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OSMIUM TETROXIDE AND OXONE: DEVELOPMENT OF AN ORGANOMETALLIC OZONOLYSIS REACTION, NOVEL OXIDATIVE METHODS AND PROGRESS TOWARDS AMPHIDINOLIDE T1.

presented by

Benjamin Ross Travis

has been accepted towards fulfillment
of the requirements for the

Ph.D. degree in Organic Chemistry

Major Professor's Signature

8/23/04

Date

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By

Benjamin Ross Travis

A DISSERTATION

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ABSTRACT

OSMIUM TETROXIDE AND OXONE: DEVELOPMENT OF AN ORGANOMETALLIC OZONOLYSIS REACTION, NOVEL OXIDATIVE METHODS AND PROGRESS TOWARDS AMPHIDINOLIDE T1.

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Numerous oxidative and reductive processes are reported in literature. However, when it comes to oxidatively cleaving olefins to form aldehydes, ketones, carboxylic acids or esters, there are two primary methodologies, i) Transform the olefin into a 1,2 diol followed by cleavage with $NaIO_4$ (or other oxidants),[1,2] or ii) Ozonolysis, in which the olefin is directly transformed into a variety of functionalized products depending on the workup conditions.[3,4] We have now developed a methodology that mimics ozonolysis; i.e., directly oxidize and cleave an olefinic bond to yield carbonyl compounds.

We have pursued this goal using metal catalysts capable of activating the C-C scission under very mild conditions. Our results to date have been promising in terms of achieving the set goals. Osmium tetroxide mediated oxidative cleavage of olefins with Oxone ($2KHSO_5{\bullet}KHSO_4{\bullet}K_2SO_4$) as the preferred co-oxidant has led to oxidative cleavage of vinyl groups to yield aldehydes, carboxylic acids, methyl esters and lactones.[5,6] Additionally, we have investigated the purification of the Oxone triple salt to $KHSO_5$,[7] which has been invaluable for our kinetic studies of the aldehyde oxidation to prepare carboxylic acids and esters.[8] The oxidative cleavage methodology has now been applied to the total synthesis of tanikolde[9] and erythromycin B[10] and is currently a key step in our approach to amphidinolide T1.

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For Heather, Matthew, and Lucy

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defense. His name is Matthew Ross Travis and is the most precious thing in the world. My family (Heather, Matthew, and Lucy (the St. Bernard)) is what brings joy into my life and is the reason I could finish this thesis with my sanity intact.

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LIST OF ABBREVIATIONS

Å	angstrom
AA	arachidonic acid
Ac	acetyl
ACN	acetonitrile
AD	asymmetric dihydroxylation
Ar	Aryl
aq	aqueous
Bp	dihydrobispyrazolylborate
CH_2Cl_2	dichloromethane
CI	chemical ionization
CSA	camphorsulfonic acid
Cy	cyclohexyl
DBU	1,8-diazabicyclo[5,4,0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
de	diasteromeric excess
DI	deionized
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminum hydride
DIPEA	diisopropylethyl amine
DMAP	4-(dimethylamino)pyridine
DMDO	dimethyl dioxirane

DME	dimethoxyethane
DMF	N,N-dimethylformamide
DMP	dess-martin periodinane
DMSO	dimethyl sulfoxide
ED_{50}	Effective Dose to 50 percent
ee	enantiomeric excess
EI	electric ionization
eq	equation
equiv	equivalent
FAB	fast atom bombardment
GC	gas chromatography
h	hour
HMPA	hexamethyl phosphoramide
HRMS	high resolution mass spectrometry
HWE	Horners-Wadsworth-Emmons reaction
IBX	2-iodoxybenzoic acid
KHMDS	potassium bis(trimethylsilyl)amide
LiHMDS	lithium bis(trimethylsilyl)amide
*m*CPBA	*m*-chloroperbenzoic acid
Mes	mesityl
mL	milliliter
ML	methyl lineolate
mmol	millimole

MS	mass spectrometry
NaHMDS	sodium bis(trimethylsilyl)amide
NBS	N-bromosuccinimide
NMM	*n*-methylmorpholine
NMO	*n*-methylmorpholine-*n*-oxide
NMR	nuclear magnetic resonance
NMP	N-methyl-2-pyrrolidinone
NOE	nuclear Overhauser effect
OsO_4	osmium tetroxide
Ph	phenyl
PMB	p-methoxybenzyl
PPTS	pyridinium para-toluenesulfonate
PTSA	*p*-toluenesulfonic acid
RT	room temperature
TBAF	tetrabutylammonium fluoride
TBA-OX	tetra-*n*-butylammonium peroxymonosulfate
TBS	*t*-butyldimethylsilyl
THF	tetrahydrofuran
THP	tetrahydropyran
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl

Chapter 1. Osmium Tetroxide and Oxone: A Brief Review

1.1. Introduction

Over the past twenty-five years in organic chemistry an enormous amount of progress has been achieved. This includes numerous modifications for existing processes to make them milder, higher yielding, and cheaper not to mention catalytic and/or asymmetric. At the outset of the Ph.D. research that will be discussed herein we realized the obvious, oxidations and reductions are key reactions for organic chemists. In particular, our laboratory had an interest in oxidative chemistries to prepare 2,3,5-trisubstituted tetrahydrofuran (2,3,5-THF) diols, which are known metabolites of arachidonic acid (AA) metabolism. Additionally, an example of a natural product that contains such a substitution pattern exists in a class of compounds known as the *Anneaceous* acetogenins, specifically mucoxin (See Chapter 2).

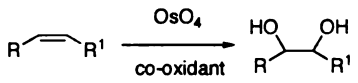
We were interested in examining various oxidative processes including chromium oxidations of alcohols and aldehydes (Jones, PCC, PDC, etc), hydroxylations, dihydroxylations, aminohydroxylations, epoxidations, aziridinations, metal assisted oxidative cleavage of alkenes and alkynes, the oxidative cleavage of diols, and ozonolysis.[11-20] We believed that the importance of these reactions cannot be overstated, and that the need for new, more efficient, and milder reactions with unique properties would only increase the repertoire of tools organic chemists could use to tackle the syntheses of complex molecules on both laboratory and industrial scales or for high valued commodities and pharmaceuticals. It is with these ambitious aims that we approach organic synthesis methodology.

The question, however, was with what approach we should tackle our specific problem: An efficient way to prepare 2,3,5-trisubstitutedtetrahydrofuran diols. Our answer to this question has led us down a wandering path that has allowed for the development of methodologies in several areas and focuses on two reagents, osmium tetroxide (OsO_4) and Oxone® ($2KHSO_5 \bullet KHSO_4 \bullet K_2SO_4$). These reagents, when used in conjunction, allow unique reactions to proceed with unexpected ease. It is interesting to note that individually, both OsO_4 and $KHSO_5$ (the active peroxysulfate portion of Oxone) have had an interesting history of discovery and implementation and as such will be reviewed briefly throughout the remainder of this chapter.

1.2. Osmium Tetroxide

Osmium tetroxide has long been known for its reactivity towards unsaturated species to provide *cis*-diols.[1,2] Hofmann first demonstrated this using catalytic OsO_4 with sodium or potassium chlorate to dihydroxylate alkenes, and Milas later extended this work by demonstrating that hydrogen peroxide is also an effective oxidant for this process (Scheme I-1).[21-23]

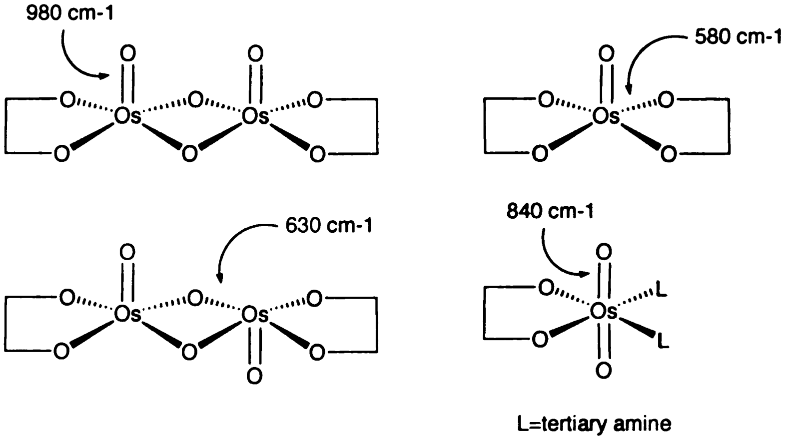
Scheme I-1. Dihydroxylation of olefins with osmium tetroxide



R and R^1 = numerous possibilities
Co-oxidant = $KClO_3$, H_2O_2, *t*BuOOH,
NMO, $NaClO_4$, oxygen, $NaIO_4$, $K_3Fe(CN)_6$

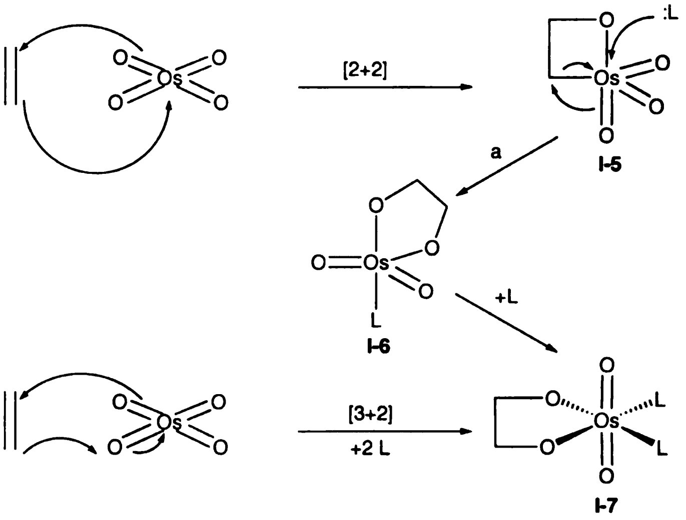
Criegee was the first to demonstrate that the dihydroxylation pathway was directly linked to OsO_4 by performing stoichiometric reactions to generate diols.[24,25] He suggested that osmium(VI) ester complex was an intermediate, which could either be hydrolyzed directly to yield OsO_3 or reoxidized to the osmium(VIII) ester. The osmium(VI) ester complex is generally green and has infrared bands near 980 cm^{-1} (Os=O stretching), 580 cm^{-1}, and 630 cm^{-1} (Os—O stretching) (Figure I-1). Crystal structures have revealed three predominate forms of osmate esters, two are dimeric monoesters and the other is a diester. All of these osmate ester forms predominate in a square pyramidal geometry. The addition of tertiary amines has been shown to increase the rate of osmate ester formation, and the resultant crystals are typically brown, octahedral complexes. Here the O=Os=O asymmetric stretching frequency is typically near 840 cm^{-1} (Figure I-1). Many related osmium crystal structures, along with numerous examples of normal dihydroxylation, have now been reviewed in the literature.[26,27]

Figure I-1. Typical osmate ester structures and typical IR stretching bands



While the intermediacy of an osmate ester has not been the subject of debate in dihydroxylation chemistry, the route by which the osmate is formed has been. The two schools of thought have been either a direct [3+2] cycloaddition[28,29] or a [2+2] cycloaddition followed by ring expansion. Sharpless *et al* in 1977 initially favored the [2+2] cycloaddition pathway based upon the observation that nucleophilic attack upon carbonyls occurs on carbon, not oxygen. Thus, by analogy, the more electropositive osmium center should favor attack (Scheme I-2).[30,31] Additionally, metallocyclobutanes are well known in olefin metathesis chemistry.[31-34] The differences in the two pathways potentially explain the differences in rate of dihydroxylation in the presence or absence of a tertiary amine whereby the ligand could potentially promote the osmium-carbon bond cleavage and the subsequent ring expansion. Twenty years later, Houk, Singleton, Sharpless *et al* essentially recounted the [2+2] cycloaddition pathway after comparing high-precision experimental kinetic isotope effects with high-level transition structure calculations in which their experimental results match quite favorably with their calculations with a [3+2] mechanism and not the [2+2] osmaoxetane or the ring expansion.[35]

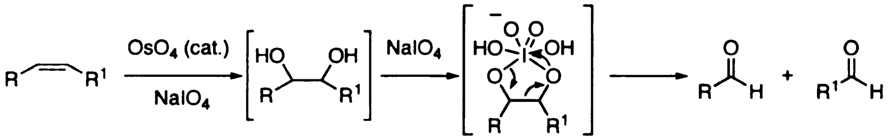
Scheme I-2. Initial cycloaddition—[2+2] versus [3+2]



a) Possible route of interconversion from osmaoxetane (**I-5**) to osmate ester (**I-7**)

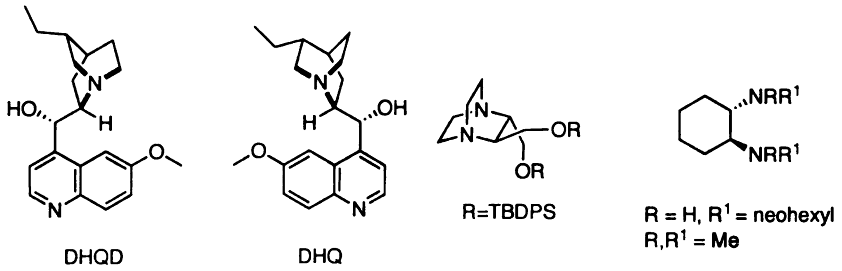
In addition to hydrogen peroxide and potassium chlorate, various other oxidants are effective co-oxidants including *t*BuOOH, NMO, $NaClO_4$, oxygen, $NaIO_4$ and $K_3Fe(CN)_6$ (Scheme I-1).[21,22,36-43] Selectivity and over oxidation are known problems of the *cis*-dihydroxylation process but can generally be avoided by the appropriate choice of oxidant, solvent, and reaction temperature. In the case of $NaIO_4$, this over oxidation is most prominent and is referred to as the Lemieux-Johnson reaction (Scheme I-3).[44,45] Here, in one pot, the normal resultant diol can independently be oxidatively cleaved into two respective aldehydes. Unfortunately, the $NaIO_4$ reaction is not selective for just the newly formed diol but for any diol present in the molecule, making prior protection of vicinal diols a necessity. In addition, further over oxidation (to carboxylic acids) makes this reaction less desirable.

Scheme I-3. Lemieux-Johnson oxidative cleavage of olefins



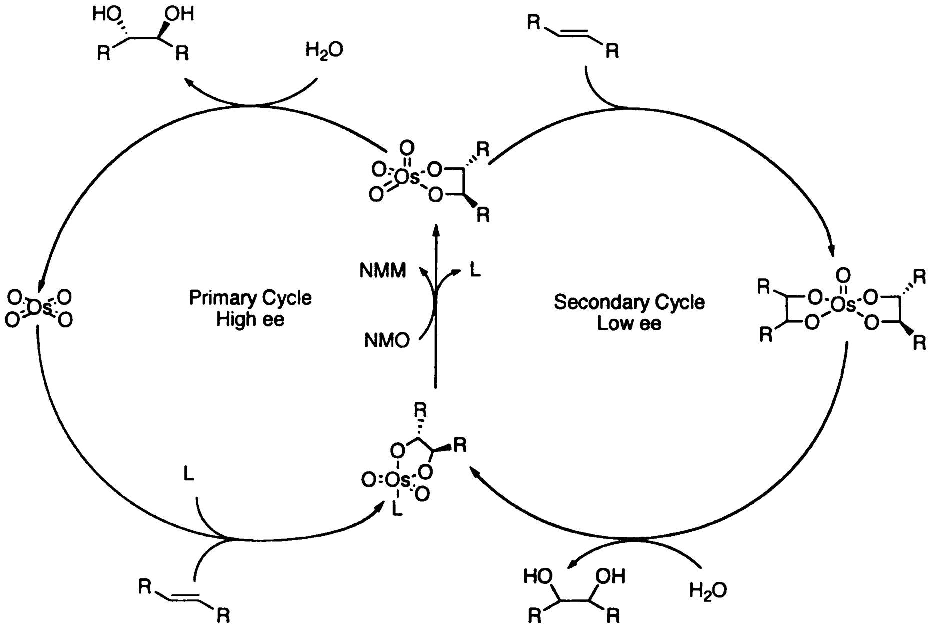
It has been noted that over the last two decades asymmetric reactions have become an invaluable asset to organic chemists. This has definitely been true for dihydroxylation chemistry such that numerous ligands have now been developed for asymmetric dihydroxylation.[1] Several general features and classes of ligands emerge as good asymmetric inductors (Figure I-2). The most prominent feature of such ligands is a tertiary amine. This element is crucial to enhance the rate of the dihydroxylation overall and was first noted by Criegee utilizing pyridine and stoichiometric amounts of OsO_4.[24,25] Sharpless and Hentges began their asymmetric efforts based on the pyridine observation using chiral pyridine derivatives.[46] However, these attempts failed due to low OsO_4 affinity, and changing to the chichona alkaloids proved to be essential for their research.[46] 1,4-Diazabicyclo[2.2.2]octane derivatives failed to give useful enantiomeric excess (<41% ee). More recently, chiral diamines have provided good to excellent enantiomeric excesses, but their bidentate nature provides stable chelates which are resistant to hydrolysis. Therefore stoichiometric oxidative conditions are required.[47-49]

Figure I-2. Ligands for asymmetric dihydroxylation

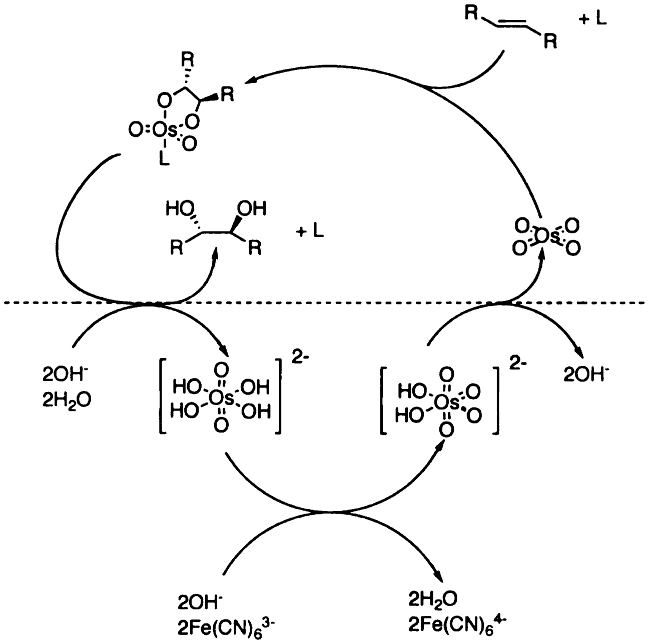


The first examples of chichona alkaloids as chiral auxiliaries for asymmetric dihydroxylation reaction were also stoichiometric in OsO_4 and were thus cost prohibitive to run on large scale. Introduction of NMO as a co-oxidant eliminated this problem but initially provided lower enantiomeric excesses than with the comparable stoichiometric reaction.[50] The problem was found to be a competitive second achiral catalytic cycle involving a bisosmate (Scheme I-4). Slow addition of the olefin substrate helped to alleviate the second catalytic cycle,[51] but the real advance came by using $K_3Fe(CN)_6$ as the co-oxidant in a biphasic system.[52] This modification essentially eliminated the second catalytic cycle because only OsO_4 remains in the organic phase while the co-oxidant and the reduced osmium(VI) species are found in the aqueous layer. Finally, utilization of $K_2OsO_4 \cdot 2H_2O$ as a nonvolatile source of osmium has allowed for the preparation and sale of a premixed system conventionally referred to as “AD-mix,” and the introduction of methanesulfonamide has greatly decreased reaction times. Additionally, reactions enantiomeric excesses remain unchanged or are even enhanced (Scheme I-5).[37] Moreover, complementary cinchona alkaloids can selectively dihydroxylate either the α or β face of the olefin which can be predicted using a reliable mnemonic.[53,54] The substrate scope for this chiral *cis*-dihydroxylation is very general, and numerous examples can be found in the literature.[1,2]

Scheme I-4. The second catalytic cycle



Scheme I-5. Optimized AD conditions with cinchona alkaloid ligands



1.3. Oxone

1.3.1. History

Caro's acid (H_2SO_5), first reported in 1898, has had an intriguing 100 year history.[55,56] For nearly a decade the constitution of Caro's acid was not known, and several references debate various possible formulas, the most probable of which were $H_2S_2O_9$ and H_2SO_5. Even after fifty years of research, the constitution of Caro's acid was only "generally accepted" as H_2SO_5. However, persistence prevailed, and in 1984 two independently obtained crystal structures of the potassium salt were published.[57,58] These results confirmed not only the constitution of Caro's acid as H_2SO_5 but also the structure of the $KHSO_5$ salt as a peroxysulfate unambiguously. Caro's acid is a potentially explosive substance that proved to be difficult to isolate, purify, and identify, but it now exists as a shelf stable triple salt ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) sold under the trademark name of Oxone.[59-63]

While Oxone is a convenient and cheap triple salt (~\$10/Kg), there is only ~50% of active oxidant per mol of the triple salt. Several methods have been developed to prepare the pure potassium salt of peroxymonosulfate, yet these purified oxidants have not proven to be synthetically useful, most probably due to the less than convenient procedures necessary to purify the oxidant. For example, in 1985, Appleman *et al.* isolated and characterized pure $KHSO_5$ and $KHSO_5 \cdot H_2O$ by passage of sodium peroxydisulfate ($Na_2S_2O_8$) through a cationic ion exchange resin followed by hydrolysis of the peroxydisulfate at 50 °C to yield equal molar peroxymonosulfate and bisulfate. Adjustment of the pH with $KHCO_3$ and lyophylization yielded the purified $KHSO_5 \cdot H_2O$.[64] The purification of $KHSO_5 \cdot H_2O$ was revisited by Connick *et al.* in the early 90's along with a modified method for its preparation.[65] Essentially a straightforward filtration protocol starting from Oxone, followed by evaporation and crystallization, resulted in the isolation of analytically pure $KHSO_5 \cdot H_2O$. Again, this method received little attention from organic chemists, perhaps due to its limitations upon scale-up where the removal of large volumes of water is required.

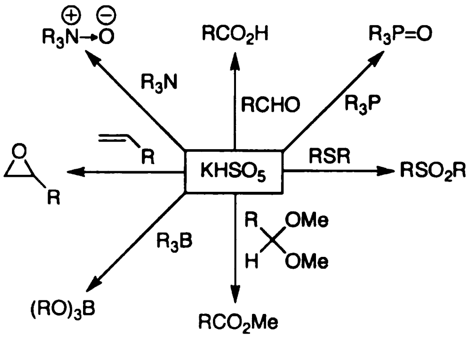
Prior to either Appleman or Connick's attempts to purify $KHSO_5$, Adam[66] in 1979 utilized the bis(trimethylsilyl)peroxymonosulfate prepared from bis(trimethylsilyl)peroxide with SO_3 for the Baeyer-Villiger reaction of ketones to esters. In the mid 80's, Dehmlow *et al.* reported a methodology to prepare several tetraalkyl ammonium salts of Oxone by cationic exchange of Oxone. These include ammonium peroxymonosulfate, tetra-*n*-butylammonium peroxymonosulfate (TBA-OX), tetra-*n*-pentylammonium peroxymonosulfate, and tetra-*n*-hexylammonium peroxymonosulfate.[67,68] However, only in 1988 did Trost and coworkers popularize TBA-OX as an organic soluble form of Oxone that was capable of oxidizing sulfides to sulfones under anhydrous conditions.[68] In 2000, Hajipour developed a method to prepare $Ph_3PBnHSO_5$ (TPPB-OX).[69-71] This interesting phosphonium salt has been used for the oxidative deprotection of TMS and THP ethers, among other things.

The active oxidant within the mixture of Oxone, peroxymonosulfate (HSO_5^-), has been the subject of study in various fields ranging from atmospheric science to physical, computational, and organic chemistry. For example, HSO_5^- is proposed to be an intermediate in atmospheric oxidation of sulfur, and it is hypothesized that 35% of the total sulfur species in clouds exist as HSO_5^-.[72,73] The standard electrochemical potential of HSO_5^- and the mode of HSO_5^- decomposition have also been evaluated, but reaching numerical consensus have been issues of contention.[74-79] Other physical characteristics have been less debatable, and in the mid-eighties the molecular and vibrational spectra of $KHSO_5$ and $KHSO_5 \cdot H_2O$ in aqueous solution were reported by IR and Raman along with two independently solved crystal structures.[57,58] These data have been revisited and confirmed by computational experimentation. Organic chemists have also found peroxymonosulfate to be an intriguing molecule, especially since it has been utilized for numerous organic transformations.

1.3.2. Organic Transformations

Over the past twenty years, Oxone has become a very popular oxidant for the preparation of dimethyl dioxirane *in situ* from acetone and buffered water to epoxidize olefins.[80-86] Additionally, Oxone has been quite remarkable for its effective oxidations of boron, sulfur, nitrogen, and phosphorous.[68,87-93] However, the earliest use of the free acid (Caro's Acid, H_2SO_5), before its constitution was fully understood, was in Baeyer-Villiger chemistry.[66] This area has also grown significantly over recent years and now includes oxidations of α- and β-ketones, aldehydes, or α-amino acids with Oxone to name a few.[94-99]

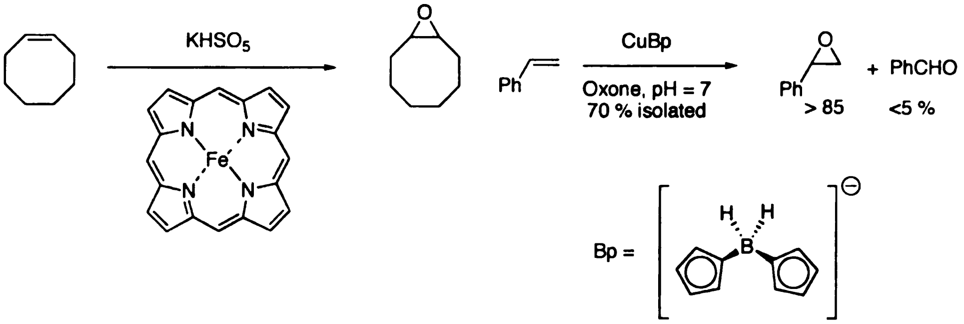
Scheme I-6. Known oxidative pathways for Oxone



1.3.2.1. Epoxidation of Olefins

There are some examples of epoxidation in which $KHSO_5$ is simply the oxygen donor to an active metal complex that subsequently undergoes epoxidation. Meunier for one has used iron metalloporphyrins to epoxidize simple olefins where aqueous $KHSO_5$ was the active oxidant.[100-102] Copper dihydrobispyrazolylborate (CuBp) with pH 7 buffered Oxone proved to also be an efficient epoxidation protocol however, small amounts of oxidative cleavage were observed.[103]

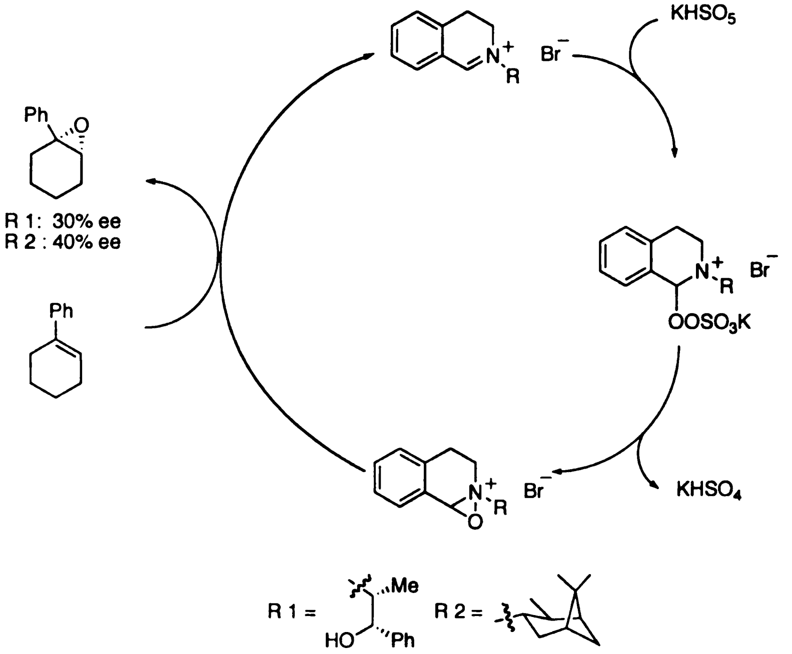
Scheme I-7. Epoxidations with metalloporphyrins and CuBp



In addition to metal complexes that transfer oxygen, there are several examples where organic molecules themselves act as the oxygen electrophile. For instance, oxaziridinium salts are one such example and contain highly electrophilic oxygens that can be transferred effectively to alkenes or thioethers; however, the isolation of such salts can be quite difficult. Oxone has been shown to effectively oxidize the requisite iminium salt to the oxaziridinium salt[104] *in situ* thus allowing the iminium salt to be used in substoichiometric quantities (10 mol %).[105-107] Modifications to prepare chiral iminium salts do indeed provide epoxidation products with varying levels of enantiomeric excess (% ee) (Scheme I-8).[108,109]

The primary role of organic compounds to serve as oxygen donors has been in the area of DMDO epoxidation. A significant advance in this area was to move away from the acetone-derived oxidant DMDO and instead prepare dioxiranes of chiral ketones. Examples include fructose-derived ketones by Shi *et al.*, [3.2.1] chiral ketobicycles by Armstrong *et al.*, and modified 1,1'-biphenylketones that can now *in situ* generate chiral dioxiranes which in turn provide chiral epoxides.[110-124] This asymmetric application has proven general and allows for a wide variety of olefins to be epoxidized with high % ee.

Scheme I-8. Iminium salts as epoxidation catalysts



Scheme I-9. General catalytic epoxidation with dioxiranes

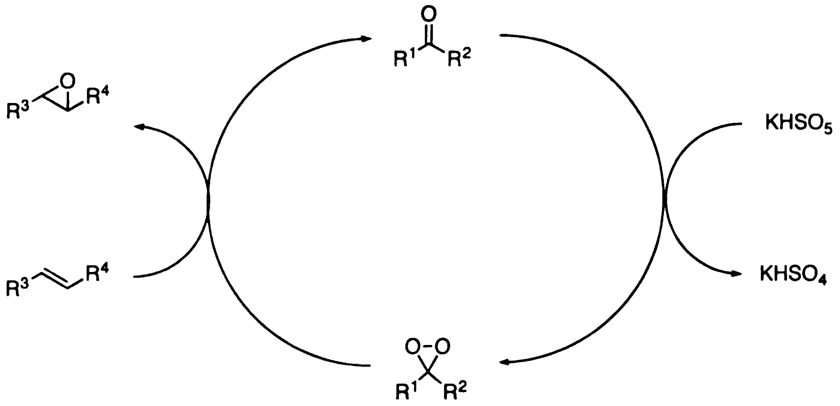
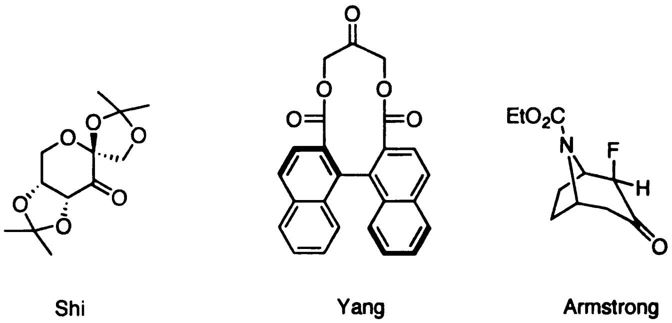


Figure I-3. Chiral ketone precursors for dioxirane epoxidations[114,118,124]



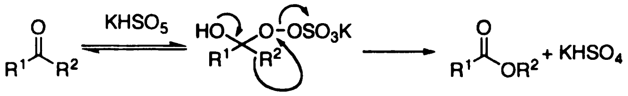
1.3.2.2. Heteroatom Oxidation

Other advances include selective oxidations of boron, nitrogen, phosphorous, and sulfur containing compounds (Scheme I-6).[68,87-93] Most generally, boronic acids or boronic esters are oxidatively hydrolyzed to the corresponding alcohol, while nitrogen, phosphorous, and sulfur are oxidized to their respective oxides. Interestingly, with extra oxidant sulfur will fully oxidize to the corresponding sulfones.

1.3.2.3. Ketones, Aldehydes, and Acetals

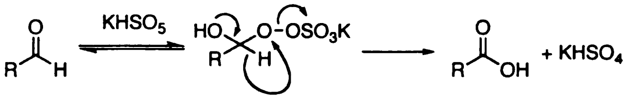
In the area of oxygen oxidations, first on the scene were Baeyer and Villiger, who noted Caro's acid's ability to convert a variety of ketones to esters.[56,125] Kennedy and coworkers[126] and Robinson and coworkers[127] also contributed to this body of knowledge utilizing Caro's acid. In the late 70's, Adam[66] utilized the bis(trimethylsilyl)peroxymonosulfate and noted remarkable reactivity towards ketones providing esters at low temperature, and in 1991 Hirano demonstrated that cyclic ketones could be converted to the corresponding lactones by absorbing Oxone onto wet alumina.[128]

Scheme I-10. Generalized Baeyer-Villiger reaction with $KHSO_5$



Work by Baumstark in 1989 has demonstrated that aldehyde oxidations can be promoted by dimethyl dioxirane (DMDO) to generate carboxylic acids, while Webb's group in 1998 also oxidized aldehydes to acids with Oxone in a manner that supposedly does not generate DMDO *in situ.*[95,96] Related oxidations by Curini in 1999 demonstrated that acetals could undergo oxidation to esters with Oxone in acetonitrile at elevated temperature, and Wang demonstrated this again in 2001 utilizing an ethanolic Caro's acid solution.[129,130] In a similar sense to an acetal oxidation, THP protected alcohols can be unmasked by Oxone in acetonitrile as shown by both Curini and Mohammadpoor-Baltork.[129,131]

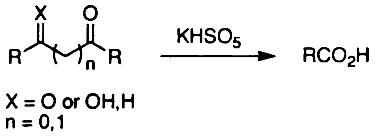
Scheme I-11. Baeyer-Villiger oxidation of aldehydes



Baeyer-Villiger oxidation of ketones that contain an α- or β-heteroatom substitution tend to promote the oxidative cleavage pathway. Oxidation of α-diones with Oxone was shown to be feasible in 1988 by Panda, but with a very limited scope.[99] A study by Ashford and Grega[94] reported that β-diones could be oxidatively cleaved to the corresponding one carbon deleted carboxylic acid using

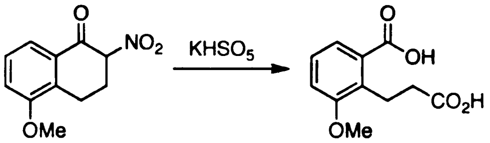
Oxone—$NaHCO_3$—acetone—water. Paradkar demonstrated that α-amino acids oxidatively decarboxylate generally providing a one carbon shorter acid, this oxidative cleavage is analogous to α-ketols that will be discussed in Chapter 6.[98]

Scheme I-12. Oxidation of α- and β-diones or α-ketols



Cyclic α-nitro ketones oxidatively cleave to provide diacids or diesters with Oxone or methanolic Caro's acid and heat as shown by Ballini.[132,133] Again, this process is analogous to the Nef reaction, which has been performed under milder conditions by Ceccherelli in a phosphate buffered methanol solution with Oxone.[134]

Scheme I-13. Oxidation of α-nitro ketones *via* the Nef reaction

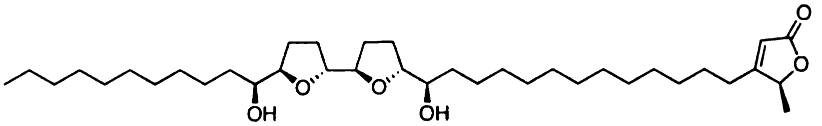


Chapter 2. 2,3,5-Trisubstituted Tetrahydrofurans

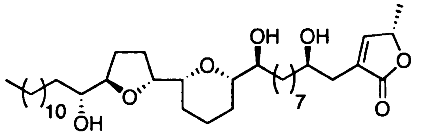
2.1. Introduction

The development of methodologies to prepare substituted 2,5-disubstituted tetrahydrofurans (THF's) stereoselectively has become an area of great interest due to the increasing reports of their biological activity in areas such as polyether antibiotics and *Annonaceous* acetogenins.[135,136] Comparatively, 2,3,5-trisubstituted THF-diols are fairly rare subclasses of either the *Annonaceous* acetogenins or polyether antibiotics and are therefore much less studied. A notable exception includes the non-classical acetogenin mucoxin a bis-THF natural product where one THF ring is 2,3,5-trisubstituted.

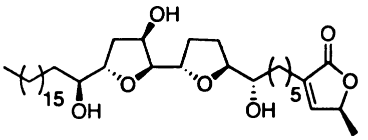
Figure II-1. Representative examples of *Annonaceous* acetogenins



Uvaricin(first isolated Acetogenin) **II-1**



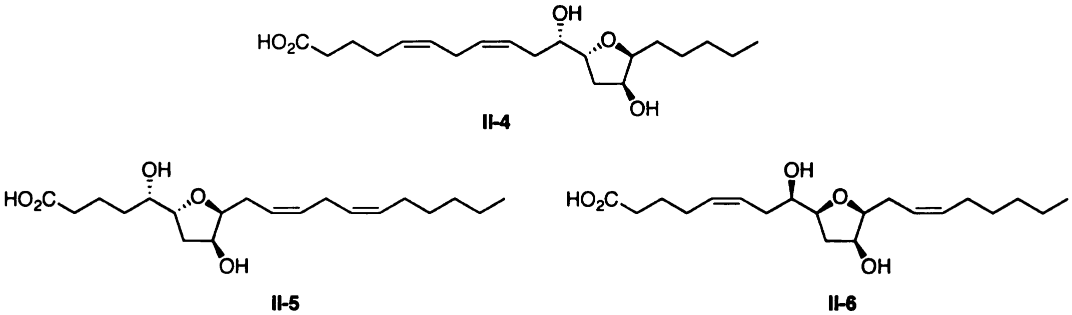
Muconin (nonclassical-THP) **II-2**



Mucoxin (nonclassical-hydroxylated THF) **II-3**

Aside from the new reports within the *Annonaceous* acetogenins and polyether antibiotics a recent discovery within arachidonic acid (AA) metabolism suggests that 2,3,5-AA-THF-diols may have an important biological function within the cell.[137] Here, the implicated 2,3,5-AA-THF-diols (**II-4** to **II-6**), have as of yet undetermined relative regiochemistry and stereochemistry (Figure II-2); however, twenty four possibilities can be envisioned from the three possible vicinal diepoxides. In addition, the biological response of the AA-THF-diols seems significant (See section 2.1.2). Therefore, our interest in 2,3,5-THF diols is promoted on two fronts that have previously been known to be both biologically rich and diverse: *Annonaceous* acetogenins and arachidonic acid (AA) metabolism.

