3$) $\delta$ 156.1, 139.3, 129.6, 128.3, 126.1, 80.9, 69.8, 40.9, 33.9, 32.0, 30.3, 29.6, 29.4, 28.6, 27.6, 26.4, 22.9, 14.3; IR (neat) 3357, 2930, 2856, 1719, 1515, 1456, 1367, 1252, 1172, 1092, 872, 743, 702 cm$^{-1}$. 
To (4-octyloxy-5-phenylpentyl)carbamic acid tert-butyl ester (0.050 g, 0.123 mmol) in dichloroethane (5 mL) and toluene (1 mL) in a borosilicate flask at 20 °C were added N-methylquinolinium hexafluorophosphate (0.001 g, 0.003 mmol), sodium acetate (0.100 g, 1.22 mmol), and sodium thiosulfate (0.100 g, 0.595 mmol). The mixture was stirred at room temperature while bubbling air gently and irradiating for 2 h. The reaction mixture was filtered, and then concentrated. No desired cyclization product was obtained, and small quantities of several unidentifiable side products were isolated.

To (4-octyloxy-5-phenylpentyl)carbamic acid tert-butyl ester (0.050 g, 0.123 mmol) in dichloroethane (5 mL) and toluene (1 mL) in a borosilicate flask at 20 °C were added N-methylquinolinium hexafluorophosphate (0.001 g, 0.003 mmol), methanol (0.003 g, 0.123 mmol), sodium acetate (0.100 g, 1.22 mmol), and sodium thiosulfate (0.100 g, 0.595 mmol). The mixture was stirred at room temperature while bubbling air gently and irradiating for 3 h. The reaction mixture was filtered, and then concentrated. No desired cyclization product was obtained, starting material (0.010 g, 20%), and small quantities of several unidentifiable side products were isolated, along with (4-Methoxy-4-octyloxy-butyl)-carbamic acid tert-butyl ester. 

\[ \text{H NMR (300 MHz, CDCl}_3\text{) } \delta 4.57 (bs, 1H), 4.39 (t, J = 5.6, 1H), 3.51-3.38 (m, 6H), 3.28 (s, 3H), 1.41-1.15 (m, 25H), 0.85 (m, 3H). \]

**Hexanoic acid [1-benzyl-5-(4-nitrobenzenesulfonylamino)pentyl]amide (50)**

Dry EtOAc (2 mL) was added to a reaction flask containing Pd/C (0.25 g) fitted with an H₂ balloon. The system was evacuated, then purged
with \( \text{H}_2 \) five times to ensure a \( \text{H}_2 \) atmosphere, and the reaction mixture was then stirred for 1h. (5-Azido-2-octyloxy-pentyl)benzene (0.11 g, 0.34 mmol, in 2 mL EtOAc) was added and the pump/purge with \( \text{H}_2 \) technique was repeated five times. The reaction mixture was stirred for 1.5h, then filtered over Celite. The Celite was washed with EtOAc (100 mL) and the filtrate was concentrated. The resulting residue was dissolved in \( \text{CH}_2\text{Cl}_2 \) (10 mL) and the temperature was decreased to 0 °C before triethylamine (0.13 g, 1.37 mmol) and 4-nitrobenzenesulfonyl chloride (0.11 g, 0.51 mmol) were added. The reaction mixture was stirred for 18h, then quenched with \( \text{H}_2\text{O} \). The two layers were separated, and the organic layer was washed with saturated NaCl (2 x 10 mL), dried (MgSO\(_4\)) and concentrated. The resulting residue was purified by flash chromatography to afford the desired product (0.09 g, 61%). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 8.46 (d, \( J = 7.2 \) Hz, 2H), 8.17 (d, \( J = 7.3 \) Hz, 2H), 7.37 (m, 5H), 6.11 (t, \( J = 5.7 \) Hz, 1H), 5.60 (d, \( J = 8.9 \) Hz, 1H), 4.30 (m, 1H), 3.07 (dd, \( J = 5.8, 12.0 \) Hz, 2H), 2.87 (t, \( J = 6.2 \) Hz, 2H), 2.22 (add, \( J = 3.1, 7.2, 11.1 \) Hz, 2H), 1.67-1.26 (m, 12H), 0.97 (t, \( J = 7.3 \) Hz, 3H); 173.61, 149.97, 146.32, 137.90, 129.36, 128.58, 128.39, 126.67, 124.42, 49.50, 43.02, 41.33, 37, 01, 33.89, 31.43, 28.84, 25.59, 22.62, 22.49, 22.31, 17.00, 14.07; IR (neat) 3378, 3287, 2930, 2859, 1643, 1524, 1350, 1156, 1093, 847, 740 cm\(^{-1}\); HRMS (EI) calcd for (M+H) \( \text{C}_{24}\text{H}_{34}\text{N}_{3}\text{O}_{5}\text{S} \) 476.221918, found 476.218065.

**Hexanoic acid [1-(4-nitro-benzenesulfonyl)-piperidin-2-yl]-amide (51)**

To 4-nitro-N-(5-octyloxy-6-phenyl-hexyl)benzenesulfonamide (10) (0.040 g, 0.084 mmol) in dichloroethane (5 mL) and toluene (1 mL) in a borosilicate flask at 20 °C were added \( N \)- methylquinolinium hexafluorophosphate (0.002 g, 0.007 mmol), sodium acetate (0.100 g, 1.21 mmol), and sodium thiosulfate (0.100 g, 0.632 mmol). The mixture
was stirred at room temperature while bubbling air gently and irradiating for 5 h, then filtered, and concentrated. The resulting residue was purified by flash chromatography to yield the desired product 11 (0.021 g, 64%): $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.30 (d, $J$ = 8.9, 2H), 8.04 (d, $J$ = 8.9, 2H), 6.10 (m, 1H), 5.90 (m, 1H), 3.80 (m, 1H), 2.91 (dt, $J$ = 8.3, $J$ = 3.2), 1.79 (m, 4H), 1.22 (m, 10H), 0.84 (t, $J$ = 6.8); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 172.0, 150.0, 146.0, 128.8, 124.5, 58.4, 42.0, 36.6, 31.4, 31.1, 25.2, 22.4, 18.8, 14.0; IR (neat) 3313, 2939, 2861, 1650, 1527, 1354, 1147, 1097, 924, 740 cm$^{-1}$; HRMS (El) calcd for C$_{17}$H$_{26}$N$_3$O$_5$S 384.1593, found 384.1583.

Methyl N-(diphenylmethylene)glycinate (52)

To a stirring solution of benzophenone immine (1.21 g, 6.66 mmol) in CH$_2$Cl$_2$ (20 mL) was added glycine methyl ester hydrochloride (0.83 g, 6.66 mmol). The reaction mixture was stirred at room temperature for 18 h, then filtered to remove NH$_4^+$Cl and concentrated. The resulting residue was purified by flash chromatography (30% EtOAc in hexanes) to afford the desired product (1.43 g, 85%): $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.68-7.18 (m, 10H), 4.23 (s, 2H), 3.75 (s, 3H).

3-(Trifluoromethyl)phenylalanine (53)

To a suspension of sodium hydride (60% dispersion in mineral oil, 0.15 g, 3.95 mmol) in DMF (10 mL) at 0 ºC was added methyl N-(diphenylmethylene)glycinate (52) (1.00 g, 3.95 mmol, in 5 mL DMF). The reaction mixture was stirred for 15 min. before 3-(trifluoromethyl)benzyl chloride (0.61 g, 3.95 mmol) was added. The reaction mixture was stirred for 2 h at room temperature, then was quenched with ice chips. The reaction mixture was extracted into ether, washed with saturated NaCl, dried (MgSO$_4$) and
concentrated. The resulting residue was purified by flash chromatography (5% EtOAc in hexanes). The resulting residue was dissolved in 6N HCl (5 mL) and heated to reflux for 6.5h. The reaction mixture was then cooled to 0 ºC and stirred for 1h. The reaction mixture was filtered and the hydrochloride salt was washed with cold acetone. The hydrochloride salt was dissolved in MeOH (10 mL) and the temperature was decreased to 0 ºC. The pH was increased to 9 by dropwise addition of 15% NaOH and the reaction mixture was stirred for 15 min. The reaction mixture was concentrated and the resulting residue was redissolved in EtOAc (5 mL) and washed with saturated NaCl (5 mL). The organic layer was dried (MgSO₄) and concentrated to afford the desired product (0.84 g, 92%): ¹H NMR (300 MHz, D₂O) δ 7.51 (m, 2H), 7.41 (m, 2H), 3.94 (ddd, J = 1.9, 5.6, 7.6 Hz, 1H), 3.22 (dd, J = 5.4, 14.6 Hz, 1H), 3.08 (dd, J = 7.8, 14.6 Hz, 1H).

5-(3-Hydroxypropyl)-2,2-dimethyl-4-(3-trifluoromethylbenzyl)oxazolidine-3-carboxylic acid tert-butyl ester (54)

To a suspension of lithium aluminum hydride (0.27 g, 7.24 mmol) refluxing in THF (25 mL) was added 3-(trifluoromethyl)phenylalanine (0.84 g, 3.62 mmol) was added in small portions. The reaction mixture was stirred for 18 h, then cooled to 0 ºC and quenched with 15% NaOH (1.5 mL) and water (5 mL). Di-tert-butyl-dicarbonate (0.95 g, 4.34 mmol, in 5 mL CH₂Cl₂) was added. The reaction was stirred at 60 ºC for 6 h, cooled and filtered through a pad of Na₂SO₄ and concentrated. The resulting residue was added dropwise to a solution of oxalyl chloride (0.73 g, 5.76 mmol) and DMSO (0.51 g, 6.59 mmol) in CH₂Cl₂ (30 mL) at -78 ºC. The reaction mixture was stirred for 1 h, then quenched with triethylamine (1.66 g, 16.4 mmol), warmed to room temperature and quenched with water (5
mL). The two layers were separated and the organic layer was washed with saturated NaCl (15 mL), dried (MgSO₄) and concentrated. The resulting residue was dissolved in THF (10 mL) and the temperature was decreased to 0 °C. Allyl magnesium bromide (1.0 M in THF, 9.85 mL, 9.85 mmol) was added and the reaction mixture was stirred at room temperature for 2 h, then quenched with saturated NH₄Cl and extracted into EtOAc. The organic layer was dried (MgSO₄) and concentrated. The resulting residue was purified by flash chromatography (5% EtOAc in hexanes). To a solution of the resulting residue in toluene (10 mL) was added PPTS (0.02 g) and dimethoxypropane (4.06 g, 39.54 mmol). The reaction mixture was heated to reflux for 3 h, then cooled to room temperature, concentrated and purified by flash chromatography (5% EtOAc in hexanes). To a stirring solution of the resulting residue was dissolved in THF (5 mL) and the temperature was decreased to 0 °C. BH₃ (1.0 M in THF, 5.07 mL, 5.07 mmol). The reaction was allowed to stir for 1 h, then quenched at 0 °C with a solution of basic hydrogen peroxide [(2 mL) 20% aqueous NaOH (1 mL), 30% aqueous hydrogen peroxide (1 mL)] and saturated Na₂SO₃ (2 mL). and saturated Na₂SO₃ (2 mL). The reaction mixture was stirred for an addition hour, then was extracted with ethyl acetate, washed with saturated NaCl, dried (MgSO₄) and concentrated. The resulting residue was purified by flash chromatography (50% EtOAc in hexanes) to afford the desired product (0.03 g, 2%).: ¹H NMR (300 MHz, CH₃Cl) δ 7.49 (m, 4H), 4.26 (dd, J = 6.3, 11.4 Hz, 1H), 4.10 (m, 1H), 3.83 (bs, 1H), 3.56 (m, 2H), 3.14 (m, 1H), 2.88 (m, 1H), 1.53 (m, 13H), 1.40 (s, 3H), 1.29 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 140.27, 140.39, 133.54, 133.20, 132.97, 130.74, 129.09, 128.85, 126.80, 126.23, 123.60, 123.8193.35, 92.72, 80.61, 80.38, 80.0163.64, 63.02, 62.52, 60.85, 60.67, 36.85, 36.52, 35.86, 31.01, 29.99, 29.07, 28.65, 28.47, 28.18, 27.85, 27.62, 27.00, 26.33, 25.09, 23.89; IR (neat) 3447, 2978, 2933, 2866, 1678, 1399,
1326, 1170, 1125, 1069; HRMS (EI) calcd for C_{21}H_{31}NO_{4}F_{3} (M+H) 418.220519, found 418.219120.

To 5-(3-hydroxypropyl)-2,2-dimethyl-4-(3-trifluoromethylbenzyl)oxazolidine-3-carboxylic acid tert-butyl ester (54) (0.030 g, 0.0718 mmol) in dichloroethane (2.5 mL) and toluene (0.5 mL) in a borosilicate flask at 20 ºC were added N- methylquinolinium hexafluorophosphate (0.002 g, 0.007 mmol), sodium acetate (0.060 g, 0.714 mmol), and sodium thiosulfate (0.060 g, 0.379 mmol). The mixture was stirred at room temperature while bubbling air gently and irradiating for 2.5 h, then filtered, and concentrated. The reaction mixture was purified by flash chromatography (45% EtOAc in hexanes) to provide the desired product 42 as a single diastereomer (0.010 g, 56%).

[5-Hydroxy-1-(3-trifluoromethyl-benzyl)pentyl]carbamic acid tert-butyl ester (55)

To a suspension of lithium aluminum hydride (0.21 g, 5.44 mmol) refluxing in THF (25 mL) was added 3-(trifluoromethyl)phenylalanine (0.63 g, 2.27 mmol) was added in small portions. The reaction mixture was stirred for 18 h, then cooled to 0 ºC and quenched with 15% NaOH (1.5 mL) and water (5 mL). Di-tert-butyl-dicarbonate (0.59 g, 2.72 mmol, in 5 mL CH_{2}Cl_{2}) was added. The reaction was stirred at 60 ºC for 6 h, cooled and filtered through a pad of Na_{2}SO_{4} and concentrated. To a solution of the resulting residue in CH_{2}Cl_{2} (5 mL) at 0 ºC was added Dess-Martin periodinane (0.15 g, 0.35 mmol). The reaction mixture was stirred at room temperature for 1h, then quenched slowly with saturated NaHCO_{3} (1.5 mL). The two layers were separated and the organic layer was washed with saturated NaCl (5 mL), dried (MgSO_{4}) and concentrated. To a solution of the resulting
residue in THF (5 mL) at 0 ºC was added allylmagnesium bromide (1.0 M in THF, 0.35 mL, 0.35 mmol). The reaction mixture was stirred at 0 ºC for 30 min, then quenched with saturated NH₄Cl (1.5 mL) and warmed to room temperature. The reaction mixture was extracted into EtOAc (10 mL), washed with saturated NaCl (5 mL), dried (MgSO₄) and concentrated. The resulting residue (in 1 mL DMF) was added to a suspension of sodium hydride (60% dispersion in mineral oil, 0.02 g, 0.38 mmol) in DMF (5 mL) at 0 ºC. The reaction mixture was stirred for 30 min. before methyl iodide (0.05 g, 0.33 mmol) was added. The reaction mixture was stirred for 3 h, then quenched with ice chips and extracted into Et₂O. The organic layer was washed with saturated NaCl (5 mL), dried (MgSO₄) and concentrated. To a solution of the resulting residue in THF (5 mL) at 0 ºC was added BH₃ (1.0 M in THF, 0.49 mL, 0.49 mmol). The reaction was allowed to stir for 1 h, then quenched at 0 ºC with a solution of basic hydrogen peroxide [(2 mL) 20% aqueous NaOH (1 mL), 30% aqueous hydrogen peroxide (1 mL)] and saturated Na₂SO₃ (2 mL). The reaction mixture was stirred for an additional hour, then was extracted with ethyl acetate, washed with saturated NaCl, dried (MgSO₄) and concentrated. The resulting residue was purified by flash chromatography (60% EtOAc in hexanes) to afford the desired product (0.04 g, 2%): ¹H NMR (300 MHz, CH₃Cl) δ 7.42 (M, 4H), 3.66 (m, 2H), 3.51 (m, 1H), 3.45 (s, 3H), 3.25 (m, 1H), 2.73 (m, 2H), 2.54 (bs, 1H), 1.76-1.67 (m, 4 H), 1.34 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 155.95, 140.28, 132.49, 128.81, 125.75, 123.17, 122.46, 83.00, 82.68, 82.02, 79.75, 63.06, 62.71, 58.39, 58.18, 58.07, 35.11, 34.90, 34.09, 29.79, 28.75, 28.25, 28.15, 27.49, 27.15, 26.61, 26.39, 24.12 IR (neat) 3369, 2978, 2933, 1806, 1739, 1711, 1505, 1326, 1159, 1120; HRMS (EI) calcd for C₁₆H₂₁NO₃F₃ (M–C₃H₇O) 332.147354, found 332.147026.
1.6. References


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2. The aqueous Prins reaction

2.1. Introduction

I. Introduction

The Prins reaction, first discovered in 1899, is the condensation of an alkene and formaldehyde in the presence of an acid at an elevated temperature to afford either an allylic alcohol, a 1,3-diol, or a 1,3-dioxane (Figure 2.1). The product composition is dependent on the specific alkene as well as the reaction conditions. The reaction appears to proceed partly by an electrophilic addition of a protonated aldehyde to an alkene, and partly through an ene reaction when the reaction is initiated thermally in the absence of a catalyst. Despite numerous investigations into the mechanism and extensive postulation, it is generally accepted that the complex product mixtures that arise are a result of general acid catalysis, but are not consistent with a mechanism of simple carbenium ion formation.
The initial electrophilic addition of the protonated aldehyde to the olefin is generally considered to proceed in a stepwise manner leading to the formation of carbenium ion 1. This carbenium ion can then react further with any of the species present in the reaction mixture to form the allylic alcohol 2, 1,3-diol 3, or the 1,3-dioxane 4. Each of these products may in turn react further increasing the complexity of the product composition.

One method of controlling the product distribution of the Prins reaction is through controlling the formation of the cationic intermediates. Incorporating a silyl group into the nucleophilic component of the reaction either in the allylic (5) or vinyl (8) position encourages the formation of cationic intermediates 6 and 9, (Figure 2.2). These cations, unlike cation 1, are thermodynamically stabilized by hyperconjugation of the adjacent carbon-silicon bond, and kinetically unstable with respect to loss of the silicon group. Therefore, homoallylic alcohols (7) are formed specifically.
Figure 2.2: Generally accepted Prins mechanism involving allyl and vinylsilanes

Unlike Prins reactions of alkenes, reactions incorporating allylsilanes are often catalyzed with Lewis acids rather than protic acids. Protic acids can induce protodesilylation in competition with carbon-carbon bond formation, whereas Lewis acids are less likely to attack the carbon-carbon double bond. The existence of cationic intermediate 6 has not yet been proved for this type of reaction. However, circumstantial evidence is provided through the observed formation of oxepins without loss of the silyl group.47

Allylsilanes are thermally stable with respect to allylic shift of the silyl group. Consequently, regioisomeric allylsilanes react in a reliable manner with the electrophile always bonding to the terminus of the allyl unit remote from the silyl group, to afford regiospecific products, as shown in Figure 2.3. Under Lewis acidic conditions, carbon-carbon bond formation occurs exclusively at the γ-carbon of the allylsilane, with clean allylic transposition leading to the formation of homoallylic alcohols.48
Acetals and ketals serve as exceptional electrophiles for Prins reactions. When these intermediate oxocarbenium ions are tethered to alkenes, intramolecular additions occur to generate cyclic oxocarbenium ions from which a variety of products can arise depending on the method of termination. This variant of the Prins reaction, cyclic acetal ionization under strongly acidic conditions and intramolecular electrophilic addition of a pendent alkene, provides a powerful method for access into cyclic ethers through carbon-carbon bond construction.

Early examples of intermolecular Prins reactions of mixed acetals to form tetrahydrofurans\(^49\) are known. Overman has greatly expanded the scope of the reaction and has successfully used intramolecular pinacol-terminated Prins cyclization reactions as the key strategic element in the total synthesis of a variety of natural products.\(^50\) Through the ionization of cyclic acetals, intramolecular Prins cyclization, and termination via pinacol rearrangement, as shown in Figure 2.4, Overman has accessed highly functionalized acyltetrahydrofuran derivatives.

**Figure 2.4: Pinacol-terminated Prins cyclization**

![Pinacol-terminated Prins cyclization](image)

Tetrahydropyran\(^s\) (THP) are critical substructural motifs in a variety of biologically significant natural products, and a number of methods for the formation of these oxacycles have been developed based on the basic Prins reaction. Rychnovsky used intramolecular Prins cyclizations of saturated acetals followed by subsequent trapping with oxygen nucleophiles as an entry into oxygenated tetrahydropyrans\(^51\) (Figure 2.5).
Many have realized the utility and enhanced reactivity of allylsilanes as intramolecular traps for oxocarbenium ions generated in various ways and have exploited this reactivity. Marko has done extensive studies in this area, and developed an efficient tetrahydropyran synthesis that combines the Noyori\textsuperscript{52} method for generation of oxocarbenium ions with intramolecular silyl modified Sakurai (ISMS) reaction (Eq. 1, Figure 2.6). Marko has also coined the term “IMSC” (intramolecular Sakurai cyclization) in reference to the cyclization of hydroxy allylsilanes in sequences leading to pyrans via an “ene” type reaction\textsuperscript{53} (Eq. 2, Figure 2.6).

Recently, Keck reported a facile enantioselective synthesis of 2,6-cis-disubstituted-4-methylenetetrahydropyran systems through a two-step process\textsuperscript{54} (Figure 2.7). The first step is asymmetric allylation of an aldehyde in the presence of a BINOL titanium isopropoxide catalyst to generate the enantiopure hydroxy allylsilane. The second step, TMSOTf–promoted annulation of the silane with a second aldehyde, affords the 2,6-cis-tetrahydropyran containing an exo-methylene in the 4 position.
In a similar approach, Rychnovsky has also reported a Mukaiyama aldol-Prins (MAP) cyclization reaction effectively utilizing allylsilanes in the synthesis of tetrahydropyrans\textsuperscript{55} (Figure 2.8). The cascade reaction involves the Mukaiyama aldol condensation of an aldehyde and an alkyl enol ether to generate an intermediate oxocarbenium ion. The oxocarbenium ion is then trapped with an allylsilane in an intramolecular Prins cyclization. This method was applied in a formal total synthesis of leucascandrolide A, and has since expanded to include condensation with ketones followed by intramolecular Prins cyclization\textsuperscript{56}.

**Figure 2.8: MAP cyclization reaction**

It is known that the substitution of a carbon for a charged heteroatom in [3,3]-sigmatropic rearrangements leads to significant rate increases. Typical examples of these types of reactions are the anionic oxy-Cope rearrangement and the 2-azonia-Cope rearrangement, shown in Figure 2.9. The oxygen analog of the 2-azonia-Cope rearrangement is the oxonia-Cope rearrangement,
which has been invoked as a competitive pathway in Prins cyclizations and related transformations.\textsuperscript{57} This competitive cationic [3,3]-sigmatropic rearrangement leads to undesired stereochemical outcomes and side chain scrambling in Prins reactions.

