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I. Development of the In Situ Reductive Ozonolysis of Alkenes with Tertiary Amine N-Oxides. II. Progress toward the Asymmetric Synthesis of Peroxyplakoric Acid A3.

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I. Development of the *In Situ* Reductive Ozonolysis of Alkenes with Tertiary Amine N-Oxides.

II. Progress toward the Asymmetric Synthesis of Peroxyplakoric Acid A$_3$.

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Advisor: Patrick H. Dussault

Ozone, first discovered in the mid 1800's, is a triatomic allotrope of oxygen that is a powerful oxidant. For over a century, research has been conducted into the synthetic application and mechanism of reactions of ozone with organic compounds. One of the major areas of interest has been the ozonolysis of alkenes. The production of carbonyl compounds is the most common synthetic application of ozonolysis. The generally accepted mechanism developed by Rudolf Criegee for this reaction involves the 1,3-electrocyclic addition of ozone to the π bond of the alkene to form a 1,2,3-trioxolane or primary ozonide. The primary ozonide is unstable at temperatures above -100 $^{\circ}$C and undergoes cycloreversion to produce the carbonyl oxide and carbonyl intermediates. These intermediates then recombine in another 1,3-electrocyclic addition step to form the 1,2,4-trioxolane or final ozonide. While the final ozonide is often isolable, most synthetic applications of ozonolysis require a subsequent reductive or oxidative step to form the desired carbonyl compound.

During investigations into the nucleophilic trapping of the reactive carbonyl oxide, it was discovered that when amines were used as additives, an increased amount of

reaction time was required in order to consume all of the starting material. Surprisingly, significant amounts of aldehydes and a suppression of ozonide formation also occurred which led to the discovery that amine N-oxides formed by the ozonation of the amine additives in the reaction were intercepting the carbonyl oxide. From the observed production of aldehydes, our proposed mechanism for the *in situ* reductive ozonolysis reaction with amine N-oxides involves the nucleophilic trapping of the carbonyl oxide intermediate to produce a zwitterionic adduct that fragments into $^1O_2$, amine and the carbonyl thereby avoiding the formation of peroxidic intermediates.

With the successful total syntheses of peroxyacarnoates A and D by Dr. Chunping Xu, the asymmetric total synthesis of peroxyplakorate A_3 was investigated. The peroxyplakoric acids are cyclic peroxide natural products isolated from the Plakortis species of marine sponge that have been found to exhibit activity against malaria, cancer and fungi. Even though the peroxyplakorates differ from the peroxyacarnoates in the polyunsaturated tail and the head group, the lessons learned from the syntheses of the peroxyacarnoates have proven to be valuable in the asymmetric synthesis of peroxyplakorate A_3.

The challenges for the asymmetric synthesis of peroxyplakorate A_3 include the stereospecific formation of the 3-methoxy-1,2-dioxane core with a propionate head group and the introduction of oxidation sensitive dienyl tail in the presence of a reduction sensitive 1,2-dioxane core. It was found that the stereochemistry of two of the chiral centers could be controlled by an anti-aldol reaction of a chiral propionate followed by the stereospecific intramolecular cyclization of a hydroperoxyacetal. The regioselective ozonolysis of a 1,2-disubstituted alkene in the presence of a terminal alkyne forms the

required hydroperoxyacetal as a mixture of diastereomers. Finally, the dienyl tail is introduced by a hydrometallation/iodination of the alkyne to produce a vinyl iodide followed by a palladium catalyzed coupling reaction. While the coupling reaction was unsuccessful in these attempts, it is still believed that the intramolecular cyclization to introduce the 1,2-dioxane core could prove to be a general solution to many other cyclic peroxides natural products.

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Chapter 1

Development of the *In Situ* Reductive Ozonolysis of Alkenes with Tertiary Amine N-Oxides

In the first chapter of my dissertation I will describe the development of a new methodology for the *in situ* reductive ozonolysis of alkenes in the presence of tertiary amine-N-oxides. As background, I will first give a brief history of ozone and ozonolysis including the development of the generally accepted mechanism of alkene ozonolysis, referred to hereafter as ozonolysis. This will be followed by background of the methodology developed in the group prior to 2003. I will then explain the conflicting and sometimes misleading results of ozonolysis in the presence of tertiary amines. In the final part of this chapter, I will give the details of the refinements and results that led us to the new methodology (Scheme 1.1).
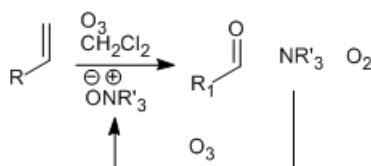
Scheme 1.1

Background

Ozone

Ozone, first described as a gas with an odor, similar to the odor during a lightning storm, was first observed at the positive electrode by Schönbein in the 1840's.[1] Ozone is an allotrope of oxygen consisting of three atoms of oxygen with a bond angle of 116.75°, a small dipole moment of 0.533 debye, and bond lengths of 1.272 Å.[2] While dioxygen has a triplet ground state, ozone is a singlet in the ground state. The five canonical resonance forms are shown in Figure 1.1.
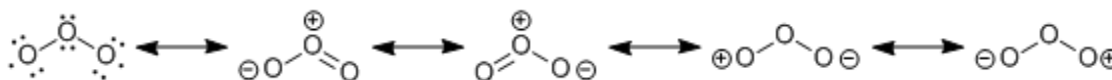
Figure 1.1: Canonical resonance forms of ozone.

The exact nature of the bonding has been debated since the 1970's beginning with Goddard's generalized valence bond (GVB) computations.[3] According to the GVB description, ozone is a biradical with spin paired, lone electrons on the terminal oxygens. This model is generally accepted by computational chemists. The calculations first assume the electrons in the s orbitals are not used in bonding. Second, singly occupied p orbitals are used to form the sigma bonding. Third, the remaining p atomic orbitals form "molecular orbitals" in which the individual atomic orbitals are not mixed and are filled with the atomic electrons. There are two different ways to populate the atomic orbitals

(Figure 1.2). In the lowest energy configuration, the unpaired electrons on the terminal

oxygens are parallel to the paired electrons on the center oxygen (Configuration A). The

terminal p orbitals are distorted into an antibonding molecular orbital configuration by

the electron repulsion with the center oxygen's paired electrons. In the higher energy

configuration, there is a pair of electrons in the parallel p orbital on one of the terminal

oxygens (Configuration B) leading to increased electron repulsion. The geometry of the

molecule is also perturbed by the electron repulsion of the terminal oxygens' lone pairs

thereby increasing the angle from the 90° of orthogonal p orbitals of the center oxygen to

approximately 116°.
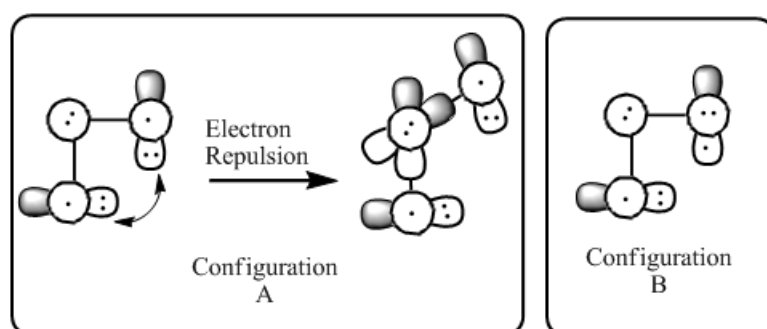
Figure 1.2: General valence bond (GVB) descriptions of ozone.

Recently, Kalemosa and Mavridis[2] have calculated the molecular orbitals for the

ground state using multireference variational methods with large basis sets and have

shown that ozone is not necessarily a biradical.[2] In the calculations, they found that the

ground state of ozone (O_3, $^1\Delta_g$) can be thought of as a combination of the first excited

state of dioxygen (O_2, $^1\Delta_g$) and the first excited state of the oxygen atom (O, ^1D) (Figure

1.3).
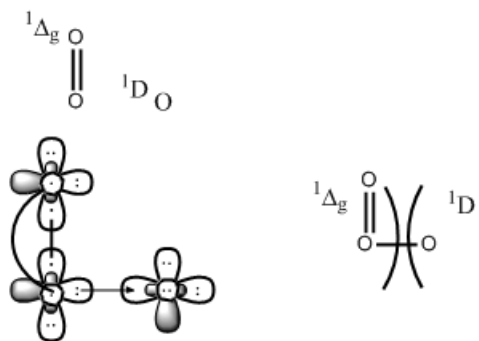
Figure 1.3: Multireference variational description of ozone.

As with the previous model, the geometry of ozone can be attributed to the electron repulsion of the terminal oxygens. The sigma bond framework is thought to be comprised of sp hybridized orbital overlap allowing more s character in the sigma bonds. The calculations are also in good agreement with dipole moment, angle and spectroscopy data determined by experiment.

A third method to envision the electronic configuration of ozone is to construct a correlation diagram according to the rules created by Walsh[4] (Figure 1.4). In this representation, ozone is predicted to have an electronic ground state wherein the electrons are also paired.
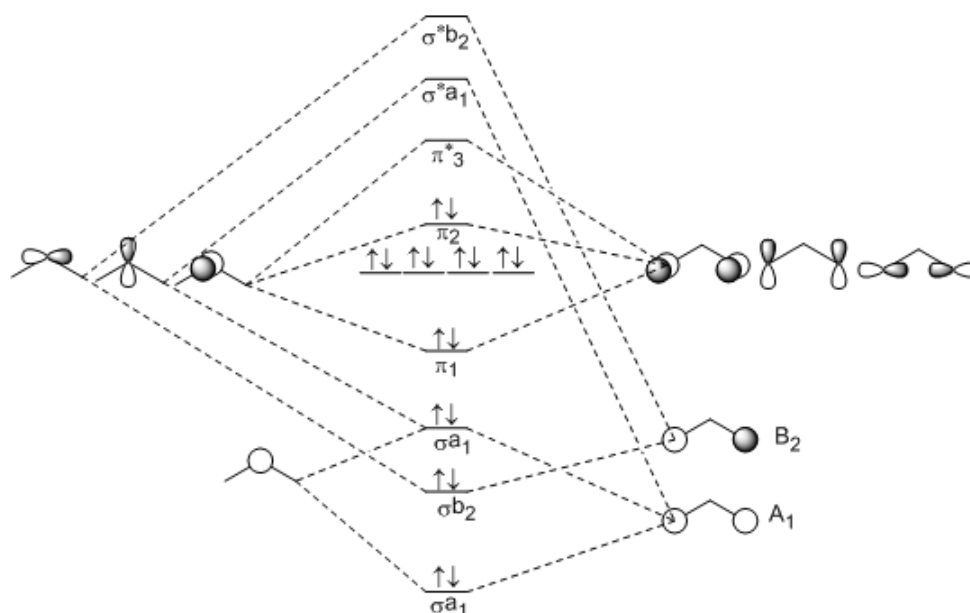
Figure 1.4: Molecular orbitals formed with Walsh rules.

Finally, because most organic chemists are comfortable with the concept of hybridization, a qualitative molecular orbital diagram can be created using sp^2 hybridized oxygens (Figure 1.5). One of the important aspects of this representation is the aspect of the vectors (direction and magnitude) of the hybridized orbitals. In this case, the sp^2 hybridized orbitals have the approximate angle of 120°, whereas in the previous representations, the angle begins at 90° and must be perturbed to 116° by the electron-electron repulsions. This representation also allows a more qualitative visualization of the lone pairs of electrons and indicates the single π bond that is delocalized over the three oxygens. This also shows nonbonding electrons delocalized between the terminal oxygens which can be used to explain the diradical nature of ozone shown in GVB theory calculations.
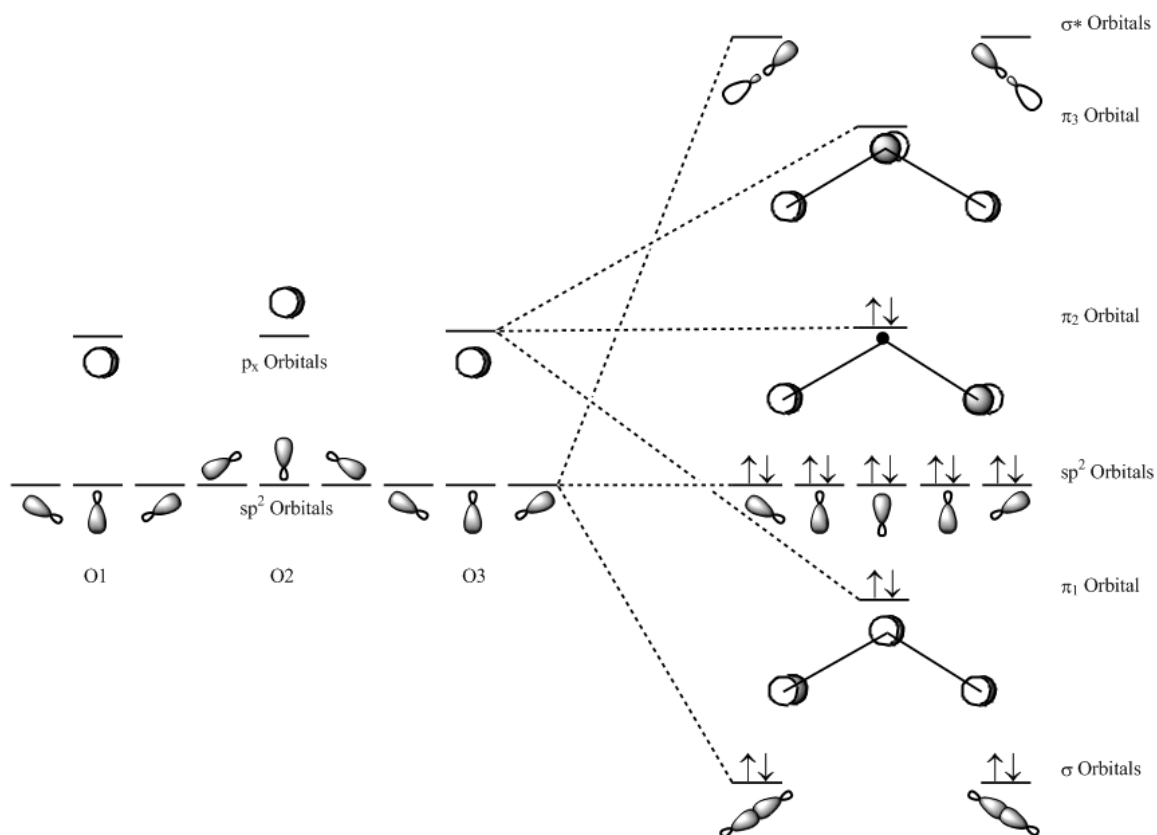
Figure 1.5: Molecular orbitals formed from the sp^2 hybridized atomic orbitals of oxygen.

While each of these descriptions of ozone has some validity, the actual electronic structure is probably best thought of as an amalgam or continuum of all of them. In some reactions, ozone could indeed react as a diradical. With that being said, the research presented in this thesis will primarily focus on two classes of solution phase reactions involving ozone. The first class is the reaction of ozone with the π bond of an alkene in a 1,3-dipolar [2 + 3] cycloaddition (hereafter called ozonolysis). The second class is the reaction of ozone as an electrophile with tertiary amines (hereafter called ozonation of amines).

Reactions of Ozone

Chemistry, like all of the sciences, poses three fundamental questions: What is it?; What can it be used for?; How or why does it work? The structure of ozone has been described, for the most part, in the first part of this chapter. The important things to consider in the description are the small dipole moment, the singlet ground state and, to a lesser degree, the geometry. This part of the chapter is concerned with the second two questions. First, I will describe some of the uses of ozone with an emphasis on the reactions of ozone and olefins. Second, I will describe the generally accepted Criegee mechanism for ozonolysis and its impact on the *in situ* reductive ozonolysis reaction.

Over the past hundred or so years, ozone has been used in a variety of reactions. By the end of the 19th century, ozone had been introduced to the chemistry world as an active reagent capable of oxidizing a great many compounds. With the commercially available von Siemens ozonator, research into ozone reactions truly came into its own. Carl Harries was one of the first researchers to systematically study the reactions of ozone and publish results. Although his primary interest initially involved rubber, he published nearly 100 papers on his research into ozone reactions. Prior to this period, ozone reactions were a curiosity and the products were seldom isolated. Harries developed standard procedures for ozonolysis reactions sometime around 1903[5].

Since that time, the reactions of many organic compounds have been investigated in detail. Long[6] and Bailey[5, 7] have written extensive reviews on the subject including the reactions with organic and inorganic compounds. It is not the purpose, nor within the

scope of this dissertation, to provide details for every type of reaction with ozone. It is, however, important to review two types of reactions that are the focus of the studies in this chapter of this thesis: the ozonolysis of alkenes and the ozonation of tertiary amines (Scheme 1.2).
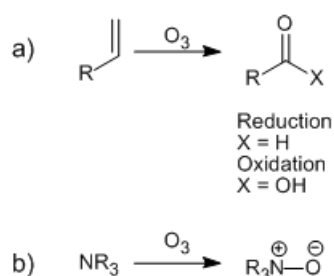
Scheme 1.2: a) Ozonolysis of alkenes b) Ozonation of tertiary amines.

Ozonation of Amines

Before delving into ozonolysis of alkenes, I will first discuss the ozonation of tertiary amines. While ozonolysis is the primary reaction used by modern chemists, ozone can also be used to oxidize other compounds. In fact, in the early 20th century, it was found that waste water could be purified with ozone.[5] One of the benefits of using ozone for water purification was the elimination of odor caused by sulfur containing compounds. From the description of ozone (Figure 1.1), it can be seen that it can act as an electrophile, nucleophile, 1,3-dipole or diradical. In the case of water purification, ozone reacts as an electrophile in the presence of nucleophilic sulfides. Therefore, ozone is capable of oxidizing sulfides to sulfoxides and, to a lesser extent, sulfones. There are also competing side chain oxidations (Scheme 1.3) which will have some significance in this discussion of the ozonation of tertiary amines.[8]
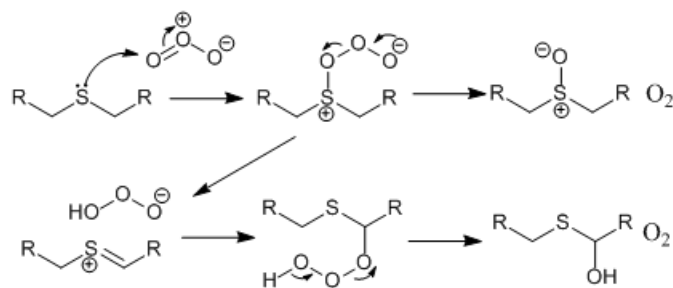
Scheme 1.3: Ozonation of sulfides

The ozonation of tertiary amines is analogous to the ozonation of sulfur containing compounds. Bailey et al. studied the ozonation of amines in some detail over 30 years ago.[9] In these investigations it was found that the products in these reactions will vary depending on the temperature of the reaction, solvent and the substrate amine. Oxidation of the nitrogen (affording N-oxides, nitroxides and nitroalkanes) and side chain oxidation are the main competing reactions although radical reactions may also occur, especially in chlorinated solvents.

Based on the ionization potentials of aromatic amines, it has been suggested that the initial step in the ozonation of amines is a single electron transfer (Pathway B, Scheme 1.4).[10] While it is possible for this to occur, and the ozonate anion radical has been detected by EPR spectroscopy in the ozonation of primary amines, the amine cation and ozonate anion radical can reversibly combine to form the amine-ozone adduct (Pathway C, Scheme 1.4). Another possibility for the reaction to occur is by the formation of the amine-ozone adduct directly (Pathway A, Scheme 1.4).
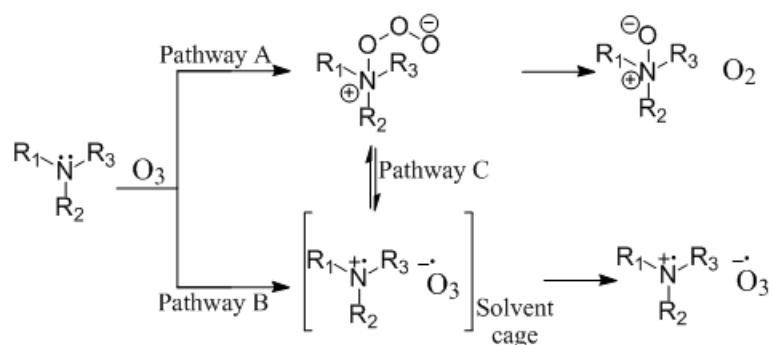
Scheme 1.4: Ozonation of amines

The two pathways that are relevant to this research are amine-N-oxide formation and side chain oxidation. Fragmentation of tertiary amine-ozone adducts forms amine-N-oxides and singlet oxygen (Scheme 1.4). Although Bailey et al. has reported low yields of tertiary amine-N-oxides[9d] (except in the case of the ozonation of tri-n-butylamine in chloroform, methylene chloride and methanol),[9e] Shulman,[11] as well as, our preliminary investigations using ^{1}H NMR suggest the N-oxides are the major product. While N-oxides are the major products in our investigation, this reaction is complicated by side chain oxidations. The side chain oxidations become even more complicated when considering product distributions because the initial products from the initial reaction can also react with ozone.

Side chain oxidation can occur in two ways. First, in a similar manner as the Polonovski reaction,[12] the amine-ozone adduct can undergo intramolecular proton transfer accompanied by N-O cleavage. This is followed by nucleophilic addition of the hydroxide to the iminium ion (Pathway B, Scheme 1.5) affording the hemiaminal and dioxygen. Second, Bailey has proposed that the tertiary amine can undergo a 1,3-dipolar

insertion followed by fragmentation.[9d] Bailey has suggested that the manner in which the

side chain oxidation occurs depends on the type of substituents on the amine. The

product in either case is the hemiaminal which then undergoes further reactions including

hydrolysis, elimination and further oxidations (Pathway A, Scheme 1.5).
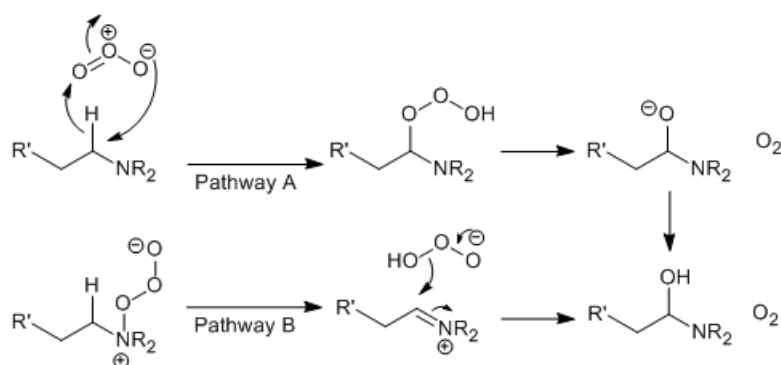
Scheme 1.5: Side chain oxidation of amines

Ozonolysis of Alkenes

The ozonolysis of alkenes was and still is an important reaction in organic

chemistry. In the early days of ozonolysis research, ozonolysis was used for two main

reasons. First, the reaction was used for the efficient syntheses of valuable small

molecules such as vanillin[13] (and derivatives) and sensitive dialdehydes such as

adipaldehyde. This provided economic, as well as, scientific reasons for the development

of ozonolysis.[6, 14] Second, because of a lack of modern spectroscopic techniques,

ozonolysis was routinely used to characterize terpenes, lipids and natural polymers.[6, 15]

More recently, ozonolysis has been used in the multistep synthesis of natural products[16]

and steroids.[17] The transformations in Figure 1.6 show the utility of the ozonolysis

reaction.
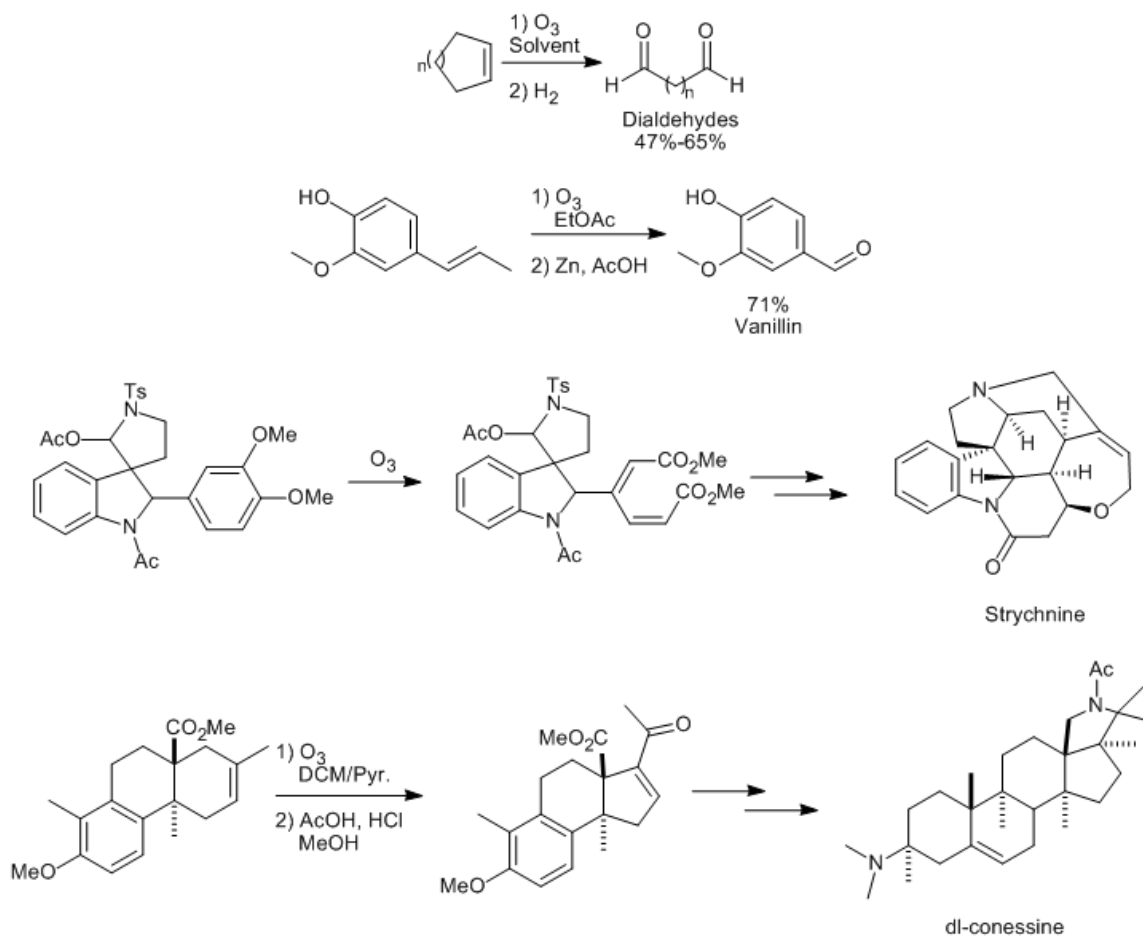
Figure 1.6: The utility of ozonolysis.

It can be seen from the transformations shown in Figure 1.6 that one of the main reasons for the importance of ozonolysis in synthesis is the ability to cleave the double bond in an alkene to regiospecifically obtain aldehydes and ketones or carboxylic acids. The alkene, therefore, can be thought of as a masked or protected carbonyl that can be revealed at the appropriate step. With the discovery of the medicinal properties of artemisinin, a wormwood peroxidic natural product, there has also been great interest in the use of ozonolysis to prepare hydroperoxyacetals and related peroxides (Figure 1.7).[18]

Artemisinin

Furodysinin hydroperoxide

Chondrillin
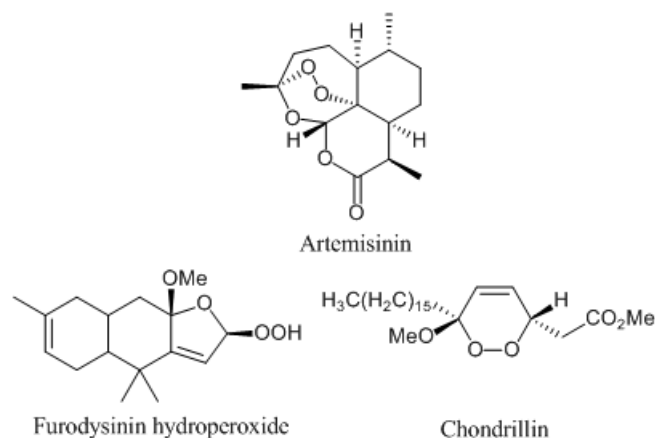
Figure 1.7: Examples of peroxide containing natural products

Although ozonolysis can furnish different types of products depending on the reaction conditions and substrates, the two major products are typically ozonides or hydroperoxyacetals (Scheme 1.2). In the early years of ozonolysis, products were often explosive oligomeric peroxides, at times thought to be the normal products. In some cases these oligomers were used to verify proposed mechanisms or indicate the limits of the reaction. The modern organic chemist can tailor the reaction conditions to obtain the desired product and limit the amount of side products. Studies have been done to examine the effects of substrates, solvent, temperature, concentrations and workups. Standard procedures have been written up to optimize the reaction conditions for ozonolysis reactions.

The 1,2,4-trioxolanes (ozonides) and hydroperoxyacetals are relatively stable and can be isolated in most cases. However, because the final desired products are usually aldehydes, ketones or carboxylic acids, isolation of the ozonolysis products is seldom done and a second reductive or oxidative work up step is done on the reaction mixture.

The ozonide or hydroperoxyacetals can be selectively obtained by controlling the reaction conditions. In most cases, the final ozonide can be selectively formed at low temperatures in a non-participating solvent such as methylene chloride, while the hydroperoxyacetal can often be selectively formed in sterically unhindered polar protic solvents such as methanol. The factors controlling the formation of these products will be discussed below.

Mechanism of Ozonolysis

While Criegee is often credited with the elucidation of the mechanism for ozonolysis, the history of the investigation of the reaction mechanism began at the turn of the 20th century with Harries. Harries was insightful in proposing the structure of the 1,2,3-trioxolane or primary ozonide (PO) as an initial intermediate from the attack of ozone on the π bond of an olefin. To account for the different types of products typically seen in ozonolysis, he proposed that the PO could rearrange or react with other compounds to afford ketones, aldehydes or carboxylic acids, as well as other peroxidic products (Figure 1.8).[6]
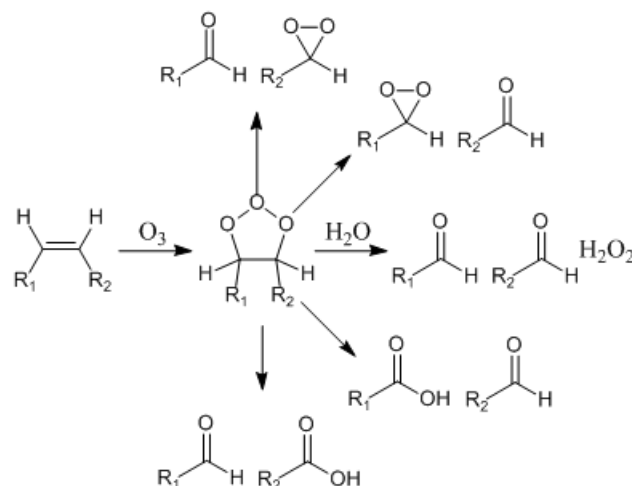
Figure 1.8: Harries' proposed 1,2,3-trioxolane rearrangement products.

Unfortunately, the methods at that time were inadequate to determine the initial structure and his evidence for the 1,2,3-trioxolane was insufficient to prove the structure. Harries' evidence consisted of reformation of mesityl oxide from the pyrolysis of mesityl ozonide and the reformation of fumaric acid from fumaric acid ozonide. Because these compounds are hindered alkenes and contain electron withdrawing groups, the rate of the reaction was slow. It is likely the ozonolysis was not complete. Consequently, upon standing or pyrolysis the ozonide formed from the reaction would be lost leaving only starting material. Indeed, the reactions were repeated by Pummerer and Briner[6] who did not obtain starting material after the reaction and concluded that Harries' observations were incorrect.