Figure II-2. Representative examples of implicated 2,3,5-AA-THF diols



II-4

II-5

II-6

2.1.1. *Annonaceous* Acetogenins

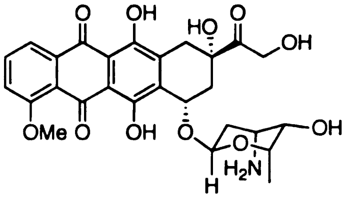
Annonaceous acetogenins are typically found in tropical and sub-tropical regions and are derived from C32 or C34 fatty acids. Traditionally, extracts of many species belonging to this family have been used in folk medicines as insecticides, fungicides, antiparasitics, antimalarials, emetics, antitumor agents, and as a cure for snake bites. The natural products isolated, purified, and tested from within this family of compounds have proven to be highly bioactive, to be selectively cytotoxic against a variety of human tumor cell lines, and to posses sub-nanamolar IC_{50} values. This has culminated in a wide variety of interest from researchers in chemical, biological, and medicinal sciences.[136,138-141]

Classical acetogenins (**II-1**) generally contain one or more 2,5-disubstituted THF rings within the long fatty acid chain. Much less common are the non-classical acetogenins, which contain THP (**II-2**) or hydroxylated 2,3,5-trisubstituted THF rings (**II-3**).

In the early eighties the first acetogenin uvaricin (**II-1**) was discovered from an ethanolic root extract of *Uvaria accuminata* and determined to be a potent antilukemic (P-388) agent.[142,143] Upon structural elucidation, a novel C34 scaffold was discovered. Since then biological studies of over 400 related compounds have allowed the *Annonaceous* acetogenins to emerge as a new class of highly potent bioactive compounds.[144-146]

Mucoxin (**II-3**) is the first non-classical acetogenin to contain a 2,3,5-trisubstituted THF ring. McLaughlin isolated it in 1996 from the bioactive leaf extracts of *Rollinia mucosa*. Mucoxin (ED_{50} = 3.7×10^{-3} mg/mL) was found to be more potent and selective *in vitro* against MCF-7, a human tumor cell line, as compared to adriamycin[147-149] (**II-7**) (ED_{50} = 1.0×10^{-2} mg/mL), which is a well studied antitumor agent. Our interest in this 2,3,5-trisubstituted THF ring scaffold has made this molecule one of great interest in our laboratory such that we are pursuing its total synthesis.[144,150]

Figure II-3. Structure of adriamycin[147]



II-7: Adriamycin, Synthesis: Smith 1977

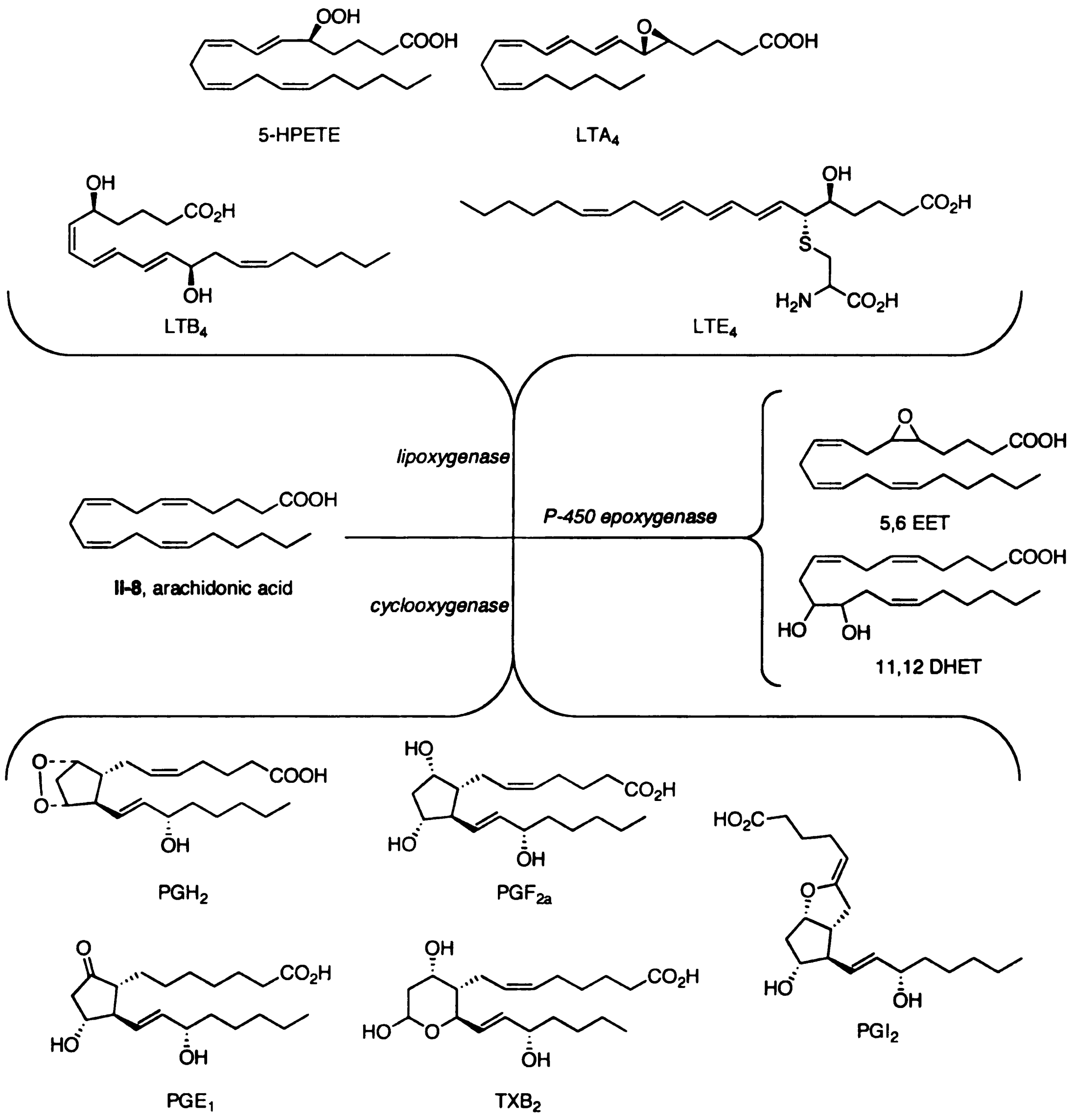
2.1.2. Arachidonic Acid Metabolism

Arachidonic acid (AA) is a C20 polyunsaturated fatty acid that plays an important role in the production of prostanoids (which include prostacyclins, prostaglandins, and thromboxanes) and leukotrienes.[151-153] Prostanoids and leukotrienes have critical roles in pulmonary and vascular physiology (i.e. pain, fever, and regulation of blood pressure) as well as in the onset of inflammation, asthma, and cancer.[154-156] Prostanoids and leukotrienes are derived from the cyclooxygenase and lipoxygenase metabolic pathways. They have both been highly scrutinized over the years, and each contains a great number of compounds that are rich in biological activity and structural diversity. This has prompted much research focused on the enzymes and receptors involved in AA metabolism along with the total synthesis of many of these compounds. (Scheme II-1).[157-160]

The third least scrutinized metabolic pathway is that of P-450 epoxgenase (Scheme II-1). Biologically significant compounds such as 5,6 EET (5,6 epoxide of AA), a potent stimulator of prolactin release and an effective vasodilator, along with 11,12 DHET (11,12 diol of AA), a Na^+/K^+ ATPase inhibitor, are just two of the metabolites that have been well studied and synthesized.[161-167] The emphasis placed upon the P-450 metabolic pathway, however, has had a narrow focus, specifically on compounds that are derived from monooxygenation of AA. Metabolites derived from dioxygenation, their respective hydrolytic metabolites, and their presumed biological relevance have not been examined in detail.[137,167-169]

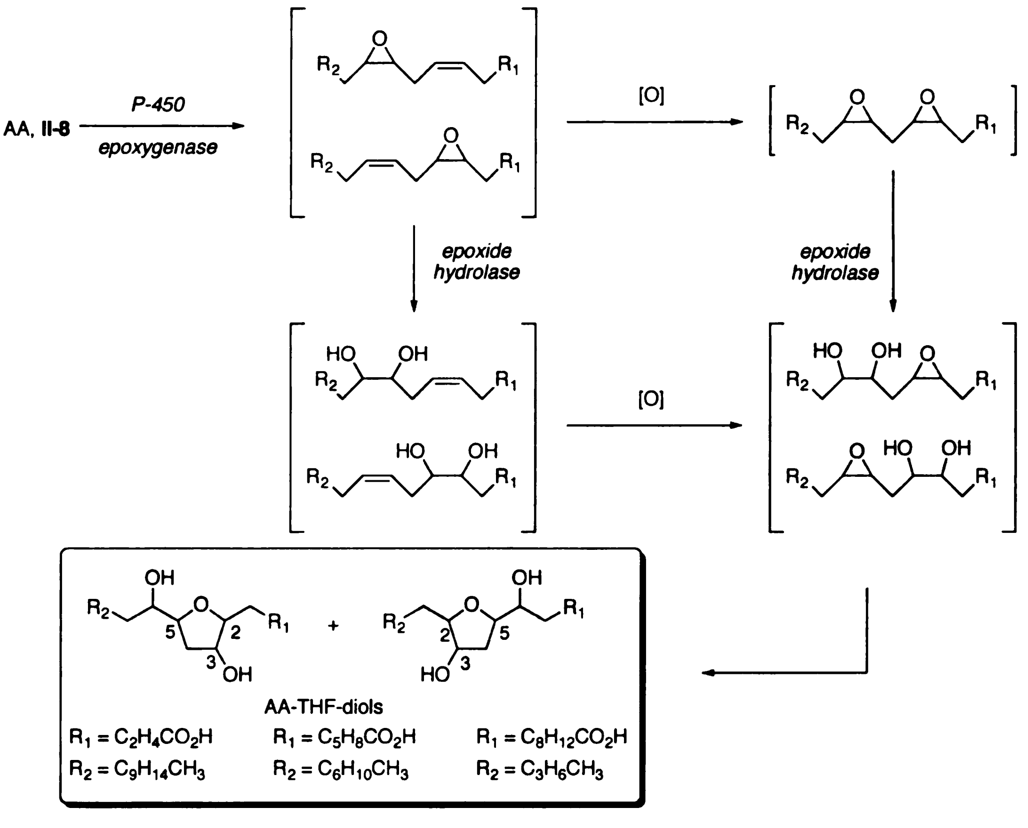
Recently, a new class of AA metabolite has been found that appears to be derived from the hydrolysis of an AA vicinal diepoxide along the P-450 pathway.[137] The resultant compounds are termed arachidonic acid tertahydrofuran diols (AA-THF-diols) (Figure II-2). Since monoepoxides and their respective diols by way of hydrolysis are known, it is probable that the hydrolytic products of higher order epoxides exist.

Scheme II-1. AA metabolites *via* three different enzymatic pathways



Moghaddam *et al.* have demonstrated through *in vitro* experimentation that, when AA-monoepoxides are exposed to clofibrate treated mouse liver microsomes, AA-diepoxides are generated. In addition, synthetically prepared AA diepoxides, when treated with the same microsomes, can produce AA-THF-diols.[137] Here the AA-THF-diols were compared *via* derivitization and subsequent GC-MS fragmentation analysis to an authentic synthetically prepared sample. These *in vitro* studies in which AA-THF-diols are prepared allow for a reasonable biosynthetic pathway to be proposed (Scheme II-2). Additionally, AA-THF-diols have now been found *in vivo*; lipids isolated from liver extracts of clofibrate treated mice were derivatized similarly to the *in vitro* experiments, and the AA-THF-diols were identified unambiguously by GC-MS fragmentation analysis.[170]

Scheme II-2. Proposed biosynthesis of AA-THF-diols



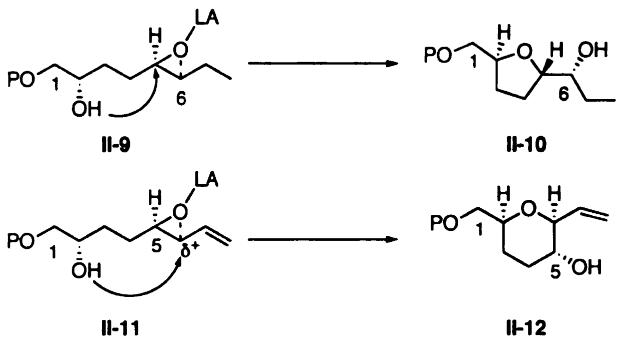
Interestingly, the mixture of synthetic AA-THF-diols (100 mM) also exhibit a pronounced biological effect in that upon their incubation with rat pulmonary alveolar epithelial cells, a rapid increase in intracellular Ca^{+2} ion concentration was observed.[170] Notably, this response appears to be dose and time dependent. These are significant results in that intracellular Ca^{+2} ion levels play a crucial role in controlling physiological processes such as signal transduction and cell homeostasis. Notably, AA and AA-monoepoxides did not exhibit an increase in intracellular Ca^{+2} at all while AA-diepoxides initially showed no increase, but after a few minutes of incubation intracellular Ca^{+2} ion levels began to increase with a slow, and transient rise in intracellular Ca^{+2} levels. This finding suggests that the AA-diepoxides are not initially active; however, as they are metabolized AA-THF-diols form by interconversion from the AA-diepoxides, and a modest level of activity is then detectable. This biological activity along with the unique structural feature of AA-THF-diols has been the thrust of our research group's interest in devising a variety of new ways to prepare substituted THF rings, specifically 2,3,5-trisubstituted-THF-diols. Included in the next sections is the brief description of three of our group's approaches, followed by my own.

2.1.3. Approaches to 2,3,5-Trisubstituted THF Diols

Numerous strategies have been developed to provide quick and facile entry into 2,5-disubstituted THFs, 2,3,5-trisubstituted THFs, and 2,6-disubstituted tetrahydropyrans (THPs).[171-182] [183-188] Perhaps the most common methods utilize a regiochemically controlled opening of epoxides (Scheme II-3). Synthetically, this is an excellent approach because of the relative ease in which innumerable substrates can be prepared in a chiral fashion. These substrates are generally prepared utilizing a variety of well precedented asymmetric methods including but not limited to asymmetric dihydroxylation and asymmetric epoxidation.[1,2,189] A regiochemically defining substituent such as an alkyl or hydroxy group is introduced adjacent to the epoxide such that a Lewis acid promoted epoxide opening leads to preferential nucleophilic attack at C-5; therefore, it is possible to direct the path of ring opening in an *exo* fashion (**II-9** to

II-10). Conversely, when substituents such as an allyl, propargyl, or phenyl sulfide group can be introduced adjacent to the epoxide such that a Lewis acid promoted epoxide opening leads to preferential nucleophilic attack at C-6; therefore, it is possible to direct the path of ring opening in an *exo/endo* fashion (**II-11** to **II-12**). By controlling the intramolecular regiochemistry in the cyclization of epoxy-alcohols, a very versatile strategy for stereodefined THFs and THPs has been established.[171-182]

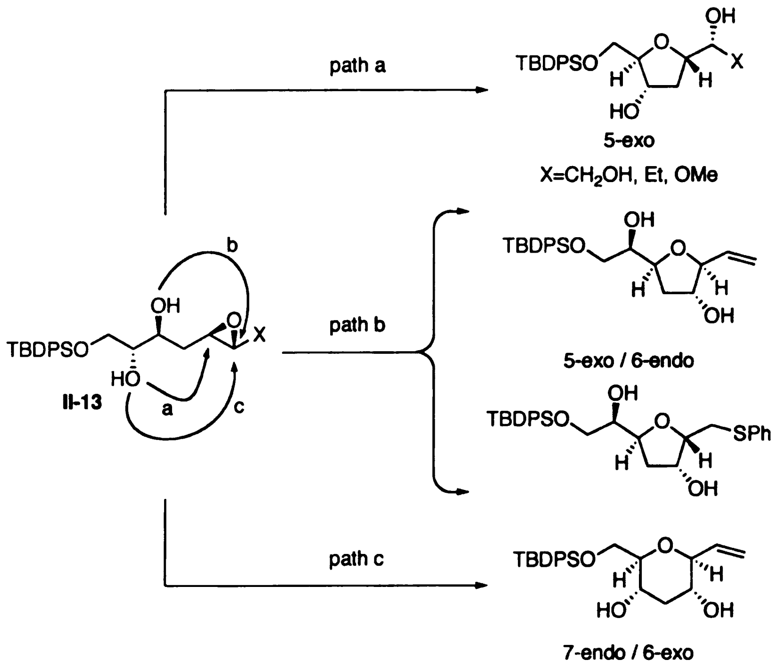
Scheme II-3. Regiochemically controlled epoxide openings



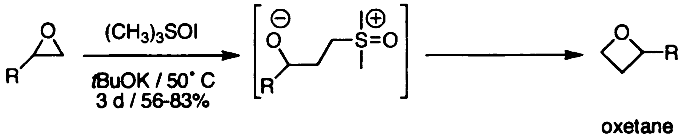
Notably, most synthetic strategies have had a single hydroxyl group acting as the nucleophile, and thus product diversity from competing nucleophiles was not an issue. Our initial approach to 2,3,5-trisubstituted THFs addresses this issue specifically. Can a non-differentiated epoxy-diol (**II-13**) participate in a selective regiochemically controlled epoxide opening? Our research has bourne out that this is indeed a viable option to produce 2,3,5-trisubstituted THFs or tetrahydropyrans (THPs) in good yield with excellent regio- and stereocontrol (Scheme II-4).[190]

An alternative approach to THF rings that has been developed in our laboratory also utilizes a directed epoxide ring opening with trimethylsulfoxonium iodide. Generally this method is applicable to form oxetane rings (Scheme II-5), but when an allylic epoxyalcohol is subjected to the same reaction conditions, an initial Payne rearrangement followed by nucleophilic ring opening provides the dianion (Scheme II-6). Here either alkoxide may attack to displace DMSO intramolecularly, but in these instances the formation of the THF core proceeds preferentially and in good yield.

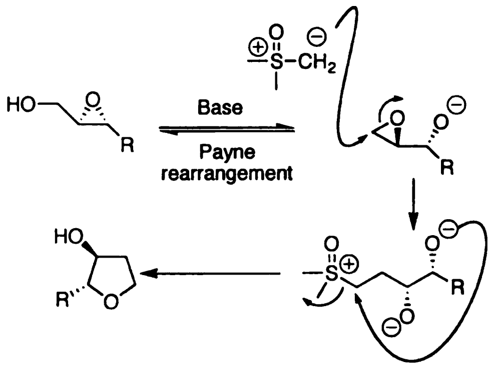
Scheme II-4. Regiochemically controlled epoxide openings—competing nucleophiles



Scheme II-5. Trimethylsulfoxonium iodide epoxide opening to form oxetanes

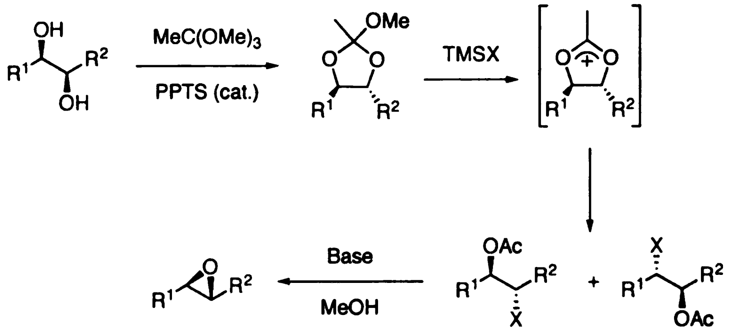


Scheme II-6. Trimethylsulfoxonium iodide epoxide opening to form THFs

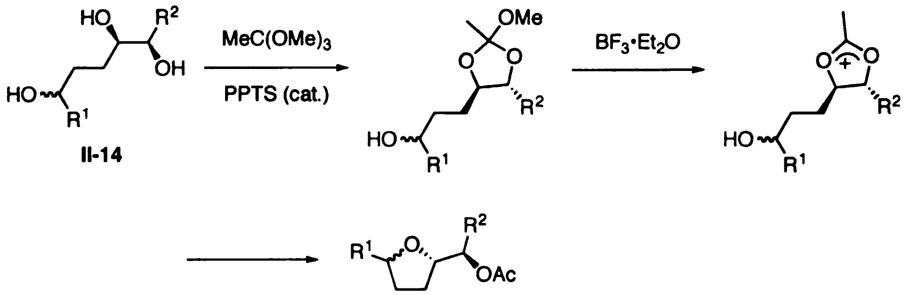


A third approach to THF rings developed in our laboratory again utilizes an intramolecular ring closure. This particular idea stemmed from dihydroxylation chemistry where protection of *syn* diols as their orthoester is utilized as a method to generate an epoxide in a stereospecific fashion (Scheme II-7). We hoped that placement of a nucleophilic oxygen four carbons away (**II-14**) could serve as an intramolecular trap for the intermediate acetoxonium ion to provide an ester protected THF ring (Scheme II-8). Again this method was successful and proved very useful in the construction of the second THF ring in mucoxin.

Scheme II-7. Conversion of *syn* diols to epoxides *via* an orthoester



Scheme II-8. Intramolecular trapping of an orthoester to prepare THFs



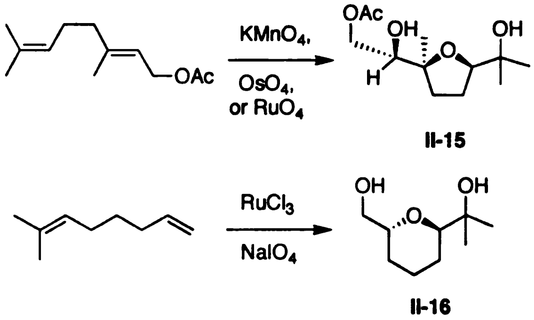
These powerful and compelling results are a definite addition to existing literature. The directed epoxide opening methodology and the orthoester method have both been utilized in the total synthesis of the proposed structure of mucoxin. The ylide chemistry is currently being used for the preparation of haterumalide NA. However, our underlying interest in these 2,3,5-trisubstituted THF substructures has prompted us to investigate other alternative routes to 2,3,5-THF-diols, as will be discussed in the remainder of this chapter.

2.2. Oxidative Cyclization Approach to 2,3,5-Trisubstituted THF Diol Core

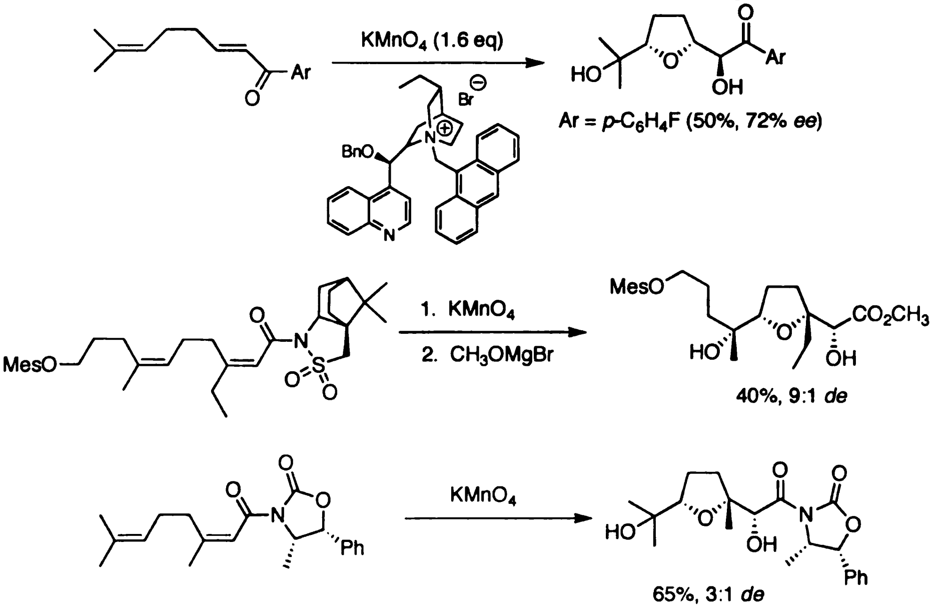
In 1965 Klein and Rojhan demonstrated that the oxidation of geranyl acetate with potassium permanganate ($KMnO_4$) did not provide the expected tetraols but instead underwent a stereospecific oxidative cyclization to provide the 2,5-bis-hydroxymethyltetrahydrofuran **II-15** in 70% yield (Scheme II-9).[191] The oxidative cyclization of other related 1,5-dienes continues to be an intriguing approach for the synthesis of 2,5-disubstituted THF diols, and its synthetic utility has only gained interest over the past 40 years. This can be understood due to the excellent relative stereochemical control and the high degree of oxygenation that occurs in one simple transformation. Recently, the 1,5-diene oxidative cyclization has been reported with not only $KMnO_4$,[191-195] but also OsO_4[196-198] and RuO_4 [199-205]as oxidants. The reaction generally provides the desired THF products in 40-80% yield with excellent stereoselectivity. A similar methodology has recently been reported for 1,6-dienes in which $RuCl_3$ mediated oxidation stereoselectively prepares 2,6-disubstituted tetrahydropyran-diols such as **II-16** (Scheme II-9).[199]

Interestingly, the asymmetric potential of this reaction had not been explored at all until very recently. Brown and co-workers[206] have demonstrated that the stoichiometric permanganate mediated oxidative cyclization of 1,5-dienes in the presence of chiral tertiary ammonium salts affords enantiomerically enriched THF rings (Scheme II-10). This reaction was substrate specific and required an aryl α,β-unsaturated ketone to undergo a selective reaction. In this system, the degree of enantiomeric excess, was affected by changing the reaction temperature or solvent. As one may expect more polar solvents and higher temperatures led to decreases in the enantiomeric excess and the best conditions were determined to be in DCM at –30 ˚C with HOAc and $KMnO_4$. Previous to this study, there were only two reports that achieve control of absolute stereochemistry through oxidative cyclization of 1,5-dienes containing either Oppolzer's chiral sultam or Evans' norephedrin based oxazolidone (Scheme II-10).[193,207]

Scheme II-9. Oxidative cyclization of 1,5- and 1,6-dienes

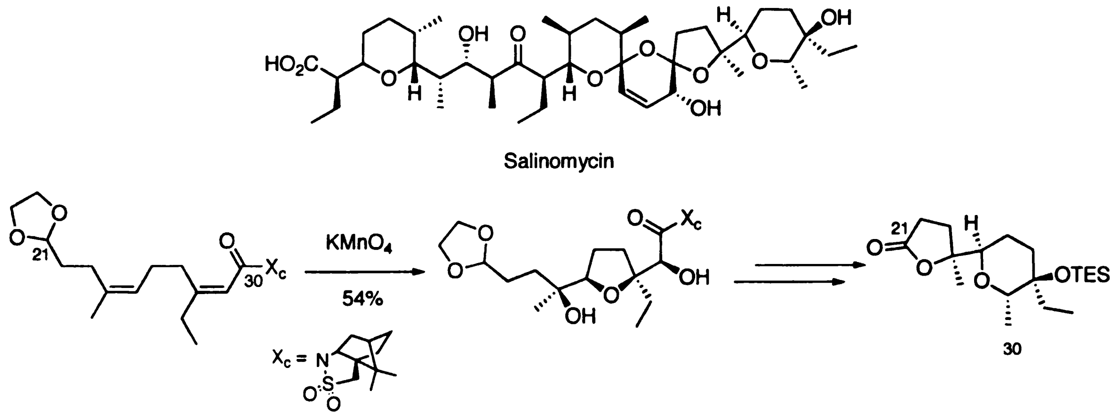


Scheme II-10. **Examples of enantioenriched oxidative cyclizations**

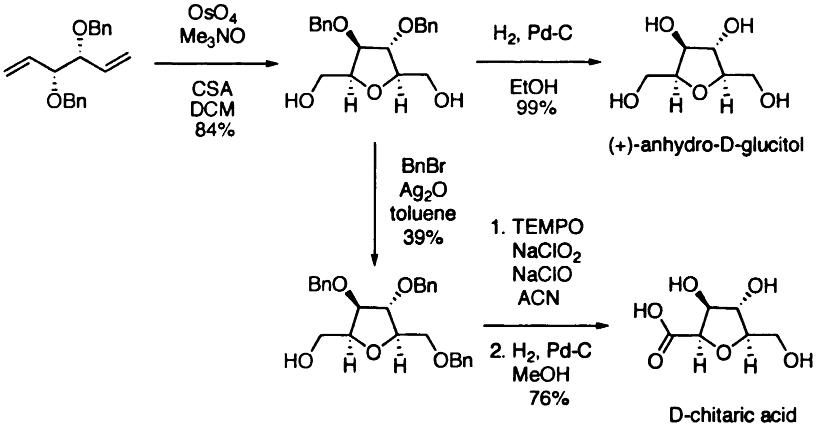


The potential in this field lies in the highly stereoselective nature of the oxidative cyclization which yields functionalized oxygenated products from simple dienes. In addition, the added benefit of chiral induction has increased the value of this reaction tremendously. The popularity of such a 1,5-diene oxidative cyclization reaction can be seen in its recent utilization in the total synthesis of complex natural products such as salinomycin (Scheme II-11) and sugar derivatives including (+)-anhydro-D-glucitol and D-chitaric acid (Scheme II-12). These synthetic efforts demonstrate the utility of the oxidative cyclization of 1,5-dienes. Our synthetic interests of course lie in the area of 2,3,5-trisubstituted THF diols. We believed an analogous approach utilizing 1,4-dienes may provide an efficient entry to our desired THF core.

Scheme II-11. Preparation of C-21 to C-30 of salinomycin



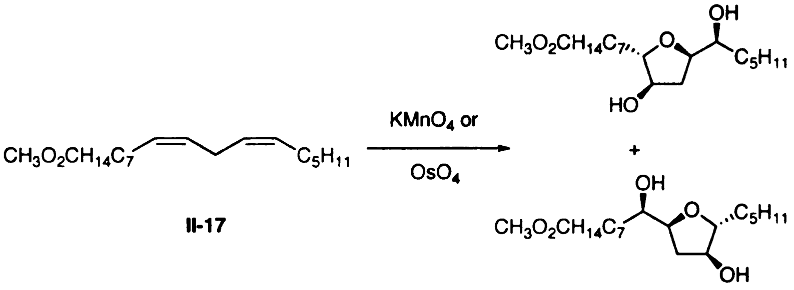
Scheme II-12. Synthesis of (+)-anhydro-D-glucitol and D-chitaric acid.



2.2.1. Initial Results

As previously mentioned we are interested in studying 2,3,5-trisubstituted tetrahydrofuran-diols (THF-diols) isolated from the oxidative metabolism of arachidonic acid (AA, **II-5**) (Scheme II-3).[137] This has led us to investigate the feasibility of securing these structural motifs by the unprecedented oxidative cyclization of 1,4-dienes (Scheme II-13). As a starting point, we utilized protocols for the 1,5-diene and 1,6-diene systems. Methyl linoleate (**II-17**) was chosen as an initial substrate due to its structural similarities to the desired substrate AA. We believed that methyl linoleate would be an ideal model system since the THF-diols derived from the bis-epoxides were known. Moreover, the system is inherently simpler since there are only two oxidizable olefins.

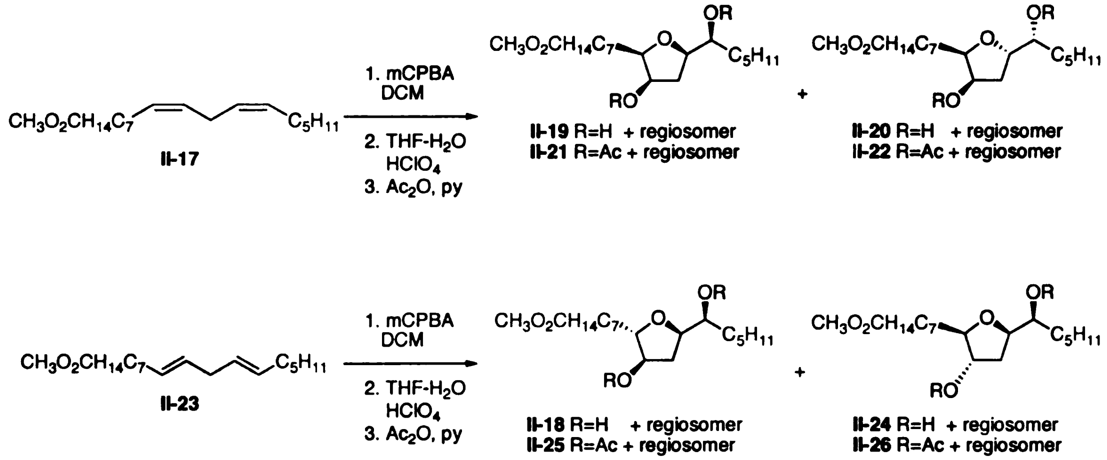
Scheme II-13. Putative oxidative cyclization pathway



II-18 and **II-18-regioisomer**

Our initial attempts utilized $KMnO_4$ in aqueous acetone (9:1) providing the desired 2,3,5-trisubstituted THF-diols (**II-18** and **II-18-regiosomer**) as a 1:1 regioisomeric mixture in a very modest 20% yield (Table 1) (referred to as **II-18** only throughout the remainder of this chapter). Analysis of ^{1}H, ^{13}C, HMQC, and COSY NMR identified the products as **II-18**, and the corresponding peracetylated compounds allowed the relative ring stereochemistry to be defined as 2-*trans*-3,5-*cis*. Similar to other 2,3,5-trisubstituted THF-diol stereoisomers obtained from linoleic acid oxidation and cyclization reported previously, these compounds were also inseparable using standard chromatographic techniques.[208] Verification of the ring stereochemistry was also established by simple bis-epoxidation of ML or 9,12-*trans* ML with *m*CPBA, subsequent $HClO_4$ ring closure, and finally peracetylation as described in literature.[208,209] This provided easy access to all four relative ring stereochemistries either as free hydroxyls or the acetates as standards (Scheme II-14).

Scheme II-14. 2,3,5-THF diols from bis-epoxides



Attempts to increase the yield in this system by adjusting the pH were unsuccessful. However, $TsOH{\bullet}H_2O$ and CO_2 did not reduce the yield and provided 18% and 23% respectively. $BF_3{\bullet}Et_2O$ did reduce the yield of the cyclized products to 10%

and DIPEA and $NaHCO_3$ produced no cyclized product at all. Other cyclization attempts were performed with $KMnO_4$ and ML using $TsOH•H_2O$ as an additive in various solvents, EtOH, DCM, Et_2O, and THF. Unfortunately, no reaction occurred most likely due to the lack of solubility of $KMnO_4$ (Table II-1).

Table II-1. Initial attempts to prepare 2,3,5-THF-diol **II-18**

Entry	Oxidant	Solvent	Additive	Yield **II-18** (%)
1	$KMnO_4$	Acetone-H_2O (9:1)		20
2	$KMnO_4$	Acetone-H_2O (9:1)	CO_2	23
3	$KMnO_4$	Acetone-H_2O (9:1)	$BF_3•Et_2O$	10
4	$KMnO_4$	Acetone-H_2O (9:1)	DIPEA	0
5	$KMnO_4$	Acetone-H_2O (9:1)	$NaHCO_3$	0
6	$KMnO_4$	Acetone-H_2O (9:1)	$TsOH•H_2O$	18
7	$KMnO_4$	EtOH	$TsOH•H_2O$	NR
8	$KMnO_4$	DCM	$TsOH•H_2O$	NR
9	$KMnO_4$	Et_2O	$TsOH•H_2O$	NR
10	$KMnO_4$	THF	$TsOH•H_2O$	NR
11	OsO_4	Acetone-H_2O (9:1)	$NaIO_4$	21
12	$RuCl_3•nH_2O$	EtoAc/ACN/H_2O	$NaIO_4$	12

With promising results we chose to move away from $KMnO_4$, primarily due to the great amount of excess reagent needed, and shifted our focus toward other metal-oxo oxidants. Attempts to cyclize ML with catalytic OsO_4 and $NaIO_4$ did provide **II-18** in 21% yield while oxidative cyclization with catalytic $RuCl_3$ and $NaIO_4$ was an inefficient process, providing only a 12% yield of **II-18** (Table II-1).[199] Detailed analysis of all of these initial reactions revealed that 1,2-diols and tetraols were present in the crude reaction mixture. We suspected that these alcoholic byproducts could have come from a competitive hydrolytic pathway of the intervening osmate ester. Aldehydes were also found in both $KMnO_4$ and $NaIO_4$ reactions. Such reagents are known to oxidatively cleave diols to yield the aldehydic products.[210-212]

2.2.2. Improvement Strategies

In an attempt to hinder the hydrolysis of the intermediate osmate ester, numerous anhydrous solvents were used with OsO_4 and different co-oxidants. With only a few exceptions, compound **II-18** was formed to no appreciable degree (Table II-2). To summarize these results, using standard conditions (ML, $NaIO_4$, OsO_4 1:4:0.05), no product was observed with CH_2Cl_2, toluene, ethyl acetate, diethyl ether, *t*-BuOH, and hexanes. In all cases starting material was recovered with trace amounts of diols being produced. THF and acetonitrile respectively yielded 8% and 10% of the desired product **II-18**. Notably, DMF provided compound **II-18** in an improved yield of 30%. Two possible explanations for the modest reactivity of the more polar solvents such as acetonitrile, THF, and DMF is that there is a charge stabilizing effect, assuming the mechanism involves a charged species. The higher yield could also be due to better solvation of the reagents in the more polar solvents.

With OsO_4 as the oxidant we attempted to vary the co-oxidant in acetone-water. These results showed that only a few of these provided the desired compounds in greater than 10% yield (Table II-3). Primarily, the products obtained were diols and/or aldehydes. NMO with or without $TsOH{\bullet}H_2O$, KIO_3, *t*-BuOOH, H_2O_2, and DMP did not yield any THF-diol products. Using AD-mix-β in the presence of methanesulfonamide also did not provide any desired cyclization product. The co-oxidants that did yield products were $KClO_3$, 2-iodoxybenzoic acid (IBX), KIO_4, and Oxone. Interestingly, Oxone, a mono potassium peroxysulfate salt, was unique not only because it provided yields comparable to the initial $KMnO_4$ and OsO_4-$NaIO_4$ systems, but also this reaction had fewer number of byproducts, thus making the work-up more facile.

Table II-2. Solvent effects on the cyclization of ML

Entry	Oxidant	Solvent	Additive	Yield **II-18** (%)
1	OsO_4	$NaIO_4$	Acetone-H_2O (9:1)	21
2	OsO_4	$NaIO_4$	DCM	0
3	OsO_4	$NaIO_4$	Et_2O	0
4	OsO_4	$NaIO_4$	*t*-BuOH	0
5	OsO_4	$NaIO_4$	ACN	10
6	OsO_4	$NaIO_4$	Hexanes	0
7	OsO_4	$NaIO_4$	EtOAc	0
8	OsO_4	$NaIO_4$	Toluene	0
9	OsO_4	$NaIO_4$	DMF	30
11	OsO_4	$NaIO_4$	THF	8

Various other co-oxidant/solvent reactions variations provided no improvement. For instance when ML was treated with OsO_4 and Oxone in THF the reaction proceeded providing **II-18** but in only 17%. Using *t*-BuOH-H_2O had no effect on the yield as compared to standard $NaIO_4$ conditions (Table II-3, entry 1), and changing to a purely biphasic system (toluene-H_2O) even with Adogen 464 as a phase transfer catalyst provided no cyclized product. The rate of addition of the co-oxidant $NaIO_4$ was also varied from the standard one portion addition. This was achieved by dissolving the co-oxidant in either DMF or acetone-H_2O and then slowly adding the solution *via* syringe pump over the course of 10 h. These attempts had absolutely no effect on the yield of the isolated product, which remained at 30% and 20%, respectively.