**Figure 2.9:** Heteroatom substituted [3,3]-sigmatropic rearrangements

In his studies of Lewis acid-induced $\pi$-cyclization reactions of a variety of $\alpha$-methoxy oxocarbenium ions, Speckamp found that the oxonia-Cope rearrangement played an important role in the formation of 5- and 6-membered cyclic ethers. The influence of the [3,3]-sigmatropic rearrangement on the regio- and stereochemical outcome of the cyclization reaction was examined through the influence of side chain substituents, the type of $\pi$-nucleophile (allyl- or vinylsilane) and the cyclization of enantio-pure substrates. The controlling factors in whether or not rearrangement would occur were found to be the nature of the $\pi$-nucleophile, with vinylsilanes more apt to rearrange to form the allylsilane, and the substitution pattern of the oxocarbenium ion intermediate, with rearrangement occurring to form the more stable sigmatropisomer. Retention of stereochemical integrity was observed in the cyclization of enantiopure substrates. However, oxonia-Cope cyclization was observed in Prins cyclization reactions of vinylsilanes.
In the course of studies on the synthesis of 2,6-disubstituted dihydropyrans, Roush found the oxonia-Cope rearrangement to be a competitive reaction pathway in intramolecular Prins cyclization reactions of allylsilanes.\(^{58}\) The goal of the study was the development of a novel method for the synthesis of 2,6-\textit{trans}-disubstituted dihydropyrans through the reaction of a $\beta$-hydroxyallylsilane with an aldehyde in the presence of a Lewis acid to generate an intermediate oxocarbenium ion that would subsequently undergo intramolecular Prins cyclization (Figure 2.10). The strong stereoelectronic preference of silyl substituents to adopt an axial orientation in reactions that develop cationic character in the $\beta$-position was expected to be the origin of the \textit{trans} selectivity.

**Figure 2.10:** Origin of 2,6-\textit{trans}-dihydropyran selectivity

In initial studies to optimize reaction conditions, the isolated products, surprisingly, consisted of 2,6-\textit{cis}-disubstituted dihydropyrans rather than the targeted \textit{trans} diastereomer. Attempts to extend the method to include a variety of $\beta$-hydroxyallylsilane-aldehyde combinations and achieve the desired \textit{trans} selectivity led only to complex reaction mixtures with side chain exchange (Figure 2.11).

**Figure 2.11:** 2,6-\textit{cis}-substituted dihydropyrans with side chain exchange
The unexpected exchange of allylsilane side chains and the preferential 2,6-cis-disubstituted dihydropyran formation was explained through the facile oxonia-Cope rearrangement prior to intramolecular Prins cyclization, as shown in Figure 2.12. The reaction was initially predicted to proceed through oxocarbenium ion intermediate 12, which could cyclize via a chair transition state to give the desired product, 13. However, oxonia-Cope rearrangement occurs at a faster rate than intramolecular Prins cyclization to give oxocarbenium ion intermediate 14, placing the alkyl substituent in the thermodynamically unfavorable axial position. Intermediate 14 can then isomerize through a reversible nucleophilic addition to give 15, which is structurally equivalent to intermediates proposed by Speckamp in observed oxonia-Cope rearrangements of vinylsilanes in attempted intramolecular Prins cyclizations. Intermediate 15 can cyclize directly to form the 2,6-cis-disubstituted dihydropyran, 17. The intermediacy of 14 and 15 also account for the observed side chain scrambling, where the addition of TMSOH creates the opportunity for release of one aldehyde equivalent and recombination with another.
Rychnovsky demonstrated recently that oxonia-Cope rearrangements are faster than intramolecular Prins cyclization reactions when simple alkenes are employed as nucleophiles. The oxonia-Cope rearrangement was first observed when an unexpected epimerization product was isolated from an intramolecular Prins cyclization (Figure 2.13). The α-acetoxy ether was cyclized in the presence of SnBr₄ to produce the desired product and its C₃ epimer. The intermediate oxocarbenium ion could cyclize directly to afford the desired product, or undergo oxonia-Cope rearrangement via a chair transition state and then cyclize to give the desired product. However, oxonia-Cope rearrangement of oxocarbenium ion through a boat transition state, ring flip and subsequent cyclization through a chair transition state explains the formation of the undesired C₃ epimer.
Due to the unexpected boat transition state invoked in the oxonia-Cope rearrangement, Rychnovský sought further evidence of the intermediacy of 25 in the formation of the undesired epimer by treatment of the starting material with TMSOTf. The reaction produced the $E$ and $Z$ alkenes 26 and 27 (Figure 2.14), both of which presumably arise from the hydrolysis of oxocarbenium ion intermediates 24 and 25. Thus, it was concluded that the oxonia-Cope rearrangement plays an important role in the Prins cyclization of simple alkenes, providing unexpected outcomes.

**Figure 2.13:** Proposed mechanistic pathway for epimerization

**Figure 2.14:** Test of proposed oxonia-Cope boat transition state
III. Substrate Design

Tetrahydropyrans serve as the core of numerous marine natural products and are key structural features in a variety of polyether antibiotics and pheromones. They also are the structural core of the majority of carbohydrates, which are the most abundant biological molecules on earth. Numerous methods exist for the synthesis of highly functionalized tetrahydropyrans, such as hetero Diels-Alder reactions, oxiranyl anions, carbonyl ylides, Claisen rearrangements, ring opening of epoxides, iodolactonization, and ring closing metathesis. During the course of the present work towards the total synthesis of (+)-dactylolide the development of a new method for the construction 2,6-cis-disubstituted-4-methylenetetrahydropyrans became of interest.

As shown through the work of Overman and Rychnovsky, the ionization of cyclic acetals followed by intramolecular Prins cyclization provides a powerful entry into 2,4,6-trisubstituted tetrahydropyrans through carbon-carbon bond construction. The incorporation of allylsilanes in intramolecular Prins reactions has led to the formation of 2,6-cis-disubstituted-4-methylenetetrahydropyrans. Based on the combination of these two results, the design of substrates that will efficiently and stereoselectively undergo intramolecular Prins cyclization at ambient temperature with mild Lewis acids that will tolerate other acid sensitive functional groups contained within the molecule should be possible.
The general cyclization substrate consists of a cyclic α,β-unsaturated acetal with a pendent allylsilane (Figure 2.15). Given that Prins cyclization is initiated through ionization, it was postulated that this step could be facilitated through the use of cyclic α,β-unsaturated acetals. The use of cyclic acetals allows for the convergent condensation of highly functionalized aldehydes and 1,3-diols, alleviating the need for lengthy synthetic sequences and numerous protecting group manipulations. Employment of an α,β-unsaturated acetal provides a relatively stable conjugated oxocarbenium ion upon ionization. This is expected to thermodynamically disfavor the oxonia-Cope rearrangement which is often a competitive reaction pathway in Prins cyclizations and has been known to lead to stereorandomization and sidechain scrambling. Substrates are also designed with a pendent electron rich olefin in the form of an allylsilane, which is expected to expedite the cyclization step. Finally, as the objective is to develop a method applicable to advanced synthetic intermediates, cyclization reactions involving secondary ethers were examined to determine if the reaction is in any way inhibited, or oxacene formation becomes a competitive reaction pathway.
2.2. Results and Discussion

An intramolecular Prins cyclization reaction was first observed in the Floreancig labs in the course of efforts towards the total synthesis of (+)-dactylolide. Construction of the core of the molecule, a 2,6-cis-disubstituted-4-methylenetetrahydropyran, was envisioned to occur through an electron transfer initiated cyclization (ETIC) reaction.\textsuperscript{62} However, during the synthesis of a model substrate for the ETIC reaction, the intramolecular Prins cyclization provided an undesired, although serendipitous result.

The reaction attempted was the addition of trimethylsilyl propyne into acetal 28 in the presence of titanium tetrachloride, as shown in Figure 2.16. The desired product, propargyl ether 29, was not detected; rather, the only isolable product was a single diastereomer at the 2 and 6 positions of tetrahydropyran 30. Tetrahydropyran 30 was postulated to arise from the intramolecular Prins cyclization with the pendent vinyl bromide upon ionization of the acetal and termination by trapping with chloride. Because of the interest in the generation of 2,6-cis-disubstituted-4-methylenetetrahydropyrans, utilizing pendent allylsilanes in the development of a novel method for intramolecular Prins cyclization reactions of cyclic acetals to provide these moieties became the primary focus.

**Figure 2.16:** Initially observed intramolecular Prins cyclization
Synthesis of the test substrate, cyclic acetal 34 containing a pendent allylsilane, began with 1,3-propane diol (Scheme 2.1). Monoprotection of the diol as the tert-butyldiphenylsilyl ether followed by Dess-Martin periodinane oxidation afforded the aldehyde, which was then reacted with 2,3-dibromopropene in the presence of metallic tin$^{63}$ and HBr to give homoallylic alcohol 32. The silyl ether was removed with TBAF, and the diol was condensed with commercially available heptaldehyde to provide acetal 33. Palladium-mediated coupling of the vinyl bromide with trimethylsilylmethylmagnesium chloride afforded the cyclization substrate, 34, in good yield. These conditions will be used as the standard allylsilane formation conditions.

**Scheme 2.1: Synthesis of initial Prins substrate**

Reagents: a) TBDPSCl, NaH, DMF, b) DMPI, NaHCO$_3$, CH$_2$Cl$_2$, c) 2,3-dibromopropene, HBr, Sn, Et$_2$O:H$_2$O (1:1) (42% over 3 steps), d) TBAF, THF, 32%, e) heptaldehyde, PTSA, PhH, reflux, 64%, f) Me$_3$SiCH$_2$MgCl, Pd(PPh$_3$)$_4$, THF, 88%

Intramolecular Prins cyclization of cyclic acetal 34 was performed using the same conditions under which the Prins reaction was initially observed. The acetal was treated with two equivalents of titanium tetrachloride in methylene chloride at -78 °C, and 2,6-cis-substituted-4-methylenetetrahydropyran 35, was isolated as a single diastereomer (Scheme 2.2). The cis stereochemical relationship between the C2 and C6 methines was confirmed through the strong correlation observed in the NOESY spectrum. The origin of the cis selectivity is assumed to be the preference of the two alkyl groups to adopt a pseudoequitorial orientation in the transition state.

**Scheme 2.2: Intramolecular Prins cyclization with an allylsilane**
With adequate proof that the cyclization reaction could be performed with complete stereoselectivity, and in accord with the desire to carry out this transformation on advanced synthetic intermediates, intramolecular Prins cyclizations of a variety of \(\alpha,\beta\)-unsaturated acetals were examined. Cyclic \(\alpha,\beta\)-unsaturated acetal 39 served as the primary cyclization substrate, and also as the substrate on which cyclization reaction conditions would be optimized. Cyclic \(\alpha,\beta\)-unsaturated acetal 39 was synthesized in the same manner as cyclic acetal 34, excepting the substitution of crotonaldehyde for heptaldehyde in the acid mediated acetal formation (Scheme 2.3).

**Scheme 2.3:** \(\alpha,\beta\)-Unsaturated acetal synthesis

Intramolecular Prins cyclization of cyclic \(\alpha,\beta\)-unsaturated acetal 39 to form 2,6-cis-substituted-4-methylenetetrahydropyran 40 was carried out using a variety of organic solvents and both Lewis and Brønstead acids (Scheme 2.4), the results of which are shown in Table 2.1.

**Scheme 2.4:** Cyclization with specifically designed substrate

The initial conditions, using titanium tetrachloride as the Lewis acid, proved too harsh and led only to decomposition of the starting material. Switching to BF\(_3\)•OEt\(_2\) afforded the desired cyclized tetrahydropyran in a moderate yield, as did reaction with trimethylaluminum. Use of the mild Lewis acids cerium chloride and cerium bromide also provided the desired tetrahydropyran in moderate yield. However, the lack of solubility of the cerium coupled with
the associated nucleophilic counterions played a major role in the reaction, leading to the incorporation of both chlorine and bromine into the cyclized products (42) and promoting formation of the protodesylilated product 41 in varying yields. In situ generation of a soluble cerium (III) source through the combination of ceric ammonium nitrate and hydroquinone proved ineffective at initiating the cyclization reaction. Use of p-toluenesulfonic acid yielded a 1:1 mixture of the desired cyclized product in combination with protodesilylated product 41. Both acetic acid and Montmorillonite K-10 clay also proved ineffective at initiating intramolecular Prins cyclization. Through the reaction conditions examined, it became clear that the enhanced reactivity afforded as a result of the α,β-unsaturated acetal required that cyclization be initiated with a mild Lewis acid bearing non-nucleophilic counterions to avoid decomposition, unproductive protodesilylation and incorporation of the counterion into the desired product.

**Table 2.1: Intramolecular Prins cyclization with Lewis/Brønstead acids**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis/Brønstead acid</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Product (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TiCl₄</td>
<td>CH₂Cl₂</td>
<td>-78 ºC</td>
<td>decomposition</td>
</tr>
<tr>
<td>2</td>
<td>BF₃•OEt₂</td>
<td>CH₂Cl₂</td>
<td>-78 ºC</td>
<td>40 (52%)</td>
</tr>
<tr>
<td>3</td>
<td>AlMe₃</td>
<td>CH₂Cl₂</td>
<td>r.t.</td>
<td>40 (55%)</td>
</tr>
<tr>
<td>4</td>
<td>CeCl₃</td>
<td>CH₃CN</td>
<td>r.t.</td>
<td>40 (57%), 41 (22%)</td>
</tr>
<tr>
<td>5</td>
<td>CeCl₃</td>
<td>THF</td>
<td>r.t.</td>
<td>No rxn</td>
</tr>
<tr>
<td>6</td>
<td>CeCl₃</td>
<td>THF:H₂O</td>
<td>r.t.</td>
<td>No rxn</td>
</tr>
<tr>
<td>7</td>
<td>CeCl₃ on silica</td>
<td>CH₂Cl₂</td>
<td>r.t.</td>
<td>No rxn</td>
</tr>
<tr>
<td>8</td>
<td>CeBr₃</td>
<td>CH₃CN</td>
<td>r.t.</td>
<td>40 (47%), 41 (12%)</td>
</tr>
<tr>
<td>9</td>
<td>CAN/Hydroquinone</td>
<td>CH₃CN</td>
<td>r.t.</td>
<td>No rxn</td>
</tr>
<tr>
<td>10</td>
<td>PTSA</td>
<td>CH₂Cl₂</td>
<td>r.t.</td>
<td>40 (55%), 41 (3%)</td>
</tr>
<tr>
<td>11</td>
<td>PPTS</td>
<td>CH₂Cl₂</td>
<td>r.t.</td>
<td>decomposition</td>
</tr>
<tr>
<td>12</td>
<td>Montmorillonite K-10</td>
<td>CH₃CN</td>
<td>r.t.</td>
<td>No rxn</td>
</tr>
<tr>
<td>13</td>
<td>AcOH</td>
<td>CH₂Cl₂</td>
<td>r.t.</td>
<td>No rxn</td>
</tr>
</tbody>
</table>

Kobayashi’s Lewis acid surfactant combined catalyst (LASC)⁶⁴ provided a solution to this problem. LASCs are composed of water-stable Lewis acidic cations, such as scandium (III) ions, and anionic surfactants, such as dodecyl sulfate that form stable colloidal dispersions...
rapidly in the presence of water. These catalysts act both as a Lewis acid, as well as a surfactant to simultaneously activate substrate molecules and form a hydrophobic reaction environment, effectively utilizing the concept of organic microsolvation to allow for rapid organic reactions in water. Kobayashi successfully employed these catalysts in carbon-carbon bond forming reactions such as aldol, allylation, and Mannich-type reactions, but had not demonstrated that they could be employed in reactions where the reactive electrophilic intermediates could be irreversibly consumed by water. Therefore, it was pleasing to observe that the addition of 10 mol % ScCl₃ to a suspension of allylsilane 39 and 30 mol% of sodium dodecylsulfate (SDS) in water rapidly generated a colloidal dispersion that afforded a 71% yield of the desired 2,6-cis-substituted-4-methylenetetrahydropyran 40 as a single diastereomer in the first aqueous Prins cyclization reaction (Scheme 2.5). The cis stereochemical relationship of the C2 and C6 protons was verified through the strong correlation observed in the NOESY spectrum.

**Scheme 2.5: Initial aqueous Prins reaction**

The aqueous Prins reaction conditions are mild and procedurally simple. The reaction is performed in water at ambient temperature without need for organic cosolvents. The reaction mixture appears as a colloidal dispersion in which the cyclization reaction proceeds efficiently and stereoselectively inside micelles. Micelles are generated *in situ* by the addition of Lewis acid into a rapidly stirring suspension of the cyclization substrate and the surfactant (Figure 2.17).
Only a catalytic amount of both the Lewis acid and surfactant are needed to effect reaction. In the absence of the cyclization substrate, with simply the combination of the Lewis acid and surfactant in water, the reaction mixture appears homogeneous and no micelle formation is observed. Stirring a mixture of the water soluble Lewis acid and the cyclization substrate in water for extended periods of time failed to yield any of the desired cyclization product and resulted in recovery of the starting material with minimal acetal hydrolysis.

**Figure 2.17: Schematic of aqueous Prins reaction**

Based on the inability to hydrate the exocyclic olefin by resubjecting the resulting tetrahydropyran to the reaction conditions, and the inability to effect reaction in the absence of the surfactant, it is postulated that all starting materials, intermediates and products are contained within the hydrophobic interior of the micelle for the duration of the reaction. Nucleation by the cyclization substrate and micelle formation occurs upon addition of the Lewis acid to the suspension. Once viable micelles are formed, the substrate can be envisioned to diffuse through the hydrophobic interior to the periphery of the micelle where it can encounter and coordinate to the Lewis acidic cations. Ionization of the acetal ensues to form the intermediate oxocarbenium...
ion which is rapidly trapped with the pendent allylsilane resulting in the formation of a 2,6-cis-disubstituted-4-methylene tetrahydropyran, as shown in Figure 2.18.

**Figure 2.18: Intramolecular Prins contained within a micelle**

The effect of surfactant chain length on micelle and stability was examined. As summarized in Table 2.2, the dodecanesulfonate provided the best yields, while surfactants with shorter or longer alkyl chains resulted in lower yields. In addition to surfactant alkyl chain length, concentration proved to be a significant factor in micelle formation. Achievement of a critical micelle concentration was necessary for formation and maintenance of viable micelles for extended reaction times. The critical micelle concentration could typically be achieved by performing the reaction at a 0.5 M concentration with respect to the cyclization substrate, 10 mol% of the Lewis acid ScCl$_3$•6H$_2$O and 40 mol% of sodium dodecylsulfate.
Table 2.2: Optimal surfactant chain length

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis Acid</th>
<th>Surfactant</th>
<th>Concentration (with respect to substrate)</th>
<th>Product (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ScCl₃•6H₂O</td>
<td>NaO₄SC₁₀H₂₁</td>
<td>0.5 M</td>
<td>40 (64%), 40a (20%)</td>
</tr>
<tr>
<td>2</td>
<td>ScCl₃•6H₂O</td>
<td>NaO₄SC₁₂H₂₅</td>
<td>0.5 M</td>
<td>40 (74%), 40a (23%)</td>
</tr>
<tr>
<td>3</td>
<td>ScCl₃•6H₂O</td>
<td>NaO₄SC₁₈H₃₀</td>
<td>0.5 M</td>
<td>40 (50%), 40a (9%)</td>
</tr>
</tbody>
</table>

In an effort to make the cyclization a more cost effective reaction, the use of various cerium (III) salts was examined. Cerium was the Lewis acid of choice based on cost as well as predicted compatibility with reactions in aqueous media. Cerium has a hydrolysis constant (pKₐ) of 8.3 and an exchange rate constant for substitution of inner-sphere water ligands (WERC) of 2.7x10⁸ M⁻¹s⁻¹, making it an ideal Lewis acid for use in aqueous conditions. The appropriate range for sufficient Lewis acidity of a metal cation in water is a pKₐ between 4.3 and 10.8. A value of less than 4.3 indicates that the metal cation is easily hydrolyzed. Conversely, any metal cation with a pKₐ value greater than 10.8 is deemed too stable. A WERC value greater than 3.2x10⁶ M⁻¹s⁻¹ is also required for sufficient Lewis acidity. The cost/benefit analysis of the various cerium (III) salts based on a 0.4 mmol scale reaction with respect to the cyclization substrate is shown in Table 2.3. Although slightly less reactive than Ce(OTf)₃-based micelles, Ce(NO₃)₃•6H₂O provides an attractive alternative to ScCl₃•6H₂O that effectively catalyzes the intramolecular Prins cyclization at a fraction of the cost.
Table 2.3: Cost/benefit analysis of cerium III salts

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis Acid</th>
<th>Scale (with respect to Lewis acid)</th>
<th>Surfactant</th>
<th>Product (%)</th>
<th>Cost/rxn</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ScCl₂•6H₂O</td>
<td>0.04 mmol</td>
<td>NaO₄SC₁₂H₂₅</td>
<td>40 (74%)</td>
<td>$0.20</td>
</tr>
<tr>
<td>2</td>
<td>CeCl₃•6H₂O</td>
<td>0.04 mmol</td>
<td>NaO₄SC₁₂H₂₅</td>
<td>40 (67%)</td>
<td>$0.01</td>
</tr>
<tr>
<td>3</td>
<td>Ce(OTf)₃•H₂O</td>
<td>0.04 mmol</td>
<td>NaO₄SC₁₂H₂₅</td>
<td>40 (77%)</td>
<td>$0.33</td>
</tr>
<tr>
<td>4</td>
<td>Ce(NO₃)₃•6H₂O</td>
<td>0.04 mmol</td>
<td>NaO₄SC₁₂H₂₅</td>
<td>40 (76%)</td>
<td>$0.003</td>
</tr>
</tbody>
</table>

The extent to which the hydrophobic nature of the molecule influences the aqueous Prins reaction was examined through the cyclization reaction of 45. Cyclic α,β-unsaturated acetal 45 was synthesized in the same manner as acetal 34, excepting the substitution of 2-decenal for heptaldehyde in the acid mediated acetal formation (Scheme 2.6). Intramolecular Prins cyclization was performed using ScCl₃-micelle conditions, to afford the desired tetrahydropyran 46 in a 73% yield, indicating that increasing the hydrophobicity of the substrate has a negligible effect on reaction yield.

Scheme 2.6: Synthesis of tetrahydropyran 46

As the objective is to develop a method applicable to advanced synthetic intermediates, cyclization reaction involving secondary ether 52 was examined to determine if reaction was in any way inhibited, or oxacene formation became a competitive reaction pathway (Scheme 2.7). The synthesis of 52 began with protection of the primary alcohol as the pivalate ester, followed by protection of the secondary alcohol as the silyl ether. The pivalate ester was removed with sodium methoxide in methanol and the resulting alcohol was oxidized with Dess-Martin periodinane to provide aldehyde 48. Aldehyde 48 was then reacted with 2,3-dibromopropene in...
the presence of metallic tin and HBr to afford the resulting homoallylic alcohol, which followed by silyl ether deprotection afforded diol 50. The diol was condensed with crotonaldehyde to provide cyclic acetal 51, which was converted to the allylsilane 52 by the standard palladium-mediated coupling with trimethylsilylmethylmagnesium chloride. Intramolecular Prins cyclization of 52 using Ce(NO₃)₃-based micelles provided tetrahydropyran 53 in 80% yield indicating that the secondary ether does not inhibit cyclization or lead to competitive oxecene formation.

Scheme 2.7: Prins cyclization of secondary ether 54

Reagents: a) Piv-Cl, Et₃N, CH₂Cl₂, b) TBDPSCI, imidazole, DMF, c) Na, MeOH, d) DMPI, CH₂Cl₂, 48% over 4 steps, e) Sn, HBr, Et₂O:H₂O, f) TBAF, THF (91% over 2 steps), g) PTSA, PhH, reflux, 70%, h) Me₃SiCH₂MgCl, Pd(PPh₃)₄, THF, 68%, i) Ce(NO₃)₃·6H₂O, SDS, H₂O, 80%.