In 1925, Staudinger postulated the existence of the molozonide wherein the π bond of the olefin reacts with the terminal and center oxygens to form a four membered

ring which, as shown in Scheme 1.6, can then polymerize, undergo cleavage of the sigma

bond or rearrange to the 1,2,4-trioxolane (isozonide or final ozonide).
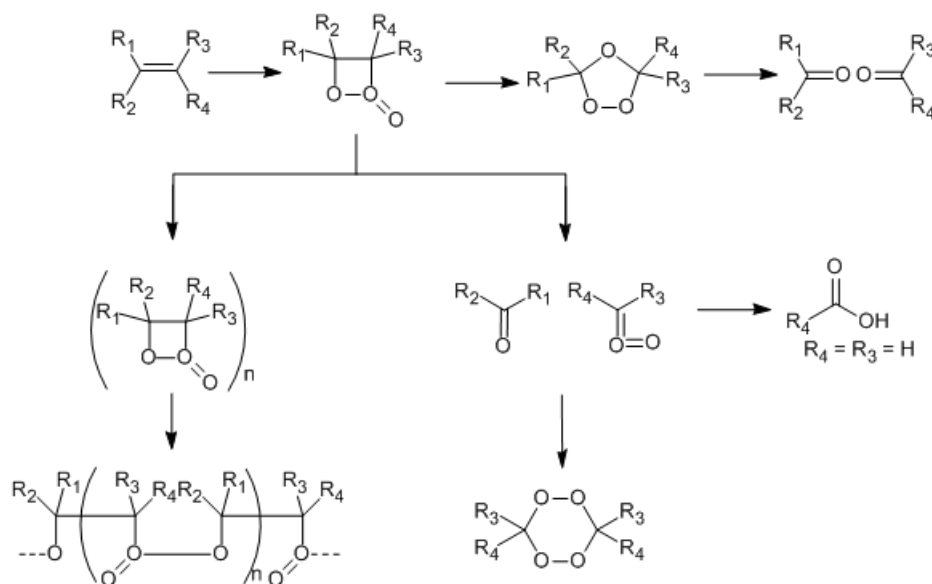
Scheme 1.6: Staudinger postulated the molozonide and isozonide

There are two aspects to this proposed mechanism that are significant. First,

Staudinger based his molozonide intermediate on the analogous peroxide moloxide

(dioxirane) intermediate as proposed by Engler and Bach in the autoxidation of organic

compounds.[19] In the case of the rearrangement of the moloxide, a carboxylic acid is

produced whereas the molozonide rearranges to the stable isozonide (Scheme 1.7).[20]

Second, Staudinger did propose a carbonyl oxide type intermediate that undergoes

rearrangement to the carboxylic acid.
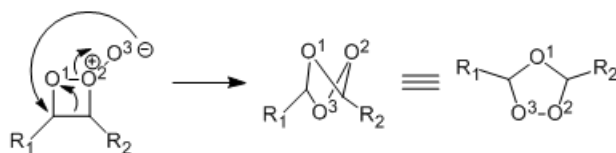
Scheme 1.7: Staudinger molozonide rearrangement

Criegee Mechanism

The Criegee mechanism consolidates Harries' initial ozone alkene adduct, Staudinger's carbonyl oxide type intermediate and the isozonide. The general mechanism, in its simplest form, consists of three consecutive steps, the formation of the PO, fragmentation of the PO to form the carbonyl oxide (CO) and formation of the final ozonide (FO) (Scheme 1.8).
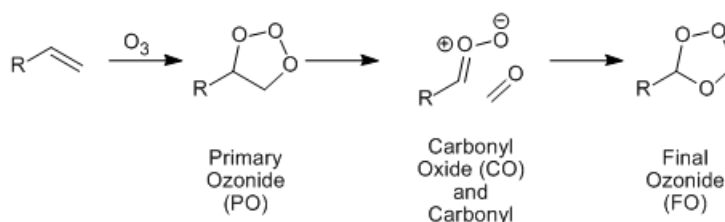
Scheme 1.8: Criegee intermediates

Initial reaction of ozone and the π bond

When Criegee first envisioned the highly unstable initial intermediate in ozonolysis, he left the structure indeterminate. Since then, the 1,2,3-trioxolane has been verified by low temperature spectroscopy,[21] low temperature reaction with isopropyl magnesium bromide[22] and abnormal intramolecular trapping.[23] The formation of the primary ozonide can, in theory, be accomplished either stepwise or in a concerted step. Stepwise, the π bond of the alkene can be coordinated, attacked as an electrophile, nucleophile or radical. This is followed by cyclization or rearrangement to the PO

(Scheme 1.9). Solvent effects are minimal on the rate of the reaction which suggests

nucleophilic and electrophilic stepwise mechanisms are unlikely. The lack of appreciable

epoxide products for unhindered alkenes[24] suggests the π coordination mechanism is a

minor pathway. Finally, the lack of initiation of alkene polymerization indicates the

biradical stepwise mechanism is also unlikely.
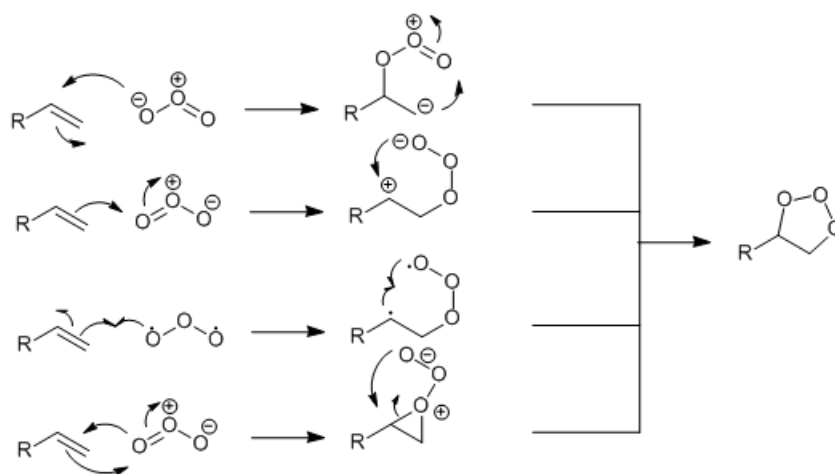
Scheme 1.9: Pathways for the stepwise addition of ozone to alkenes

The concerted mechanism consists of either a biradical or [2+3] 1,3-dipolar cycloaddition

to the π bond of the alkene. As both of these are 6 π electron reactions, the concerted

stepwise reaction is thermally allowed according to Woodward-Hoffmann rules (Scheme

1.10). It is entirely possible that some or all of the mechanistic pathways occur to some

degree but the concerted [2+3] 1,3-dipolar cycloaddition is generally considered the

major mechanistic pathway in solution phase.

Concerted formation of the primary ozonide
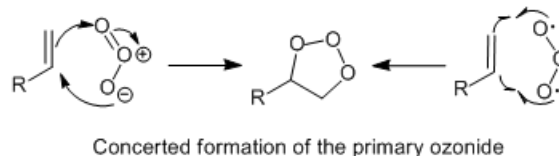
Scheme 1.10: Pathways for the concerted addition of ozone to alkenes

Pericyclic Fragmentation of the Primary Ozonide

Regardless of how the primary ozonide is formed, the next step is nearly spontaneous at temperatures above -100 °C. The cycloreversion could in principle occur in a stepwise fashion but is generally considered to be a concerted fragmentation evidenced by both secondary isotope effects and calculations.[25] This fragmentation forms the carbonyl oxide (CO), a very reactive intermediate that has yet to be detected in an ozonolysis reaction, and a carbonyl compound. While this step is straight forward and relatively simple, the stereochemical and regiochemical aspect merit a brief discussion.

Stereochemical Aspects of Carbonyl Oxide Formation and Reactions

Bunnelle has written an extensive review of carbonyl oxides that includes a section devoted to the generation, stereochemistry and regiochemistry of the carbonyl oxide in the ozonolysis of alkenes.[26] The stereochemistry of the fragmentation has been studied by Bailey and Bauld, among others, by investigating the stereochemistry of the secondary ozonide. The disrotatory, thermally allowed fragmentation of the PO produces,

in principle, either the syn or anti stereoisomers of the CO depending on the geometry of the starting alkene.

According to Bauld and Bailey, the stereochemistry of the PO is defined by the initital concerted reaction step. Thus, the configuration of the alkene is translated to the PO; E-alkene forms the trans-primary ozonide with substituents either diaxial or diequatorial and Z-alkene forms the cis-primary ozonide with axial and equatorial substituents. Assuming the fragmentation is governed by the path of least motion, the anti-carbonyl oxide is formed from an equatorial substituent in the primary ozonide and the syn-carbonyl oxide is formed by an axial substituent. Whether the substituents are axial or equatorial can be determined by sterics (Figure 1.9).
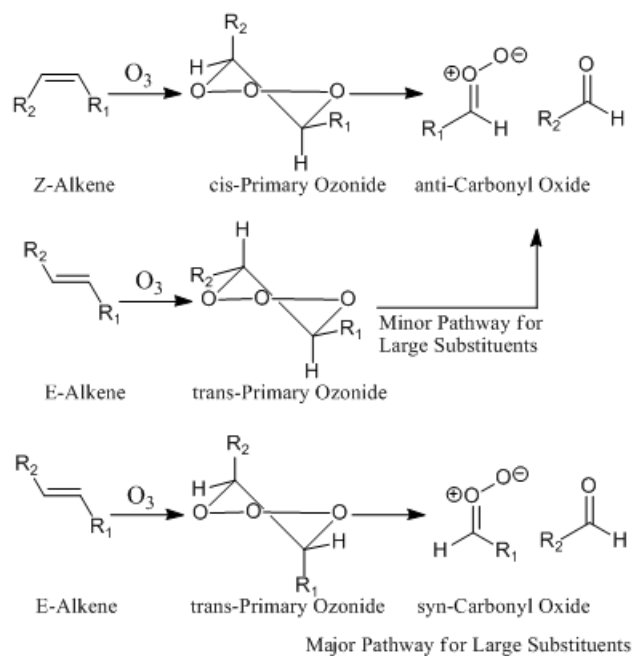
Figure 1.9: Bauld-Bailey stereochemistry of the primary ozonide and carbonyl oxide.

Kuczkowski has proposed a slight variation on the stereochemical outcomes of the PO.[25] In this case, the PO is an O-envelope conformer instead of the C-C half chair. As with the Bauld-Bailey mechanism, the stereochemistry of the PO depends on the configuration of the starting alkene and the substituents are axial or equatorial based on sterics with large substituents in the equatorial position and small substituents in the axial position. The stereochemistry of the resulting carbonyl oxides are then developed from the previous principles (Figure 1.10).
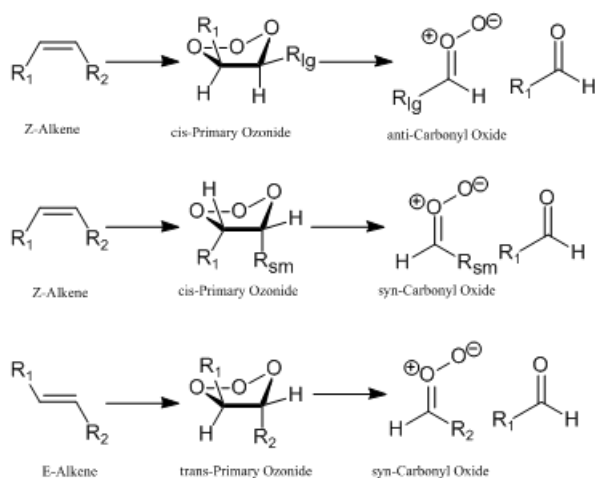
Figure 1.10: Kuczkowski stereochemistry of the PO and CO

Bauld, Bailey[5] and Kuczkowski[27] have developed rules on the stereochemical outcome of the PO fragmentation and they are summarized in Table 1.1. While the stereochemistry of the CO does not directly play a part in the present research, it might be relevant to future extensions of these studies.

Table 1.1: Bauld-Bailey and Kuczkowski rules

Alkene	Bauld-Bailey Rules			Kuczkowski Rules		
	PO Config.	PO Conformation	CO Config.	PO Config.	PO Conformation	CO Config.
1-Alkene	—	—	—	—	equatorial	anti
Z	—	—	—	cis	equatorial (Large Substituent)	anti
Z	cis	axial, equatorial	anti	cis	axial (Small Substituent)	syn
E	trans	axial, axial	syn	trans	axial	syn
E	trans	equatorial, equatorial	anti	—	—	—

The second aspect in this step is the regiochemistry of the fragmentation. The regiochemistry of the fragmentation involves the direction of the fragmentation to form the carbonyl oxide and is directly relevant to my research. In general, the concerted fragmentation of the PO can form two sets of CO and carbonyls (Figure 1.11).
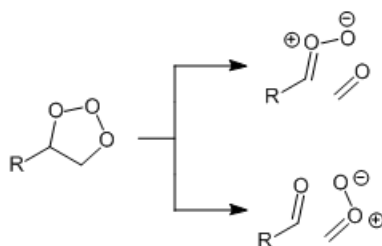
Figure 1.11: Regiochemistry of the PO fragmentation

There has been much research into the direction of fragmentation of the PO. Fliszár has studied the regiochemistry of the fragmentation extensively, both by

calculations and experiments, and has concluded that there are two phenomena that seem to direct the carbonyl oxide formation.[28] First, inductive effects of electron donating groups stabilize the incipient partial positive carbon in the CO. Second, "hyperconjugation" can also stabilize the carbonyl oxide. The effect of hyperconjugation is also probably related to a stabilization of 3.3 kcal/mol of the eclipsed syn CO calculated by Cremer using MP2 with 6-31G* basis set wherein the eclipsed conformation allows a π interaction with the alpha hydrogens (Figure 1.12).[29] The hyperconjugation and inductive effects can counter each other to some extent but the inductive effects are, in most cases, more important, especially when the group is in the equatorial position of the primary ozonide.
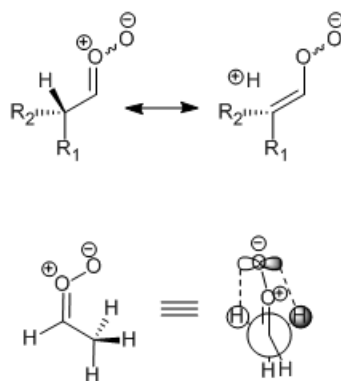
Figure 1.12: Hyperconjugation and molecular orbital overlap stabilization of the carbonyl oxide

The general trend is that the CO will preferentially form on the carbon that can stabilize the formation of the carbocation. Therefore, the influence of groups in directing the formation of the carbonyl oxide has been found to be in the order $CH_3 > COOH > H > OCH_3 > CN > CH_2OH > CH_2I > OCOCH_3 > COOCH_3 > CH_2Br > CH_2Cl > CH_2CN$.

Unfortunately, the regiochemistry and the stereochemistry are interrelated and can complicate this trend.

Concerted [2+3] 1,3-dipole cycloaddition of the carbonyl oxide and carbonyl compound

The final step in a normal ozonolysis reaction is a second [2 + 3] 1,3-dipolar cycloaddition. The CO intermediate undergoes a pericyclic reaction with the carbonyl forming the final ozonide. The normal final ozonide is the reaction between the carbonyl compound and CO formed in the previous step and can be complicated by other carbonyls. Before the cyclization can occur, the two compounds must reorient and it is here that AM1 calculations show a stabilization of the complex (Figure 1.13).[30]
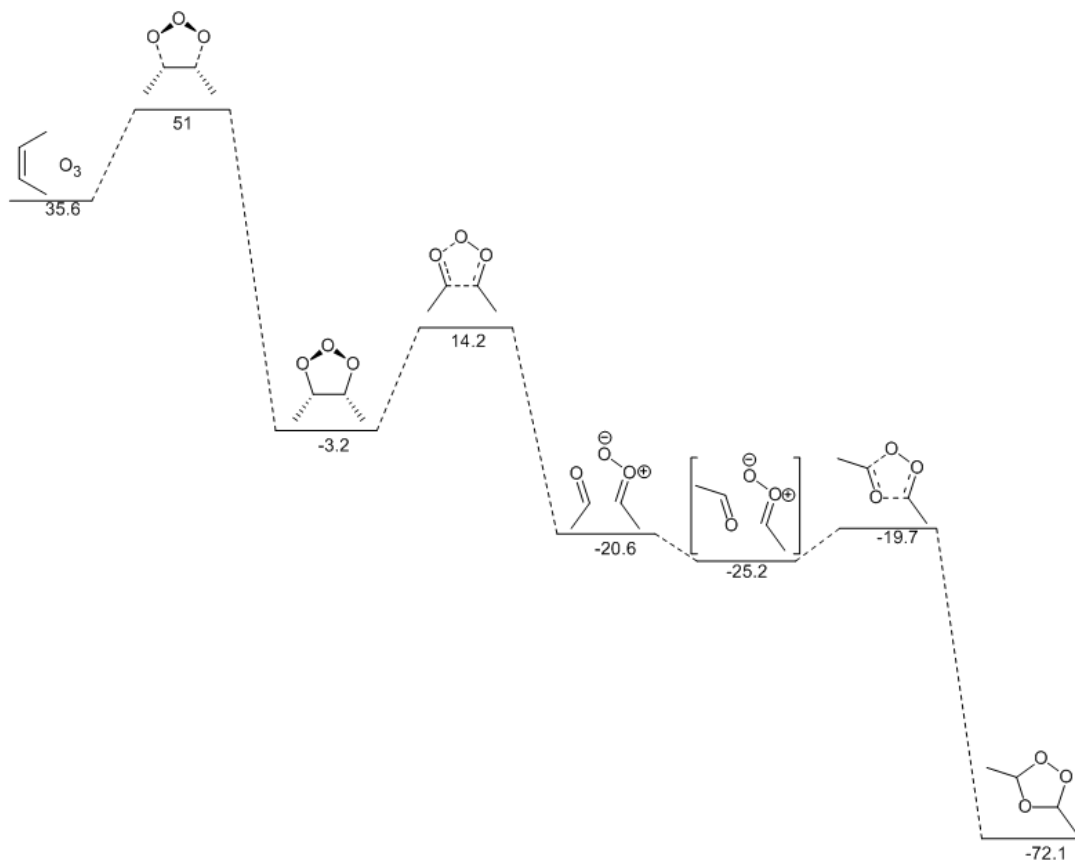
Figure 1.13: AM1-calculated energy profile for *cis*-dimethylethylene + ozone reaction, including the dipole complex (DC). The heats of formations (kcal/mol) for all intermediates and transition states are given.

As overviewed in Scheme 1.11, the CO can be intercepted by nucleophiles, carbonyls or other carbonyl oxides. The addition of protic nucleophiles, such as methanol, produces hydroperoxyacetals or hydroperoxyketals depending on the carbonyl oxide. If there is an excess of a second carbonyl, a cross-ozonide can form and finally, when the endogenous carbonyl does not react with the CO, oligomers, dimers or polymers can form. In this research, it is the interception of the carbonyl oxide by other nucleophiles that is the important aspect.
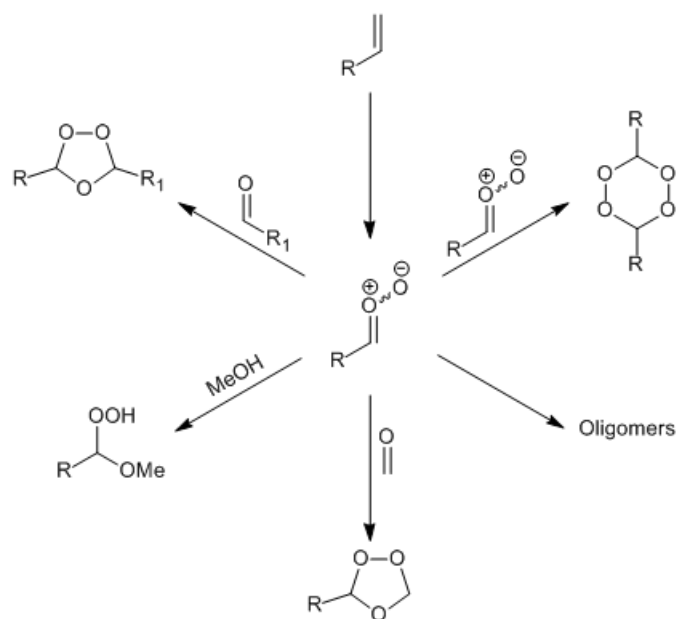
Scheme 1.11: Products of the trapping of the carbonyl oxide

Results and Discussion

In Situ Reductive Ozonolysis with Tertiary Amine N-Oxides

Background: Before going into the discussion of the results of this research, it should be mentioned that much of this work has been published.[31] The following section describes our investigations into methods for the reductive ozonolysis based upon selective reactions of the short-lived carbonyl oxide intermediates. The net impact of our discovery is a method for the direct conversion of alkenes to aldehydes and/or ketones without the formation of potentially hazardous peroxide intermediates.

I will first describe the standard procedures developed in our lab for the ozonolysis of alkenes. Although other solvents may be used in an ozonolysis reaction in which the desired product is the ozonide, the alkene is normally dissolved in freshly distilled methylene chloride at approximately 0.15 M. Because of safety issues when screening reactions, usually, only 3 mmol of alkene are reacted but larger amounts have been used. The reaction is then cooled to -78 ^{o}C in a dry ice/acetone bath and ozone is introduced through a disposable pipette. At this temperature, the solution acquires a blue hue due to the accumulation of excess ozone when all of the alkene has reacted. Variations on the method of ozone introduction have also been used such as a fritted gas stone or fritted funnel. The fritted apparatuses allow smaller gas bubbles and increased mixing but are inconvenient to use. If the reaction is done at higher temperatures, the use of an indicator dye such as Sudan Red III can be used to determine the end of the reaction.[32] In these instances, the reaction is complete when the solution changes from pink to colorless. Alternatively, because the Osmonics ozone generator used in the

Dussault lab has been calibrated to deliver approximately 1 mmol of ozone per minute at 0.75 amps, time can be used to determine when the reaction is complete. This can be problematic if less reactive alkenes are used but for most alkenes studied in this lab, it has not been a problem and the introduction of ozone is stopped after 1.25 equivalents by time. Many TLC dips can be used to monitor the reaction as well. For ozonolysis reactions where the product is peroxidic, a peroxide specific dip consisting of N,N-p-dimethylphenylenediamine in acetic acid, water and methanol is used. This TLC dip can differentiate between ozonides, hydroperoxyacetals and carbonyls by the color of the developed spots. After heating, the spots corresponding to aldehyde appear yellow, spots corresponding to ozonides appear dark red, while the spots corresponding to hydroperoxyacetals appear bright red prior to heating.[33] While TLC can be a very good method to monitor the progress of the reaction, care must be used to minimize exposure to ozone. In most cases, the isolation of the peroxidic product is accomplished by flash column chromatography or HPLC.

Additives can also be present in the reaction using the standard procedures described. For example, the use of methanol or other unhindered alcohol as an additive in the reaction produces hydroperoxyacetals in good yields. This trapping of the carbonyl oxide by nucleophiles is routinely done in the Dussault lab and is, in part, the basis for this research. It can be seen from Table 1.2 that the product distribution in the ozonolysis reaction depends on the reactants and the carbonyl oxide.[34]

3a: R₁ = Me 4a: R₁ = Me
3b: R₁ = iPr 4b: R₁ = iPr
3c: R₁ = Ph 4c: R₁ = Ph

5 6
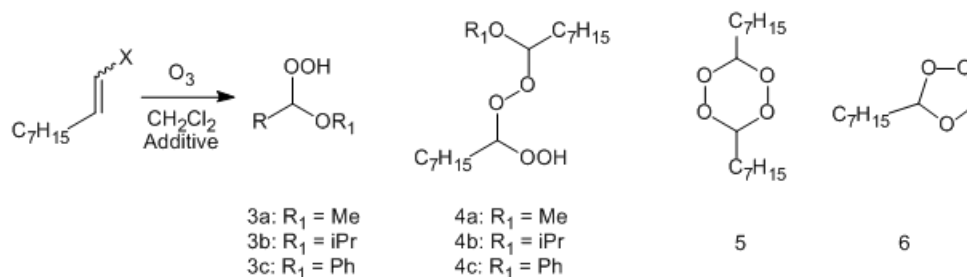
Table 1.2: Initial screening of nucleophilic alcohols

X =	R$_1$ =	Additive	Yield			
			3a-c	4a-c	5	6
OMe		None			4 %	
OMe	Me	MeOH	75 %	8 %		
OMe	iPr	iPrOH	68 %	11 %		
OMe	Ph	PhOH	12 %	20 %	8 %	
H		None				96 %
H	Me	MeOH	66 %	4 %		10 %
H	iPr	iPrOH	12 %	32 %		32 %
H	Ph	PhOH	16 %	27 %		14 %

As stated previously, not only is ozonolysis a method used to synthesize

peroxides such as ozonides and hydroperoxyacetals, it is also a powerful method of

introducing the carbonyl functionality in synthetic intermediates. For most synthetic

applications, the peroxidic products from ozonolysis are further transformed in either an

oxidative or reductive second step without isolation due to the safety hazards associated

with peroxidic products. While an oxidative step affords carboxylic acids and ketones

and can be accomplished with hydrogen peroxide, the most common second step in

synthesis is a reductive step which affords aldehydes and ketones. Unfortunately, the

most common reagents for reduction such as triphenylphosphine,[35] borane,[36] zinc and

acetic acid,[37] platinum and hydrogen[6] and lithium aluminum hydride[38] or sodium

borohydride[39] can be incompatible with other functionality in the final product or make

the isolation of final products difficult. Dimethyl sulfide is another common reagent that

is very mild and relatively easy to remove by aqueous washes from the product but can

often lead to incomplete reduction and safety hazards.[40]

Former members in the Dussault group were interested in developing a method

which circumvented the formation of the kinetically stable but thermodynamically

unstable ozonide or any other peroxidic products. Of the three intermediates in an

ozonolysis reaction (PO, CO and FO), the group targeted the interception of the carbonyl

oxide because it can act theoretically as an electrophile, nucleophile or dipolarophile.

Previously, it has been shown that carbonyl oxides can react as an electrophile in

the presence of protic nucleophiles and dipolarophiles in the presence of carbonyls.

Although Adam has proposed that photogenerated carbonyl oxides react as nucleophiles

with thianthrene-5-oxide (a thiasulfoxide probe for oxygen transfer reagents),[41] it was

believed that the sulfoxide could be reacting as a dipolarophile (Scheme 1.12).
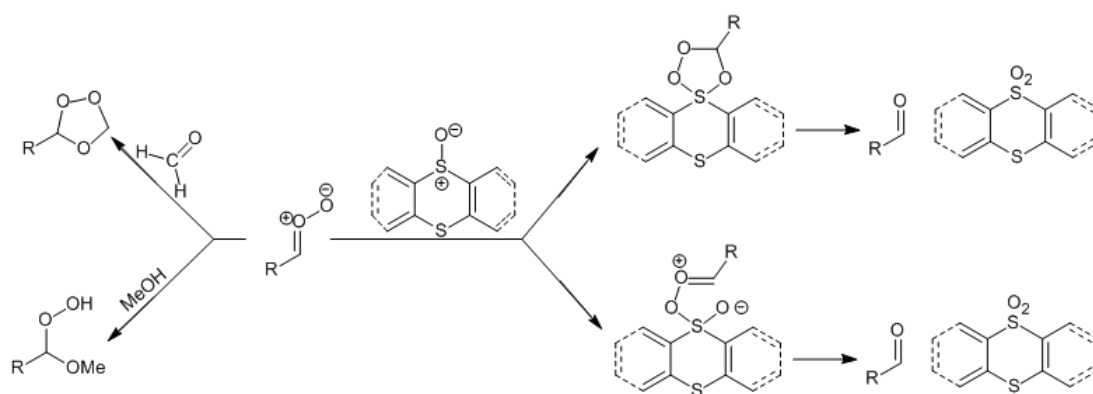
Scheme 1.12: Thiasulfoxide rationale for sulfoxide trap

Because of the thiasulfoxide research, our group became interested in the potential of using inexpensive sulfoxides as *in situ* reducing agents. If the CO could be trapped by a sulfoxide, in much the same way that the carbonyl compound reacts with the CO, the resulting relatively unstable heteroozonide would undergo a cycloreversion reaction to the carbonyl compound and a sulfone.[41] This is because, unlike the carbonyl, the sulfur atom in the sulfoxide is not in its highest oxidation state. The group selected 1-decene as the alkene model for screening reactions for three reasons. First, 1-decene is well behaved as a substrate forming predominately the nonanal-O-oxide. Second, the rate of the reaction of 1-decene with ozone is relatively fast. Finally, ozonides and hydroperoxyacetals from the reaction are fairly stable and can be isolated with little difficulty.

Kyle Mott, Dr. Joe Raible and Paul Unverzagt began this project with the investigation of reactions conducted in the presence of dimethylsulfoxide (DMSO). In this initial investigation, there were some promising but curious results. When 2 equivalents of DMSO were used at -78 °C, the ratio of ozonide to aldehyde was 1.5:1. This is in stark contrast with a normal ozonolysis reaction in the absence of DMSO where the ozonide can be isolated in >95% yield. Unfortunately, attempts to optimize the reaction conditions resulted in only slight improvement in the yields of the aldehyde.[31b]

A key development in this research was the observation by Joe Raible that the use of both triethylamine and DMSO appeared to increase the aldehyde to ozonide ratio. This approach, initially pursued on the hypothesis that the amine would coordinate with

the DMSO and might enhance the nucleophilicity of sulfoxide's oxygen, was

complicated by the discovery that the relative yields of ozonide and aldehyde were also

sensitive to the moisture content of the methylene chloride used as a reaction solvent.

The results of these initial reactions are shown in Table 1.3.
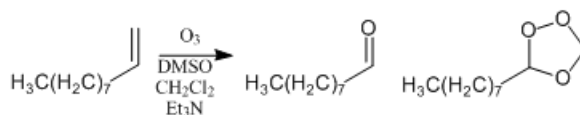
Table 1.3: Initial screening of amines in ozonolysis

DMSO	Et$_3$N	Wet/Dry Solvent	Temperature	Aldehyde	Ozonide
0 eq.	0 eq.	NR	-78 ^{o}C or 0 ^{o}C	Trace	>95%
2 eq.	0 eq.	NR	-78 ^{o}C	35%	52%
2 eq.	0 eq.	NR	0 ^{o}C	61%	22%
2 eq.	1 eq.	Dry	-78 ^{o}C	43%	17%
2 eq.	1 eq.	Wet	-78 ^{o}C	65%	29%
2 eq.	1 eq.	Wet	0 ^{o}C	84%	12%

To make matters more confusing, control studies revealed that ozonolysis in the presence

of triethylamine achieved yields of aldehyde comparable to those obtained in the

presence of either DMSO or DMSO and triethyl amine. Furthermore, higher yields of

aldehyde were once again consistently obtained for reaction in wet methylene chloride.

Initially, triethylamine was used in the reaction but afterwards, other tertiary and

secondary amines were screened and it was found that, with the exception of pyridine, the

reaction consistently gave good yields of the aldehyde (Table 1.4). These results were

confusing for several reasons. First, given that amines are relatively good reductants, the

hypothesis was that the formation of the desired reduction product (aldehydes) was a result of the reaction of the carbonyl oxide and the amine. However, there was little precedent for this reaction in the literature. Second, if the formation of aldehyde was the result of carbonyl oxide being reduced by the amine, the reaction yields would increase steadily with increased amounts of amine. Kyle Mott found that this is not the case since the use of excess amine resulted in slower reaction rates and recovered alkene.
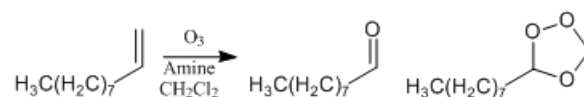
Table 1.4: Screening of amines in ozonolysis under different conditions

Amine	Wet/Dry Solvent	Temperature	Aldehyde	Ozonide
Et$_3$N	Wet	-78 °C	79%	13%
Et$_3$N	Dry	-78 °C	50%	30%
Et$_3$N	Wet	0 °C	75%	14%
Et$_3$N	Wet	0 °C	64%	14%
NMM	Wet	0 °C	68%	12%
NMM	Dry	0 °C	57%	10%
Morpholine	Dry	0 °C	62%	10%
Morpholine	Wet	0 °C	56%	18%
Et(i-Pr)$_2$N	Dry	0 °C	58%	9%
(C$_{12}$H$_{25}$)$_2$NMe	Wet	0 °C	55%	15%
DABCO	Dry	0 °C	48%	10%
Pyridine	Dry		16%	11%

To begin my investigation into this mystery, the ozonolysis of 1-decene with 1 equivalent of triethylamine at -78 °C was repeated with similar results. Because this reaction seemed to be capricious and the role of water was unknown, the reaction was run under anhydrous conditions. With the exclusion of water from the reaction, there were two working hypotheses. The first hypothesis, proposed in 1958 by Slomp[42] and later in 1971 by Prokrovskaya,[43] was that there was an oxygen transfer from the carbonyl oxide to the nucleophilic amine. While this seems unlikely, the fact that amine-N-oxides were observed as a side product, seemed to lead credence to the hypothesis. The second hypothesis was that the amine was acting as nothing more than a base that deprotonated and fragmented the ozonide (Scheme 1.13).[44]
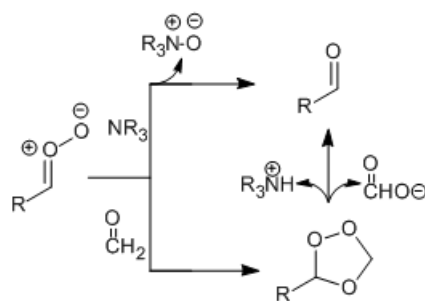
Scheme 1.13: Possible pathways for ozonolysis with amine additives

The first hypothesis is largely based on the ionization potentials of amines and the presence of the amine-N-oxides as by products. From the previous section on the ozonation of amines, it is obvious, in hindsight, that ozone was the oxidant rather than the carbonyl oxide. The decrease in the reaction rate and the recovery of starting alkene can be attributed to the ozonation of the amines. In addition, the ozonolysis of 1-decene with an amine as an additive produced intense fuming that does not occur without the amine.

If the rate of reaction of the amines is comparable to or faster than the rate of reaction of alkene, then the amine oxidation would compete with the alkene oxidation.[45] The second hypothesis is also thought to be incorrect. Although the decomposition of monosubstituted ozonides by amines is relatively fast and exothermic, the formate produced as a byproduct in this pathway was not evident in significant amounts by ^{1}H NMR of the crude samples in the ozonolysis of 1-decene with triethylamine.

These observations, along with the realization that the rate of the ozonation of amines was relatively fast, led to the conclusion that the ozone was reacting first with the amine to form the amine-N-oxide. A new pathway was hypothesized in which the addition of the amine-N-oxide to the carbonyl oxide formed an adduct that could fragment into an amine and an aldehyde. To test this new hypothesis, the ozonolysis of 1-decene with one equivalent of N-methylmorpholine-N-oxide (NMMO) resulted in the isolation of nonanal in good yield. Furthermore, in contrast to the ozonolysis in the presence of one equivalent of amine, there was no fuming during the reaction and the time to completion was comparable to a reaction in the absence of any additive.
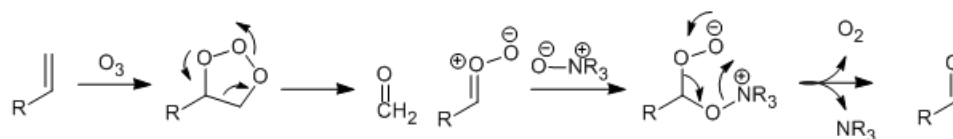
Scheme 1.14: Hypothesized mechanism for ozonolysis with amine-N-oxides

Although the ozonolysis of 1-decene with one equivalent of NMMO resulted in good yields of nonanal, the ozonide was still being produced, albeit as a minor product. This prompted the reinvestigation of previous ozonolysis reactions with triethylamine. First, the reaction was run in two steps beginning with the ozonation of triethyl amine,

during which the intense fuming occurred. The triethyl amine-N-oxide (TEANO)

produced in this manner was used in the next step without purification. The alkene was

subsequently added and allowed to react with ozone. The results were as predicted with

the isolation of aldehyde in 80% yield.

Although the amine produced from the fragmentation of the adduct should, in

theory, be oxidized back to the amine oxide with ozone, the formation of the ozonide

indicated that the amine-N-oxide was probably not catalytic. Still, these results

encouraged us to attempt to optimize the reaction and reduce the formation of the ozonide.

In order to accomplish this, the reaction was first run with increasing equivalents of

NMMO, a relatively inexpensive and easily handled compound that gave good initial

results. These screening reactions, shown in Table 1.5, resulted in the discovery that with

three equivalents of NMMO only a trace amount of ozonide was observed by TLC and at

five equivalents of NMMO, the ozonide formation is completely suppressed.

Because we had good evidence for the trapping of the carbonyl oxide by the

amine-N-oxides, other N-oxides were next screened to see if the reaction was general.

The other amine-N-oxides tested were trimethylamine-N-oxide (TMANO), 1,4-

diazabicyclo[2.2.2]octane N-oxide (DABCO-N-oxide) and pyridine-N-oxide. TMANO

was thought to be more nucleophilic and would therefore perform better as a trap.