Table II-3. Co-oxidant effects on the cyclization of ML

Entry	Oxidant	Co-oxidant	Solvent	Additive	Yield **II-18** (%)
1	OsO_4	$NaIO_4$	Acetone-H_2O (9:1)		21
2	OsO_4	NMO	Acetone-H_2O (9:1)		0
3	OsO_4	NMO	Acetone-H_2O (9:1)	TsOH•H_2O	0
4	OsO_4	*t*-BuOOH	Acetone-H_2O (9:1)		0
5	OsO_4	KIO_3	Acetone-H_2O (9:1)		0
6	OsO_4	KIO_4	Acetone-H_2O (9:1)		20
7	OsO_4	$KClO_3$	Acetone-H_2O (9:1)		8
8	OsO_4	IBX	Acetone-H_2O (9:1)		5
9	OsO_4	DMP	Acetone-H_2O (9:1)		0
10	OsO_4	Oxone	Acetone-H_2O (9:1)		20
11	OsO_4	Oxone	THF		17
12	OsO_4	Oxone	DMF		30
13	OsO_4	AD-mix b	*t*-BuOH-H_2O (1:1)	Methane sulfonamide	0
14	OsO_4	$NaIO_4$	*t*-BuOH-H_2O (1:1)		20
15	OsO_4	$NaIO_4$	Toluene-H_2O (1:1)	Adogen 464	0
16	OsO_4	$NaIO_4$	DMF	syringe pump	30
17	OsO_4	$NaIO_4$	Acetone-H_2O (9:1)	syringe pump	20

With DMF as the solvent, Oxone-based reactions also yielded 30% of the desired oxidatively cyclized products. Changing the temperature in the DMF–Oxone system with hopes of reducing the rates of competing reactions and to increase the yield of the desired product **II-18** did not result in any improvements (Table II-4). Experiments at both 0 °C and –40 °C actually lowered the yield of **II-18** providing 20% and 12%, respectively. Elevating the temperature to 50 °C was also ineffective and lowered the yield to 13%. Adding 4Å molecular sieves reduced the yield to 9%, and other OsO_4

reactions in DMF utilizing IBX or DMP resulted in little or no conversion 10% and 0%, respectively.

Table II-4. Temperature and oxidant effects of ML cyclization in DMF

Entry	Oxidant	Co-Oxidant	Solvent	Additive	Yield **II-18** (%)
1	OsO_4	$NaIO_4$	DMF		30
2	OsO_4	Oxone	DMF		30
3	OsO_4	Oxone	DMF	4A Sieves	9
4[a]	P-OsO_4	Oxone	DMF		30
5	OsO_4	Oxone	DMF	-40 °C	14
6	OsO_4	Oxone	DMF	0 °C	22
7	OsO_4	Oxone	DMF	50 °C	13
8	OsO_4	IBX	DMF		10
9	OsO_4	DMP	DMF		0

a) P-OsO_4: Polymer bound OsO_4 where the polymer is derived from 4-vinylpyridine

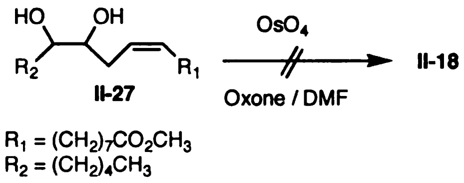
2.2.3. Optimized Reaction Conditions

While the results of our optimization studies did not increase the isolated yield, we still believe this to be an intriguing reaction since it sets four stereocenters in a simple, one pot reaction. This prompted us to see if the reaction was scaleable. Using our best reaction conditions for the oxidative cyclization, i.e., Oxone (4 equiv.) and OsO_4 (0.05 equiv. 2.5% in *t*-BuOH) in DMF (0.2 M), we scaled the reaction up to 5 mmol (1.5 g) of ML. This did indeed provide **II-18** in 30% yield. Detailed analysis of the reaction byproducts in this instance showed no diol or aldehyde products as seen with $NaIO_4$ or $KMnO_4$. Instead, this reaction revealed only the formation of carboxylic acids from oxidatively cleaved olefins. The OsO_4 assisted oxidative cleavage of olefins will be discussed more in subsequent chapters. As a final note the amount of catalyst need not be 5 mol%. Successful reactions were carried out with as little as 0.5 mol%, a ten-fold decrease in catalyst providing an identical yield of **II-18** in 30%.

2.2.4. Mechanistic Proposal

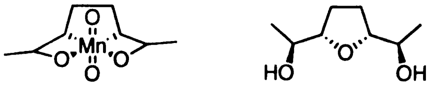
Again noting the potential usefulness of this reaction we felt that it was necessary to analyze the reaction mechanism as compared to others reported.[194,197,213-216] A very simple explanation for the oxidative cyclization could be based on Walba's research. Walba reported an oxidative cyclization using a Cr(VI) compound to prepare 2,5-disubstituted THF rings from 5,6-dihydroxyalkenes.[213] Analogous to Walba's observations, we thought that the diol of one of the olefins in **II-27** might be a possible intermediate, so it was independently synthesized from the corresponding monoepoxide. While Walba's mechanism with Cr(VI) might be an alternative explanation for the observed cyclization in our systems, treatment of **II-27** with conditions that yield oxidative cyclization did not produce any THF-diol product (Scheme II-15). This was true not only for the DMF–Oxone system but also for the $NaIO_4$–acetone–H_2O system. This suggests that the diol is not involved as a possible reaction intermediate to the oxidatively cyclized products **II-18**.

Scheme II-15. Diols do not oxidatively cyclize



Our second hypothesis was based conjointly on the works of Walba, Baldwin, and Piccialli. In 1979, Walba and coworkers proposed that the 2,6-octadienes they were working with underwent a double [2+2] cycloaddition of $KMnO_4$ to form **II-28,** and this putative bis-metaloxetane can rearrange and eliminate to yield diol **II-29** (Figure II-4).[214,215]

Figure II-4. Bis-metaloxetane intermediate and resultant THF-diol

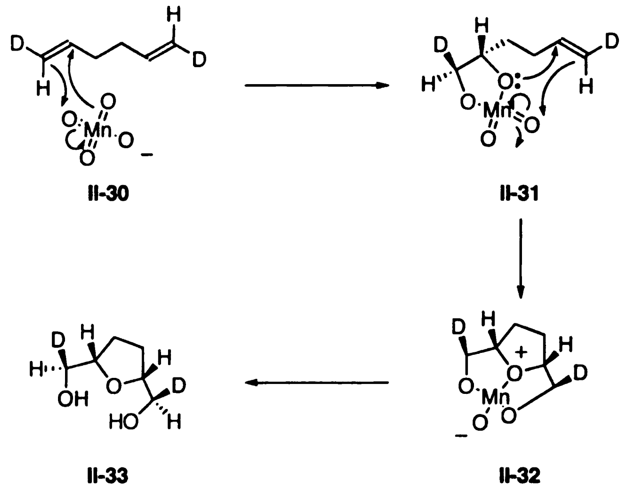


II-28 **II-29**

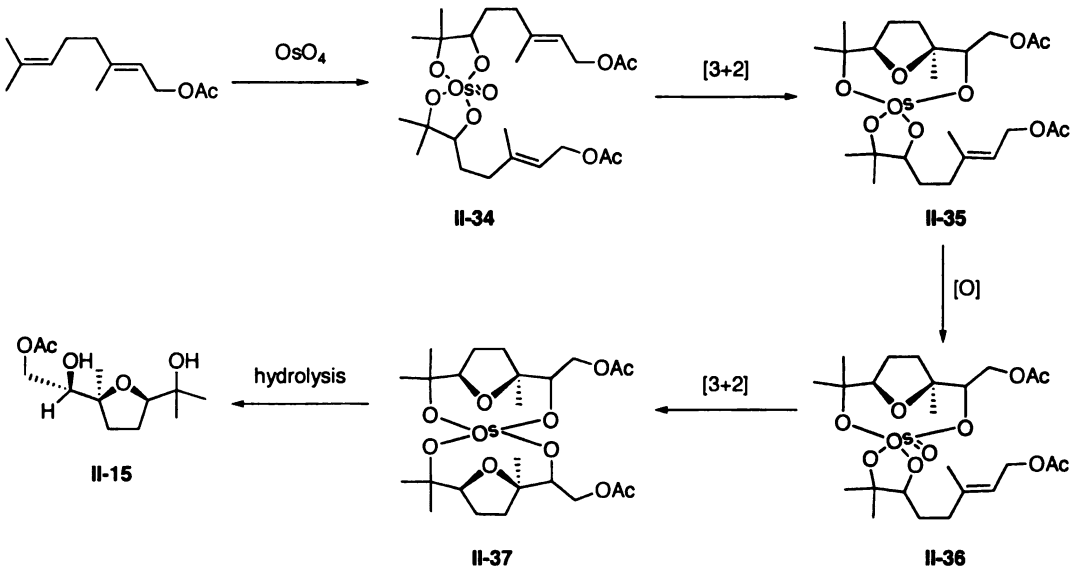
In our case with OsO_4 we did not discount the bis-metaloxetane theory out of hand. Several studies by Sharpless were highly in favor of an OsO_4 [2+2] reaction with olefins.[216] More recently, however, experimental and theoretical calculations by Houk, Sharpless, and Singleton favored the [3+2] cycloaddition of OsO_4 to olefins and found that the [2+2] formation of the osmaoxetane and the subsequent ring expansion are prohibitively high energy processes (~42 kcal/mol and ~30 kcal/mol, respectively).[35]

Baldwin's mechanistic proposal in 1979 was based on an initial MnO_4^- [3+2] cycloaddition to **II-31** followed by a second [3+2] cycloaddition to provide **II-32** (Scheme II-16).[194] Hydrolysis would then provide the desired THF diol **II-33**. Piccialli and coworkers, using OsO_4 as a catalyst, also propose a concerted [3+2] cycloaddition to form the THF diol core. The relative stereochemistry of their products is analogous to that of 1,5-dienes reported previously (Scheme II-17).[197] The first step of their mechanism involves formation of the isolated oxidized bis-osmate ester **II-34**. Then a [3+2] cycloaddition followed by oxidation of the osmate provides **II-35**. It is postulated that this intermediate also undergoes a [3+2] cycloaddition to yield **II-36**, and finally, hydrolysis of the bis osmium complex **II-37** yields the cyclized product **II-15** and regenerates OsO_4 after reoxidation of the metal.

Scheme II-16. Proposed KMnO4 oxidative cyclization via an initial [3+2] cycloaddition

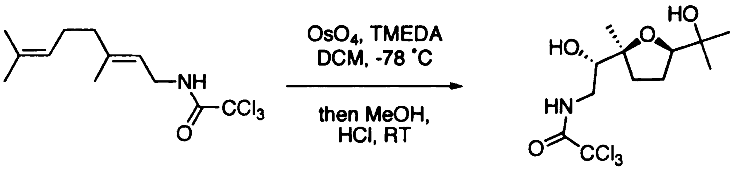


Scheme II-17. Proposed OsO4 oxidative cyclization via an initial [3+2] cycloaddition



More recently Donohoe[198] and coworkers have demonstrated that stoichiometric OsO_4 reactions with TMEDA as a ligand and 1,5-dienes produce an osmate ester that, upon treatment of this complex with MeOH and HCl, provide high yields of the desired THF diol (Scheme II-18). In this instance, since there is no additional oxidant, the cyclization is presumed to occur with an initial Os(VI) species ultimately providing a reduced Os(IV) species after hydrolysis.

Scheme II-18. Oxidative cyclization with stoichiometric OsO4 and TMEDA



In our reactions with 1,4-dienes we have obtained no evidence for or against a bis-osmate but can find no initial fault with this interpretation. Assuming, however, that the reaction proceeds in an analogous mechanism to that proposed by Piccialli mono-osmate, **II-38** would be oxidized generating **II-39** (Scheme II-19). A [3+2] rearrangement could provide **II-40**. At this point hydrolysis, or oxidation followed by hydrolysis, provide the desired product **II-18**. We believe that, based on a mono-osmate, that an alternate mechanism may still exist where intermediate **II-39** is further activated by the co-oxidant Oxone (Scheme II-19). **II-41** could then undergo a [3+2]-like rearrrangement in which the last step is the expulsion of bisulfate. The intermediacy of **II-41** may be responsible for the solvent dependence of the reaction.

Alternatively, Donohoe's interpetation could be equally as valid whereby **II-38** could directly cyclize *via* a [3+2] in the presence of a coordinating ligand to prepare **II-42**. This proposed intermediate could be hydrolyzed, or oxidized and then hydrolyzed, to provide the desired product **II-18** (Scheme II-19). Unfortunately, a similar experiment conducted with ML did not provide the desired cyclized product but instead cleanly afforded the normal dihydroxylation product (**II-27**).

Scheme II-19. Proposed mechanistic pathways for the 1,4 diene oxidative cyclization

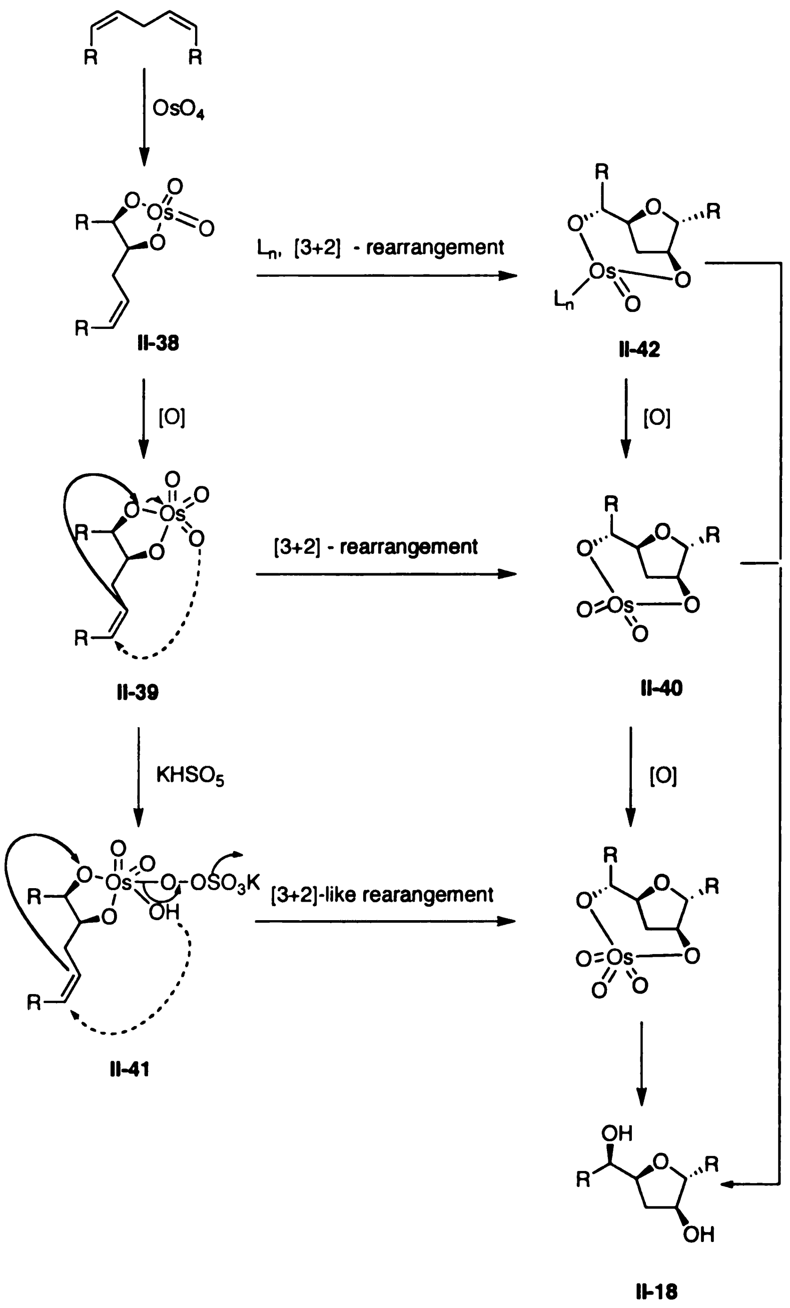
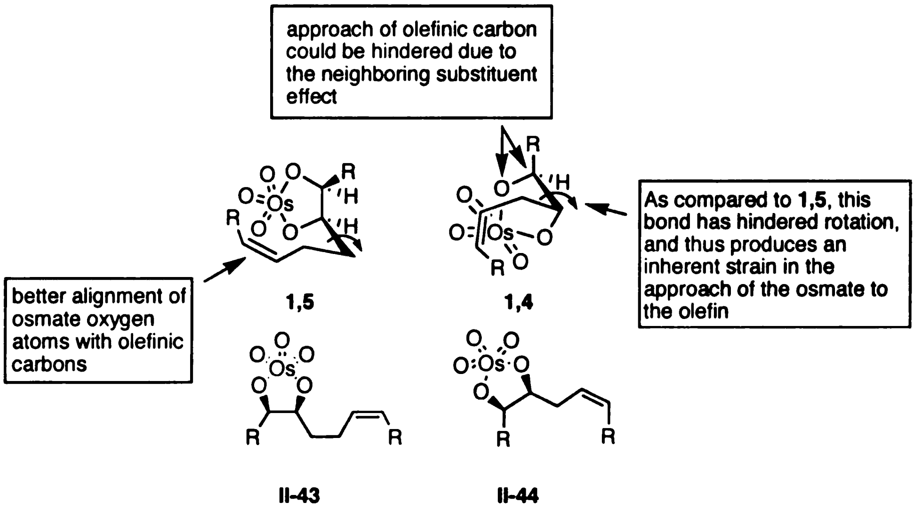


Figure II-5 illustrates a three-dimensional representation of two proposed reactive intermediates obtained from a 1,5-diene, **II-43**, and a 1,4-diene, **II-44**. The approach of the olefinic carbon to the osmate ester oxygen, which will eventually become the THF ring oxygen, is hindered by the neighboring alkyl group. This is not the case with the

1,5-diene in which the neighboring group is a methylene and does not pose a bulky presence. In the 1,5-diene example, there is good overlap between the olefin and both oxygen atoms that are incorporated into the 2,5-THF-diol product. However, the strain of the 1,4-diene, **II-44**, hinders the approach of the olefinic carbon towards the osmate ester oxygen and thus could prevent a good overlap of the atoms participating in the cycloaddition (Figure II-5). The relatively hindered approach and the overcoming of steric congestion could very well be the cause for the reaction to proceed with 1,4-dienes, but only in modest yields.

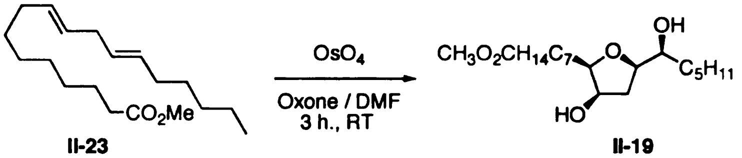
Figure II-5. Standard and 3-D projections of reactive intermediates **II-43** and **II-44**



2.2.5. Other Substrates

Based on the aforementioned [3+2] cycloaddition pathway and the observed stereoselectivity in the oxidative cyclization of **II-17** we predicted that under the same reaction conditions 9,12-*trans*-methyl lineolate, **II-23**, would produce **II-21** with an all *cis* relative stereochemistry. This reaction did unambiguously provide the known all-*cis* THF-diol **II-21** in a comparable 30% yield (Scheme II-20).[208]

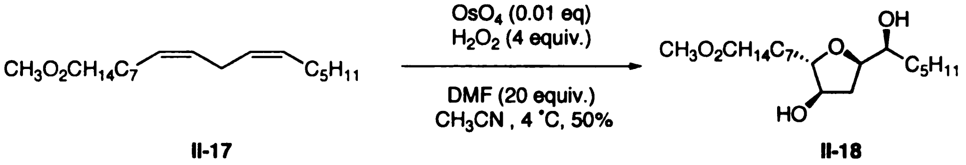
Scheme II-20. Oxidative cyclization of 9,12-*trans*-methyl lineolate (**II-23**)



2.2.6. Final Improvements

During the course of our efforts to improve the selectivity of the oxidative cleavage of olefins to aldehydes (See chapter 5.2.3) we came across several systems that we believed were applicable to perform an oxidative cyclization of a 1,4-diene. While most of these new systems failed or provided no improvement, the utilization of acetonitrile with DMF, H_2O_2, and OsO_4 provided the desired product in an improved 50% yield (Scheme II-21). Again, attempts to further optimize these conditions did not increase the yield.

Scheme II-21. Final improvements of the oxidative cyclization of ML



2.2.7. Conclusions

In summary, the oxidative cyclization of 1,4-dienes is a feasible reaction and proceeds stereoselectively through a predictable [3+2] rearrangement and has both a solvent and temperature dependence. Currently, a maximum of 50% yield has been obtained. This result has been attributed to the strain of the proposed transition state of **II-44** and the competing oxidative pathways, notably, the oxidative cleavage of the olefins, which will be discussed in the subsequent chapters, and the hydroxylations yielding diols and tetraols. The reaction is amenable to scale up with the oxidative cyclization of **II-17** (1.5 g, 5 mmol) providing a 30% yield of **II-18** following our initially developed protocol.

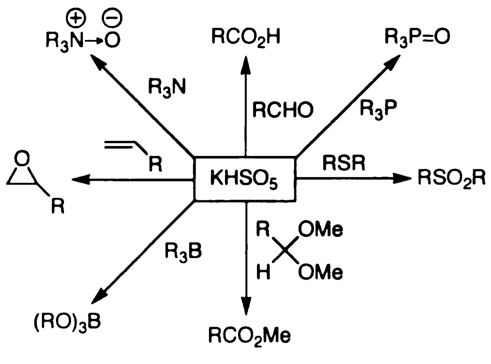
Chapter 3. Preparation of Purified Oxone and its Soluble Form by Simple and Efficient Methods

3.1. Introduction

As discussed earlier, Caro's acid (H_2SO_5) has had an intriguing history.[56,217] A potentially explosive substance that proved to be difficult to isolate, purify, and identify now exists as a shelf stable triple salt ($2KHSO_5{\bullet}KHSO_4{\bullet}K_2SO_4$) sold under the trademark name of Oxone.[59-63] The focus of this chapter is on the active oxidant within the triple salt mixture, potassium peroxymonosulfate ($KHSO_5$).

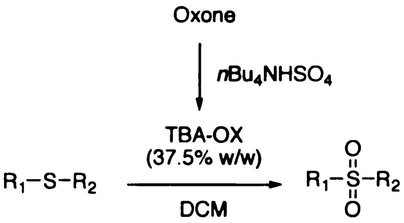
Over the past twenty years, Oxone has become a popular oxidant for the preparation of dimethyl dioxirane *in situ* from acetone and buffered water to epoxidize olefins.[80] Other advances include selective oxidations of boron, nitrogen, phosphorous, and sulfur containing compounds, while it has also been shown to oxidize acetals and aldehydes to acids or esters (Scheme III-1).[68,87,89-92,95,96,129,218-221] Generally, these oxidations are performed in water, methanol, acetone, DMF, or a miscible mixture including one of the latter solvents. The need for aqueous and/or pH controlled reactions is perhaps the most significant drawback in the use of Oxone for applications in organic chemistry.

Scheme III-1. Known oxidative pathways for Oxone



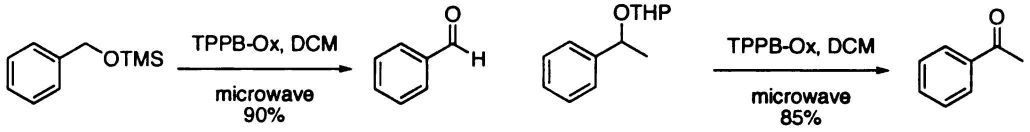
To overcome the need for aqueous conditions, several tetraalkyl ammonium salts of Oxone have been reported. These include ammonium peroxymonosulfate, tetra-*n*-butylammonium peroxymonosulfate (TBA-OX), tetra-*n*-pentylammonium peroxymonosulfate, and tetra-*n*-hexylammonium peroxymonosulfate.[67,68] In 1985, Dehmlow and coworkers. reported a methodology to prepare TBA-OX (67.5% w/w) and other tetraalkyl ammonium salts of peroxymonosulfate by cationic exchange from Oxone. However, only in 1988 did Trost and coworkers popularized TBA-OX as an organic soluble form of Oxone that was capable of oxidizing sulfides to sulfones under anhydrous conditions (Scheme III-2). This reagent was prepared from cationic exchange of the bulk potassium ions, and thus yielded a soluble version of the triple salt; i.e., tetra-*n*-butylammonium salts of sulfate and bisulfate were also formed. The oxidative activity of this soluble Oxone was 37.5% of the actual weight.

Scheme III-2. Anhydrous oxidation of sulfides to sulfones with TBA-OX



A second type of soluble peroxymonosulfate has been recently described by Hajipour and coworkers.[69-71] The reported benzyltriphenylphosphonium peroxymonosulfate (TPPB-OX) has the ability to perform some of the oxidative reactions that are well developed for Oxone (Scheme III-3). These include various oxidations of alcohols the deprotection of acetals, trimethylsilyl ethers and tetrahydropyranyl ethers to yield the corresponding alcohols.

Scheme III-3. Selective oxidative deprotections with TPPB-OX



3.2. Initial Purification Methods

While Oxone is a convenient and cheap triple salt (~\$10/Kg), there is only ~50% of active oxidant per mol of the triple salt. Several methods have been developed to prepare the pure potassium salt of peroxymonosulfate, yet these purified oxidants have not been used in synthesis, most probably due to the less than convenient procedures necessary to purify the oxidant. Appleman and coworkers isolated and characterized pure $KHSO_5$ and $KHSO_5 \cdot H_2O$ by passage of sodium peroxydisulfate ($Na_2S_2O_8$) through a cationic ion exchange resin followed by hydrolysis of the peroxydisulfate at 50 °C to yield equal molar peroxymonosulfate, $KHSO_5$, and bisulfate, $KHSO_4$. Adjustment of the pH with $KHCO_3$ and lyophylization yielded the purified $KHSO_5 \cdot H_2O$.[222] This resulted in one of two reported crystal structures of $KHSO_5 \cdot H_2O$. Interestingly, both reports were published within months of each other.[57,223] The purification of $KHSO_5 \cdot H_2O$ was revisited by Connick *et al.* in the early 90's along with a modified method for its preparation.[65] Essentially a straightforward filtration protocol starting from Oxone, followed by evaporation and crystallization resulted in the isolation of analytically pure $KHSO_5 \cdot H_2O$. Again, this method received little attention from organic chemists perhaps due to its limitations upon scale-up where the removal of large volumes of water is required.

3.3. Purification Method Development

We have developed a modified, straightforward, and stepwise procedure for the preparation of pure $KHSO_5 \bullet H_2O$ (>98% activity) from Oxone that does not require laborious water removal. Additionally, a method for the preparation of analytically pure tetra-*n*-butylammonium peroxymonosulfate (TBA-OX) from $KHSO_5 \bullet H_2O$ has been developed, along with a one step procedure to purify and solubilize the commercial Oxone triple salt with $n Bu_4NHSO_4$. Furthermore, the chemical reactivity of commercially available Oxone has been compared with that of pure $KHSO_5 \bullet H_2O$ and two soluble forms of the oxidant.

3.3.1. Preparation of Purified Oxone.

From a preparative point of view, comparison of the two reported methods to obtain $KHSO_5 \bullet H_2O$ in pure form favors the method described by Connick *et al.*[65] The procedure is easier since the starting material is Oxone, which contains the active oxidant and does not lose activity over time. This method provides the desired pure $KHSO_5 \bullet H_2O$, but requires a laborious removal of water, which is followed by crystallization of the product. This limits the scale on which the procedure can be performed easily. In order to satisfy our need for large amounts of purified Oxone, we have devised a preparative scheme that is not only facile, easy, and reproducible, but also amenable to large scale production (0.5 mol).

To prepare the purified oxidant, commercially available Oxone was added to deionized (DI) water (1:1 w/w) and swirled for 5 min until the noticeable fizzing subsided. Molecular oxygen is the gas evolved during the mixing of Oxone with water. This was shown by bubbling the gas through a suspension of CuI in aqueous NH_4OH.

The solution turned blue immediately as Cu^{+2} was generated through oxidation of Cu^{+} with oxygen. The overall loss of oxidant is less than 2% (measured via iodometric titration of the solution after the evolution of gas had ceased), and is probably due to the decomposition of Oxone by trace metal ions present in the solution.[77,224]

Potassium peroxymonosulfate is more soluble in H_2O than the corresponding sulfate salts and is dissolved preferentially. However, keeping the slurry for a prolonged time allows the salts to equilibrate and lower yields are obtained. The cold slurry (~10 °C) was filtered and washed with minimal amounts of cold DI H_2O. The initial pH of this clear solution was about 1.0. The pH of the filtrate was adjusted to 3.5 using solid $KHCO_3$ while continuously stirring the solution. At the endpoint a noticeable pink color was observed along with the formation of some precipitate. We found that overshooting the endpoint resulted in a reduced yield of the purified material. If need be, the pH can be readjusted with a few drops of concentrated H_2SO_4. This pink slurry was filtered and the solid was washed with MeOH (2 volumes) and combined with the original water filtrate resulting in the formation of more precipitate. The precipitate was again filtered and washed with MeOH (1 volume). The slightly cloudy solution containing water and MeOH (1:3 v/v) was placed in a freezer overnight to crystallize the purified product. The thick slurry was filtered and washed with Et_2O to provide $KHSO_5{\bullet}H_2O$ in 45% yield (based on oxidative equivalence as compared to Oxone). The crop was found to be 99.1% pure after triplicate iodometric titration. A second crop (4%) could be obtained if the filtrate containing the water, methanol, and ether mixture was again place in the freezer overnight. This material showed negligible loss of activity over a prolonged period of time (6 months) when stored on the bench top in an amber bottle. The hydrated pure $KHSO_5$ can be dried under vacuum at room temperature to yield pure anhydrous $KHSO_5$. Although we have not had any incidents of rapid decomposition or explosion with Oxone (triple salt or purified) when heated, the oxidizing activity is lost at 70 °C, and thus drying the sample should be carried out at room temperature. Also noteworthy is that dry $KHSO_5$ does not seem to be a contact explosive. This was tested by repeatedly hammering a sample on a smooth flat surface. The two major advantages of the latter procedure are the immediate crystallization of $KHSO_5 \bullet H_2O$ that provides analytically pure product, and the fact that large volumes of water need not be removed via evaporation. The only limit to perform this procedure effectively on a large scale is the need for a few large erlenmeyers.

There is a significant advantage for converting the commercially available Oxone to purified $KHSO_5 \bullet H_2O$ since less weight of salt is required. Oxone's ($2KHSO_5 \bullet KHSO_4 \bullet K_2SO_4$) molecular weight of 615 g/mol is equivalent to 307 g/mol of oxidizing equivalence. This is significantly more than that of $KHSO_5 \bullet H_2O$, 170 g/mol. Thus, the use of purified Oxone results in more oxidant per mol of salt. This significantly reduces the amount of oxidant needed, which could be a major factor when doing large-scale chemistry.

3.3.2. Preparation of Soluble Oxone (TBA-OX).

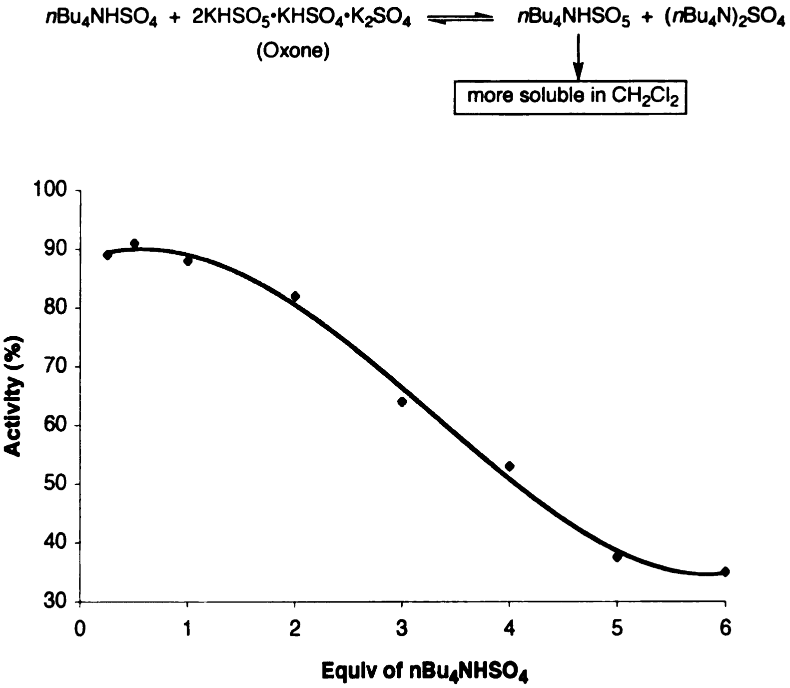
3.3.2.1. Background

As mentioned previously *n*Bu_4NHSO_5 (TBA-OX) has been prepared by both the Dehmlow and Trost groups with 61% and 37.5% activity, respectively.[67,68] While the preparative methods are similar, it is necessary to explain the differences to better understand how it has led us to obtain >98% active TBA-OX with only minor modifications. Dehmlow's procedure requires the preparation of two solutions, a concentrated aqueous solution of Oxone and a solution of $n\mathrm{Bu_4NHSO_4}$. The latter two solutions were mixed together overnight and the TBA-OX was isolated by extraction into CH_2Cl_2. In contrast, Trost's procedure utilizes 5 equiv of $n\mathrm{Bu_4NHSO_4}$ per each equiv of Oxone. The two reagents are mixed for 30 min in water, which is followed by extraction into CH_2Cl_2 to provide 37.5% active TBA-OX. The recovered activity is less than the activity of the starting Oxone. The latter two examples yield products with different activities, probably due to two factors; time of mixing prior to extraction and the ratio of $n\mathrm{Bu_4NHSO_4}$ and Oxone used for preparation of soluble Oxone. Optimization of both factors should lead to the isolation of a more pure product with higher activity.

3.3.2.2. TBA-OX Method Development: Preparation from Oxone.

We have found that the solubility of $n\mathrm{Bu_4NHSO_5}$ in CH_2Cl_2 (352 mg/mL) is higher than the solubility of $n\mathrm{Bu_4NHSO_4}$ in the same solvent (168 mg/mL). Thus, it should be possible to preferentially extract $n\mathrm{Bu_4NHSO_5}$ in favor of $n\mathrm{Bu_4NHSO_4}$. It is plausible that the excess amount of $n\mathrm{Bu_4NHSO_4}$ used in Trost's extraction procedure counterbalances the higher solubility of TBA-OX and leads to the extraction of $n\mathrm{Bu_4NHSO_4}$ along with TBA-OX. To illustrate this point Oxone (1 equiv) and varying amounts of $n\mathrm{Bu_4NHSO_4}$ were used to extract TBA-OX into CH_2Cl_2. As can be seen from Figure III-1, lowering the equivalence of $n\mathrm{Bu_4NHSO_4}$ used in the extraction greatly enhances the purity of the extracted TBA-OX (range of 35% to 91%), presumably due to the higher solubility of $n\mathrm{Bu_4NHSO_5}$ in CH_2Cl_2. Therefore, by utilizing 1 equiv of $n\mathrm{Bu_4NHSO_4}$ in a single extraction, 88% of the oxidative equivalence is obtained in soluble form (TBA-OX). Overall, much higher extraction efficiencies are realized with less $n\text{Bu}_4\text{NHSO}_4$. Additionally we do not find it necessary to mix the solids for an extended amount of time, but instead simply mixing both solids in water followed by an immediate extraction provided reproducible results. We attribute the success of this procedure to the fact that KHSO_5 dissolves preferentially over KHSO_4 and K_2SO_4, and that $n\text{Bu}_4\text{NHSO}_5$ is more soluble in CH_2Cl_2 as compared to $n\text{Bu}_4\text{NHSO}_4$ in the same solvent.

Figure III-1. Extraction of TBA-OX from Oxone into CH2Cl2 with various equiv of nBu4NHSO$_4$



3.3.2.3. TBA-OX Method Development: Preparation from $\text{KHSO}_5\bullet\text{H}_2\text{O}$

Utilizing the same extraction technique, the preparation of analytically pure TBA-OX is feasible simply by extracting pure $\text{KHSO}_5\bullet\text{H}_2\text{O}$ (1 equiv) with $n\text{Bu}_4\text{NHSO}_4$ (1.2 equiv). In fact, single extraction with purified $\text{KHSO}_5\bullet\text{H}_2\text{O}$ yields >98% active TBA-OX. The two methods described above use stoichiometric amounts of $n\text{BuNHSO}_4$ to easily prepare pure TBA-OX. The highly purified TBA-OX (>98%) has been stable for more than 6 months at room temperature in an amber vial. Moreover, removal of residual water from the purified TBA-OX under vacuum has met with no problems. This should allow for the use of TBA-OX in anhydrous form for oxidations in organic solvents without the necessity for using a great excess of oxidant or mixed tetrabutylammonium salts. It should be noted that heating of TBA-OX at 70 °C in order to speed up the drying led to the decomposition of the oxidant (complete loss of activity).

3.4. Solubility

The latter experiments strongly suggest that solubility plays a major role in obtaining pure $n\mathrm{Bu}_4\mathrm{NHSO}_5$. To demonstrate this further we have compared the solubility of $KHSO_5 \cdot H_2O$ and TBA-OX. $KHSO_5 \cdot H_2O$ possesses very poor solubility in CH_2Cl_2 such that a 1:6 (w/w) mixture of $KHSO_5 \cdot H_2O$ and TBA-OX resulted in 99% recovery of the $KHSO_5 \cdot H_2O$ after filtration. To ensure that the oxidative equivalence measured by iodometric titrations of the organic phase are not a result of $KHSO_5 \cdot H_2O$'s partial solubility in CH_2Cl_2, purified $KHSO_5 \cdot H_2O$ was vigorously stirred with CH_2Cl_2 and the filtrate was titrated for oxidizing activity. The iodometric titrations showed less than 1% activity present in the organic filtrate based on the starting amount of $KHSO_5 \cdot H_2O$.

The soluble salt forms of Oxone have a good solubility profile with various organic solvents, therefore, making it possible to use a large number of organic solvents for the oxidations (Table III-1). This is clearly an advantage over traditional Oxone chemistry, which uses water in a large number of the reported reactions. Oxone (triple salt) is practically insoluble in all solvents except water, although, the $KHSO_5$ portion of Oxone does have solubility in other solvents such as DMF. $KHSO_5 \cdot H_2O$ is also soluble in water, however, it exhibits notable solubility in DMF (100 mg/mL) and slight solubility in MeOH. TBA-OX is completely soluble in DMF, acetone, water, $CHCl_3$, CH_2Cl_2, CH_3NO_2, CH_3CN, and MeOH at 100 mg/mL (this is not to say the solutions are saturated). Other solvents such as EtOAc, hexanes, CCl_4, benzene, THF, and Et_2O were not able to dissolve TBA-OX. Comparably, $Ph_3BnPHSO_5$ was soluble only in MeOH, $CHCl_3$, CH_2Cl_2, and DMF and insoluble in all other solvents tested. Since these salts all exhibit a lack of solubility in solvents such as hexanes or ether, we feel that this could perhaps be beneficial since it can provide an easy route to remove the oxidant and its by-products (usually $XHSO_4$) by simple precipitation from the reaction mixture upon addition of hexanes or ether.