The mild nature of the reaction conditions, specifically their compatibility with other acid-sensitive functional groups contained within the cyclization substrate, was examined through the cyclization of cyclic α,β-unsaturated acetal 57 (Scheme 2.8). Synthesis of the acetal commenced with protection of 3-butenol as the methoxymethyl ether, followed by cross metathesis with acrolein using Grubbs 2nd generation catalyst to provide aldehyde 55. The aldehyde was condensed with diol 43 to form acetal 56 using p-toluenesulfonic acid and magnesium sulfate in methylene chloride. The vinyl bromide was converted to the allyl silane using the standard palladium mediated coupling conditions to provide acetal 57. Intramolecular Prins cyclization of cyclic α,β-unsaturated acetal 57 with Ce(NO₃)₃-based micelles provided tetrahydropyran 58 in reasonable yield, indicating the compatibility of these reaction conditions with acid-sensitive functional groups.
Scheme 2.8: Prins cyclization with an acid-sensitive functional group

Cyclization reaction of 1,3-dioxolanes was examined, as shown in Scheme 2.9. The synthesis of cyclic acetal 64 began with the protection of 1,4-butene diol with tert-butyldimethylsilyl chloride and sodium hydride in DMF to afford the bis-silyl ether. Ozonolysis followed by reduction with triphenylphosphine provided aldehyde 60. Allylation of aldehyde 60 with 2-bromoallyltrimeethylsilane 67 followed by silyl deprotection afforded diol 62. Acid mediated condensation of diol 62 with decenal provided cyclic acetal 63. The vinyl bromide was converted to the allylsilane through palladium mediated coupling with trimethylsilylmethylzinc bromide 68 (prepared in situ from trimethylsilylmethylmagnesium bromide and zinc bromide). While reaction of cyclic acetal 64 with both the ScCl3- and Ce(NO3)3-based micelles afforded the desired tetrahydropyran 65, the ScCl3-based micelles provided higher yields. The major byproduct isolated only from Ce(NO3)3-based micelle reactions was the tertiary alcohol 66 rather than the exocyclic olefin.
Cyclization of enantiomerically enriched cyclic α,β-unsaturated acetal (-)-72 was examined in order to determine if oxonia-Cope rearrangement was indeed a competitive reaction pathway in the intramolecular Prins cyclization. The starting material for the synthesis, as shown in Scheme 2.10, was (+)-(S)-methyl lactate, which was protected as the benzyl ether using benzyl bromide in the presence of silver (I) oxide. The ester was reduced with DIBAL-H to provide aldehyde 68. Allylation with 2-bromoallyltrimethylsilane in the presence of tin tetrachloride provided allyl alcohol 69 in 45:1 diastereoselectivity and 79% ee. The benzyl protecting group was removed with titanium tetrachloride to give diol 70, which was subjected to acid mediated condensation with decenal to provide vinyl bromide 71. The vinyl bromide was converted to the allylsilane through palladium-mediated coupling with trimethylsilylmethylzinc bromide to provide cyclic α,β-unsaturated acetal (-)-72. In accord with the cyclization of cyclic α,β-unsaturated acetal 64, ScCl₃-based micelles provided higher yields of the desired tetrahydropyran (+)-73. Tetrahydropyran (+)-73 was isolated as a single diastereomer, and the cis stereochemical relationship of the C2/C6 methine protons was confirmed through the strong correlation observed in the NOESY spectrum. HPLC analysis of the benzyl ester of tetrahydropyran (+)-73 showed no loss of ee, indicating that the oxonia-Cope rearrangement is not a competitive reaction pathway in intramolecular Prins cyclization reactions of cyclic α,β-unsaturated acetals.
Scheme 2.10: Synthesis of enantioenriched cyclic -unsaturated acetal (-)-72

In addition to 2,6-cis-disubstituted-4-methylenetetrahydropyran (+)-73, the protodesilylated product (-)-74 and tertiary alcohol 75 were isolated as byproducts of the reaction. Resubjecting tetrathydropyran (+)-73 to the cyclization reaction conditions for an extended time failed to yield tertiary alcohol 75 and resulted in the complete recovery of starting material. Therefore, tertiary alcohol 75 is proposed to result from intramolecular Prins cyclization of alkene (-)-74 followed by trapping of the intermediate cation with either water or dodecyl sulfate. The enhanced reactivity afforded through the use of 1,3-dioxolanes allows for significantly faster cyclization reactions than those of 1,3-dioxanes, as well as for the use of less nucleophilic, unactivated olefins as nucleophiles.

Methyl glycolate severed as the starting material for the synthesis of the racemate of tetrahydropyran 73, which was used for HPLC analysis of enantiomeric excess. Methyl glycolate was protected with benzyl bromide in the presence of silver (I) oxide. The benzyl ether was then alkylated with methyl iodide and reduced with DIBAL-H to provide the racemate of aldehyde.
The aldehyde was carried through the synthesis in the same manner to ultimately yield rac-73.

2.3. Conclusion

An innovative variant of the Prins cyclization has been developed in which cyclization reactions occur efficiently and stereoselectively under mild conditions when cyclic α,β-unsaturated acetals are ionized in the presence of allylsilanes to provide 2,6-cis-disubstituted-4-methylenetetrahydropyrans. These cost-effective reactions are procedurally simplistic, and utilize the environmentally benign solvent, water, without need for organic cosolvents. The reactions are catalyzed by Lewis acid surfactant combined catalysts (LASCs) generated in situ through the combination of either Lewis acid ScCl₃·6H₂O or Ce(NO₃)₃·6H₂O and the surfactant sodium dodecylsulfate (SDS) in the presence of the cyclization substrate in water at ambient temperature. These reaction conditions effectively utilize the concept of organic microsolvation to provide a sufficiently anhydrous environment to protect oxocarbenium ion intermediates from hydrolysis. Both α,β-unstaurated 1,3-dioxanes and 1,3-dioxolanes having pendent electron rich olefins in the form of allylsilanes react under these conditions to provide a variety of 2,6-cis-disubstituted-4-methylenetetrahydropyrans. The reaction conditions are sufficiently mild so as to tolerate the incorporation of acid-sensitive functional groups within the cyclization substrate.

Table 2.4 provides a summary of the cyclic α,β-unsaturated acetals subjected to intramolecular Prins cyclization reactions using the aqueous Prins reaction conditions. Reactions are performed using either 10 mol % ScCl₃·6H₂O or Ce(NO₃)₃·6H₂O, 30-60 mol % SDS, at 0.5 M with respect to the acetal and isolated yields of purified products are reported.
Table 2.4: Summary of intramolecular Prins cyclization substrates

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<th>% Yield</th>
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</table>
2.4. Experimental

**General Procedures.** All reactions were performed in oven or flame-dried glassware under a positive pressure of N₂ with magnetic stirring unless otherwise noted.

**Materials.** Tetrahydrofuran and diethyl ether were dried by passage through an activated alumina column under positive N₂ pressure. Methylene chloride was distilled under N₂ from CaH. Analytical TLC was performed on E. Merck pre-coated (25 mm) silica gel 60F-254 plates. Visualization was done under UV (254 nm). Flash chromatography was done using ICN SiliTech 32-63 60 Å silica gel. Reagent grade ethyl acetate, diethyl ether, pentane and hexanes (commercial mixture) were purchased from EM Science and used as is for chromatography.

**Instrumentation.** 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 CH₂Cl₂ and then evaporating the CH₂Cl₂. Proton (¹H NMR) and carbon (¹³C NMR) nuclear magnetic resonance spectra were recorded on Bruker Avance 300 spectrometers at 300 MHz and 75 MHz, respectively. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. The solvent peak was used as a reference value, for ¹H NMR: CDCl₃ = 7.27 ppm, for ¹³C NMR: CDCl₃ = 77.23. Data are reported as follows: (s = singlet; d = doublet; t = triplet; q = quartet; dd = doublet of doublets; dt = doublet of triplets; b = broad). HPLC analysis was performed with a HP series 1100 instrument using either a Chiralcel OD-H or OJ or CHIRAPAK AD column.
5-Bromo-hex-5-ene-1,3-diol (36)

To 1,3-propanediol (1.00 g, 13.14 mmol) in THF (20 mL) was added sodium hydride (60% dispersion in mineral oil, 0.54 g, 13.14 mmol). The reaction mix was stirred for 30 min. then tert-butyldichlorosilane (3.62 g, 13.14 mmol) was added. The reaction mixture was stirred for 1.5 h then quenched with ice chips, extracted into ether, dried (MgSO₄), and concentrated. The resulting residue was dissolved in CH₂Cl₂ (20 mL) under N₂ and the temperature was decreased to 0 ºC before Dess-Martin periodinane (6.70 g, 15.77 mmol) was added. The reaction mixture was stirred at 23 ºC for 30 min. then quenched with saturated aqueous NaHCO₃ (5 mL) and saturated aqueous Na₂S₂O₃ (5 mL). The reaction mixture was stirred for an additional 20 min. before the two layers were separated. The organic layer was dried (MgSO₄), and concentrated. To a stirring suspension of tin powder (1.95 g, 16.42 mmol) in an ether-water mixture (25 mL:12.5 mL) were added a few drops of HBr, 2,3-dibromopropene (3.15 g, 15.76 mmol) and the resulting residue (in 10 mL of ether). The reaction mixture was stirred for 18 h before it was filtered through a pad of Celite. The filtrate was washed with brine. The organic layer was dried (MgSO₄), concentrated, and filtered through a plug of silica gel. The resulting residue was dissolved in THF (10 mL) under N₂ and tetrabutylammonium fluoride (1.72 g, 5.56 mmol) was added. The reaction mixture was stirred for 1 h, then concentrated and purified by flash chromatography (5% hexanes in EtOAc) to afford the desired product (0.84 g, 32%).: ¹H NMR (300 MHz, CDCl₃) δ 5.70 (s, 1H), 5.51 (s, 1H), 4.16 (m, 1H), 3.85 (m, 3H), 2.62 (dd, J = 14.4, 7.8 Hz, 1H), 2.55 (dd, J = 14.3, 4.9 Hz, 1H), 1.75 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 130.5, 119.6, 69.2, 61.1, 49.6, 37.8; IR (neat) 3349, 2939, 1736, 1634, 1442, 1372, 1255, 1050, 886 cm⁻¹; HRMS (EI): m/z calcld for C₄H₅BrO (M – C₂H₅O) 147.952376, found 147.9523.
Trimethyl[2-(2-propenyl[1,3]dioxan-4-ylmethyl)allyl]silane (39)

This procedure is representative of a standard acetal formation followed by palladium mediated coupling to afford the desired cyclization substrate. To 36 (0.20 g, 1.02 mmol) in benzene (5 mL) was added crotonaldehyde (0.08 g, 0.82 mmol) and p-toluenesulfonic acid (cat.). The reaction mixture was refluxed for 2 h, then cooled to room temperature and triethylamine (0.2 mL) was added. The reaction mixture was stirred for 20 min. then extracted into ether, washed with 10% aqueous NaOH and brine, dried (MgSO₄), and concentrated. The resulting residue was flashed through a silica gel column (10% EtOAc in hexanes) then dissolved in THF (5 mL). Palladium tetrakistriphenylphosphine (0.03 g, 0.03 mmol) was added followed by trimethylsilylmethylmagnesium chloride (1.0 M in ether, 3.29 mmol, 3.29 mL). The reaction mixture was heated to reflux for 3 h, then cooled to room temperature and quenched with saturated aqueous NH₄Cl. The reaction mixture was extracted into ethyl acetate, washed with H₂O, dried (MgSO₄), and concentrated. The resulting residue was purified by flash chromatography (10% triethylamine, 5% EtOAc in hexanes) to afford the desired product (0.15 g, 92%).

1H NMR (300 MHz, CDCl₃) δ 5.91 (dq, J = 15.5, 6.5 Hz, 1H), 5.57 (m, 1H), 4.95 (d, J = 5.1 Hz, 1H), 4.66 (s, 1H), 4.61 (s, 1H), 4.15 (m, 1H), 3.80 (m, 2H), 2.38 (dd, J = 13.9, 5.7 Hz, 1H), 2.10 (dd, J = 13.9, 7.5 Hz, 1H), 1.75 (d, J = 1.5 Hz, 1H), 1.72 (d, J = 1.5 Hz, 1H), 1.64 (m, 2H), 1.55 (d, J = 2.9 Hz, 3H), 0.04 (s, 9H); 13C NMR (75 MHz, CDCl₃) δ 143.6, 129.8, 129.0, 110.0, 101.0, 75.9, 66.9, 45.1, 31.5, 27.6, 19.6, -1.4; IR (neat) 3069, 2952, 1723, 1658, 1440, 1374, 1374, 1309, 1287, 1258, 1192, 1054, 974, 836 cm⁻¹; HRMS (EI): m/z calcd for C₁₄H₂₆O₂Si (M⁺) 254.170209, found 254.170992.
2-(4-Methylene-6-propenyl-tetrahydropyran-2-yl)-ethanol (40)

To a suspension of cerium chloride (0.19 g, 0.79 mmol) in acetonitrile (5 mL) was added 39 (0.10 g, 0.39 mmol). The reaction mixture was sonicated for 3 h, then quenched by the addition of saturated aqueous NaHCO₃. The reaction mixture was extracted with ether (2 x). The combined organic layers were dried (MgSO₄) and concentrated. The resulting residue was purified by flash chromatography (2% Et₂O in pentanes) to afford the desired product 2 (0.04 g, 57%): ¹H NMR (300 MHz, CDCl₃) δ 5.71 (dq, J = 15.4, 1.0 Hz, 1H), 5.49 (ddq, J = 16.9, 6.2, 1.5 Hz, 1H), 4.75 (d, J = 1.7 Hz, 1H), 4.74 (d, J = 1.7 Hz, 1H), 3.79 (m, 3H), 3.58 (m, 1H), 2.76 (bs, 1H), 2.22 (dd, J = 15.0, 11.2 Hz, 2H), 2.05 (dd, J = 12.5, 12.3 Hz, 2H), 1.85 (m, 5H); ¹³C NMR (75 MHz, CDCl₃) δ 143.5, 131.9, 127.2, 109.0, 79.2, 78.7, 61.4, 41.1, 40.8, 38.4, 17.8; IR (neat) 3410, 3069, 2916, 2850, 1701, 1650, 1440, 1389, 1309, 1258, 1185, 1054 cm⁻¹; HRMS (EI): m/z calcd for C₁₁H₁₈O₂ (M⁺) 182.130680, found 182.130982.

4-(2-Methylallyl)-2-propenyl-[1,3]dioxane (41)

41 results from desilylation of the starting material (0.02 g, 22%): ¹H NMR (300 MHz, CDCl₃) δ 5.91 (m, 1H), 5.54 (ddq, J = 15.5, 4.9, 1.3 Hz, 1H), 4.92 (d, J = 4.9 Hz, 1H), 4.79 (s, 1H), 4.73 (s, 1H), 4.13 (dd, 11.4, 4.8 Hz, 1H), 3.79 (m, 2H), 2.38 (dd, J = 13.9, 6.3 Hz, 1H), 2.16 (dd, 13.9, 6.7 Hz, 1H), 1.74 (s, 3H), 1.71 (d, J = 6.5 Hz, 3H), 1.61 (ddd, 23.8, 11.8, 4.9 Hz, 1H), 1.42 (d, J = 13.3 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 141.6, 130.4, 128.5, 113.0, 100.8, 75.4, 66.7, 44.7, 31.1, 23.0, 17.8; IR (neat) 3076, 2960, 2916, 2850, 2727, 1687, 1636, 1440, 1367, 1316, 1243, 1134, 1076, 1010, 960, 887 cm⁻¹; HRMS (EI): m/z calcd for C₁₁H₁₇O₂ (M⁺) 181.122855, found 181.122805.
This procedure is representative of a standard aqueous Prins reaction. To trimethyl[2-(2-propenyl[1,3]dioxan-4-ylmethyl)ally]silane (0.10 g, 0.39 mmol) in H₂O (1 mL) was added sodium dodecylsulfate (0.03 g, 0.12 mmol) followed by cerium nitrate hexahydrate (0.01 g, 0.04 mmol). Micelles formed immediately upon the addition of the cerium nitrate and the reaction mixture was stirred at 1100 rpm for 18 h. The reaction mixture was extracted into ether, washed with 10% aqueous HCl, dried (MgSO₄), and concentrated. The resulting residue was purified by flash chromatography (20% EtOAc in hexanes) to afford the desired product 2 (0.06 g, 76%).

**Trimethyl-[2-(2-non-1-enyl-[1,3]dioxan-4-ylmethyl)-ally]-silane (45)**

This cyclization substrate was obtained using standard acid mediated acetal formation conditions with 36 (0.50 g, 2.56 mmol) and trans-2-decenal (0.39 g, 2.56 mmol). A portion of the resulting residue (250 mg, 0.75 mmol) was subjected to standard palladium-mediated coupling conditions using palladium tetrakistriphenylphosphine (0.09 g, 0.08 mmol) and trimethylsilylmethylmagnesium chloride (1.0 M in ether, 3.77 mmol, 3.77 mL) to afford the desired cyclization substrate (0.18 g, 71%): ¹H NMR (300 MHz, CDCl₃) δ 5.92 (dt, J = 14.9, 6.6 Hz, 1H), 5.53 (ddt, J = 15.1, 5.0, 1.4 Hz, 1H), 4.95 (d, J = 5.0 Hz, 1H), 4.65 (s, 1H), 4.61 (s, 1H), 4.15 (ddd, 11.4, 4.8, 1.2 Hz, 1H), 3.82 (m, 2H), 2.38 (dd, J = 13.9, 5.5 Hz, 1H), 2.08 (m, 3H), 1.72 – 1.26 (m, 14H), 0.87 (t, J = 6.5 Hz, 3H), 0.03 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 144.0, 135.4, 127.4, 110.0, 101.1, 76.3, 66.8, 45.1, 32.2, 32.0, 31.4, 29.4, 29.3, 28.9, 27.5, 22.8, 14.4, -0.58; IR (neat) 2952, 2923, 2850, 1672, 1636, 1461, 1352, 1243, 1134, 1018, 967, 858 cm⁻¹; HRMS (EI): m/z calcd for C₂₀H₃₈O₂Si (M⁺) 338.264109, found 338.263779.
2-(4-Methylene-6-non-1-enyl-tetrahydropyran-2-yl)ethanol (46)

Trimethyl-[2-(2-non-1-enyl-[1,3]dioxan-4-ylmethyl)-allyl]-silane (45) (0.10 g, 0.29 mmol) was subjected to standard aqueous Prins cyclization conditions using scandium chloride hexahydrate (0.004 g, 0.03 mmol) and sodium dodecylsulfate (0.03 g, 0.09 mmol) to afford the desired product (0.06 g, 73%): \(^1\)H NMR (300 MHz, CDCl₃) \(\delta 5.66\) (dtd, \(J = 15.4, 6.6, 0.9\) Hz, 1H), \(5.47\) (ddt, \(J = 15.4, 6.2, 1.3\) Hz, 1H), \(4.73\) (s, 2H), \(3.79\) (t, \(J = 5.0\) Hz, 2H), \(3.74\) (m, 1H), \(3.57\) (m, 1H), \(2.76\) (s, 1H), \(2.26 – 1.97\) (m, 6H), \(1.80\) (m, 2H), \(1.26\) (m, 10H), \(0.87\) (t, \(J = 6.9\) Hz, 3H); \(^1^3\)C NMR (75 MHz, CDCl₃) \(\delta 144.2, 132.7, 130.5, 108.9, 79.3, 78.7, 61.3, 41.2, 40.8, 38.4, 32.4, 32.0, 29.8, 22.8, 14.1\); IR (neat) 3396, 2923, 2850, 1650, 1461, 1425, 1352, 1309, 1054, 960, 894 cm\(^{-1}\); HRMS (EI): \(m/z\) calcd for C\(_{17}\)H\(_{30}\)O\(_2\) (M\(^+\)) 266.224580, found 266.225400.

2,2-Dimethylpropionic acid 3-hydroxy-butyl ester

To 1,3-butanediol (1.50 g, 16.64 mmol) in CH\(_2\)Cl\(_2\) (15 mL) at 0 °C was added triethylamine (7.58 g, 74.89 mmol) followed by pivaloyl chloride (2.20 g, 18.31 mmol). The reaction mixture was stirred for 4 h at room temperature then quenched with H\(_2\)O. The two layers were separated and the organic layer was dried (MgSO\(_4\)), concentrated and purified by flash chromatography (40% EtOAc in hexanes) to afford the desired product (79%, 2.28 g): \(^1\)H NMR (300 MHz, CDCl₃) \(\delta 4.36\) (m, 1H), \(4.11\) (m, 1H), \(3.86\) (m, 1H), \(2.05\) (br s, 1H), \(1.74\) (m, 2H), \(1.26\) (d, \(J = 4.8\) Hz, 3H), \(1.18\) (s, 9H).\(^1\)
Trimethyl-[2-(6-methyl-2-propenyl-[1,3]dioxan-4-ylmethyl)-allyl]-silane (52)

To 2,2-dimethyl-propionic acid 3-hydroxybutyl ester (2.28 g, 13.08 mmol) in DMF (15 mL) was added triethylamine (1.58 g, 15.70 mmol) followed by tert-butylchlorodiphenylsilane (3.95 g, 14.39 mmol). The reaction mixture was stirred for 48 h, and then quenched with H₂O. The two layers were separated and the organic layer was dried (MgSO₄), and concentrated. Sodium (0.299 g, 13.08 mmol) was dissolved in MeOH (20 mL) under N₂ at 0 ºC. The resulting residue (in 5 mL of MeOH) was added drop wise. The reaction mixture was heated to 40 ºC for 12 h, then cooled to room temperature, quenched with H₂O and extracted with EtOAc. The organic layer was dried (MgSO₄), concentrated and purified by flash chromatography (20% EtOAc in hexanes) to afford the desired primary alcohol (2.05 g, 48%). The resulting alcohol was dissolved in CH₂Cl₂ (30 mL) under N₂ and the temperature was decreased to 0 ºC before Dess-Martin periodinane (3.19 g, 7.50 mmol) was added. The reaction mixture was stirred for 1 h at room temperature. The temperature was then decreased to 0 ºC and the reaction mixture was quenched with saturated aqueous NaHCO₃ and saturated aqueous Na₂S₂O₃. The reaction mixture was warmed to room temperature and stirred for 30 min. before the two layers were separated. The organic layer was dried (MgSO₄) and concentrated. To a stirring suspension of tin powder (0.93 g, 7.82 mmol) in an ether-water mixture (15 mL:7 mL) were added a few drops of HBr, 2,3-dibromopropene (1.87 g, 7.50 mmol) and the resulting residue (in 5 mL of ether). The reaction mixture was stirred for 18 h before it was filtered through a pad of Celite. The filtrate was washed with brine, dried (MgSO₄), and concentrated. The resulting residue was dissolved in THF (15 mL) and TBAF (1.26 g, 4.84 mmol). The reaction mixture was stirred for 3h, then filtered through a plug of silica (EtOAc) to afford the desired diol (0.76 g, 91%).
The cyclic α,β-unsaturated acetal was obtained using standard acid mediated acetal formation conditions with 6-bromo-hept-6-ene-2,4-diol (0.50 g, 2.39 mmol), crotonaldehyde (0.15 g, 2.15 mmol) and p-toluenesulfonic acid. The resulting residue was purified by flash chromatography. The all cis-substituted product was isolated and subjected to standard palladium mediated coupling conditions using palladium tetrakistriphenylphosphine (0.06 g, 0.05 mmol) and trimethylsilylmethylmagnesium chloride (1.0 M in ether, 5.35 mmol, 5.35 mL) in THF (10 mL) to afford the desired cyclization substrate (0.19 g, 68%): \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 5.95 (dq, \(J = 15.5, 6.5\) Hz, 1H), 5.59 (m, 1H), 4.97 (d, \(J = 5.3\) Hz, 1H), 4.65 (s, 1H), 4.61 (s, 1H), 3.80 (m, 1H), 2.36 (dd, \(J = 13.8, 5.7\) Hz, 1H), 2.09 (dd, \(J = 13.8, 7.5\) Hz, 1H), 1.74 (dd, \(J = 6.5, 1.4\) Hz, 3H), 1.58 (m, 2H), 1.25 (m, 5H), 0.02 (s, 9H); \(^1\)\(^3\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 144.3, 130.3, 128.9, 109.8, 100.7, 74.1, 72.8, 44.9, 38.7, 27.5, 21.9, 14.2, -1.09; IR (neat) 2943, 2906, 2857, 1714, 1419, 1376, 1235, 1124, 1100, 1032, 842 cm\(^{-1}\); HRMS (EI): \(m/z\) calcd for C\(_{15}\)H\(_{28}\)O\(_2\)Si (M\(^+\)) 268.185859, found 268.185834.