Unfortunately, anhydrous TMANO was found to be expensive and hydrated TMANO

had limited solubility in dichloromethane. It was thought that DABCO-N-oxide and

pyridine-N-oxide would be superior N-oxides because side chain oxidation is not really

possible under normal circumstances. While the DABCO-N-oxide had to be formed *in*

situ by the ozonation of DABCO prior to the addition of alkene, pyridine-N-oxide was

commercially available. Unfortunately, although one equivalent of DABCO-N-oxide is reported, it is only partially soluble in methylene chloride so it is difficult to determine the actual amount used. The pyridine-N-oxide produced an intensely colored solution but still good yields of aldehydes (Table 1.5).

Table 1.5: Results of ozonolysis with amine-N-oxides

Amine-N-Oxide (eq.)	Aldehyde Yield (%)	Ozonide Yield (%)
NMMO (1)	88	0 (trace by TLC)
NMMO (3)	94	0 (trace by TLC)
NMMO (5)	94	0 (none by TLC)
TEANO (1)	80	Trace
TMANO (1)	68	12
DABCO-N-Oxide (1)	62	10
Pyridine-N-Oxide (1)	58	9

Next, methyl oleate, a 1,2-disubstituted cis-alkene, and 2-methylundecene, a 1,1-disubstituted alkene, were ozonized in order to examine the generality of the reaction. While the reductive ozonolysis reactions were successful, the yields of aldehyde for the methyl oleate were difficult to reproduce due to the volatility. The ozonolysis of methyl oleate had to be repeated many times in order to get yields of pure aldehyde and methyl 9-oxononanoate at the same time. These products were often isolated individually in the 90% range but as a set of products, the best yields of pure product were 74% for nonanal and 96% for methyl 9-oxononaoate. The yield for the ozonolysis reaction of 2-methylundecanene was moderate at only 54% possibly due to a side reaction or a slower nucleophilic addition to the carbonyl oxide.

In order to directly discriminate between the amine-N-oxide nucleophilic trapping of the carbonyl oxide and the base fragmentation of the ozonide developed by Hon,[46] it was first thought that we could isotopically label the oxygen of the amine-N-oxide. Unfortunately, Fred Zinnel, the undergraduate student working in the lab at the time, found the oxidation of amines to be difficult or cost prohibitive for labeled oxygen. Therefore, indirect means of confirming our proposed mechanism were explored. First, an experiment was run in which 1-phenylcyclopent-1-ene was ozonized with and without 5 equivalents of NMMO. Second, an experiment in which there was competitive trapping with methanol and NMMO in the ozonolysis of 1-decene.

In the first experiment, 1-phenylcyclopent-1-ene was chosen as the substrate because during ozonolysis, it forms the ozonide almost exclusively,[47] and it is also known to undergo base-promoted fragmentation to the keto acid.[48] First, 1-phenylcyclopentene was ozonized with no additives after which, 5 equivalents of NMMO were added. This resulted in the formation of the keto acid almost exclusively from the base mediated fragmentation of the ozonide. Next, the reaction was repeated with equivalents of NMMO as an additive. This resulted in a four to one ratio of keto acid to keto aldehyde. While the ozonide was formed in both reactions, the formation of keto aldehyde indicates that NMMO did indeed react with the carbonyl oxide as predicted (Scheme 1.15).
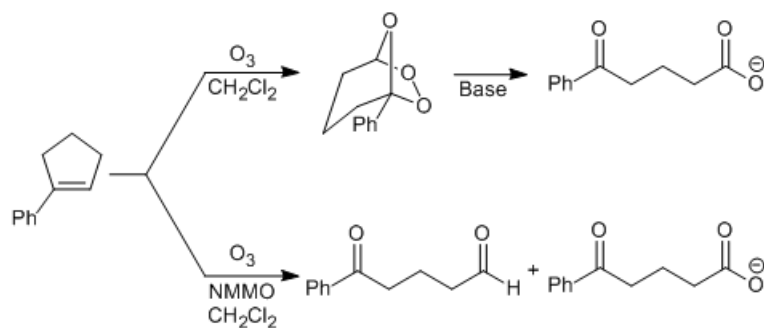
Scheme 1.15: Ozonolysis of 1-phenylcyclopentene with amine-N-oxide additive

In the second set of experiments, the amine-N-oxide and methanol were used as competitive nucleophiles for the carbonyl oxide derived from the ozonolysis of 1-decene. It is known that the ozonide is formed with no methanol present, whereas with methanol, the formation of the hydroperoxyacetal is the major product. With one equivalent of NMMO and methanol, the ozonolysis of 1-decene resulted in aldehyde being produced as the major product (Scheme 1.16).
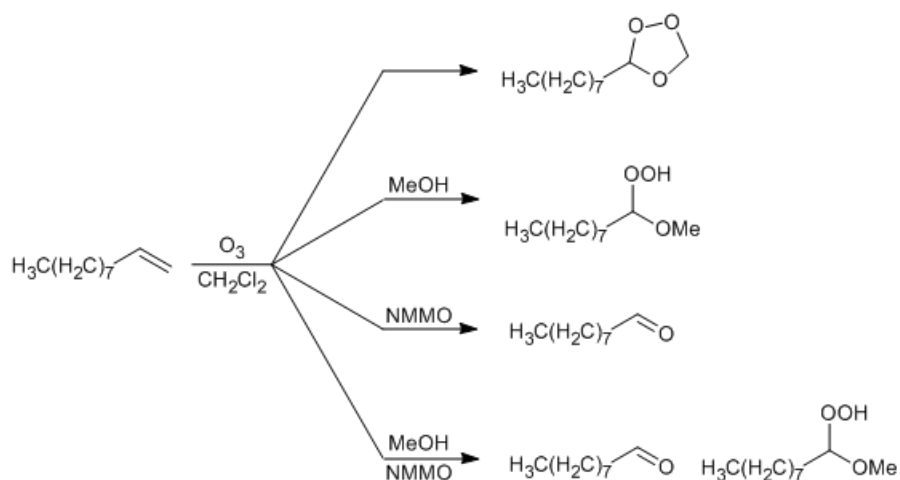
Scheme 1.16: Competitive nucleophilic trapping

Finally, an exploratory tandem reaction was run where 1-decene was ozonized in the presence of 2.5 equivalents of NMMO followed by the addition of ethyl magnesium bromide. The resulting 3-undecanol was isolated in 53% yield. While this is only a moderate yield, the reaction was not optimized. This result may suggest that ozonolysis may be used in other tandem reactions thereby decreasing waste and time.

Final notes on ozonolysis:

As a final note on the implications of this research, the proposed mechanism has had some impact on some of the other research in this lab. The fragmentation of the adduct formed by the nucleophilic trapping of the carbonyl oxide with amine-N-oxides produces singlet oxygen. While it would be difficult to use the singlet oxygen produced in ozonolysis, similar peroxidic compounds have been found to fragment in the same manner. Dr. Ghorai found that geminal dihydroperoxides can be transformed into "monoprotected" acetates, carbonates and sulfonates. These compounds then fragment to produce singlet oxygen when treated with base (Scheme 1.17).[49] Other compounds have since been used in the same manner and it is possible that other leaving groups may also be used to produce singlet oxygen.
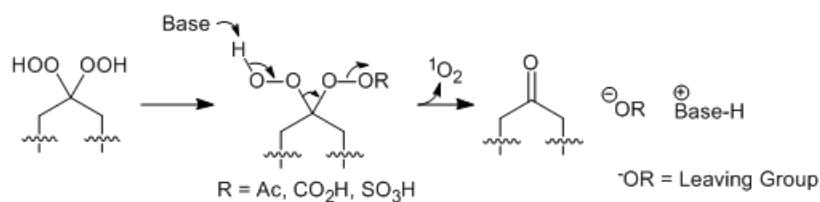
Scheme 1.17: Base mediated fragmentation of "monoprotected" geminal dihydroperoxides

Further experiments need to be completed for the ozonolysis reaction in general and the *in situ* reductive ozonolysis reaction, specifically. For ozonolysis in general, an optimization of a method for screening reaction conditions needs to be accomplished. One of the challenges in the method development was the time commitment for screening the reactions. While the ozonolysis reactions took only minutes to complete, the isolation and purification of the products was more time consuming. In the beginning of the project, I had attempted to streamline the screening process by using ^{1}H NMR spectroscopy with an internal standard. Unfortunately, by the time I had developed a prototype method, I was finished with the project. Later, Joy Kotschwar, an undergraduate student working in the lab, attempted to use both TLC analysis and HPLC chromatograms to screen ozonolysis reactions. I believe that with different TLC developing dips and TLC imaging software, the screening of ozonolysis reactions with and without additives could be streamlined. Once a screening method is developed and optimized, there are four variables that need to be tested. First, different solvents can be used in addition to the common ozonolysis solvents. Second, the concentration can be varied in order to ascertain its effect on oligomer and aldehyde formation. Third, different ozone delivery methods should be tested. I have used a type of fritted funnel in an attempt to increase the mixing and surface area of ozone bubbles but did not do any extensive comparison with the pipette delivery method. In addition, a dropping funnel could be used to add a saturated solution of ozone to the reaction flask. Finally, the temperature can be varied. All of these variables must be tested in the ozonolysis reaction first without any additives. Once a baseline is established for each set of

conditions, amine N-oxide additives can be tested at various equivalents in order to improve the method.

Experimental

General Experimental Procedure: All purchased chemicals were used without further purification. THF was distilled over benzophenone and sodium metal. Dichloromethane was distilled over calcium hydride. Methanol was dried with molecular sieves. Ozone was generated at approximately 1 mmol per minute as a 2-4% mixture of O_3/O_2 stream by an Osmonics V-series ozone generator. Molybdate dip (25 g ammonium molybdate tetrahydrate, 10 g ceric sulfate and 1 L 10% sulfuric acid) was used as general TLC developing dip. A peroxide specific dip[33] (1.2 g N,N-dimethyl-*p*-phenylenediamine dihydrochloride, 100 mL methanol, 20 mL water and 1 mL acetic acid) was used for peroxide containing compounds and an olefin dip (0.316 g potassium permanganate in 100 mL water) was used as an olefin compound specific dip. NMR spectra were obtained with 300, 400 or 500 MHz Bruker spectrometers using $CDCl_3$ as the solvent unless otherwise noted. Chemical shifts are reported in ppm. IR spectra were obtained with a Nicolet Avatar 360 FT-IR ESP spectrometer.
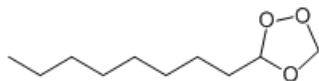
Typical procedure for ozonolysis of alkenes: To a flame dried 100-mL round bottom flask was added 3.0 mmol of decene, 20 mL of methylene chloride. The stirred solution was cooled to -78 °C and a solution of 2% O_3/O_2 (nominal output of 1 mmol O_3/min) was introduced directly above the solution via a glass pipette for 3.3 min.

(nominally 1.1 equiv ozone relative to alkene). This mode of ozone addition furnished

the most consistent results. The solution was then sparged with O_2 for 2 min. and

warmed to rt then concentrated. The residue was purified by flash chromatography using

2.5% ethyl acetate/hexane. Ozonide; $R_f = 0.6$ (15% ethyl acetate/hexane); ^{1}H NMR

(CDCl$_3$) δ 5.18 (1H, s), 5.12 (1H, t, $J = 5.0$ Hz), 5.02 (1H, s), 1.75-1.68 (2 H, m), 1.49-

1.19 (12 H), 0.88 (3H, t, $J = 6.8$ Hz); ^{13}C NMR (CDCl$_3$) δ 103.79, 93.93, 31.80, 31.08,

29.37, 29.36, 29.13, 23.83, 22.61, 14.01
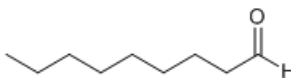
Typical procedure for ozonolysis of alkenes with amine-N-oxide additives: To a

flame dried 100-mL round bottom flask was added 3.0 mmol of decene, 20 mL of

methylene chloride, and 9.0 mmol of N-methylmorpholine-N-oxide (NMMO). The

stirred solution was cooled to 0 °C and a solution of 2% O_3/O_2 (nominal output of 1 mmol

O_3/min) was introduced directly above the solution via a glass pipette for 6.6 min.

(nominally 2.2 equiv ozone relative to alkene). This mode of ozone addition furnished

the most consistent results. The solution was then sparged with O_2 for 2 min. and warmed

to rt. Following confirmation of the absence of ozonide (TLC), the solution was

concentrated and the residue was purified by flash chromatography using 5% diethyl

ether/pentane. Alternatively, the crude reaction was quenched into pH 6 phosphate buffer

and extracted with ether prior to concentration and chromatography. Nonanal; $R_f = 0.52$

(15% ethyl acetate/hexane); ^{1}H NMR (CDCl$_3$) δ 9.75 (1H, t, $J = 1.7$ Hz), 2.41 (2H, dt, J

$= 1.7$ and 7.3 Hz), 1.62 (2 H, apparent quint, 7.3 Hz), 1.37-1.23 (10 H), 0.87 (3H, t, $J =$

6.4 Hz); ^{13}C NMR (CDCl$_3$) δ 202.8, 43.9, 31.8, 29.3, 29.13, 29.06, 22.6, 22.1, 14.0.
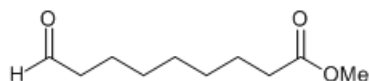
Methyl 9-oxononanoate: $R_f = 0.25$ (10% ethyl acetate/hexane); ^{1}H NMR (CDCl$_3$) δ 9.70 (1H, t, $J = 1.8$ Hz), 3.60 (3H, s) 2.36 (2H, dt, $J = 1.8$ and 7.3 Hz), 2.34 (2 H, t, $J = 7.3$ Hz) 1.6-1.5 (4 H), 1.3-1.2 (6 H); ^{13}C NMR (CDCl$_3$) δ 202.69, 174.13, 100.00, 51.39, 43.79, 33.95, 28.92, 28.88, 28.84, 24.78, 21.92.
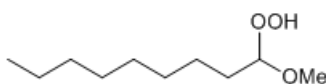
Typical procedure for ozonolysis of alkenes with methanol as an additive: To a flame dried 100-mL round bottom flask was added 3.0 mmol of decene, 20 mL of methylene chloride, and 42.0 mmol of anhydrous methanol. The stirred solution was cooled to 0 °C and a solution of 2% O$_3$/O$_2$ (nominal output of 1 mmol O$_3$/min) was introduced directly above the solution via a glass pipette for 3.3 min. (nominally 1.1 equiv ozone relative to alkene). This mode of ozone addition furnished the most consistent results. The solution was then sparged with O$_2$ for 2 min. and warmed to rt. The reaction mixture was then washed with sodium bicarbonate and dried with anhydrous sodium sulfate. The solution was concentrated and the residue was purified by flash chromatography using 15% ethyl acetate/hexane. Hydroperoxyacetal: $R_f = 0.25$ (15% ethyl acetate/hexane); ^{1}H NMR (CDCl$_3$) δ 8.3 (1H, s), 4.76 (1H, t, $J = 5.8$ Hz), 3.52 (3H, s), 1.78-1.58 (2 H, m), 1.46-1.21 (12 H), 0.90 (3H, t, $J = 7.0$ Hz); ^{13}C NMR (CDCl$_3$) δ 108.86, 55.78, 31.84, 31.27, 29.43, 29.37, 29.19, 24.62, 22.65, 14.09.
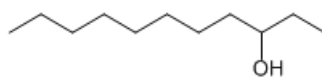
To a flame dried 100-mL round bottom flask was added 3.3 mmol of decene, 20 mL of methylene chloride, and 8.2 mmol of N-methylmorpholine-N-oxide (NMMO). The stirred solution was cooled to 0 $^{\circ}$C and a solution of 2% O_3/O_2 (nominal output of 1 mmol O_3/min) was introduced directly above the solution via a glass pipette for 6.6 min. (nominally 2.2 equiv ozone relative to alkene). The solution was then sparged with O_2 for 2 min. and concentrated. The crude product was then redissolved in 20 mL THF. 2.8 mL of a solution of 3 M ethylmagnesium bromide in diethyl ether was added slowly to this solution at -40 $^{\circ}$C and allowed to stir as it warmed to rt. After TLC indicated the absence of aldehyde, the solution was quenched with 20 mL of water, diluted with diethyl ether and washed with 10% HCl. The organic layer was then washed with brine and dried over anhydrous sodium sulfate. The crude product was then concentrated by vacuum and purified with flash column chromatography (25% ethyl acetate/hexane) to give 301 mg of the alcohol in 53% yield. R_f = 0.25 (25% ethyl acetate/hexane); ^{1}H NMR (CDCl$_3$) δ 3.53-3.46 (1H, m), 1.80 (1H, br s), 1.55-1.20 (3H), 0.92 (3 H, t, 7.5 Hz), 0.87 (3H, t, J = 6.7 Hz); ^{13}C NMR (CDCl$_3$) δ 73.22, 37.11, 32.07, 30.22, 29.96, 29.81, 29.48, 25.86, 22.80, 14.14, 9.96.
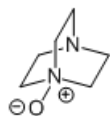
3 mmol of 1,4-diazabicyclo[2.2.2]octane (DABCO) was dissolved in 20 mL of dichloromethane in a flame dried 100 mL round bottom flask with a stir bar. The stirred solution was cooled to 0 $^{\circ}$C and a solution of 2% O_3/O_2 (nominal output of 1 mmol O_3/min) was introduced directly above the solution via a glass pipette for 3.3 min.

(nominally 1.1 equiv ozone relative to DABCO). The solution was then sparged with O_2

for 2 min. and warmed to rt. A small aliquot of the solution was removed for ^{1}H NMR

after which 3.0 mmol of 1-decene was then added to the solution and again a solution of

2% O_3/O_2 (nominal output of 1 mmol O_3/min) was introduced directly above the solution

via a glass pipette for 6.6 min. (2.2 equiv ozone relative to alkene). The solution was

then worked up by standard procedures. The ^{1}H NMR spectrum of 1,4-

diazabicyclo[2.2.2]octane-N-oxide indicated the clean formation of the desired product

which was very different from the singlet of DABCO; ^{1}H NMR (CDCl$_3$) δ 3.22-3.06

(Presumably 12H, m).

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Chapter 2

Progress toward the Asymmetric Synthesis of

Peroxyplakoric Acid A$_3$

In this chapter, I will describe the progress made toward the asymmetric synthesis of peroxyplakoric acid A$_3$. Specifically, I will describe a successful asymmetric approach to the 3-methoxy-1,2-dioxane core of this class of natural products that should be applicable to other cyclic peroxides. The key step in this synthesis is the stereospecific cyclization of a hydroperoxy acetal to afford the 3-methoxy-1,2-dioxane core. A boron mediated anti-selective asymmetric aldol reaction sets the stage for this cyclization and sets the stereochemistry of the propionate head group for the peroxyplakoric acids. While we did not complete the synthesis of peroxyplakoric acid A$_3$, this strategy for the asymmetric synthesis of the peroxyplakoric acids is demonstrated to be feasible and potentially applicable to other 1,2-dioxanes.
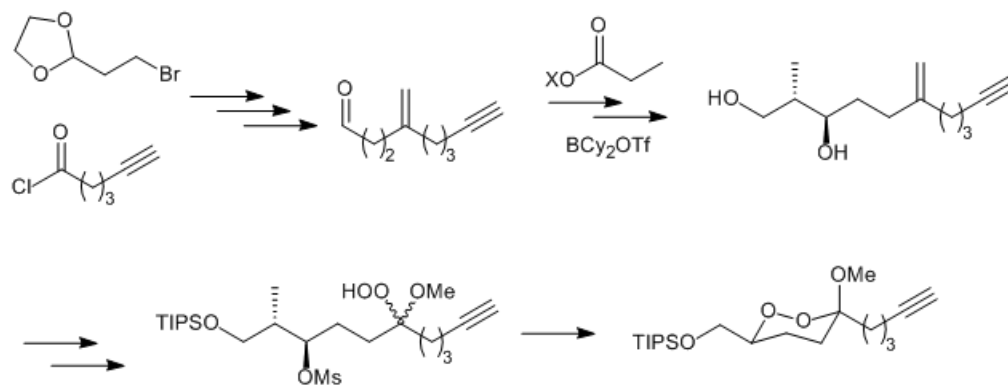
Scheme 2.1

Background

As in the previous chapter on ozonolysis, it should be mentioned that much of this work has also been published.[1] The peroxyplakoric acids are a family of cyclic peroxides isolated from various species in the *Plakortis* genus of marine sponges. These compounds have three distinguishing features: a propionate head group; a diene tail group; and a methoxy-1,2-dioxane core. The compounds are divided into the "A" and "B" series, which differ only in the stereochemistry at C_6 of the 1,2-dioxane core, S for the "A" series and R for the "B" series. Individual compounds within a series (A_1, A_2, A_3) differ only in the nature of the alkyldienyl tail (Figure 2.1). The peroxyplakoric acids, like many cyclic peroxides, have been shown to have antifungal, antimalarial and antiviral activity.[2] Before going into the details of the synthesis, I will first discuss cyclic peroxides in general.

"A" Series	R	"B" Series
A_1		B_1
(**1a**)		(**2a**)
A_2		
(**1b**)		—
A_3		B_3
(**1c**)		(**2c**)
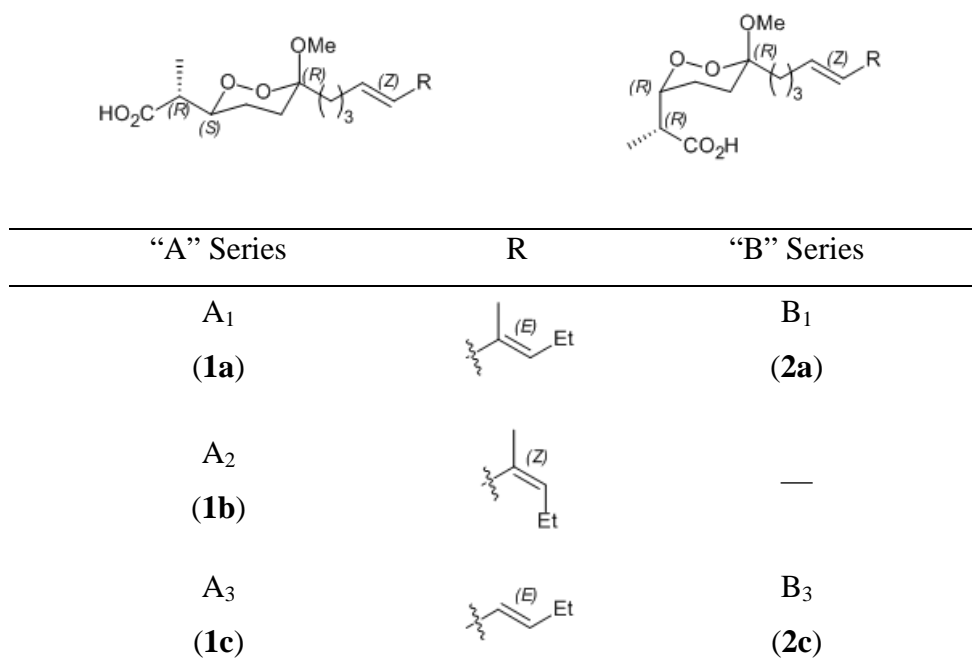
Figure 2.1: Peroxyplakoric acids

Casteel[2] has written two comprehensive reviews of peroxide containing natural products. Rahm[3] has written a review specifically on the metabolites of the *Plakortis* genus marine sponges. Suffice to say that cyclic peroxides in nature occur more often than one would expect. As stated in the first chapter of this synthesis, the antimalarial activity of artemisinin has caused an increased interest in the search for other peroxide containing natural products. As a result, several compounds of interest have been isolated and tested for biological activity. It is difficult to categorize the many types of peroxide natural products and I will, therefore, focus on selected examples of the six membered cyclic peroxyketals that are related to the peroxyplakorates (Figure 2.2).
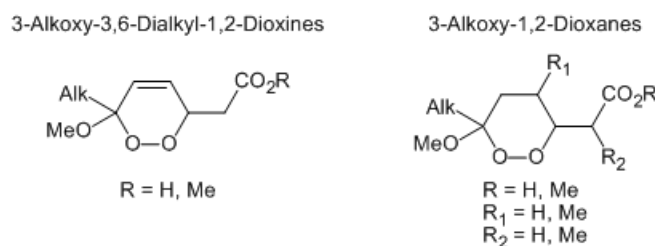
Figure 2.2: 1,2-Dioxines and 1,2-dioxanes

Before going into detail about dioxanes and dioxines, I must clarify some of the terms that I will be using to describe these peroxide natural products. First, these compounds all share a common six membered cyclic peroxide core which I will refer to as a 1,2-dioxane or 1,2-dioxine. Second, as a result of this core description, I will use the terms head group and tail to describe the propionate or acetate substituents on C_3 of the dioxane and the large alkyl group on C_6, respectively (systematic numbering system). Third, when referring to the substitution of the peroxide core, the numbering system will

reflect the priority of the core. The systematic and peroxide core numbering systems are shown in Figure 2.3.
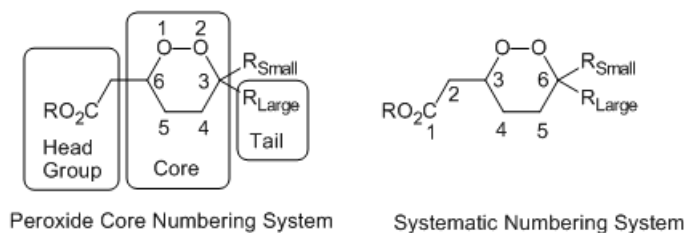
Figure 2.3: Numbering schemes

1,2-Dioxines

R = H, Me
R_1 = Et, OMe, Me
R_2 = Alkyl Chain
R_3 = H, Et
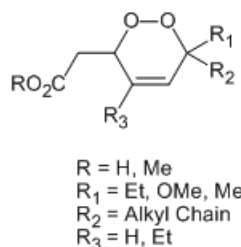
Figure 2.4: 1,2-dioxines

1,2-Dioxines are six membered cyclic peroxides with an endocyclic π bond. It might be tempting to imagine these compounds being formed by an singlet oxygen addition to a diene starting material but the optical activity of these natural products suggest that these 1,2-dioxines are the product of a stereospecific enzyme mediated process. There have been less than a dozen tetraalkyl substituted 1,2-dioxines isolated and identified from *Plakortis* marine sponges. The majority of these compounds have a

3,5-diethyl substitution pattern along with the carboxyl head group and alkylated tail.

The remaining dioxines are 3-methoxy substituted. These compounds usually have a

methyl acetate or acetic acid head group. The variability in the individual members of

these compounds is the stereochemistry of C_3 and C_6 of the 1,2-dioxine core and the

length, branching and degree of unsaturation of the alkyl tail. I will specifically only

discuss a few of the 3-methoxy-1,2-dioxines beginning with chondrillin and plakorin.

Chondrillin and Plakorin
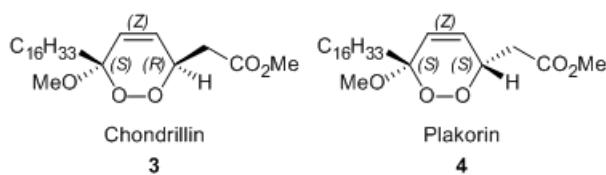
Figure 2.5: Chondrillin and Plakorin

Chondrillin (**3**), shown along with the C_3 epimer plakorin (**4**) in Figure 2.5, is a

3,6-dialkyl-3-methoxy-1,2-dioxine that was first isolated from marine sponges of the

genus *Chondrilla* by Wells in 1976.[4] It was also later isolated from *Plakotis lita* by De

Guzman[5] and Christophersen[6] along with plakorin. In the Wells' paper, it was concluded

that the stereochemistry of C_3 was *S* based on the circular dichroism and ORD studies of

the hydrogenated hydroxyketo ester product. Unfortunately, this turned out to be

incorrect as the subsequent asymmetric synthesis of chondrillin, *ent*-chondrillin (***ent*-3**),

plakorin and *ent*-plakorin (***ent*-4**) (Scheme 2.2 shows the synthesis of the *ent*-chondrillin

and plakorin pair) by members of the Dussault group established that chondrillin is

(3*R*,6*S*) and plakorin is (3*S*,6*S*).[7] This is a prime example for the importance of

asymmetric synthesis of natural products. Often, the structure and stereochemistry of a natural product can be confirmed or even defined by the synthesis of the compound in the lab.
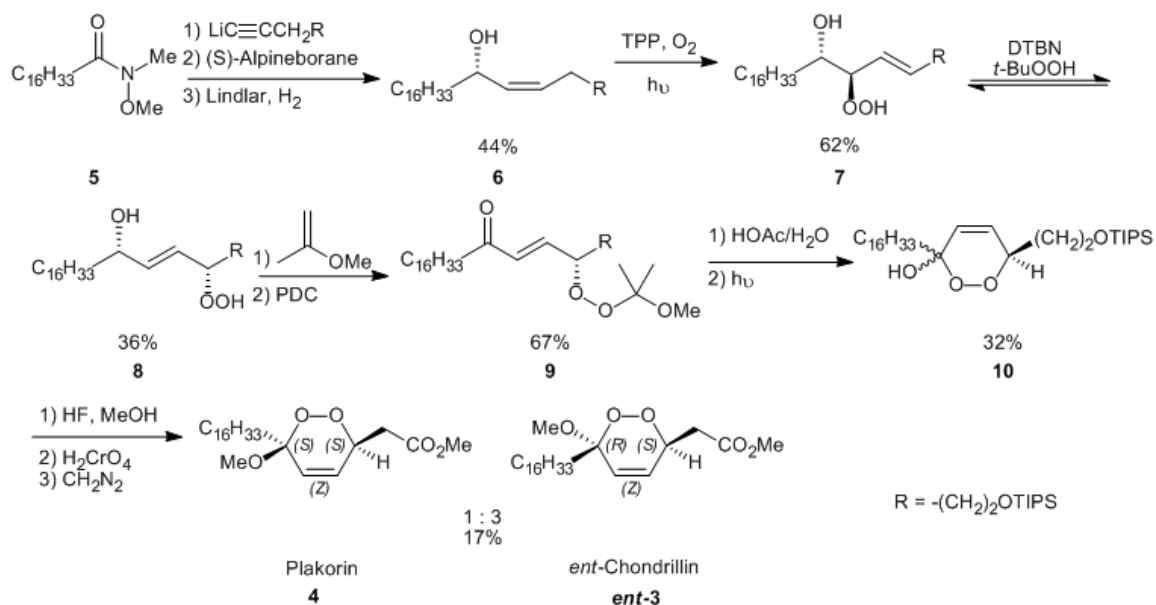
Scheme 2.2: Synthesis of plakorin and *ent*-chondrillin

Chondrillin and plakorin have been tested for biological activity. Chondrillin was found to have an *in vitro* IC_{50} of 5 µg/mL against P388 leukemia cells[6] although one reference indicates an ED_{50} of > 10 µg/mL (interestingly, the stereochemistry of chondrillin is incorrect in this reference).[5] Plakorin was found to be an activator of sarcoplasmic reticulum calcium-ATPase as well as having an in vitro $IC_{50} = 0.85$ µg/mL against murine lymphoma L1210 cells and an $IC_{50} = 1.8$ µg/mL against human epidermoid carcinoma KB cells.[2a]

Xestin A and Xestin B
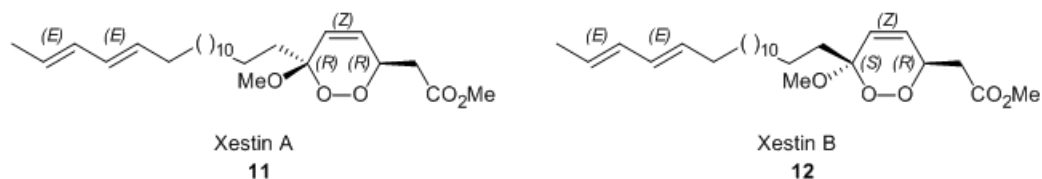
Figure 2.6: Xestin A and xestin B

Xestin A (**11**) and xestin B (**12**) (Figure 2.6) are methoxy-1,2-dioxine compounds that have been isolated by the Crews[8] group from *Xestospongia* species of marine sponges. Xestin B was found to have the same relative configuration as chondrillin, whereas, xestin A was found to be the C_6 epimer. Both of these compounds have an octadecadienyl tail. Other compounds isolated from this marine sponge were found to vary in the alkyl chain branching and saturation as well as the stereochemistry. Xestin A and xestin B have shown to have IC_{50}'s of 0.3 µg/mL and 3.0 µg/mL, respectively against the P388 leukemia cell line.[8-9] Xestin A was also found to be active against other tumor cell lines.[8]

1,2-Dioxanes

R = H, Me
R_1 = Et, OMe, Me
R_2 = Alkyl Chain
R_3 = H, Et
R_4 = H, Me
R_5 = H, Me

R_1 = OMe, Alkyl
R_2 = Alkyl Chain
R_3 = H, Alkyl
R_4 = H, Alkyl
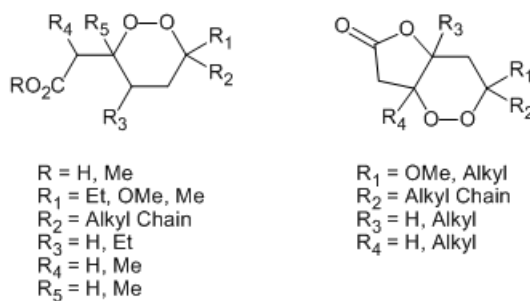
Figure 2.7: 1,2-Dioxanes

While a number of 1,2-dioxine compounds have been isolated from marine sponges, the number of 1,2-dioxanes isolated has been much greater. As with the 1,2-dioxines, the dioxanes can have a variety of substitution patterns, substituents and stereochemistry (Figure 2.7). Attempting to categorize all of the different structural families of 1,2-dioxanes would be beyond the scope of this dissertation so just a few of the examples of the alkylated 1,2-dioxanes are shown in Figure 2.8. I will only go into detail about the peroxyacarnoates and manadic acids because they are the most relevant to our research on the peroxyplakoric acids.
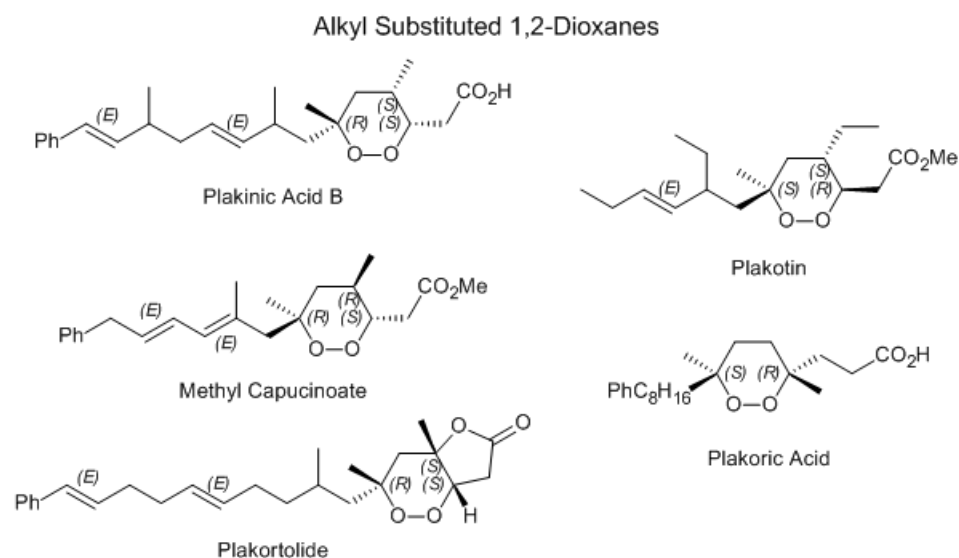
Figure 2.8: Alkyl substituted 1,2-dioxanes

Manadic Acids

$[\alpha]_D^{18°} = +83.9$ (MeOH, c = 43.8) $[\alpha]_D^{18°} = +130.3$ (MeOH, c = 4.0)

Manadic Acid A   Manadic Acid B

12   **13**
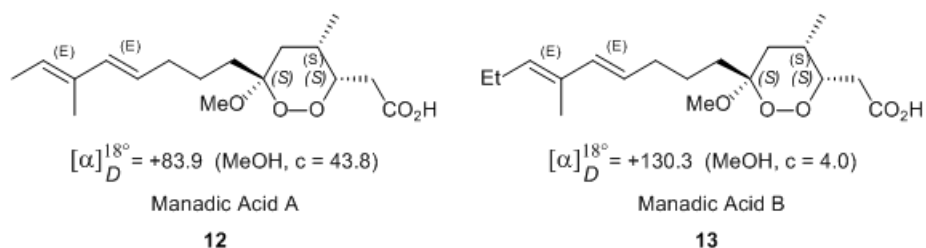
Figure 2.9: Manadic acids

The two manadic acids (**12** and **13**)shown in Figure 2.9 were isolated and

identified from a species of marine sponge belonging to the genus Plakortis in 1995.[10]

These compounds have a 3-methoxy-5-methyl-1,2-dioxane core with an acetic acid head

group and a polyunsaturated tail. While the manadic acids and the peroxyplakorates

differ in the methyl substitution of the 1,2-dioxane core and the head group, the two

families share an unsaturated tail. Manadic acids A and B have the same stereochemistry

and only differ in the dienyl tail so it is not surprising that the optical rotations for these

compounds are of the same sign and similar magnitude. The manadic acids were tested

against several tumor cell lines but showed only moderate activity in the P388 assay

(manadic acids A and B had IC$_{50}$'s = 0.5 μg/mL).[10]

Peroxyacarnoic Acids
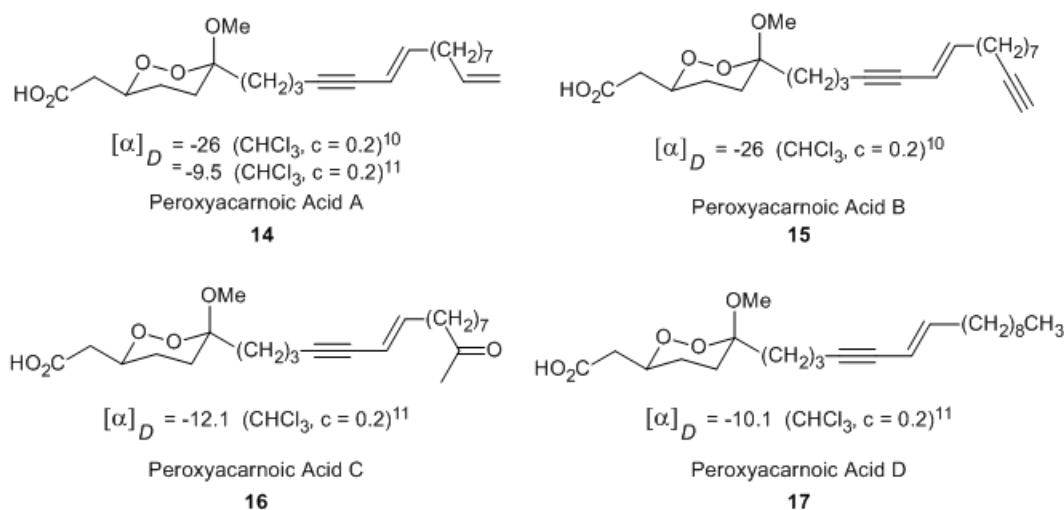
Figure 2.10: Peroxyacarnoic acids

The peroxyacarnoates A (**14**) and B (**15**) (Figure 2.10) were isolated in 1998 by

Kashman and co-workers from the marine sponge *Acarnus* cf. *bergquistae*.[11] The

structures were elucidated by 1D and 2D NMR spectroscopy and tentatively assigned the

same absolute stereochemistry as the peroxyplakoric acids (3*S*,6*R*) based on the negative

values for optical rotations. Unfortunately, this assumption may be less diagnostic than it

appears because all of the methyl peroxyplakorates have a negative optical rotation.