Table III-1. Solubility profiles of various $XHSO_5$ salts

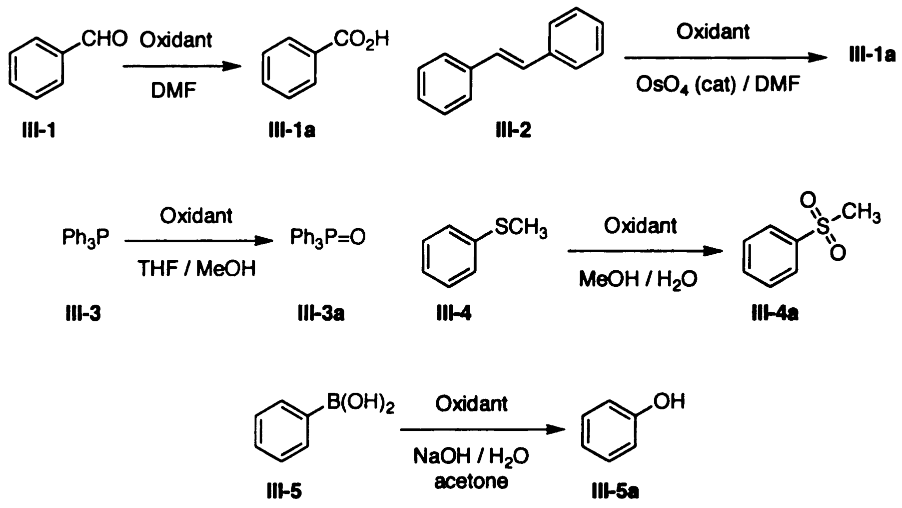
Solvent	Oxone	$KHSO_5 \cdot H_2O$	TBA-OX	TPPB-OX
DMF	A	B	C	C
Acetone	D	D	C	D
Water	C	C	C	D
$CHCl_3$	D	D	C	C
CH_2Cl_2	D	D	C	C
CH_3NO_2	D	D	C	D
CH_3CN	D	D	C	D
MeOH	D	B	C	C
EtOAc	D	D	D	D
Hexanes	D	D	D	D
Benzene	D	D	D	D
CCl_4	D	D	A	D
THF	D	D	A	D
Et_2O	D	D	D	D

A) slightly soluble; B) ~100 mg/mL; C) >100 mg/mL; D) insoluble

3.5. Peroxysulfate Salts as Oxidizing Reagents

As discussed above, Oxone is an effective oxidant in many types of transformations. Having at hand a simple method to secure both pure $KHSO_5{\bullet}H_2O$ and its pure soluble form, TBA-OX, a comparison of their reactivity was pursued. Through a set of simple experiments Oxone, $KHSO_5{\bullet}H_2O$, TBA-OX, and $Ph_3PBnHSO_5$ (TPPB-OX) were compared directly in five different reaction manifolds. The results are summarized in Table III-2. Essentially, Oxone and $KHSO_5{\bullet}H_2O$ showed no significant differences in reactivity or yield of isolated products in the reactions studied, namely, oxidation of benzaldehyde to benzoic acid, oxidative cleavage of *trans*-stilbene to benzoic acid, oxidation of triphenylphosphine to triphenylphosphine oxide, oxidation of thioanisol to methylphenylsulfone, and oxidative cleavage of phenylboronic acid to phenol. On the other hand, TBA-OX was ineffective in oxidizing benzaldehyde to benzoic acid and not very effective in cleaving the C-B bond of phenylboronic acid providing phenol in only 40%. However, as reported by others for the less pure TBA-OX, it was efficient in oxidation of both phosphorous and sulfur. Use of TBA-OX for oxidative cleavage of olefins was attempted with *trans*-stilbene. Although, both Oxone and $KHSO_5{\bullet}H_2O$ yielded benzoic acid as the oxidation product, TBA-OX led to the isolation of benzaldehyde as the sole product in 88% yield. Clearly, the soluble form of Oxone has attenuated activity. This is a beneficial outcome since selectivity can be exercised based on the oxidant utilized for the reaction. TPPB-OX is a rather poor oxidant for the reactions illustrated here except for the oxidation of triphenylphosphine, which resulted in a 98% yield of triphenylphosphine oxide.

Table III-2. Oxidation of various functionalities with Oxone and soluble Oxone.[a]



Substrate		Product		Oxone	KHSO$_5$	TBA-OX	TPPB-OX
benzaldehyde	**III-1**	benzoic acid	**III-1a**	97%	94%	N.R.[b]	N.R.[b]
trans-stilbene	**III-2**	benzoic acid	**III-1a**	95%	97%	88%[c]	25%[c]
triphenylphosphine	**III-3**	triphenylphosphine oxide	**III-3a**	98%[d]	99%	97%	98%
thioanisol	**III-4**	methylphenylsulfone	**III-4a**	95%[d]	90%	91%	52%
phenylboronic acid	**III-5**	phenol	**III-5a**	86%[d]	80%	40%	30%

a) See experimental for reaction details. b) Starting material was recovered (90% for TBA-OX, 85% for TPPB-OX). c) Yield of **III-1**. d) Yield reported in literature.

3.6. Work-up Protocols

During the course of our study we found that using purified reagents showed only minor reactivity differences, and that the work-up was facile for all substrates on a 1 mmol scale. However, extraction and chromatography are more tedious upon scale-up. To investigate this further we evaluated the oxidation of triphenylphosphine with Oxone, $KHSO_5 \cdot H_2O$, $n$$Bu_4NHSO_5$ (30%, containing other $n$$Bu_4N$-sulfate salts) and $n$$Bu_4NHSO_5$ (98%) on a 10 mmol scale. Not surprisingly, the starting material was cleanly converted to the corresponding triphenylphosphine oxide over a 2 h period with all the oxidants utilized. In a typical experiment, removal of the organic solvent under reduced pressure by 50% was followed by precipitation of the salts with Et_2O. The precipitation was completed upon storing of the filtrate in the freezer for 3 h, and the salts were removed by filtration to provided excellent yields of the product (>95 % in all cases after removal of solvent). Oxidation with pure *n*Bu_4NHSO_5 led to only 3% of the tetrabutylammonium salts left over in the final product. However, when 30% active *n*Bu_4NHSO_5 was used the product was contaminated with 35% of tetrabutylammonium salt. Both Oxone and $KHSO_5{\bullet}H_2O$ yielded clean products, but less Et_2O was required for precipitation and washing using the purified reagents. Thus, for large-scale reactions it is advantageous to use purified oxidant to reduce the amount of solvent needed for purification. Also, use of pure soluble oxidants yields products of higher purity after a simple filtration of the tetrabutylammonium salts.

3.7. Conclusions

Oxone is a cheap commercially available oxidant that easily oxidizes numerous functional groups. In this study, we have developed a facile procedure for the preparation of pure $KHSO_5{\bullet}H_2O$ in a straightforward and efficient manner, which is amenable to large-scale production. An improved procedure for the preparation of *n*Bu_4NHSO_5 (soluble Oxone) has also been developed that requires much less *n*Bu_4NHSO_4 and delivers high purity in a single extraction from either Oxone or $KHSO_5{\bullet}H_2O$. The purified Oxone ($KHSO_5{\bullet}H_2O$) was as effective as Oxone, but only required half the mass of oxidant, thus making the reaction work-ups more facile. Column chromatography was generally not necessary with either Oxone or $KHSO_5{\bullet}H_2O$ reactions. The high purity of TBA-OX led to easier purification since less tetrabutylammonium ions were present. TBA-OX was also unique in that it does not oxidize aromatic aldehydes, but remained as effective as Oxone in the oxidative cleavage reaction, thus providing an alternate oxidant for procuring aldehydes instead of carboxylic acids.

Chapter 4. Osmium Tetroxide Promoted Catalytic Oxidative Cleavage of Olefins. An Organometallic Ozonolysis

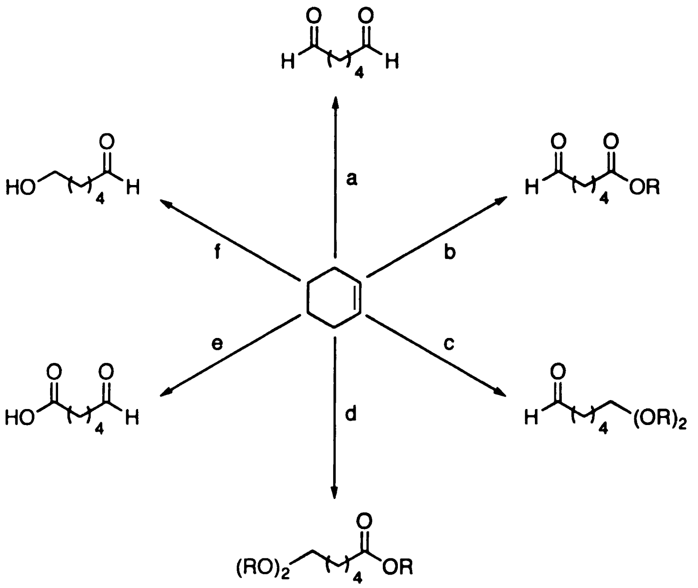
4.1. Introduction

Oxidative cleavage of olefins is one of the paramount reactions developed in organic chemistry. Many oxidative pathways discussed in the literature can be summarized into two main methodologies; i) Transformation of olefins into 1,2-diols followed by cleavage with $NaIO_4$ or other oxidants[225], or ii) Ozonolysis, in which the olefin is directly cleaved into a variety of functionalized products depending on the workup conditions.[3,4,226]

The standard method for the direct oxidative cleavage of olefins is ozonolysis. This reaction has been well-developed and yields aldehydes or carboxylic acids upon reductive or oxidative workup, respectively.[226] Simple modification of the workup also gives rise to terminally differentiated functionality, such as combinations of ester-aldehydes, acetal-aldehydes, acetal-esters, and carboxylic acids in combination with acetals and alcohols.[18-20]

A lingering problem with ozonolysis is the major concern for safety; serious accidents due to explosions have been reported.[227-231] Under normal conditions, ozonolysis reactions form ozonides and can also produce peroxides. These by-products are hazardous and can lead to explosions upon concentration. This has been a point of concern for the pharmaceutical industry during large-scale reactions, and also the paper recycling industry, which utilizes ozonolysis during the decolorization process of recycled paper.

Scheme IV-1. Various pathways of ozonolitic workup

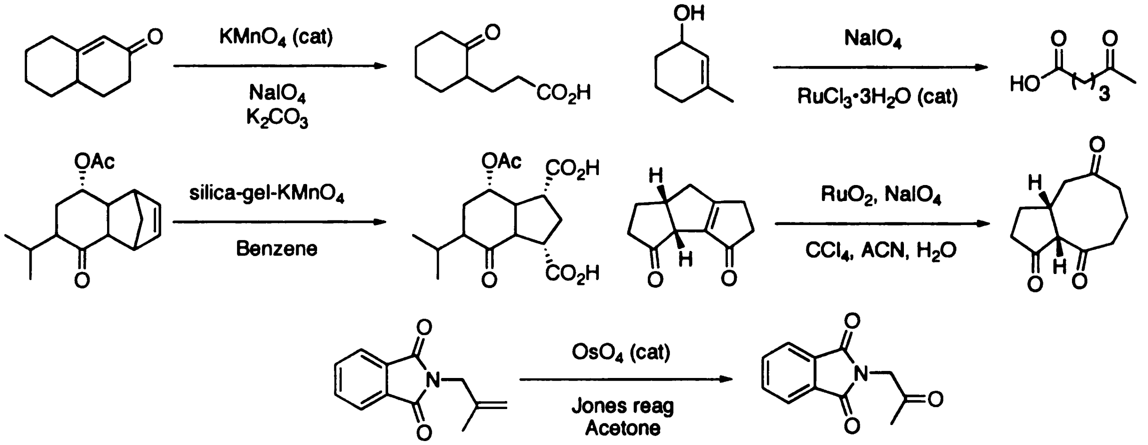


a) 1. O_3, CH_3COCO_2Me, -78°C 2. PPh_3
b) 1. O_3, ROH, $NaHCO_3$ 2. Ac_2O, TEA
c) 1. O_3, ROH, TsOH 2. DMS. $NaHCO_3$
d) 1. O_3, ROH, TsOH 2. Ac_2O, TEA
e) 1. O_3, CH_3COCO_2Me, -78°C 2. TEA
f) 1. O_3, CH_3COCO_2Me, -78°C 2. $LiBH_4$ 3. PPh_3

As important as ozonolysis has proven to be in synthetic chemistry, there are relatively few alternate reactions that duplicate the same transformation; i.e., the direct cleavage of olefins in one step without the intermediacy of 1,2-diols. Ruthenium catalyzed oxidative cleavage of olefins with $RuCl_3$ or RuO_4 to aldehydes with various co-oxidants has been reported, although it is not clear whether or not diol intermediates are generated.[232-234] Direct oxidative cleavage of olefins with OsO_4, without the intermediacy of 1,2-diols, has been suggested by using either hydrogen peroxide or *t*-butyl hydrogen peroxide as co-oxidants, albeit in low yields.[23,36] In these instances mixtures of over oxidized products such as α-hydroxy ketones, aldehydes, and carboxylic acids are present.

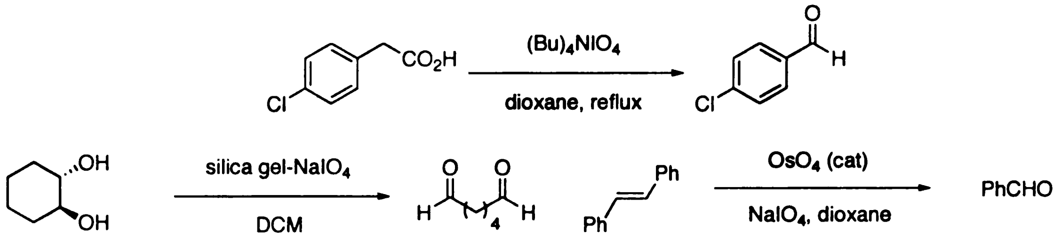
Alternatively, the Lemieux-Johnson reaction, which typically uses $NaIO_4$, and its variants are widely used for the one pot oxidative cleavage of 1,2-diols, and can be coupled to the dihydroxylation of olefins with Os, Mn, Ru, and W oxides. Potassium permanganate ($KMnO_4$), for example, is a cheap and useful oxidant but is not soluble in many organic solvents and is often non-specific.[14,212,235-237] Much work in this area has focused on the use of various phase transfer catalysts and solid supported reagents to modify the reactivity and selectivity of permanganate, but while these reactions are all milder and more selective than permanganate itself, this has not proven to be a general solution to the problem (Scheme IV-2).[236,238-243]

Scheme IV-2. Reactions with Os, Mn, and Ru oxides



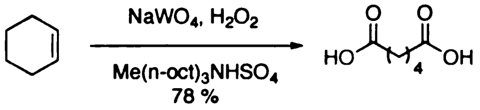
Sodium periodate ($NaIO_4$) is another useful reagent for oxidations including cleaving diols.[16] This reagent is also limited by its insolubility in organic solvents. Quaternary alkyl ammonium periodate,[244,245] potassium metaperiodate along with phase transfer catalysts,[246] and silica gel supported $NaIO_4$[247] are reported examples that increase the solubility and reactivity of the oxidant. These modifications have been successful to some extent; however, the drawback of these reactions is the necessary intermediacy of diol precursors to the cleavage. Alternatively, catalytic OsO_4 and $NaIO_4$ have been used together to oxidatively cleave olefins in a one-pot procedure.[211] Unfortunately, this reaction often produces undesirable byproducts. This fact necessitates that the diol precursor is independently prepared before a separate periodate cleavage. Ultimately, this becomes a two-step process instead of a more desirable one-pot method. Also, other 1,2-diols within target molecules need to be protected.

Scheme IV-3. General periodate oxidations



Noyori and coworkers have also developed a "green" route for the direct oxidation of olefins to carboxylic acids with catalytic Na_2WO_4 and hydrogen peroxide as the terminal oxidant (Scheme IV-4). This is an elegant procedure for production of high valued compounds such as adipic acid from cyclohexene in large quantities using cheap oxidants, however, it is not very general in its scope and is not tolerant of many functional groups.[248]

Scheme IV-4. Green oxidative cleavage of cyclohexene with Na_2WO_4

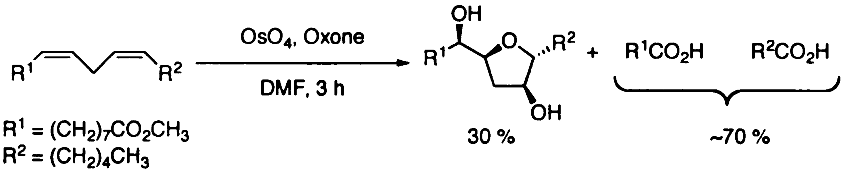


Development of the many oxidative cleavage methodologies is a testimony to the importance of this reaction for synthetic chemists. Ultimately, organic chemists will utilize the most appropriate conditions for their particular transformation amongst the large body of possible reaction tools. Thus, it is very important to pursue other reaction manifolds that could be more efficient, milder, and act as a substitute for established transformations.

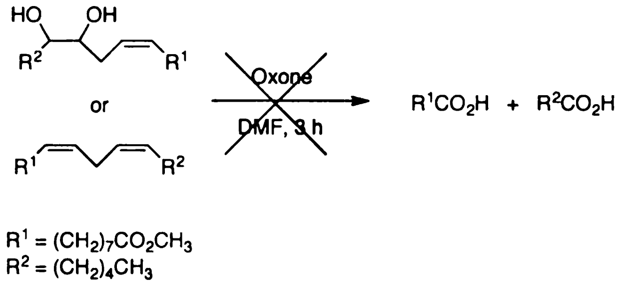
4.2. Initial Observations

Our interest in this area stemmed from previous work in the oxidative cyclization of 1,4-dienes, in which OsO_4 and various co-oxidants were used to promote the desired cyclization pathway.[249] Low yields of the cyclized products were attributed to a large number of side reactions including diol and tetrol formation, oxidative cleavage to aldehydes when $NaIO_4$ was used as a co-oxidant, and the formation of carboxylic acids especially when Oxone was used as the co-oxidant (Scheme IV-5). We noted early on that OsO_4 was necessary for the cleavage reactions with Oxone because subjecting either methyl lineolate or its diol to the reaction conditions without OsO_4 did not provide oxidized products, but instead returned the starting material untouched (Scheme IV-6).

Scheme IV-5. Initial OsO4—Oxone results

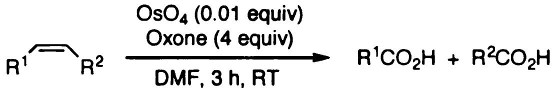


Scheme IV-6. Requirement of OsO4 for the oxidative cleavage of olefins



Further investigation into the nature of the over-oxidized products and optimization of that side reaction has led to a selective oxidative cleavage of olefins to yield carboxylic acids using catalytic OsO_4 and Oxone in DMF (Scheme IV-7). Herein, we report initial observations on a mild, organometallic alternative to ozonolysis.

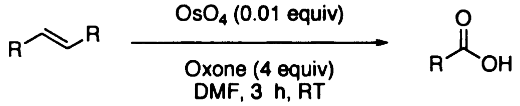
Scheme IV-7. Selective oxidative cleavage with OsO4—Oxone—DMF



4.3. Results

Initially, we investigated the oxidative cleavage of olefins in simple alkyl and aromatic compounds (Table IV-1). Both *cis*- and *trans*-stilbene, **IV-1** and **IV-2**, cleanly provided two equivalents of benzoic acid, **IV-1a**, in 95% yield. *trans*-Cinnamic acid **IV-3**, styrene **IV-4**, and methyl cinnimate, **IV-5**, were also easily converted to **IV-1a** in 97%, 94%, and 96% yields, respectively. Cyclohexene, **IV-6**, and cyclooctene, **IV-7**, provided the corresponding adipic acid, **IV-6a**, and suberic acid, **IV-7a**, in good yields. Additionally, simple alkyl olefins such as 1-decene, **IV-8**, 1-nonene, **IV-9**, and *trans*-2-nonene, **IV-10**, all provided the appropriate alkyl carboxylic acids in 93%, 90%, and 93%, respectively. Similarly, methyl oleate **IV-11**, provided a clean conversion to nonanoic acid, **IV-8a**, and nonanedioic acid monomethyl ester, **IV-11a**.

Table IV-1. Oxidative cleavage of simple olefins[a]



Entry	Substrate	Product	Yield[b] (%)
1	*cis*-stilbene, **IV-1**	benzoic acid, **IV-1a**	95
2	*trans*-stilbene, **IV-2**	**IV-1a**	95
3	*trans*-cinnamic acid, **IV-3**	**IV-1a**	97
4	styrene, **IV-4**	**IV-1a**	94
5	methyl cinnimate, **IV-5**	**IV-1a**	96
6	cyclohexene, **IV-6**	adipic acid, **IV-6a**	50 (94)[c]
7	cyclooctene, **IV-7**	suberic acid, **IV-7a**	82 (92)[c]
8	1-decene, **IV-8**	nonanoic acid, **IV-8a**	93
9	1-nonene, **IV-9**	octanoic acid, **IV-9a**	90
10	2-*trans*-nonene, **IV-10**	heptanoic acid, **IV-10a**	93
11	methyl oleate, **IV-11**	**IV-8a** + **IV-11a**	80 (93)[c]

a) All reactions were performed with olefin (1 equiv), Oxone (4 equiv), and OsO_4 (0.01 equiv) in DMF for 3 h at RT. b) Isolated yields. c) GC yield.

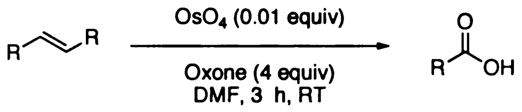
A number of mono-substituted, 1,1-disubstituted, 1,2-disubstituted, tri-substituted, and tetra-substituted olefins containing a variety of functional groups were also subjected to the oxidative cleavage (Table IV-2). In most cases a yield of 80% or greater of the desired ketene or carboxylic acid was obtained.

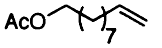
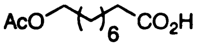
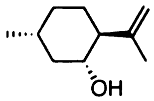
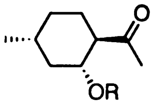
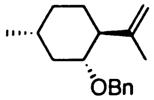
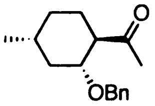
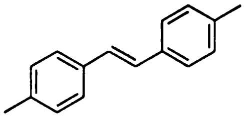
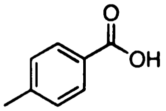
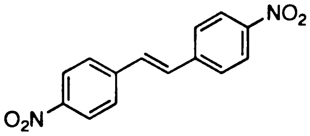
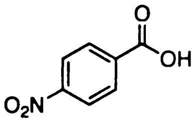
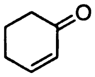
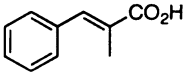
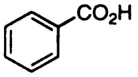
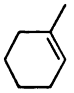
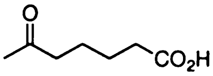
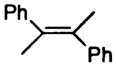
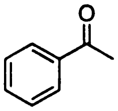
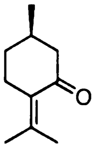
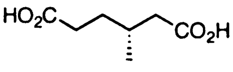
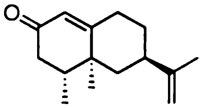
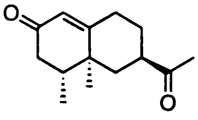
Acetate **IV-12** reacted smoothly to provide the carboxylic acid **IV-12a** in 93% yield. (-)-Isopulegol, **IV-13**, was oxidized to furnish the desired hydroxyketone **IV-13a** and formate **IV-13b** in 78% total yield. The formate could be easily hydrolyzed with base; therefore, it is clear that the alcohol functionality is immune to oxidation. The benzyl-protected isopulegol **IV-14** provided 80% of the desired ketone **IV-14a**. Substituted stilbenes, **IV-15** and **IV-16** were also cleanly converted into the corresponding acid products, **IV-15a** and **IV-16a** without difficulty in 91% and 95% yield, respectively.

Interestingly, α-methyl cinnamic acid, **IV-18**, and 1-methyl cyclohexene, **IV-19**, (examples of trisubstituted olefins) did not deliver the desired product in high yields under standard conditions. Seemingly, the hydrolysis of the osmate intermediate leads to the formation of the observed diol side product, presumably as a result of the acidity of Oxone. However, addition of solid $NaHCO_3$ to the reaction substantially improved the results, leading to high yields of the oxidatively cleaved trisubstituted olefins **IV-18** and **IV-19**. Cleavage of the tetrasubstituted olefin **IV-20** in presence of $NaHCO_3$ was also successful in yielding acetophenone, **IV-20a**.

α,β-Unsaturated systems pose an interesting case since their cleavage would yield an α-dicarbonyl functionality. Oxidation of 2-cyclohexenone (Table IV-2, entry 6) provided pentanedioic acid, most probably via the α-dicarbonyl intermediate which decarboxylates under the oxidative conditions. Baeyer-Villiger like oxidative cleavage of α-dicarbonyls have been reported previously with peroxy compounds, and is likely the operative route in the latter oxidation.[99,250] 1,2-Cyclohexanedione, subjected to the same reaction conditions (without OsO_4) was also oxidized to adipic acid (See Chapter VI), thus demonstrating the lability of the α-dicarbonyl functionality. In a similar fashion, (+)-pulegone, **IV-21**, yielded the dicarboxylic acid **IV-21a** via the intermediacy of an α-diketone along with small amounts of **IV-21b** (16%), the simple hydrolyzed Baeyer-Villiger product.

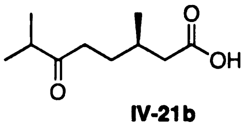
Table IV-2. Oxidative cleavage of assorted olefins[a]



Entry	Substrate		Product		Yield (%)[b]
1		**IV-12**		**IV-12a**	93
2		**IV-13**		**IV-13a** R=H **IV-13b** R=CHO	44 34
3		**IV-14**		**IV-14a**	80
4		**IV-15**		**IV-15a**	91
5		**IV-16**		**IV-16a**	95
6		**IV-17**		**IV-17a**	92
7		**IV-18**		**IV-1a**	82
8		**IV-19**		**IV-19a**	80
9		**IV-20**		**IV-20a**	85
10		**IV-21**		**IV-21a**	67
11		**IV-22**		**IV-22a**	60
12		**IV-23**	Recovered SM	**IV-23**	96

[a]All reactions were performed with olefin (1 equiv), Oxone (4 equiv), and OsO_4 (0.01 equiv) in DMF for 3 h at RT. [b]Isolated yields.

Figure IV-1. Structure of **IV-21b**



IV-21b

Treatment of nootkatone, **IV-22**, containing dissimilar olefins under standard conditions furnished ketone, **IV-22a**, showing that selectivity in oxidation is also obtainable. Lastly, alkyne **IV-23** was subjected to the cleavage conditions, however, it proved immune to oxidation and starting material was recovered, thus indicating selectivity for alkenes vs. alkynes.

4.4. Mechanistic Proposal

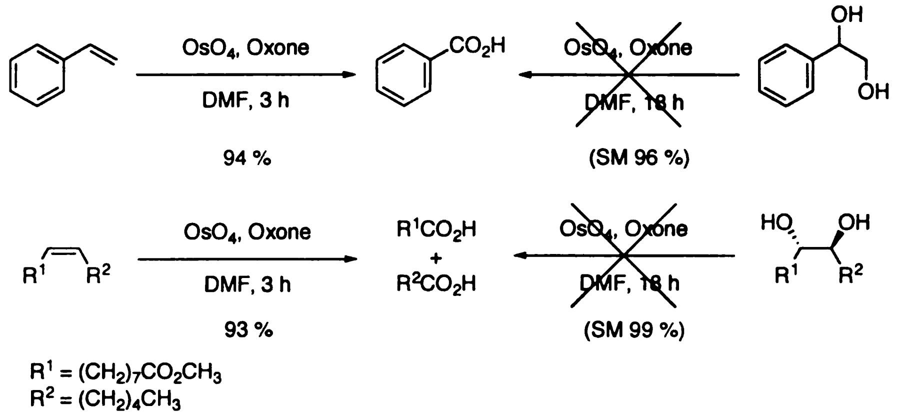
Oxone, a mono potassium peroxysulfate salt, is known to be an effective oxidant for numerous transformations. For instance, Oxone is well known to prepare sulfones or sulfoxides from sulfides, oxides of both phosphorous and nitrogen, and several reports have shown that Oxone can also be used to oxidize aldehydes to carboxylic acids.[68,87-92,95,96,218,221,251] We believe that in this system Oxone functions in three distinct oxidizing roles: 1) oxidizes the initially formed osmate back to Os(VIII), 2) promotes the oxidative cleavage to an intermediate aldehyde, and 3) independently oxidizes the aldehyde to the carboxylic acid.

We are not certain as to the mechanism of the oxidative cleavage, however, we do propose the intermediacy of an osmate ester, which undergoes the cleavage. We do not believe that the 1,2-diol is an intermediate of this reaction for two reasons: i) The oxidation of olefins with the OsO_4-Oxone system proceeds just as well under anhydrous conditions; i.e, there is no hydrolysis of the osmate ester. ii) Submission of 1,2-diols to this reaction does not yield products, and in fact starting diol is recovered quantitatively.

To highlight the fact that 1,2-diols do not oxidize under our reaction conditions to yield product, and thus are not intermediates during the cleavage, two test reactions were performed with both styrene glycol and methyl 9,10-dihydroxyoctadecanoate. In both cases, their corresponding olefin counterparts: i.e. styrene and methyl 9,10-octadecanoate were also subjected to the oxidative cleavage reaction simultaneously [Oxone (2 equiv), OsO_4 (0.01 equiv), 3 h, RT]. The reactions were monitored by ^1H NMR, TLC and GC and clearly showed that the olefins were cleanly oxidized to their corresponding carboxylic acids; however, the diols in both cases remained untouched and were recovered in quantative yields.

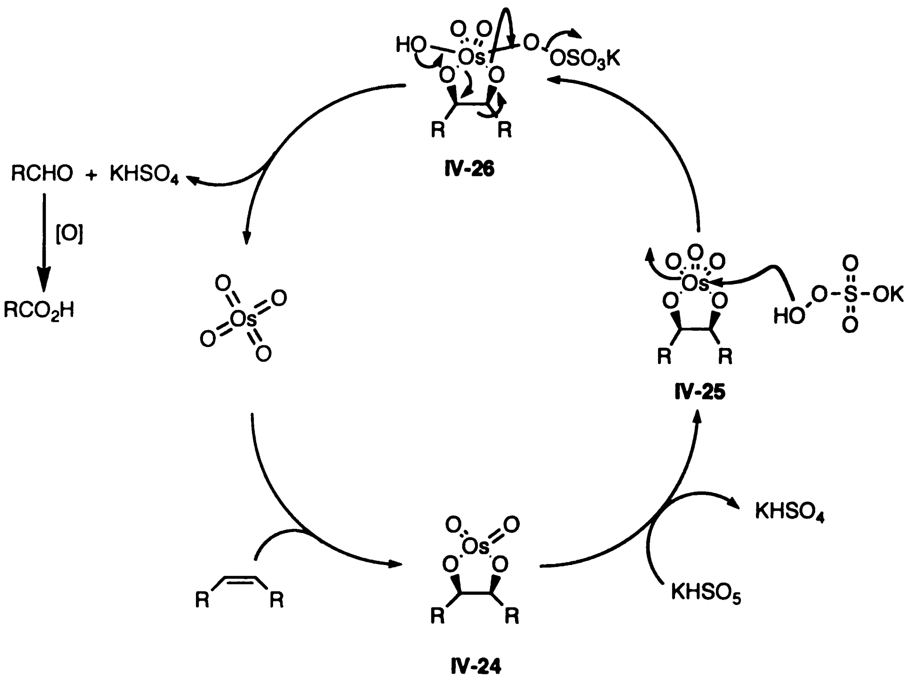
OsO_4 does not cleave 1,2-diols independently either. From the latter experiment and literature precedent it is clear that Oxone also does not cleave or oxidize alcohols or 1,2-diols without other co-factors present. Thus it is reasonable to assume that this oxidative cleavage proceeds without the formation of an intermediate 1,2-diol, and in fact the osmate ester is activated for the direct cleavage of the C-C bond.

Scheme IV-8. Diols are not intermediates



Scheme IV-9 depicts our proposed mechanism, in which osmate **IV-24** is oxidized by Oxone to furnish **IV-25**, which is subsequently attacked by the same to yield intermediate **IV-26**. Fragmentation of **IV-26** regenerates OsO_4 and produces two aldehydes, which can undergo further oxidation to yield carboxylic acids.

Scheme IV-9. Proposed catalytic cycle



To highlight the utility of this reaction, the oxidative cleavage of **IV-2** was successfully scaled to 50 mmol (9 g) and the amount of OsO_4 required was greatly reduced from 1 mol % to 0.02 mol % (5000 turnovers). The isolated yield of this reaction remains high at 95%; 88% after crystallization from chloroform.

4.5. Other Examples

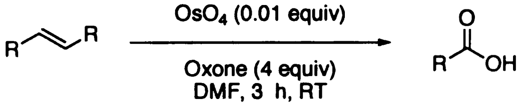
Since our initial publication in this area, several new substrates have been examined. In general we continued to be interested in aromatic olefins, which had different functionalities on one side of the olefin and various other alkyl olefins (Table IV-3). Trisubstituted olefin, **IV-27**, underwent clean reaction with the addition of $NaHCO_3$ as previously seen in 98%. The conjugated ketone **IV-28** and the long chain alkyl aromatic **IV-29** provided reasonable yields at 83% and 90% respectively. Table IV-

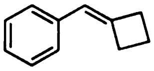
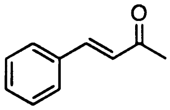
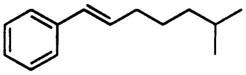
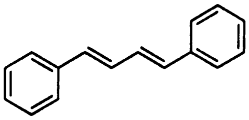
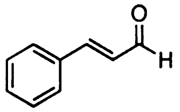
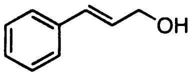
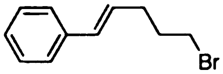
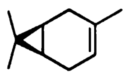
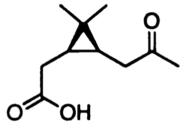
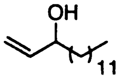
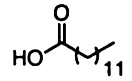
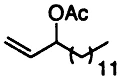
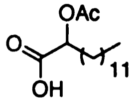
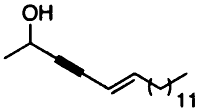
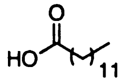
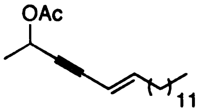
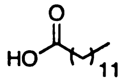
3, entry 4, which contains a conjugated diene, has been reported to be problematic for complete oxidative cleavage, but in this instance there were no complications and provided **IV-1a** in 93% yield. Cinnamyl aldehyde, **IV-31**, did not oxidatively cleave very well providing a modest 41% yield. There is no seemingly good explanation because even if cinnamyl aldehyde underwent a Michael addition of $KHSO_5$ instead of direct osmium assisted oxidative cleavage the resultant 1,3-ketol should still be able to progress to benzoic acid (See Chapter 6). Cinnamyl alcohol, **IV-32**, and 1-bromo-5-phenyl-4-pentene, **IV-33**, however, proceeded in 84% and 98% yield without incident.

The trisubstituted cyclic olefin careen, **IV-34**, proved to be a very difficult substrate to oxidatively cleave. Addition of $NaHCO_3$ continued to be necessary, but the best attainable yield was 44% of the desired acid product **IV-34a**. Analysis of the reaction byproducts demonstrated that the diol, **IV-34b**, and the formylated diol, **IV-34c**, were the major byproducts (Figure IV-2).

The allylic alcohol **IV-35** was subjected to normal oxidative cleavage conditions, but the resultant product was not the expected α-hydroxyacid but instead an even further oxidized product where the α-hydroxyacid functionality cleaved and provided the simple acid product **IV-35a** in 95% yield. This cleavage could be stopped by protection as the acetate providing α-acetoxyacid, **IV-36a**, in 86% yield. We had some hope that the homoallylic alcohol might serve as an intramolecular trap to provide the acid-ester **IV-37b**, but this product was not seen at all and the only isolable product was pentanoic acid in 98% yield (Figure IV-3). The last two examples were pursued because we had previously reported that alkynes do not undergo oxidative cleavage with our DMF—OsO_4—Oxone system. We hoped to be able the isolate the alkynyl acid from the.

Table IV-3. Additional oxidative cleavage examples[a]

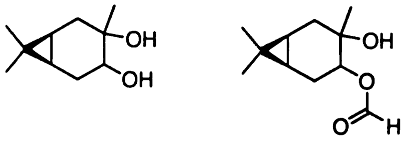


Entry	Substrate		Product		Yield (%)[b]
1		**IV-27**	benzoic acid	**IV-1a**	98
2		**IV-28**	benzoic acid	**IV-1a**	83
3		**IV-29**	benzoic acid	**IV-1a**	90
4		**IV-30**	benzoic acid	**IV-1a**	93
5		**IV-31**	benzoic acid	**IV-1a**	41
6		**IV-32**	benzoic acid	**IV-1a**	84
7		**IV-33**	benzoic acid	**IV-1a**	98
8		**IV-34**		**IV-34a**	44
9		**IV-35**		**IV-35a**	95
10		**IV-36**		**IV-36a**	86
11		**IV-37**	pentanoic acid	**IV-37a**	98
12		**IV-38**		**IV-35a**	93
13		**IV-39**		**IV-35a**	97

[a] All reactions were performed with olefin (1 equiv), Oxone (4 equiv), and OsO_4 (0.01 equiv) in DMF for 3 h at RT. [b] Isolated yields.

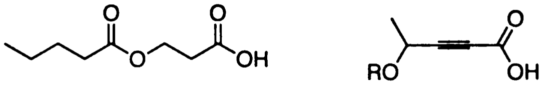
left hand portion of the eneyne, but this product could not be found for either the free alcohol, **IV-38**, or the acetate, **IV-39**, yet the long chain acid, **IV-35a**, was recovered in good yield for both substrates, 93 % and 97 % respectively

Figure IV-2. Side products from Table IV-3 entry 7



IV-34b **IV-34c**

Figure IV-3. Desired products from Table IV-3 entries 11, 12 and 13



R = H, Ac

4.6. Conclusions

During the course of our investigation we have been able to show that a simple, mild, and efficient oxidative cleavage of olefins takes place with OsO_4 and Oxone in DMF, to provide ketones or carboxylic acids. Modification of the reaction to deliver aldehydes exclusively is in progress. This reaction can be considered as an organometallic alternative to ozonolysis

Chapter 5. Extension of the Oxidative Cleavage Methodology

5.1. Introduction

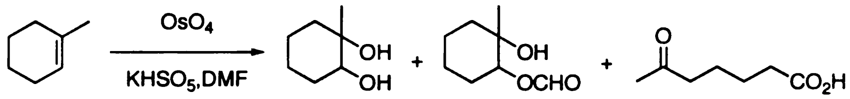
In the ozonolysis of olefins, aldehydes, carboxylic acids, and esters can be obtained depending on the work-up procedure. In our previous studies on the oxidative cleavages of olefins, carboxylic acids were obtained exclusively by using an OsO_4—Oxone—DMF system (See Chapter 4).[6] Our laboratory was interested in developing a suitable oxidative cleavage system that would provide easy access to aldehydes, esters, and lactones as well. These attempts are described below.