1-(4-Methylene-6-propenyltetrahydropyran-2-yl)propan-2-ol (53)

2-Bromo-6-(\textit{tert}-butyl-diphenyl-silanyloxy)-hept-1-en-4-ol (52) (0.10 g, 0.37 mmol) was subjected to standard aqueous Prins cyclization conditions using cerium nitrate hexahydrate (0.01 g, 0.04 mmol) and sodium dodecylsulfate (0.05 g, 0.19 mmol), to afford the desired product (0.06 g, 80%): \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 5.70 (dq, \(J = 15.4, 6.2\) Hz , 1H), 5.51 (ddq, \(J = 15.4, 6.2, 1.3\) Hz, 1H), 4.74 (s, 2H), 4.03 (m, 1H), 3.78 (m, 1H), 3.58 (m, 1H), 2.15 (m, 4H), 1.63 (m, 5H), 1.18 (d, \(J = 6.2\) Hz, 3H); \(^1\)\(^3\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 143.8, 131.4, 127.7, 109.3, 79.7, 79.1, 68.3, 44.5, 41.0, 40.8, 23.6, 18.0; IR (neat) 3418, 3069,
2923, 2850, 1643, 1440, 1309, 1061, 960, 887 cm\(^{-1}\); HRMS (EI) \(m/z\) calcd for C\(_{12}\)H\(_{20}\)O\(_2\) (M\(^+\)) 196.146330, 0.06 g found 196.146690.

**5-Methoxymethoxypent-2-enal (55)**

To 3-butenol (1.00 g, 13.86 mmol) in CH\(_2\)Cl\(_2\) (10 mL) at 0 °C was added \(N, N'\)-diisopropylethylamine (2.68 g, 20.80 mmol), and chloromethyl methyl ether (1.67 g, 20.80 mmol). The reaction mixture was stirred for 1.5 h at room temperature, then poured into a separatory funnel containing Et\(_2\)O: 1N HCl and extracted. The organic layer was dried (MgSO\(_4\)) and concentrated. To a solution of the resulting residue in CH\(_2\)Cl\(_2\) (10 mL) was added acrolein (0.49 g, 8.61 mmol) and tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene] [benzylidine]ruthenium (IV) dichloride (Grubbs second generation catalyst) (0.18 g, 0.22 mmol). The reaction mixture was heated to reflux for 18 h, cooled to room temperature and concentrated. The resulting residue was purified by flash chromatography (30% Et\(_2\)O in pentanes) to afford the desired product (0.17 g, 28%): \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 9.55 (d, \(J = 7.8\) Hz, 1H), 6.88 (dt, \(J = 15.7, 6.7\) Hz, 1H), 6.22 (dd, \(J = 15.7, 7.8\) Hz, 1H), 4.65 (s, 2H), 3.73 (t, \(J = 6.2, 2H\)), 3.37 (s, 3H), 2.64 (m, 2H).

**4-(2-Bromoallyl)-2-(4-methoxymethoxy-but-1-enyl)-[1,3]dioxane (56)**

To 36 (0.23 g, 1.21 mmol) in CH\(_2\)Cl\(_2\) (5 mL) at -20 °C was added 5-methoxymethoxypent-2-enal (0.17 g, 1.21 mmol), \(p\)-toluenesulfonic acid (0.02 g, 0.12 mmol), and anhydrous MgSO\(_4\) (0.17 g, 1.39 mmol). The reaction mixture was stirred for 18 h, quenched with saturated aqueous NaHCO\(_3\) (2 mL) and allowed to warm to room
temperature. The two layers were separated, and the organic layer was dried (MgSO₄) and concentrated. The resulting residue was purified by flash chromatography (20% Et₂O in pentanes) to afford the desired product (0.29 g, 76%): ¹H NMR (300 MHz, CDCl₃) δ 5.92 (dt, J = 15.7, 6.7 Hz, 1H), 5.66 (s, 1H), 5.60 (ddt, J = 15.7, 4.6, 1.4 Hz, 1H), 5.48 (d, J = 1.5 Hz, 1H), 4.96 (d, J = 4.6 Hz, 1H), 4.60 (s, 2H), 4.11 (dd, J = 11.4, 4.9 Hz, 1H), 3.99 (m, 1H), 3.80 (dt, J = 11.9, 2.6 Hz, 1H), 3.57 (t, J = 6.7 Hz, 2H), 3.33 (s, 3H), 2.75 (dd, J = 14.4, 6.7 Hz, 1H), 2.49 (dd, J = 14.4, 6.3 Hz, 1H), 2.36 (m, 2H), 1.64 (m, 1H), 1.48 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 131.6, 128.9, 119.6, 100.5, 96.4, 74.2, 66.7, 66.5, 55.3, 47.7, 32.6, 30.5; IR (neat) 2945, 2916, 2850, 1694, 1629, 1432, 1352, 1243, 1149, 1134, 1032, 974; HRMS (EI) m/z calcd for C₁₃H₂₀O₄Br (M⁺) 319.054495, found 319.054353.

{2-[2-(4-Methoxymethoxybut-1-enyl)-[1,3]dioxan-4-ylmethyl]allyl}-trimethylsilane (57)

To 56 (0.29 g, 0.92 mmol) in THF (5 mL) was added trimethylsilylmethylmagnesium chloride (1.0 M in Et₂O, 4.59 mmol, 4.59 mL) and palladium tetrakistriphenylphosphine (0.05 g, 0.05 mmol). The reaction mixture was heated to reflux for 3h, cooled to 0 °C, and quenched with saturated aqueous NH₄Cl. The reaction mixture was warmed to room temperature and extracted into Et₂O. The organic layer was dried (MgSO₄) and concentrated. The resulting residue was purified by flash chromatography (10% triethylamine, 20% Et₂O in pentanes) to afford the desired product (0.24 g, 80%): ¹H NMR (300 MHz, CDCl₃) δ 5.93 (dt, J = 15.7, 6.7 Hz, 1H), 5.63 (ddt, 15.7, 3.4, 1.3 Hz, 1H), 4.97 (d, J = 4.7 Hz, 1H), 4.65 (s, 1H), 4.63 (s, 3H), 4.15 (dd, J = 11.4, 4.9 Hz, 1H), 3.80 (m, 2H), 3.60 (t, J = 6.8 Hz, 2H), 3.35 (s, 3H), 2.37 (m, 2H), 2.10 (dd, J = 13.9, 7.3 Hz, 2H) 1.53 (m, 2H), 1.24 (s, 2H), 0.35 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 143.2, 131.4, 129.2, 110.0,
100.6, 96.5, 75.7, 66.8, 55.3, 44.8, 32.6, 31.2, 27.3, -1.19; IR (neat) 3076, 2952, 2850, 1687, 1621, 1367, 1243, 1149, 1112, 1047, 967, 850; HRMS (EI): m/z calcld for C_{17}H_{31}O_{4}Si (M^{+}) 327.199163 found, 327.199646.

2-[6-(4-Methoxymethoxybut-1-enyl)-4-methylenetetrahydropyran-2-yl]ethanol (58)

{2-[2-(4-Methoxymethoxybut-1-enyl)-[1,3]dioxan-4-ylmethyl]allyl}-trimethylsilane (57) (0.10 g, 0.304 mmol) was subjected to standard aqueous Prins cyclization conditions using scandium chloride hexahydrate (0.004 g, 0.03 mmol) and sodium dodecylsulfate (0.04 g, 0.12 mmol) to afford the desired product (0.04 g, 53%): 1H NMR (300 MHz, CDCl₃) δ 5.65 (m, 2H), 4.75 (d, J = 1.6 Hz, 1H), 4.74 (d, J = 1.6 Hz, 1H), 4.61 (s, 2H), 3.73 (t, J = 5.1 Hz, 3H), 3.57 (t, J = 6.8 Hz, 3H), 3.35 (s, 4H), 2.33 (m, 2H), 2.17 (m, 4H), 1.80 (m, 2H); 13C NMR (75 MHz, CDCl₃) δ 143.7, 132.4, 128.5, 109.2, 96.4, 78.9, 78.8, 67.1, 61.4, 55.2, 40.7, 40.5, 38.0, 32.8; IR (neat) 3440, 3069, 2930, 2880, 1658, 1425, 1352, 1316, 1149, 1105, 1047, 960, 901; HRMS (EI): m/z calcld for C_{14}H_{24}O₄ (M^{+}) 256.167460, found 256.167673.

(tert-Butyldimethylsilanyloxy)-acetaldehyde (60)

Ozone was bubbled through a solution of 1,4-bis(tert-butyldimethylsilanyloxy)but-2-ene (3.00 g, 9.47 mmol) in CH₂Cl₂ (30 mL) at -78 °C. The flow of ozone was stopped after 45 min. and triphenylphosphine (2.48 g, 9.47 mmol) was added to the reaction mixture. The mixture was allowed to stir for 12 h while slowly warming to room temperature. The reaction
mixture was concentrated to a third of its volume, placed directly on a silica gel column and purified by flash chromatography (CH$_2$Cl$_2$) to afford the desired aldehyde (3.03 g, 51%): $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.71 (s, 1H), 4.23 (s, 2H), 0.94 (s, 9H), 0.11 (s, 6H).

**Trimethyl[2-(2-non-1-enyl[1,3]dioxolan-4-ylmethyl)allyl]silane (64)**

To a solution of (2-bromo-allyl)-trimethylsilane (1.85 g, 9.58 mmol) in CH$_2$Cl$_2$ (15 mL) at -78 ºC was added 60 (1.11 g, 6.39 mmol) followed by titanium tetrachloride (1.51 g, 7.98 mmol). Then reaction mixture was stirred for 35 min., then cannulated into a stirring saturated aqueous NaHCO$_3$ (25 mL) at 0 ºC. The mixture was stirred while warming to room temperature. The two layers were separated. The water layer was washed with ethyl acetate. The combined organic layers were dried (MgSO$_4$) and concentrated. The resulting residue was purified by flash chromatography (5% EtOAc in hexanes) to afford the desired product (1.10 g, 59%). To 4-bromo-1-(tert-butyldimethylsilanyloxy)pent-4-en-2-ol (1.10 g, 3.73 mmol) on THF (10 mL) under N$_2$ was added tetrabutylammonium fluoride (1.07 g, 4.11 mmol). The reaction mixture was stirred for 12 h then concentrated. The crude mixture was purified by flash chromatography (EtOAc). The resulting residue was subjected to standard acid mediated acetal formation conditions using trans-2-decenal (0.51 g, 0.51 g 3.28 mmol). A solution of zinc bromide (0.71 g, 3.15 mmol) in THF (3 mL) was added dropwise to a solution of trimethylsilylmethylmagnesium chloride (1.0 M in ether, 3.15 mmol, 3.15 mL) and was stirred for 18 h. A solution of the resulting residue from the acetal formation in THF (2 mL) was added, followed by palladium tetrakistriphenylphosphine (0.04 g, 0.03 mmol). The reaction mixture was stirred for 18 h, and was then quenched with saturated aqueous NH$_4$Cl. The two layers were separated and the aqueous layer was washed with ether. The organic layers were combined, dried.
(MgSO₄), concentrated and purified by flash chromatography (10% triethylamine, 5% ether in pentanes) to afford the desired product: 

\[ ^1H \text{ NMR (300 MHz, CDCl}_3 \] \delta 5.91 (m, 1H), 5.48 (m, 1H), 5.32 (d, \( J = 6.6 \text{ Hz}, 1H \)), 5.20 (d, \( J = 6.8 \text{ Hz}, 1H \)), 4.64 (m, 1H), 4.60 (s, 1H), 4.26 (m, 1H), 4.14 (dd, \( J = 8.1, 6.0 \text{ Hz}, 1H \)), 3.96 (dd, \( J = 7.7, 6.5 \text{ Hz}, 1H \)), 3.61 (dd, \( J = 7.7, 6.4 \text{ Hz}, 1H \)), 3.52 (dd, \( J = 8.1, 6.9 \text{ Hz}, 1H \)), 2.40 (m, 2H), 2.21 (m, 2H), 1.25 (m, 12H), 0.02 (s, 9H); ^{13}C \text{ NMR (75 MHz, CDCl}_3 \] \delta 143.8, 143.6, 138.0, 137.2, 126.9, 109.7, 104.7, 103.9, 75.6, 74.8, 70.5, 69.8, 42.6, 42.1, 32.2, 32.0, 29.0, 28.9, 27.6, 22.8, 14.2, 11.12; IR (neat) 3061, 2945, 2923, 1730, 1665, 1463, 1461, 1403, 1243, 1127, 1061, 967, 850; HRMS (EI): \( m/z \) calcd for C₁⁹H₃₆O₂Si (M⁺) 324.248459, found 324.247900.

(4-Methylene-6-non-1-enyl-tetrahydropyran-2-yl)methanol (65)

(4-Methylene-6-non-1-enyl-tetrahydropyran-2-yl)methanol (65) (0.05 g, 0.15 mmol) was subjected to standard aqueous Prins cyclization conditions using scandium chloride hexahydrate (0.002 g, 0.02 mmol) and sodium dodecylsulfate (0.04 g, 0.15 mmol) to afford the desired product (0.03 g, 77%): 

\[ ^1H \text{ NMR (300 MHz, CDCl}_3 \] \delta 5.70 (dt, \( J = 15.5, 6.5 \text{ Hz}, 1H \)), 5.49 (dd, \( J = 15.5, 6.4 \text{ Hz}, 1H \)), 4.77 (s, 2H), 3.79 (m, 1H), 3.61 (m, 2H), 3.47 (m, 1H), 2.05 (m, 7H), 1.57 (m, 3H), 1.26 (m, 10H), 0.88 (t, \( J = 5.5 \text{ Hz}, 3H \)); ^{13}C \text{ NMR (75 MHz, CDCl}_3 \] \delta 143.8, 133.2, 130.3, 109.4, 79.2, 78.6, 66.1, 41.2, 36.3, 32.5, 32.0, 29.8, 29.3, 22.8, 14.3; IR (neat) 3418, 3069, 2930, 2850, 1650, 1461, 1345, 1098, 1054, 967, 894; HRMS (EI): \( m/z \) calcd for C₁₆H₂₈O₂ (M⁺) 252.208930, found 252.209094.
2-Benzylpropionic acid methyl ester (+)-67

To a suspension of silver oxide (4.45 g, 19.21 mmol) in ether (15 mL) was added methyl-(S)-(−)-lactate (1.00 g, 9.60 mmol) and benzyl bromide (2.45 g, 14.40 mmol). The reaction mixture was stirred for 48 h, then filtered through a pad of Celite and concentrated. The resulting residue was purified by flash chromatography (10% Et2O in pentanes) to afford the desired product (1.09 g, 63%): 1H NMR (300 MHz, CDCl3) δ 7.35 (m, 5H), 4.72 (d, J = 11.6 Hz, 1H), 4.48 (d, J = 11.6 Hz, 1H), 4.09 (q, J = 6.9 Hz, 1H), 3.76 (s, 3H), 1.44 (d, J = 6.8 Hz, 3H); 13C NMR (75 MHz, CDCl3) δ 173.8, 137.6, 128.5, 128.1, 74.1, 72.1, 52.0, 18.8; [α]D23 -92.3º (CDCl3, c 0.37); lit: [α]D23 78.5º (CDCl3, c 0.37) for the (R)-(−) enantiomer.

2-Benzyl-5-bromo-hex-5-en-3-ol (+)-69

To (+)-67 in CH2Cl2 (10 mL) at -98 ºC was added diisobutyl aluminum hydride (1.0 M in hexanes, 3.33 mmol, 3.33 mL). The reaction mixture was stirred for 1 h, then quenched with ethyl acetate (2 mL) and stirred for 10 min. before a solution of saturated sodium, potassium tartrate (10mL) was added. The reaction mixture was warmed to room temperature and stirred for 2 h before the two layers were separated. The water layer was washed with CH2Cl2 and the combined organic layers were dried (MgSO4) and concentrated. The resulting residue was added to a solution of (2-bromo-allyl)-trimethyl-silane (0.64 g, 3.33 mmol) under N2 at -78 ºC in CH2Cl2 (10 mL). Tin (IV) chloride (1.0 M in CH2Cl2, 5.55 mmol, 5.55 mL) was added and the reaction mixture was stirred for 45 min. before being quenched with H2O (10 mL). The reaction mixture was warmed to room temperature and the two layers were separated. The aqueous layer was washed with CH2Cl2 and the combined organic layers were dried (MgSO4)
and concentrated. The resulting residue was purified by flash chromatography (10% Et₂O in pentanes) to afford the desired product (0.46 g, 62%): ¹H NMR (300 MHz, CDCl₃) δ 7.32 (m, 5H), 5.66 (d, J = 1.3 Hz, 1H), 5.15 (d, J = 1.5 Hz, 1H), 4.70 (d, J = 11.5 Hz, 1H), 4.47 (d, J = 11.5 Hz, 1H), 3.85 (m, 1H), 3.52 (dq, J = 4.8, 6.2 Hz, 1H), 2.60 (d, J = 6.1 Hz, 2H), 1.28 (d, J = 6.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 138.4, 130.8, 128.7, 128.0, 119.4, 76.5, 72.6, 71.1, 45.5, 15.8; IR (neat) 3447, 3083, 3061, 3025, 2952, 2923, 2872, 1621, 1505, 1447, 1374, 1207, 1069, 901, 734, 698 cm⁻¹; HRMS (EI): m/z calcd for C₁₃H₁₇O₂ (M⁺) 284.041191, found 284.041088; [α]D²³ 14.7º (CHCl₃, c 5.0).

The ee was determined to be 80% by chiral HPLC analysis using a chiracel OD-H column. Conditions: Hex:i-PrOH 90:10, 0.80 mL/min.

4-(2-Bromo-allyl)-5-methyl-2-non-1-enyl-[1,3]dioxolane (-)-71

To (+)-69 (0.31 g, 1.08 mmol) in CH₂Cl₂ (10 mL) at 0 ºC was added titanium (IV) chloride (0.25 g, 1.36 mmol). The reaction mixture was stirred for 2h, and then quenched with saturated aqueous NaHCO₃ (5 mL) and allowed to warm to room temperature. The reaction mixture was extracted into ethyl acetate, and the aqueous layer was washed (5 x) with ethyl acetate. The combined organic layers were dried (MgSO₄) and concentrated and flashed through a silica gel plug using ethyl acetate. To a solution of the resulting residue in CH₂Cl₂ (5 mL) at -20 ºC under N₂ was added trans-2-decenal (0.12 g, 0.78 mmol), p-tolunesulfonic acid (0.01 g, 0.08 mmol), and anhydrous MgSO₄ (0.11 g, 0.89 mmol). The reaction mixture was stirred for 18 h, then was quenched with saturated aqueous NaHCO₃ (2 mL) and warmed to room temperature. The two layers were separated and the organic layer was dried (MgSO₄) and concentrated. The resulting residue was purified by flash chromatography.
(5% Et$_2$O in pentanes) to afford the desired product (0.22 g, 85%): $^1$H NMR (300 MHz, CDCl$_3$) δ 5.93 (dt, $J = 15.3$, 6.6 Hz, 1H), 5.75 (m, 1H), 5.53 (d, $J = 1.7$ Hz, 1H), 5.47 (m, 1H), 5.36 (d, $J = 6.8$ Hz, 1H), 5.30 (d, $J = 6.9$, Hz, 1H), 3.87 (m, 2H), 2.79 (m, 1H), 2.58 (dtd, $J = 13.4$, 4.3, 0.85 Hz, 1H), 2.05 (m, 2H), 1.37 (d, $J = 5.9$ Hz, 3H), 1.26 (m, 10H), 0.87 (t, $J = 6.5$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 138.0, 137.7, 129.3, 129.2, 127.1, 127.0, 119.4, 103.7, 103.5, 81.0, 79.9, 78.0, 76.6, 45.2, 44.7, 32.2, 32.0, 29.3, 28.8, 22.8, 18.3, 18.2, 15.4, 14.2; IR (neat) 3105, 2952, 2930, 1672, 1629, 1454, 1410, 1374, 1316, 1214, 1127, 1083, 1061, 974, 894; HRMS (EI): m/z calcd for C$_{16}$H$_{26}$O$_2$Br (M$^+$) 329.11616, found 329.110518; [α]$_D^{23}$ -10.9º (CH$_2$Cl$_2$, c 5.7).

**Trimethyl[2-(5-methyl-2-non-1-enyl-[1,3]dioxolan-4-ylmethyl)allyl]silane (-)-72**

A solution of zinc bromide (0.57 g, 2.54 mmol) in THF (3 mL) was added dropwise to a solution of trimethylsilylmethylmagnesium chloride (1.0 M in ether, 2.54 mmol, 2.54 mL) and was stirred for 18 h. A solution of (-)-71 (0.17 g, 0.508 mmol) in THF (2 mL) was added, followed by palladium tetrakistriphenylphosphine (0.03 g, 0.03 mmol). The reaction mixture was stirred for 18 h, and was then quenched with saturated aqueous NH$_4$Cl. The two layers were separated and the aqueous layer was washed with ether. The organic layers were combined, dried (MgSO$_4$), concentrated and purified by flash chromatography (5% Et$_2$O in pentanes, the silica was neutralized with 10% triethylamine in pentanes) to afford the desired cyclization substrate (0.15 g, 89%): $^1$H NMR (300 MHz, CDCl$_3$) δ 5.19 (dt, $J = 15.3$, 6.6 Hz, 1H), 5.50 (m, 1H), 5.34 (d, $J = 6.7$ Hz, 1H), 5.30 (d, $J = 6.8$ Hz, 1H), 4.72 (s, 1H), 4.63 (s, 1H), 3.74 (m, 2H), 2.33 (m, 1H), 2.05 (m, 3H), 1.57 (s, 3H), 1.26 (m, 12H), 0.88 (t, $J = 6.8$ Hz, 3H), 0.04 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 143.5, 143.4, 138.2, 138.0,
127.0, 110.3, 103.4, 103.2, 82.1, 80.7, 78.5, 66.0, 41.5, 32.2, 31.9, 29.3, 28.8, 27.1, 22.8, 18.2, 14.3, -1.1; IR (neat) 3069, 2952, 2916, 2850, 1680, 1629, 1454, 1410, 1381, 1250, 1163, 1120, 1076, 1047, 960, 843; HRMS (EI): m/z calcd for C_{20}H_{38}O_2Si (M^+) 338.264109, found 338.263645; [\alpha]_D^{23} -12.8^\circ (CH_2Cl_2, c 5.0).