Although the purified peroxyacarnoates were too unstable to be tested, the chloroform

extracts from the sponge were tested for biological activity and found to have

cytotoxicity against P388, A549, HT29 cell lines with IC$_{50}$'s $= 0.1$ µg/mL.[11]

Peroxyacarnoates C (**16**) and D (**17**) (Figure 2.10) were isolated in 2001 by

Fontana and co-workers from *Acarnus bicladotylota*, an Indian marine sponge.[12]

Structurally, these were found to be very similar to peroxyacarnoates A and B, including

the stereochemistry of the 1,2-dioxane core. Again, the long chain tail was found to be the point of difference for these compounds, compound C has an oxoenyne tail and compound D has an enyne saturated tail. The optical rotations for the methyl esters of these compounds can be seen in Figure 2.10. It is unclear why the optical rotation from methyl peroxyacarnoate A is different from the two studies.

Peroxyplakoric Acids
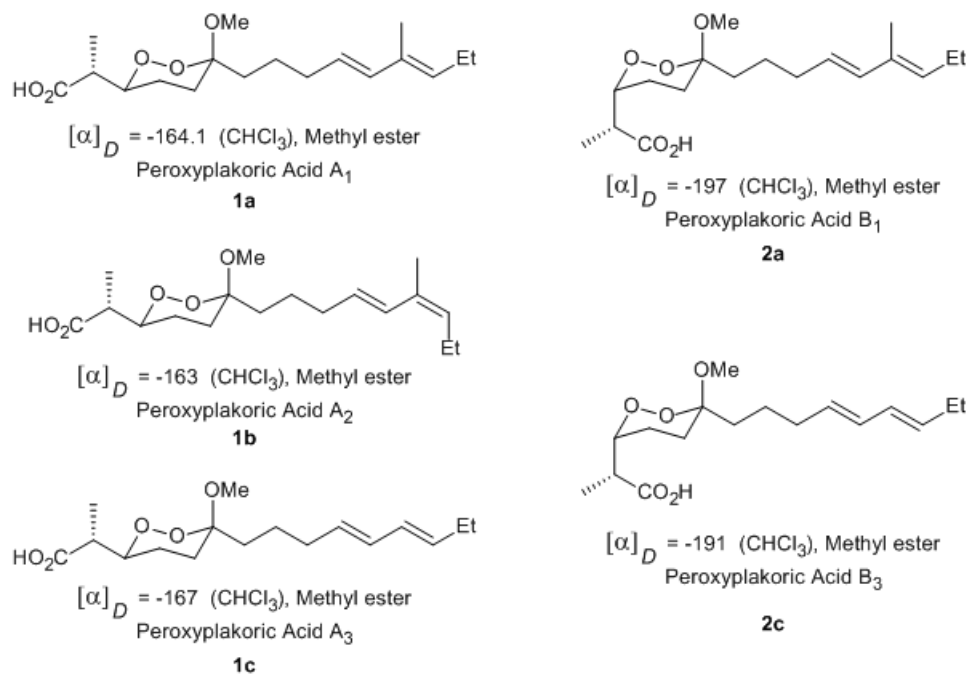
Figure 2.11: Peroxyplakoric acids

As stated earlier, the peroxyplakoric acids (Figure 2.11) were isolated from an unknown species of *Plakortis* by Kobayashi in 1993.[13] The crude mixture of these natural products showed strong antifungal activity against *Candida albicans*[13] and later,

methyl peroxyplakorates A_3 (**1c**) and B_3 (**2c**) were shown to have moderate antimalarial

activity against *Plasmodium falciparum* with $IC_{50} = 0.15$ µM for A_3 and $IC_{50} = 0.12$ µM

for B_3.[14] The structures of the methyl esters were determined by 1D and 2D NMR

spectroscopy in the same manner as other cyclic peroxides. While the polyunsaturated

alkyl tail is similar to those found in other 1,2-dioxanes, peroxyplakorates seem to be

unique from other cyclic peroxyketal natural products in having a propionate head group.

This was established by the correlation through long-range coupling (COLOC) of the

carbonyl carbon and the methyl protons of the propionate. The relative stereochemistry

was determined by nuclear Overhauser enhancement spectroscopy (NOESY) and by a

comparison of the spectra of similar compounds. Finally, the absolute chemistry of

peroxyplakoric acid A_3, methyl ester was determined by the application of the Mosher

method (Scheme 2.3). First, the propionate head group was reduced to the primary

alcohol followed by esterification with (*R*)-α-methoxy-α-trifluoromethylphenylacetic

acid (MPTA) and (*S*)-MPTA to establish the stereochemistry of the methyl group

(Scheme 2.3, Path A). By the comparison of the ^{1}H NMR spectra of the two esters, the

methyl group of the propionate head group was determined to have an (*R*) absolute

stereochemistry. Next, the 1,2-dioxane core was reduced to the hydroxyketone.

Comparison of the chemical shift changes for C_3 upon formation of the (*R*)- and (*S*)-

MPTA derivatives allowed the assignment of (*S*) stereochemistry at C_3 (Scheme 2.3, Path

B). With this data it was possible to assign the absolute stereochemistry of

peroxyplakoric acid A_3, and, in a similar manner, the remaining peroxyplakoric acids.[13]
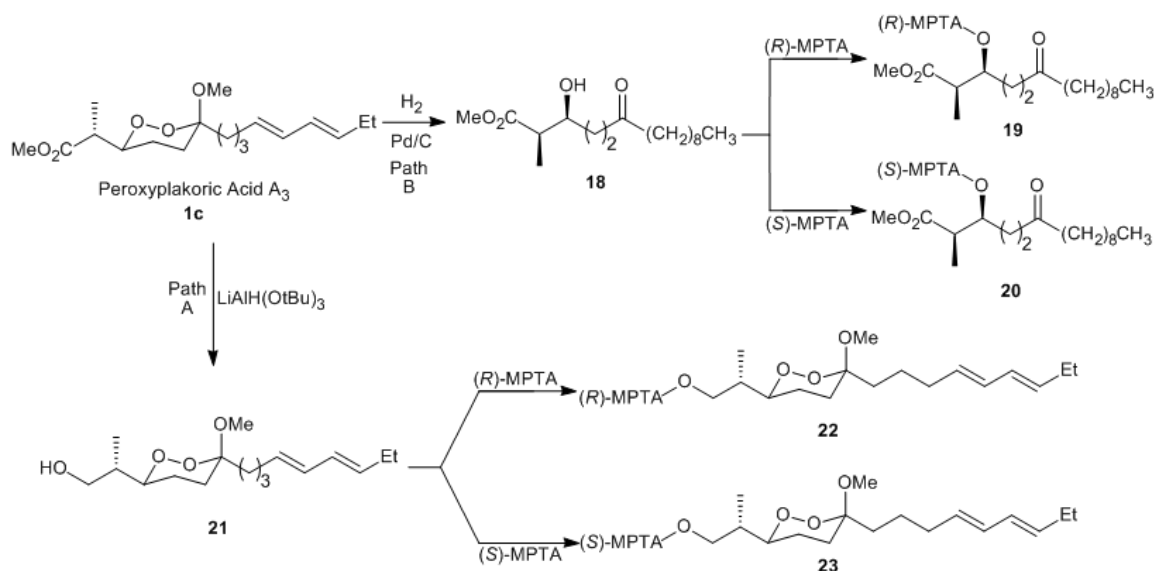
Scheme 2.3: Stereochemical determination with Mosher's acid

Before outlining a retrosynthetic analysis of the peroxyplakoric acids, it is useful to discuss the lessons learned from the synthesis of related compounds. The synthesis of these compounds can be divided into three parts; the 1,2-dioxane core, the dienyl tail and the propionate head. First, I will talk about methods to create the 1,2-dioxane core of the molecule. Second, I will discuss methods to incorporate the dienyl tail focusing on metal-mediated sp^2-sp^2 and sp-sp^2 couplings. Finally, because this is an asymmetric synthesis, I will focus on the stereochemical aspects of the synthesis. In the process of discussing these aspects of these compounds, I will go into some detail about the strategies employed by Kobayashi and Wu to form the 1,2-dioxane core, and the approach applied by Xu, et al., for the incorporation of the dienyl tail in the total synthesis of peroxyacarnoate A and D.[15]

3-Methoxy-1,2-Dioxane Core

The methods to introduce the peroxide will be divided into two main areas. First, I will discuss reactions with singlet or triplet oxygen. Second, I will discuss nucleophilic reactions of hydroperoxides.[16] It should be noted that oxygen can be used to form alkyl hydroperoxides as well as being used to form the cyclic peroxides.

"Concerted [4+2]" Singlet Oxygen Reaction

The [4+2] electrocyclic addition of singlet oxygen to 1,3-dienes is one of the oldest methods of generating 6-membered cyclic peroxides. Generation of singlet oxygen from the ground state triplet oxygen is accomplished by the use of light and photosensitizers such as Rose Bengal, methylene blue and others. One of the first reports of the use of singlet oxygen in this way was by Windaus and Brunken in 1928 when they isolated the cyclic peroxide of ergosteryl acetate (Scheme 2.4).[16-17]
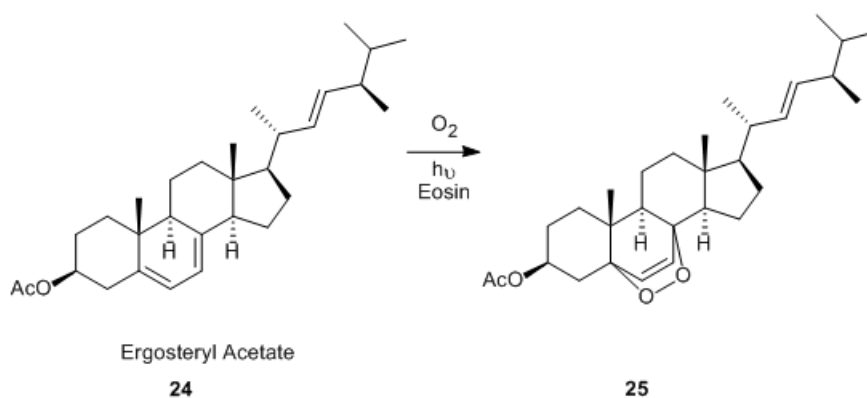
Scheme 2.4: Ergosteryl acetate oxidation with oxygen

While the [4+2] cycloaddition is often syn-stereospecific, the competing side reactions can produce unexpected products. Investigations in the synthetic pathway for the mycaperoxides have shown that singlet oxygenation of trisubstituted dienes can result in "ene" allylic oxidation due to the diene's inability to adopt the s-*cis* conformation.[18] Additionally, O'Shea and Foote found that while the cycloaddition of singlet oxygen to (*E,E*)-2,4-hexadiene produced the expected cis-1,2-dioxine, the photooxidation of (*E,Z*)- and (*Z,Z*)-2,4-hexadiene also produced the cis-1,2-dioxine instead of the expected trans-cyclic peroxide. In addition, 4-methoxy-2-hydroperoxides and oxetanes were also formed in the reaction when methanol was used as a solvent indicating a stepwise reaction pathway (Scheme 2.5).[19]
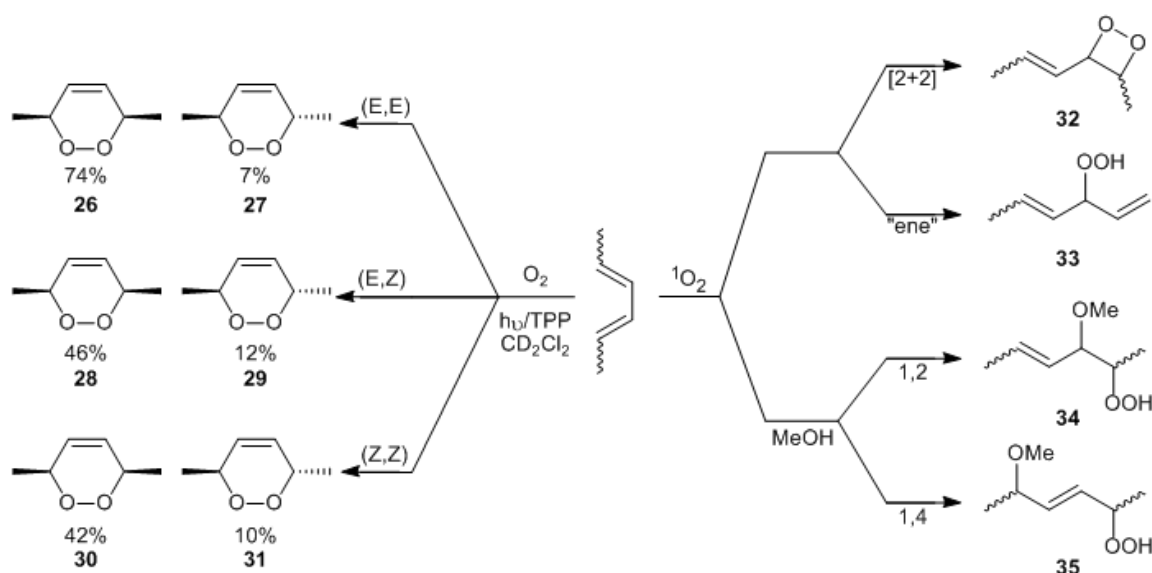
Scheme 2.5: Oxidation with singlet oxygen

Regardless of the reaction mechanistic pathway, the six-membered cyclic peroxide can be formed in this manner and the 1,2-dioxine core can then be reduced by

diimide[20] or undergo further reactions to obtain the desired saturated core. For example,

the synthesis of 6-epiplakotolide E was accomplished by Jung in 2002. The key step was

the photooxidation of the silyl protected 4,6-dimethyl-16-phenylhexadeca-3,5-dien-1-ol

to form the 1,2-dioxine which was further transformed by an iodolactonization and

radical dehalogenation (Scheme 2.6).[21] Other examples of the use of singlet oxygen to

introduce the hydroperoxide precursor for the cyclization will be given later.
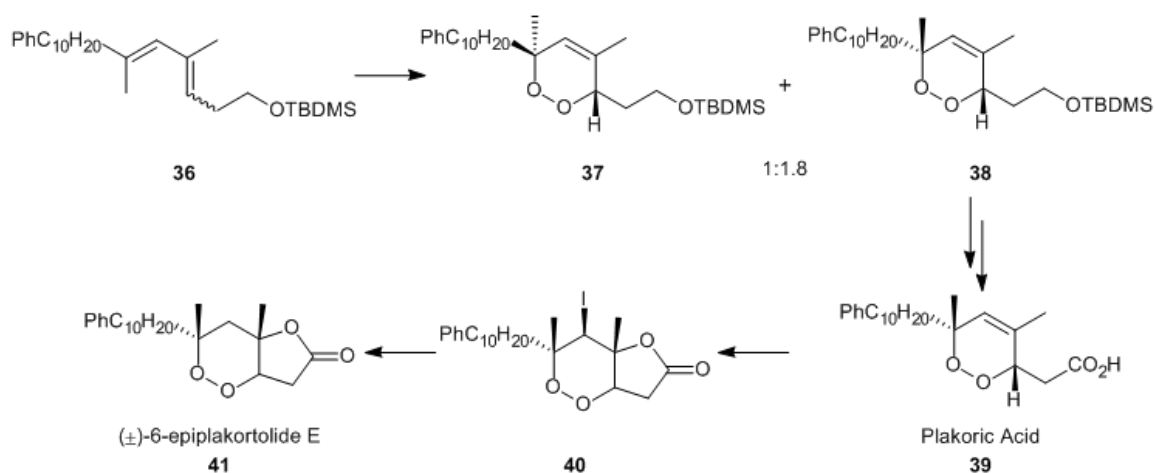
Scheme 2.6: Racemic synthesis of 6-epiplakortolide

In 2006, La Clair published a synthesis of (+)-hexacyclinol wherein the key step

was a purported singlet oxygen [2+2+2] cyclization involving two isolated π bonds to

form a "1,2-dioxane" (Scheme 2.7).[22] Rychnovsky[23] proposed a revised structure to the

compound based on theoretical calculations and in subsequent syntheses[24] and an X-ray

crystal structure[25] have shown that hexacyclinol is the diepoxide related to

panepophenanthrin shown in Figure 2.12.
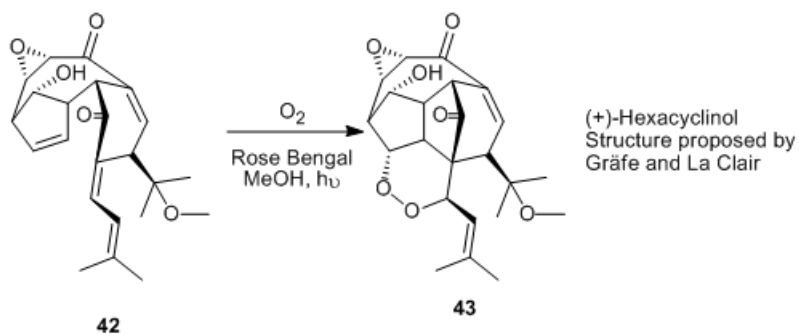
Scheme 2.7: La Clair synthesis of hexacyclinol
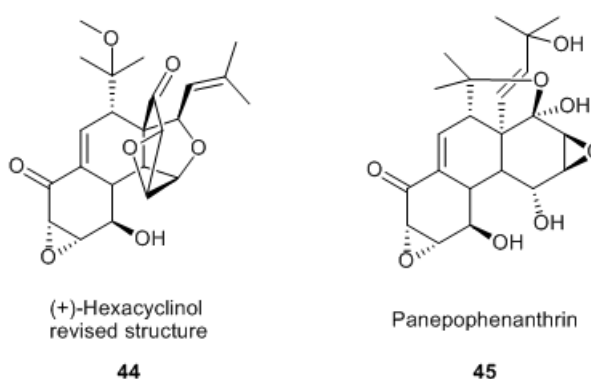
Figure 2.12: Revised hexacyclinol structure and its relationship to panepophenanthrin

Triplet Oxygen Trapping

Oxygen in its triplet ground state can also be used to form the 6-membered cyclic peroxide. The oxygen is used to introduce peroxide diradical followed either by cyclization or hydrogen abstraction. Formally, this reaction is spin forbidden but cyclic peroxides can form through radical autoxidation or in the presence of additives, facilitating formation of radicals or radical cations. Barton and co-workers found that the addition of many different Lewis acids allowed the reaction of ergosteryl acetate and triplet oxygen to occur in minutes and in quantitative yields (Scheme 2.8).[26]
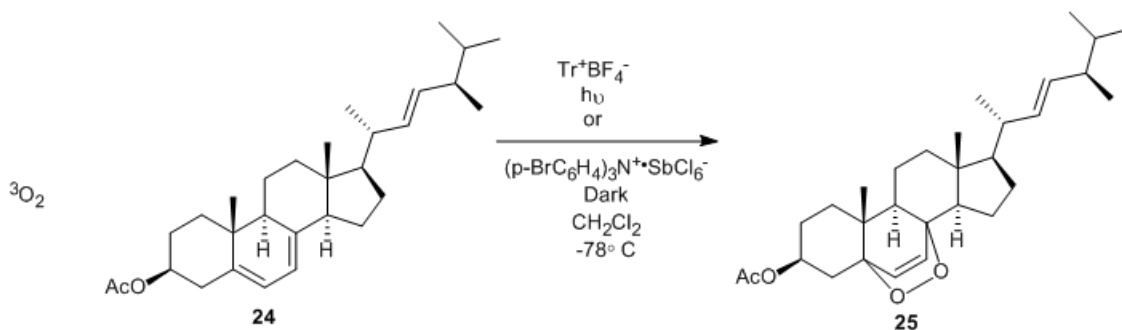
Scheme 2.8: Oxidation with triplet oxygen in the presence of additives

The authors propose that the electrophilic catalyst (E) complexes with either the diene or the peroxyenyl diradical which then undergoes spin conversion followed by cyclization (Scheme 2.9).[26] An alternative explanation is provided by the analogous oxidation with triplet oxygen in the presence of triphenylpyrylium tetrafluoroborate (TPT).[27] It has been proposed that the reaction involves the excitation of the electrophilic catalyst (in this case TPT) followed by a single electron transfer step. Triplet oxygen can then add to the radical cation and, in the Tr$^+$ reactions, the cyclization occurs after a second single electron transfer (Scheme 2.10). Other reactions where the hydroperoxides are formed will be introduced in the next section.
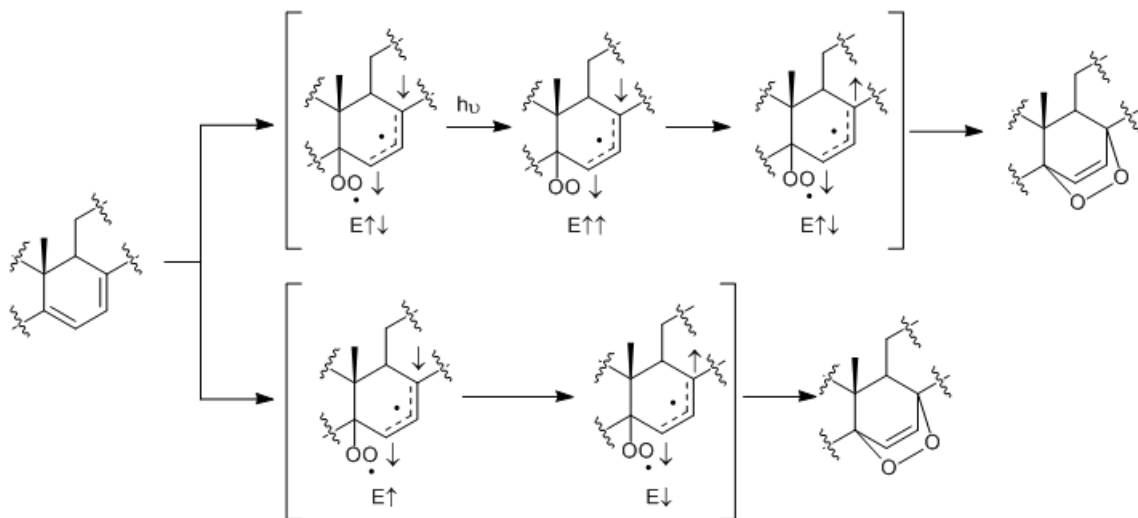
Scheme 2.9: Proposed intermediates
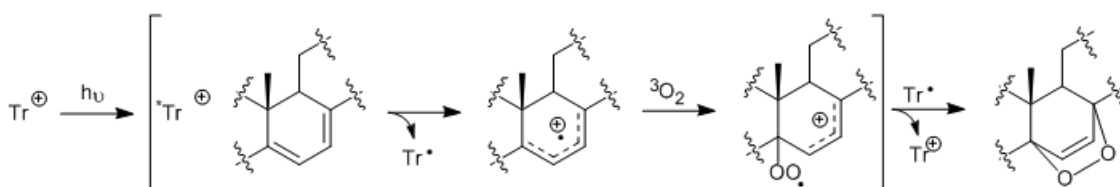
Scheme 2.10: Alternative mechanism for the trityl cation photosensitized oxygenation

Addition to Alkenes

Two methods of addition to alkenes to form cyclic peroxides are presented here. The first is the electrophile-assisted intramolecular nucleophilic addition of alkyl hydroperoxides to alkenes. The second is the radical cyclization of *in situ* generated alkyl peroxide radicals. The carbon centered radical formed after cyclization is then usually trapped by oxygen or a halogen.

Radical Cyclization

In 1975, in their investigations of the prostaglandins, the Porter lab showed that the fatty acid hydroperoxides underwent radical cyclization to form bicyclic hydroperoxy

dioxolanes.[28] The initial peroxide radical is generated by reagents such as di-t-butylperoxyoxalate (DBPO), excited state acetophenone,[29] di-t-butyl hyponitrite (DTBN),[30] or N-iodosuccinimide (NIS).[31] The peroxide radical ring closure is followed by the trapping of the carbon centered radical by molecular oxygen or, in the case of NIS, iodine (Scheme 2.11). It was later found that the 5-membered ring closure occurs preferentially over 6 membered ring closure.[29, 31]
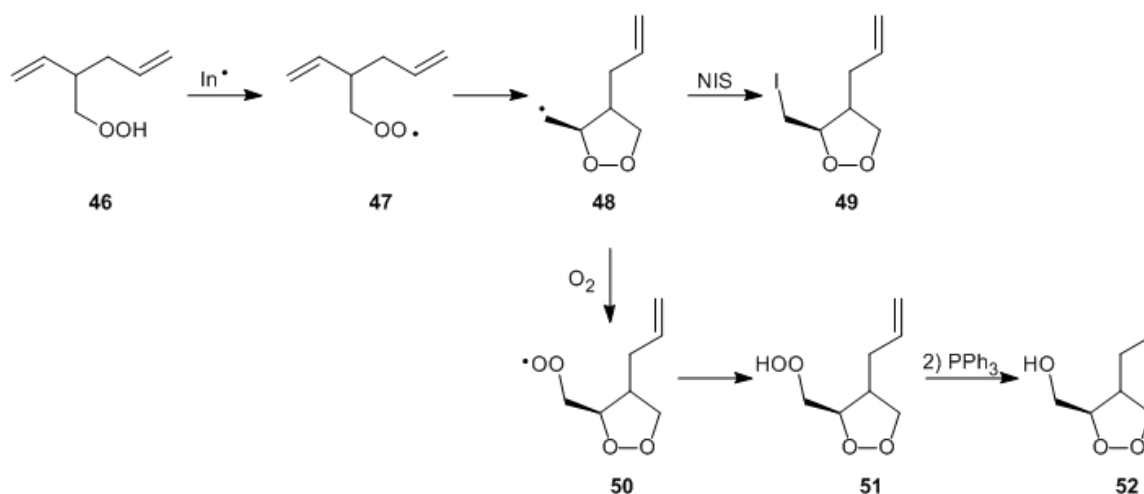
Scheme 2.11: Radical cyclization of hydroperoxy alkenes

Electrophile Assisted Cyclization

Electrophilic cyclizations of unsaturated hydroperoxides have also been reported. Mercuric nitrate was used for the hydroperoxide dioxane and dioxolane cyclizations as early as 1976.[32] Other mercuric salts have since been applied to this cyclization reaction. The organomercurial products can be reduced or halogenated. N-bromosuccinimide, bromine and iodine have also been used in the cyclization reaction.