5.2. New Oxidative Cleavage Methodologies

5.2.1. Preparation of Aldehydes with $KHCO_3$

In the oxidations of olefins with OsO_4—Oxone—DMF we noted that the immediate products of oxidation were aldehydes, which could be observed *via* GC.[6] However, the reactions did not stop at the aldehyde oxidation state and simply reducing the amount of Oxone to less than equivalent amounts did not provide the aldehydes either. Instead carboxylic acids were the major products. We believed that by increasing the rate of the oxidative cleavage of the intermediate osmate ester that we may overcome the facile oxidation of aldehydes, thus being able to isolate the desired aldehyde products. One way we thought to promote the rate of oxidative cleavage was through the use of additives. This idea came about from the fact that the addition of $NaHCO_3$ to tri and tetra substituted olefins had improved the yield of the desired acid cleavage reactions.[6] In those instances we believed that the problem was also the oxidative cleavage rate because the major byproducts were the hydrolyzed osmate and the structurally related formylated diol (Figure V-1). Additionally, additives such as methanesulfonamide and pyridine are frequently used in dihydroxylation reactions to increase the rate of hydrolysis of the intermediate osmate ester.[1]

Figure V-1. Products from the oxidative cleavage of methylcyclohexene



For an initial screen we wanted to know if simply adding enough base as an additive would prevent the oxidation of benzaldehyde, **V-1a** to benzoic acid **V-1b**. When we added 1 to 4 equiv of $NaHCO_3$ and 1 equiv of Oxone to benzaldehyde in DMF the over-oxidation was not prevented and clean conversion to **V-1b** occurred. Interestingly, by changing the additive to $KHCO_3$ (1 to 4 equiv), a majority of the starting material could be maintained overnight with using 4 equiv of base (Table V-1).

Table V-1. Oxidations of benzaldehyde in the presence of base[a]

Entry	Substrate	Solvent	Base	Equivalents	**V-1a**[b]	**V-1b**[b]
1	Benzaldehyde, **V-1a**	DMF	$NaHCO_3$	1	0	100
2	**V-1a**	DMF	$NaHCO_3$	2	0	100
3	**V-1a**	DMF	$NaHCO_3$	3	0	100
4	**V-1a**	DMF	$NaHCO_3$	4	0	100
5	**V-1a**	DMF	$KHCO_3$	1	0	100
6	**V-1a**	DMF	$KHCO_3$	2	0	100
7	**V-1a**	DMF	$KHCO_3$	3	20	80
8	**V-1a**	DMF	$KHCO_3$	4	83	17

a) All reactions were performed with olefin (1 equiv), Oxone (1.2 equiv), Base and OsO_4 (0.01 equiv) in DMF (0.1 M) for 18 h at RT. b) Conversions determined as compared to the relative areas of all peaks from a GC analysis.

With this result we chose to now directly investigate the oxidative cleavage of *trans*-stilbene, **V-1** with $KHCO_3$ and $NaHCO_3$. Using $KHCO_3$ as an additive, no carboxylic acid products could be detected in the reactions with one or more equivalents of base. With half an equivalent, however, the reaction showed a majority of the acid product. Reactions with $NaHCO_3$ again showed no carboxylic acid products, but lower conversions. The success with $KHCO_3$ could not be extended to the alkyl olefin, 1-decene, **V-2**, where a mixture of the starting material, nonanal, **V-2a**, and nonanoic acid, **V-2b**, were obtained (Table V-2 entry 14).

Table V-2. Oxidative cleavage of **V-1** with base[a]

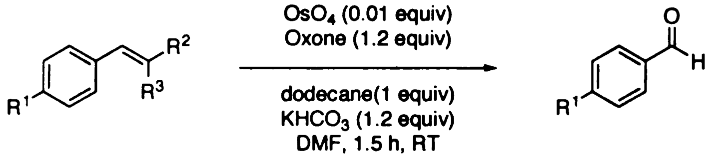
Entry	Substrate	Solvent	Base	Equivalents	**V-1**[b]	**V-1a**[b]	**V-1b**[b]
1	*trans*-stilbene. **V-1**	DMF	None	—	23	ND	77
2	**V-1**	DMF	$KHCO_3$	0.5	15	5	80
3	**V-1**	DMF	$KHCO_3$	1	ND	100	ND
4	**V-1**	DMF	$KHCO_3$	2	ND	100	ND
5	**V-1**	DMF	$KHCO_3$	3	ND	100	ND
6	**V-1**	DMF	$KHCO_3$	4	ND	100	ND
7	**V-1**	DMF	$KHCO_3$	5	ND	100	ND
8	**V-1**	DMF	$NaHCO_3$	2.5	12	88	ND
9	**V-1**	DMF	$NaHCO_3$	5	45	55	ND
10	**V-1**	DMF	$MeSO_3NH$	1	2	98	ND
11	**V-1**	MeOH	None	—	40	ND	60[c]
12	**V-1**	MeOH	$KHCO_3$	5	400	60	ND
13	**V-1**	MeOH	$MeSO_3NH_2$	1	20	98	ND
14	1-decene, **V-2**	DMF	$KHCO_3$	5	14	9	77
15	**V-2**	DMF	$MeSO_3NH$	1	10	13	77

a) All reactions were performed with olefin (1 equiv), Oxone (1.2 equiv), Base and OsO_4 (0.01 equiv) in the appropriate solvent (0.1 M) for 18 h at RT. b) Conversions determined as compared to the relative areas of all peaks from a GC analysis. c) 60 % refers to methyl benzoate.

A few of other additives were also tried with mixed success. The choice of these additives, methanesulfonamide and imidazole, was based on Shi's observation that the Baeyer-Villiger decomposition of their ketone catalyst is prevented under basic conditions.[118,120] While methanesulfonamide provided **V-1a** for aryl olefins, it was again not successful in stopping the cleavage of **V-2** at the aldehyde stage. Imidazole proved to be more basic or reactive than desired and decomposed the active $KHSO_5$ very rapidly resulting in no oxidative cleavage at all. It is plausible that the imidazole was oxidized to the corresponding N oxide.

Oxidations of various substrates under our optimized conditions provided benzaldehyde in varying yields. *Trans*-stilbene, styrene, methyl cinnimate and **V-5**, provided high yields of the desired product at 96%, 92%, 94%, and 94%, respectively. **V-9** and **V-10** along with cinnamyl aldehyde and cinnamyl alcohol provided somewhat lower yields at 70%, 68%, 80%, and 73%, respectively. In the third subgroup, however, the yields drop off precipitously providing only 56% and 60% product from the two cinnamic acid derivatives, and only a 45 % and 47 % yield from 1,4-diphenylbutadiene, **V-11**, and the long chain alkyl-aryl olefin, **V-12**.

Table V-3. Oxidative cleavage of aryl olefins to aldehydes



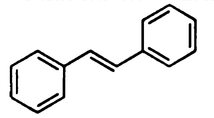
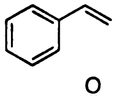
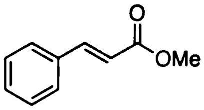
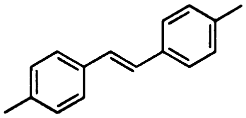
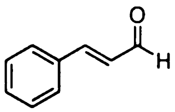
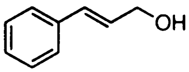
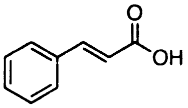
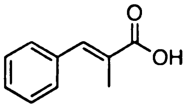
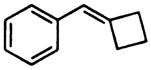
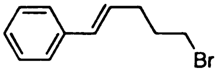
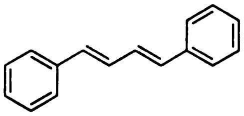
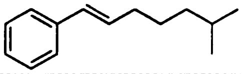
Entry	Substrate		*Product*	GC Yield (%)^b
1		**V-1**	**V-1a**	100
2		**V-3**	**V-1a**	92
3		**V-4**	**V-1a**	94
4		**V-5**	**V-5a**	94
5		**V-6**	**V-1a**	80
6		**V-7**	**V-1a**	73

Table V-3. cont'd.

Entry	Substrate		*Product*	GC Yield (%)[b]
7		**V-8**	**V-1a**	56
8		**V-9**	**V-1a**	60
9		**V-10**	**V-1a**	70
10		**V-11**	**V-1a**	68
11		**V-12**	**V-1a**	47[c]
12		**V-13**	**V-1a**	45

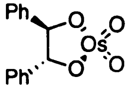
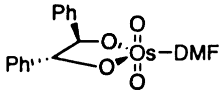
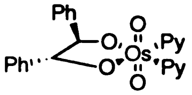
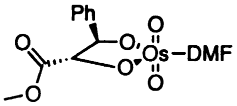
a) All reactions were performed with olefin (1 equiv), Oxone (1.2 equiv), $KHCO_3$ (1.2 equiv), dodecane (1 equiv) and OsO_4 (0.01 equiv) in DMF (0.1M) for 18 h at RT. b) Yields determined as compared to a GC standard curve with dodecane as an internal standard. c) Oxone (2.4 equiv) and $KHCO_3$ (2.4 equiv) were added in for this substrate

Currently, we attribute the differences in the selectivity between aryl and alkyl olefin cleavages to a difference in the relative rates between the OsO_4 promoted cleavage and Oxone promoted oxidation of aldehydes. We think that for alkyl olefins the rate of oxidation of the aldehyde is much faster than the rate of cleavage of the osmate ester. The exact role of $KHCO_3$ in preventing the over-oxidation of aryl aldehydes is not clear at present but possibly the slightly increased bacisity, due to the added $KHCO_3$, slows down the Baeyer-Villiger oxidation. Overall, we feel that Oxone is well suited for the complete oxidation of olefins to carboxylic acids, but may generally be less suited for the preparation of aldehydes. This has led us to study and search for other oxidants to affect an oxidative cleavage and this is discussed in subsequent sections of this chapter.

5.2.2. Finding a New Oxidant via OsO_4 Complexes

Our initial strategy to find a new oxidative cleavage oxidant was to prepare a few stoichiometric osmium complexes of *t*-stilbene.[23-27,252] This was easily accomplished at low temperature in THF with OsO_4, *t*-stilbene, and an appropriate ligand (none, DMF or pyridine) (Table V-4).

Table V-4. Osmate esters of **V-1** and **V-4**[a]

Entry	Substrate	Ligand	Product		Yield (%)[b]
1	**V-1**	——		**V-14**	95[c]
2	**V-1**	DMF		**V-15**	64
3	**V-1**	Py		**V-16**	86
4	**V-4**	DMF		**V-17**	71

a) All reactions were performed with substrate (1 equiv), ligand (3 equiv) in THF (0.2 M) at 0 °C and then precipitated at –20 °C. b) Isolated yields. c) ^1H NMR yield

The ligand free complex was not isolable, but could be identified by UV and NMR. This complex showed good stability as a cold solution, but upon warming it decomposed to provide benzaldehyde as the sole product. The DMF complex could be isolated under nitrogen as a brown solid and was determined to contain only one DMF ligand by NMR. However, when stored under nitrogen the solid compound remained stable either cold or at room temperature. When left to stand in an air atmosphere the brown solid turned to a black solid and no complex remained, only benzaldehyde. The DMF complex was also stable as a cold solution, but decomposed slowly when left at room temperature. The pyridine complex showed two pyridine ligands for every one stilbene by NMR and this isolable brown solid was stable in air and in solution at room

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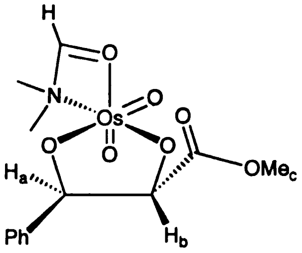
temperature. All three complexes could be cleaved *via* addition of $KHSO_5$ to a solution of the complex in DCM providing only benzaldehyde. Furthermore, the DMF complex could very quickly and cleanly be converted to benzaldehyde with NMO, H_2O_2, or even air. These intriguing results provided our first insight into the fact that other oxidants may be suitable for the desired oxidative cleavage reaction and in various solvents.

In addition to the complex with *trans*-stilbene we also prepared a complex of methyl cinnimate with DMF. After isolating the pure complex of methyl cinnimate the ^1H NMR was recorded. Interestingly, it showed eight distinctive doublets for both olefinic protons (H_a and H_b) and eight doublets (Me_c) for the methyl ester, which we believe could suggest a *cis* conformational relationship between a bidentate DMF and the olefin. We have no evidence for the structure drawn in Figure V-2, however this picture could potentially describe why there are eight different doublets and eight different methyl groups. The reasoning is as follows: there are two distinct rotations for the olefin, two distinct faces of the olefin and two rotations for a bidentate DMF, this would provide 2^3 possibilities which is eight. There are of course alternatives including a bisosmate, or dimeric/polymeric osmate, but they are perhaps as unlikely as our proposal. To investigate this further a stable DMF containing osmium complex needs to be prepared and crystallized. A possible substrate for this work would be 4-nitro-methyl cinnimate.

Figure V-2. Proposed structure of one of eight *cis* complexes



Again our complex, **V-17**, was susceptible to oxidative cleavage with a variety of oxidants including NMO, H_2O_2, and air.

5.2.3. Preparation of Aldehydes with H_2O_2

A drawback of the earlier described Oxone/DMF system to promote oxidative cleavage is its utility in large-scale synthesis. The need to remove large volumes of DMF together with the large amounts of inorganics will result in the system being unattractive for the isolation of products at the end of the reaction especially in the case of small molecules. To circumvent this problem, several modifications were attempted with the hope to develop a more convenient and suitable system for the use in a large-scale preparation. We also wanted to see if the direct oxidative cleavage of the osmate ester intermediate was a unique property of the Oxone—DMF combination or if the cleavage would be promoted by other oxidants as well. This section describes the results of our modifications on the Oxone/DMF system.

As can be seen from Table V-5, our test reaction with H_2O_2—DMF with methyl cimmimate at RT led to the recovery of starting material. We surmised that this was most probably due to the rapid decomposition of H_2O_2 in the presence of OsO_4 and DMF, which was observed as the evolution of oxygen.[253,254] Cooling to 0 °C did not prevent decomposition completely but did provide a 27% conversion to benzaldehyde. Encouraged by this result, we decided to carry out the cleavages in ACN at 0 °C. We reasoned that ACN would be more convenient to use and facilitate easy work-up protocols. In the case of ACN at 0 °C, an 18% conversion to benzaldehyde was observed while the remaining was unreacted starting material (Table V-5).

To improve the yield of the oxidative cleavage, the reaction was carried out in varying amounts of DMF. ACN would remain the primary solvent, DMF would now be considered as the "additive" and H_2O_2 would be used at a slight excess to gauge the reaction outcome. As can be seen from Table V-5, addition of DMF up to 20 equiv steadily improved the percent conversion of the benzaldehyde product. More surprising was the decrease in conversion when the amount of DMF was further increased to 100 equiv. We surmised that the decomposition of H_2O_2 again became rapid with the increased equivalents of DMF and thusly provided a decrease in conversion.

Since the addition of a relatively small amount of DMF seemed to promote the cleavage effectively, different commonly used organic solvents with varying amounts of DMF were pursued. These results are summarized in Table V-5. Thus, all the solvents showed appreciable amounts of benzaldehyde, although, the best results were observed in DCM or ACN. In most cases increasing DMF beyond 20 equiv proved to be detrimental, therefore, we decided to carry out further cleavages with 20 equiv. of DMF in ACN.

Table V-5. Varying amounts of additive in various solvents[a]

Entry	Solvent	DMF	SM[b]	Aldehyde[b]
1	DMF	——	100[c]	ND
2	DMF	——	73	27
3	Acetonitrile	0	46	54
4	Acetonitrile	1	64	36
5	Acetonitrile	5	11	89
6	Acetonitrile	10	13	87
7	Acetonitrile	20	4	96
8	Acetonitrile	50	6	94
9	Acetonitrile	100	56	44
10	DCM	5	59	41
11	DCM	10	45	55
12	DCM	20	4	96

Table V-5. cont'd.[a]

Entry	Solvent	DMF	SM[b]	Aldehyde[b]
13	DCM	50	ND	100
14	DCM	100	ND	100
15	Hexanes	20	47	46
16[d]	Hexanes	50	1	97
17[d]	Hexanes	100	48	17
18[e]	EtOAc	20	51	45
19[e]	EtOAc	50	65	30
20	EtOAc	100	97	3
21	Toluene	20	14	86
22	Toluene	50	34	66
23	Toluene	100	53	47

a) All reactions were performed with methyl cinnimate, **V-4**, (1 equiv), H_2O_2 (3 equiv), DMF (0-100 equiv), and OsO_4 (0.01 equiv) in solvent (0.1M) for 18 h at 0—4 °C. b) Conversions determined as compared to the relative areas of all peaks from a GC analysis. c) Reaction carried out at RT d) Diol contaminant: entry 16, 2%; entry 17, 35 % e) Acid contaminant: entry 18, 4%; entry 19, 5 %

We had observed the best cleavage reactions for our model system in ACN with 20 equiv. DMF and 3 equiv. H_2O_2 at 0 °C, and therefore, this system was chosen as our standard reaction condition. We preferred this to DCM and toluene where the reactions were biphasic and very efficient stirring was necessary. In fact, we observed significantly different conversions for the same reaction in DCM based on the stirring rate.

We next decided to screen a series of oxidants other than H_2O_2 to affect the cleavage in ACN with 20 equiv DMF. The oxidants chosen were NMO, AcOOH, *t*BuOOH, urea H_2O_2, $KHSO_5$, and $NaIO_4$. Some of these were chosen in order to keep the system completely anhydrous. We felt that in an anhydrous system the potential hydrolytic pathway would be shut down resulting in exclusive oxidative cleavage. Here in addition to our standard methyl cinnimate we also chose four other olefins to do simultaneous comparisons.

As can be seen in Table V-6, $KHSO_5$ and *t*BuOOH led mostly to over oxidation providing the carboxylic acid, while NMO was not generally a very efficient oxidant and yielded unreacted starting material or diol. AcOOH, urea H_2O_2, $NaIO_4$, and H_2O_2 were also evaluated in this system and again gave mixed results. All four oxidants provide significant amounts of aldehyde for the aromatic olefins tested, **V-3**, **V-4**, and **V-17**. The alkyl cases, **V-2** and **V-18**, remained most difficult except for $NaIO_4$, but distinguishing an osmate oxidative cleavage from in iodate oxidative cleavage would be difficult. Otherwise, only H_2O_2 looked promising for alkyl aldehyde production. Hence we chose H_2O_2 as the oxidant of choice for further studies.

Table V-6. Various oxidants and substrates

Entry	Oxidant	Substrate	SM	Aldehyde	Acid	Diol
1	30% H_2O_2	**V-3**	28	72	ND	ND
2	30% H_2O_2	**V-7**	ND	100	ND	ND
3	30% H_2O_2	**V-4**	ND	100	ND	ND
4	30% H_2O_2	**V-2**	4	19	6	71
5	30% H_2O_2	**V-18**	ND	26	17	56
6	AcOOH	**V-3**	ND	100	ND	ND
7	AcOOH	**V-7**	ND	100	ND	ND
8	AcOOH	**V-4**	ND	100	ND	ND
9	AcOOH	**V-2**	14	10	26	50
10	AcOOH	**V-18**	33	ND	ND	67
11	*t*BuOOH	**V-3**	ND	28	72	ND
12	*t*BuOOH	**V-7**	23	9	7	61
13	*t*BuOOH	**V-4**	ND	ND	100	ND
14[d]	*t*BuOOH	**V-2**	94	ND	ND	ND
15	*t*BuOOH	**V-18**	93	ND	ND	7
16	urea H_2O_2	**V-3**	ND	70	30	ND
17	urea H_2O_2	**V-7**	ND	100	ND	ND

Table V-6. cont'd.

Entry	Oxidant	Substrate	SM	Aldehyde	Acid	Diol
18	urea H_2O_2	**V-4**	ND	100	ND	ND
19	urea H_2O_2	**V-2**	28	ND	ND	72
20	urea H_2O_2	**V-18**	30	ND	ND	70
21	$KHSO_5$	**V-3**	ND	26	74	ND
22	$KHSO_5$	**V-7**	ND	46	54	ND
23	$KHSO_5$	**V-4**	ND	86	14	ND
24	$KHSO_5$	**V-2**	5	ND	95	ND
25	$KHSO_5$	**V-18**	ND	ND	100	ND
26	NMO	**V-3**	ND	70	30	ND
27	NMO	**V-7**	50	30	20	ND
28	NMO	**V-4**	100	ND	ND	ND
29	NMO	**V-2**	20	ND	ND	80
30	NMO	**V-18**	7	ND	ND	93
31	$NaIO_4$	**V-3**	ND	100	ND	ND
32	$NaIO_4$	**V-7**	ND	100	ND	ND
33	$NaIO_4$	**V-4**	ND	100	ND	ND
34	$NaIO_4$	**V-2**	ND	58	16	26
35	$NaIO_4$	**V-18**	ND	38	15	47

a) All reactions were performed with substrate (1 equiv), oxidant (3 equiv), DMF (20 equiv) and OsO_4 (0.01 equiv) in ACN (0.1M) for 18 h at 0—4°C. b) Conversions determined as compared to the relative areas of all peaks. c) **V-18** is 2-trans-nonene. d) Epoxide contaminant: entry 14, 6%.

With several factors clearly scoped out, i.e. solvent, amount of DMF, and oxidant, we chose to investigate the source of osmium that may promote cleavage (Table V-7). If effective, $OsCl_3$ and $K_2OsO_4{\bullet}H_2O$ would prove to be cheaper and easier to handle sources of osmium. Additionally polymer bound OsO_4 would facilitate an easier work-up. As seen in Table V-7 when our previous oxidative conditions were used (DMF—Oxone), all reactions behave well providing the desired carboxylic acid **V-1b** or **V-2b**. However, with the modified conditions (ACN—DMF—H_2O_2) only $OsCl_3$ was effective in the cleavage of methyl cinnimate as compared to the original OsO_4. However in the oxidative cleavage of decene $OsCl_3$ and OsO_4 provided mixtures of products while potassium osmate and polymer bound OsO_4 provided no cleaved products and returned only starting material. With these results we felt that using other osmium sources for the oxidative cleavage reaction was potentially valuable but not worth pursuing further at this time.

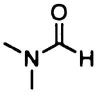
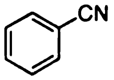
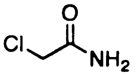
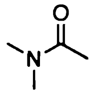
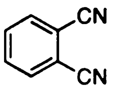
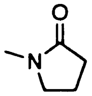
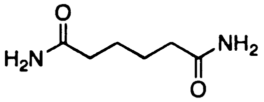
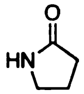
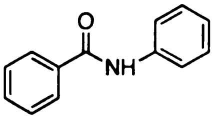
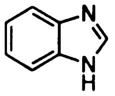
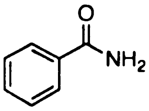
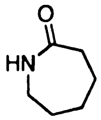
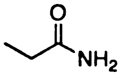
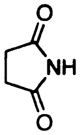
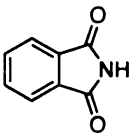
Table V-7. Various osmium tetroxide sources

Entry	Substrate	Osmium Source	Conditions[a]	Product	Yield (%)[b]
1	**V-4**	$K_2OsO_4 \cdot 2H_20$	A	**V-1b**	87
2	**V-4**	$OsCl_3$	A	**V-1b**	90
3	**V-4**	Pyridine polymer	A	**V-1b**	88
4	**V-4**	OsO_4	A	**V-1b**	96
5	**V-4**	$K_2OsO_4 \cdot 2H_20$	B	—	NR
6	**V-4**	$OsCl_3$	B	**V-1a**	100[c]
7	**V-4**	Pyridine polymer	B	—	NR
8	**V-4**	OsO_4	B	**V-1a**	100[c]
9	**V-2**	$K_2OsO_4 \cdot 2H_20$	A	**V-2b**	72
10	**V-2**	$OsCl_3$	A	**V-2b**	83
11	**V-2**	Pyridine polymer	A	**V-2b**	72
12	**V-2**	OsO_4	A	**V-2b**	93
13	**V-2**	$K_2OsO_4 \cdot 2H_20$	B	—	NR
14	**V-2**	$OsCl_3$	B	—	—[d]
15	**V-2**	Pyridine polymer	B	—	NR
16	**V-2**	OsO_4	B	—	—[d]

a) Condition A: All reactions were performed with substrate (1 equiv), Oxone (4 equiv), and osmium source (0.01 equiv) in DMF (0.1M) for 3 h at RT. B: All reactions were performed with substrate (1 equiv), H_2O_2 (3 equiv), DMF (20 equiv) and osmium source (0.01 equiv) in ACN (0.1M) for 18 h at 0—4 °C. b) Isolated Yields c) Yields of aldehydes determined as compared to a GC standard curve with dodecane as an internal standard. d) Conversions determined as compared to the relative areas of all peaks and the reactions provided a comparable mixture of products as Table V-6 entry 4.

The only other variant that needed to be explored before testing the standard condition as an alternative to the initial Oxone/DMF system was to change the "additive" which as previously mentioned in this section is DMF. We chose to study other amide based ligands as the exact role of DMF in these reactions was not clear. However, our previous results on solvent changes demonstrated that several amide based solvents promoted either oxidative cleavage or aldehyde oxidation. The results were compared in ACN and can be seen in Table V-8. A much smaller amount of ligand (0.4 equiv) was chosen to determine if there was indeed a ligand effect. Additionally, the reactions were carried out using methyl cinnimate as the model substrate and H_2O_2 (3 equiv) as the oxidant. We observed what does appear to be a ligand effect and in fact several ligands performed equal to or better than DMF. However, when the "better" ligands (γ-caprolactam and pyrolidinone) were evaluated with varying amounts of ligand the reaction did not proceed cleanly to the aldehyde and instead carboxylic acids began to

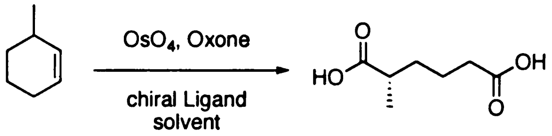
Table V-8. Oxidative cleavage with various additives[a]

Additive	Conversion (%)	*Additive*	Conversion (%)[b]
	12		8
	10		18
	4		19
	6		28
	8		0
	17		31
	23		5
	7		

a) All reactions were performed with **V-4** (1 equiv), H_2O_2 (3 equiv), ligand (0.4 equiv) and OsO_4 (0.01 equiv) in ACN (0.1 M) for 18 h at 0—4 °C. b) Conversions determined as compared to the relative areas of all peaks.

form. This is an intriguing area to investigate because of its potential to start an oxidative cleavage / kinetic resolution project. For instance, if an appropriate chiral ligand, perhaps amide based, could bind to OsO_4 and then create a preference for the face of attack, a kinetic resolution / oxidative cleavage may be realized (Scheme V-1).

Scheme V-1. Envisioned oxidative cleavage / kinetic resolution

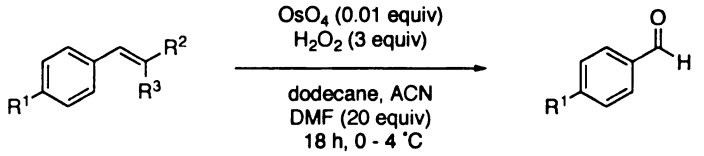


Based on all of the above considerations a system comprising of ACN (0.1 M), DMF (20 equiv.), H_2O_2 (2 – 3 equiv.) and OsO_4 (0.01 equiv.) at 0 – 4 °C was chosen to study the cleavage of various types of olefins (Table V-9).

Having chosen ACN—DMF—OsO_4—H_2O_2 as the standard system we subjected a series of aryl and alkyl olefins to cleavage under these conditions (Table V-9). The reactions were primarily monitored by GC. Most aryl olefins showed benzaldehyde in quantitative yield (measured with an internal standard) except styrene, **V-3**, and cinnamyl aldehyde, **V-6**, which provided 72% and 55% of benzaldehyde, respectively. In cases where the disubsituted olefin contained mixed aryl and alkyl components (Table V-9, entries 10,12 and 15) the ^{1}H NMR spectra of the crude reaction showed a 1:1 mixture of benzaldehyde and the corresponding alkyl aldehyde. This was an interesting finding because alkyl olefins did not work well in this system previously. Alternatively, significant amounts of diol resulting from the hydrolysis of alkyl olefins were observed. We felt that the hydrolysis of alkyl osmate esters was a facile reaction and overshadows the desired cleavage process. On the other hand, in the case of aryl olefins the cleavage process seems to be more facile than hydrolysis and hence the water present in the 30%

H_2O_2 had no deleterious effect on the cleavage process of aryl and mixed aryl-alkyl olefins.

Table V-9. Oxidative cleavage of various olefinic substrates with H_2O_2[a]



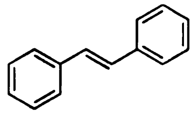
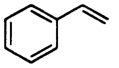
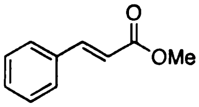
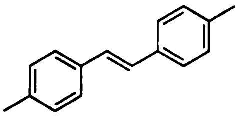
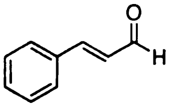
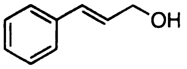
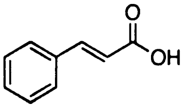
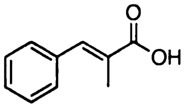
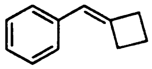
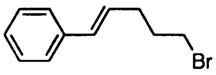
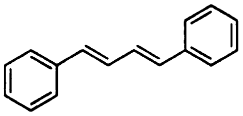
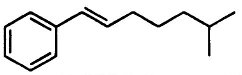
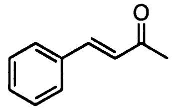
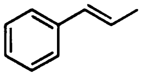
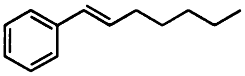
Entry		Substrate	*Product*	GC Yield (%)[b]
1		**V-1**	**V-1a**	97
2		**V-3**	**V-1a**	72
3		**V-4**	**V-1a**	100
4		**V-5**	**V-5a**	100
5		**V-6**	**V-1a**	55
6		**V-7**	**V-1a**	100
7		**V-8**	**V-1a**	100
8		**V-9**	**V-1a**	100
9		**V-10**	**V-1a**	100
10		**V-11**	**V-1a**	100
11		**V-12**	**V-1a**	50[c]
12		**V-13**	**V-1a**	96

Table V-9. cont'd.[a]

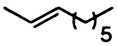
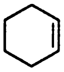
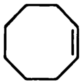
Entry		Substrate	Product	GC Yield (%)[b]
13		**V-19**	**V-1a**	100
14		**V-20**	**V-1a**	100
15		**V-21**	**V-1a**	70

a) All reactions were performed with olefin (1 equiv), H_2O_2 (3 equiv), DMF (20 equiv), dodecane (1 equiv) and OsO_4 (0.01 equiv) in ACN (0.1 M) for 18 h at 0-4 °C. b) Yields determined as compared to a GC standard curve with dodecane as an internal standard. c) H_2O_2 (6 equiv) was added in for this substrate.

Not unexpectedly, alkyl olefins performed poorly under these conditions (Table V-10) providing a mixture of oxidized products. An interesting result, however, was the reaction with cyclohexene **V-22**, and cyclooctene **V-23** (Table V-10, entry 3,4). In the reaction with **V-22** the observed products were the α-hydroxyketone (15%) and the dione (85%) (Figure V-3). Notably, **V-25** was isolated as its dimer and **V-26** was isolated in good yield. There was no observable cleavage to adipaldehyde. Cyclooctene, **V-23**, and methylcyclohexene, **V-24**, again provided the α-hydroxyketone, **V-25**, and the α-dione in good yield (Table V-10 and Figure V-3).

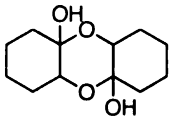
In an attempt to stop the hydrolysis process we exchanged DMF for silica in hopes that it would be an effective absorbent and ligand simultaneously (Table V-11). Additionally, we thought that silica supported peroxide may be a stronger oxidant than peroxide itself because the silica would provide a large oxophilic leaving group and that the resultant water would then stay bound to the silica. Under these conditions **V-22** afforded the α-hydroxyketone **V-25** exclusively in 95 % yield. A control experiment without silica or DMF provided only 8 % of **V-25** along with starting material.

Table V-10. Oxidations of Alkyl olefins with H_2O_2[a,b]

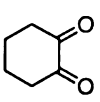
Entry	Substrate	SM	Aldehyde	Acid	Diol	Hydroxyketone	Dione	Epoxide
1	 **V-2**	4	19	6	71			
2	 **V-18**		26	17	56			
3	 **V-22**					15 (12)[c]	85 (80)[c]	
4	 **V-23**	4				78 (70)[c]	10 (7)[c]	8

a) All reactions were performed with olefin (1 equiv), H_2O_2 (3 equiv), DMF (20 equiv), dodecane (1 equiv) and OsO_4 (0.01 equiv) in ACN (0.1 M) for 18 h at 0-4 °C. b) Conversions determined as compared to the relative areas of all peaks from a GC analysis. c) Numbers in parenthesis represent isolated yields.

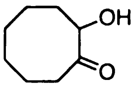
Figure V-3. Structures of isolated products from Table V-10



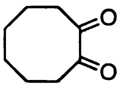
V-25



V-26



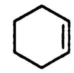
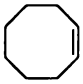
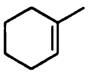
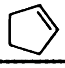
V-27



V-28

Noting that the conversion of cyclohexene to **V-25** could be achieved easily without DMF we subjected a number of alkyl olefins to these new oxidative conditions ACN—OsO_4—H_2O_2—SiO_2 (Table V-11). It was observed that cyclopentene, **V-30**, could be cleanly cleaved to glutaraldehyde, **V-30a**, but was isolated in only 50% yield, while the higher order cyclic olefins again provided good yields of the α-hydroxyketone and α-dione. The selectivity for the cleavage of linear alkyl olefins was not improved with the silica modification (Table V-11, entry 1 and 2).

Table V-11. Oxidations of alkyl olefins in the presence of SiO_2

Entry	Oxidant	Substrate	SM	Aldehyde	Acid	Diol	Hydroxyketone	Dione	Epoxide
1		**V-2**	32		15	52			
2		**V-18**		33	12	54			
3		**V-22**					100 (95)^c		
4		**V-23**	4				58 (55)^c	26 (20)^c	12
5		**V-24**			100 (97)^c				
6		**V-30**		100 (50)^c					

a) All reactions were performed with olefin (1 equiv), H_2O_2 (3 equiv), SiO_2 (1 g/mmol) and OsO_4 (0.01 equiv) in ACN (0.2 M) for 18 h at 0-4 °C. b) Conversions determined as compared to the relative areas of all peaks from a GC analysis. c) Numbers in parenthesis represent isolated yields.

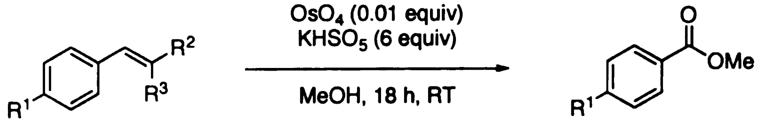
5.2.4. Preparation of Esters with $KHSO_5$

Prior investigations in our laboratory have successfully used Oxone coupled with OsO_4 to oxidatively cleave olefins to prepare carboxylic acids. We have also demonstrated that Oxone can effectively oxidize aldehydes to carboxylic acids or esters by a simple change in the solvent. Additionally, we have developed practical methods to prepare analytically pure $KHSO_5$ or nBu$_4$NHSO$_5$, which simplify mechanistic undertakings, and we have since realized the added advantage of differences in reactivity between the two purified salt forms. We felt that we could further expand our oxidation chemistry by coupling the esterification and oxidative cleavage reactions to perform an oxidative cleavage / esterfication in one pot.

As stated earlier, our observation that MeOH effectively transformed aldehydes into esters allowed us to consider the possibility of oxidatively cleaving an olefin in MeOH to an ester. To this end under standard reaction conditions (OsO_4 (1 mol %), $KHSO_5$ (6 equiv), MeOH), **V-1** and **V-3**, were cleanly converted to the corresponding esters in 90% and 72%, respectively. Other aromatic olefins were successfully transformed into the corresponding aryl ester without difficulty (Table V-12, entries 4,5,7-12). Analysis by ^{1}H NMR and GC/MS showed that the alkyl portions for **V-11** and **V-13** were cleanly converted to their corresponding esters in a 1:1 ratio as compared to methyl benzoate, but these compounds were not isolated. Surprisingly *t*-cinnamic acid, **V-8**, did not cleave, instead it provided an 80% yield of methyl 2-hydroxy-3-methoxy-3-phenylpropionate, **V-31**. Interestingly, only starting material was obtained when **V-8** was subjected to identical conditions without OsO_4. Methyl cinnimate, **V-4**, was again surprising in that it did not react even at elevated temperatures. Currently we do not understand the significant reactivity differences with the latter two aromatic olefins.

Primary alkyl olefins such as **V-2** and 10-acetoxy-1-decene, **V-32**, subjected in the same way were also cleanly converted into alkyl esters in 70% and 68% yield, respectively. Notably the acetate was hydrolyzed off during the reaction affording **V-33**. However, attempts to broaden the scope were met with limited success. Cyclooctene, **V-23** only provided 26% of the desired diester. Reaction with 2-nonene or methyl oleate provided no oxidatively cleaved product, but instead analysis by NMR showed that the products were the regioisomeric hydroxy-methoxy 1,2 addition products, **V-34a/b** and **V-36a/b**.

Table V-12. Oxidative cleavage of olefins to esters[a]



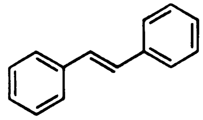
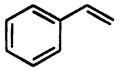
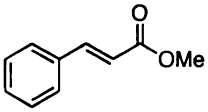
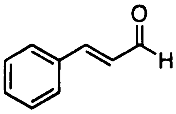
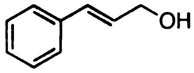
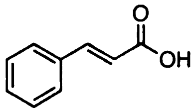
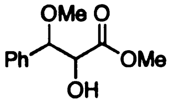
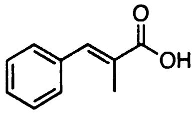
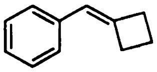
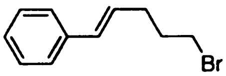
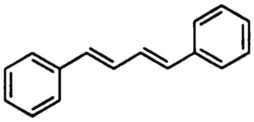
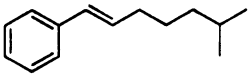
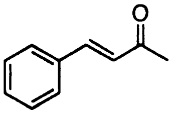
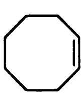
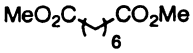
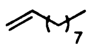
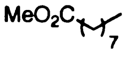
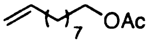
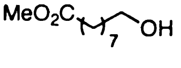
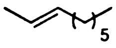
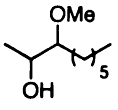
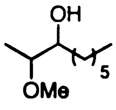
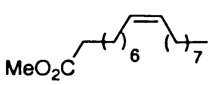
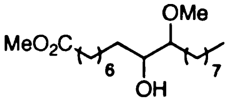
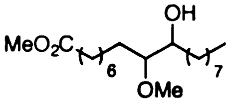
Entry	Substrate		Product	Yield (%)[b]
1		**V-1**	**V-1c**	90
2		**V-3**	**V-1c**	72
3[c]		**V-4**	**V-4**	—
4		**V-6**	**V-1c**	69
5		**V-7**	**V-1c**	74
6		**V-8**	 **V-31**	80[c]
7		**V-9**	**V-1c**	83
8		**V-10**	**V-1c**	78
9		**V-11**	**V-1c**	66
10		**V-12**	**V-1c**	66[c]
11		**V-13**	**V-1c**	90
12		**V-19**	**V-1c**	70
13		**V-23**	 $MeO_2C(CH_2)_6CO_2Me$ **V-23c**	26

Table V-12. cont'd.