1-(4-Methylene-6-non-1-enyltetrahydropyran-2-yl)ethanol (+)-73

Trimethyl[2-(5-methyl-2-non-1-enyl-[1,3]dioxolan-4-ylmethyl)allyl] (-)-72 (0.05 g, 0.15 mmol) was subjected to standard aqueous Prins cyclization conditions using scandium chloride hexahydrate (0.002 g, 0.01 mmol) and sodium dodecylsulfate (0.04 g, 0.15 mmol) to afford the desired product (0.02 g, 51%): 1H NMR (300 MHz, CDCl_3) δ 5.69 (dtd, J = 15.5, 5.8, 0.76 Hz, 1H), 5.47 (ddt, J = 15.5, 6.2, 1.2 Hz, 1H), 4.78 (s, 2H), 3.74 (m, 1H), 3.66 (m, 1H), 3.11 (m, 1H), 2.81 (s, 1H), 2.22 (m, 2H), 2.02 (m, 4H), 1.27 (m, 10H), 1.18 (d, J = 6.3 Hz, 3H), 0.88 (t, J = 6.4 Hz, 3H); 13C NMR (75 MHz, CDCl_3) δ 143.9, 132.7, 130.5, 109.5, 82.9, 79.1, 70.7, 41.2, 36.7, 32.5, 32.0, 29.3, 22.8, 18.4, 14.2; IR (neat) 3440, 3076, 2916, 2850, 1650, 1469, 1367, 1250, 1061, 967, 887; HRMS (EI): m/z calcd for C_{17}H_{30}O_2 (M^+) 266.224580, found 266.224580; [\alpha]_D^{23} +0.218^\circ (CH_2Cl_2, c 16.0).

2-(1-Hydroxyethyl)-4-methyl-6-non-1-enyl-tetrahydropyran-4-ol (75)

(0.006, 12%): 1H NMR (300 MHz, CDCl_3) δ 5.68 (dt, J = 15.4, 6.8 Hz, 1H), 5.47 (dd, J = 15.6, 6.1 Hz, 1H), 4.17 (m, 1H), 3.85 (m, 1H), 3.64 (m, 2H), 3.16 (m, 1H), 2.04 (m, 2H), 1.62 (m, 4H), 1.36 (s, 3H), 1.27 (m, 10H), 1.17 (d, J = 6.3 Hz, 3H), 0.89 (t, J = 6.8, 3H); 13C NMR (75 MHz, CDCl_3) δ 133.0, 130.3, 79.9, 75.7, 73.6, 70.7, 69.5, 46.4, 44.6, 41.9, 40.18, 32.5, 32.0, 29.9, 29.3, 26.3, 22.8, 18.3, 14.3; IR (neat) 3374, 2952, 2923, 2858,
1469, 1367, 1294, 1090, 1054, 967; HRMS (EI): \( m/z \) calcd for \( \text{C}_{17}\text{H}_{32}\text{O}_{3} (\text{M}^+) \) 284.235145, found 284.235687.

**Benzoic acid 1-(4-methylene-6-non-1-enyltetrahydropyran-2-yl)ethyl ester**

To (+)-73 (0.02 g, 0.08 mmol) in \( \text{CH}_2\text{Cl}_2 \) (1 mL) was added benzoyl chloride (0.01 g, 0.11 mmol), anhydrous pyridine (1 mL), and a catalytic amount of DMAP. The reaction was stirred for 18 h, then concentrated and purified by flash chromatography (5% Et\(_2\)O in pentanes) to afford the desired product (0.02 g, 81%): \(^1\text{H} \text{NMR} (300 \text{ MHz, CDCl}_3) \delta 8.05 \text{ (d, } J = 7.0 \text{ Hz, 2H), 7.56 \text{ (dd, } J = 7.3, 7.3 \text{ Hz, 1H), 7.45 \text{ (dd, } J = 7.2, 6.5 \text{ Hz, 2H), 5.66 \text{ (dt, } J = 15.5, 6.4 \text{ Hz, 1H), 5.52 \text{ (dd, } J = 15.5, 5.8 \text{ Hz, 1H), 5.27 \text{ (m, 2H), 4.78 \text{ (s, 2H), 3.76 \text{ (m, 1H), 3.52 \text{ (m, 1H), 2.15 \text{ (m, 6H), 1.40 \text{ (d, } J = 6.5 \text{ Hz, 3H), 1.27 \text{ (m, 10H), 0.86 \text{ (t, } J = 6.9 \text{ Hz, 3H); } ^{13}\text{C NMR} (75 \text{ MHz, CDCl}_3) \delta 166.2, 144.1, 133.0, 132.4, 130.8, 130.4, 129.8, 128.4, 109.5, 79.2, 72.3, 41.2, 35.7, 32.5, 32.0, 29.3, 22.8, 15.7, 14.3; IR (neat) 3061.8, 2923.6, 2850.9, 1716.3, 1650.9, 1592.7, 1447.2, 1352.7, 1309.1, 1280.0, 1170.9, 1112.7, 960.0, 887.2; HRMS (EI): \( m/z \) calcd \( \text{C}_{24}\text{H}_{34}\text{O}_{3} (\text{M}^+) \) 370.250795 found, 370.252609; [\( \alpha \)]\(_D\)\(^{23}\) 0.986° (\( \text{CH}_2\text{Cl}_2 \), \( c \) 5.0).

The ee was determined to be 86% by chiral HPLC analysis using a chirapak AD column. Conditions: Hex:"/PrOH 90:10, 0.40 mL/min.

**Benzyloxy-acetic acid methyl ester**

To a suspension of silver (I) oxide (5.15 g, 22.20 mmol) in Et\(_2\)O (10 mL) was added methyl glycolate (1.0 g, 11.10 mmol) and benzyl bromide (2.85 g, 16.65 mmol). The reaction mixture was heated to reflux and stirred for 18 h, cooled to room temperature, filtered through a pad of...
Celite and concentrated. The resulting residue was purified by flash chromatography (10% Et₂O in pentanes) to afford the desired product (82%, 1.64 g): ¹H NMR (300 MHz, CDCl₃) δ 7.33 (m, 5H), 4.64 (s, 2H), 4.15 (s, 2H), 3.77 (s, 3H).

2-Benzylxoy-propionic acid methyl ester

To a stirring solution of lithium bis(trimethylsilyl)amide (1.0 M in THF, 5.55 mmol, 5.55 mL) and hexamethylphosphoramide (0.05 g, 0.28 mmol) at -78 ºC was added benzyloxy-acetic acid methyl ester (0.50 g, 2.77 mmol). The reaction mixture was stirred for 30 min, and then iodomethane (1.96 g, 13.87 mmol) was added. The reaction mixture was stirred for 3 h, then quenched with saturated aqueous NH₄Cl and allowed to warm to room temperature. The reaction mixture was extracted into Et₂O and the aqueous layer was washed with Et₂O. The combined organic layers were dried (MgSO₄), and concentrated. The resulting residue was purified by flash chromatography (10% Et₂O in pentanes) to afford the desired product (0.25 g, 46%): ¹H NMR (300 MHz, CDCl₃) δ 7.35 (m, 5H), 4.72 (d, J = 11.6 Hz, 1H), 4.48 (d, J = 11.6 Hz, 1H), 4.09 (q, J = 6.9 Hz, 1H), 3.76 (s, 3H), 1.44 (d, J = 6.8 Hz, 3H).

The racemic form of benzoic acid 1-(4-methylene-6-non-1-enyltetrahydropyran-2-yl)ethyl ester was synthesized in the same manner as the enantiopure form starting from 2-Benzylxoy-propionic acid methyl ester. The racemic form was used as a standard for HPLC analysis and ee determination.
2.5. References


56 Patterson, B.; Rychnovsky, S. D. “Mukaiyama aldol-Prins cyclization with ketones” *Synlett*, 2004, 3, 543-545.


3. Efforts towards the total synthesis of (+)-dactylolide

3.1. Introduction

I. Background

Over 70% of the earth’s surface is covered by water.\textsuperscript{71} The oceans endow us with a complex biological environment that consists of an extensive assemblage of life forms. These life forms thrive in extreme habitats and continuously endure tremendous variations in pressure, salinity, and temperature, as well as attack from a wide array of predators. Consequently, they have developed unique metabolic and physiological capabilities that ensure survival. It is this potential for the production of unique bioactive metabolites, unlike any isolated from terrestrial organisms, that drives the isolation and analysis of these marine systems. Sponges and marine bacteria serve as fertile sources for these structurally diverse, bioactive molecules. Although isolated from phylogenetically diverse marine sources, macrolides are emerging as an increasingly interesting and important category of molecule based on the wide spectrum of biological and pharmacological properties they exhibit.

Macrolactones are a class of macrolides that provide a great number of cytotoxic agents. (+)-Dactylolide (1) is one such cytotoxic macrolactone recently isolated from the Vanuata sponge \textit{Dactylospongia} sp. by Riccio and coworkers\textsuperscript{72} (Figure 3.1). The crude extract from this sponge was selected based on preliminary pharmacological screening. The biologically active metabolites were obtained following methanol extraction of the lyophilized organism. The methanolic extract was then subjected to a modified Kupchan partition procedure to afford four extracts. Mycothiazole,\textsuperscript{73} latrunculin A,\textsuperscript{74} isolaulimalide\textsuperscript{75} and laulimalide were isolated as pure
compounds after medium pressure liquid chromatography of the most active CCl₄ extract. (+)-Dactylolide was isolated as a pure metabolite following elution with 80% hexanes under medium pressure liquid chromatography and further purification by C-18 reverse phase HPLC (MeOH/H₂O 70:30).

**Figure 3.1:** (+)-Dactylolide (1) and (-)-Zampanolide (2)

![Chemical structures of (+)-Dactylolide (1) and (-)-Zampanolide (2)](image)

Extensive spectroscopic analysis revealed the structure of 1². (+)-Dactylolide possesses a hydrocarbon skeleton bearing three remote stereogenic centers. The major architectural elements are the highly unsaturated 20-membered macrolactone containing two di- and two trisubstituted olefins, the α-acyloxyaldehyde, and the remote C19 stereocenter. The core of the molecule is composed of a 2,6-cis-disubstituted-4-methylenetetrahydropyran, giving rise to the two remaining C11 and C15 stereocenters. While the relative stereochemistry of the core was determined during the initial structural analysis, the absolute stereochemistry and the assignment of the C19 stereocenter was not made until completion of the first total synthesis by Smith⁷⁶ in 2001.

(+)-Dactylolide’s cytotoxicity was expressed through a 63% inhibition against L1210 (lymphatic leukemia of mice) and 40% inhibition against SK-OV-3 (carcinoma of the ovaries) tumor cell lines at 3.2 µg/mL. Other interesting examples of macrolides that bear close structural relationship to (+)-dactylolide are the sphinxolides and reidispongiolides (Figure 3.2). This new class of cytotoxic macrolides are characterized by a very similar 26-membered macrolactone ring which has proven effective against human bronchopulmonary, nasopharyngeal, breast and
colon tumor cell lines, as well as murine leukemia. In particular, the cytotoxicity of the sphinxolides is associated with cell cycle arrest in G2-M and induction of apoptosis. Sphinxolides were found to cause rapid loss of microfilaments in cultured cells without affecting microtubule organization, and potently inhibited actin polymerization in vitro. More importantly, both the sphinxolides and reidispongiolides were shown to circumvent multidrug resistance mediated by overexpression of either P-glycoprotein or MPR. Therefore, these macrolides, as well as (+)-dactylolide may be efficacious in treatment of drug resistant tumors.

**Figure 3.2: Sphinxolides and reidispongiolides**

![Structure of Sphinxolides and Reidispongiolides](image)

R=H, R'=Me Reidispongiolide A
R=H, R'=H Reidispongiolide B
R=OH, R'=Me Sphinxolide B
R=OH, R'=H Sphinxolide D

### II. Previous Syntheses

Smith’s interest in the total synthesis of (+)-dactylolide stemmed from its structural similarity to (-)-zampanolide (2), another cytotoxic marine macrolide (Figure 3.1). Although isolated in 1996 from the Okinawan sponge *Fasciospongia rimosa*, (-)-zampanolide’s skeletal structure is also a sparsely functionalized 20-membered macrolactone incorporating a 2,6-cis-disubstituted-4-methylenetetrahydropyran, differing only in the stereochemical configuration about the tetrahydropyran ring and bearing an unusual N-acyl hemiaminal side chain. The absolute stereochemistry of (-)-zampanolide was unknown until Smith reported the first total
synthesis and tentative stereochemical assignment of the non-naturally-occurring antipode, (+)-zampanolide. Assuming that (+)-dactylolide and (-)-zampanolide would be biosynthetically related and possess the same relative stereochemical assignment at the C19 center, Smith employed the advanced intermediate (-)-AB (Figure 3.3) from his total synthesis of (+)-zampanolide in the first total synthesis and determination of the absolute stereochemical configuration of (+)-dactylolide³.
Smith arrived at (+)-dactylolide in a total of thirty-five steps, with the longest linear sequence involving thirteen steps and the key Petasis-Ferrier\textsuperscript{80} rearrangement to form the 2,6-cis-disubstituted-4-methylenetetrahydropyran core. Three strategic disconnections led to the formation of the macrocycle. Scission of the C2-C3 olefin afforded the Horner-Emmons macrocyclization\textsuperscript{81} substrate 3. Disconnection of the acyl phosphonate linkage provided the commercially available diethylphosphonoacetic acid, 5. Disconnection of the C17-C18 bond simplifies to the higher order cuprate\textsuperscript{82} coupling of vinyl bromide (-)-AB and epoxide 4.
Cleavage of the C9-C8 olefin gave rise to the Kocienski-Julia olefination partners (-)-B and (+)-A.

The Petasis-Ferrier rearrangement was effectively utilized by Smith for the formation of the 2,6-cis-disubstituted-4-methylenetertahydropyran core in the synthesis of sulfone (-)-B (Figure 3.4). Trimethylsilyl ether (+)-6 was synthesized in five steps from a known aldehyde, using a Brown asymmetric allylation to set what will ultimately become the C11 stereocenter. Following condensation of 2(E)-3-bromobut-2-enal and (+)-6, a 10:1, inseparable mixture of dioxanones (+)-8 was isolated. Reaction of the mixture of dioxanones (+)-8 with the Petasis-Tebbe reagent (Cp$_2$TiMe$_2$) furnished (+)-9 as a 6:1, inseparable mixture of enol ethers. Treatment of the mixture of enol ethers with one equivalent of dimethylaluminum chloride at -78 °C effected the Petasis-Ferrier rearrangement to provide a separable mixture of cis-pyranoones, affording the desired pyranone (+)-12 in 59% yield.

**Figure 3.4:** Petasis-Ferrier rearrangement

Standard Wittig reaction with pyranone (+)-12 provided the exocyclic methylene to complete the tetrahydropyran core of the molecule (Figure 3.5). Removal of the BPS protecting group followed by introduction of the thiotetrazole using the Mitsunobu protocol provided (+)-
The sulfide was then oxidized to the sulfone to afford advanced intermediate (-)-B. Thus, the 2,6-cis-disubstituted-4-methylenetetrahydropyran core of (+)-dactylolide was realized in the longest linear sequence of the total synthesis. Starting from a known aldehyde, a total of thirteen steps were utilized to furnish (-)-B in a 12% overall yield, with key cyclization reaction involving the Petasis-Ferrier rearrangement.

Figure 3.5: Completion of advanced intermediate (-)-B

Following the construction of the 2,6-disubstituted-4-methylenetetrahydropyran core, completion of the molecule proceeded quickly and uneventfully (Figure 3.6). The most difficult step involved reaction of the higher order cuprate of (-)-AB with epoxide ⁴, only providing the desired secondary alcohol in moderate yield. Acylation with the commercially available diethylphosphonoacetic acid ⁵ afforded (-)-17 in excellent yield. Subsequent selective desilylation of the primary silyl ether, oxidation to the aldehyde with Dess-Martin periodinane (DMPI) and Horner-Emmons macrocyclization provided (-)-18 in good yield. Following two successive deprotection oxidation steps Smith arrived at the natural product (+)-dactylolide, assigning both the absolute and relative stereochemistries.
Hoye recently reported the total synthesis of the antipode, (-)-dactylolide 20, coupled with a synthetic effort towards zampanolide, in which the key transformations involved a unique macrocyclization and Prins cyclization for the formation of the 2,6-cis-disubstituted-4-methylenetetrahydropyran core. The strategic disconnections are shown in Figure 3.6. Bond scission A gives rise to the titanium (IV)-mediated epoxide opening by a carboxylic acid (Box A, Figure 3.7). Formation of bond B was envisioned through a C8-vinyl anion addition to a C7-aldehyde (Box B, Figure 3.7). Construction of the 2,6-cis-disubstituted-4-methylenetetrahydropyran core was envisioned to occur via a Prins cyclization reaction between a C15-enal and an allylsilane (Box C, Figure 3.7).
Figure 3.7: Strategic bond disconnections in the Hoye synthesis

Synthesis of the 2,6-\textit{cis}-disubstituted-4-methylenetetrahydropyran core is shown in Figure 3.8. Condensation of aldehyde 21 and silyl ether 22 in the presence of camphorsulfonic acid (CSA) provided intermediate oxocarbenium ion 22a, which underwent intramolecular Prins cyclization to form 2,6-\textit{cis}-disubstituted-4-methylenetetrahydropyran 23. Tetrahydropyran 23 was isolated as a single diastereomer in good yield. Initial attempts at cyclization using Lewis acids (BF$_3$•OEt$_2$ or TMSOTf) provided better yields, but unacceptable 2:1 cis/trans stereoselectivity. Removal of the pivalate protecting group followed by DMPI oxidation furnished aldehyde 24. Aldehyde 24 was transformed via a Takai reaction into iodoalkene 25 with 4:1 \textit{E}:\textit{Z} selectivity. The silyl ether was removed with TBAF to reveal the allyl alcohol. Deprotection of the silyl ether with the fluoride source TBAF proved beneficial in that the minor, inseperable \textit{Z} isomer underwent facile E2-elimination to give the more polar, seperable alkyne. Sharpless asymmetric epoxidation\textsuperscript{88} provided advanced intermediate 26, setting the C19 stereocenter with 25:1 diastereoselectivity.
Figure 3.8: Hoye's Prins cyclization to form the core of (-)-dactylolide

The final manipulations for macrolactonization and completion of the synthesis are shown in Figure 3.9. The C7-C8 bond of tetrahydropyran 28 was formed via addition of the vinyl lithium derived from vinyl iodide 26 into aldehyde 27. Protecting group manipulations followed by oxidation to the carboxylic acid provided the key macrocyclization substrate 29. Exposure of 29 to titanium isopropoxide and heat afforded a modest yield of the macrolactone via Lewis acid assisted opening of the epoxide by the carboxylic acid inverting the C19 stereocenter. The efficiency of the cyclization was limited by unproductive macrolactone formation through closure at C20 rather than C19, and C1 isopropyl ether formation. Given the accumulation of undesired side products with extended reaction times, macrolactonization was never carried to more than 50% conversion. Silyl ether removal, chemoselective oxidation of the allylic alcohol and final cleavage of the diol with lead tetraacetate provided (-)-dactylolide, 20. The natural product was realized in thirteen total steps through the coupling of three highly advanced intermediates.
III. Retrosynthesis

Both Smith and Hoye used convergent strategies focusing on advanced intermediates derived from chiral pool materials as well as asymmetric catalysis that could be applied in unified syntheses of both dactylolide and zampanolide. The benchmark for our synthesis of (+)-dactylolide was set by Smith at a total of thirty-five steps, but more importantly construction of the 2,6-cis-4-methylene-tetrahydropyran core in thirteen steps. Given the development of the aqueous Prins cyclization method we believed that the synthesis could be achieved in far fewer steps through a highly convergent route effectively utilizing the Prins cyclization as the key transformation on a late stage synthetic intermediate. The aqueous Prins cyclization method was
developed as an efficient and stereoselective entry into 2,6-cis-4-methylene-tetrahydropyrans via intramolecular cyclization reaction of a cyclic α,β-unsaturated acetal with a pendent allylsilane. The use of cyclic α,β-unsaturated acetals as cyclization substrates allows for the condensation of two highly functionalized advanced intermediates that can undergo the key transformation, thus dramatically decreasing the number of synthetic manipulations required for completion of the synthesis.

The retrosynthetic analysis is outlined in Figure 3.10. Following in the footsteps of Smith, scission of the C2-C3 olefin provides Horner-Emmons macrocyclization substrate 42. Disconnection of the C1 acylphoshonate linkage leads to the commercially available diethylphosphonoacetic acid 5 and secondary alcohol (-)-41. Reverse allylic transposition of the secondary alcohol from C9 to C7 provides selenoxide-selenate rearrangement substrate (+)-40. Disconnection of the C14-C15 tetrahydropyran bond gives rise to the intramolecular Prins cyclization substrate cyclic α,β-unsaturated acetal (+)-39. Cleavage of the cyclic α,β-unsaturated acetal of (+)-39 yields the known enal (+)-38 as well as diol (-)-37. α,β-unsaturated aldehyde (+)-38 arises from a copper-pybox catalyzed vinylogous aldol reaction. Diol (-)-37 also ultimately comes from the vinylogous aldol reaction of enal 35 and silyl ketene acetal 36. α,β-unsaturated aldehyde 36 can be envisioned to arise from a cross metathesis reaction of the commercially available diethylacrolein acetal with skipped diene 33. Scission of what will ultimately become the C5-C6 bond gives rise to the starting materials vinyl stannane 31 and allylbromide.
3.2. Results and Discussion

The key transformation in our highly convergent route to (+)-dactyloide involves an intramolecular Prins cyclization of a cyclic α,β-unsaturated acetal with a pendent allylsilane. The desired cyclic α,β-unsaturated acetal (+)-39 results from the condensation of two highly functionalized advanced intermediates enal (+)-38 and diol (-)-37, followed by conversion of the ester to the allylsilane. Both enal (+)-38 and diol (-)-37 were synthesized using vinylogous aldol reactions (Figure 3.10).

The synthesis of enal (+)-38 is shown in Scheme 3.1. p-Methoxy benzyloxy acetaldehyde 43 was prepared in three steps from 1,4-butene diol. Protection of 1,4-butene diol as the bis-PMB
ether followed by Sharpless asymmetric dihydroxylation and silica gel-supported sodium metaperiodate cleavage cleanly provided the aldehyde in good yield. Ozonolysis reactions of either PMB-protected allyl alcohol or the bis-PMB-protected 1,4-butene diol were low yielding and difficult to purify. The [Cu((R,R)PhPyBox)](SbF₆)₂•2Cl catalyzed vinylogous aldol reaction between p-methoxy benzyloxy acetaldehyde 43 and enolsilane 44 provided the desired aldol adduct, α,β-unsaturated ester (+)-45 as a single (E)-olefin isomer in good yield and excellent enantioselectivity (82%, 95% ee).

Scheme 3.1: Synthesis of enal (+)-38

This vinylogous aldol reaction developed by Evans aptly provides the desired enatio- as well as regioselectivity (through avoidance of unwanted A₁,₃ strain) for the generation of the necessary ε-hydroxy-α,β-unsaturated carbonyl structure. The transition state for the vinylogous aldol is depicted in Figure 3.11, showing re-face attack of the diene. No product arising from α-addition of the silylketene acetal was observed, only that of γ-addition.

Figure 3.11: Vinylogous aldol transition state
Following the vinylogous aldol reaction, secondary alcohol (+)-45 (Scheme 3.1) was protected as the tert-butylidemethylsilyl ether using tert-butylidemethylsilyl chloride and imidazole in DMF. The α,β-unsaturated ester was reduced to the allylic alcohol with lithium aluminum hydride and then oxidized to enal (+)-38 with manganese dioxide in good yield. Enal (+)-38, one major coupling partner needed for cyclic α,β-unsaturated acetal formation, containing what would ultimately become the C19 stereocenter of (+)-dactylolide and bearing the correct geometry for the C16-C17 olefin, was realized in four steps in high yield and excellent enantioselectivity.