In 1996, the Dussault lab demonstrated the 6-exo cyclization of alkyl hydroperoxyacetals by peroxymercuration and peroxyiodination with good yields (Table 2.1).[33] The limited diastereoselectivity of this reaction is attributed to the 5-exo closure to the peroxonium ion seen in the oxygen transfer reactions.[34]
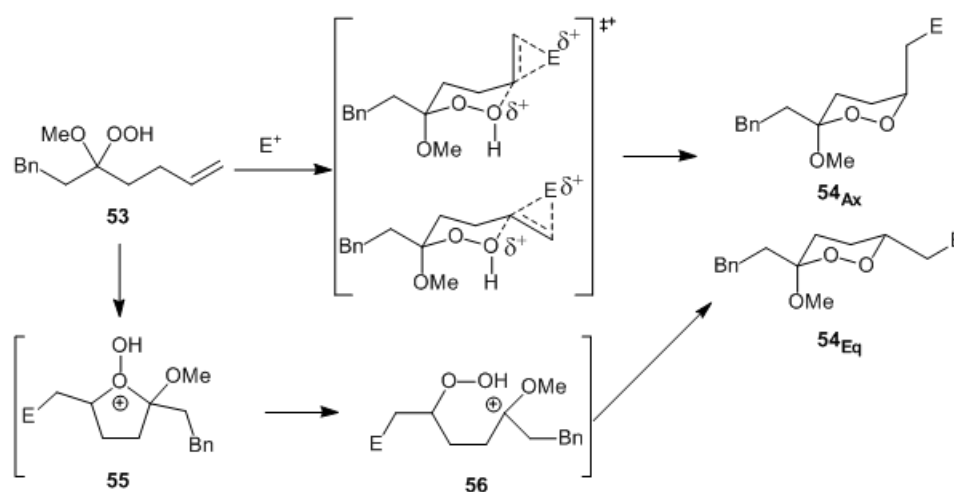
Scheme 2.12: Electrophile assisted cyclization of hydroperoxy alkenes

Table 2.1: assisted cyclization of hydroperoxy alkenes

Source of E^+	Temp.	Yield	Ax.:Eq.
Pyridine/I_2	0 °C	50%	1:1
KOt-Bu/I_2	rt	48%	1:1.7
KOt-Bu/I_2 18-crown-6	rt	34%	1:2.5
1) Hg(OAc)$_2$ 2) KBr	rt	55%	3:1
1) Hg(OAc)$_2$ 2) KBr	-78 °C	46%	1.5:1

Other groups have since explored the electrophile assisted peroxidation of alkenes using other electrophiles. The Nojima group has used other halonium sources such as bis(collidine)iodine hexafluorophosphate (BCIH),[35] N-Iodosuccinimide (NIS)[36,37] and N-bromosuccinimide (NBS).[37a] The Terent'ev group has tried to optimize the peroxyiodination for intermolecular additions.[38] The need for separate removal of the electrophile (HgX, I) in a subsequent step is a disadvantage to these types of reactions. In 2009, the Woerpel group found a way to obviate the need for the subsequent step by using a palladium(II) catalyst to form allylic 1,2-dioxanes.[39]

Nucleophilic Addition to Carbonyls

Nucleophilic addition to carbonyls has had much success in the cyclization of peroxides. The cyclization of hydroperoxyacetal carbonyls generated *in situ* by ozonolysis has been demonstrated by Nojima.[40] A related strategy was employed by Yoshida in the oxygenation of unsaturated ketones with thiophenol[41] (Scheme 2.13). In the first strategy, the hydroperoxide is installed by the methanolic trapping of the carbonyl oxide. In the second strategy, the peroxide radical or hydroperoxide generated by thiol-mediated radical oxygenation of the alkene adds to the carbonyl.
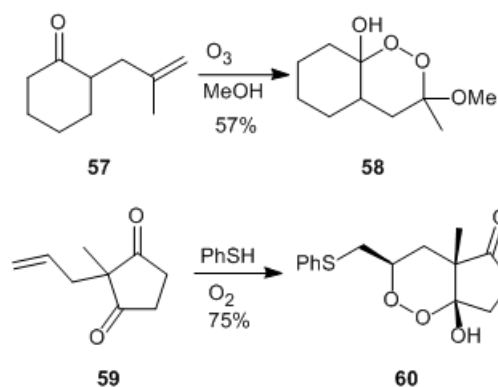
Scheme 2.13: Nucleophilic and radical cyclization of carbonyls

The Dussault lab was able to use the nucleophilic addition of a hydroperoxide to a carbonyl effectively in the synthesis of plakorin and chondrillin. The key step in the synthesis was the introduction of the hydroperoxide nucleophile via a stereospecific allylic rearrangement. The rearranged hydroperoxide was then protected after which the alcohol was oxidized to the ketone. Cyclization to the 1,2-dioxine occurred spontaneously after deprotection of the peroxide and photoisomerization of the unsaturated ketone (Scheme 2.14).[7b] This strategy was inspired by Snider's observations during the racemic synthesis of chondrillin and plakorin.[42]
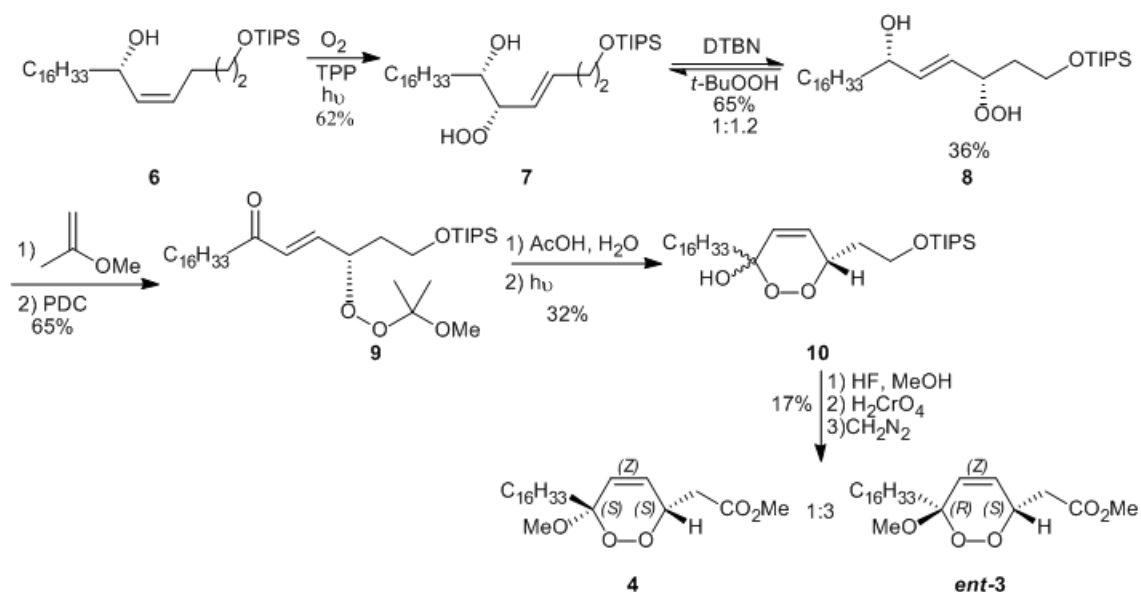
Scheme 2.14: Plakorin and *ent*-chondrillin synthesis

It should also be mentioned that the nucleophilic addition to carbonyl oxides is related to this type of reaction. The carbonyl oxide is a very reactive intermediate in the

ozonolysis of alkenes that can be trapped by protic nucleophiles to produce a

hydroperoxide. Ozonolysis of unsaturated hydroperoxides produces the hydroperoxy

cyclic peroxide which can then be reduced to the peroxy alcohol.[29] In 2001, Tokuyasu

synthesized several yingzhaosu A analogues by the ozonolysis of unsaturated

hydroperoxides and hydroperoxyacetals.[37a] The synthesis of a bicyclic 3-hydroperoxy-

1,2-dioxane and 3-6-methoxy-3-hydroperoxy-1,2-dioxane shown in Scheme 2.15.
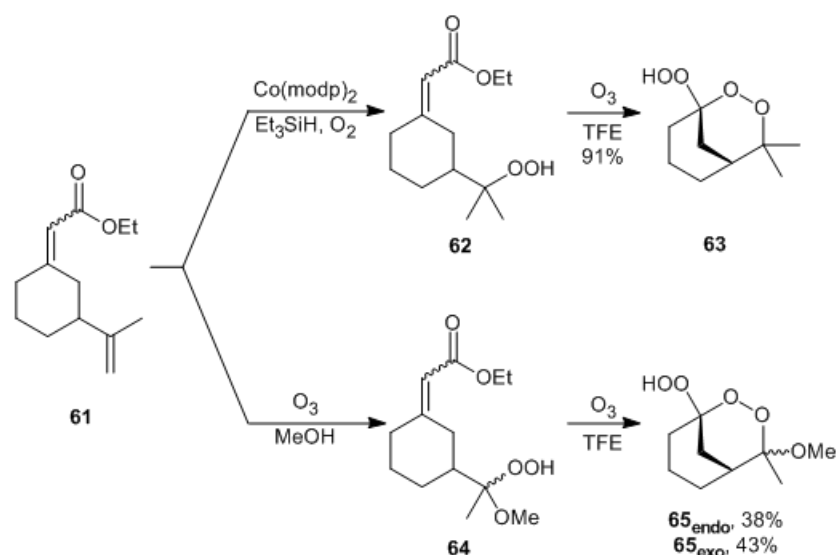
Scheme 2.15: Nucleophilic cyclization to carbonyl oxides

Nucleophilic Addition to α,β-Unsaturated Carbonyls

Nucleophilic conjugate addition to α,β-unsaturated carbonyls has also been

applied to the synthesis of the 1,2-dioxane core. This method has been applied to the

synthesis of peroxide natural products and natural product analogues. In this section I

will discuss the development on this method, the problems associated with the conjugate

addition, and the successful application of this method to the synthesis of

peroxyacarnoates A and D and several analogues.

Yingzhaosu A
66
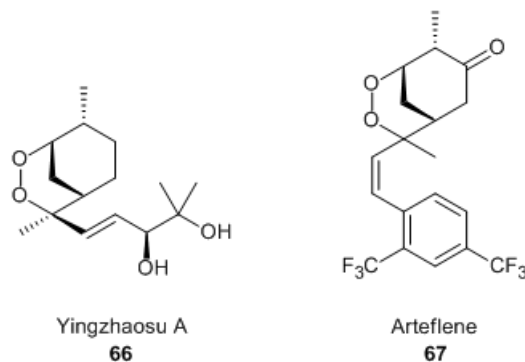
Arteflene
67

Figure 2.13: Yingzhaosu A and arteflene

I will begin with the synthesis of yingzhaosu A analogues in 1998 by the Posner

group. Yingzhaosu A and arteflene (Figure 2.13) are bicyclic endoperoxides that have

potent antimalarial activity (yingzhaosu A IC_{50} = 115 nM[43], arteflene IC_{50} = 15 nM[44]).

The cyclic peroxide is believed to be an essential pharmacophore. The common core of

yingzhaosu A and arteflene can be derived from *R*-carvone. In order to install the

hydroperoxide, Posner and O'Neill[44] elected to form the hydroperoxyacetals by the

ozonolysis of *R*-carvone in the presence of alcohols. The resulting hydroperoxyacetals

underwent cyclization by conjugate addition when they were subjected to sodium

methoxide in methanol (Scheme 2.16). The yields and antimalarial activities of the

isolated diastereomers were only moderate (Table 2.2).
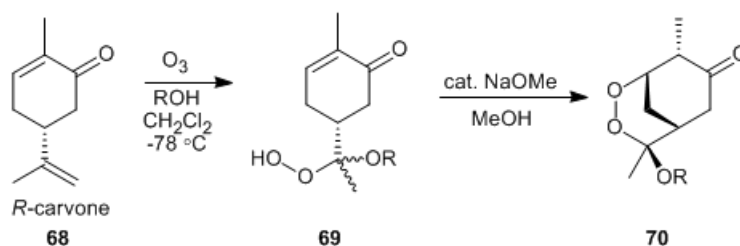
Scheme 2.16: Hydroperoxyacetal cyclization of *R*-carvone

Table 2.2: 3-Alkoxy-1,2-dioxane derivatives of *R*-carvone

R	Yield	Antimalarial IC_{50}
CH_3	38%	666 nM
C_2H_5	32%	615 nM
C_4H_9	35%	503 nM
C_5H_{11}	28%	126 nM
C_8H_{17}	24%	123 nM

The second class of 1,2-dioxane synthesis also relies on the conjugate addition to

an α,β-unsaturated carbonyl. In 2001, Kobayashi et al. studied both the introduction of

the hydroperoxyacetal and the cyclization. While ozonolysis of alkenes in the presence

of alcohols is a convenient method for the introduction of the hydroperoxyacetal, the

method can be incompatible with other functional groups (i.e. more reactive π bonds).

The Kobayashi lab investigated the hemiketalization of ketones in methanol with urea

hydrogen peroxide (UHP) in the presence of a variety of Lewis acids. A screening of

Lewis acids and reaction conditions identified $Sc(OTf)_3$ as an excellent catalyst in which

the best yields of methoxyhydroperoxy acetals were obtained with catalytic scandium

triflate and 7.5 equivalents of UHP (Table 2.3).[45]
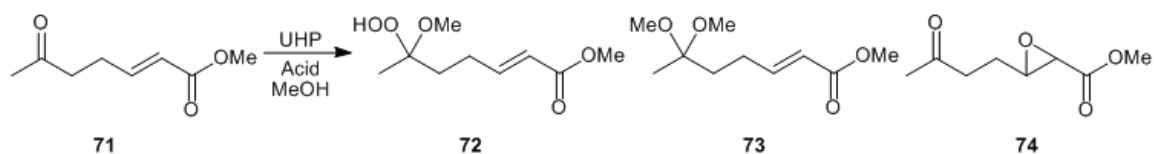
Table 2.3: Optimization of hydroperoxidation of ketones with UHP

Conc. of 1 (M)	Equivalents UHP	Acid (Conc. in M)	Conc. of Acid (M)	Yield			
				71	**72**	**73**	**74**
0.5	1	Conc. H_2SO_4	0.03	37%	10%	0%	43%
0.5	2.5	TsOH	0.03	16%	35%	12%	28%
0.5	10	TsOH	0.03	13%	24%	11%	44%
0.5	2.5	TsOH	0.03	42%	37%	13%	0%
0.5	10	TsOH	0.03	38%	45%	8%	0%
0.025	20	TsOH	0.03	9%	72%	6%	7%
0.025	20	$SnCl_4$	0.03	27%	30%	22%	10%
0.025	20	TMSOTf	0.03	26%	31%	28%	7%
0.025	20	$Sc(OTf)_3$	0.03	9%	29%	12%	45%
0.025	20	$Yb(OTf)_3$	0.03	61%	10%	13%	8%
0.025	20	$La(OTf)_3$	0.03	52%	17%	16%	7%
0.025	20	$Sc(OTf)_3$	0.003	14%	57%	11%	16%
0.025	7.5	$Sc(OTf)_3$	0.003	6%	83%	7%	0%

With the conditions for the formation of the hydroperoxyacetal optimized, the authors tried to find the best conditions for the cyclization (Scheme 2.17). By screening different reagents, concentrations and solvents, they found that the optimal conditions employed diethyl amine in 1,1,1,3,3,3-hexafluoro-2-propanol (Table 2.4). Because the epoxide is formed exclusively under strongly basic conditions, the authors propose that the ester enolate intermediate formed by the conjugate addition is stabilized or protonated

by the polar, acidic alcohol. It is interesting to note that the formation of the epoxide is

also observed to some extent during the introduction of the hydroperoxyacetal. This

could result from the ester enolate initially formed by the conjugate addition of hydrogen

peroxide (i.e. cyclization occurs spontaneously after the hydroperoxyacetal is formed).[45]

Thus, a delicate balance between the conjugate addition, decomposition and epoxidation

is inherent in this reaction. Although the reasons are unclear, for 1,2-dioxanes with tails

larger than methyl, the best results for the cyclization occurred with 2,2,2-trifluoroethanol

as the solvent rather than 1,1,1,3,3,3-hexafluoro-2-propanol.[14]
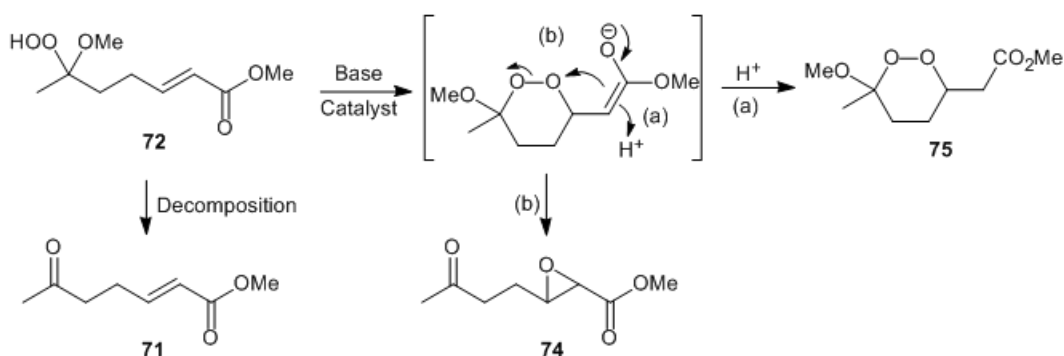
Scheme 2.17: Optimization of the cyclization of hydroperoxy-α,β-unsaturated carbonyls

Table 2.4: Optimization of the cyclization of hydroperoxy-α,β-unsaturated carbonyls

Reagent	Conc. (M)	Solvent	Yield			
			75	71	72	74
NaOMe	0.1	MeOH	0%	0%	0%	98%
NaOMe	0.01	MeOH	8%	0%	0%	89%
NaOMe	0.001	MeOH	8%	12%	61%	15%
TsOH	0.005	CH₃CN	0%	95%	0%	0%
Et₂NH	0.01	MeOH	29%	0%	0%	67%
Et₂NH	3 eq.	THF	0%	0%	0%	98%
Et₂NH	3 eq.	CH₂Cl₂	0%	0%	0%	100%

Reagent	Conc.	Solvent	Yield			
Et$_2$NH	0.01	CF$_3$CH$_2$OH	53%	0%	0%	44%
Et$_2$NH	0.1	CF$_3$CH$_2$OH	31%	0%	0%	67%
Et$_2$NH	0.001	CF$_3$CH$_2$OH	22%	8%	48%	20%
Et$_2$NH	0.01	(CF$_3$)$_2$CHOH	72%	24%	0%	2%
Et$_2$NH	0.01	(CF$_3$)$_3$COH	0%	88%	0%	5%

Because the peroxyacarnoates are structurally similar to the Kobayashi

compounds, it was thought the method could be used to introduce the 1,2-dioxane core in

the synthesis of peroxyacarnoates A and D (Figure 2.10). Unfortunately, when Xu

attempted the hydroperoxidation, only a trace amount of product was isolated.[1a, 15]

Undaunted, Xu transformed the ketone into the methylene which was selectively

ozonized in methanol to form the hydroperoxyacetal in 68% yield. Subsequent

cyclization under Kobayashi's conditions produced the 1,2-dioxane core as a 6:1 ratio of

the trans:cis in 35% yield (Scheme 2.18).[1a, 15]
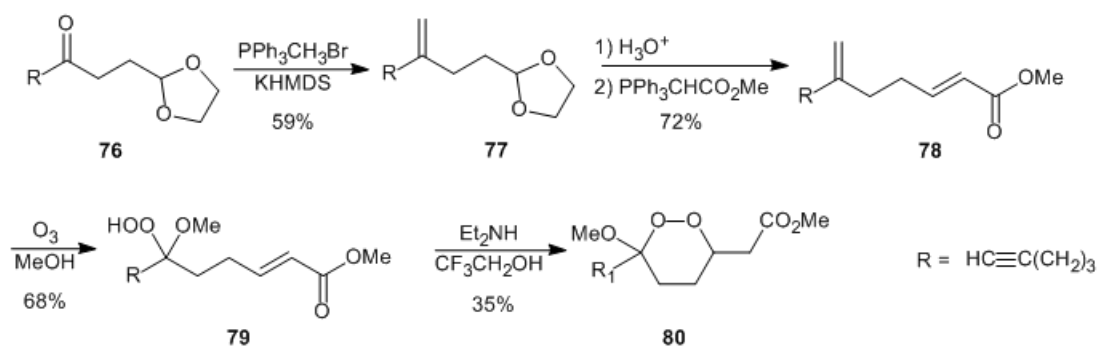
Scheme 2.18: Synthesis of 3-methoxy-1,2-dioxane core for the peroxyacarnoates

In 2005, Wu and co-workers attempted to use the Kobayashi method to synthesize nine different 1,2-dioxanes and found the method to be capricious. They varied the tail and ester and found that while the ester moiety did not appear to affect the synthesis, only the simplest of alkyl chains could be incorporated into the tail (Table 2.5). Consistent with Xu's observations, Wu et al., experienced much lower yields for the hydroperoxidation and the cyclization compared with Kobayashi's results.[46]
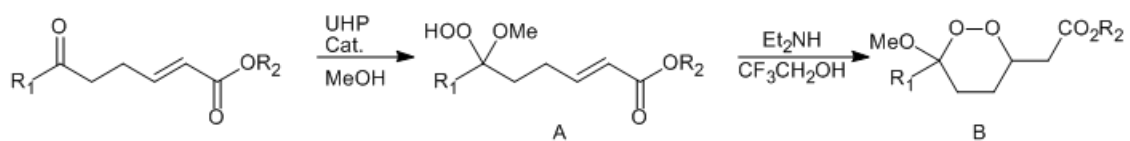
Table 2.5: Wu, et al. results with Kobayashi conditions

R_1	R_2	A Yield	B Yield
C_4H_9	Et	37%	50%
C_4H_9	CH_2Ph	35%	45%
CH_2Ph	Et	30%	35%
CH_2Ph	CH_2Ph	11%	31%
Me	Et	37%	31%
CH_2CO_2Et	Et	NR	0%
H	Et	0%	NA
i-Pr	Et	0%	NA
CO_2Me	Et	0%	NA

One final aspect to the nucleophilic addition to an α,β-unsaturated carbonyl is the issue of stereochemistry. The methoxy group of the 1,2-dioxane core can either be cis or trans in relation to the head group. In the Kobayashi method of cyclization, there is no control of this relationship nor is there any control of the absolute stereochemistry. In

2008, Lu et al. published a report on the enantioselective peroxidation of α,β-unsaturated ketone using a cinchona alkaloid catalyst (Scheme 2.19).[47] The catalyst is thought to direct the incoming hydroperoxide and suppress the competing epoxidation reaction. The yields, enantiomeric excess and ratio of peroxide to epoxide were very good to excellent (Table 2.6) although longer reaction times and higher temperatures favor the epoxide (not shown). While the authors used an intermolecular reaction of hydroperoxides with enones, it is easy to imagine the potential of this reaction for a cyclization, although forming the necessary imidinium ion from hydroperoxy esters may prove to be a challenge.
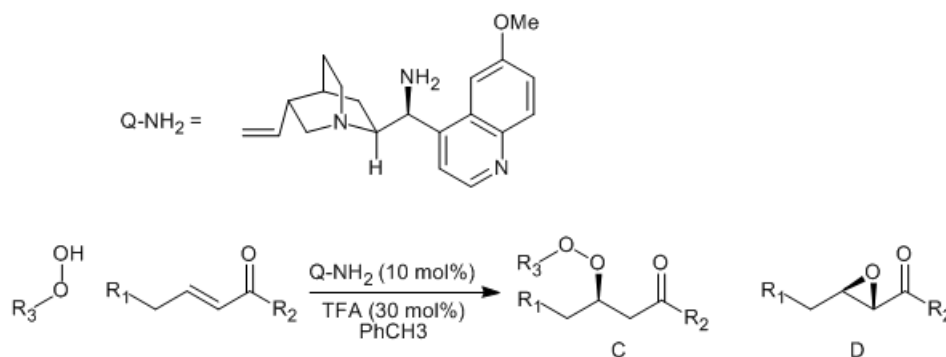
Scheme 2.19: Enantioselective hydroperoxide addition to α,β-unsaturated carbonyls

Table 2.6: Enantioselective hydroperoxide addition to α,β-unsaturated carbonyls

R_1	R_2	R_3	Temp	Time (h)	C:D	C Yield	A ee
Bn	Me	$C(CH_3)_3$	23 °C	4	92:8	85%	91%
H	Me	$C(CH_3)_3$	23 °C	4	94:6	88%	84%
Et	Me	$C(CH_3)_3$	23 °C	4	94:5	91%	90%
n-Bu	Me	$C(CH_3)_3$	23 °C	4	93:7	86%	93%
$(CH_2)_2OBn$	Me	$C(CH_3)_3$	23 °C	4	90:10	65%	91%

R$_1$	R$_2$	R$_3$	Temp	Time (h)	C:D	C Yield	A ee
H	Et	C(CH$_3$)$_3$	23 °C	4	95:5	90%	89%
H	n-Bu	C(CH$_3$)$_3$	23 °C	4	94:6	89%	87%
Et	n-Bu	C(CH$_3$)$_3$	23 °C	4	86:14	64%	94%
Bn	Me	C(CH$_3$)$_2$Ph	0 °C	16	86:14	74%	94%
H	Me	C(CH$_3$)$_2$Ph	0 °C	12	77:23	70%	92%
Et	Me	C(CH$_3$)$_2$Ph	0 °C	12	88:12	75%	92%
n-Bu	Me	C(CH$_3$)$_2$Ph	0 °C	16	87:13	77%	95%
(CH$_2$)$_2$OBn	Me	C(CH$_3$)$_2$Ph	0 °C	12	90:10	82%	96%
H	Et	C(CH$_3$)$_2$Ph	0 °C	24	89:11	75%	94%
H	n-Bu	C(CH$_3$)$_2$Ph	0 °C	24	85:15	66%	96%
Et	n-Bu	C(CH$_3$)$_2$Ph	0 °C	24	65:35	55%	97%
Bn	Me	C(CH$_3$)$_2$OCH$_3$	0 °C	19	77:23	60%	92%
Et	Me	C(CH$_3$)$_2$OCH$_3$	0 °C	24	86:14	70%	95%
n-Bu	Me	C(CH$_3$)$_2$OCH$_3$	0 °C	24	88:12	62%	95%
H	Et	C(CH$_3$)$_2$OCH$_3$	0 °C	17	95:5	63%	95%
n-Hex	Et	C(CH$_3$)$_2$OCH$_3$	0 °C	24	78:22	42%	94%
H	n-Bu	C(CH$_3$)$_2$OCH$_3$	0 °C	24	95:5	60%	94%

Nucleophilic Substitution

The final method of forming the 1,2-dioxane core that I will discuss is the intramolecular nucleophilic substitution by a hydroperoxide at an sp^3 center. As can be seen from the previous section, the hydroperoxide acts as a nucleophile in reactions with activated alkenes and carbonyls. In fact, early methods of preparing hydroperoxides and alkyl peroxides were nucleophilic substitution under acidic[48] or basic conditions.[49]

Cookson also developed a method for synthesizing alkyl peroxides using alkyl halides,

alkyl hydroperoxides and silver acetate. The yields for the method were good even for

tertiary alkyl halide substrates and tertiary hydroperoxides.[50] In the process of

investigating the oxidation of arachidonic acid, Porter adopted the Cookson method to

synthesize 2,3-dioxabicyclo[2.2.1]heptane,[51] prostaglandin H_2 methyl ester,[52]

prostaglandin H_2[53] and prostaglandin G_2[54], presumably in an S_N2, stereospecific

pathway[51] (Example of the prostaglandin endoperoxide syntheses shown in Scheme

2.20).[54]
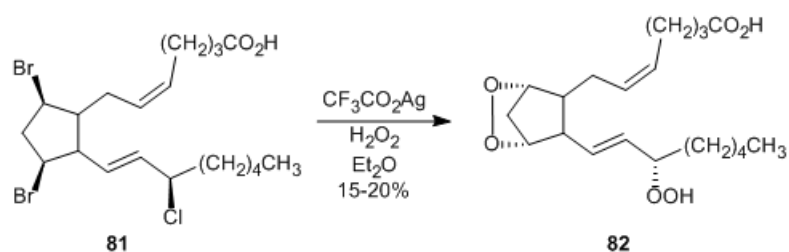
Scheme 2.20: Nucleophilic cyclization

Acidic conditions can be used to open both oxetanes and epoxides. The first

example that I will discuss is the total synthesis of all four stereoisomers of yingzhaosu C.

Xu et al. envisioned forming the 1,2-dioxane core by the intramolecular epoxide opening

thereby controlling the stereochemistry of the closure by the stereochemistry of the

epoxide. The synthesis begins with the Sharpless asymmetric epoxidation of 6-(4-

methylphenyl)-2,6-heptadiene followed by protection of the alcohol as an acetate. The

introduction of the silyl protected peroxide by a modified Isayama[55] method followed.

After removal of the silyl group, the diastereomeric hydroperoxides were stirred with

Amberlyst-15 to afford a 50:50 mixture of diastereomeric 1,2-dioxanes. The

diastereomers were then separated after deprotection of the alcohol (Scheme 2.21).[56]

i) 1) L-(+)-DIPT, Ti(OiPr)$_4$, t-BuOOH, CH$_2$Cl$_2$ 2) Ac$_2$O/Pyr
ii) 1) Et$_3$SiH, O$_2$, Co(modh)$_2$ 2) KF/18-crown-6, THF
iii) 1) Amberlyst-15, CH$_2$Cl$_2$ 2) K$_2$CO$_3$/MeOH, then H$_2$C$_2$O$_4$ 2H$_2$O
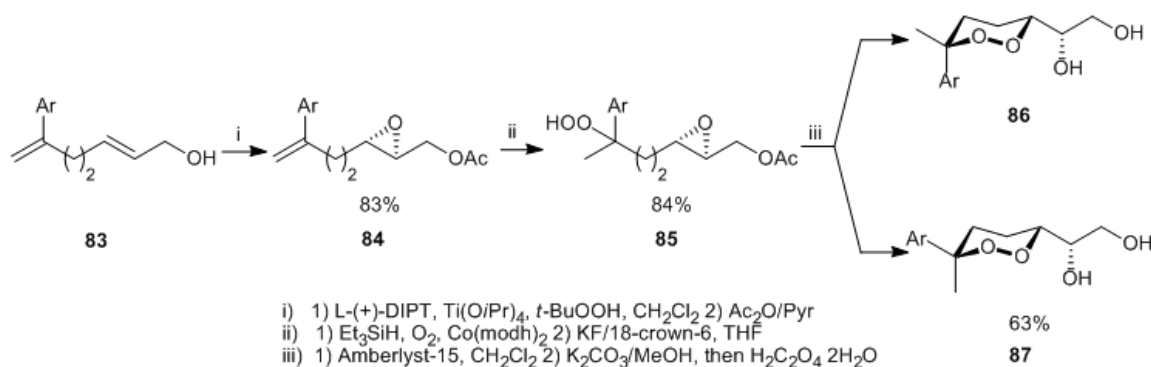
Scheme 2.21: Yingzhaosu C synthesis

The second example of 1,2-dioxane and 1,2-dioxolanes formation under acidic

conditions is the intramolecular opening of secondary and tertiary oxetanes by

hydroperoxides. In 2005, Dai successfully synthesized 1,2-dioxolanes, 1,2-dioxanes and

3-alkoxy-1,2-dioxolanes by the intramolecular oxetane opening.[57] The reaction occurs

with good stereoselectivity and good yields. While both 1,2-dioxolanes and 1,2-dioxanes

could be synthesized from alkyl hydroperoxides, only 3-alkoxy-1,2-dioxolanes could be

synthesized from the analogous hydroperoxyacetals. Attempts to prepare a methoxy-1,2-

dioxane product by a 6-exo cyclization instead afforded the 2-hydroperoxy-5-

methoxyoxepane as the major product. In this reaction, the rate of the 5-exo methoxy

migration is faster than the 6-exo hydroperoxide cyclization (Scheme 2.22).
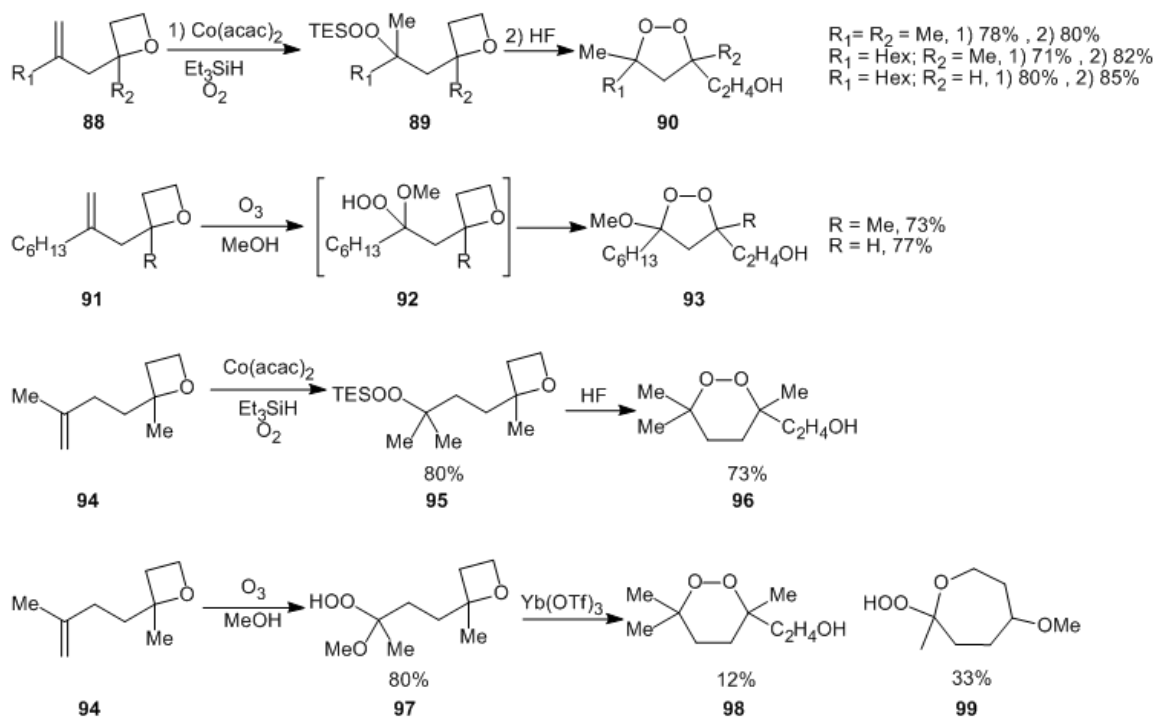
Scheme 2.22: Cyclization by oxetane opening

The older method of nucleophilic substitution under basic conditions was used in the Dussault lab as a means of assessing the diastereoselectivity of the nucleophilic addition to the carbonyl oxide during ozonolysis. In 1995, Zope ozonized 5-iodo-3-phenylpentene in methanol at -78 $^\circ$C. The hydroperoxyacetal, isolated in 46% yield and a 67:33 diastereomeric ratio, was subsequently subjected to cesium hydroxide in dimethyl formamide to form the 3-methoxy-4-phenyl-1,2-dioxane in 71% yield. Because the substitution reaction did not influence the stereochemistry of the peroxide-bearing center, the ratio of alkoxy-dioxanes could be used to determine the facial selectivity for the addition to a chiral carbonyl oxide (Scheme 2.23).[58]
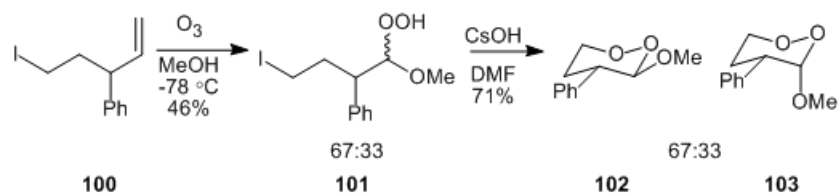
Scheme 2.23: Nucleophilic cyclization of primary iodides

A more recent example of this reaction being employed in the Dussault lab was the synthesis of spiro-bisperoxyketals.[59] In 2008, Ghorai was able to synthesize several examples of spiro-bis-peroxides using two methods. The first was the acid catalyzed intramolecular peroxyketalization of tertiary hydroperoxides. The reaction resulted in very good yields of bis-1,2-dioxolanes, bis-1,2-dioxanes and bis-1,2-dioxepanes (Acid Catalyzed Cyclization, Scheme 2.24). The second method used was the base promoted intramolecular cyclization of *gem*-dihydroperoxy bis-mesylates using potassium tert-butoxide and 18-crown-6 ether. This proved to be a very fast reaction which produced bis-1,2-dioxolanes and bis-1,2-dioxanes in very good yields (Base Promoted Cyclization Scheme 2.25).
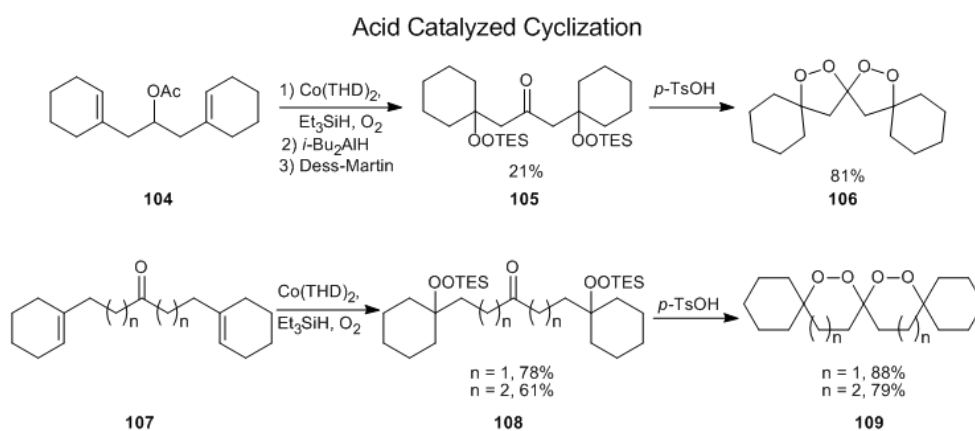
Scheme 2.24: Acid catalyzed cyclization

Base Promoted Cyclization
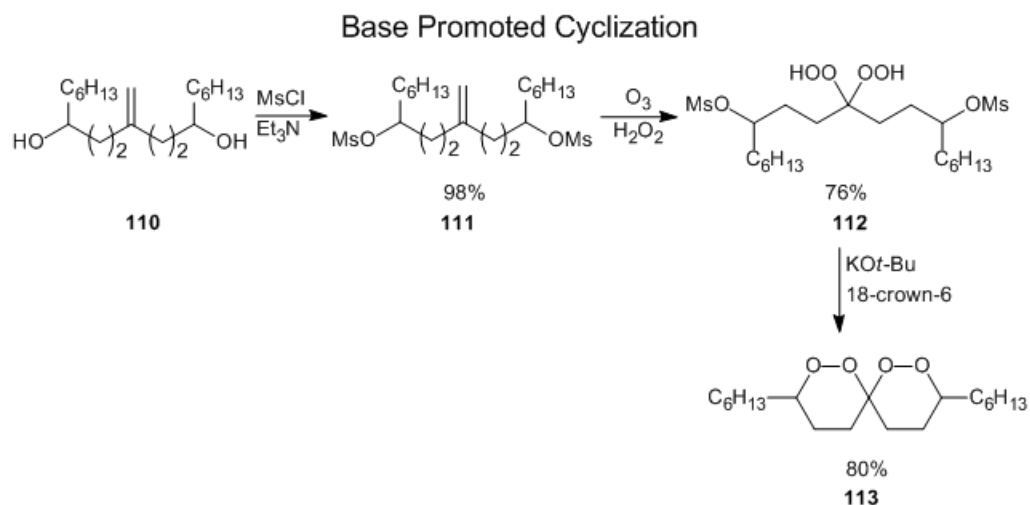
Scheme 2.25: Base promoted cyclization

Progress in the Peroxyplakorate A$_3$ Synthesis

A discussion of the synthesis of the 1,2-dioxane core in cyclic peroxide natural products was presented in the previous section. I will now discuss the challenges and the rationale for the planned asymmetric synthesis of peroxyplakoric acid A$_3$ methyl ester. The challenges encountered in the synthesis include control of relative and absolute stereochemistry and the introduction of both reduction- and oxidation-sensitive functionality. In order to overcome these challenges, the lessons learned from previous syntheses become important.