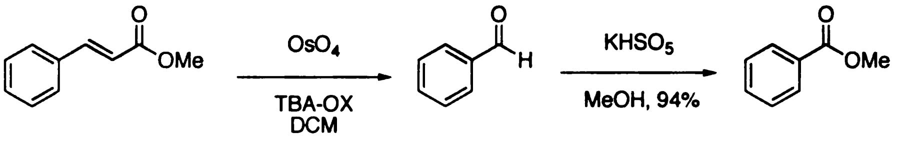
Entry	Substrate		Product	Yield (%)[b]
14		**V-2**	 **V-2c**	70
15		**V-32** V-33		68
16[d]		**V-18**	 **V-34a**  **34b**	30[c]
17[d]		**V-35**	 **V-36a**  **V-36b**	52[c]

a) All reactions were performed with olefin (1 equiv), $KHSO_5$ (6 equiv), and OsO_4 (0.01 equiv) in MeOH (0.1 M) for 18 h at RT. b) Isolated yields. c) No reaction was seen even when the reaction was elevated to 50 °C. d) Regioisomeric mixtures of the hydroxy and methoxy.

Attempts to do the oxidative cleavage / esterification on alkyl substrates in mixed solvents i.e. DMF/MeOH resulted in a mixture of products including carboxylic acids, esters and the hydroxy-methoxy addition product. Additional studies in this area are ongoing to determine if the cleavage reaction can be accelerated in alcoholic solvents such that the addition byproduct is minimized.

As an alternative strategy, one could oxidatively cleave the olefin to prepare aldehydes and then modify the oxidation state by adding the appropriate solvent and an additional amount of oxidant. A proof of concept experiment was performed along this line where methyl cinnimate, which notably did not react under the latter cleavage conditions, was converted to the aldehyde with $n\mathrm{Bu_4NHSO_5}$ and OsO_4 in DCM. Subsequent dilution with MeOH and addition of $KHSO_5$ cleanly provided the desired methyl benzoate (Scheme V-2). This modification is currently not applicable to alkyl olefins because their selective oxidation to aldehydes has not been accomplished.

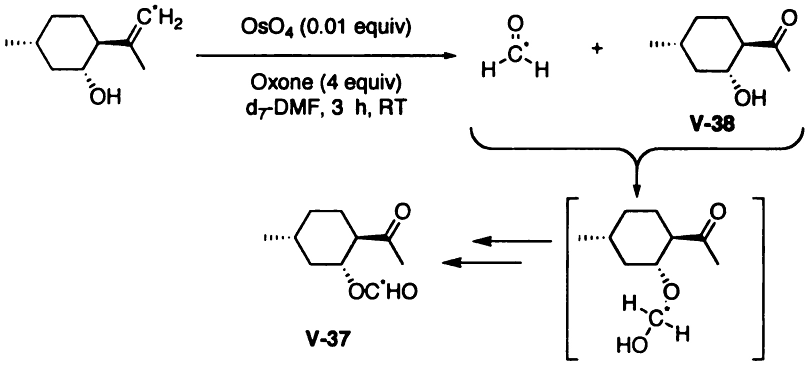
Scheme V-2. One pot oxidative cleavage with two different oxidants



5.2.5. Preparation of Lactones with Oxone

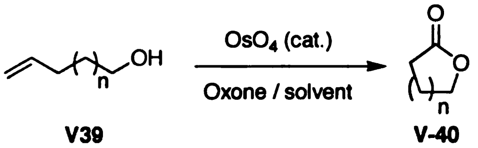
Previously we had noted that the oxidative cleavage of (-) isopulegol in Oxone—DMF furnished formate ester, **V-37**, along with the desired hydroxyketone, **V-38**. By performing this reaction in d_7-DMF we were able to unambiguously establish that the formate of **V-37** did not come from the solvent. Therefore, the formate must be obtained from an intramolecular formate transfer reaction and by a presumed hemiacetal oxidation (Scheme V-3).[6] In Scheme V-3 please note that the label on the olefinic carbon is for carbon tracking purposes and not a ^{13}C labeling of that carbon.

Scheme V-3, Intramolecular trapping of an aldehyde with an alcohol



The formation of hemiacetals and their subsequent oxidation to esters has also been observed in the low temperature NMR experiments of oxidation of benzaldehyde to methyl benzoate with Oxone in d_4-MeOH (See Chapter 6). These observations led us to believe that suitably positioned hydroxyolefins could be converted to their corresponding lactones by an intramolecular trapping of the intermediate hemiacetals. The envisioned reaction is shown in Scheme V-4 (direct conversion of **V-39** to **V-40**).

Scheme V-4. Envisioned one pot oxidative lactonization

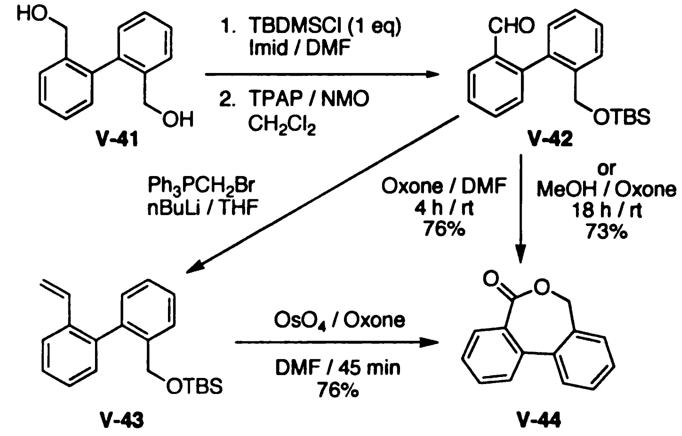


Other methods that have been reported for the conversion of hydroxy olefins to lactones via oxidative cyclization require stoichiometric chromium or permanganate reagents. Schlecht and Kim[255] have used chromium trioxide in acetic acid/acetic anhydride and Chandrasekaran and co-workers[256,257] have used a pentavalent $(BiPyH_2)CrOCl_5$ reagent to effect the transformation of various γ- and δ-hydroxy olefins to the corresponding lactones. However, these particular sets of reaction conditions are only useful for hydroxy olefins containing a tertiary alcohol group, otherwise, oxidation of the alcohol to the corresponding carboxylic acid or ketone is a major problem.

Chandrasekaran and co-workers soon devised a solution to this problem in the form of cetyltrimethylammonium permanganate, which can be used in the oxidative cyclization of primary, secondary, or tertiary alkenols to the corresponding lactones.[258] Chandrasekaran also reported the use of $KMnO_4$ in the presence of copper sulfate and a small amount of water as effective in the oxidative cyclization of ω-hydroxy alkenes to ω-lactones under mild conditions.[259] We wish to report on our success in developing a new and mild system for effecting this transformation involving catalytic OsO_4 in the presence of Oxone as the oxidant.

Our initial efforts centered on the proof of concept depicted in Scheme V-5. Bis-(hydroxymethyl) biphenyl **V-41** was mono-protected and the free hydroxyl was oxidized to yield aldehyde **V-42**. Upon treatment of **V-42** with either Oxone in DMF or in MeOH, *in situ* deprotection of the silyl group occurred concomitantly with oxidation of the hydroxy aldehyde intermediate to the lactone **V-44**. Olefination of **V-42** to deliver **V-43** provided the prerequisite silyl-protected alkenol poised for a tandem oxidative cleavage/oxidative lactonization to deliver **V-44**. Treatment of **V-43** with catalytic OsO_4 (1 mol %) and Oxone in DMF led to the isolation of **V-44** in good yields, thus demonstrating the intramolecular trapping of the unmasked hydroxyl upon oxidative cleavage of the olefin.

Scheme V-5. Oxidative lactonization: proof of concept

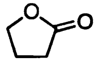
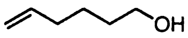
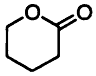
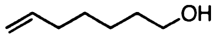
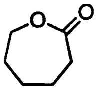
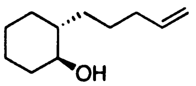
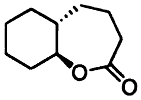
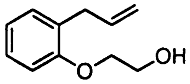
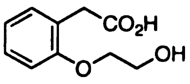
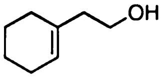
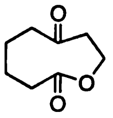
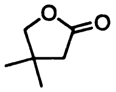
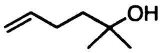
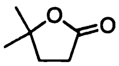
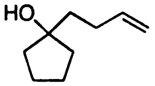
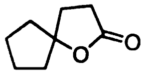
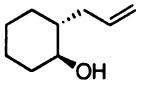
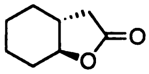
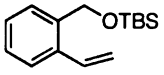
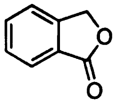
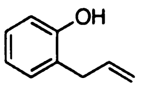
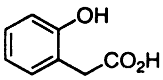
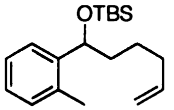
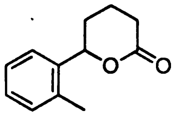
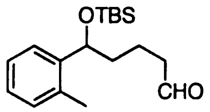
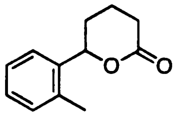


DMF was chosen as the initial solvent to study due to fast reaction times and higher yields of product as compared to other solvents. It was found that the use of a 0.1 M solution of the alkenol in DMF with 4.0 equivalents of Oxone and 1.0 mol % OsO_4 was effective at converting primary, secondary, and tertiary alcohols to the corresponding lactones in good yields (Table V-13).

Subsequent experiments focused on the conversion of alkenols to their corresponding lactones. *The remainder of the work presented here regarding oxidative lactonizations has been performed by Jennifer Schomaker, a graduate student in our laboratory, and is being shown and discussed for completeness of the oxidative story.* Specifically, the conversion of 4-penten-1-ol and 5-hexen-1-ol to butyrolactone and valerolactone were initially investigated (Table V-13, entries 1 and 2). These lactones were obtained in good yields, thus demonstrating that alkyl-substituted olefins can also undergo the lactonization in preference to oxidation to carboxylic acids.

While the formation of five- and six-member lactones was facile as expected, the yield dropped precipitously on formation of caprolactone (Table V-13, entry 3). Longer chain alken-1-ols gave no discernable amounts of lactone, and the carboxylic acids were isolated as the sole products. This is likely due to the small equilibrium presence of the cyclized hemiacetals for larger rings. Therefore, following oxidative cleavage, the oxidation of the intermediate aldehyde to carboxylic acids predominates. The yield of seven-member lactones could be improved provided conformational freedom was restricted (Scheme V-5 and Table V-13, entry 4). Attempts to form an eight-member lactone (Table V-13, entry 5) was unsuccessful and led only to the carboxylic acid product **V-49a**, albeit in good yield. We were disappointed with these results, since we had hoped that this protocol could be extended to the formation of macrocyclic ring systems, thus providing the opportunity for masking a carboxylic acid as an alkene during the course of a synthesis. While this might still prove a viable strategy for more highly substituted systems with preferred conformations that could increase the cyclic hemiacetal intermediate necessary for lactonization, another route to larger macrocycles can be pursued by tethering an alcohol functionality to an endocyclic double bond (Table V-13, entry 6).[260]

Table V-13. Oxidative lactonization of alkenols

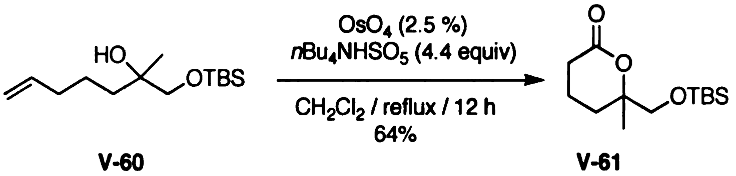
Entry	Substrate		Product		Yield (%)^{a}
1		**V-45**		**V-45a**	73^{b}
2		**V-46**		**V-46a**	68^{b}
3		**V-47**		**V-47a**	42^{b}
4		**V-48**		**V-48a**	59
5		**V-49**		**V-49a**	69
6		**V-50**		**V-50a**	45
7		**V-51**		**V-51a**	84^{c}
8		**V-52**		**V-52a**	85^{c}
9		**V-53**		**V-53a**	73
10		**V-54**		**V-54a**	82
11		**V-55**		**V-55a**	76
12		**V-56**		**V-56a**	52
13		**V-57**		**V-57a**	65
14		**V-58**		**V-57a**	76^{d}

a) Isolated yields, unless specified otherwise. b) GC yields determined by using 1,2,3,4-tetramethylbenzene or dodecane as an internal standard. c) NMR yields. d) The reaction conditions are the same except for omitting OsO_4.

Entries 7 and 8 in Table V-13 illustrate the effect of substitution on the yield of lactonization. The anticipated Thorpe-Ingold effect[261] for alkenol **V-51** did result in higher yields of **V-51a**. However surprisingly, the tertiary alcohols **V-52** and **V-53** with steric crowding of the hydroxyl groups reacted efficiently to yield **V-52a** and the spirolactone **V-53a**, respectively. Fused 5/6 and 6/7 ring systems **V-54a** and **V-48a** could be obtained in good isolated yields (Table V-13, entries 10 and 4). Protected benzylic alcohol **V-55** with an olefinic appendage was also lactonized under the same reaction conditions. However, phenolic systems such as **V-56** did not undergo oxidative lactonization, presumably because of the tempered nucleophilicity of the hydroxyl group (Table V-13, entry 12). Oxidative lactonization of the silyl-protected alkenol **V-57** yielded **V-58a**, once again demonstrating the *in situ* deprotection/lactonization sequence under the reaction conditions. Aldehyde **V-59**, presumably the intermediate in the oxidative lactonization of **V-58**, also yields **V-58a** in good yields upon treatment only with Oxone.

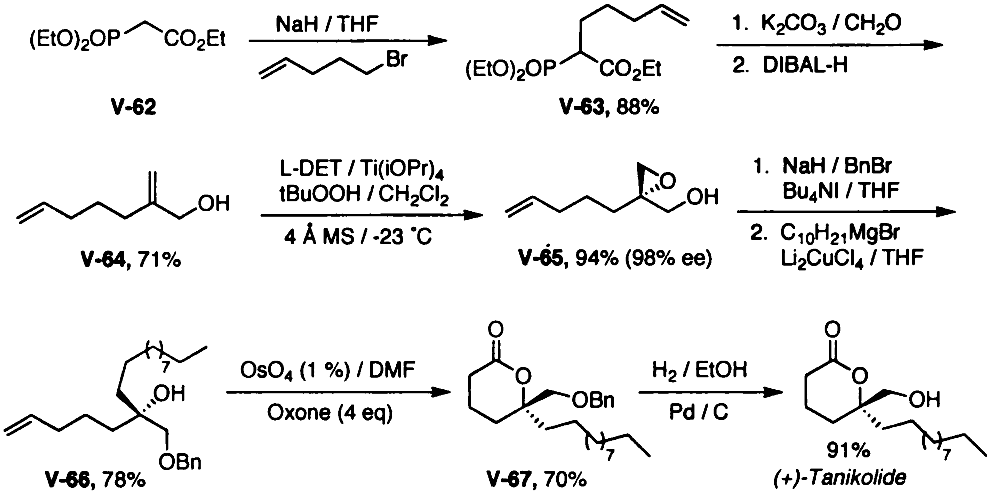
The use of a soluble form of Oxone ($n\text{Bu}_4\text{NHSO}_5$)[7] was briefly studied. Difficulty in separating excess oxidant and oxidation by-products from highly polar products was not trivial, and thus, $n\text{Bu}_4\text{NHSO}_5$ is not recommended for use with water-soluble lactones. However, $n\text{Bu}_4\text{NHSO}_5$ is a convenient reagent for more non-polar substrates and, unlike the Oxone/DMF system, allows for silyl groups to be retained during the lactonization (Scheme V-6). The reason for the observed difference in reactivity between $n\text{Bu}_4\text{NHSO}_5$ and Oxone is not apparent, however, it could be a result of Oxone's much higher water content and its inherent acidity that could lead to the hydrolysis of silyl ethers. Previous report by Sabitha and co-workers has demonstrated the ability of Oxone to deprotect TBDMS groups in aqueous MeOH.[262] As such, the tandem oxidative cleavage/oxidative lactonization of the tertiary alcohol **V-60** with *n*Bu_4NHSO_5 in dichloromethane provided lactone **V-61** in good yields without the deprotection of the TBS group.

Scheme V-6. Oxidative lactonization with TBA-OX



The oxidative lactonization has now been applied in an eight step total synthesis of (+)-Tanikolide. This elegant synthesis, which was executed by Jennifer Schomaker, begins with alkylation of the ylide **V-62** to prepare **V-63**. HWE reaction and DIBAL-H reduction provide the alcohol **V-64**. SAE, benzyl protection and a copper mediated grignard addition provide **V-66**. This substrate is now poised for the oxidative lactonization to prepare **V-67** in 70% yield. Hydrogenation affords the desired natural product (+)-Tanikolide (Scheme V-7).[9]

Scheme V-7. Total synthesis of (+)-Tanikolide *via* an intramolecular oxidative lactonization



5.3. Conclusions

In our initial study (See Chapter 4) we found that Oxone is an excellent oxidant for the oxidation of aldehydes, for the re-oxidation of Os(VI) to Os(VIII) and that the solubility of Oxone in DMF played a key factor in the overall process. We have now seen throughout this chapter that small changes (i.e. $KHCO_3$ or MeOH) in our initial reaction conditions can provide different products selectively such as aldehydes or esters. Additionally, appropriate placement of an oxygen nucleophile can successfully prepare lactones. Furthermore we have now determined that successful oxidative cleavage does not require Oxone or DMF specifically, but that the reaction can be successful with H_2O_2 in ACN utilizing small amounts of a coordinating ligand. All of these conditions are mild and use environmentally friendly co-oxidants and small amounts of OsO_4 (as little as 0.02 mol %) such that large-scale reactions are feasible.

Chapter 6: Oxidation of Aldehydes and α- and β-Diones or α-Ketoalcohols to Provide Carboxylic Acids and Esters.

6.1. Introduction

Carboxylic acids and esters may seem to be fairly innocuous targets for novel synthetic methodology given the numerous methods already available. However, with our intent to pursue "green oxidations" we believe there still is a lot of room for potential growth. Oxone is a mild and green oxidant that is useful for numerous synthetic transformations.[80,87,89,90,92,95-97,129,220,221,240,263,264] We have found that it is quite effective in complete oxidative cleavage of olefins to carboxylic acids in one pot.[8,265] Our data suggests the intermediacy of aldehydes in this oxidation, and thus we began to probe the aldehyde oxidation independently.

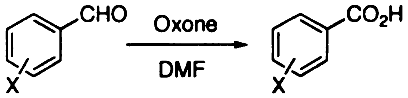
We have now completed the optimization of this aldehyde oxidation to carboxylic acids and in the process have also discovered a new route for the direct conversion of aldehydes, α- or β-diones and α-ketols to esters.[5,6,8,249] The scope and limitations for these oxidative processes and our current mechanistic understanding are presented. These methods are quite attractive, since as opposed to most methodologies that utilize Cr, Mn, Re, Ru, or other transition metal oxides, the environmentally benign reagent Oxone mediates these highly efficient oxidations.[263,266-273]

6.2. Oxidations of Aldehydes

6.2.1. Preparation of Carboxylic Acids

Initially, oxidation of aryl aldehydes to carboxylic acids with Oxone in DMF were investigated, the results of which are summarized in Table VI-1. In most cases the desired carboxylic acids were obtained in >85% yield. Electron withdrawing (NO_2, CF_3, and CN) and electron neutral (CO_2Me, Ph, Me, H) benzaldehdyes were oxidized efficiently (Table VI-1, entries 1-10). Halogenated benzaldehydes, including both Br and Cl, were also oxidized effortlessly to their corresponding halogenated benzoic acids in good yields (Table VI-1, entries 9-11). However, electron rich substrates such as 4-hydroxybenzaldehyde and *p*-anisaldehyde provided the formate esters **VI-13b** and **VI-15b** as the major products in 62% and 58% yield, respectively (Scheme VI-1). This is consistent with previous observations for the oxidation of electron rich aromatic rings that are presumed to undergo a Baeyer-Villiger reaction where the phenolic or Dakin products were obtained. Conversely, the electron rich *p*-acetoxybenzaldehyde **VI-14** proceeds smoothly to the desired carboxylic acid (Table VI-1, entry 14) in 90% yield.

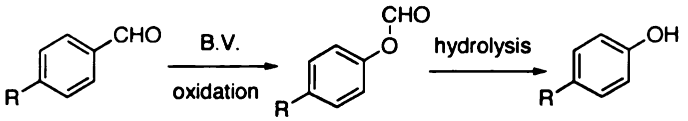
Table VI-1. Oxone oxidations of aromatic aldehydes[a]



Entry	X		Product	Yield (%)[b]
1	2-NO_2	**VI-1**	**VI-1a**	90
2	3-NO_2	**VI-2**	**VI-2a**	95
3	4-NO_2	**VI-3**	**VI-3a**	95
4	4-CF_3	**VI-4**	**VI-4a**	95
5	4-CN	**VI-5**	**VI-5a**	85
6	4-CO_2Me	**VI-6**	**VI-6a**	95
7	H	**VI-7**	**VI-7a**	97
8	4-Me	**VI-8**	**VI-8a**	97
9	2-Cl	**VI-9**	**VI-9a**	90
10	4-Cl	**VI-10**	**VI-10a**	97
11	3-Br	**VI-11**	**VI-11a**	97
12	3-OH	**VI-12**	**VI-12a**	63
13	4-OH	**VI-13**	**VI-13a**	19[c]
14	4-OAc	**VI-14**	**VI-14a**	90
15	4-OMe	**VI-15**	**VI-15a**	31[d]
16	Ph	**VI-16**	**VI-16a**	90

a) Aldehyde (1 equiv), Oxone (1 equiv), DMF (0.2 M), 3 h, RT. b) Isolated yields. c) 62% yield of **VI-13b**. d) 58% yield of **VI-15b**.

Scheme VI-1. Dakin products from electron rich aromatic aldehydes



VI-13, R = OH
VI-15, R = OMe

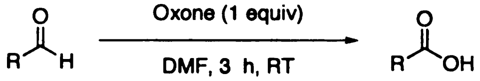
VI-13b, R = OH
VI-15b, R = OMe

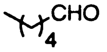
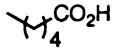
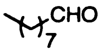
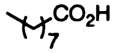
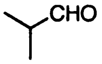
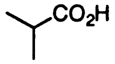
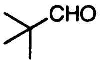
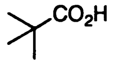
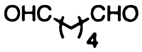
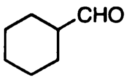
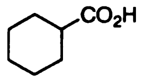
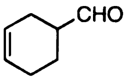
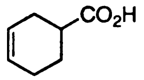
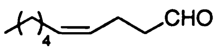
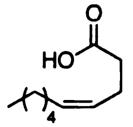
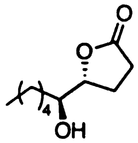
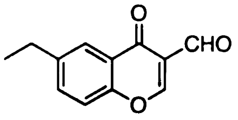
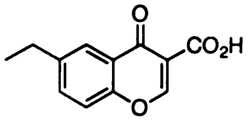
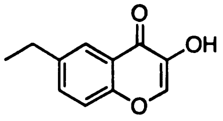
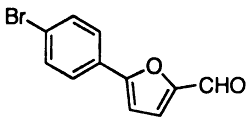
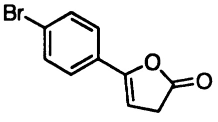
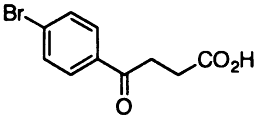
VI-18, R = OH
VI-19, R = OMe

The potential scope of this method was evident when the protocol was extended to simple aliphatic aldehydes (Table VI-2, entries 1-7). In most cases the oxidation proceeds with high efficiency and yields of greater than 90% were obtained. While affording clean reactions, smaller aliphatic aldehydes (Table VI-2, entries 3 and 4), provided low yields due to isolation difficulties from DMF. 1,2,3,4-tetrahydrobenzaldehye, which contains a double bond, oxidized effectively to **VI-26a** in 93% yield. Conversely, *cis*-4-decenal, **VI-27**, which also contains a double bond, was a unique substrate in that in addition to providing the desired acid, (**VI-27a**, 53%) a significant amount of the γ-lactone (**VI-28**, 32%) was isolated (Table VI-2, entry 8). Oxidation of the electron rich aldehydes **VI-29** and **VI-31** again provided primarily the Dakin products (Table VI-2, entries 9 and 10). Interestingly, the oxidation of 5-(4-bromophenyl)-furfural **VI-31** leads to the 1,4-dicarbonyl system **VI-33** through a simple oxidative process upon hydrolysis of the dehydrolactone **VI-32** (>70% yield).

A key feature of the oxidation protocol to carboxylic acids is its inherent simplicity. A mixture of the aldehyde (1 equiv) and Oxone (1 equiv) in DMF (0.1 - 1.0 M) is stirred for 3 h at RT. There is no need for rigorous exclusion of air or moisture in order to affect a clean oxidation, however, the reactions continue to work even with these added precautions. In most cases, a simple pass through a plug of silica is enough to obtain highly pure products.

Table VI-2. Oxidation of assorted aldehydes[a]

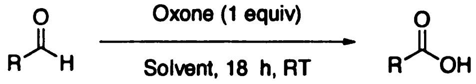


Entry	Substrate		Product		Yield (%)[b]
1		**VI-20**		**VI-20a**	99
2		**VI-21**		**VI-21a**	97
3		**VI-22**		**VI-22a**	33
4		**VI-23**		**VI-23a**	47
5		**VI-24**		**VI-24a**	84
6		**VI-25**		**VI-25a**	97
7		**VI-26**		**VI-26a**	93
8		**VI-27**		**VI-27a**	53
				**VI-28**	32
9		**VI-29**		**VI-29a**	34
				**VI-30**	52
10		**VI-31**		**VI-32**	42
				**VI-33**	30

a) Aldehyde (1 equiv), Oxone (1 equiv), DMF (0.2 M), 3 h, RT. b) Isolated yields.

Previous reports concerning the oxidation of aldehydes with Oxone were performed in aqueous acetone or acetonitrile. However, we have found that DMF is also effective for the oxidation; and in some cases superior to aqueous conditions. To test the range of solvents that may promote this oxidation, a number of cyclic and linear hydrocarbons, ethers, esters, and amides were screened against benzaldehyde, **VI-7** (Table VI-3). Surprisingly, very few solvents provided the desired carboxylic acid product even after extended reaction times of up to 36 h. The absence of reactivity is not attributed to the lack of solubility of Oxone because a comparable study using TBA-OX ($n\mathrm{Bu_4NHSO_5}$), a soluble version of Oxone, provided similar results. Interestingly, other amide based solvents such as NMP, HMPA, and DMA were as effective as DMF in the oxidation of **VI-7** with Oxone providing >96% yield of **VI-7a** in all cases.

Table VI-3. Oxidation of **VI-7** to **VI-7a** in various solvents[a,b]



Entry	Solvent	Yield (%)[c]
1	DMF	97
2	HMPA	99
3	NMP	97
4	DMA	96
5	tBuOH	99
6	MeOH	96[d]
7	H_2O	85
8	Acetonitrile	52
9	DCM	20
10	Et_2O	0
11	THF	0
12	Benzene	0
13	Hexane	0
14	EtOAc	0

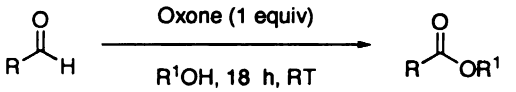
a) **VI-7** (1 mmol), Oxone (1 mmol), solvent (5 ml), RT b) Reactions were run for 6 h and checked by GC. Reactions that still showed **VI-7** were then checked after 18 h and 36 h. All reactions were then worked-up according to the standard procedure and the yield of **VI-7a** (or **VI-7b** entry 6) was calculated. c) Isolated yields d) Isolated product was **VI-7b** not **VI-7a**.

6.2.2. Preparation of Esters

As a fortuitous extension of the solvent study, the oxidation of aldehydes with Oxone in alcoholic solvents cleanly provided high conversion to esters. Thus, the oxidation of benzaldehyde in methanol did not yield the expected carboxylic acid, but instead the methyl ester was obtained (Table VI-4 entry 1). This oxidative pathway complements other known methods that directly convert aldehydes to esters such as oxidation in presence of alcohol with Br_2 or I_2, NBS/AIBN, PDC, HCN/MnO_2 or performed electrochemically.[274-278] Additionally, we found that other alcohols such as ethanol, propanol, and isopropanol could also provide esters in excellent yields, although *tert*-butanol exclusively provided the acid product (Table VI-4, entries 1-9).

The direct oxidation of a variety of aryl and alkyl aldehydes to their corresponding methyl esters is also listed in Table VI-4 (entries 10-21). In the case of electron rich aromatic substrates, as with the oxidations to carboxylic acids in DMF (Scheme VI-1), the Dakin products were observed. Thus, 4-hydroxybenzaldehyde, **VI-13**, and *p*-anisaldehyde, **VI-13**, provided primarily phenols **VI-18** and **VI-19** in 77% yield (Scheme VI-1, Table VI-4) for both along with small amounts of the corresponding esters (Table 4, entries 14 and 15). Additionally, **VI-31** provided 75% yield of the 1,4-dicarbonyl ester product, **VI-34** (methyl ester of **VI-33**). On the other hand, electron withdrawing substituents showed slow conversion to the esters (Table VI-4, entries 10 and 11) initially providing mixtures of the presumed monomethyl and dimethyl acetals in addition to the ester products. The identity of the acetals was proven to be incorrect and will be discussed later in this chapter. However, by heating the reactions to reflux overnight the observation of incomplete reaction was overcome and clean conversion to the desired methyl esters **VI-3b** and **VI-5b** occurred.

Table VI-4. Oxidation of aldehydes to esters[a]



Entry	Substrate	Solvent	Product	Yield (%)[b]
1	**VI-7**	MeOH	**VI-7b**	96
2	**VI-7**	EtOH	**VI-7c**	90
3	**VI-7**	*n*-PrOH	**VI-7d**	94
4	**VI-7**	*i*-PrOH	**VI-7e**	95
5	**VI-7**	*t*-BuOH	**VI-7a**	98
6	**VI-20**	MeOH	**VI-20b**	93
7	**VI-20**	EtOH	**VI-20c**	95
8	**VI-20**	*i*-PrOH	**VI-20e**	90
9	**VI-20**	*t*-BuOH	**VI-20a**	98
10	**VI-3**	MeOH	**VI-3b**	98[c]
11	**VI-5**	MeOH	**VI-5b**	98[c]
12	**VI-8**	MeOH	**VI-8b**	94
13	**VI-10**	MeOH	**VI-10b**	98
14	**VI-13**	MeOH	**VI-13b**	9[d]
15	**VI-15**	MeOH	**VI-14b**	19[d]
16	**VI-21**	MeOH	**VI-21b**	92
17	**VI-22**	MeOH	**VI-22b**	91[e]
18	**VI-23**	MeOH	**VI-23b**	76[e]
19	**VI-24**	MeOH	**VI-24b**	98
20	**VI-25**	MeOH	**VI-25b**	98
21	**VI-31**	MeOH	**VI-34**[f]	75

a) Aldehyde (1 equiv), Oxone (1 equiv), ROH (0.2 *M*), 18 h, RT. b) Isolated yields. c) These reactions were carried out at 50 °C for 18 h. d) The phenol products **VI-18** (77%) and **VI-19** (77%) were isolated as the major products for entries 14 and 15. e) GC yield. f) Methyl ester of **VI-33**.

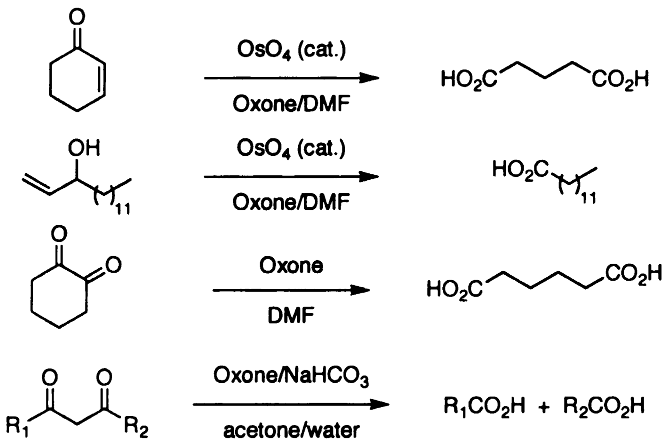
Noteworthy, is the fact that *iso*-propyl esters are made with ease. However, as mentioned above, *tert*-butyl esters cannot be accessed, most probably due to the sterics of the bulky alcohol. Although at this time conversion of aldehydes to esters proceed best if the reaction is performed in the alcoholic solvent (in order to prevent the formation of carboxylic acids), studies are underway with mixed solvents and show promising indications that the oxidation to carboxylic acids could be retarded in favor of esterification. Thus it could be possible to lessen the amounts of alcohol used in the oxidation.

6.3. Oxidations of α-Diones, β-Diones and α-Ketols

We have further extended our esterification protocol to include substrates such as α-diones, β-diones and α-ketols which represent a common structural motif in organic molecules. We noted that oxidative cleavage of α-ketoalcohols, α-diones, and β-diones to their corresponding dicarboxylic acids is a well precedented process with reagents such as calcium hypochlorite, sodium percarbonate, copper perchlorate, basic peroxide, bisthmuth and rhenium and in Ashford and Grega's report, β-diones could be oxidatively cleaved to the corresponding one carbon deleted carboxylic acid using Oxone-$NaHCO_3$-acetone-H_2O.[94,266-270,279] Additionally vanadium based systems have been reported to convert α-ketoalcohols or α-diones into the corresponding methyl or ethyl esters in presence of the appropriate alcohol (Scheme VI-2).[280,281]

Our own results in the related area of oxidative cleavage of olefins indicated that neither α,β-unsaturated carbonyls nor α-hydroxyolefins provided the expected α-ketoacids or α-hydroxyacids, but instead the one carbon deleted product. Moreover, 1,2-cyclohexanedione when treated with Oxone—DMF provided adipic acid exclusively (Scheme VI-2).

Scheme VI-2. Prior studies with Oxone cleavages



Since the data suggested that oxidative conversion of α-ketoalcohols, α-diones, and β-diones to carboxylic acids was well precedented there was little need for our group to pursue it further, but the preparation of esters seemed to be less general. We thought that these same classes of molecules may provide the corresponding diesters using ROH as an interactive solvent. We have now developed a methodology to effectively oxidatively cleave α-diones, β-diones and α-ketols to diesters in one simple transformation using the environmentally benign reagent $KHSO_5$, prepared easily from Oxone,

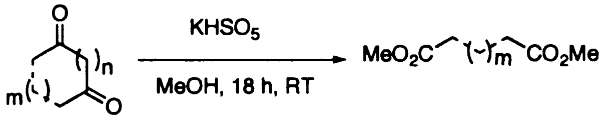
6.3.1. Preparation of Esters

To test this hypothesis we have now subjected several α-diones or β-diones and α-hydroxyketones to our oxidative protocol. Under normal conditions, the oxidations were performed in the chosen alcoholic solvent at RT for 18 h with the purified (>95%) dry version of Oxone, $KHSO_5$ (4 equiv). It should be noted that even though $KHSO_5$ was used in all the studies cited in this report, similar reactivity and yield were obtained if Oxone (triple salt containing $KHSO_5$) was utilized.

As can be seen from Table IV-5, oxidation of α-hydroxyketones, and α- and β-diones in methanol provided good to excellent yields of the desired dimethyl esters. For instance ketoalcohols, (Table IV-5, entries 1 and 2) provided products in 98% and 69% yield, respectively, and cyclic α-diones (Table IV-5, entries 3 and 4) convert efficiently to their corresponding dimethyl esters. Various other cyclic β-diones afforded the desired dimethyl esters in 78-99% yield. α-Branching did not affect the reaction (Table IV-5, entry 6); however, bis α-branching in the 1,3-dione **IV-41** did hinder the reaction significantly providing the tertiary ketoalcohol **IV-41a** in a modest 65% yield. Interestingly, **IV-41a** does not undergo further oxidation without heating, presumably due to steric constraints that hinder nucleophilic attack of the oxidant at the carbonyl carbon. Heating the reaction to 50 °C, however, did initiate the oxidative cleavage, but with poor conversion leading to only 54% of the desired diester with 22% of the starting material being recovered (Table IV-5, entry 16). The structurally related cyclic tertiary hydroxyketone, **IV-50**, reacted at room temperature providing an inseparable 4:1 mixture of the dimethyl ester and the keto ester in a modest 50% yield. Benzil and benzoin (**IV-46** and **IV-47**) were also notable because they required heating to 50 °C for a facile reaction. Additionally, the α-dione **IV-48** did not yield the expected diester, providing anhydride **IV-48a** in 98% yield, while **IV-49** did not provide the diester exclusively affording both the dimethyl and monomethyl esters in 19 and 64% yield, respectively. Conversion of **IV-48** to the cyclic anhydride **IV-48a** and not the diester (and conversely the oxidation of **IV-49** to **IV-49a** and **IV-49b**) is probably related to the observations made by Blanc in acetylation of 1,5 and 1,6-dicarboxylic acids, and in particular the differences in the reaction of the latter two compounds.[282,283]

Reactions in EtOH and *i*PrOH (Table IV-6) proved to be quite reluctant to yield diesters exclusively, and instead a reproducible mixture of mono- and di- esters were obtained. Notably, the overall yield of these products remains high (51-86%). Benzil and benzoin (**IV-46** and **IV-47**) again proved to be more difficult substrates requiring heating to 50 °C. Generally the yield of diethyl esters were higher than the corresponding diisopropyl esters, however, significant amounts of monoesters were isolated in all reactions. Reactions with *t*BuOH provided the diacid exclusively. This is in agreement with our previous observations, which demonstrated that oxidation of aldehydes in *t*BuOH with Oxone provided carboxylic acids without any trace of the desired ester.[8]

Table VI-5. Oxidation of α-diones, β-diones and α-ketols in MeOH[a]



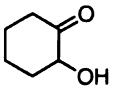
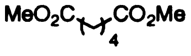
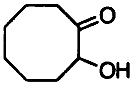
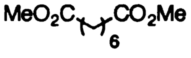
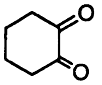
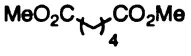
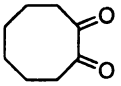
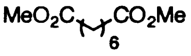
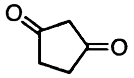
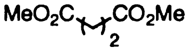
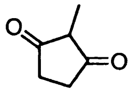
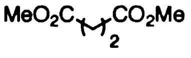
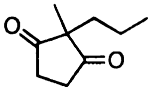
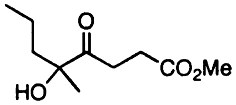
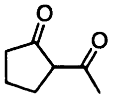
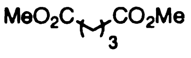
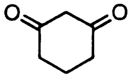
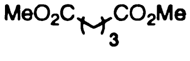
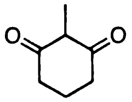
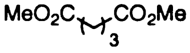
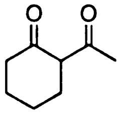
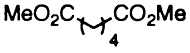
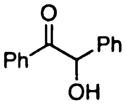
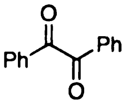
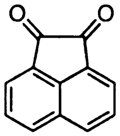
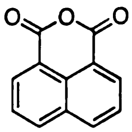
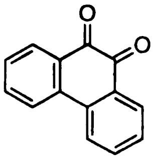
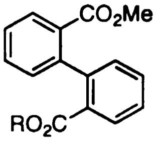
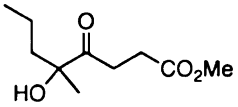
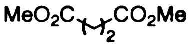
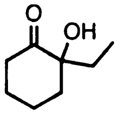
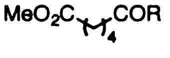
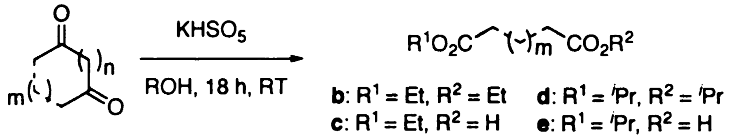
Entry	Substrate		Product		Yield (%)[b]
1	 (dimer)	**VI-35**		**VI-35a**	98
2		**VI-36**		**VI-36a**	69
3		**VI-37**		**VI-35a**	90
4		**VI-38**		**VI-36a**	79
5		**VI-39**		**VI-39a**	85
6		**VI-40**		**VI-39a**	80
7		**VI-41**		**VI-41a**	65
8		**VI-42**		**VI-42a**	86

Table VI-5. cont'd.