A vinylogous aldol reaction was also used in the production of diol (-)-37, the second coupling component necessary for cyclic α,β-unsaturated acetal formation. The synthesis of the aldehyde required for the vinylogous aldol reaction, and what would ultimately become the C3-C9 segment, is shown in Scheme 3.2. Preparation of the C4-C5 trisubstituted (Z)-olefin started with Red-Al reduction of 2-butyn-1-ol followed by quenching with tributyltin chloride to give (Z)-3-tributylstannyl-but-2-en-1-ol 31 in good yield. The primary alcohol was protected as the tert-butylidiphenylsilyl ether to afford vinylstannane 48. Palladium mediated coupling of vinylstannane 48 and allyl bromide provided the skipped diene 33 in good yield. Cross metathesis using Grubbs 1st generation catalyst, followed by in situ formic acid hydrolysis provided α,β-unsaturated enal 35 in high yield with excellent (E)-selectivity. The observed selectivity is proposed to result from the reversibility of the cross metathesis reaction, tending toward the formation of the more thermodynamically stable E-isomer. This type of self editing, reversible mechanism was exploited by Smith in his synthesis of (-)-cylindrocyclophanes A and F.94
Support for this idea is also provided through the work of Grubbs on ring closing metathesis, as well as by Hoveyda in his work on the total synthesis of fluvirucin B1.

**Scheme 3.2: Synthesis of aldehyde 35**

With aldehyde 35 in hand the stage was set for the second vinylogous aldol reaction. The vinylogous aldol reaction was first examined using the unique chemistry developed by Carreira for the catalytic generation of a chiral Cu(II) dienolate initiated by a (R)-Tol-BINAP·Cu(II)-fluoride complex that is generated in situ through the reaction of (R)-Tol-BINAP·Cu(II)-triflate with the anhydrous fluoride source (Bu₄N)Ph₃SiF₂ (TBAT) as shown in Scheme 3.3. The three salient features of this vinylogous aldol reaction were its application in the total syntheses leucascandrolide A for the formation of a similar dioxenone, combined with the inexpensive, commercially available BINAP ligand, as well as the high yields and enantioselectivities observed by Carreira. However, in test reactions involving cinnamaldehyde and silyl ketene acetal 36 the observed yields and enantioselectivities were considerably less than expected or previously reported in the literature.
Scheme 3.3: Carreira vinylogous aldol

\[
\begin{align*}
\text{Reagents: } & a) (R)-\text{Tol-BINAP, Cu(OTf)}_2, (\text{Bu}_4\text{N})\text{Ph}_3\text{SiF}_2, \text{THF, } -78^\circ \text{C, } 51\%, 42\% \text{ ee} \\
\end{align*}
\]

The desired mechanistic pathway involved desilylation by the in situ generated metal fluoride with concomitant generation of a chiral enolate through complexation with the chiral metal complex, as shown in Figure 3.12. The low enantioselectivity was proposed to result from the in situ generation of copper (II) fluoride in competition with the generation of the chiral \((R)-\text{Tol-BINAP-Cu(II)-fluoride}\). Copper (II) fluoride then entered into the catalytic cycle to catalyze the racemic aldol reaction. Given the difficulty in obtaining the desired yields and enantioselectivities, coupled with the success of the alternative Denmark vinylogous aldol, further development of this reaction was not pursued.

Figure 3.12: Carreira vinylogous aldol catalytic cycle

Reaction of aldehyde 35 with silyl ketene acetal 36 in the presence of Denmark’s chiral bisphosphoramidé \((S,S)-\text{E}^{99}\) and silicon tetrachloride provided dioxenone (-)-52 in good yield and excellent enantioselectivity (65%, 93% ee), as shown in Scheme 3.4.
Scheme 3.4: Denmark vinylogous aldol

The reaction is unique in that the active chiral Lewis acid is generated in situ through the coordination of the weak Lewis acid silicon tetrachloride to the strongly Lewis basic bisphosphoramidate \((S,S)\)-E to form a catalytically active pentacoordinate silicon species. Extensive studies by Denmark on solution and solid phase bisphosphoramide•SnCl₄ complexes suggest that the reaction proceeds through the hexacoordinate cationic silicon assembly \(52a\) shown in Scheme 3.4. In allylation as well as aldol reactions higher enantioselectivities were observed using a tethered bisphosphoramide rather than two equivalents of a phosphoramidate. The restriction provided by a five-methylene unit tether in \((S,S)\)-E dictates the coordination environment about the reactive silicon center, forcing it to adopt an octahedral geometry. Thus, in the transition structure, the aldehyde would coordinate trans to a chloride at the most Lewis basic site, consequently increasing its electrophilicity. Support for the reaction proceeding through an open transition state was furnished by Denmark’s observation that in bisphosphoramide silicon tetrachloride catalyzed aldol reactions the geometrical integrity of the nucleophile had no effect on the enantio- or diastereoselectivity of the products. Denmark further discounted the possibility of a closed Zimmerman-Traxler type transition state through NMR studies on the stability of silyl ketene acetals in the presence of silicon tetrachloride and HMPA, in which no isomerization or metathesis of the silyl ketene acetal was observed.
Following the Denmark vinylogous aldol reaction, synthesis of diol (-)-37 was completed uneventfully in a total of three steps in high yield an excellent enantioselectivity, as shown in Scheme 3.5. Conversion of dioxenone (-)-52 to β-hydroxy keto ester (-)-54 was accomplished through a thermal retro-Diels-Alder reaction leading to intermediate ketene 53 formation through acetone extrusion and subsequent trapping with 1-butanol. β-Hydroxyketone (-)-54 was subjected to diastereoselective sodium borohydride reduction in the presence of the chelating reagent diethylmethoxyborane to provide 1,3-syn diol (-)-37 in high yield and 99:1 d.e.

Scheme 3.5: Synthesis of diol (-)-37

With the successful synthesis of 1,3-syn diol (-)-37 and enal (+)-38, the focus became formation of the key advanced intermediate, cyclic α,β-unsaturated acetal (+)-39. In the development of the aqueous Prins reaction, cyclic acetals were generated under protic conditions either by refluxing with concomitant azeotropic removal of water, or at low temperature utilizing the dehydrating reagent magnesium sulfate. However, all attempts at acetal formation under protic conditions, including the use of Montmorillonite K-10 clay, Amberlyst-15 resin and trans-acetalization with the diethylacetal of enal (+)-38 proved ineffective, and led to E/Z isomerization of the aldehyde. Acetalization under Lewis acidic conditions (TMSOTf, WCl₆) was also unproductive. Yet, as shown in Scheme 3.6, successful acetalization was accomplished
using conditions developed by Noyori\textsuperscript{107} employing catalytic TMSOTf and stoichiometric silyl ethers. Formation of the bis-trimethylsilyl ether (-)-55 with trimethylsilyl chloride and DMAP in DMF, followed by TMSOTf catalyzed reaction with enal (+)-38 afforded the desired cyclic $\alpha,\beta$-unsaturated acetal (+)-39 in good yield.

**Scheme 3.6:** Formation of cyclic $\alpha,\beta$-unsaturated acetal (+)-39

The central transformation in the synthesis involved intramolecular Prins cyclization to form the 2,6-\textit{cis}-4-methylene-tetrahydropyran core of the (+)-dactylolide. The transformation was envisioned to occur upon ionization of the cyclic $\alpha,\beta$-unsaturated acetal followed by cyclization with the pendent allylsilane. Therefore, conversion of the butyl ester in cyclic $\alpha,\beta$-unsaturated acetal (+)-39 to the allylsilane was necessary. The literature protocol for the conversion of a functionalized ester to an allylsilane consists of a two step procedure involving the addition of a premixed solution of anhydrous cerium (III) chloride and trimethylsilylmethylmagnesium chloride to the ester to afford the tertiary alcohol. Mild acid treatment of the crude tertiary alcohol with silica gel then initiates Peterson elimination to form the desired allylsilane.\textsuperscript{108} When cyclic $\alpha,\beta$-unsaturated acetal (+)-39 was stirred with a premixed solution of anhydrous cerium (III) chloride and trimethylsilylmethylmagnesium chloride followed by quenching with 5\% HCl, the product isolated from the reaction mixture was not the
expected tertiary alcohol, but rather the 2,6-\textit{cis}-4-methylene-tetrahydropyran core of the molecule (+)-40, as shown in Scheme 3.7.

**Scheme 3.7: Intramolecular Prins Cyclization**

![Reaction Scheme](image)

Reagents: a) i. Me$_3$SiCH$_2$MgCl, CeCl$_3$, THF, -78°C to r.t. ii. 1N HCl, -78°C to r.t. 42%

The one pot transformation from cyclic $\alpha,\beta$-unsaturated acetal (+)-39 to the 2,6-\textit{cis}-4-methylene-tetrahydropyran (+)-40 is shown in Figure 3.13. Under the reaction conditions, the organosilane carries out a double addition into the ester to provide tertiary alcohol 56. Upon quenching with 5% HCl the tertiary alcohol undergoes Peterson elimination to form the allylsilane (-)-57. It is believed that trace amounts of cerium survived the work-up protocol and went on to catalyze the Prins cyclization, because 2,6-\textit{cis}-4-methylene-tetrahydropyran (+)-40 was only observed following work-up and concentration of the crude reaction mixture.
In an effort to better understand the results of the one pot ester-to-Prins transformation the quenching and work-up procedures were altered. Repeating the quenching and work-up procedure, followed by allowing the crude product to stand at room temperature overnight led only to decomposition of what appeared to be the desired Prins product by TLC. Refluxing the organic layer obtained after work-up in ether prior to concentration resulted in isolation of only the E/Z isomerized aldehyde (+)-38. As shown in Scheme 3.8, quenching with ethyl acetate followed by basic work-up with saturated NaHCO₃ provided tertiary alcohol 56, which could be converted to allylsilane through stirring with silica gel in CH₂Cl₂. Quenching with saturated NH₄Cl afforded allylsilane (-)-57. However, washing allylsilane (-)-57 with a 1.0 M solution of cerium (III) chloride failed to effect Prins cyclization, as did stirring with silica gel for prolonged periods of time.
Scheme 3.8: Altered quenching method

Given the ability to cleanly isolate allylsilane (-)-57, conversion to the Prins cyclization product (+)-40 was attempted using a variety of Lewis and Bronstead acids as shown in Table 3.2. Prins cyclization could only be affected using both PPTS and the pyridine salt of camphorsulfonic acid (PCSA). Cyclization with PPTS resulted in protodesilylation, as well as the desired tetrahydropyran (+)-40. The addition of MgSO₄ to PPTS catalyzed Prins cyclization increased reaction yield, and provided only the desired tetrahydropyran (+)-40. Subjecting allylsilane (-)-57 to the reaction conditions developed for the aqueous Prins reaction failed to yield any of the desired tetrahydropyran (+)-40, but rather resulted in complete decomposition of the starting material. Under these reaction conditions viable micelle formation was not observed. Neither the critical micelle concentration required was achieved, nor was a surfactant of ideal chain length for viable micelle formation identified. All attempts at performing the Prins cyclization in the presence of a mild Lewis acid at ambient temperature also proved ineffective.

Despite the ability to isolate allylsilane (-)-57 and effect Prins cyclization with PPTS, in terms of overall yield and step count the most synthetically practical route to tetrahydropyran (+)-40 remains the one pot ester-to-Prins transformation. Isolation of the tertiary alcohol followed by Peterson elimination to give allylsilane (-)-57 and subsequent Prins cyclization with PPTS is a lengthy, inefficient means for the preparation of the tetrahydropyran (+)-40. Protodesilylation is a competitive, unproductive reactive pathway in this route that significantly
decreases reaction yield, and affords the side product (-)-58 that can not be further manipulated for useful synthetic transformations. Therefore, efforts will continue to be focused on optimizing the one pot ester-to-Prins transformation.

**Table 3.1: Screening of viable Prins cyclization conditions**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis/Brønstead Acid</th>
<th>Solvent</th>
<th>Product (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ScCl$_3$•6H$_2$O, SDS</td>
<td>H$_2$O</td>
<td>Decomposition</td>
</tr>
<tr>
<td>2</td>
<td>Me$_3$Al</td>
<td>CH$_2$Cl$_2$</td>
<td>Decomposition</td>
</tr>
<tr>
<td>3</td>
<td>Ce(OTf)$_3$</td>
<td>CH$_3$CN</td>
<td>Decomposition</td>
</tr>
<tr>
<td>4</td>
<td>ScCl$_3$•6H$_2$O</td>
<td>CH$_3$CN</td>
<td>No rxn</td>
</tr>
<tr>
<td>5</td>
<td>Sc(OTf)$_3$</td>
<td>CH$_3$CN</td>
<td>Decomposition</td>
</tr>
<tr>
<td>6</td>
<td>EuCl$_3$</td>
<td>CH$_3$CN</td>
<td>Decomposition</td>
</tr>
<tr>
<td>7</td>
<td>CeCl$_3$</td>
<td>EtOAc</td>
<td>No rxn</td>
</tr>
<tr>
<td>8</td>
<td>CeCl$_3$, I$_2$</td>
<td>EtOAc</td>
<td>No rxn</td>
</tr>
<tr>
<td>9</td>
<td>CeCl$_3$, SiO$_2$</td>
<td>EtOAc</td>
<td>No rxn</td>
</tr>
<tr>
<td>10</td>
<td>SiO$_2$</td>
<td>CH$_2$Cl$_2$</td>
<td>No rxn</td>
</tr>
<tr>
<td>11</td>
<td>SnCl$_4$ on SiO$_2$</td>
<td>CH$_2$Cl$_2$</td>
<td>Decomposition</td>
</tr>
<tr>
<td>12</td>
<td>TMSOTf</td>
<td>CH$_2$Cl$_2$</td>
<td>Decomposition</td>
</tr>
<tr>
<td>13</td>
<td>MgCl$_2$</td>
<td>EtOAc</td>
<td>No rxn</td>
</tr>
<tr>
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<td>---</td>
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</tr>
<tr>
<td>14</td>
<td>Montmorillonite K-10</td>
<td>CH₂Cl₂</td>
<td>No rxn</td>
</tr>
<tr>
<td>15</td>
<td>Pyridinium camphorsulfonate</td>
<td>CH₂Cl₂</td>
<td>(+)-40 (47%)</td>
</tr>
<tr>
<td>16</td>
<td>PTSA</td>
<td>CH₂Cl₂</td>
<td>Decomposition</td>
</tr>
<tr>
<td>17</td>
<td>PPTS</td>
<td>CH₂Cl₂</td>
<td>(+)-40 (48%), (-)-58 (29%)</td>
</tr>
<tr>
<td>18</td>
<td>PPTS, MgSO₄</td>
<td>CH₂Cl₂</td>
<td>(+)-40 (66%)</td>
</tr>
</tbody>
</table>

*All reactions conducted at room temperature

In Figure 3.13, the atoms involved in intramolecular Prins cyclization are highlighted in red for clarity. In accord with the observed diastereoselectivity in the development of the aqueous Prins reaction, only a single diastereomer of (+)-40 was isolated. The cis stereochemical relationship between the C11 and C15 protons was conformed through the strong correlation observed in the NOESY spectrum of (-)-59. The origin of the cis selectivity is understood to be the preference of the two alkyl groups to adopt a pseudoequitorial orientation in the transition state for the Prins reaction. α,β-Unsaturated ketone (-)-59 was used in spectral studies in preference to (+)-40 simply for ease of analysis.

Having successfully constructed the core of the molecule through intramolecular Prins cyclization, the focus shifted to allylic transposition of the C7 alcohol to C9. Initially, the feasibility of allylic transposition via a Wharton epoxy ketone fragmentation¹⁰⁹ was probed. 2,6-cis-4-Methylene-tetrahydropyran (+)-40 was converted to α,β-epoxy ketone (-)-60, as shown in Scheme 3.9. However, all attempts to affect the transformation using hydrazine under the conditions developed by Wharton or at low temperature using conditions developed by Luche¹¹⁰ failed to yield any of the desired transposed allylic alcohol.
Fearing that facile, self condensation to form azine 61 was inhibiting fragmentation, the reaction was attempted using 1,2-bis(tert-butyldimethylsilyl)hydrazine (BTBSH)\(^{111}\) in the presence of Sc(OTf)_3. BTBSH is known to react with ketones and aldehydes in the presence of a Lewis acid, and to date has been employed in Wolff-Kischner-type reduction reactions, Barton vinyl iodide preparation, and the synthesis of gem-dihalides.\(^{112}\) The use of the N-silyl hydrazone was expected to enhance stability and prevent azine formation, allowing for isolation of a stable hydrazone which could then be subjected to Wharton fragmentation conditions. However, reaction of BTBSH with epoxy-ketone (-)-60, as shown in Scheme 3.10, led only to decomposition of the starting material. No identifiable side products were isolated and no starting material was recovered.
Scheme 3.10: Hydrazone formation with BTBSH

![Scheme 3.10: Hydrazone formation with BTBSH](image)

Allylic transposition via the Wharton fragmentation gave way to an allyl selenoxide-selenate [2,3] sigmatropic rearrangement,\(^\text{113}\) as all attempts employing hydrazine or BTBSH proved ineffective. The [2,3] sigmatropic rearrangement of selenoxides provides a powerful pathway for allylic transposition of alcohols. Tetrahydropyran (+)-40 was converted to selenide 40a with phenylselenocyanate and tributyl phosphine. Selenide 40a was then treated with peroxide and pyridine to effect oxidation to the selenoxide, followed by [2,3] sigmatropic rearrangement to provide allylic alcohol (-)-62 (Scheme 3.11). Allylic alcohol (-)-62 was isolated as a single isomer with complete stereocontrol in the formation of the trans C8-C9 olefin. The complete selectivity is attributed to the propensity of the large alkyl groups to preferentially occupy pseudoequitorial positions in the five-membered transition state. This result also is in accord with observations made by Otera in his work on [2,3] sigmatropic rearrangements of allylic sulfoxides, in which rearrangements were found to occur with extremely high E-selectivity when a substituent branched at the β position of the sulfinyl group was involved. Thus, formation of the E-isomer is thermodynamically, as well as kinetically, favored, so as to avoid A\(_{1,3}\) strain that would be imposed by the presence of the THP ring in the Z-isomer.
Following the selective [2,3]-selenoxide-selenate rearrangement, preparations to close the macrocycle began. Global deprotection of the silyl ethers using TBAF to provide triol 63, followed by double allylic oxidation with MnO$_2$ led only to decomposition (Scheme 3.12).

Subsequent to the failed double allylic oxidation, the strategy became protection of the C9 alcohol as the PMB ether, followed by global silyl deprotection and selective oxidation of the primary alcohol in the presence of the secondary alcohol. Thus, following acylation with the commercially available diethylphosphonoacetic acid 5 and Horner-Emmons macrocyclization a global deprotection of the PMB ethers followed by a double oxidation would provide the (+)-dactylolide. As shown in Scheme 3.13, the C9 alcohol was protected as the PMB ether using sodium hydride and $p$-methoxybenzyl chloride in DMF. Protection under acidic conditions using $p$-methoxybenzyl trichloroacetimidate failed to yield any of the desired PMB ether. The use of HF-pyridine for global silyl deprotection provided a 40% yield of the desired diol, (-)-41 and 27% yield of primary alcohol 64, which could be resubjected to the reaction conditions to
provide \((-\text{-}41\). Global silyl deprotection with TBAF proved less favorable, providing only a 27% yield of the desired diol \((-\text{-}41\), with no other isolable products. Selective oxidation of the primary, allylic alcohol in the presence of the secondary alcohol was accomplished using one equivalent of Dess-Martin periodinane to provide aldehyde \((-\text{-}65\) in 64% yield.

**Scheme 3.13: Selective oxidation**

![Scheme 3.13: Selective oxidation](image)

Reagents: a) PMBCl, NaH, TBAI, DMF, b) HF-pyridine, THF, 40%, c) DMPI, CH₂Cl₂, 64%

Precedence for acylation with the commercially available diethylphosphonoacetic acid \(5\), followed by Horner-Emmons macrocyclization was established through the work of Smith \(^3\) in the first total synthesis of \((+\)-dactylolide. An advanced intermediate prepared by Smith differs from \((-\text{-}65\) only in that the C9 hydroxyl group is protected as a TBS ether, rather than a PMB ether. Efforts towards the completion of the molecule are on going. However, advanced intermediate \((-\text{-}65\) was attained in seventeen total steps, with the longest linear sequence involving seven steps for the preparation of diol \((-\text{-}37\). Thus, this highly convergent route clearly underscores the efforts of Smith who set the benchmark at thirty-five total steps with a longest linear sequence of thirteen steps.
3.3. Conclusion

A highly convergent route towards the total synthesis of the marine macrolide (+)-dactylolide is currently being pursued. The route involves the condensation of two highly functionalized segments of the molecule, an $\alpha,\beta$-unsaturated aldehyde and a 1,3-$\text{syn}$-diol, to form a cyclic $\alpha,\beta$-unsaturated acetal. Both enantiopure segments arise from vinylogous aldol reactions, providing the three necessary stereocenters. The 1,3-$\text{syn}$-diol is reached in the longest linear sequence of the synthesis, utilizing only seven steps from commercially available starting materials. The key synthetic transformation involves intramolecular Prins cyclization of a cyclic $\alpha,\beta$-unsaturated acetal with a pendent allylsilane to provide the 2,6-$\text{cis}$-disubstituted-4-methylenetetrahydropyran core of the molecule efficiently and stereoselectively. The transformation can be achieved either through the in situ generation of the allylsilane in a one pot ester-to-Prins cyclization reaction, or in a lengthier, step-wise manner in which the allylsilane is isolated. Other key transformations include a completely $\text{trans}$ selective selenoxide-selenate [2,3] sigmatropic rearrangement and the selective oxidation of a primary allylic alcohol in the presence of a secondary alcohol with Dess-Martin periodinane. Thus far the synthesis entails seventeen total steps, with the longest linear sequence involving seven steps, well below the bench mark established by Smith at thirty-five total steps. Precedence for the conversion of the most advanced intermediate attained in this effort to the natural product was also established through the work of Smith.
3.4. Experimental

**General Procedures.** All reactions were performed in oven or flame-dried glassware under a positive pressure of N₂ with magnetic stirring unless otherwise noted.

**Materials.** Tetrahydrofuran and diethyl ether were dried by passage through an activated alumina column under positive N₂ pressure. Methylene chloride was distilled under N₂ from CaH. Analytical TLC was performed on E. Merck pre-coated (25 mm) silica gel 60F-254 plates. Visualization was done under UV (254 nm). Flash chromatography was done using ICN SiliTech 32-63 60 Å silica gel. Reagent grade ethyl acetate, diethyl ether, pentane and hexanes (commercial mixture) were purchased from EM Science and used as is for chromatography.