An asymmetric synthesis of the peroxyplakoric acid family must address five elements of stereochemistry: two stereocenters of the 1,2-dioxane core, one stereocenter in the head group and two geometric centers in the alkyldiene tail. The asymmetric synthesis of the peroxyplakoric acids, as well as other cyclic peroxides, must address

these stereochemical aspects. The "A" series of compounds differ from the "B" series of compounds only in the stereochemistry of the C_6 position 1,2-dioxane core, therefore it was imagined that the ability to control this center would allow access to both series of compounds. Likewise, the individual members of the series only differ in the tail and a method of introducing different diene tails would allow access to all of the peroxyplakoric acids. While the stereochemistry of the head group is applicable at this time only to the peroxyplakoric acids, the method could potentially be applied to analogues of other peroxides with a similar propionate head group may have better biological activity. Finally, as can be seen in Figure 2.14, several families of peroxides have similar polyunsaturated tails so it would be beneficial to use a general method that can be used for a variety of compounds.
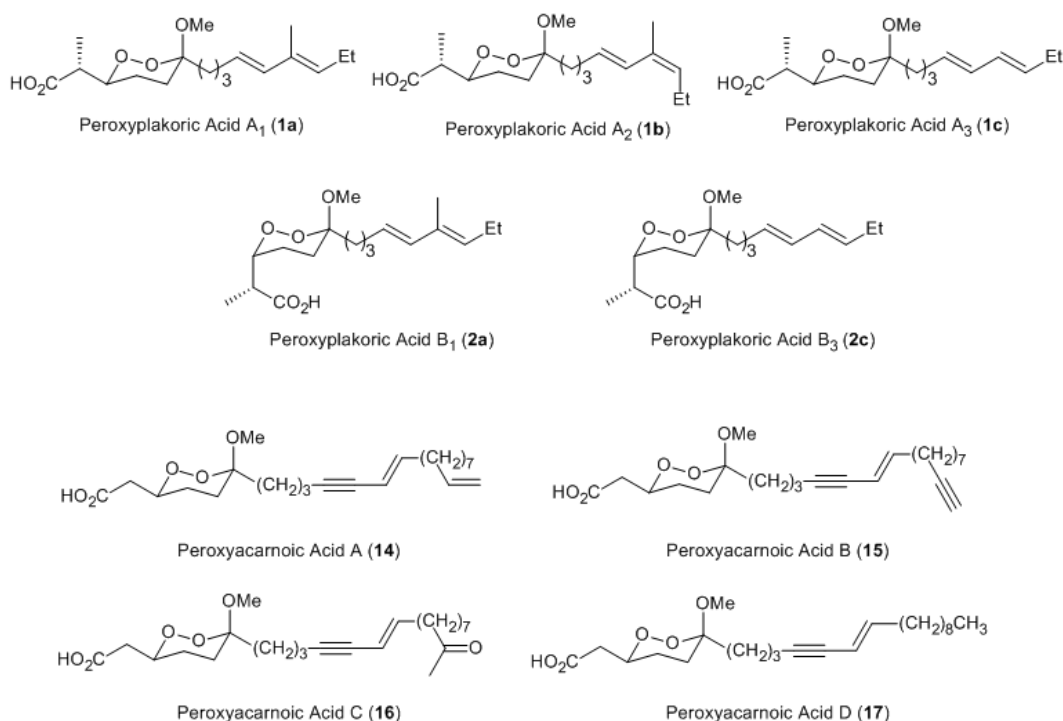
Figure 2.14: Similar unsaturated tails of peroxyplakoric acids and Peroxyacarnoic acids

In the retrosynthesis shown in Scheme 2.26, it was envisioned that the oxidation

sensitive dienyl tail would be installed by a palladium-mediated Negishi reaction late in

the synthesis. In order to control the stereochemistry of the peroxyplakoric acid core, the

best approach was thought to be an intramolecular nucleophilic substitution method of a

mesylate. Chemoselective methanolic ozonolysis would provide the necessary

hydroperoxyacetal precursor as a mixture of epimers (**115**). It was our hope that after the

cyclization, the 1,2-dioxane core would undergo acid catalyzed epimerization. Finally,

the stereochemistry of the propionate head group would be controlled by a boron

mediated asymmetric aldol reaction which would also provide the necessary alcohol

precursor of the methansulfonate (**117**).
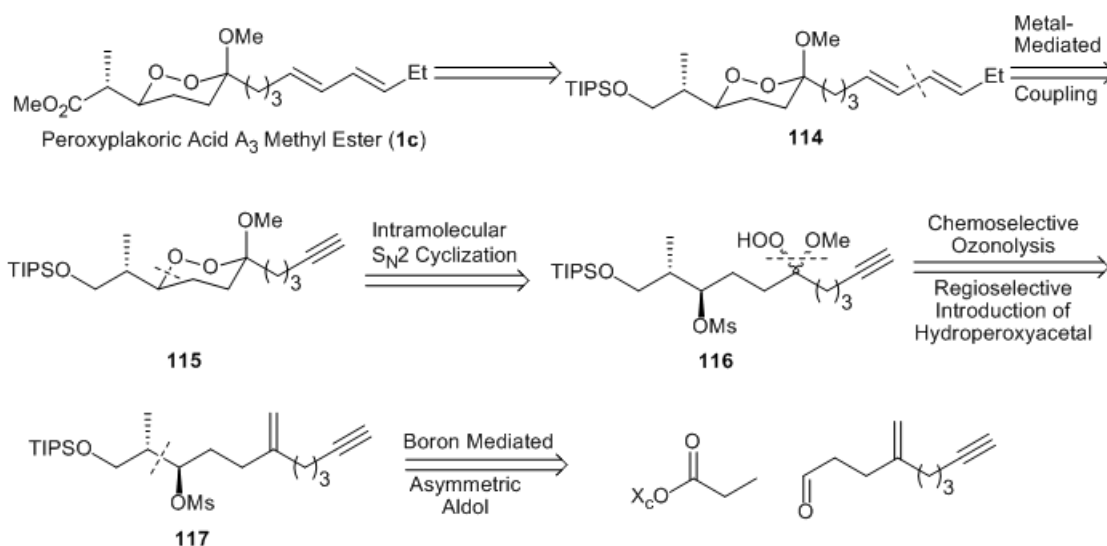
Scheme 2.26: Retrosynthetic analysis of peroxyplakoric acids

Metal Mediated Coupling Reactions

First, I will discuss the palladium catalyzed coupling reaction. There are many different palladium catalyzed coupling reactions that vary, primarily, in the nature of the nucleophilic coupling partner. The Sonogashira reaction couples an alkyl halide with a terminal alkyne using palladium, copper iodide and base. The Stille reaction couples an alkyl, vinyl or acyl halide with organotin compounds. The Negishi reaction couples an alkyl halide with an organozinc compounds. The generalized catalytic cycle shown in Scheme 2.27 begins with the oxidative addition of an alkyl halide to the palladium. This is followed by a transmetallation with the organometallic compound. Finally, a reductive elimination occurs to form the coupled product and regenerates the active palladium catalyst.
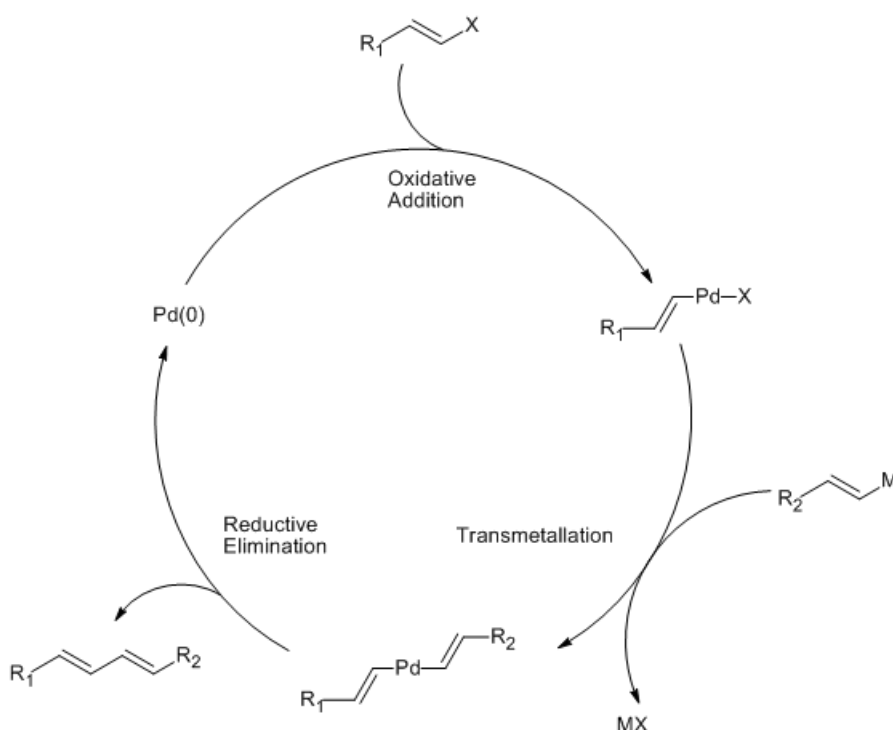
Scheme 2.27: Catalytic cycle for palladium coupling reactions

Eary and Zope found that peroxides were compatible with the performance of a number of palladium catalyzed reactions (Scheme 2.28). During their investigations, they found that acyclic peroxides could be used for the palladium catalyzed alkylation, acylation, Heck, and Stille reactions.[60] In Xu's synthesis of the peroxyacarnoates, the 1,2-dioxane core was found to be stable to the Stille and the Suzuki reactions but the reactions were slow and yields were low. Fortunately, although Eary's work had suggested acyclic peroxides were reduced under the conditions of the Sonogashira reaction, Xu was able to successfully use this reaction for the final coupling reaction in the peroxyacarnoate synthesis (Scheme 2.29).[15]
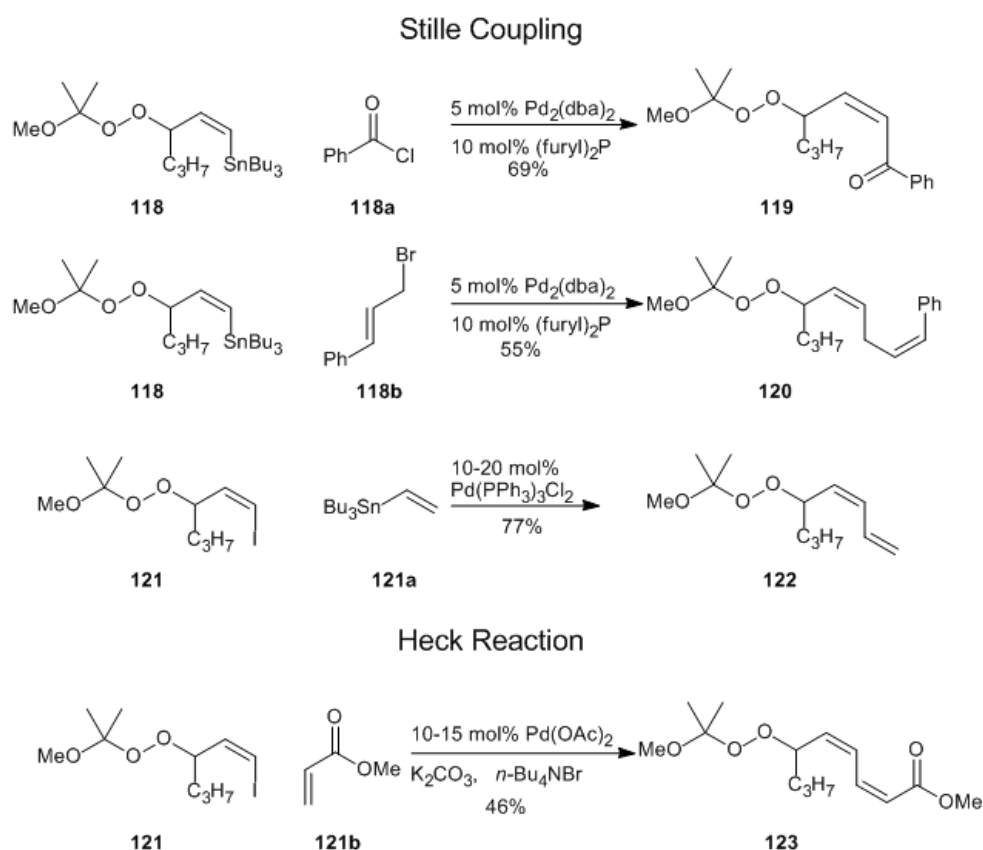
Scheme 2.28: Representative palladium coupling reactions of peroxides

Sonogashira Reaction
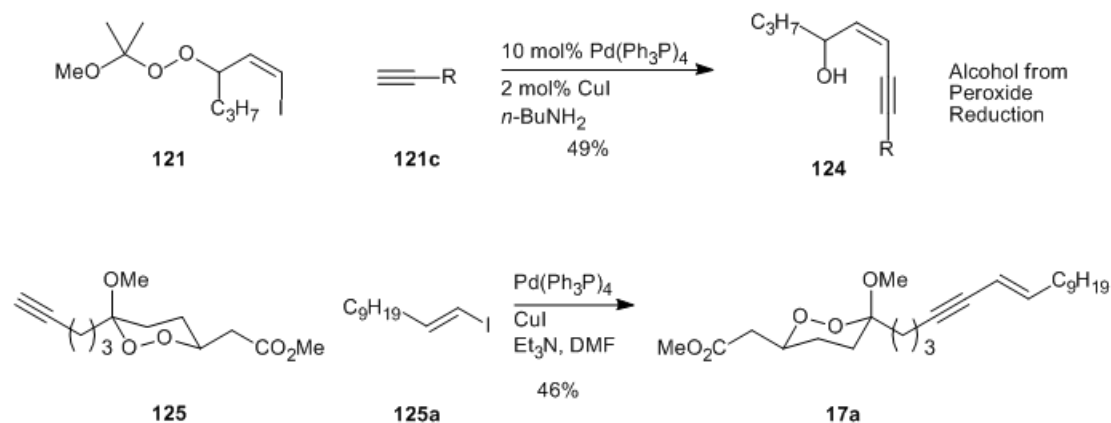
Scheme 2.29: Sonogashira reaction with peroxides

While these palladium catalyzed coupling reactions were found to be compatible with the 1,2-dioxane core, it was determined from Xu's observations in the peroxyacarnoate syntheses that the Stille coupling gave low yields. In addition, the Sonogashira reaction affords the conjugated enyne tail, therefore, it was envisioned that the Negishi coupling would provide the diene directly.

The Negishi reaction, originally discovered in 1977,[61] was a method to couple vinyl halides and alkynyl zincs but has also been used to couple vinyl halides and vinyl zincs. The synthesis of β-carotene demonstrates the utility of this reaction both as a sp-sp^2 and sp^2-sp^2 coupling method.[62] The synthesis also demonstrates carbometalation (and by extension hydrometallation), transmetallation of zirconium and zinc, and illustrates the differences in the reactivity of vinyl iodides and vinyl bromides (Scheme 2.30).

i. Me$_3$Al (2 eq.), Cp$_2$ZrCl$_2$ (1 eq.),CH$_2$Cl$_2$
ii. **127** (1.05 eq.), ZnCl$_2$ (1.05 eq.), 2.5 mol% Pd$_2$(dba)$_3$, 10 mol% TFP, DMF
iii. K$_2$CO$_3$, MeOH
iv. **126** (0.5 eq.), ZnCl$_2$ (1.05 eq.), 2.5 mol% Pd$_2$(dba)$_3$, 10 mol% TFP, DMF
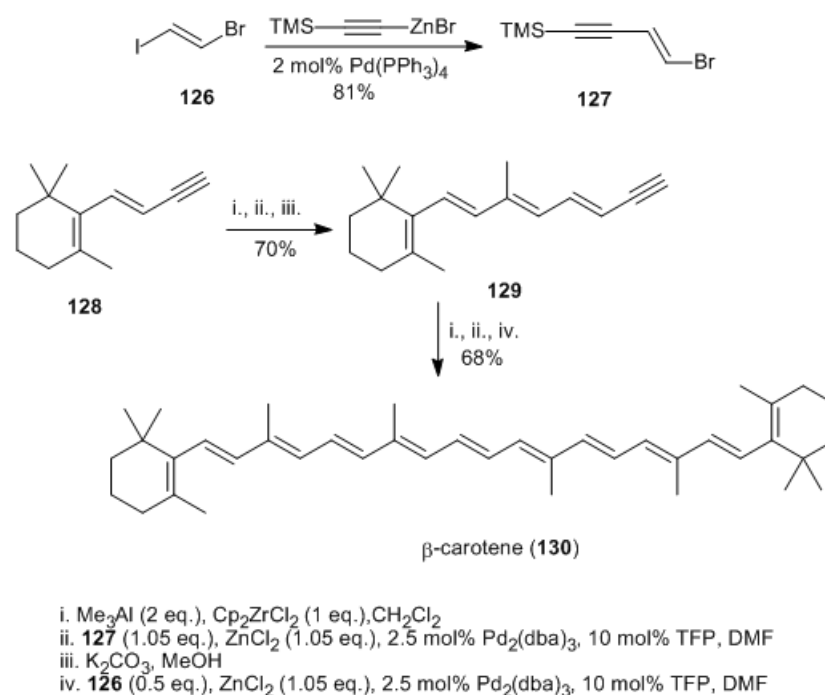
Scheme 2.30: Negishi reaction for the synthesis of • -carotene

The Negishi coupling catalytic cycle and the reaction sequence for the formation

of the vinyl iodide and vinyl zinc are shown in Scheme 2.31. Hydrometallation of the

alkyne with Schwartz's reagent produces the vinyl zirconium intermediate that can either

be transformed into the vinyl iodide or the vinyl zinc. One advantage to this mild method

is the ability to produce either the nucleophilic or electrophilic coupling partner from the

alkyne.
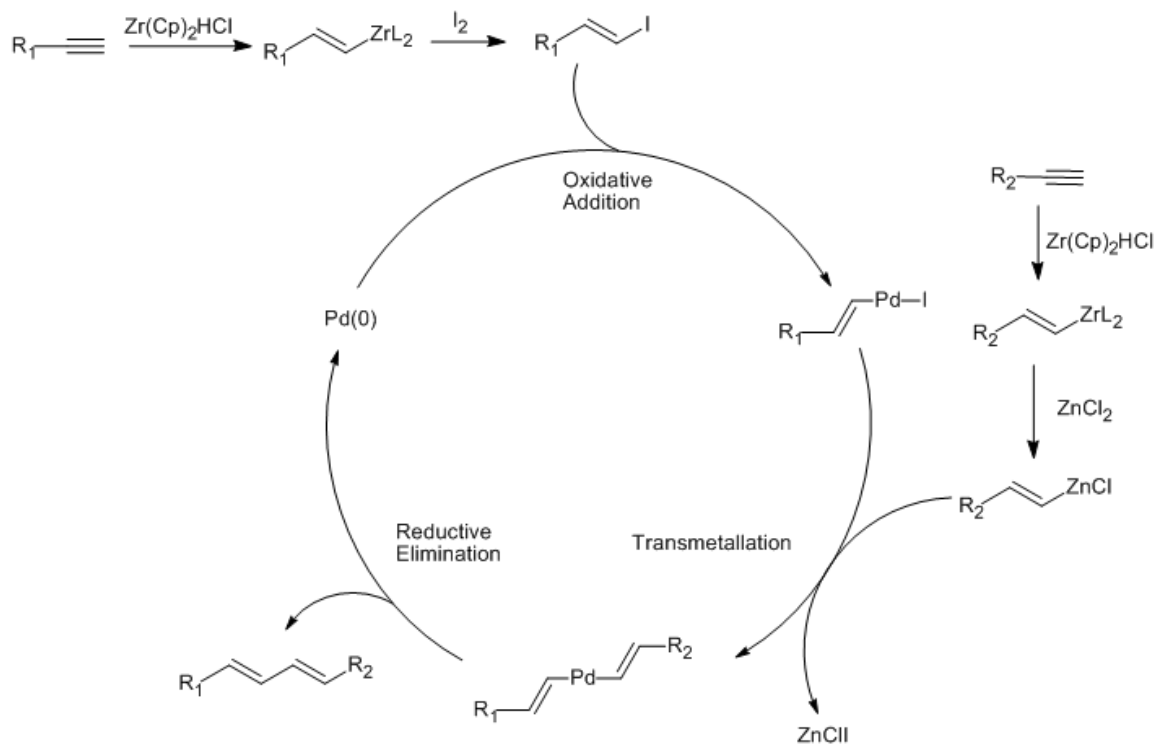
Scheme 2.31: Catalytic cycle for the Negishi coupling

Asymmetric Aldol

An asymmetric aldol reaction was envisioned as a way of controlling not only the stereochemistry of the propionate head group but also the C_6 of the 1,2-dioxane core thereby allowing access to either the A or B series of the peroxyplakorates. The inversion of the stereochemistry planned for the intramolecular substitution reaction requires that an anti-aldol reaction be employed for the "A" series and a syn-aldol for the "B" series of the family (Figure 2.15). Along with the established methods for the syn-aldol, recent advances in the asymmetric anti-aldol allow access to both intermediates.
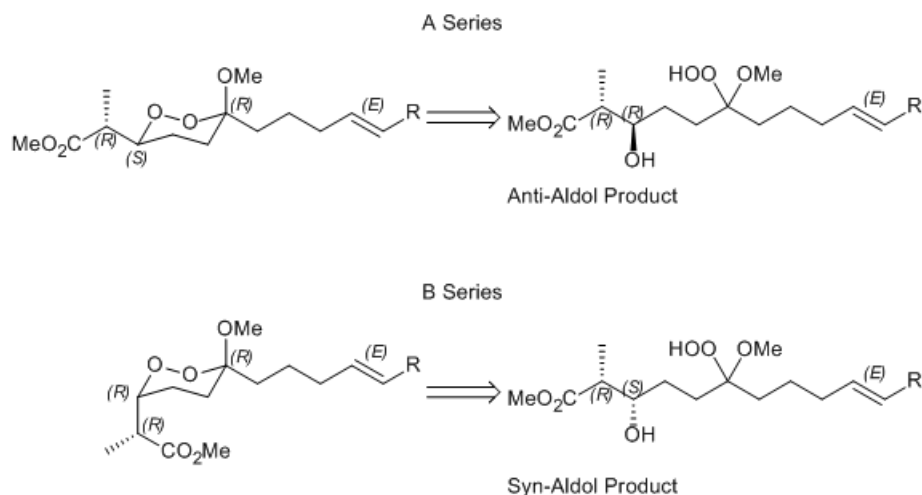
Figure 2.15: Retrosynthetic analysis for the asymmetric aldol

In general, the aldol reaction is a powerful method of forming carbon-carbon bonds. The reaction occurs between an enolate or enol and a carbonyl, usually an aldehyde. The challenge is the control of both the relative (syn or anti diastereoselectivity) and absolute stereochemistry (enantioselectivity) for the propionate aldol reaction needed for the peroxyplakorates. Since it would be nearly impossible to comprehensively discuss the stereoselective aldol, I will focus on using chiral auxiliaries to control the stereochemistry.

The Zimmerman-Traxler model, developed in 1957, is an excellent method to predict the stereochemical outcome of the asymmetric aldol reaction.[63] In this model, a metal or boron is tightly coordinated to both the enolate and the aldehyde in a chair-like transition state with the substituents oriented in such a way as to reduce the dipole moment, steric repulsions and 1,3-allylic strain. Of the four possible conformations, transition state B is favored by E-enolates while transition state D is favored by Z-

enolates (Figure 2.16). This has the effect of producing the syn-aldol product for Z-enolates and the anti-aldol product for E-enolates.
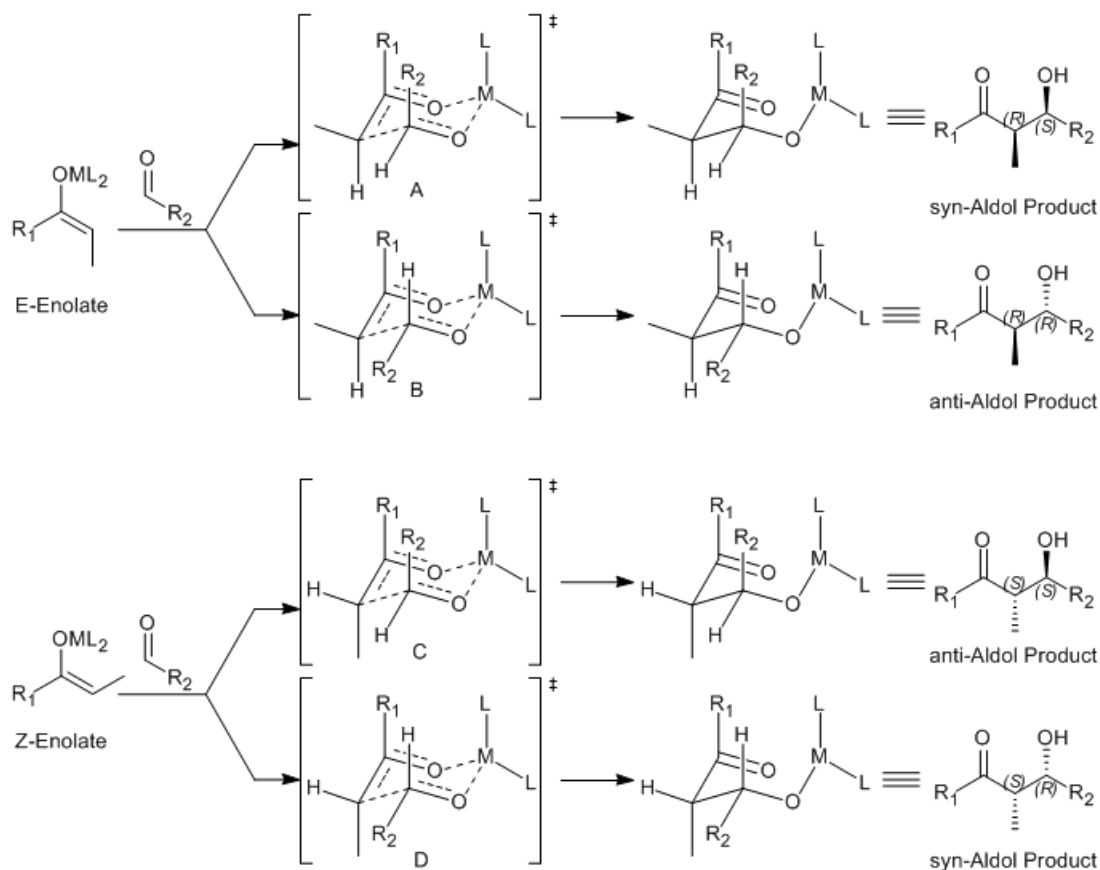
Figure 2.16: Zimmerman-Traxler model

In 1981, Evans et al. published the results of the investigations of using the oxazolidinone as a chiral auxiliary in the aldol reaction.[64] In these investigations, it was found that excellent diastereoselectivity for the syn-aldol product could be achieved. In addition, by using either (S)-4-isopropyloxazolidin-2-one or (4R,5S)4-methyl-5-phenyloxazolidin-2-one as the chiral auxiliary, the reaction afforded products with excellent control of absolute stereochemistry (Table 2.7). Besides the enantio- and

diastereoselectivity, this method offers two other advantages. First, the products of the

aldol reaction can often be easily separated due to the inherent chirality of the

oxazolidinone. Second, the chiral auxiliary can be removed and recycled.
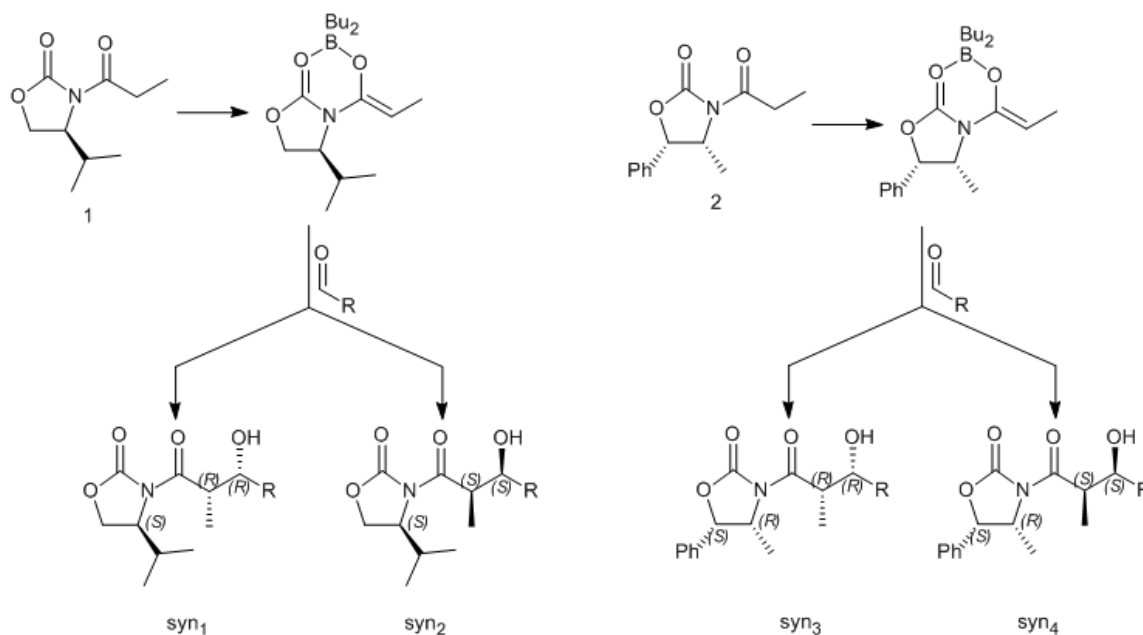
Table 2.7: Evans asymmetric aldol

Imide	R =	(R,R):(S,S)	Yield of major
1	Me₂CH	497:1	78%
2	Me₂CH	<1:500	91%
1	Bu	141:1	75%
2	Bu	<1:500	95%
1	Ph	>500:1	88%
2	Ph	<1:500	89%

There are some aspects of the boron mediated Evans asymmetric aldol that should

be addressed. First, under the reaction conditions typically used, the enolate is generated

first under kinetic control typically with stoichiometric amounts of a bulky amine which

affords the Z-enolate.[65] After the enolate is formed, the carbonyl is added and the

reaction proceeds through a chair-like transition state where the boron is tightly

coordinated to the carbonyl and the enolate. Second, the chiral auxiliary is oriented in the

pseudoaxial position in order to maximize the resonance of the nitrogen. The

oxazolidinone carbonyl is also oriented away from the boron in order to minimize the

dipole moment of the transition state.[66] This orientation allows the approach of the

carbonyl from one face with its substituents preferentially in the equatorial position in the

chair-like transition state. The Z-enolate geometry affords the syn-aldol product while

the specific stereochemistry of the oxazolidinone controls the enantioselectivity of the

reaction (Scheme 2.32).
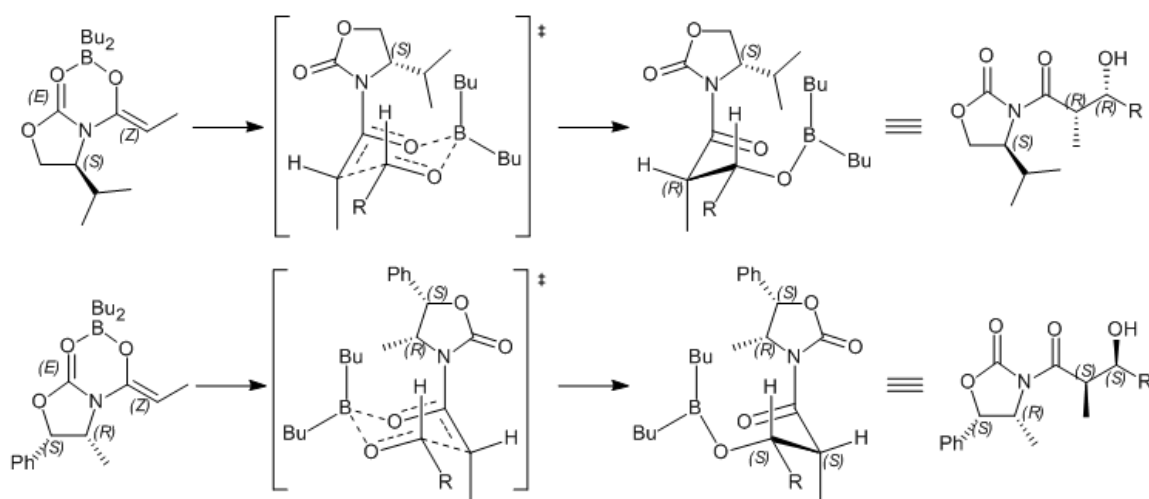
Scheme 2.32: Transition state rationale for the Evans asymmetric aldol