Entry	Substrate		Product		Yield (%)[b]
9		**VI-43**		**VI-42a**	99
10		**VI-44**		**VI-42a**	86
11		**VI-45**		**VI-35a**	78[c]
12		**VI-46**	$PhCO_2Me$	**VI-46a**	73
13		**VI-47**	$PhCO_2Me$	**VI-47a**	77
14		**VI-48**		**VI-48a**	98
15		**VI-49**		**VI-49a** R=Me **VI-49b** R=H	19 64
16		**VI-49a**		**VI-43a** **VI-49a**	54 22
17		**VI-50**	 R = OMe:Et = 4:1	**VI-35a:VI-51**	50

a) Dione (1 equiv), $KHSO_5$ (4 equiv), MeOH (0.2 *M*), 18 h, RT. b) Isolated yields. c) These reactions were carried out at 50 °C for 18 h.

Table VI-6. Oxidation of α-diones, β-diones and α-ketols in EtOH and iPrOH[a]



b: R^1 = Et, R^2 = Et **d**: R^1 = ^{i}Pr, R^2 = ^{i}Pr
c: R^1 = Et, R^2 = H **e**: R^1 = ^{i}Pr, R^2 = H

Entry	Substrate	Solvent (ROH)	Product	Yield (%)[b]
1	**VI-35**	EtOH	**VI-35b: VI-35c**	49:25
2	**VI-37**	EtOH	**VI-35b: VI-35c**	44:28
3	**VI-39**	EtOH	**VI-39b: VI-39c**	61:25
4	**VI-40**	EtOH	**VI-39b: VI-39c**	42:38
5	**VI-44**	EtOH	**VI-42b: VI-42c**	61:14
6	**VI-45**	EtOH	**VI-35b: VI-35c**	35:48
7[c]	**VI-46**	EtOH	**VI-46b: VI-46c**	25:37[c]
8[c]	**VI-47**	EtOH	**VI-46b: VI-46c**	44:37[c]
9	**VI-48**	EtOH	**VI-48a**	98
10	**VI-35**	*i*-PrOH	**VI-35d: VI-35e**	34:45
11	**VI-37**	*i*-PrOH	**VI-35d: VI-35e**	33:18
12	**VI-39**	*i*-PrOH	**VI-39d: VI-39e**	31:31
13	**VI-40**	*i*-PrOH	**VI-39d: VI-39e**	30:38
14	**VI-44**	*i*-PrOH	**VI-42d: VI-42e**	24:45
15	**VI-45**	*i*-PrOH	**VI-35d: VI-35e**	40:43
16[c]	**VI-46**	*i*-PrOH	**VI-46d: VI-46e**	15:51
17[c]	**VI-47**	*i*-PrOH	**VI-46d: VI-46e**	38:43
18	**VI-48**	*i*-PrOH	**VI-48a**	90

a) Aldehyde (1 equiv), $KHSO_5$ (4 equiv), ROH (0.2 *M*), 18 h, RT. b) Isolated yields. c) These reactions were carried out at 50 °C for 18 h.

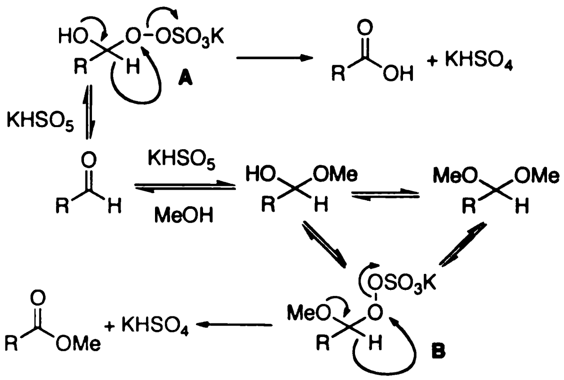
6.4. Mechanistic Interpretation

6.4.1. Aldehyde Oxidations

Studies in our laboratory demonstrated Oxone's effectiveness in the oxidative transformations of aldehydes to carboxylic acids and esters. While related studies had been conducted for the preparation of carboxylic acids from aldehydes, or esters from acetals our modified protocols now easily provids carboxylic acids or esters directly from aldehydes. Interestingly, the focus of prior work provides little insight into the oxidative role of Oxone.

Baumstark demonstrated that the aldehyde oxidation was promoted by dimethyl dioxirrane (DMDO), which could be either distilled away from Oxone or made *in situ*, and proceeded through a radical process.[95] Webb's oxidative protocol of aldehydes was said not be able to generate DMDO *in situ*; therefore, he attributed the oxidation purely to Oxone.[96] Additionally, Curini demonstrated that acetals could undergo oxidation to esters with Oxone but provided no mechanistic insight.[129] Herein, we discuss several experiments that allow us to propose a singular putative mechanism for the oxidation of aldehydes to their corresponding carboxylic acids or esters.

Scheme VI-3. Proposed mechanism of Oxone promoted oxidations

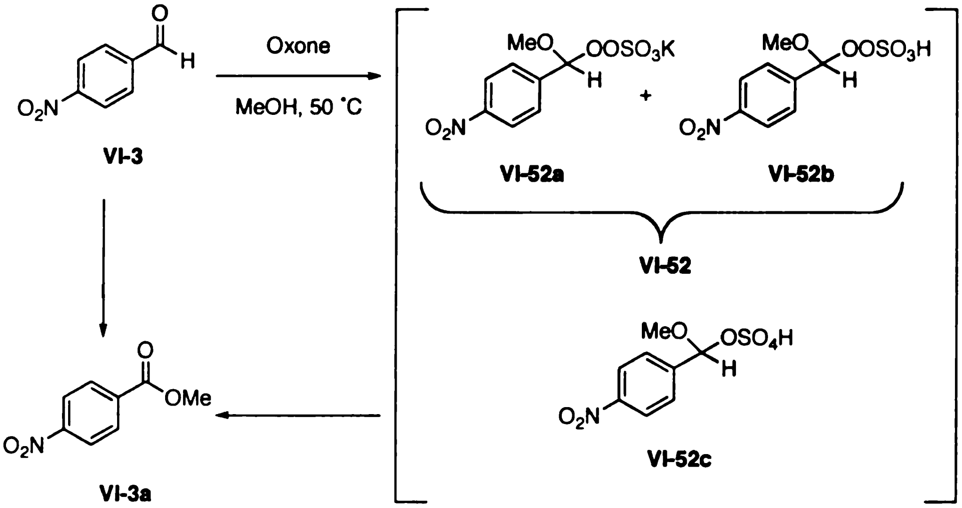


6.4.1.1. Initial Observations

Several empirical observations were key in pursuing the mechanistic studies of the oxidation process. Firstly, we observed phenolic products from the oxidation of aldehydes possessing electron donating substituents, i.e *p*-anisaldehyde. Baumstark demonstrated that if the oxidation proceeds through a radical based mechanism the phenolic products could be avoided by the exclusion of light and air.[95] In our oxidations of *p*-anisaldehyde with Oxone in DMF the product ratio did not change in the absence of light and oxygen, thus suggesting that radicals are not generated in these reactions.

Secondly, oxidation of aldehydes with electron withdrawing substituents such as 4-nitrobenzaldehyde, **VI-3**, in the presence of methanol provided a mixture of unknown acetals, **VI-52**. These acetals were not the monomethyl or dimethylacetal as confirmed by NMR experiments and are suspected to be peroxysulfate acetals. Elevating the reaction temperature in these cases from 20 °C to 50 °C cleanly provided the desired ester, **VI-3a**. Additionally, subjecting the mixture **VI-52** to MeOH at 50 °C did produce the desired ester along with some starting material **VI-3**. Noting that the ^{1}H NMR of **VI-52** looked like two distinct acetals we attempted to separate them by crystallization, which was unsuccessful. We found that careful chromatography could provide two distinct acetals **VI-52a** and **VI-52b** in small quantities along with a majority of aldehyde **VI-3** due to hydrolysis of **VI-52**. Treatment of those two compounds at 50 °C in MeOH showed clean conversion to the ester for **VI-52a** while **VI-52b** converted in a 1:1 ratio of SM and ester. IR and ^{1}H NMR analysis also revealed that **VI-52a** contained an OH group while **VI-52b** did not. The IR's of these compounds also showed characteristic signals for nitro and sulfate. Raman spectroscopy was uninformative and attempts to obtain single crystals were unsuccessful. The ^{1}H NMR shift of the benzylic methyne proton in the proposed peroxysulfate acetal is in agreement with that of known peroxy acetals[284,285] and therefore we propose that **VI-52b** is the potassium salt while **VI-52a** is the free base. An alternative structure to **VI-52a** could be the inverted peroxysulfate acetal **VI-52c**, however, we believe that compound **VI-52c** should not undergo clean conversion to **VI-3a.** We suspect that the electron withdrawing nitro group prevents the peroxysulfate acetal from undergoing a facile Baeyer-Villiger conversion.

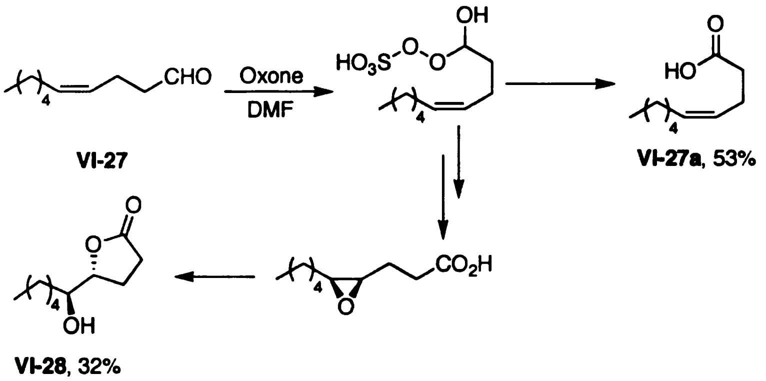
Scheme VI-4. Presumed structures, **VI-52**, of isolated acetal intermediates



Our third observation was that the conversion of *cis*-4-decenal yielded significant amounts of the γ-lactone side product (Scheme IV-5). The side product **VI-28** was curious and we subsequently investigated its origins. It was determined that Oxone is not an epoxidizing reagent under the utilized reaction conditions, as evident by the lack of reactivity of the olefin moiety in oxidation of 1,2,3,6-tetrahydrobenzaldehyde **VI-26** (Scheme VI-6). Additionally, subjecting 2-nonene to Oxone under identical reaction condition did not yield any epoxide and the starting olefin was recovered quantitatively.

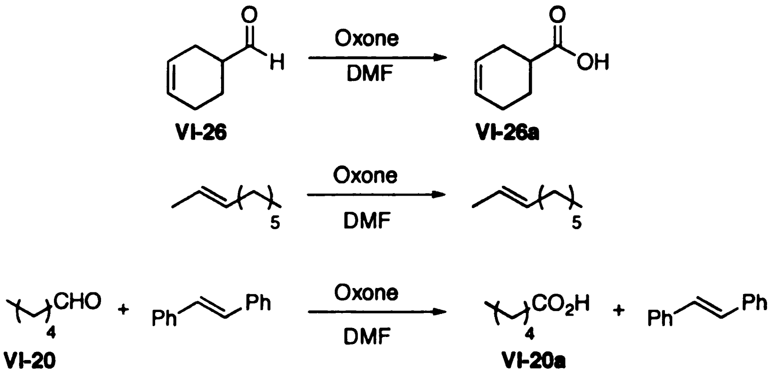
Furthermore, epoxides were not observed in the oxidation of hexanal with *t*-stilbene present as a scavenger,

Scheme VI-5. Intramolecular epoxidation provides γ-lactone



While, the lactone **VI-28** is most probably derived from the intramolecular ring opening of an intermediate epoxide (based on the stereochemistry of the product, which was determined by decoupling experiments), it certainly is not derived from an intermolecular epoxidation event. We hypothesize that an intermediate peroxy species could intramolecularly epoxidize the olefin (Scheme VI-5), as has been observed in unsaturated fatty peroxyacids.[286]

Scheme VI-6. Oxone does not epoxidize under identical conditions



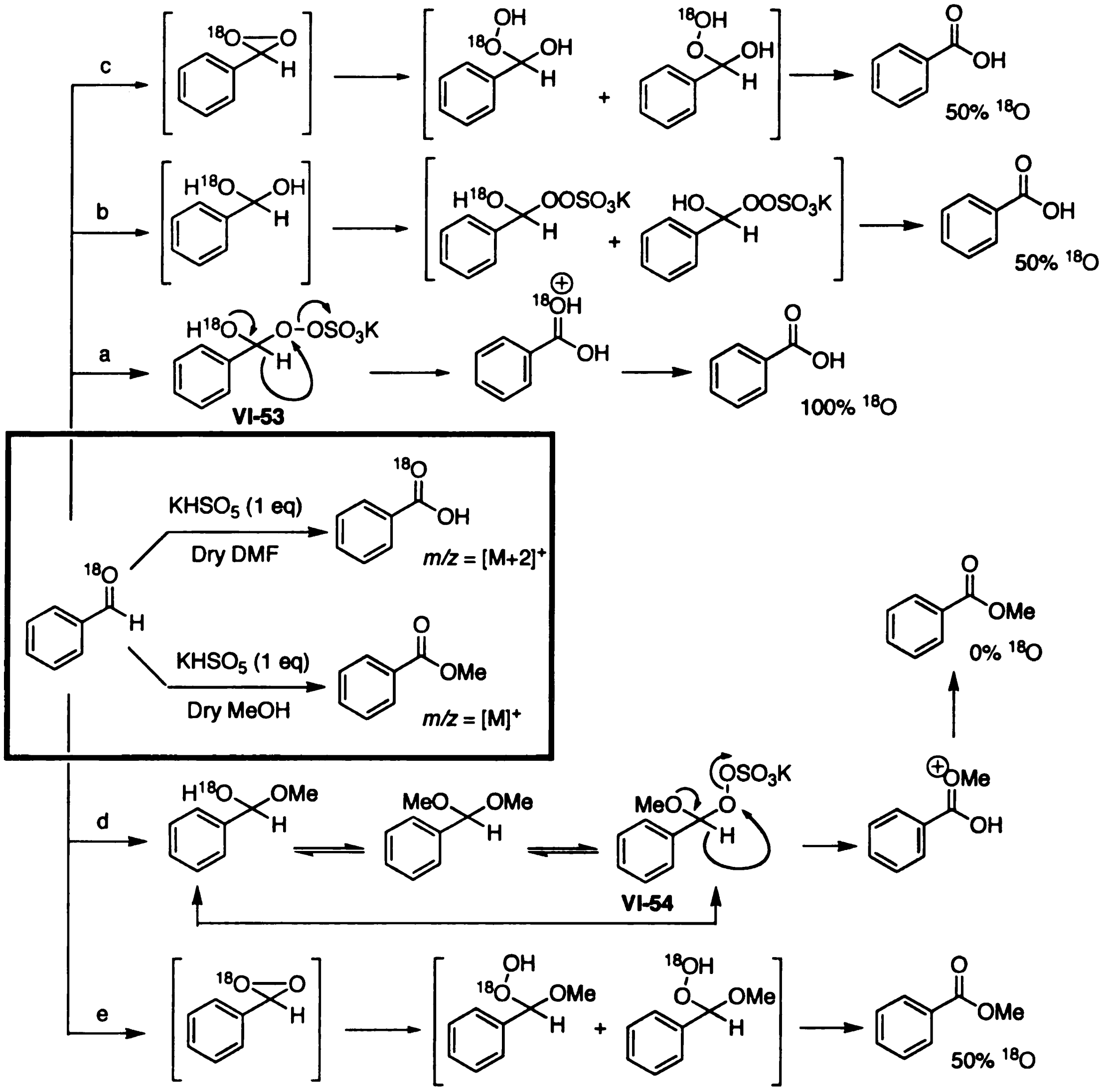
6.4.1.2. Results

6.4.1.2.1. NMR and GC Experiments

To better understand the mechanism of the two reactions discussed here, preparation of carboxylic acids and esters from aldehydes, the oxidation of ^{18}O-labeled benzaldehyde to benzoic acid and methyl benzoate were studied and the products were analyzed by mass spectrometry. ^{18}O-Labeled aldehyde was obtained with ease from $H_2{}^{18}O$ and benzaldehyde, and was used in oxidative studies with 1 equiv of anhydrous $KHSO_5$. Scheme VI-7 depicts the possible routes for the oxidation of an aldehyde to carboxylic acid (routes *a*, *b* and *c*) and ester (routes *d* and *e*). In short, if the oxidation to benzoic acid involves either the formation of a dioxirane (route *c*) or the gemdiol of the aldehyde (route *b*), the isolated product would contain 50% of the original ^{18}O-label. However, the nucleophilic attack of Oxone in route *a* and subsequent Baeyer-Villiger rearrangement of intermediate **VI-53** will lead to benzoic acid with full retention of the label. The isolated benzoic acid, obtained from the oxidation of the labeled benzaldehyde in DMF, was analyzed by GC/MS and was shown to have fully retained the oxygen label, thus suggesting route *a* as the path to carboxylic acids.

Similarly, the oxidation of benzaldehyde to methyl benzoate was investigated with the ^{18}O-labeled aldehyde. In the oxidations with MeOH, as in the previous examples, the intermediacy of a dioxirane would lead to the product with 50% of the original ^{18}O-label (route *e*, Scheme VI-7). However, formation of the hemi-acetal, and either the direct conversion to peroxide **VI-54**, or its formation through the dimethyl acetal, followed by a Baeyer-Villiger rearrangement would yield the product with no retention of the label (route *d*). The oxidation of ^{18}O-labeled benzaldehyde was performed with 1 equiv of $KHSO_5$ in dry methanol, and the isolated methyl benzoate was analyzed by GC/MS. The product did not exhibit any $[M+2]^+$ peak, thus suggesting that route *d* was operative in this reaction.

Scheme VI-7. ^{18}O labeled oxidations of benzaldehyde

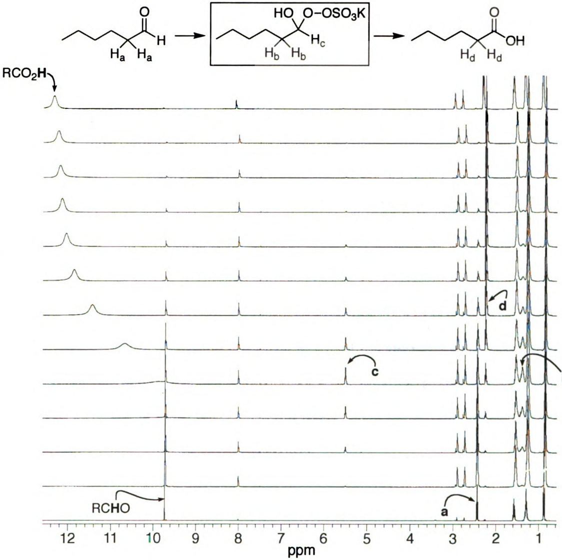


Further proof for the suggested mechanisms are provided through low temperature NMR studies. Oxidation of benzaldehyde and hexanal in d_7-DMF and d_4-MeOH at 10 °C were carried out using purified anhydrous $KHSO_5$. Figure VI-2 depicts a series of NMR traces collected during the oxidation of hexanal in d_7-DMF. As expected, the evolution of product signals is counterbalanced with the disappearance of resonances from hexanal. However, also present are a set of transient signals H_b and H_c that buildup in concentration as the reaction progresses. The transient resonance at δ 5.51 (H_c) is assigned to the hemiacetal proton of intermediate peroxy species. The chemical shift of this proton correlates well with the expected shift for hemiacetals.[287] The transient signal H_b (Figure VI-1) also falls within the expected region for a methylene neighboring a hemiacetal.[287] The upfield shift of $H_a \rightarrow H_b$ is indicative of the loss of the carbonyl functionality within the putative intermediate. The downfield shift of $H_b \rightarrow H_d$ signifies the regeneration of the carbonyl group, which in this case is the carboxylic acid. As expected the integration ratio of H_b:H_c is 2:1.

A similar transient signal was observed in the oxidation of benzaldehyde in d_7-DMF at δ 6.63, which was assigned to the benzylic proton of the corresponding peroxy hemiacetal. Since the oxidation in benzaldehyde is facile, there was little accumulation of the intermediate species as can be seen by the low intensity of the signal at δ 6.63. On the other hand, aromatic substrates with electron withdrawing groups such as 4-nitrobenzaldehyde showed slower conversion to product, therefore, we carried out the oxidation of this substrate in d_7-DMF and pure $KHSO_5$ at 10 °C. A transient signal at δ 6.77 was observed which was significantly stronger as compared to that in benzaldehyde suggesting accumulation of the putative reactive intermediate as a result of $KHSO_5$ addition to the aldehyde.

Oxidation of benzaldehyde and hexanal to their corresponding methyl ester in d_4-MeOH also exhibited transient signals at δ 5.67 and δ 4.69, respectively. These resonances were assigned as the intermediate peroxy methylacetals corresponding to structure **VI-54** in Scheme VI-7. The signals for intermediate hemiacetal and dimethyl acetal of both aldehydes were also present in the spectra, although, by the end of the reaction only the signals of the product could be observed.

Figure VI-1. NMR study of hexanal oxidation[a]



a) Oxidation of hexanal in d_7-DMF with Oxone at 10 ˚C (10 min elapsed between each spectrum) exhibits transient signals **b** and **c** that are assigned to the a-methylene and the hemiacetal proton of the boxed intermediate, respectively.

6.4.1.2.2. Kinetics

Emperical observations and subsequent analytical evidence have lead us to conclude that there is an initial nucleophilic attack with $KHSO_5$ on the aldehydic functionality which further promotes a Baeyer-Villiger rearrangement to yield the corresponding carboxylic acids or esters. Furthermore, by using $KHSO_5$ in its pure form we can reasonably suggest that neither radicals nor dioxiranes are involved in this mechanistic process.

The empirical evidence here supports a Baeyer-Villiger type of mechanism and to verify that conclusion we undertook a kinetic study of this oxidation using our most straightforward example with benzaldehyde. We found significant limitations when trying to employ GC or UV methods and found that for the kinetic study of this oxidation reaction an iodometric initial rate method was most desirable where pseudo first order kinetics were maintained by keeping a large excess of the aldehyde relative to $KHSO_5$. *All work related to the kinetics of the* $KHSO_5$ *promoted aldehyde oxidation were performed by Jun Yan, a graduate student in the Borhan laboratory, in collaboration with myself.*

Table VI-7. Rate constants of the oxidation of benzaldehyde by $KHSO_5$ at 298 K

[PhCHO], M	$10^2[KHSO_5]$, M	$[H_2SO_4]$, M	$10^3 k_1$, s^{-1}
2.46	0.83	1.00	5.51
2.46	1.27	1.00	5.34
2.46	1.63	1.00	5.88
2.46	2.19	1.00	5.69
2.46	2.79	1.00	5.88
0.49	1.50	1.00	0.74
0.98	1.50	1.00	2.03
1.48	1.50	1.00	2.82
2.02	1.50	1.00	4.13
2.46	1.50	1.00	5.88
2.46	1.00	0.30	4.33
2.46	1.00	0.50	4.71
2.46	1.00	0.75	4.47
2.46	1.00	1.00	5.12
2.46	1.00	1.25	5.00
2.46	1.00	1.50	5.52

Analysis of Table VI-7 allows one to see that the oxidation of benzaldehyde by $KHSO_5$ is first order in both substrate and $KHSO_5$ and zero order in acid concentration. It is therefore in accordance with the following observation, that the rate law for the disappearance of $KHSO_5$ is given as follows:

$$-d[KHSO_5] / dt = k\,[PhCHO][KHSO_5]$$

where k is a second order rate constant.

A temperature study between 261 K and 327 K revealed a marked increase in rate as the temperature was raised. Higher temperatures were not evaluated due to the inherent lack of stability of $KHSO_5$ at elevated temperatures. Analysis of the rate constants at various temperatures allowed us to determine both the enthalpy of activation and entropy of activation. Table VI-8 depicts the rate constant at various temperatures along with the plot of $-\ln(k_r/T)$ versus $1/T$.

The enthalpy of activation ($\Delta H^{\neq}$) was calculated from the slope of the plot:

$$\text{the slope of the plot} = \Delta H^{\neq}/R$$

$$\Delta H^{\neq} = R * (\text{the slope}) = 3.767E10^3 * 8.314 = 31.319E10^3 \text{ J mol}^{-1}$$

$$\Delta H^{\neq} = 31.319 \text{ KJ mol}^{-1}$$

followed by the calculation of entropy of activation ($\Delta S^{\neq}$) from the intercept of the plot:

$$\text{the intercept of the plot} = \Delta S^{\neq}/R + \ln(h/k)$$

$$\Delta S^{\neq} = R[\ln(h/k) - \text{the intercept of the plot}]$$

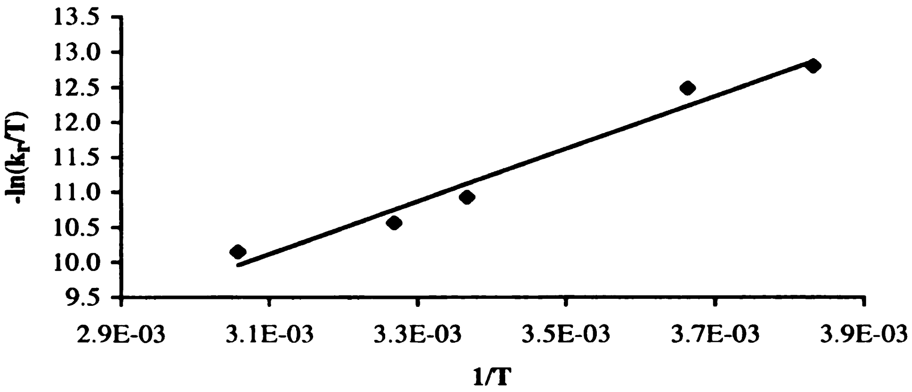
$$= 8.314\,[\ln(6.626e\text{-}34/1.38e\text{-}23) + 1.564]$$

$$= -184.5 \text{ J mol}^{-1} \text{ K}^{-1}$$

Table VI-8. Temperature effects on rate

Temperature (K)	10^3 Rate Constant (s^{-1})
261	0.72
273	1.03
297	5.32
306	7.97
327	12.70

$[KHSO_5]$ = 0.010 M; [PhCHO] = 2.5 M; $[H_2SO_4]$ = 1.0 M



The magnitudes of $\Delta H^{\neq}$ and $\Delta S^{\neq}$ reflect the transition-state structure. In particular, the reacting bonds will be both partially formed and partially broken. The energy required for bond reorganization is reflected in the higher potential energy of the activated complex and corresponds to the enthalpy of activation, $\Delta H^{\neq}$. The entropy of activation is a measure of the degree of order produced in the formation of the activated complex. If the number of translational, vibrational, or rotational degrees of freedom is reduced by proceeding from the transition state to the product, there will be an overall decrease in the total entropy of the system.

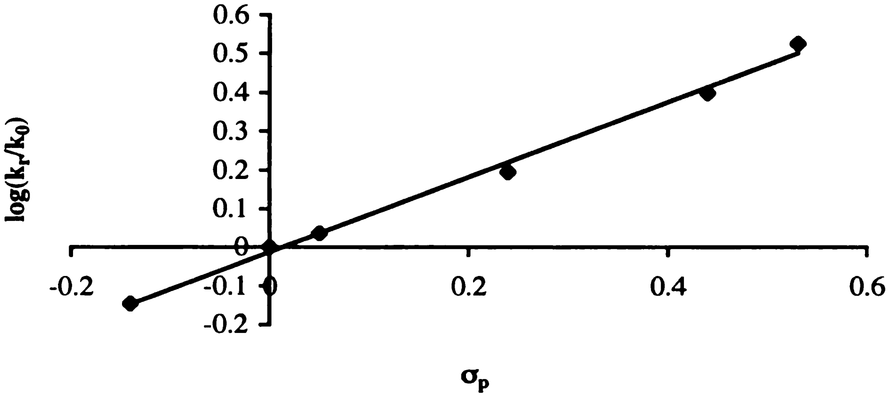
Here, the temperature effect, studied in the range of 261-327 K, shows a relatively low positive $\Delta H^{\neq}$ term demonstrating that bond making accompanies bond breaking. Additionally, a negative entropy of activation is observed, which reveals that the initially neutral reagents generate a charged intermediate species.[288,289] In comparison to other reported Baeyer-Villiger oxidations, which have small positive enthalpies of activation between 6 and 16 kcal mol^{-1} and negative entropies of activation between - 46 and - 171 J mol^{-1} K^{-1}, this reaction has very similar trends, with an enthalpy of activation at 31.32 KJ mol^{-1} or 7.48 kcal mol^{-1} and a slightly more negative entropy of activation at -184.5 J mol^{-1} K^{-1}. These results are in accordance with the known Baeyer-Villiger oxidation mechanism.[290]

The pseudo-first order rate constant was determined by using benzaldehyde and various substituted benzaldehydes under comparable conditions (Table VI-9). Since some of the substituted aldehydes did not have very good solubility in DMF they did not all have the same initial concentration. Even though the starting concentrations were different, by maintaining the concentrations of aldehydes in great excess over $KHSO_5$ the observed rate constant (k_{obs}) could be determined and could then be converted to a comparable rate constant (k_r) thus eliminating the effect of the starting concentrations of aldehydes ($k_r = k_{obs}$ / [aldehyde][H_2SO_4]).

Table VI-9. Substitutent effect at 298 K^a

substrate	10^3 k_{obs} (s^{-1})	[aldehyde], M	10^3 k_r (s^{-1})	log(k_r/k_0)	σ_p
H	5.32	2.46	2.16	0	0
p-Me	3.28	2.05	1.55	-1.46E-01	-0.14
p-Ph	4.68	1.99	2.35	3.59E-02	0.05
p-Cl	6.80	2.00	3.39	1.95E-01	0.24
p-CH_3OOC	4.33	0.80	5.40	3.98E-01	0.44
p-CF_3	14.92	2.06	7.25	5.25E-01	0.53

a) [$KHSO_5$] = 0.010 M; [H_2SO_4] = 1.0 M



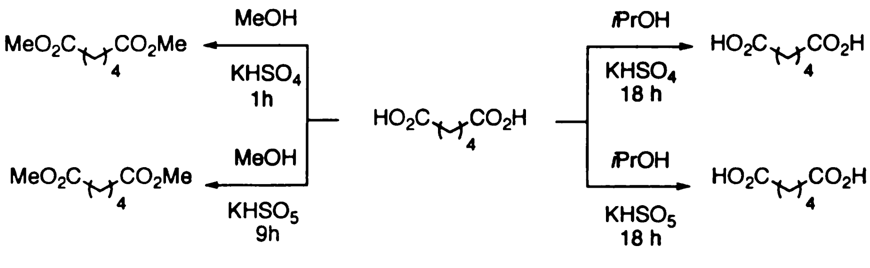
We found that the Hammett relationship that can be obtained from the substitutent effect data is well correlated with σ_p but poorly with σ^+ or σ^-, suggesting less importance of resonance effect in a transition state (Table VI-9). The slope of the Hammett plot about σ_p provides a r value of 0.97. Further inspection of the Hammett equation shows that reactions, which are favored by electron-donating groups, result in a positive ρ value. Additionally, the ρ value is not particularly large suggesting that the reaction is not very sensitive to substituent effects and furthermore implies that there is a relatively small redistribution of charge in the transition state. Again, as in comparison to known Baeyer-Villiger oxidation data, ρ has a typical value of 1.1-1.8 when a hydrogen migration occurs, which compares favorably to our ρ value of 0.97. Alternatively, Baeyer-Villiger oxidations provide negative ρ values when other groups migrate.

6.4.2. α-Diones, β-Diones and α-Ketols

The mixed products observed during the oxidation in ethanol and isopropanol prompted a mechanistic study for their origins. Of interest was to ascertain whether diesters are generated via Fisher esterification of monoesters; i.e., monoesters or dicarboxylic acids are the product of the oxidation, or different and competing mechanisms lead to mono and diesters. To address these two differing mechanistic interpretations adipic acid was treated with $KHSO_5$ or $KHSO_4$ in both MeOH and *i*PrOH. $KHSO_4$, the byproduct of the oxidative reaction, can be utilized in general acidic Fisher esterifications, but generally under heated or microwave assisted conditions.[291-293] Incubation of adipic acid for 18 h in *i*PrOH with either $KHSO_5$ or $KHSO_4$ did not lead to any detectable amounts of esterified product as analyzed by GC. Alternatively, adipic acid in MeOH and $KHSO_4$ led to the generation of dimethyl adipate in 1 h, however, the same reaction with $KHSO_5$ did not yield any esterified product within 5 h. Conversion to the diester was observed after 9 h, presumably due to the auto-decomposition of $KHSO_5$ to $KHSO_4$ in the wet alcoholic solvent. The presumed auto-decomposition was verified by iodometric titration[6] indicating that simply stirring MeOH and $KHSO_5$ for 9 h led to a 1% loss in oxidative activity, thus slowly generating the more acidic $KHSO_4$ that could be responsible for catalyzing the esterification. Moreover, addition of adipic acid (0.25

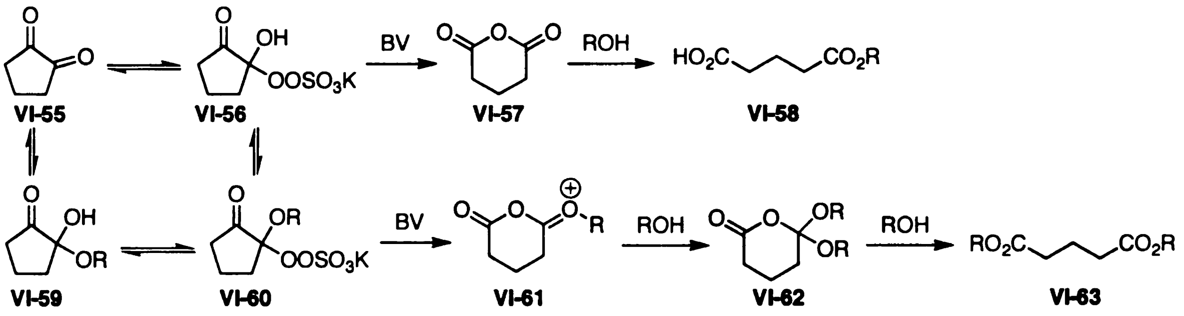
equiv) led to increased decomposition of $KHSO_5$ (4%) during the 9 h span. Considering the fact that the oxidation of cyclohexanedione **VI-37** to dimethyl adipate is nearly complete in 3 h, it seems unlikely that **VI-37** is converted to adipic acid, which in turn is esterified under the reactions conditions. More evidence of the latter is realized with experiments that demonstrate neither $KHSO_5$ nor $KHSO_4$ can convert simple acids to isopropyl esters, but yet mono and diisopropyl esters are isolated upon oxidation of α- or β-diones and α- hydroxyketones. Although it is not possible to present a detailed mechanistic picture from these experiments, it seems likely that the oxidative cleavage of the functional groups presented here is faster than Fischer esterification of their corresponding carboxylic acids, and that the mechanism for the formation of the isolated mono and diesters most probably occurs via different mechanisms. In other words, one can imagine diesters can originate directly from the oxidation without the intermediary of monoesters, although it can not be ruled out (at least for the generation of dimethyl esters) that some supplementary Fischer esterification of monoesters to diesters is occurring.

Scheme VI-8. Not just a Fischer esterification

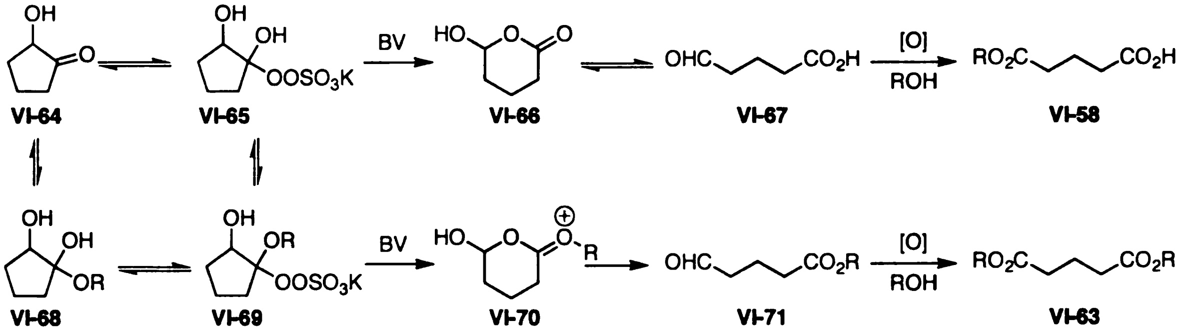


Schemes VI-9 – VI-11 depict possible routes to both monoesters and diesters from α-diones, β-diones and α-ketoalcohols. The route to monoesters would most probably involve the intermediacy of a peroxyhemiacetal, which upon Baeyer-Villegar like rearrangment would lead to the carboxylic acid functionality of the monoesters. This is shown for α-diones and α-hydroxyketones (intermediates **VI-56** and **VI-65**), which upon oxidative rearrangement lead to either the monoester **VI-58** or the aldehyde **VI-67**. Further oxidation of the aldehyde **VI-67** with Oxone in the alcoholic solvent would lead to the monoester **VI-58**. Conversely, the intermediacy of a peroxyacetal such as **VI-60** or **VI-69** could lead to the isolation of the diesters without the need for esterification of a monoesters and proceed to the diester **VI-63** directly. In a similar manner, β-diones could also lead to either mono or diesters. Presumably, α-hydroxyketone **VI-78** is produced as an intermediate to the final product, although we have not observed this via NMR spectroscopy. Subsequent Baeyer-Villiger oxidation could provide monoester **VI-80** or diester **VI-82** (Scheme VI-11).