**Instrumentation.** 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 CH₂Cl₂ and then evaporating the CH₂Cl₂. Proton (¹H NMR) and carbon (¹³C NMR) nuclear magnetic resonance spectra were recorded on Bruker Avance 300 and Bruker Avance 500 spectrometers at 300 MHz and 75 MHz, and 500 MHz and 100 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 ¹H NMR: CDCl₃ = 7.27 ppm, for ¹³C NMR: CDCl₃ = 77.23. Data are reported as follows: (s = singlet; d = doublet; t = triplet; q = quartet; dd = doublet of doublets; dt = doublet of triplets; b = broad). HPLC analysis was performed with a HP series 1100 instrument using either a Chiralcel OD-H or OJ or CHIRAPAK AD column.
bis p-Methoxybenzyl ether

To a stirring suspension of sodium hydride (60% dispersion in mineral oil, 1.18 g, 31.12 mmol) under N₂ at 0 °C in DMF (30 mL) was added but-2-ene-1,4-diol (1.21 g, 13.83 mmol). The reaction was stirred for 30 min. and p-methoxybenzyl chloride (4.33 g, 27.66 mmol) was added. The reaction mixture was stirred for 18 h at room temperature, then was quenched by the addition of ice chips, and extracted into hexanes. The organic layer was dried (MgSO₄) and concentrated. The resulting residue was purified by flash chromatography (20% EtOAc in hexanes) to afford the desired product (3.37 g, 74%): ¹H NMR (300 MHz, CDCl₃) δ 7.29 (d, J = 6.5 Hz, 2H), 6.91 (d, J = 6.8 Hz, 2H), 5.80 (adt, J = 3.8, 1.0 Hz, 1H), 4.48 (s, 2H), 4.07 (dd, J = 3.8, 1.0 Hz, 2H), 3.82 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 159.39, 130.40, 129.69, 113.95, 72.04, 65.62, 55.49.

p-methoxy benzyloloxy acetaldehyde (43)

To a stirring solution of AD-mix-β (1.4 g/mmol substrate, 7.00 g) in 1:1 tert-butyl alcohol and H₂O (25 mL:25 mL) at 0 °C was added bis p-methoxybenzyl ether (1.64 g, 5.00 mmol). The reaction mixture was warmed to room temperature and stirred for 18 h. The temperature was then decreased to 0 °C and sodium sulfite (1.5 g/mmol substrate, 7.5 g) was added in bulk. The reaction mixture was allowed to stir for 1 h while warming to room temperature, then was extracted into CH₂Cl₂. The aqueous layer was washed with CH₂Cl₂ (2 x 25 mL) and the combined organic layers where dried (MgSO₄) and concentrated. The resulting residue was dissolved in CH₂Cl₂ (15 mL) and sodium periodate immobilized on silica gel (2.0 g/mmol substrate, 5.52 g) was added. The reaction mixture was stirred vigorously for 30 min., then was filtered. The filter cake was washed with CH₂Cl₂ (2 x 20 mL) and the filtrate was
concentrated. The resulting residue was purified by vacuum distillation (bp 120 – 125 °C, 2 mm Hg) to afford the desired product (1.44 g, 80%): \( ^1 \)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 9.69 (s, 1H), 7.28 (d, \( J = 8.6 \) Hz, 2H), 6.88 (d, \( J = 8.6 \) Hz, 2H), 4.56 (s, 2H), 4.07 (s, 2H), 3.80 (s, 3H); \( ^{13} \)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 200.89, 159.96, 132.21, 129.84, 114.30, 75.27, 73.58, 55.47.

(1-Ethoxy-3-methyl-buta-1,3-dienyloxy)-trimethyl-silane (44)

To a solution of diisopropylamine (4.45 g, 44.00 mmol) in THF (50 mL) at 0 °C under N\(_2\) was added n-butyllithium (1.6M in hexanes, 27.5 mL, 44.00 mmol). The reaction mixture was stirred at 0 °C for 30 min., then the temperature was decreased to -78 °C. 3-Methyl-but-2-enoic acid ethyl ester (5.12 g, 40.00 mmol) was added and the reaction mixture was stirred for 30 min. before trimethylsilyl chloride (6.52 g, 60.00 mmol) was added. The reaction mixture was stirred for an additional 20 min., then was allowed to warm to room temperature. The reaction mixture was concentrated under reduced pressure and the resulting residue was dissolved in dry pentanes and filtered. The filtrate was concentrated and the resulting residue was purified by distillation (bp 63 – 75 °C, 2 mm Hg) to afford the desired product (5.95, 74%): \( ^1 \)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 4.77 (d, \( J = 2.2 \) Hz, 1H), 4.52 (m, 1H), 4.23 (s, 1H), 3.80 (q, \( J = 6.9 \) Hz, 2H), 1.93 (s, 1H), 1.30 (t, \( J = 6.9 \) Hz, 3H), 0.25 (s, 9H); \( ^{13} \)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 156.76, 140.77, 107.28, 81.09, 63.65, 23.92, 14.62, 0.65.

5-Hydroxy-6-(4-methoxybenzyloxy)-3-methyl-hex-2-enoic acid ethyl ester (+)-45

To a solution of (+)-2,6-bis[(4R)-4phenyl-2-oxazolin-2-yl]pyridine (0.124 g, 0.337 mmol) in CH\(_2\)Cl\(_2\) (13 mL) was added CuCl\(_2\) (0.045 g, 0.337 mmol). The
reaction mixture was stirred vigorously for 1 h to give a fluorescent green suspension. AgSbF$_6$ (0.232 g, 0.675 mmol, in 10 mL CH$_2$Cl$_2$) was added via cannula. The reaction mixture was wrapped in foil and stirred for 3 h. The resulting mixture was filtered directly into the reaction flask through and oven-dried glass pipet, tightly packed with cotton, to remove the white AgCl precipitate, yielding active catalyst (R,R)-[Cu(Ph-pybox)](SbF$_6$)$_2$ as a clear blue solution. To the solution of active catalyst at -78 ºC was added 43 (2.25 g, 11.21 mmol, in 17 mL CH$_2$Cl$_2$). (1-Ethoxy-3-methylbuta-1,3-dienyloxy)trimethylsilane (44) (2.69 g, 13.45 mmol) was added drop wise over 30 min. The reaction was stirred at -78 ºC for 4 h, and then was filtered through a pad of silica (1.5 cm thick). The filtrate was concentrated, and the resulting residue was dissolved in THF (20 mL). HCl (1N) was added and the reaction mixture was allowed to stand for 20 min., then was diluted with ether (25 mL) and the two layers were separated. The organic layer was dried (MgSO$_4$) and concentrated. The resulting residue was purified by flash chromatography (40% EtOAc in hexanes) to afford the desired product (2.82 g, 82 %); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.29 (d, $J$ = 8.6 Hz, 2H), 6.93 (d, $J$ = 8.6 Hz, 2H), 5.76 (s, 1H), 4.47 (s, 2H), 4.16 (q, $J$ = 7.1 Hz, 2H), 4.04 (m, 1H), 3.83 (s, 3H), 3.51 (dd, $J$ = 9.3, 3.3 Hz, 1H), 3.37 (dd, $J$ = 7.0, 2.3 Hz, 1H), 2.32 (m, 2H), 2.22 (s, 3H), 1.30 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 166.63, 159.52, 155.89, 129.99, 129.61, 118.26, 114.03, 73.73, 73.26, 68.44, 59.77, 55.43, 44.79, 19.08, 14.46; [$\alpha$]$_D^{23}$ 1.25º (CH$_2$Cl$_2$, c 9.4).

The ee was determined to be 95% by chiral HPLC analysis using a chirapak AD column. Conditions: Hex:i-PrOH 95:5, 1.0 mL/min.
5-(tert-Butyldimethylsilanyloxy)-6-(4-methoxybenzyloxy)-3-methylhex-2-enoic acid ethyl ester (+)-46

To a stirring solution of (+)-45 (4.63 g, 15.04 mmol) in DMF was added imidazole (1.12 g, 16.54 mmol) followed by tert-butyldimethylsilyl chloride (2.49 g, 16.54 mmol). The reaction mixture was stirred for 18 h, then was quenched with ice chips and partitioned between water and hexanes. The organic layer was dried (MgSO₄) and concentrated. The resulting residue was purified by flash chromatography (20% EtOAc in hexanes) to afford the desired product (5.65 g, 89%).

1H NMR (300 MHz, CDCl₃) δ 7.24 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 5.70 (s, 1H), 4.45 (s, 2H), 4.15 (m, 2H), 3.98 (m, 1H), 3.81 (s, 3H), 3.38 (dd, J = 9.5, 5.3 Hz, 1H), 3.32 (dd, J = 9.5, 5.8 Hz, 1H), 2.42 (dd, J = 13.1, 4.4 Hz, 1H), 2.23 (dd, J = 13.1, 7.7 Hz, 1H), 2.18 (d, J = 1.2 Hz, 3H), 0.85 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); 13C NMR (75 MHz, CDCl₃) δ 166.62, 159.22, 156.40, 130.35, 129.33, 118.56, 113.79, 74.15, 73.07, 69.92, 59.46, 55.32, 46.36, 25.85, 19.51, 18.15, 14.41, -4.40, -4.87; [α]D23 10.6º (MeOH, c 0.64).

5-(tert-Butyl-dimethyl-silanyloxy)-6-(4-methoxybenzyloxy)-3-methyl-hex-2-enal (+)-38

To a solution of lithium aluminum hydride (0.179 g, 4.73 mmol) in ether (15 mL) was added dropwise (+)-46 (1.00 g, 2.36 mmol, in 5 mL ether). The reaction mixture was stirred for 1 h, then was cooled to 0 °C and quenched with a saturated solution of sodium potassium tartrate (10 mL). The reaction mixture was warmed to room temperature and stirred for 4 h. The two layers were separated. The water layer was washed with ether (2 x 15 mL), and the combined organic layers were dried (MgSO₄) and concentrated. The resulting residue (in 5 mL CH₂Cl₂) was added to a suspension of activated manganese (IV) oxide
(2.00 g, 23.12 mmol) under N\textsubscript{2} in CH\textsubscript{2}Cl\textsubscript{2} (10 mL). The reaction mixture was stirred for 18 h, and then was filtered through a pad of celite and was concentrated. The resulting residue was purified by flash chromatography (5% EtOAc in hexanes) to afford the desired product (0.720 g, 80\%): \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 10.00 (d, \(J = 8.1\) Hz, 1H), 7.27 (d, \(J = 8.5\) Hz, 2H), 6.90 (d, \(J = 8.6\) Hz, 2H), 5.93 (d, \(J = 8.1\) Hz, 1H), 4.45 (s, 2H), 4.03 (m, 1H), 3.82 (s, 3H), 3.40 (dd, \(J = 9.4, 5.1\) Hz, 1H), 3.32 (dd, \(J = 9.4, 6.2\) Hz, 1H), 2.51 (dd, \(J = 13.2, 4.3\) Hz, 1H), 2.20 (s, 3H), 0.87 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta\) 191.11, 161.13, 159.42, 130.28, 130.09, 129.51, 113.96, 74.05, 73.24, 70.22, 55.45, 46.14, 25.95, 18.64, 18.26, -4.24, -4.65; \([\alpha]_{D}^{23}\) 2.05º (CH\textsubscript{2}Cl\textsubscript{2}, c 0.52).

\(\textbf{(Z)-3-Tributylstannanylobut-2-en-1-ol (31)}\)

\[
\text{SnBu}_3\text{HO}^{31}
\]

To a solution of 2-butyn-1-ol (4.21 g, 60.0 mmol) in THF (120 mL) at 0 °C was added Red-Al® (65 % wt solution in toluene, 18.66 g, 60.0 mmol) dropwise over 30 min. After the addition was complete the reaction mixture was warmed to room temperature and stirred for 3 h. Tributyltin chloride (39.05 g, 120 mmol) was added dropwise over a period of ten min. The reaction mixture was stirred for 18 h then was quenched with H\textsubscript{2}O and filtered through a pad of Celite. The two layers were separated and the water layer was extracted with Et\textsubscript{2}O. The combined organic layers were washed with 10 % KF, dried (MgSO\textsubscript{4}) and concentrated. The resulting residue was purified by flash chromatography (gradient from hexanes to 20% EtOAc in hexanes) to afford the desired product (17.95 g, 83 %): \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 6.28 (t, \(J = 6.7, {^3}J_{\text{Sn-H}} = 123\) Hz, 1H), 4.03 (t, \(J = 5.7\) Hz, 2H), 1.96 (s, \(J_{\text{Sn-H}} = 41\) Hz, 3H), 1.55 – 1.27 (m, 13H), 0.92 (m, 15H).
tert-Butyldiphenyl(3-tributylstannylbut-2-enyloxy)silane (48)

To a stirring solution of 31 (1.00 g, 2.77 mmol) in DMF was added imidazole (0.23 g, 3.32 mmol) followed by tert-butyldiphenylsilyl chloride (0.91 g, 3.32 mmol). The reaction mixture was stirred for 3 h, then was quenched with ice chips and partitioned between water and hexanes. The organic layer was dried (MgSO₄) and concentrated. The resulting residue was purified by flash chromatography (5% EtOAc in hexanes) to afford the desired product (1.35 g, 81%): ¹H NMR (300 MHz, CDCl₃) δ 7.71 (m, 4H), 7.41 (m, 5H), 6.26 (tq, J = 6.5, 1.5 Hz, 3J₅-H,trans 127 Hz, 1H), 4.07 (d, J = 6.3 Hz, 2H), 1.94 (d, J = 0.97 Hz, 3J₅-H 41 Hz, 3H), 1.44 – 1.21 (m, 12H), 1.06 (s, 9H), 0.83 (m, 15H); ¹³C NMR (75 MHz, CDCl₃) δ 141.48, 139.68, 135.73, 134.00, 129.63, 127.70, 66.58, 29.21, 27.45, 26.94, 13.77, 10.00; IR (neat) 3069, 2952, 2923, 2850, 1949, 1818, 1461, 1425, 1374, 1112, 1083, 1047, 821, 741, 698; HRMS (EI) calced for C₂₄H₄₃OSiSn (M-C₄H₉) 543.210519, found 543.207774.

tert-Butyl-(3-methylhexa-2,5-dienyloxy)diphenylsilane (33)

To a stirring solution of 48 (0.50 g, 0.833 mmol) in toluene (10 mL) was added palladium tetrakistriphenylphosphine (0.048 g, 0.042 mmol) followed by allyl bromide (0.101 g, 0.833 mmol). The reaction mixture was heated to reflux for 18 h, then cooled to room temperature and was partitioned between Et₂O and sat. NH₄Cl. The organic layer was dried (MgSO₄) and concentrated. The resulting residue was purified by flash chromatography to afford the desired product (0.234 g, 80%): ¹H NMR (300 MHz, CDCl₃) δ 7.71 (m, 4H), 7.41 (m, 5H), 5.62 (m, 1H), 5.48 (t, J = 6.3 Hz, 1H), 4.96 (m, 1H), 4.91 (m, 1H), 4.23 (d, J = 6.3 Hz, 2H), 2.62 (d, J = 6.5 Hz, 2H), 1.70 (s, 3H), 1.06 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 135.91,
7-(\textit{tert}-Butyldiphenylsilanyloxy)-5-methylhepta-2,5-dienal (35)

![Structural formula](image)

To a stirring solution of 33 (2.0 g, 5.71 mmol) and acrolein diethylacetal (1.85 g, 14.26 mmol) in CH$_2$Cl$_2$ (6 mL) under N$_2$ was added (Grubbs 1$^{\text{st}}$ generation catalyst, 0.117 g, 0.142 mmol). The reaction mixture was heated to reflux for 18 h, then cooled to room temperature and a solution formic acid in CH$_2$Cl$_2$ (1:8) (4 mL) was added. The reaction mixture was stirred for 3 h, then was concentrated to one third of its original volume and was purified by flash chromatography (eluting with 100 mL CH$_2$Cl$_2$, then 10% EtOAc in hexanes) to afford the desired product (1.92 g, 89%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.45 (d, $J = 7.8$ Hz, 1H), 7.71 (m, 4H), 7.42 (m, 5H), 6.61 (dt, $J = 15.5$, 6.6 Hz, 1H), 6.01 (ddt, $J = 15.5$, 7.8, 1.5 Hz, 1H), 5.60 (t, $J = 5.9$ Hz, 1H), 4.19 (d, $J = 6.4$ Hz, 2H), 2.86 (d, $J = 6.5$ Hz, 2H), 1.72 (d, $J = 1.2$ Hz, 3H), 1.06 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 193.71, 155.18, 135.82, 133.97, 133.68, 133.01, 129.89, 127.89, 127.75, 60.75, 35.74, 27.05, 23.64, 19.37; IR (neat) 3061, 2960, 2923, 2865, 1687, 1469, 1425, 1389, 1112, 1047, 974, 814, 698; HRMS (EI) m/z calcd for C$_{20}$H$_{21}$O$_2$Si (M$^+$) 321.131084, found 321.130751.

Silyl ketene acetal (36)

To a stirring solution of diisopropylamine (2.22 g, 22.00 mmol) in THF (20 mL) at 0 °C was added $n$-butyllithium (1.6M in hexanes, 13.75 ml, 22.00 mmol) drop wise
over 15 min. The reaction was stirred at 0 °C for 30 min., then the temperature was decreased to -78 °C. 2,2,6-Trimethyl-[1,3]dioxin-4-one (2.84 g, 20.00 mmol) was added drop wise over 10 min. and the resulting bright orange solution was stirred at -78 °C for 60 min. Chlorotrimethylsilane (2.61 g, 24.00 mmol) was added over 10 min. and the reaction mixture was stirred for an additional 30 min. at -78 °C, then was warmed to room temperature. The reaction mixture was then filtered through a pad of oven dried anhydrous Na2SO4 and concentrated. The resulting residue was purified by kugelrohr distillation (65 °C at 0.2 mm Hg, temperature must not exceed 65 °C in order to avoid decomposition) to afford the desired product as a bright orange liquid (3.76 g, 88%): 1H NMR (300 MHz, CDCl3) δ 4.65 (s, 1H), 4.08 (s, 1H), 3.98 (s, 1H), 1.56 (s, 6H), 0.26 (s, 9H).

**Dioxenone (-)-52**

To a stirring solution of (S,S)-N,N’-bis[4,5-dihydro-3,5-dimethyl-4-(3H-dinaphtho[2,1-d:1’,2’-f][1,3,2]-2-oxodiazaphosphino)]-N,N’-dimethyl-1,5-pentanediamine (0.04 g, 0.05 mmol) and 35 (1.92 g, 5.07 mmol) in CH2Cl2 (20 mL) at -78 °C was added silicon tetrachloride (0.94 g, 5.57 mmol). The silyl ketene acetal 36 (1.19 g, 5.57 mmol, in 5 mL of CH2Cl2) was added via syringe pump over 3h. The reaction mixture was stirred at -78 °C for 18h, then was added via cannula to a stirring room temperature solution of 1M KH2PO4. The resulting biphasic mixture was allowed to warm to room temperature before filtration through a pad of Celite. The filtrate was washed with 10% KF and the organic layer was dried (MgSO4) and concentrated. The resulting residue was purified by flash chromatography (40% EtOAc in hexanes) to afford the desired product (1.73 g, 65%): 1H NMR (300 MHz, CDCl3) δ 7.70 (m, 4H), 7.42 (m, 6H), 5.55–5.53 (m, 3H), 5.28 (s, 1H), 4.31 (m, 1H), 3.98 (s, 1H), 1.56 (s, 6H), 0.26 (s, 9H).
4.19 (d, $J = 6.4$ Hz, 2H), 2.59 (d, $J = 6.3$ Hz, 2H), 2.37 (d, $J = 3.7$ Hz, 1H), 2.34 (d, $J = 1.8$ Hz, 1H), 1.67 (m, 9H), 1.04 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 168.51, 160.92, 135.89, 135.89, 135.10, 134.38, 132.56, 130.26, 129.81, 127.86, 125.20, 106.10, 95.56, 69.71, 60.97, 41.87, 35.15, 27.15, 25.59, 25.15, 23.49, 19.44; IR (neat) 3454, 3069, 3047, 2996, 2923, 2850, 1723, 1629, 1425, 1367, 1280, 1200, 1098, 952, 901, 814, 734, 705 cm$^{-1}$; HRMS (EI): $m/z$ calcd for C$_{27}$H$_{31}$O$_5$Si (M-C$_4$H$_9$) 463.194078, found 463.194100.

The ee was determined to be 93% (88.3, 3.2) by chiral HPLC analysis using a chiracel OD-H column. Conditions: Hex:i-PrOH 95:5, 0.90 mL/min. Retention time: minor 13.9, major 15.6

**β-hydroxy keto ester (-)-54**

The dioxenone (-)-52 (0.62 g, 1.19 mmol) was dissolved in anhydrous 1-butanol (23 mL). The 1-butanol was degassed by passing a stream of N$_2$ through for 2h prior to reaction. The reaction mixture was plunged into a preheated oil bath (140 °C) and allowed to reflux for 1h, then was cooled to room temperature and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (20% EtOAc in hexanes) to afford the desired product (0.47 g, 74%): $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.70 (m, 4H), 7.42 (m, 6H), 5.49-5.34 (m, 3H), 4.49 (m, 1H), 4.20 (d, $J = 6.4$ Hz, 2H), 4.14 (t, $J = 6.7$ Hz, 2H), 3.45 (s, 2H), 2.68-2.57 (m, 4H), 1.68 (s, 3H), 1.62 (m, 2H), 1.36 (m, 2H), 1.05 (s, 9H), 0.93 (t, $J = 7.4$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 202.97, 167.11, 135.78, 135.24, 134.08, 131.75, 129.75, 129.39, 127.80, 125.92, 68.33, 65.56, 60.84, 50.10, 49.78, 35.10, 30.65, 27.01, 23.53, 19.34, 19.21, 13.83; IR (neat) 3476, 3127, 3061, 2945, 1956, 1890, 1818, 1738, 1650,
1465, 1419, 1306, 1111, 973, 825, 784, 743, 702, 609 cm⁻¹; HRMS (EI): m/z calcd for C₃₂H₄₄O₅Si (M⁺) 536.295803, found 536.293564; [α]D²³ -9.87º (CHCl₃, c 1.07).