The Evans aldol reaction is a very powerful strategy in order to synthesize the

syn-aldol product. In the past three decades since the development of this method,

several modifications have been made in the chiral auxiliaries and Lewis acid assisted reactions in order to afford the non-Evans syn and anti-aldol products.[65-67]

Investigations into the asymmetric aldol by Masamune, Abiko and Inoue have led to the development of a new chiral auxiliary method that combines norephedrine derived auxiliaries, various dialkylboryl triflates and amines to allow access to both anti- and syn-aldol products in excellent yields and diastereoselectivities.[68] The results of these studies (Table 2.8) show that dicyclohexylboryl triflate and triethyl amine produces the anti-aldol product in excellent yields and diastereoselectivities. The use of the enantiomeric chiral auxiliary was also shown to afford enantiomeric products.[68b] It is also interesting to note that by altering the chiral auxiliary, amine base and dialkylboryl triflate, it is also possible to produce the syn-aldol in excellent yields and diastereoselectivity. This would, in principle, allow the synthesis of the entire family of peroxyplakoric acids from a single class of chiral auxiliaries.
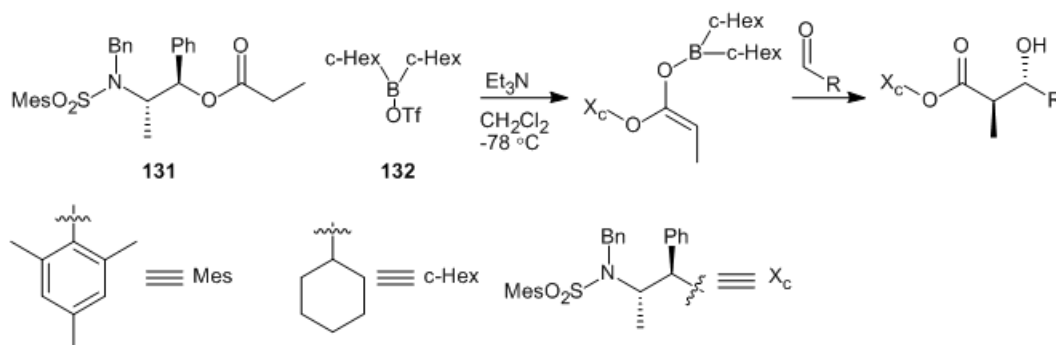
Table 2.8: Masamune asymmetric aldol

R	Yield	ds for anti
Me-	92%	97:3
Et-	90%	96:4
n-Pr-	95%	95:5

i-Pr-	95%	98:2
c-Hex-	95%	95:5
t-Bu-	91%	>99:1
Ph-	96%	95:5
(E)-CH$_3$CH=CH-	93%	98:2
CH$_2$=C(CH$_3$)-	97%	96:4
BnOCH$_2$CH$_2$-	94%	95:5
BnOCH$_2$C(CH3)$_2$-	98%	96:4

Results and Discussion

In the results and discussion section I will first discuss the synthesis of the chiral

propionate and achiral aldehyde starting materials for the 1,2-dioxane core cyclization

reaction. Next, I will discuss the cyclization reaction and finally, the coupling of the

dienyl tail. As a side note, it is during this time that I developed a Microsoft Excel based

spreadsheet that could be used as an electronic notebook. The spreadsheet calculates all

of the amounts of reagents, solvents and workup solutions based on the original reference

procedure. It also serves as a checklist for all characterizations, including optical rotation

calculations. It is also during this period that I developed a method for creating parsing

or splitting trees for complex ^{1}H NMR spin systems using ChemDraw from

Cambridgesoft (an example of the chiral propionate H$_{AB}$ splitting pattern is shown in

Figure 2.17).
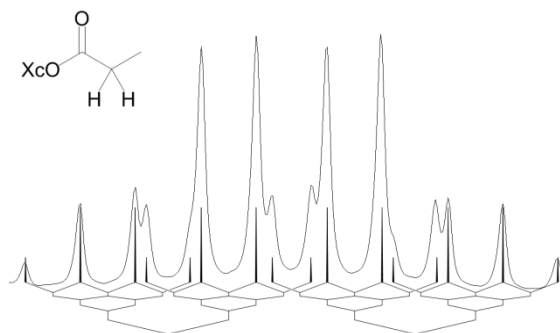
Figure 2.17: Example of splitting tree created in ChemDraw

Chiral Auxiliary Propionate Synthesis

The chiral propionate synthesis was accomplished according to the published

procedure[68c] and was relatively straight forward with the exception of purification. It

begins with the small scale synthesis of the (1*R*, 2*S*)-2-(*N*-mesitylenesulfonyl)amino-1-

phenyl-1-propanol (**131**) by the reaction of (1*R*, 2*S*)-norephedrine, triethylamine and

mesitylenesulfonyl chloride in dichloromethane. The reaction proceeded smoothly and

purification was accomplished by recrystallation. Next, the (1*R*, 2*S*)-2-(*N*-

mesitylenesulfonyl)amino-1-phenyl-1-propanol (**131a**) was alkylated with benzyl

bromide to afford (1*R*, 2*S*)-2-(*N*-benzyl-*N*-mesitylenesulfonyl)amino-1-phenyl-1-

propanol (**131b**) which was purified by flash column chromatography. Finally, the

propionate ester was synthesized by dropwise addition of propionyl chloride to the

alcohol. Purification was accomplished by recrystallization with ethyl acetate.

Throughout this synthesis, especially upon scale-up, the crystalline products were

difficult to characterize due to the difficulty of completely removing solvents. Often, the

solid would need to be heated during evaporation and would become a sticky, foamy

solid. The synthesis is shown in Scheme 2.33.
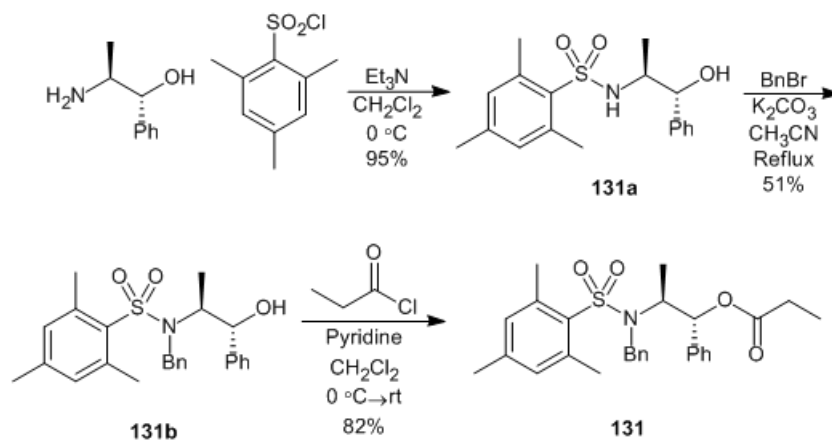
Scheme 2.33: Chiral propionate synthesis

Aldehyde Synthesis

The enynal needed for the asymmetric aldol was next synthesized by standard procedures. First, 1-(1,3-dioxolan-2-yl)-8-nonyn-4-one (**76**) was synthesized by a reaction of 2-(1,3-dioxolan-2-yl)ethyl magnesium bromide and 5-hexynoyl chloride generated *in situ* from hexynoic acid and oxalyl chloride. The resulting 1-(1,3-dioxolan-2-yl)-8-nonyn-4-one was purified by flash column chromatography. Next, the Wittig reaction with methyltriphenylphosphonium bromide and potassium bis(trimethylsilyl)amide in THF transformed the ketone to 2-(3-methylene-7-octynyl)-1,3-dioxolane (**77**) which was purified by flash column chromatography (Scheme 2.34). Due to the instability of the aldehyde, the final deprotection of the 1,3-dioxolane with aqueous hydrochloric acid was completed only after the dicyclohexylboryl triflate was made.
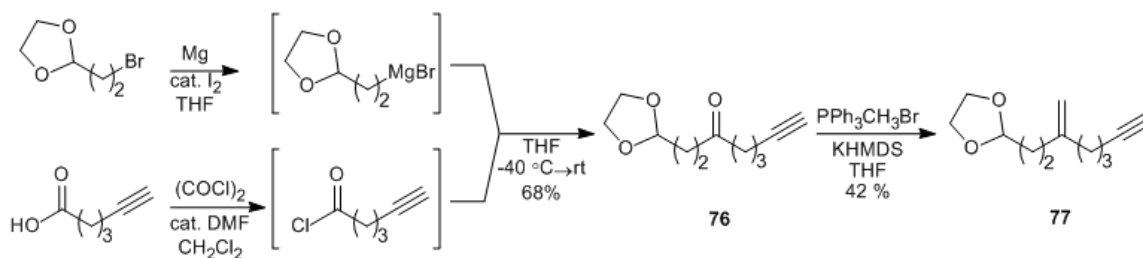
Scheme 2.34: Aldehyde synthesis

Asymmetric Aldol

Before the asymmetric aldol reaction could be run, dicyclohexylboryl triflate (**132**) needed to be synthesized, again according to procedure (Scheme 2.35).[68c] This proved to be more challenging than I had first thought. The first step in the synthesis was the hydroboration of cyclohexene. Borane dimethyl sulfide complex was added dropwise to two equivalents of cyclohexene in THF after which a white solid formed. The solvent was then removed by vacuum, the solid was resuspended in hexane and trifluoromethysulfonic acid was added dropwise.

The solid dissolved as the acid was added and a yellow oily bottom layer formed. After removing as much of the yellow layer as possible, the remaining liquid was allowed to crystallize in the freezer overnight. The removal of the remaining liquid afforded white crystals which were redissoved in hexane to make a 1 M solution. As a side note, this solution rarely lasted more than a few days before it turned yellow. This is apparently an issue with the amount of trifluoromethylsulfonic acid and the purity of the cyclohexene. During my final preparation of this compound, I added slightly less than one equivalent of the acid to the reaction and employed freshly distilled cyclohexene. As

a result, the solution of final product remained clear and colorless for a much longer period of time.
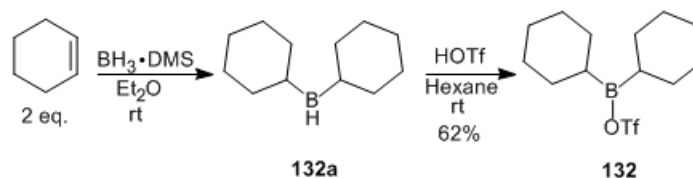
Scheme 2.35: Boryltriflate synthesis

Once the boryl triflate reagent (**132**) was made, the 1,3-dioxolane (**77**) was deprotected with aqueous hydrochloric acid and the resulting crude product was purified as much as possible by flash column chromatography leaving only trace amounts of protected aldehyde. It was believed the trace amounts of protected aldehyde would not affect the asymmetric aldol reaction and could be recovered.

For the asymmetric aldol reaction, the chiral propionate (**131**) was first dissolved in dichloromethane after which triethyl amine was added. The 1 M solution of the boryl triflate (**132**) was then added slowly and the reaction allowed to stir at -78 °C. After two hs a dichloromethane solution of the aldehyde (**77a**) was added slowly and the reaction stirred for another h. The reaction was allowed to warm to rt slowly and then quenched with a 0.1 M pH 7 phosphate buffer. The reaction was completed by the removal of the boronate through digestion with methanol and hydrogen peroxide (Scheme 2.36). Purification by flash column chromatography afforded predominately the anti-aldol product (**133**) in excellent diastereoselectivity. The optical rotation of this product ($[\alpha]_D^{20}$ 19.5 (c 0.87, CHCl$_3$)) caused some confusion because the previously reported rotation

$([\alpha]_D^{20} = 31.8$ (c = 0.48, CHCl$_3$))[1a] did not match. The error was revealed, however, after

the removal of the chiral auxiliary afforded the diol with an optical rotation of $[\alpha]_D^{20} =$

31.7 (c = 1.1, CHCl$_3$) which is identical to the previously reported diol optical rotation.[1a]

It is my belief that the optical rotation for the aldol product in Xu's dissertation was a

transcription error because of the similarity between the two values.
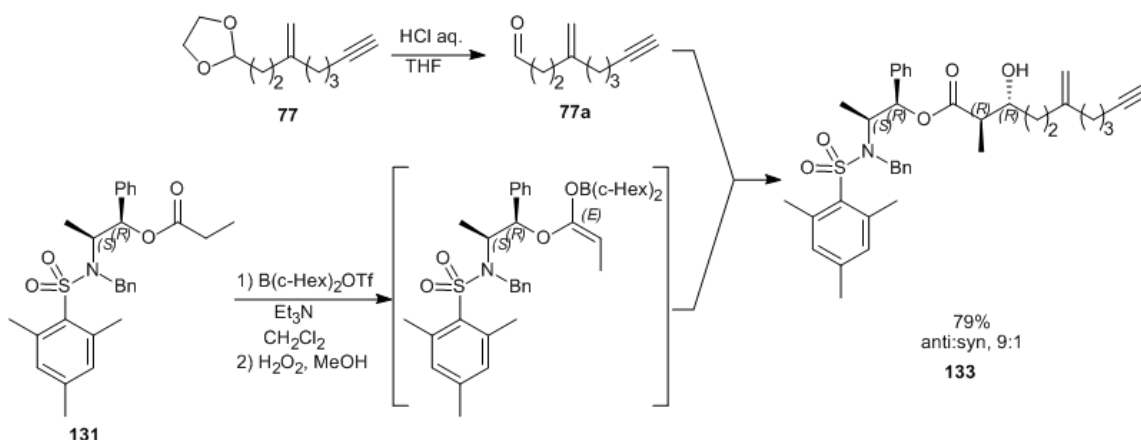
Scheme 2.36: Asymmetric aldol

Removal of the chiral auxiliary alcohol with lithium aluminum hydride resulted in

the recovery of the chiral alcohol and the diol product. The workup procedure seemed a

little capricious. Both sodium sulfate decahydrate and sodium hydroxide procedures

were tried and gave comparable yields.[68c, 69] After the diol was purified with flash

column chromatography, the primary alcohol was protected with triisopropylsilyl

chloride. The secondary alcohol was then transformed into the mesylate with

methanesulfonyl chloride (Scheme 2.37).
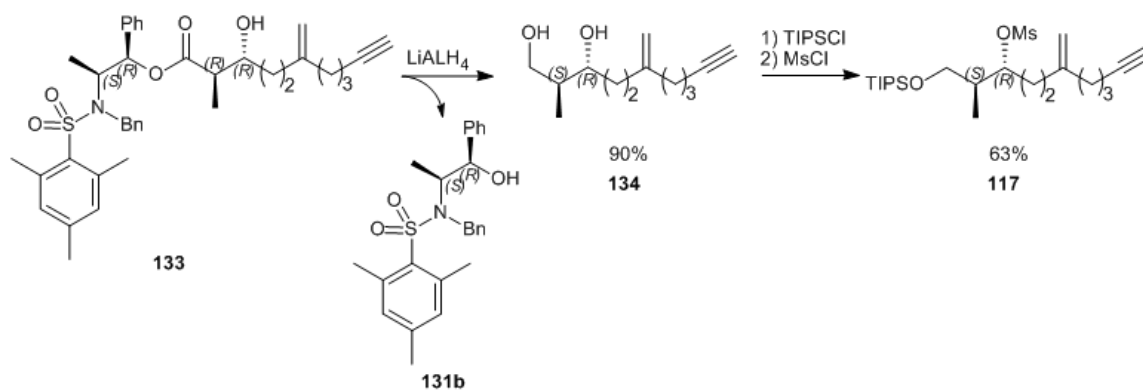
Scheme 2.37: Chiral auxiliary removal, alcohol protection and mesylation

This TIPS protected mesylate is the common intermediate for the 3-methoxy-1,2-dioxane core of the A series of peroxyplakoric acids. It should also be noted that the only difference in the synthesis up until this point between the A and B series of peroxyplakoric acids is the choice of asymmetric aldol conditions. In order to synthesize the 1,2-dioxane core of the B series, the octahydroanthracenyl (OHA) sulfonimide version of the chiral auxiliary, dibutylboryl triflate and diisopropylethyl amine would be used to give the syn-aldol product.

1,2-Dioxane Core Synthesis

With the TIPS protected mesylate (**117**) in hand, chemoselective methanolic ozonolysis of the olefin was accomplished during which the reaction was monitored by TLC. The first time this reaction was attempted on a small scale, the product was purified as a mixture of hydroperoxyacetal epimers by flash column chromatography. Attempts at further purification by HPLC failed. Unfortunately, when the reaction was tried again, the hydroperoxyacetal decomposed to the ketone (**116a**). Although it was not

possible to definitely determine the cause of the decomposition, the lab changed silica

vendors during this period (Scheme 2.38).
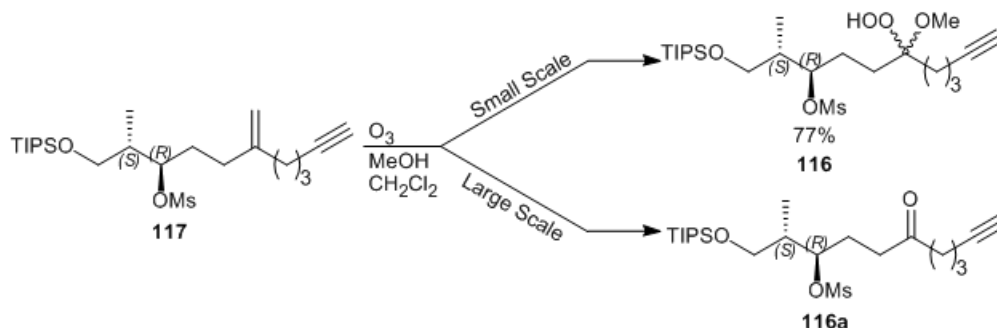
Scheme 2.38: Initial methanolic ozonolysis

The ozonolysis reaction was modeled using other alkenes with mixed results. In a

final attempt, a model alkenyl mesylate was ozonized in the presence of 14 equivalents of

octanol in dichloromethane and immediately subjected to the cyclization conditions. This

resulted in the 3-alkoxy-1,2-dioxane being formed in 78% yield (Scheme 2.39).
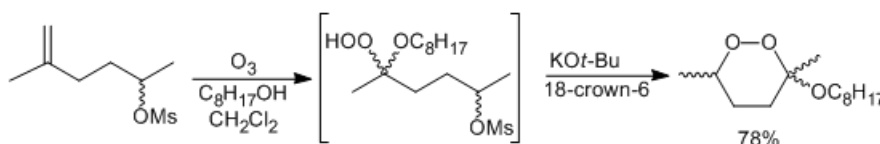
Scheme 2.39: Model one pot ozonolysis and cyclization

When the TIPS protected mesylate was used as the substrate in the same manner,

I was relieved to have formed the cyclized product in 75% yield for the two steps as a

mixture of the two diastereomers (~55:45 ratio of the desired product by ^{1}H NMR) that

could be separated by careful chromatography (Scheme 2.40). Attempts to epimerize the

undesired diastereomer with methanol and hydrochloric acid resulted in decomposition to

the ketone.
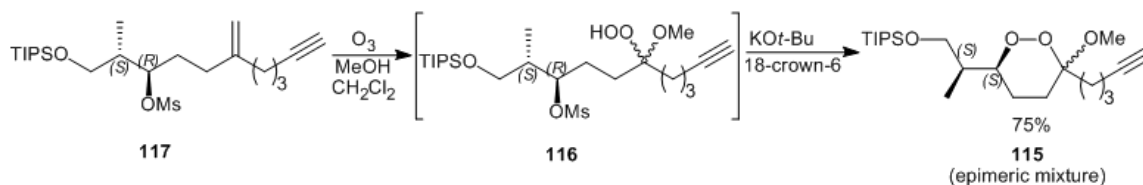
Scheme 2.40: 3-methoxy-1,2-dioxane core synthesis

Dienyl Tail Coupling

With the successful synthesis of the core of the peroxyplakoric acids by an

intramolecular substitution reaction, the coupling reaction of the tail could be attempted.

First, it was believed that the dioxane was too valuable to transform into the vinyl iodide

as had already been accomplished previously.[1a] While the reaction had been mild enough

for the dioxane core, terminal alkene was always a side product, presumably due to trace

amounts of water. It was hoped to decrease the linear sequence of reactions and limit the

side reaction by coupling the dioxanyl containing organometallic with the butenyl iodide

instead. In order to synthesize the butenyl iodide, I attempted hydrozirconation followed

by the addition of iodine. Unfortunately, while the reaction was successful by TLC,

yields of the isolated product were extremely low. The transformation was also tried

with alane and while the yield of the vinyl iodide was moderate using the higher

molecular weight 1-decyne, the butynyl iodide was still problematic. In the end, the

vinyl iodide (**135**) was synthesized from the 1,2-dioxane (**115**). The terminal alkene side

product (**135a**) could be reduced with careful exclusion of water but was always present (Scheme 2.41).
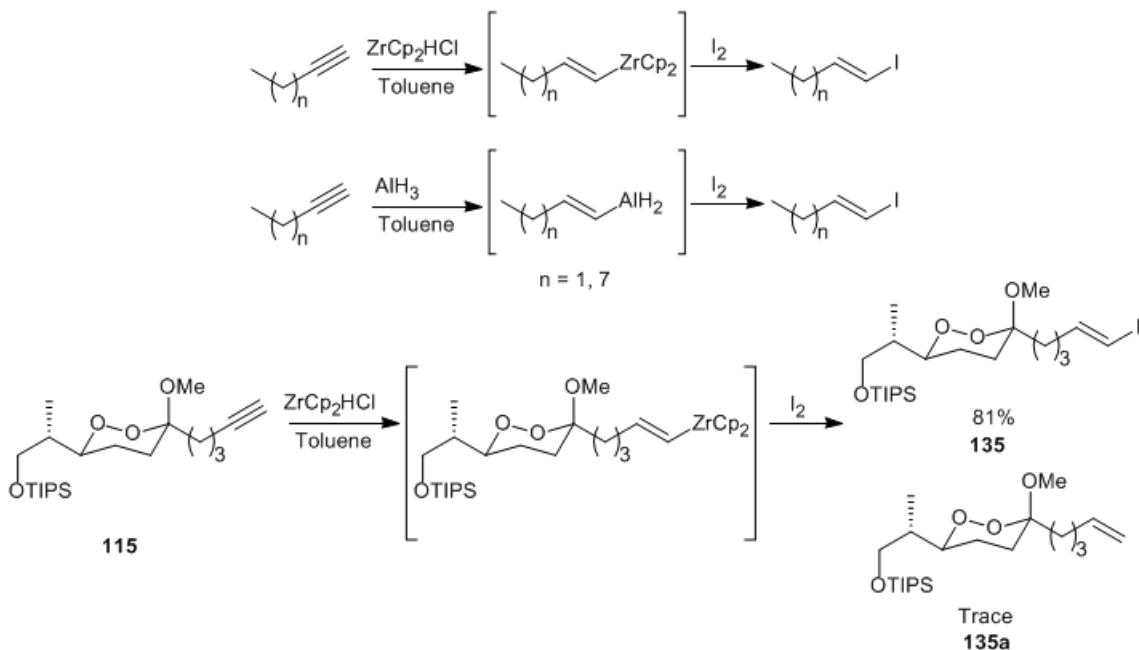
Scheme 2.41: Hydroziconation followed by iodination

With the vinyl iodide synthesized (**135**), the Negishi coupling to form the tail was attempted. Butyne was first condensed into a graduated cylinder at -78 °C and the volume used to estimate the amount of butyne needed for the reaction. It was then transferred to a flask and diluted with solvent (1:1 THF:toluene) and stirred. The reaction was allowed to warm to 0 °C, ZrCp$_2$HCl was added and the reaction was allowed to stir. After the reaction had stirred for an h, another portion of ZrCp$_2$HCl was added in order to drive the reaction to completion. The reaction was allowed to warm briefly and vented with nitrogen in order to help remove any excess butyne. The reaction was then cooled back to 0 °C and zinc chloride was added after which the solution became an orange

color. Finally, a solution of vinyl iodide (**135**) in THF was added followed by the first

portion of palladium tetrakistriphenylphosphine (Pd(PPh$_3$)$_4$). The reaction was monitored

by TLC, and after five minutes, another portion of the palladium catalyst added. When

TLC indicated most of the starting material had reacted, the reaction was diluted with

hexane and filtered through a silica plug. Unfortunately, after purification by flash

column chromatography, ^{1}H NMR indicated a lack of the desired product with a clear

triplet and a doublet of quartets for a substituted ethyl group. While both the desired and

undesired products have a doublet of quartets, the coupling constant was too small for the

expected diene product indicating long range coupling (Scheme 2.42).
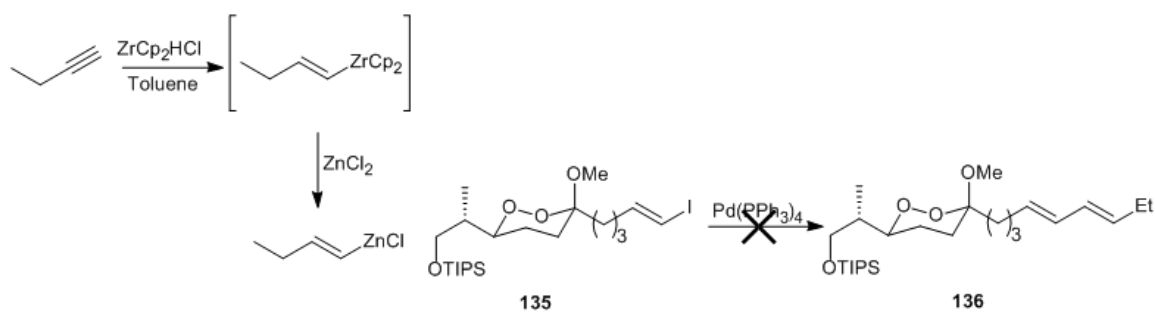
Scheme 2.42: Initial attempt at Negishi coupling

The reaction was modeled using iododecene and decyne while more starting

dioxane was being synthesized. The ^{1}H NMR spectrum of the model reaction indicated

that the expected product was formed. After obtaining the same product when the

reaction was run a second time, by carefully examining the correlation spectroscopy

(COSY) spectrum, I was able to identify the product as the 3-methoxy-1,2-dioxane with a

conjugated enyne tail (Scheme 2.43); the long range cross peak ($=CH\!\!\!=\!\!\!=\!\!\!CH_2Me$) was

difficult to see.
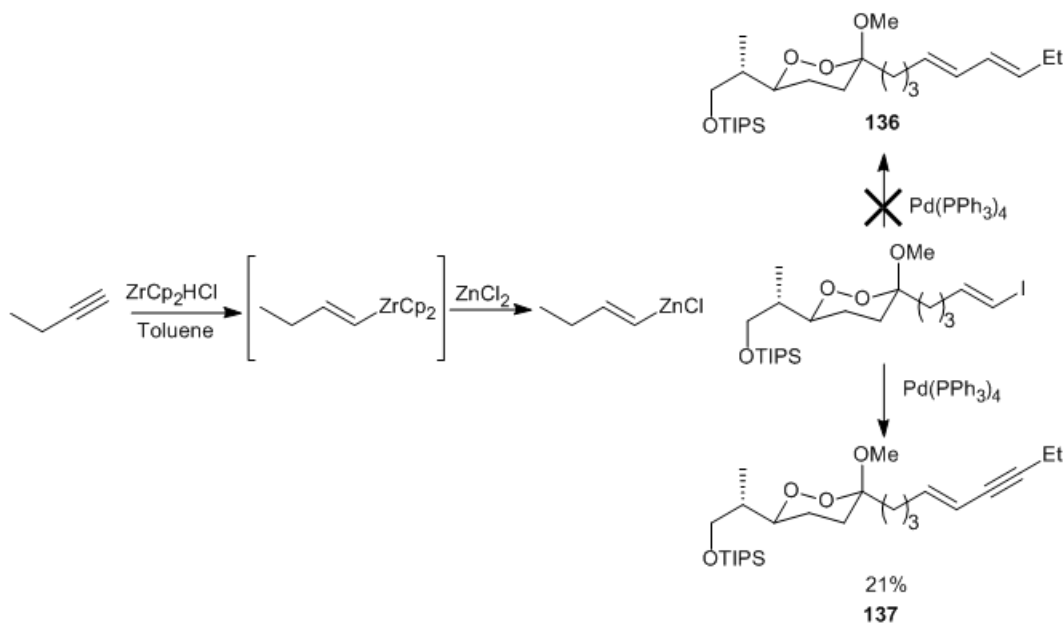
Scheme 2.43: Final attempt of Negishi coupling and product identification

A possible explanation for the formation of the enyne product (**137**) is that a

copper salt contaminant in the palladium catalyst catalyzed the Sonogashira reaction

between the excess butyne and the vinyl iodide. Copper could have also leached from the

needles although this is unlikely considering the formation of the enyne in two separate

reactions. A second possibility is that the Negishi reaction can couple an alkynyl zinc

from the excess butyne and vinyl iodide.[61]

Regardless of the cause of the enyne product, I attempted to reduce the alkynyl π

bond. Based on the observation of the formation of the terminal alkene in the

hydrozirconation reactions, I had hoped it would be possible to use this side reaction to

reduce the conjugated enyne. This method of reduction does have some precedent with terminal alkynes,[70] unfortunately, due to the limited amount of enyne, the reaction was unsuccessful and most of the starting material was recovered. Perhaps with a change in reaction conditions, the reaction could work but at the time, I didn't want to risk what little I had left.

While peroxyplakoric acid A_3 was not synthesized, the key asymmetric aldol and stereospecific cyclization steps have been shown to be feasible. If another attempt is made in the future, there are two things I would change. First, the chiral propionate has been shown to be very stable which means that it can be synthesized prior to the enynal. Second, the Negishi palladium mediated coupling reaction would need to be examined again. The reaction was shown to give 72% yield as a mixture of the terminal alkenyl-1,2-dioxane and the coupled product by Dr. Xu and I believe the reaction could be optimized with fresh palladium catalyst and a better method of measuring the amount of butyne.

Experimental Section:

General Experimental Procedure: All purchased chemicals were used without further purification except for cyclohexene which was distilled and benzyl bromide which was pushed through an alumina plug. THF was distilled over benzophenone and sodium metal. Dichloromethane and toluene were distilled over calcium hydride. Methanol was dried with molecular sieves. Ozone was generated at approximately 1 mmol per minute as a 2-4% mixture of O_3/O_2 stream by an Osmonics V-series ozone generator. Molybdate dip (25 g ammonium molybdate tetrahydrate, 10 g ceric sulfate

and 1 L 10% sulfuric acid) and vanillin dip (3 g vanillin, 97 mL absolute ethanol and 3

mL concentrated sulfuric acid) were used as general TLC developing dips. A peroxide

specific dip[71] (1.2 g N,N-dimethyl-*p*-phenylenediamine dihydrochloride, 100 mL

methanol, 20 mL water and 1 mL acetic acid) was used for peroxide containing

compounds and an olefin dip (0.316 g potassium permanganate in 100 mL water) was

used as an olefin compound specific dip. NMR spectra were obtained with 300, 400 or

500 MHz Bruker spectrometers using $CDCl_3$ as the solvent unless otherwise noted.

Chemical shifts are reported in ppm. IR spectra were obtained with a Nicolet Avatar 360

FT-IR ESP spectrometer. Optical rotations were obtained with a Rudolph Research

Autopol III Automatic Polarimeter. Melting points are uncorrected and were obtained

with a MeltTemp.

Chiral Propionate Synthesis:

Synthesis of the chiral propionate was accomplished according to the published

procedure.[68c]
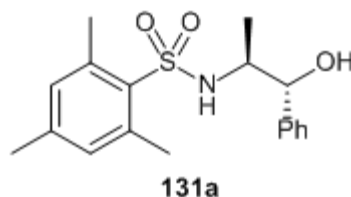
131a

(1*R*, 2*S*)-2-(*N*-Mesitylenesulfonyl)amino-1-phenyl-1-propanol (131a): To a

stirred solution of norephedrine (5.1 g, 34 mmol) and Et_3N (5.8 mL, 41 mmol) in CH_2Cl_2

(132 mL) was added mesitylenesulfonyl chloride (7.38 g, 33.7 mmol) at 0 °C. The

reaction mixture was stirred at 0 °C and allowed to warm to rt over 2 h then diluted with a

volume of diethyl ether. The mixture was washed successively with water, 1 M HCl,

water, sat. aq. NaHCO$_3$, and brine and dried over anhydrous Na$_2$SO$_4$. The filtered

organic solution was concentrated to give an oily residue, which was dissolved in CH$_2$Cl$_2$.

Addition of hexane to the solution resulted in the crystallization of the product as a white

solid. Yield: 10.76 g, 95%; R_f = 0.23 (25% EtOAc/Hexane); mp 121-122 °C; $[\alpha]_D^{20}$ -12.1

(c 2.2, CHCl$_3$); ^{1}H NMR 300 MHz (CDCl$_3$) δ 0.87 (3H, d, J = 6.8 Hz), 2.31 (3H, s), 2.95

(1H, -OH), 2.67 (6H, s), 3.50 (1H, dqd, J = 3.1, 6.8, 8.9 Hz), 4.81 (1H, d, J = 3.1 Hz, -

NH), 5.2 (1H, d, J = 8.9 Hz), 6.97 (2H, s), 7.21-7.35 (5H, m); ^{13}C NMR 75 MHz (CDCl$_3$)

δ 14.4, 20.9, 23.0, 54.7, 75.7, 126.0, 127.6, 128.3, 132.1, 134.3, 139.0, 140.5, 142.3; IR;

3502, 3298, 2980, 2939, 1601, 1564, 1452, 1402, 1333, 1316, 1154, 1135, 1083, 972

cm^{-1}.
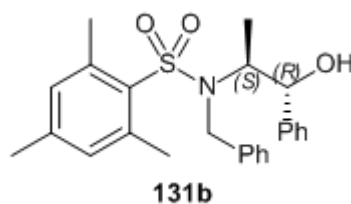
131b

(1R, 2S)-2-(N-Benzyl-N-mesitylenesulfonyl)amino-1-phenyl-1-propanol

(131b): A mixture of **131a** (9.8 g, 33 mmol), benzyl bromide (3.8 mL, 32 mmol), and

K$_2$CO$_3$ (4.9 g, 35 mmol) in CH$_3$CN (120 mL) was heated under reflux overnight. The

cooled mixture was filtered and the salt was washed with diethyl ether. The combined

filtrate and washes were concentrated, and the residue purified by flash chromatography

to afford **131b** as a white solid. Yield: 7.13 g, 51%; R_f = 0.31 (25% EtOAc/Hexane); mp

123-124 °C; $[\alpha]_D^{20}$ -5.2 (c 3.7, CHCl$_3$); ^{1}H NMR 300 MHz (CDCl$_3$) δ 1.03 (3H, d, J = 7.0

Hz), 2.14 (1H, -OH), 2.29 (3H, s), 2.65 (6H, s), 3.82 (1H, dq, J = 1.9 and 7.0 Hz), 4.54

(1H, A of AB, J_{AB} = 16.1 Hz), 4.77 (1H, B of AB, J_{AB} = 16.1 Hz), 5.00 (1H, br s), 6.93

(2H, s), 7.04-7.08 (2H, m), 7.10-7.36 (8H, m); ^{13}C NMR 75 MHz (CDCl$_3$) δ 10.1, 20.8, 22.9, 48.9, 59.5, 76.5, 125.4, 127.1, 127.2, 127.6, 128.0, 128.4, 132.0, 133.4, 138.6, 140.0, 142.2, 142.5; IR; 3510 (br), 3061, 2987, 2934, 1604, 1454, 1401, 1143, 1020 cm^{-1}.
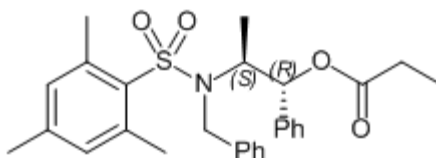
(1*R*, 2*S*)-2-(*N*-Benzyl-*N*-mesitylenesulfonyl)amino-1-phenyl-1-propyl

Propionate (131): Propionyl chloride (0.58 mL, 6.6 mmol) was added dropwise to a 0 °C

solution of **131b** (2.1 g, 5.0 mmol) and pyridine (0.52 mL, 6.4 mmol) in CH$_2$Cl$_2$ (30 mL).