1,3-syn diol (-)-37

To a stirring solution of β-hydroxy keto ester (-)-54 (1.08 g, 2.02 mmol) in THF (15 mL) at -78 ºC was added diethylmethoxyborane (0.22 g, 2.22 mmol). The reaction mixture was stirred for 30 min. before NaBH₄ (0.45 g, 12.14 mmol) was added in bulk. The reaction mixture was stirred at -78 ºC for 18h before being quenched with saturated NH₄Cl (5 mL). The reaction mixture was warmed to room temperature, diluted with Et₂O and acidified to pH 1 by the addition of 1N HCl. The two layers were separated and the aqueous layer was washed with Et₂O (3x20 mL). The combined organic layers were dried (MgSO₄) and concentrated. The resulting residue was azeotroped with MeOH (3x25 mL) and purified by flash chromatography (50% EtOAc in hexanes) to afford the desired product (0.09 g, 83 %): ¹H NMR (300 MHz, CDCl₃) δ 7.70 (m, 4H), 7.41 (m, 6H), 5.44 (m, 3H), 4.29 (m, 2H), 4.21 (d, J = 5.5 Hz, 2H), 4.12 (t, J = 6.6 Hz, 2H), 2.57 (d, J = 6.0 Hz, 2H), 2.47 (d, J = 3.6 Hz, 1H), 2.45 (d, J = 0.88 Hz, 1H), 1.68 (s, 3H), 1.65-1.50 (m, 4H), 1.35 (m, 4H), 1.05 (s, 9H), 0.94 (t, J = 7.3 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 172.75, 135.78, 135.50, 134.07, 133.42, 129.74, 128.74, 127.73, 125.77, 72.71, 68.53, 64.85, 60.85, 42.81, 41.76, 35.12, 30.73, 27.01, 23.57, 19.34, 19.28, 13.87; IR (neat) 3403, 3069, 3040, 2734, 1963, 1890, 1818, 1730, 1592, 1425, 1258, 1112, 814 cm⁻¹; HRMS (EI): m/z calcd for C₂₈H₃₅O₄Si (M–C₄H₉, H₂O) 463.230463, found 463.231124; [α]D²³ -8.57º (CHCl₃, c 1.07).
Cyclic $\alpha,\beta$-unsaturated acetal (+)-39

To a stirring solution of 1,3-syn diol (-)-37 (0.77 g, 1.44 mmol) in DMF (10 mL) was added imidazole (0.49 g, 7.23 mmol). The reaction mixture was stirred for 5 min. and chlorotrimethylsilane (0.34 g, 3.18 mmol) was added, followed by DMAP (0.01 g). The reaction mixture was stirred for 18h, then quenched with ice chips. The reaction mixture was extracted into hexanes, and the water layer was washed with hexanes (3x15 mL). The combined organic layers were dried (MgSO$_4$) and concentrated. The resulting residue was dissolved CH$_2$Cl$_2$ (10 mL) and the temperature was decreased to -78 °C before 5-(tert-butyldimethylsilanyloxy)-6-(4-methoxybenzyloxy)-3-methylhex-2-enal (0.54 g, 1.44 mmol) and TMSOTf (0.03 g, 0.14 mmol) were added. The reaction mixture was stirred for 45 min., then quenched with pyridine (0.01 g, 0.17 mmol), warmed to room temperature and washed with saturated NaHCO$_3$. The organic layer was dried (MgSO$_4$) and concentrated. The resulting residue was purified by flash chromatography (5% EtOAc in hexanes) to afford the desired product (0.91 g, 71%): $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.68 (m, 4H), 7.41 (m, 6H), 7.27 (d, $J = 8.5$ Hz, 2H), 6.88 (d, $J = 8.5$ Hz, 2H), 5.51-5.42 (m, 3H), 5.33 (d, $J = 5.9$ Hz, 1H), 5.23 (d, $J = 6.1$ Hz, 1H), 4.44 (s, 2H), 4.20 (d, $J = 6.3$ Hz, 2H), 4.09 (t, $J = 6.6$ Hz, 4H), 3.94 (m, 1H), 3.80 (s, 3H), 3.36 (d, $J = 5.3$ Hz, 2H), 2.66 (dd, $J = 15.7$, 7.0 Hz, 1H), 2.59 (d, $J = 6.1$ Hz, 2H), 2.43 (dd, $J = 15.6$, 6.0 Hz, 1H), 2.26 (dd, $J = 13.5$, 5.3 Hz, 1H), 2.14 (dd, $J = 13.5$, 6.9 Hz, 1H), 1.73 (s, 3H), 1.67 (s, 3H), 1.61 (m, 4H), 1.34 (m, 2H), 1.05 (s, 9H), 0.93 (t, $J = 7.6$ Hz, 3H), 0.86 (s, 9H), 0.03 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 170.95, 159.21, 139.37, 135.83, 135.44, 134.06, 130.84, 130.75, 129.66, 129.38, 127.79, 125.74, 125.28, 113.82, 98.38, 76.42, 74.46, 73.06, 72.75, 70.49, 64.65, 60.82, 55.40, 44.84, 41.07, 36.65, 35.22, 31.77, 30.76, 27.01, 26.07, 23.54, 22.84, 18.32, 18.15, 13.89, -4.32, -4.57; IR (neat) 3061, 2952, 2923, 2850, 1730,
2,6-cis-4-methylene-tetrahydropyran (+)-40

Cerium III chloride (2.46 g, 10.0 mmol) was dried with vigorous stirring under vacuum (0.2 mm Hg) at 150 °C for 2h, then cooled to room temperature, flushed with N2 and suspended in THF (15 mL). The suspension was sonicated for 2h, then transferred to a -78 °C cold bath. Trimethylsilylmethylmagnesium chloride (1.0M in Et2O, 10.0 mL, 10.0 mmol) was added over 20 min. to form a pale yellow suspension, which stirred for 1h. The cyclic α,β-unsaturated acetal (+)-39 (0.54 g, 0.60 mmol, in 2 mL THF) was added dropwise, and the reaction mixture was allowed to gradually warm to room temperature and stir for 18h. The temperature was then decreased to -78 °C and the reaction was quenched by the addition of 5% HCl (5 mL). The reaction mixture was warmed to room temperature, and the two layers were separated. The aqueous layer was washed with Et2O (2x25 mL), and the combined organic layers were dried (MgSO4) and concentrated using a 40 °C water bath. The flask was placed under vacuum and allowed to stand for 30 min. The resulting residue was purified by flash chromatography (10% → 15% → 20% → 30% EtOAc in hexanes) to afford the desired product (0.21 g, 42%): 1H NMR (500 MHz, CDCl3) δ 7.70 (d, J = 1.4 Hz, 2H), 7.68 (d, J = 1.5 Hz, 2H), 7.40 (m, 6H), 7.26 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 5.46 (m, 2H), 5.38 (dd, J = 6.2, 15.6 Hz, 1H), 5.22 (d, J = 7.5 Hz, 1H), 4.73 (s, 2H), 4.45 (s, 2H), 4.24 (ddd, J = 2.2, 6.2, 9.2 Hz, 1H), 4.20 (d, J = 6.4 Hz, 2H), 4.00 (ddd, J = 2.5, 7.8, 11.0 Hz, 1H), 3.95 (m, 1H), 3.80 (s, 3H), 3.53 (m, 1H), 3.32 (d, J = 5.2 Hz, 2H), 2.57 (d, J = 6.0 Hz, 2H), 2.26 (dd, J = 6.3, 13.5 Hz, 1H), 2.20 (s, 1H), 2.13 (m, 3H), 2.00 (m, 2H), 1.69 (s, 3H), 1.68
(s, 3H), 1.06 (s, 9H), 0.88 (s, 9H), 0.03 (s, 3H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \( \delta \) 159.17, 143.85, 136.97, 135.72, 135.68, 134.05, 133.63, 130.07, 129.67, 129.35, 127.98, 127.74, 125.51, 113.79, 109.17, 78.82, 75.67, 74.04, 73.03, 72.24, 70.79, 60.82, 55.36, 44.79, 43.35, 40.92, 40.65, 35.13, 26.98, 26.04, 23.52, 19.30, 18.30, 18.04, -4.32, -4.54; IR (neat) 3476, 3076, 2930, 2894, 2850, 1672, 1614, 1585, 1512, 1469, 1425, 1352, 1287, 1250, 1105, 1040, 843, 770, 698 cm\(^{-1}\); HRMS (ESI): \( m/z \) calcd for C\textsubscript{51}H\textsubscript{74}O\textsubscript{6}NaSi\textsubscript{2} (M + Na) 861.4922, found 861.4961; \([\alpha]\)\textsubscript{D}\textsuperscript{23} +0.79\(^\circ\) (CHCl\textsubscript{3}, c 1.01).

**Allylsilane (-)-57**

The desired Prins cyclization product could also be obtained in a step-wise manner. Cerium III chloride (2.46 g, 10.0 mmol) was dried with vigorous stirring under vacuum (0.2 mm Hg) at 150 °C for 2h, then cooled to room temperature, flushed with N\textsubscript{2} and suspended in THF (15 mL). The suspension was sonicated for 2h, then transferred to a -78 °C cold bath. Trimethylsilylmethylmagnesium chloride (1.0M in Et\textsubscript{2}O, 10.0 mL, 10.0 mmol) was added over 20 min. to form a pale yellow suspension, which stirred for 1h. The cyclic \( \alpha,\beta \)-unsaturated acetal (+)-39 (0.89 g, 1.00 mmol, in 2 mL THF) was added dropwise, and the reaction mixture was allowed to gradually warm to room temperature and stir for 18h. The temperature was then decreased to -78 °C and the reaction was quenched by the addition of EtOAc (5 mL). The reaction mixture was stirred at -78 °C for and addition 20 min., then was warmed to room temperature, and washed with saturated NaHCO\textsubscript{3} and brine. The organic layer was dried (MgSO\textsubscript{4}) and concentrated. The resulting residue was dissolved in CH\textsubscript{2}Cl\textsubscript{2} (10 mL) and silica gel (1.5 g) was added. The reaction mixture was stirred for 18h, then filtered. The filtrate was concentrated and the resulting residue was
purified by flash chromatography (10 % EtOAc in hexanes) to afford the desired product (0.35 g, 66%). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.69 (m, 4H), 7.41 (m, 6H), 7.26 (d, $J = 8.2$ Hz, 2H), 6.88 (d, $J = 8.6$ Hz, 2H), 5.55-5.33 (m, 4H), 5.20 (d, $J = 6.2$ Hz, 1H), 4.65 (s, 1H), 4.60 (s, 1H), 4.44 (s, 2H), 4.20 (d, $J = 6.4$ Hz, 2H), 4.07 (m, 1H), 3.95 (m, 1H), 3.81 (s, 4H), 3.36 (d, $J = 5.3$ Hz, 2H), 2.59 (d, $J = 5.8$ Hz, 2H), 2.36 (dd, $J = 13.9$, 5.7 Hz, 1H), 2.26 (dd, $J = 13.5$, 5.5 Hz, 1H), 2.15 (dd, $J = 13.4$, 6.7 Hz, 1H), 2.05 (dd, 15.5, 8.2 Hz, 1H), 1.74 (d, $J = 0.9$ Hz, 3H), 1.67 (s, 3H), 1.27 (s, 2H), 1.05 (s, 9H), 0.86 (s, 9H), 0.04 (s, 15H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 159.40, 143.57, 138.98, 135.90, 135.70, 134.35, 131.50, 131.04, 129.80, 129.45, 129.19, 127.88, 125.84, 114.01, 110.08, 98.51, 75.42, 74.71, 73.22, 70.80, 60.99, 55.54, 45.05, 44.93, 27.56, 27.17, 26.21, 23.59, 19.46, 18.43, 18.29, -1.05, -4.18, -4.46; IR (neat) 3061, 2952, 2850, 2734, 2698, 1949, 1890, 1818, 1738, 1665, 1607, 1585, 1505, 1469, 1425, 1360, 1250, 1112, 843, 778, 734 cm$^{-1}$; HRMS (ESI): $m/z$ calcd for C$_{54}$H$_{82}$O$_6$NaSi$_3$ (M + Na) 933.5317, found 933.5359; [$\alpha$]$_D^{23}$ -5.53º (CHCl$_3$, c 0.75).

To a solution of PPTS (0.54 g, 1.99 mmol) in CH$_2$Cl$_2$ (2 mL) at room temperature was added allylsilane (0.05 g, 0.05 mmol, in 1 mL CH$_2$Cl$_2$) and MgSO$_4$ (0.26 g, 2.18 mmol). The reaction mixture was stirred at room temperature for 3.5h, then placed directly on a silica gel column. The reaction mixture was purified by flash chromatography (10 % EtOAc in hexanes) to afford the desired Prins cyclization product (0.029 g, 66%).

The proto-desilated acetal was isolated as a by-product of the reaction (0.014g, 29%): $^1$H NMR (300 MHz, CDCl$_3$) δ 7.67 (m, 4H), 7.42 (m, 6H), 7.23 (d, $J = 9.8$ Hz, 2H), 6.88 (d, $J = 8.5$ Hz, 2H), 5.52-5.33 (m, 4H), 5.20 (d, $J = 6.2$ Hz, 1H), 4.79 (s, 1H), 4.74 (s, 1H), 4.43 (s, 2H), 4.20 (d, $J = 6.4$ Hz, 2H), 4.05 (m, 1H),...
3.94 (m, 1H), 3.81 (s, 4H), 3.34 (d, J = 5.3 Hz, 2H), 2.59 (d, J = 5.8 Hz, 2H), 2.35 (dd, J = 7.4, 13.9 Hz, 1H), 2.25 (dd, J = 5.5, 13.5 Hz, 1H), 2.12 (dd, J = 6.7, 13.8 Hz, 2H), 1.75 (s, 3H), 1.74 (s, 3H), 1.67 (s, 3H), 1.47 (m, 2H), 1.26 (m, 2H), 1.04 (s, 9H), 0.86 (s, 9H), 0.02 (s, 6H); 13C NMR (75 MHz, CDCl3) δ 159.49, 142.03, 138.87, 135.89, 134.46, 131.55, 131.13, 129.75, 129.40, 129.11, 127.84, 125.90, 114.07, 112.92, 98.54, 80.12, 75.17, 74.78, 73.23, 70.87, 61.02, 55.53, 45.08, 44.52, 37.14, 35.34, 27.19, 26.20, 23.51, 23.19, 19.45, 18.39, 18.23, -4.19, -4.46; IR (neat) 3069, 2938, 2858, 1607, 1512, 1469, 1425, 1367, 1301, 1243, 1105, 1032, 829, 770, 698 cm⁻¹; HRMS (ESI) calcd for C₅₁H₇₄O₆NaSi₂ (M+Na) 861.4922, found 861.4926.

**Ketone (-)-59**

To a stirring solution of 2,6-cis-4-methylene-tetrahydropyran (+)-40 (0.11 g, 0.12 mmol) in CH₂Cl₂ (5 mL) at 0 ºC was added Des-Martin periodinane (0.06 g, 0.15 mmol). The reaction mixture was stirred at room temperature for 2h, then quenched with a 1:1 mix of saturated NaHCO₃ and saturated Na₂S₂O₃ (1.5 mL). The resultant biphasic reaction mixture was stirred for 30 min, then the two layers were separated. The aqueous phase was washed with CH₂Cl₂ (10 mL), and the combined organic layer was dried (MgSO₄) and concentrated. The resulting residue was purified by flash chromatography (10% EtOAc in hexanes) to afford the desired product (0.10 g, 94%):

1H NMR (500 MHz, CDCl3) δ 7.72 (d, J = 4.0 Hz, 4H), 7.45 (m, 5H), 7.29 (d, J = 5.0 Hz, 2H), 6.91 (d, J = 5.0 Hz, 2H), 6.64 (dt, J = 3.9, 9.5 Hz, 1H), 6.02 (d, J = 9.5 Hz, 1H), 5.57 (t, J = 3.6 Hz, 1H), 5.23 (d, J = 4.5 Hz, 1H), 4.77 (s, 1H), 4.76 (s, 1H), 4.47 (s, 2H), 4.20 (d, J = 3.7 Hz, 2H), 4.01 (at, J = 5.2 Hz, 1H), 3.94 (m, 1H), 3.84 (s, 4H), 3.36 (d, J = 3.0 Hz, 2H), 2.90 (dd, J = 3.7, 9.6 Hz, 1H), 2.76 (d, J = 3.9 Hz, 2H), 2.59 (dd, J = 3.7, 9.6 Hz, 1H), 2.32 (d, J = 7.8 Hz,
1H), 2.31 (d, J = 7.8 Hz, 1H), 2.13 (m, 2H), 2.00 (at, J = 7.3 Hz, 1H), 1.93 (at, J = 7.4 Hz, 1H), 1.71 (s, 3H), 1.69 (s, 3H), 1.08 (s, 9H), 0.90 (s, 9H), 0.06 (s, 6H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 197.88, 159.31, 144.71, 144.11, 136.35, 135.81, 133.97, 133.48, 131.61, 130.83, 129.87, 129.41, 128.56, 127.89, 127.30, 113.91, 109.29, 77.23, 75.80, 74.37, 73.13, 70.17, 60.75, 55.47, 46.69, 45.21, 40.78, 40.52, 35.43, 27.05, 26.14, 23.67, 19.38, 18.40, 17.91, -4.25, -4.49; IR (neat) 3069, 2923, 2894, 2843, 1709, 1672, 1614, 1520, 1469, 1425, 1360, 1250, 1112, 829, 770, 698 cm\(^{-1}\); HRMS (ESI): \(m/z\) calcd for C\(_{51}\)H\(_{72}\)O\(_6\)NaSi\(_2\) (M Na) 859.4765, found 859.4805; \([\alpha]_D^{23}\) -8.02º (CHCl\(_3\), c 1.02).

**Allylic alcohol (-)-62**

To a stirring solution of 2,6-\(\text{cis}\)-4-methylene-tetrahydropyran (+)-40 (0.13 g, 0.15 mmol) in THF (3 mL) at 0 ºC was added phenylselenocyanate (0.03 g, 0.15 mmol) followed by tributylphosphine (0.03 g, 0.15 mmol). The reaction mixture was stirred at room temperature for 3h, then concentrated. The resulting residue was purified by flash chromatography (CH\(_2\)Cl\(_2\)) to yield the desired selenide. The selenide was dissolved in CH\(_2\)Cl\(_2\) (2 mL) and the temperature was decreased to -30 ºC. Pyridine (0.71 mL) was added, followed by 30% H\(_2\)O\(_2\) (1 mL), and the reaction mixture was stirred for 5h, then quenched with saturated NH\(_4\)Cl (1 mL). The reaction mixture was warmed to room temperature and extracted into Et\(_2\)O. The organic layer was washed with 10% HCl, dried (MgSO\(_4\)) and concentrated. The resulting residue was purified by flash chromatography (5% → 20% EtOAc in hexanes) to afford the desired product (0.07 g, 58%): \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.74 (at, \(J = 7.1\) Hz, 4H), 7.44 (m, 6H), 7.28 (d, \(J = 8.3\) Hz, 2H), 6.91 (d, \(J = 8.3\) Hz, 2H), 5.72 (dt, \(J = 4.1, 15.3\) Hz, 1H), 5.63 (t, \(J = 6.5\) Hz, 1H), 5.54 (dd, \(J = 6.4, 15.3\) Hz, 1H),...
5.29 (d, \( J = 7.5 \) Hz, 1H), 4.75 (s, 2H), 4.48 (s, 2H), 4.23 (m, 1H), 4.16 (m, 1H), 3.98 (m, 2H), 3.84 (s, 3H), 3.38 (d, \( J = 5.2 \) Hz, 2H), 3.34 (m, 1H), 2.37 (m, 4H), 2.23 (m, 2H), 2.14 (m, 2H), 2.06 (m, 2H), 1.93 (m, 1H), 1.80 (s, 3H), 1.72 (s, 3H), 1.65 (s, 1H), 1.11 (s, 9H), 0.92 (s, 9H), 0.08 (s, 6H); \(^{13}\text{C} \) NMR (100 MHz, CDCl\(_3\)) \( \delta \) 159.28, 144.60, 135.98, 135.62, 133.55, 130.55, 129.63, 129.19, 128.55, 127.66, 127.41, 127.21, 113.64, 108.78, 77.92, 75.82, 74.11, 73.13, 70.49, 70.21, 60.05, 55.23, 45.21, 40.96, 40.74, 40.23, 39.40, 26.77, 25.89, 23.89, 19.07, 18.41, 17.95, -4.24, -4.47; IR (neat) 3461, 3083, 2923, 2894, 2850, 1650, 1607, 1505, 1469, 1425, 1360, 120, 836, 770, 741, 705 cm\(^{-1}\); HRMS (ESI): \( m/z \) calcd for \( \text{C}_{51}\text{H}_{74}\text{O}_6\text{NaSi}_2 \) (M + Na) 861.4922, found 861.4948; \([\alpha]_D^{23}\) -2.32º (PhH, c 1.82).

**Diol (-)-41**

To a stirring solution of allylic alcohol (-)-62 (0.013 g, 0.015 mmol) in DMF (0.25 mL) at 0 °C was added 4-methoxybenzyl chloride (0.25 mL), tetrabutylammonium iodide (0.01 g) and sodium hydride (60% dispersion in mineral oil, 0.0009 g, 0.023 mmol). The reaction mixture was stirred for 18h at room temperature, then quenched by the addition of ice chips, and extracted into hexanes. The organic layer was dried (MgSO\(_4\)) and concentrated. The resulting residue was purified by flash chromatography (5% EtOAc in hexanes). The resulting residue was dissolved in THF (0.25 mL) and 3 drops of HF-pyridine were added. The reaction mixture was stirred at room temperature for 18h, then quenched by the careful addition of saturated NaHCO\(_3\) (1.5 mL) and extracted into EtOAc (5 mL). The water layer was washed with EtOAc (5 mL) and the combined organic layers were dried (MgSO\(_4\)) and concentrated. The resulting residue was azeotroped with benzene (3x5 mL) to remove any excess pyridine, and purified by flash chromatography (50% EtOAc in...
hexanes) to afford the desired product (0.003 g, 40%): $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.25 (d, $J = 6.5$ Hz, 2H), 7.21 (d, $J = 8.4$ Hz, 2H), 6.89 (d, $J = 8.4$ Hz, 2H), 6.87 (d, $J = 8.4$, 2H), 5.68 (m, 2H), 5.46 (dd, $J = 8.2$, 15.5 Hz, 1H), 5.32 (d, $J = 7.3$ Hz, 1H), 4.75 (s, 2H), 4.54 (d, $J = 11.5$ Hz, 1H), 4.49 (s, 2H), 4.26 (d, $J = 11.5$ Hz, 1H), 4.05 (m, 2H), 3.94 (m, 1H), 3.81 (m, 2H), 3.77 (s, 3H), 3.76 (s, 3H), 3.45 (dd, $J = 3.7$, 9.4 Hz, 1H), 3.40 (m, 1H), 3.35 (dd, $J = 6.9$, 9.3 Hz, 1H), 2.58 (m, 3H), 2.36 (m, 2H), 2.20 (m, 2H), 2.10-1.95 (m, 4H), 1.71 (s, 3H), 1.67 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 159.31, 144.27, 136.77, 135.64, 132.59, 130.25, 129.91, 128.62, 127.03, 113.83, 113.77, 108.79, 77.86, 76.75, 75.58, 73.64, 73.04, 69.58, 68.34, 58.04, 55.26, 43.66, 40.66, 40.14, 39.03, 38.54, 23.86, 17.11; IR (neat) 3418, 3076, 2930, 2858, 1650, 1607, 1585, 1512, 1447, 1360, 1294, 1170, 1040, 894, 814 cm$^{-1}$; HRMS (ESI): $m/z$ calcd for C$_{37}$H$_{50}$O$_7$Na (M + Na) 629.3454, found 629.3478 $\alpha$$_D$ -21.05º (PhH, c 0.50).

**Aldehyde (-)-65**

To a stirring solution of diol (-)-41 (0.004g, 0.006 mmol) in CH$_2$Cl$_2$ (0.25 mL) at 0 ºC was added Dess-Martin periodinane (0.003 g, 0.006 mmol). The reaction mixture was stirred at 0 ºC for 20 min., then warmed to room temperature and stirred for an additional 30 min. The temperature was then decreased to 0 ºC and the reaction mixture was quenched with saturated aqueous NaHCO$_3$ (0.5 mL) and saturated aqueous Na$_2$S$_2$O$_3$ (0.5 mL). The reaction mixture was stirred for 10 min. before the two layers were separated. The organic layer was dried (MgSO$_4$) and concentrated. The resulting residue was purified by flash chromatography (50% EtOAc in hexanes) to afford the desired product (0.0023 g, 64%): $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.91 (d, $J = 8.1$ Hz, 1H), 7.27 (d, $J = 8.0$ Hz, 2H), 7.21 (d, $J = 8.5$ Hz, 2H), 6.90 (d, $J = 8.7$ Hz, 2H), 6.87 (d, $J = 8.7$ Hz,
2H), 5.93 (d, J = 8.1 Hz, 1H), 5.71 (m, 1H), 5.44 (dd, J = 15.7, 8.1 Hz, 1H), 5.31 (d, J = 7.6 Hz, 1H), 4.77 (s, 2H), 4.51 (m, 3H), 4.25 (d, J = 11.5 Hz, 1H), 3.94-3.88 (m, 2H), 8.81 (m, 4H), 3.80 (s, 3H), 3.44 (dd, J = 9.4, 3.3 Hz, 1H), 3.33 (m, 2H), 2.94 (dd, J = 13.3, 7.9 Hz, 1H), 2.64 (dd, J = 13.1, 5.4 Hz, 1H), 2.39 (m, 2H), 2.26-1.98 (m, 6H), 1.93 (s, 3H), 1.71 (s, 3H); 13C NMR (100 MHz, CDCl₃) δ 191.25, 159.91, 144.28, 131.91, 130.90, 130.01, 129.38, 129.26, 128.71, 113.94, 113.87, 109.61, 77.77, 76.75, 75.67, 73.72, 73.10, 69.74, 68.59, 55.30, 43.59, 40.74, 40.15, 39.19, 39.01, 26.02, 17.20; IR (neat) 3461, 3069, 2923, 2850, 1680, 1614, 1595, 1294, 1243, 1178, 1061, 1032, 821; HRMS (ESI): m/z calcd for C₃₇H₄₈O₇Na (M+Na) 627.3298, found 627.3307 [α]D²³ -17.95° (PhH, c 0.20).

3.5. References


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APPENDIX A

Mechanistic and stereochemical studies of photoinduced electron transfer initiated cyclization reactions: the role of nitrogen (Supporting Information)
APPENDIX B

The aqueous Prins reaction (Supporting Information)
APPENDIX C

Efforts towards the total synthesis of (+)-Dactylolide (Supporting information)