The reaction was stirred at rt for 13 h and diluted with diethyl ether (300 mL). The

mixture was washed successively with 100 mL each of water, 1 M HCl, water, sat. aq.

NaHCO$_3$ and brine. The organic extract was then dried with anhydrous Na$_2$SO$_4$, filtered

and concentrated to give a crystalline residue, which was recrystallized from hot ethyl

acetate (4 mL/g of crude **131**) and hexane (ethyl acetate:hexane 1:2) to afford **131** as a

white solid. Yield: 1.96 g, 82%; R_f = 0.46 (25% EtOAc/Hexane); mp 146-149 °C; $[\alpha]_D^{20}$

11 (c 2.1, CHCl$_3$); ^{1}H NMR 400 MHz (CDCl$_3$) δ 1.04 (3H, t, *J* = 7.4 Hz), 1.15 (3H, d, *J*

= 7.0 Hz), 2.22 (1H, dq, *J* = 16.4 and 7.4 Hz), 2.14 (1H, dq, *J* = 16.4 and 7.4 Hz), 2.3 (3H,

s), 2.55 (6H, s), 4.08 (1H, dq, *J* = 3.9 and 7.0 Hz), 4.64 (1H, A of AB, J_{AB} = 16.6 Hz),

4.75 (1H, B of AB, J_{AB} = 16.6 Hz), 5.87 (1H, d, *J* = 3.9 Hz), 6.87 (2H, s), 6.88-6.96 (2H,

m), 7.13-7.35 (8H, m); ^{13}C NMR 100 MHz (CDCl$_3$) δ 8.5, 12.3, 20.6, 22.7, 27.1, 47.9,

56.5, 77.7, 125.6, 126.8, 127.1, 127.5, 128.1 (2C), 131.9, 133.2, 138.4, 138.5, 139.8,

142.3, 172.2; IR; 3030, 2983, 2941, 1746, 1604, 1454, 1420, 1324, 1152, 1020 cm^{-1}.

Enynal Preparation:

76
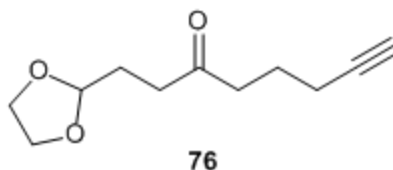
1-(1,3-Dioxolan-2-yl)-8-nonyn-4-one (76): To a solution of 3.0 g (27 mmol) 5-hexynoic acid and 2 drops of dry DMF in 89 mL dry CH_2Cl_2 was added oxalyl chloride (4.6 mL, 53 mmol) dropwise under an atmosphere of nitrogen. The reaction was stirred for 3 h and then the solvent was removed *in vacuo*. The residue was redissolved in 30 mL dry THF and the solution cooled to ca. $-40\ ^{\circ}C$ (dry ice/CH_3CN). To this was slowly added a $0\ ^{\circ}C$ solution of 2-(2-bromomagnesioethyl)-1,3-dioxolane (9.7 g, 3.6 mmol) in dry THF (70 mL). The reaction was allowed to warm to rt and then concentrated *in vacuo*. The oily residue was poured into water (100 mL). The combined ether extracts (2 x 100 mL) were washed with sat. aq. NH_4Cl and dried with Na_2SO_4. The residue obtained after concentration was purified by flash chromatography (silica, 30% EtOAc/Hexane) to afford the ketodioxolane **76** as a clear, colorless oil. Yield: 3.60 g, 68%; $R_f = 0.30$ (33% EtOAc/Hexane); ^1H NMR (CDCl$_3$) δ 4.88 (t, 1H, $J = 4.3$), 3.80-3.96 (4H, m), 2.55 (t, 2H, $J = 7.1$ Hz), 2.52 (t, 2H, $J = 7.3$ Hz), 2.20 (td, 2H, $J = 7.0$ and 2.6 Hz), 1.9 (1H, t, 2.6 Hz), 1.88 (2H, dt, $J = 4.3$ and 7.3 Hz), 1.70 (2H, quintet, $J = 7.0$ Hz); ^{13}C NMR (CDCl$_3$) δ 209.3, 103.2, 83.6, 68.9, 64.9, 41.0, 36.5, 27.5, 22.2, 17.7; IR 3282, 2940, 2888, 1712, 1412, 1374, 1139, 1102, 1034, 945, 891, 649 cm^{-1}.

77
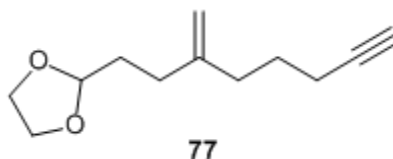
2-(3-Methylene-7-octynyl)-1,3-dioxolane (77): To a rt suspension of

methyltriphenylphosphonium bromide (16.3 g, 46 mmol) in 150 mL THF was slowly

added potassium bis (trimethylsilyl)amide (83 mL, 55 mmol, 15% w/v in toluene). The

reaction was stirred for 1 h, and then cooled to –78°C, whereupon a solution of ketone **76**

(6.0 g, 31 mmol) in THF (20 mL) was added dropwise. Once addition was complete, the

reaction was stirred for 10 min. and then allowed to warm to rt over 1 h. The reaction

solution was partitioned between water and ether and the aqueous layer extracted with

additional ether. The combined ether layers were dried with Na_2SO_4 and concentrated.

The residue was purified by flash chromatography (silica, 25% EtOAc/Hexane) to afford

the alkenyl dioxolane **77** as a clear, colorless oil. Yield: 2.53 g, 42%; R_f = 0.36 (25%

EtOAc/Hexane); ^{1}H NMR (CDCl_3) δ 4.85 (t, J = 4.7, 1H), 4.74-4.75 (2H, m), 3.79- 3.99

(4H, m), 2.19 (2H, dt, J = 2.7 and 7.1 Hz), 2.17-2.11 (4H, m), 1.94 (t, 1H, J = 2.7), 1.70-

1.80 (2H), 1.61-1.69 (2H); ^{13}C NMR (CDCl_3) δ 147.8, 109.6, 104.1, 84.2, 68.4, 64.8,

35.0, 32.0,30.0,26.4, 17.9; IR 3292, 3078, 2947, 2882, 2117, 1645, 1443, 1410, 1133,

1073, 1035, 944, 894 cm^{-1}.
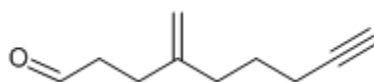
4-Methylenenon-8-ynal (2.7): Dioxolane **77** (3.5 g, 18 mmol) was dissolved in

1:1 3M. HCl/THF (30 mL). The reaction was stirred at rt for 10 h and then diluted with

50 mL water. The combined ether extracts (2 x 70 mL) were washed with sat. aq.

NaHCO$_3$ and water and then dried with Na$_2$SO$_4$. The crude aldehyde **77a** obtained after concentration was used without further purification. ^{1}H NMR (CDCl$_3$) δ 9.6 (1 H, t, J = 1.6 Hz), 4.6-4.5 (2 H, m), 2.39 (2 H, dt, J = 1.6 Hz and 7.6 Hz), 2.1 (2 H, br t, J = 7.5 Hz), 1.99 (2 H, dt, J = 2.6 and 7.1 Hz), 1.94 (2 H, br t, J = 7.9 Hz), 1.8 (1H, t, J = 2.6 Hz), 1.5-1.4 (2 H, m but overall quintet J ~ 7.4 Hz); ^{13}C NMR (CDCl$_3$) δ 201.9, 146.6, 110.1, 84.0, 68.7, 41.7, 35.0, 27.9, 26.3, 17.8.

132
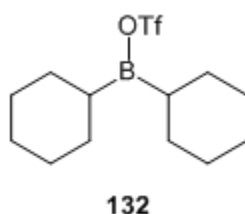
Dicyclohexyl(trifluoromethylsulfonyloxy)borane (132): Diethyl ether (33 mL) and cyclohexene (13.6 mL, 134 mmol) were added to a weighed 250 mL flame dried round bottom flask with a stir bar under nitrogen. Borane dimethylsulfide complex (5.3 mL, 56 mmol) was then added dropwise to the solution after which a white solid formed. The reaction was allowed to stir for 1 h and then allowed to stand until the solid settled. Most of the solvent was removed with a syringe. The remaining solvent was removed by high vac. The solid was then suspended in dry hexane and trifluoromethanesulfonic acid was added slowly with a glass syringe through a Teflon needle. The solution was stirred for 2 h and then allowed to stand resulting in the formation of two layers. The bottom yellow oil was removed as much as possible by syringe and the flask placed into a freezer overnight for crystallization. The remaining solvent was removed from the white crystals by syringe and the solid washed with cold hexane and dried by high vac. Finally, the solid (**132**) was dissolved in dry hexane to make a 1 M solution. Yield: 62%.

133
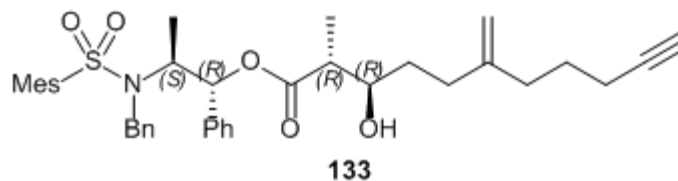
(2*R*, 3*R*)-((1*R*, 2*S*)-2-(N-benzyl-2,4,6-trimethylphenylsulfonamido)-1-phenylpropyl)-3-hydroxy-2-methyl-6-methyleneundec-10-ynoate (133)

Into an oven-dried 250 mL round-bottom flask under nitrogen was added (1*R*, 2*S*)-2-(N-Benzyl-N-mesitylenesulfonyl)amino-1-phenyl-1-propyl propionate (**131**) (3.1 g, 6.5 mmol) and 40 mL CH$_2$Cl$_2$. To this solution was added Et$_3$N (2.2 mL, 16 mmol) via syringe. The solution was cooled to -78 °C and a solution of dicyclohexylboron triflate (**132**) (1.0 M in hexane, 13 mL, 13 mmol) was added dropwise over 15 min.. The resulting solution was stirred at -78 °C for 2 h. Crude 4-methylenenon-8-ynal (**77a**) (1.2 g, 7.9 mmol) in 5 mL CH$_2$Cl$_2$ was added dropwise to the enol boronate solution. The reaction mixture was stirred for 1 h at -78 °C and was allowed to warm to rt over 1 h, then quenched by addition of 0.1 M pH 7 phosphate buffer solution (24 mL). The mixture was diluted with 120 mL methanol, after which, 30% H$_2$O$_2$ (12 mL) was added carefully. The resulting suspension was stirred vigorously overnight and then concentrated. The residue was partitioned between water (50 mL) and CH$_2$Cl$_2$ (100 mL). The aqueous layer was extracted with CH$_2$Cl$_2$ (75 mL x2). The combined organic layers were washed with water (60 mL x 3) and dried with Na$_2$SO$_4$. The filtered organic layer was concentrated and the residue was purified by flash chromatography using 15%-25% EtOAc/Hexane as the eluting solvent to afford **133** as a clear semisolid oil. Yield: 3.23 g, 79%; R_f = 0.33 (25% EtOAc/Hexane); $[\alpha]_D^{20}$ 19.5 (c 0.87, CHCl$_3$); ^{1}H NMR (CDCl$_3$)

δ 1.15 (3H, d, J = 7.3Hz), 1.19 (3H, d, J = 7.0 Hz), 1.49-1.69 (4H, m), 1.95 (1H, t, J = 2.6

Hz), 2.03-2.25 (4H, m), 2.18 (2H, td, J = 7.1 and 2.6 Hz), 2.28 (3H, s), 2.43-2.52 (1H, m),

2.49 (6H, s), 2.55 (1H, d, J = 6.8 Hz), 3.61-3.67 (1H, dtd, J = 3.5, 6.8, 9.5 Hz), 4.11-4.15

(1H, dq, 4.0 and 6.9 Hz), 4.54 (1H, B of AB, J_{AB} = 16.5 Hz), 4.75 (1H, A of AB, J_{AB} =

16.5 Hz), 4.75 (2H, s), 5.86 (d, 1H), 6.87 (2H, s), 6.88-6.90 (2H, m), 7.17-7.30 (8H, m);

^{13}C NMR (CDCl$_3$) δ 174.5, 148.2, 142.6, 140.3, 138.4, 138.2, 133.4, 132.1, 128.5, 128.4,

128.0, 127.7, 127.2, 126.0, 109.9, 84.3, 78.3, 72.8, 68.5, 56.8, 48.2, 45.5, 35.0, 32.4, 31.8,

26.5, 23.0, 21.0, 18.0, 14.1, 13.5; IR: 3532, 3299, 3031, 2981, 2942, 1737, 1604, 1454,

1381, 1321, 1153, 1013, 858, 757, 699, 659 cm^{-1}.

134
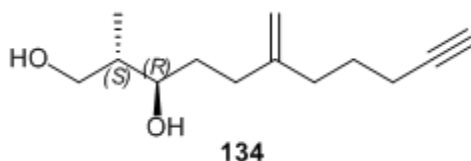
(2*S*, 3*R*)-2-Methyl-6-methyleneundec-10-yne-1,3-diol (134). To a stirred

solution of the propionate ester (**133**) (2.6 g, 4.2 mmol) in THF (40 mL) was added

lithium aluminum hydride (0.19 g, 5.0 mmol) at 0 °C. The reaction mixture was stirred at

rt for 1 h and then quenched by the careful addition of Na$_2$SO$_4$•10 H$_2$O. The mixture was

stirred vigorously for 30 min. and filtered. The residue obtained upon concentration was

resuspended in hexane (60 mL) and then filtered, resulting in recovery of the auxiliary

alcohol. The residue obtained upon concentration of the filtrate was separated by

chromatography with 1:1 ethyl acetate and hexane to afford the 1,3-diol (**134**) as a clear,

colorless oil. Yield: 0.79 g, 90%; R_f = 0.27 (50% EtOAc/Hexane); $[\alpha]_D^{20}$ 31.7 (c 1.1,

CHCl$_3$); ^{1}H NMR (CDCl$_3$) δ 4.79 (1H, s), 4.77 (1H, s), 3.77 (1H, dd, J = 3.7 and 10.8 Hz),

3.55-3.64 (2H, m), 2.90 (2H, br s), 2.04-2.22 (6H, m), 1.95 (1H, t, J = 2.6 Hz), 1.53-1.77

(5H, m), 0.89 (3H, d, J = 7.0 Hz); ^{13}C NMR (CDCl$_3$) δ 148.6, 109.7, 84.3, 76.9, 68.5,

67.5, 39.8, 34.8, 33.2, 31.7, 26.4, 17.9, 13.8; IR: 3302 (br), 2939, 1644, 1432, 1275, 1026

cm^{-1}.
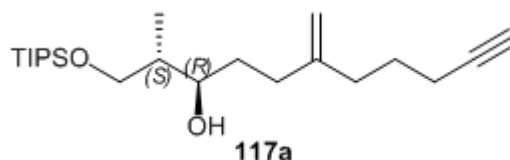
(2S, 3R)-2-Methyl-6-methylene-1-(triisopropylsilyloxy)undec-10-yn-3-ol

(117a). Diol, **(134),** (0.55 g, 2.6 mmol) was dissolved in CH$_2$Cl$_2$ (15 mL) and cooled to

0 °C. To this solution was added Et$_3$N (0.44 mL, 3.2 mmol), DMAP (32 mg, 0.26 mmol),

and triisopropylsilyl chloride (0.61 mL, 2.9 mmol) sequentially. This mixture was

warmed to rt and stirred for 15 h, and then quenched with sat. aq.. NH$_4$Cl. The aqueous

phase was extracted with Et$_2$O, and the combined organic extracts were dried with

Na$_2$SO$_4$, filtered, and concentrated in *vacuo*. The resulting crude material was purified by

column chromatography using 5% EtOAc/Hexane to afford the silyl ether (**117a**) as

colorless oil. Yield: 0.753 g, 79%; R_f =0.44 (10% EtOAc/Hexane); $[\alpha]_D^{20}$ 25.1 (c 1.2,

CHCl$_3$); ^{1}H NMR (CDCl$_3$) δ 0.85 (3H, d, J = 7.0 Hz), 1.03-1.15 (21H), 1.49-1.76 (5H),

1.92 (1H, t, J = 2.6 Hz), 2.02-2.29 (6H, m), 3.54 (1H, m), 3.66 (1H, dd, J = 7.7 and 9.9

Hz), 3.88 (1H, dd, J = 3.9 and 9.9 Hz), 3.97 (1H, d, 3.0 Hz), 4.72 (1H, s), 4.76 (1H, s);

^{13}C NMR (CDCl$_3$) δ 148.9, 109.2, 84.4, 76.5, 69.1, 68.3, 39.6, 35.1, 33.4, 31.5, 26.5,

17.94, 17.89, 13.7, 11.7; IR: 3439 (br), 3314, 2943, 2886, 1645, 1463, 1386, 1276, 1261,

1062, 996, 883, 797 cm^{-1}.

117
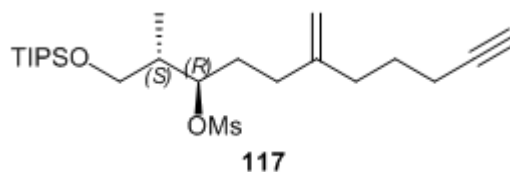
(2*S*, 3*R*)-2-Methyl-6-methylene-1-(triisopropylsilyloxy)undec-10-yn-3-
ylmethanesulfonate (117). Silyl ether (117a) (0.70 g, 1.9 mmol) was dissolved in

CH_2Cl_2 (10 mL) and the solution was cooled to 0 °C. After the addition of Et_3N (0.32

mL, 2.3 mmol) and MsCl (0.18 mL, 2.3 mmol), the reaction mixture was allowed to

warm to rt and stirred for 14 hs. The reaction mixture was diluted with CH_2Cl_2 and then

washed with sat. aq. NH_4Cl and brine and dried with Na_2SO_4. Crude mesylate obtained

upon concentration was purified by 10% EtOAc/Hexane to afford the mesylate (117).

Yield: 0.676 g, 80%; $R_f = 0.26$ (10% EtOAc/Hexane); $[\alpha]_D^{20}$ 7.0 (c *0.97*, $CHCl_3$); ^1H

NMR ($CDCl_3$) δ 0.97 (3H, d, *J* = 7.0 Hz), 1.04-1.11 (21H), 1.62-1.1.70 (2H), 1.77-1.89

(2H), 1.94 (1H, t, *J* = 2.6 Hz), 2.03-2.27 (7H), 3.00 (3H, s), 3.63 (1H, s), 3.65 (1H, s),

4.78 (2H, s), 4.89 (1H, dt, *J* = 3.9 and 8.8 Hz); ^{13}C NMR ($CDCl_3$) δ 147.5, 110.1, 85.1,

84.2, 68.5, 65.0, 39.7, 38.6, 34.9, 31.6, 28.4, 26.5, 18.0, 17.7, 11.9, 11.6; IR: 3312, 2943,

2893, 2866, 1646, 1463, 1336, 1175, 1109, 908, 884, 795, 678 cm^{-1}.

116
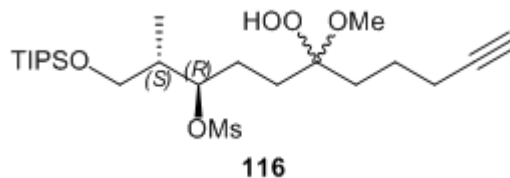
6-Hydroperoxy-6-methoxy-2-methyl-1-(triisopropylsilyloxy)undec-10-yn-3-
ylmethanesulfonate (116). A stream of O_3/O_2 was bubbled into a solution of mesylate

(117) (0.99 g, 2.2 mmol) in 19 mL methanol and 61 mL CH_2Cl_2 cooled to –78 °C. The

reaction was monitored by TLC until the starting material was absent, then, sparged with

N$_2$. The solution was allowed to warm to rt and concentrated in *vacuo.* The residue was

purified by column chromatography using 30% EtOAc/Hexane to afford 0.85 g product

as an approximate 1:1 mixture of diastereomers that were carried on to the next step.

Yield: 0.85g, 77 %. $R_f = 0.27$ (33% EtOAc/Hexane); **116R** (2*S*, 3*R*, 6*R*); ^{1}H NMR

(CDCl$_3$) δ 7.61 (1H, s), 4.87-4.91 (1H, m), 3.68 (1H, s), 3.66 (1H, s), 3.32 (3H, s), 3.04

(3H, s), 2.18-2.28 (3H, m (contains 2H, dt, *J* = 2.6 and 6.7 Hz at 2.27 ppm)), 1.99 (1H, t,

J = 2.6Hz), 1.90-1.98 (1H, m), 1.72-1.82 (5H, m), 1.50-1.63 (3H, m), 1.03-1.14 (21H, m),

0.98 (3H, d, *J* = 7.0Hz). **116S** (2*S*, 3*R*, 6*S*); ^{1}H NMR (CDCl$_3$) δ 8.08 (1H, s), 4.91-4.95

(1H, m), 3.69 (1H, s), 3.68 (1H, s), 3.34 (3H, s), 3.05 (3H, s), 2.14-2.28 (3H, m (contains

2H, dt, *J* = 2.6 and 6.7 Hz at 2.26 ppm)), 1.88-2.0 (3H, m (contains 1H, t, *J* = 2.6 Hz)),

1.66-1.80 (4H, m), 1.50-1.63 (3H, m), 1.03-1.14 (21H, m), 0.98 (3H, d, *J* = 7.0 Hz); [13]C

NMR (CDCl$_3$) δ 108.2, 108.0, 84.8, 84.3, 83.8, 83.7, 77.2,77.3, 69.0, 68.9, 48.7, 48.6,

39.6, 39.2, 38.7, 38.5, 29.6, 29.0, 27.0 24.8 24.6, 22.61, 22.60, 18.41, 18.40, 18.0, 12.1,

11.9, 11.8.
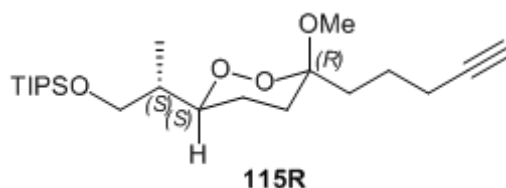
115R

(2*S*)-1-Triisopropylsiloxy-2-((3*S*,6*R*)-6-methoxy-6-(pent-4-ynyl)-1,2-dioxan-3-yl)propane (**115R**). To a solution of diastereomeric mixture of hydroperoxy acetals

(44.2 mg, 0.9 mmol) in anhydrous toluene (12 mL) was added 18-crown-6 (226.5 mg, 0.9

mmol), followed by KO*t*-Bu (91.6 mg, 0.8 mmol). The reaction mixture was stirred for

20 min., at which point additional KO*t*-Bu (91.9 mg, 0.8 mmol) was added. After an

additional 20 min., TLC indicated the disappearance of the starting material and the

solution had turned yellow. The crude reaction mixture was filtered through a short pad

of silica gel with 20% EtOAc/hexane. The filtrate was concentrated and the residue was

purified by column chromatography using 5% EtOAc/Hexane to afford 1,2 dioxane,

115R. Yield: 161mg, 47%; R_f = 0.36 (5% EtOAc/Hexane); $[\alpha]_D^{20}$ -144 (c 0.74, CHCl$_3$);

^{1}H NMR (CDCl$_3$): δ 4.05 (1H, ddd, *J* = 1.9, 6.3, 11.0 Hz), 3.68 (1H, dd, *J* = 5.2 and 9.8

Hz), 3.63 (1H, dd, *J* = 5.6 and 9.8Hz), 3.28 (3H, s), 2.19-2.24 (2H, m), 1.96 (1H, t, *J* =

2.6 Hz), 1.41- 1.92 (9H, m), 1.03-1.13 (21H, m), 1.01 (3H, d, *J* = 6.9Hz); ^{13}C NMR

(CDCl$_3$): δ 102.3, 83.8, 81.7, 68.8, 65.1, 48.4, 39.7, 31.9, 30.7, 22.9, 22.1, 18.5, 18.0,

12.7, 12.0; IR: 3312, 2943, 2866, 1462, 1238, 1109, 1066, 917, 882, 789, 746, 682 cm^{-1}.

One Pot Ozonolysis/Cyclization Method: (2*S*)-1-Triisopropylsiloxy-2-((3*S*,

6*R,S*)-6-methoxy-6-(pent-4-ynyl)-1,2-dioxan-3-yl)propane (115R,S). Mesylate **117**

(0.6811 g, 1.5 mmol) was dissolved in 20 mL CH$_2$Cl$_2$ and methanol (7.8 mL, 193 mmol).

The solution was cooled to –78 ^{o}C and treated with a stream of O$_3$/O$_2$. The reaction was

monitored by TLC until starting material was absent. The reaction mixture was then

sparged with nitrogen and allowed to warm to rt. To this solution was added 18-crown-6

(396.8 mg, 1.5 mmol), followed by KO*t*-Bu (154.2 mg, 1.4 mmol). The reaction mixture

was stirred for 20 min., at which point additional KO*t*-Bu (170.5 mg, 1.5 mmol) was

added. After an additional 20 min., TLC indicated the disappearance of the starting

material and the solution appeared yellow. The crude reaction mixture was filtered

through a short pad of silica gel with 20% EtOAc/hexane. The filtrate was concentrated

and the residue was purified by column chromatography using 5% EtOAc/Hexane to

afford the product as an approximate 1:1 mixture of diastereomers. Yield: 0.448 g, 75%.
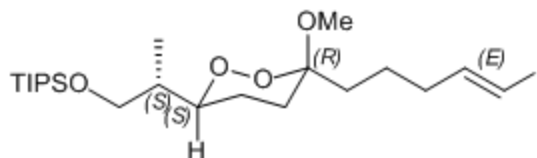
(2S)-1-Triisopropylsiloxy-2-((3S, 6R)-6-methoxy-6-((4E)-4-iodopent-4-enyl)-1,2-dioxan-3-yl)propane (**135**). 1,2-Dioxane **115R** (0.43 g, 1.1 mmol), azeotropically dried by concentration from distilled toluene (2x15 mL), was dissolved in 10 mL dry toluene. To this solution was added Cp$_2$ZrHCl (0.38 g, 1.5 mmol) under a nitrogen atmosphere. After stirring for 15 min., the solution became light orange in color. Another portion of Cp$_2$ZrHCl (0.21 g, 0.8 mmol) was added and the reaction mixture was stirred for another 15 min.. Sublimed iodine (0.41 g, 1.6 mmol) was added slowly until the dark red color became permanent. The reaction mixture was diluted with 50 mL hexane, and filtered through Celite. The filtrate was washed with sat. aq. Na$_2$S$_2$O$_3$, dried with Na$_2$SO$_4$ and concentrated. The residue was purified by column chromatography using 5-10% EtOAc/Hexane to afford a mixture of the terminal alkene reduction product (due to water) and the desired terminal E-iodoalkene (**135**) which could be separated by semi-prep HPLC (EtOAc/Hex). Yield: 0.469 g, 81%. R_f = 0.32 (5% EtOAc/Hexane); $[\alpha]_D^{20}$ -97.2 (c 0.94, CHCl$_3$); ^{1}H NMR (CDCl$_3$) δ 6.48 (1H, dt, J = 14.4 and 7.1 Hz), 6.01 (1H, dt, J = 14.4 and 1.3 Hz), 4.01-4.06 (1H, m), 3.67 (1H, dd, J = 5.2 and 9.9 Hz), 3.63 (1H, dd, J = 5.6 and 9.9 Hz), 3.24 (3H, s), 2.03-2.08 (2H, m), 1.82-1.92 (2H, m), 1.24-1.67 (7H, m), 1.03-1.12 (21H, m), 1.00 (3H, d, J = 6.9 Hz); ^{13}C NMR (CDCl$_3$) δ 145.7, 102.3, 81.7, 75.2, 65.0, 48.4, 39.6, 36.0, 32.1, 30.7, 22.9, 21.8, 18.0, 12.7, 11.9; IR: 2942, 2865, 1462, 1234, 1110, 1070, 1030, 946, 882, 788, 683, 659 cm^{-1}.
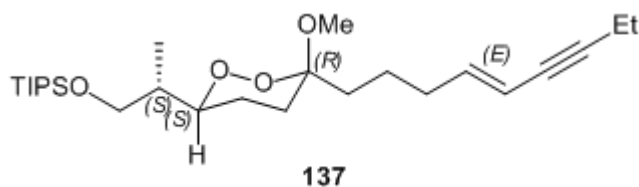
(2S)-1-triisopropylsiloxy-2-((3S, 6R)-6-methoxy-6-((4E, 6E)-nona-4-en-6-ynyl)-1,2-dioxan-3-yl)propane (137)

1-Butyne (0.12 g, 2.2 mmol) was condensed into a 50 mL flask at –78 °C under a N_2 atmosphere, and dissolved in distilled THF (4 mL) and distilled toluene (4 mL). The solution was warmed slowly to 0 °C, whereupon Cp_2ZrHCl (0.22 g, 0.85 mmol) was added. The reaction was held at 0 °C for 1 h, after which another portion of Cp_2ZrHCl (0.10 g, 0.39 mmol) was added. The reaction mixture was stirred for another hour at 0 °C after which the ice bath was removed. After 10 min., the solution was cooled to 0 °C again and $ZnCl_2$ (0.12 g, 0.88 mmol) in 2 mL dry THF was added. The reaction solution turned orange and was stirred at 0 °C for 10 min.. Vinyl iodide (**135**) (0.16 g, 0.30 mmol) was added, followed by $Pd(PPh_3)_4$ (45 mg, 0.04 mmol). The reaction was stirred at 0 °C for 5 min.. TLC indicated the presence of a significant amount of starting material, and another portion of $Pd(PPh_3)_4$ (15 mg, 0.01 mmol) was added. The reaction mixture was stirred at 0 °C for another half an h at which point TLC indicated the absence of starting material. The reaction was diluted with 20 mL hexane, and the reaction mixture was filtered through a short pad of silica gel with 30% EtOAc/Hexane. The filtrate was concentrated in *vacuo* and the residue was purified by flash chromatography (5% EtOAc/Hexane) to give 0.13 g crude product. NMR analysis of the crude product revealed that it is a mixture of

desired diene product and terminal alkene product from reduction of the vinyl iodide.

These two compounds were inseparable even with HPLC. However, the coupled and

reduced products were separable after removal of the TIPS ether (next step). ^{1}H

NMR (CDCl$_3$): δ 6.02 (1H, dt, J = 7.0, 15.7 Hz), 5.48 (1H, dquintets, J = 15.7, J = 2.0

Hz), 4.05 (1H, ddd, J = 11.3, 6.2, 2 Hz), 3.70 (1H, H$_{AB}$, dd, J = 9.8 Hz, 5.2) 3.65 (1H,

H$_{AB}$, dd, J = 9.8, 5.5 Hz), 3.27 (3H, s), 2.31 (2H, 2dq, J = 2.0, 7.5), 2.11 (2H, br q, J =

6.7 Hz), 2.0-1.23 (9 H), 1.17 (3H, t, J = 7.5 Hz), 1.11-1.05 (21 H) 1.03 (3H, d, J = 7.0

Hz);^{13}C NMR (CDCl$_3$) δ 142.1, 110.5, 102.5, 90.4, 81.7, 78.3, 65.1, 48.4, 39.7, 32.9,

32.3, 30.7, 22.9, 22.3, 18.0, 13.9, 13.0, 12.7, 11.9.
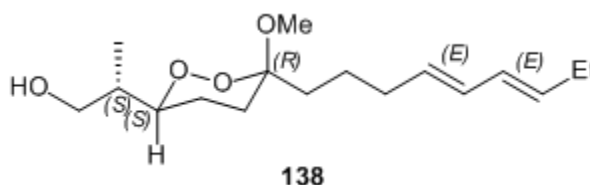
((2S)-2-((3S, 6R)-6-methoxy-6-((4E, 6E)-nona-4,6-dienyl)-1,2-dioxan-3-yl)

propan-1-ol (138)

A mixture of diene (**136**) and terminal alkene (**135a**) from the previous step was

dissolved in THF, at rt, TBAF (1M) was added dropwise to the solution until TLC

indicated the disappearance of the starting material. The reaction mixture was washed

with saturated ammonium chloride solution and water sequentially. Then the separated

organic layer was dried with Na$_2$SO$_4$, concentrated. The residue was first purified by

flash chromatography, and then by HPLC. The desired deprotected diene product (**138**)

was very easily isolated by HPLC. ^{1}H NMR (CDCl$_3$): δ 5.95-6.06 (2H, m), 5.49- 5.66

(2H, m), 4.10-4.14 (1H, m), 3.54-3.70 (m, 2H), 3.25 (3H, s), 2.04-2.20 (4H, m), 1.82-

2.01 (3H, m), 1.25-1.72 (6H, m), 0.99 (3H, t, J = 7.4 Hz), 0.96 (3H, d, J = 7.2 Hz); ^{13}C

NMR (CDCl$_3$) δ 134.5, 131.2, 131.0, 129.1, 102.8, 82.5, 65.1, 48.4, 39.1, 32.5, 32.2, 30.5,

25.6, 22.7, 21.6, 13.6, 11.9.

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