Scheme VI-9. Probable mechanistic routes for the oxidative cleavage of α-diones



Scheme VI-10. Probable mechanistic routes for the oxidative cleavage of β-diones



Finally, it was shown that a minimum of 2 equiv of $KHSO_5$ for an α-hydroxyketone **VI-35** and 1 equiv of $KHSO_5$ for α-dione **VI-44** in EtOH was necessary for their oxidation to yield the ratios of products listed in Table VI-10 (entries 1 and 2). Increasing the amount of oxidant did not change the ratio of the mono and diester products isolated. However, β-dione **VI-44** required a minimum of 3 equiv of $KHSO_5$ to yield consistent product ratios listed in Table VI-10 (entry 5). These observations are inline with the postulated mechanism depicted in Scheme VI-8 to Scheme VI-10.

Scheme VI-11. Probable mechanistic routes for the oxidative cleavage of α-hydroxyketones

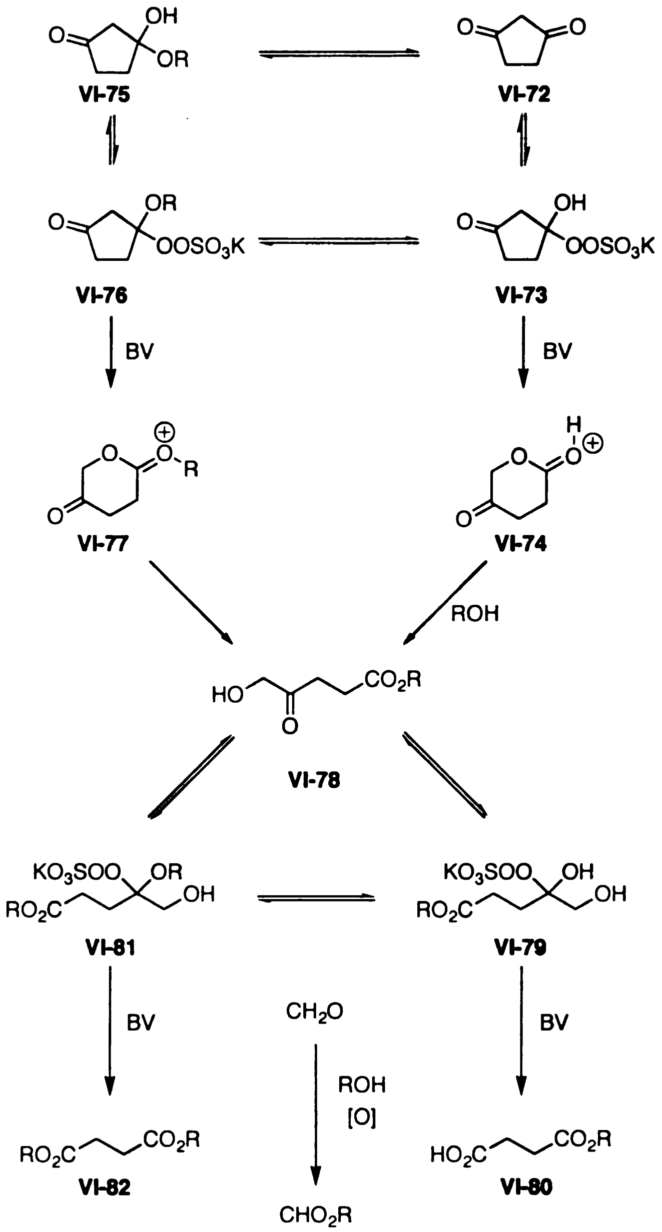


Table VI-10. Equivalents of oxidant necessary for complete conversion

Entry	Substrate	Equiv	Product	Yield(%)
1	**VI-35**	2	**VI-35b:VI-35c**	51:20
2	**VI-37**	1	**VI-35b: VI-35c**	42:33
3	**VI-44**	3	**VI-44b: VI-44c**	61:08

Summarily, we feel that the oxidative cleavage of α- or β-diones and α-ketoalcohols to esters with $KHSO_5$ is a valuable addition to the oxidative arsenal of Oxone chemistry. These results demonstrate a new methodology aimed at the direct synthesis of esters without the intermediacy of carboxylic acids from readily available α- or β-diones and α-ketoalcohols.

6.5. Conclusions

In conclusion, we have demonstrated a simple and effective one-pot protocol to oxidize aldehydes directly to carboxylic acids or esters. These reactions are facile, high yielding, and easy to work up (most do not require chromatography) and should provide a mild oxidative alternative for organic chemists. The oxidative cleavage of α- or β-diones and α-hydroxyketones to esters with $KHSO_5$ is also a valuable addition to the oxidative arsenal of Oxone chemistry. These results demonstrate a new methodology aimed at the direct synthesis of esters from α- or β-diones and α-hydroxyketones.

As demonstrated throughout this chapter, empirical observation, analytical experimentation and kinetic measurement provide sound support for a Baeyer-Villiger oxidation. An initial nucleophilic attack with $KHSO_5$ on the aldehydic functionality provides either carboxylic acids or esters depending simply on the solvent. This method is unique in that comparably harsh metal mediated processes can be replaced with the environmentally benign peroxysulfate salt $KHSO_5$. Furthermore, by using $KHSO_5$ in its pure form we can reasonably suggest that dioxiranes are not involved in this mechanistic process.

Chapter 7. Experimental Details

7.1. General Information

All commercially available starting materials were used without further purification. Commercially available starting materials were obtained from Aldrich, Fisher, Nu-Chek-Prep, and Lancaster (Table VIII-1). Some compounds were prepared as previously reported (Table VIII-1). All of the spectral data for known compounds either match those reported by Aldrich or by comparison to the literature report. Compounds that were analyzed by comparison to the Aldrich spectroscopic database are listed below and their data is not tabulated further in the experimental (Table VIII-2). ^{1}H, ^{13}C, gCOSY, gHMBC, DEPT and nOe spectra were recorded on either a 300 MHz NMR spectrometer (VARIAN INOVA) or on a 500 MHz NMR spectrometer (VARIAN VXR). IR spectra were recorded on Nicolet IR/42 spectrometer using NaCl cells. Column chromatography was performed using Silicycle (40-60 mm) silica gel. Analytical TLC was done using pre-coated silica gel 60 F_{254} plates. GC analysis was performed using HP (6890 series) GC system (Column type-AltechSE-54, 30 m x 320 mm x 0.25 mm).

7.1.1. Orgins of Starting Materials

Materials obtained from Aldrich: benzaldehyde **(III-1, V-1a, VI-7)**, *trans*-stilbene **(III-2, IV-2, V-1)**, triphenylphosphine **(III-3)**, methylphenysulfide **(III-4)**, phenylboronicacid **(III-5)**, *cis*-stilbene **(IV-1)**, *trans*-cinnamic acid **(IV-3, V-8)**, styrene **(IV-4, V-3)**, methyl cinnimate **(IV-5, V-4)**, cyclooctene **(IV-7, V-23)**, 1-decene **(IV-8, V-2)**, 1-nonene **(IV-9)**, 2-*trans*-nonene **(IV-10, V-18)**, (-)-isopulegol **(IV-13)**, 4,4`-dimethylstilbene **(IV-15, V-5)**, 4,4`-dinitrostilbene **(IV-16), 2**-cyclohexeneone **(IV-17)**, α-methyl cinnamic acid **(IV-18, V-9)** 1-methylcyclohexene **(IV-19)**, (+)-pulegone **(IV-21)**, 4-phenyl-3-buten-2-one **(IV-28, V-19)**, 1,4-diphenyl-1,3-butadiene **(IV-30, V-12)**, cinnamyl aldehyde **(IV-31, V-6)**, cinnamyl alcohol **(IV-32, V-7)**, 3-carene **(IV-34)**, 3-octene-1-1-ol **(IV-37)**, 2,2`-biphenylmethanol **(V-41)**, 4-pentene-1-ol **(V-45)**, 5-hexene-1-ol **(V-46)**, 6-heptene-1-ol **(V-47)**, 2-allylphenol **(V-56)**, 2-nitrobenzaldehyde **(VI-1)**, 3-nitrobenzaldehyde **(VI-2)**, 4-nitrobenzaldehyde **(VI-3)**, 4-trifluoromethylbenzaldehyde **(VI-4)**, 4-cyanobenzaldehyde **(VI-5)**, methyl 4-formylbenzoate **(VI-6)**, 4-methylbenzaldehyde **(VI-8)**, 2-chlorobenzaldehyde **(VI-9)**, 4-chlorobenzaldehyde **(VI-10)**, 3-bromobenzaldehyde **(VI-11)**, 3-hydroxybenzaldehyde **(VI-12)**, 4-hydroxybenzaldehyde **(VI-13)**, 4-acetoxybenzaldehyde **(VI-14)**, 4-methoxybenzaldehyde **(VI-15)**, 4-phenylbenzaldehyde **(VI-16)**, hexanal **(VI-20)**, nonanal **(VI-21)**, *iso*-butyraldehyde **(VI-22)**, 2,2,2-trimethylacetaldehyde **(VI-23)**, cyclohexanecarboxaldehyde **(VI-25)**, 1,2,3,6-tetrahydrobenzaldehyde **(VI-26)**, *cis*-4-decenal **(VI-27)**, 6-ethyl-4-oxo-4*H*-chromene-3-carbaldehyde **(VI-29)**, 5-(4-bromophenyl)furan-2-carbaldehyde **(VI-31)**, 2-hydroxy-cyclohexanone **(VI-35)**, 1,2-cyclohexanedione **(VI-37)**, 1,3-cyclopentanedione **(VI-39)**, 2-methyl-1,3-cyclopentadione **(VI-40)**, 2-

acetylcyclopentanone (**VI-42**), 1,3-cyclohexanedione (**VI-43**), 2-methyl-1,3-cyclohexanedione (**VI-44**), 2-acetylcyclohexanone (**VI-45**), benzil (**VI-46**), benzoin (**VI-47**), acenaphtyl-1,2-dione (**VI-48**), phenanthrene-9,10-dione (**VI-49**),

Materials obtained from Fischer: cyclohexene (**IV-6**),

Materials obtained from Nu-Chek-Prep: methyl lineolate **II-17**, 9,12-trans-methyl lineolate **II-23**, methyl oleate (**IV-11, V-35**),

Materials obtained from Lancaster: nootkatoone **IV-22**,

Materials prepared according to literature preparation: **(IV-12, V-32),**[294] **IV-14**[295], **IV-20,**[296] **IV-23,**[297] **(IV-27, V-10),**[298] **(IV-29)**[299] **(IV-33, V-11),**[300,301] **IV-35,**[302] **IV-36,**[303] **IV-38,**[304] **V-20,**[305] **V-21,**[306] **(V-27, VI-36)**[305] **(V-28, Vi-38),**[307] **V-48,**[308] **V-50,**[309] **V-51,**[310] **V-52,**[311] **V-53,**[312] **V-54,**[313] **V-55,**[314] **V-57,**[315] **V-58,**[316] **V-60,**[317] **VI-41,**[318] **VI-50,**[186]

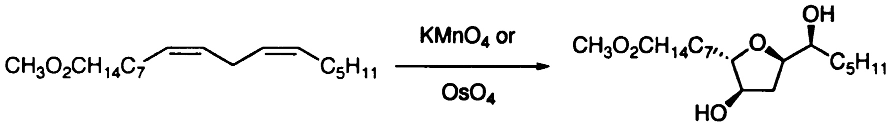
7.1.2. List of Compounds that were Compared with the Aldrich Database

Benzoic acid (**III-1a, IV-1a, V-1b, VI-7a, VI-46c**), triphenylphosphine oxide (**III-3a**), methylphenylsulfone (**III-4a**), phenol (**III-5a**), adipic acid (**IV-6a**), suberic acid (**IV-7a**), nonanoic acid (**IV-8a, VI-19a**), octanoic acid (**IV-9a**), heptanoic acid (**IV-10a**), 4-methylbenzoic acid (**IV-15a, VI-6a**), 4-nitrobenzoic acid (**IV-16a, VI-3a**), glutaric acid (**IV-17a**), acetophenone (**IV-20a**), and 3(R)-methyladipic acid (**IV-21a**), tridecanoic acid (**IV-35a**), pentanoic acid (**IV-37a**), benzaldehyde (**V-1a**), methyl benzoate (**V-1c, VI-7b, VI-46a**), methyl nonanoate (**V-2c, VI-21b**), 4-methylbenzaldehyde (**V-5a**), dimethylsuberate (**V-23c, VI-36a**), γ-butyrolactone (**V-45a**), γ-valerolactone (**V-46a**), γ-caprolactone (**V-47a**), 2-hydroxyphenylacetic acid (**V-56a**), 2-nitrobenzoic acid (**VI-1a**), 3-nitrobenzoic acid (**VI-2a**), 4-nitrobenzoic acid (**VI-3a**), methyl-4-nitrobenzoate (**VI-3b**), 4-trifluoromethylbenzoic acid (**VI-4a**), 4-cyanobenzoic acid (**VI-5a**), methyl-4-cyanobenzoate (**VI-5b**), mono-methyl terephthalate (**VI-6a**), ethyl benzoate (**VI-7c, VI-46b**), *n*-propyl benzoate (**VI-7d**), 4-methylbenzoic acid (**VI-8a**), methyl 4-methylbenzoate (**VI-8b**), 2-chlorobenzoic acid (**VI-9a**), 4-chlorobenzoic acid (**VI-10a**), methyl 4-chlorobenzoate (**VI-10b**), 3-bromobenzoic acid (**VI-11a**), 3-hydroxybenzoic acid (**VI-12a**), 4-hydroxybenzoic acid (**VI-13a**), methyl 4-hydroxybenzoate (**VI-13b**), 4-acetoxybenzoic acid (**VI-14a**), 4-methoxybenzoic acid (**VI-15a**), methyl 4-methoxybenzoate (**VI-15b**), 4-phenylbenzoic acid (**VI-16a**), hexanoic acid (**VI-20a**), methyl hexanoate (**VI-20b**), ethyl hexanoate (**VI-20c**), nonanoic acid (**VI-21a**), *iso*-butyric acid (**VI-22a**), 1,1,1-trimethylacetic acid (**VI-23a**), adipic acid (**VI-24a**), dimethyl adipate (**VI-24b, VI-35a**), cyclohexanoic acid (**VI-25a**), methyl cyclohexanoate (**VI-25b**), diethyl adipate (**VI-35b**), adipic acid monomethyl ester (**VI-35c**), diisopropyl adipate (**VI-35d**), dimethyl succinate (**VI-39a**), diethyl succinate (**VI-39b**), dimethyl glutarate (**VI-42a**), diethyl glutarate (**VI-42b**), 1,8-naphthalic anhydride (**VI-48a**)

7.1.3. List of Compounds that were Compared to Literature Reports

II-19,[208,209] **II-20,**[208,209] **II-21,**[208,209] **II-22,**[208,209] **II-27,**[319] **IV-12a,**[299] **IV-13a,**[320] **IV-19a,**[321] **IV-21b,**[322] **IV-22a,**[323] **IV-34a,**[324] **IV-34b,**[325] **VI-35d,**[132] **VI-39c,**[326], **VI-39d,**[327] **VI-39e,**[328] **VI-42c,**[329]**VI-42e,**[330] **VI-46d**[8] **VI-49a,**[331] **VI-49b,**[332]

7.2. Data for Chapter 2



II-17 **II-18**

Methyl (2-trans-3,5-cis)-8-(3-hydroxy-5-(1-hydroxyhexyl)-tetrahydrofuran-2-yl)octanoate (**II-18**):

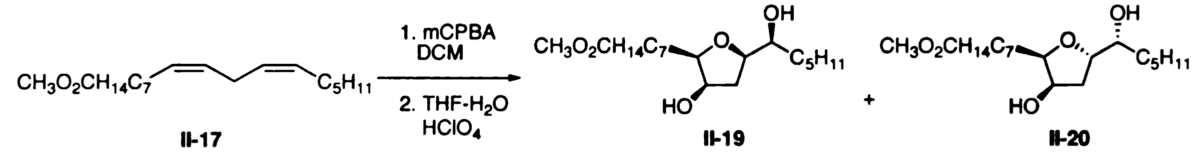
Acidic KMnO$_4$: **II-17** (200 mg, 0.68 mmol, 1 equiv) was dissolved in an acetone/H_2O (9:1) (20 mL) mixture and then *p*TsOH (117 mg, 0.68 mmol, 1 equiv) was added. Next, KMnO$_4$ (644 mg, 4.08 mmol, 6 equiv) was added in three portions over 20 min and stirred for 4 h. The reaction was then filtered through celite and washed with EtOAc. The organic layer was separated and the aqueous phase was extracted with EtOAc (10 mL x 2). The combined organics were washed with 1N HCl (30 mL) and brine (30 mL) and then dried over Na_2SO_4. The reaction was filtered and then evaporated under reduced pressure. Silica gel flash chromatography in 40% EtOAc/hexanes provided **II-18** (40 mg, 18%).

Basic KMnO$_4$: **II-17** (50 mg, 0.17 mmol, 1 equiv) was dissolved in an acetone/H_2O (9:1) (5mL) mixture and cooled to 0 °C. CO_2 was continuously bubbled through the solution followed by the addition of KMnO$_4$ (81 mg, 0.51 mmol, 3 equiv) in one portion. The reaction was stirred for 30 min at 0 °C, warmed to room temperature, and continued the CO_2 stream and stirring for 1 h. The reaction was then filtered through celite and washed with EtOAc. The organic layer was separated and the aqueous phase was extracted with EtOAc (5 mL x 2). The combined organics were washed with 1N HCl (15 mL) and brine (15 mL) and then dried over Na_2SO_4. The reaction was filtered and then evaporated under reduced pressure. Silica gel flash chromatography in 40% EtOAc/hexanes provided **II-18** (13.5 mg, 23%).

General Cyclization Protocol with OsO_4 and Various Co-oxidants: **II-17** (50 mg, 0.17 mmol, 1 equiv) was dissolved in acetone/H_2O (9:1) (5 mL) followed by the addition of OsO_4 (4% in H_2O, 0.017 mmol, 0.1 equiv). After 5 min. the co-oxidant was added (0.68 mmol, 4 equiv) and stirred for 6 h. The reaction was quenched with Na_2SO_3 (300 mg) and stirred for 1 h. The reaction was then extracted with EtOAc (5 mL) and the aqueous phase was washed with EtOAc (5 mL x 2). The combined organics were washed with 1N HCl (15 mL) and brine (15 mL) and then dried over Na_2SO_4, filtered and evaporated under reduced pressure. The reactions were purified by Silica gel flash chromatography in 10-80% EtOAc/hexanes.

General cyclization protocol with OsO_4, $NaIO_4$ and varying solvents: **II-17** (50 mg, 0.17 mmol, 1 equiv) was placed in a flame dried flask and dissolved in the appropriate solvent (5 mL). OsO_4 (2.5% in *t*-BuOH, 0.0085 mmol, 0.05 equiv) was added and stirred for 5 min under N_2. $NaIO_4$ (0.68 mmol, 4 equiv) was tehn added and stirred for 6 h. The reaction was quenched with Na_2SO_3 (300 mg) and stirred for 1 h. The reaction was then extracted with EtOAc (5 mL) and the aqueous phase was washed with EtOAc (5 mL x 2). The combined organics were washed with 1N HCl (15 mL) and brine (15 mL) and then dried over Na_2SO_4, filtered and evaporated under reduced pressure. The reactions were purified by silica gel flash chromatography in 10-80% EtOAc/hexanes.

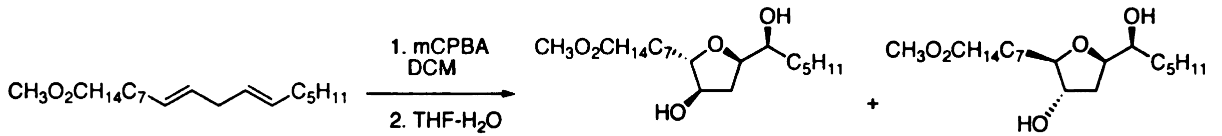
Optimized preparation with OsO_4 and Oxone in DMF: **II-17** (1.5g, 5.01 mmol, 1 equiv) was dissolved in DMF (50 mL) and OsO_4 (2.5% in *t*BuOH, 0.0085 mmol, 0.05 equiv) was added and stirred for 5 min followed by the addition of Oxone (20.37 mmol, 4 equiv), which was stirred for 3 h. The reaction was quenched with Na_2SO_3 (9 g) and stirred for 1 h. CH_2Cl_2 (150 mL) was then added and subsequently filtered through a pad of celite to remove the salts. The celite was further washed with CH_2Cl_2 (25 mL x 3), and then extracted with H_2O (200 mL x 2), 1N HCl (200 mL) and brine (200 mL). The combined organics were dried over Na_2SO_4, filtered and evaporated under reduced pressure to afford a brown oil. Silica gel flash chromatography in 30% EtOAc/hexanes provided **II-18** (535 mg, 30% yield). ^1H NMR ($CDCl_3$, 300 MHz): δ 4.05 (m, 1H), 3.98 (m, 1H), 3.93 (m, 1H), 3.78 (m, 1H), 3.63 (s, 3H), 2.26 (t, 2H, J = 7.4Hz), 2.21-2.12 (m, 1H), 1.83 (bd, 1H, J = 3.9Hz), 1.59-1.22 (b, 20H), 0.85 (s, 3H) ^{13}C ($CDCl_3$, 75 MHz): δ 174.2, 87.3, 80.2, 74.5, 71.9, 51.3, 33.9, 33.3, 32.9, 32.6, 31.6, 29.2, 29.0, 28.9, 25.8, 25.6, 24.7, 22.4, 13.9; HRMS (CI) calcd. for $C_{19}H_{37}O_5$, 345.2641 *m/z* (M+H), observed, 345.2638 *m/z*; IR (neat, NaCl, cm^{-1}) 3460, 2930, 2861, 1742, 1456, 1442, 1254, 1117, 1066, 1029.



Methyl (2,3,5-cis)-8-(3-hydroxy-5-(1-hydroxyhexyl)-tetrahydrofuran-2-yl)octanoate (**II-19**) and *Methyl (2,3-cis-5-trans)-8-(3-hydroxy-5-(1-hydroxyhexyl)-tetrahydrofuran-2-yl)octanoate* (**II-20**): [208,209]

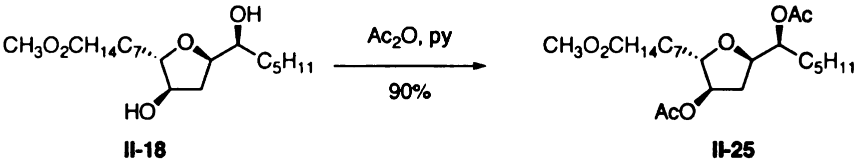
II-17 (110 mg, 0.373 mmol, 1 equiv) was dissolved in CH_2Cl_2 (15 mL). *m*CPBA (1.120 mmol, 3 equiv) was then added in one portion and the reaction was stirred for 1 h. The reaction was diluted with hexanes (50 mL) and filtered. The reaction was evaporated under reduced pressure to afford a white solid (residual *meta*-chlorobenzoic acid).

Additional hexanes (20 mL) were added, the solid was filtered and the organics were evaporated. This was repeated three times until a clear oil was obtained. This crude oil was dissolved in THF—H_2O—5% $HClO_4$ (3:1:1) (10 mL) and stirred for 3 h. The reaction was diluted with EtOAc (50 mL) washed with 5% $NaHCO_3$ (30 mL x 2) and brine (30 mL). The reaction was dried over Na_2SO_4, filtered and evaporated under reduced pressure to a clear oil. Silica gel flash chromatography in 30% EtOAc/hexanes provided **II-19** (40 mg, 31% yield) and **II-20** (44 mg, 35% yield). **VII-19** ^1H NMR ($CDCl_3$, 300 MHz): δ 4.00 (m, 1H), 3.91 (m, 1H), 3.63 (s, 3H), 3.60 (m, 1H), 3.43 (m, 1H), 2.36 (m, 1H), 2.27 (t, 2H, J = 7.8 Hz), 1.83 (dd, 1H, J = 13.2, 4.1 Hz), 1.58 (m, 6H), 1.28 (b, 14H), 0.86 (t, 3H, J = 6.0 Hz) ^{13}C ($CDCl_3$, 75 MHz): δ 174.9, 84.7, 84.6, 79.6, 74.3, 51.9, 39.1, 34.7, 32.5, 32.2, 30.0, 29.8, 29.6, 29.5, 26.6, 25.4, 25.3, 23.1, 14.5; IR (neat, NaCl, cm^{-1}) 3396, 2929, 2856, 1739, 1457, 1437, 1253, 1197, 1076, 1034. **VII-20** ^1H NMR ($CDCl_3$, 300 MHz): δ 4.20 (m, 1H), 4.00 (q, 1H, J = 8.8 Hz), 3.70 (m, 1H), 3.63 (s, 3H), 3.33 (m, 1H), 2.26 (t, 2H, J = 7.7 Hz), 1.96 (dd, 1H, J = 12.4, 7.1 Hz), 1.82 (m, 1H), 1.58 (m, 6H), 1.28 (b, 14H), 0.85 (t, 3H, J = 6.0 Hz) ^{13}C ($CDCl_3$, 75 MHz): δ 174.9, 82.9, 80.7, 74.5, 73.7, 51.9, 38.4, 33.6, 32.5, 32.3, 30.0, 29.4, 29.3, 26.6, 25.7, 25.4, 25.3, 23.0, 14.5; IR (neat, NaCl, cm^{-1}) 3470, 2931, 2858, 1740, 1457, 1437, 1252, 1120, 1070, 1026.



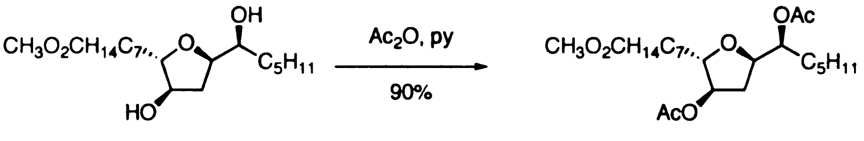
Methyl (2-trans-3,5-cis)-8-(3-hydroxy-5-(1-hydroxyhexyl)-tetrahydrofuran-2-yl)octanoate (**II-18**) and *Methyl (2,5-cis-3-trans)-8-(3-hydroxy-5-(1-hydroxyhexyl)-tetrahydrofuran-2-yl)octanoate* (**II-24**):

II-23 (150 mg, 0.51 mmol, 1 equiv) was dissolved in CH_2Cl_2 (20 mL). *m*CPBA (1.120 mmol, 3 equiv) was then added in one portion and stirred for 1 h. The reaction was diluted with hexanes (50 mL) and filtered. The reaction was evaporated under reduced pressure to afford a white solid (residual *meta*-chlorobenzoic acid). Additional hexanes (20 mL) were added, the solid was filtered and the organics were evaporated. This was repeated three times until a clear oil was obtained. This crude oil was dissolved in THF—H_2O—5% $HClO_4$ (3:1:1) (10 mL) and stirred for 3 h. The reaction was diluted with EtOAc (50 mL) and washed with 5% $NaHCO_3$ (30 mL x 2) and brine (30 mL). The reaction was dried over Na_2SO_4, filtered and evaporated under reduced pressure to a clear oil. Silica gel flash chromatography in 30% EtOAc/hexanes provided **II-18** (51 mg, 30% yield) and **II-24** (62 mg, 35% yield). *Methyl (2,5-cis-3-trans)-8-(3-hydroxy-5-(1-hydroxyhexyl)-tetrahydrofuran-2-yl)octanoate* **II-24**: ^1H NMR ($CDCl_3$, 500 MHz): δ 4.11-4.01 (m, 2H), 3.82 (m, 1H), 3.73 (m, 1H), 3.64 (s, 3H), 2.27 (t, 2H, $J = 7.3$ Hz), 2.05 (m, 2H), 1.69-1.26 (br, 20H), 0.86 (t, 3H, J=6.3Hz). ^{13}C ($CDCl_3$, 125 MHz): δ 174.3, 86.6, 80.8, 76.4, 70.8, 51.4, 34.2, 34.0, 33.2, 32.4, 31.8, 29.3, 29.1, 29.0, 25.8, 25.6, 24.9, 22.5, 14.0; HRMS (CI) calcd. for $C_{19}H_{37}O_5$, 345.2641 *m/z* (M+H), observed, 345.2642 *m/z*; IR (neat, NaCl, cm^{-1}) 3400, 2927, 2859, 1741, 1453, 1438, 1251, 1201, 1078, 1031.



Methyl (2-trans-3,5-cis)-8-(3-acetoxy-5-(1-acetoxyhexyl)-tetrahydrofuran-2-yl)octanoate **(II-25)**:

II-18 (150 mg, 0.45 mmol, 1 equiv) was dissolved in pyridine (3 mL). Ac_2O (1.35 mmol, 3 equiv) was then added and the reaction was stirred for 6 h at RT. The reaction was quenched with 1N HCl and diluted with EtOAc (15 mL). The organics were washed with 1N HCl (10 mL x 3) and brine (10 mL) dried over Na_2SO_4, filtered and evaporated under reduced pressure to a clear oil. Silica gel flash chromatography in 10% EtOAc/hexanes provided **II-25** (386 mg, 90% yield). ^1H NMR ($CDCl_3$, 300 MHz): δ 4.99-4.95 (m, 1H), 4.88-4.85 (m, 1H), 3.98-3.89 (m, 2H), 3.63 (s, 3H), 2.36-2.23 (m, 1H and t, 2H, J = 7.5Hz), 2.02 (s, 6H), 1.82-1.80 (m, 1H), 1.79-1.25 (b, 20H), 0.84 (t, 3H, J = 1Hz). ^{13}C ($CDCl_3$, 75 MHz): δ 174.2, 170.8, 170.5, 83.3, 78.1, 77.8, 74.6, 51.4, 33.9, 33.4, 32.7, 31.6, 30.9, 29.2, 29.0, 28.9, 25.4, 25.2, 25.0, 24.8, 22.4, 21.1, 13.9. HRMS (CI) calcd. for $C_{23}H_{41}O_7$, 429.2844 *m/z* (M+H), observed, 429.2849 *m/z*; IR (neat, NaCl, cm^{-1}) 2931, 2859, 1741, 1457, 1436, 1369, 1238, 1174, 1085, 1024.

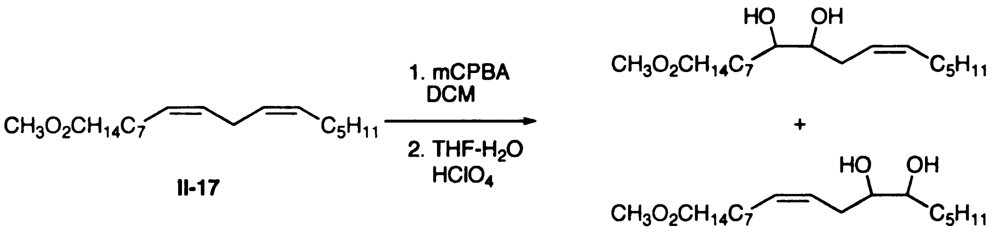


II-18

II-25

Methyl (2,5-cis-3-trans)-8-(3-acetoxy-5-(1-acetoxyhexyl)-tetrahydrofuran-2-yl)octanoate (**II-26**):

II-24 (50 mg, 0.145 mmol, 1 equiv) was dissolved in pyridine (1 mL). Ac_2O (0.435 mmol, 3 equiv) was added and the reaction was stirred for 6 h at RT. The reaction was quenched with 1N HCl and diluted with EtOAc (15 mL). The organics were washed with 1N HCl (10 mL x 3) and brine (10 mL) dried over Na_2SO_4, filtered and evaporated under reduced pressure to a clear oil. Silica gel flash chromatography (10% EtOAc/hexanes) provided **II-26** (55 mg, 88% yield). ^1H NMR ($CDCl_3$, 300 MHz): δ 5.04-5.02 (m, 1H), 4.99-4.90 (m, 1H), 4.11-4.04 (m, 1H), 3.84-3.82 (m, 1H), 3.63 (s, 3H), 2.27 (t, 2H, J = 7.4Hz) 2.03 (s, 6H), 2.15-1.83 (bm, 2H), 1.57-1.02 (b, 20H), 0.85 (t, 3H). ^{13}C ($CDCl_3$, 75 MHz): δ 174.3, 170.7, 170.5, 84.3, 79.4, 78.3, 73.9, 51.5, 34.2, 34.0, 33.0, 31.7, 31.6, 30.8, 29.2, 29.1, 29.0, 25.3, 25.1, 24.9, 22.5, 21.1, 14.0. HRMS (CI) calcd. for $C_{23}H_{41}O_7$, 429.2844 *m/z* (M+H), observed, 429.2840 *m/z*; IR (neat, NaCl, cm^{-1}) 2932, 2861, 1738, 1458, 1437, 1366, 1241, 1176, 1086, 1023.



II-27

(Z)-Methyl 9,10-dihydroxyoctadec-12-enoate and *(Z)-Methyl 12,13-dihydroxyoctadec-9-enoate* (**II-27**):[319]

II-17 (150 mg, 0.51 mmol, 1 equiv) was dissolved in CH_2Cl_2 (20 mL). *m*CPBA (0.56 mmol, 1.1 equiv) was then added in one portion and stirred for 1 h. The reaction was diluted with hexanes (50 mL) and filtered. The reaction was evaporated under reduced pressure to afford a white solid (residual *meta*-chlorobenzoic acid). Additional hexanes (20 mL) were added, the solid was filtered and the organics were evaporated. This was repeated three times until a clear oil was obtained. This crude oil was dissolved in THF—H_2O—5% $HClO_4$ (3:1:1) (10 mL) and stirred for 3 h. The reaction was diluted with EtOAc (50 mL) and washed with 5% $NaHCO_3$ (30 mL x 2) and Brine (30 mL). The reaction was dried over Na_2SO_4, filtered and evaporated under reduced pressure to a clear oil. Silica Gel flash chromatography in 30% EtOAc/hexanes provided **II-27** (118 mg, 71% yield). **II-27**: ^1H NMR ($CDCl_3$, 300MHz): δ 5.53 (m, 1H), 5.36 (m, 1H), 3.60 (s, 3H), 3.55 (m, 2H), 2.41-2.08 (m, 6H), 1.97 (m, 2H) 1.58-1.16 (br, 18H), 0.84 (t, 3H)..

7.3. Data for Chapter 3

$$2KHSO_5{\cdot}KHSO_4K_2SO_4 \longrightarrow KHSO_5{\cdot}H_2O \longrightarrow KHSO_5$$

Potassium peroxymonosulfate:

Preparation of $KHSO_5$•H_2O. Commercially available Oxone (307 g, 0.5 mol) was placed into a 2 L erlenmeyer. DI H_2O (307 mL) was added and swirled for 5 min until the noticeable fizzing subsided (internal temperature 10 °C). The slurry was filtered and washed with cold DI H_2O (30 mL). With the aid of a pH meter, the pH of the filtrate was adjusted to 3.5 using solid $KHCO_3$ (~75 g) with stirring. The initial pH of this clear solution was about 1.0 and at the endpoint a pink color is observed. We found that overshooting the endpoint resulted in a reduced yield of the purified material. If need be, the pH can be readjusted with a few drops of concentrated H_2SO_4. The pink slurry was filtered and the solid was washed with MeOH (2 x 307 mL) into the original water filtrate resulting in the formation of more precipitate in the filtrate. This precipitate was again filtered and washed with MeOH (307 mL). The slightly cloudy solution containing water (337 mL) and MeOH (921 mL) was placed in the freezer overnight to crystallize the purified product. The thick slurry was filtered and washed with Et_2O (4 x 200 mL) to yield 76.88 g, 45% yield of $KHSO_5$•H_2O and found to be 99.1% pure after triplicate iodometric titration. A second crop (6.52 g, 4% yield) could be obtained if the filtrate containing the water, methanol, and ether mixture was again place in the freezer overnight. The second crop was found to be 98.9% pure after iodometric titration.

Iodometric Titration of $KHSO_5$•H_2O. The iodometric titrations for purified $KHSO_5$•H_2O were all performed in triplicate. $KHSO_5$•H_2O (250.6 mg) was dissolved in DI H_2O (75 mL), 25% (w/w) KI (10 mL), and 10% (v/v) H_2SO_4 (15 mL). The dark brown solution was immediately titrated with 0.1003 M $Na_2S_2O_3$ to a slightly yellow endpoint. This method was adopted from the procedures developed by DuPont, Inc., and can be found at the following website: http://www.dupont.com/oxone/techinfo/index.htmL.

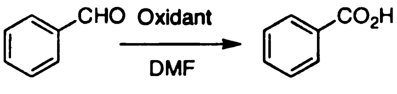
$$KHSO_5 \xrightarrow{n\text{Bu}_4NHSO_4} n\text{Bu}_4NHSO_5$$

Tetra-n-butylammonium peroxymonosulfate:

Preparation of nBu$_4$NHSO$_5$ (Method A, using KHSO$_5$•H$_2$O). Pure $KHSO_5$•H_2O (15 g, 88.2 mmol) was dissolved in DI H_2O (50 mL) and placed into a separatory funnel. A slight excess of nBu$_4$NHSO$_4$ (31.4 g, 92.6 mmol) was added to the separatory funnel and the slurry was extracted with CH_2Cl_2 (4 x 100 mL). The combined organics were dried over Na_2SO_4, and the solvent was removed under reduced pressure providing nBu$_4$NHSO$_5$ (31.5 g, 96% yield based on nBu$_4$NHSO$_4$, 98.6% activity) as a white solid.

(Method B, using Oxone). Oxone (2 g, 3.25 mmol) was dissolved in DI H_2O (20 mL) and placed into a separatory funnel. nBu$_4$NHSO$_4$ (0.25 → 6 equiv) was added to the funnel and the slurry was extracted with CH_2Cl_2 (6 x 50 mL). The combined organics were dried over Na_2SO_4, and the solvent was removed under reduced pressure to provide nBu$_4$NHSO$_5$ in 90 → 99% yield based on nBu$_4$NHSO$_4$ and ranged in activity from 35 → 91% activity based on triplicate iodometric titration.

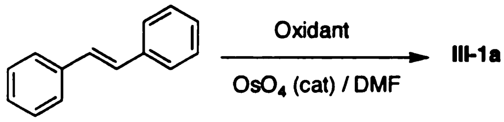
Iodometric Titration of nBu$_4$NHSO$_5$.[68] The assay was performed in triplicate using the following procedure. nBu$_4$NHSO$_5$ (200.3 mg) was dissolved in glacial acetic acid (2 mL), 10% (w/w) NaI (4 mL), and diluted with distilled THF (14 mL). The dark brown solution was immediately titrated with 0.1276 M $Na_2S_2O_3$ to reach the slightly yellow endpoint.



III-1 **III-1a**

Benzoic Acid (**III-1a**):

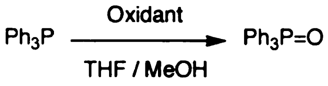
III-1 (100 mg, 0.94 mmol, 1 equiv) was dissolved in DMF (0.1 M). The appropriate HSO_5^- salt (1.1 equiv) was added in one portion and the reaction was stirred at RT for 18 h. 1N HCl (10 mL) was then added along with Et_2O (20 mL) to extract the products. The organic layer was washed with 1N HCl (10 mL x 3) and brine (10 mL), dried over Na_2SO_4, and the solvent was removed under reduced pressure. The reaction with Oxone and $KHSO_5 \cdot H_2O$ yielded benzoic acid (**III-1a**) in 97% (111 mg) and 94% (108 mg), respectively. The products were analytically pure and did not required additional purification. Oxidation with TBA-OX and $Ph_3PBnHSO_5$ led to the isolation of starting material **III-1**. The products of the latter two reactions were purified by column chromatography with CH_2Cl_2 as the eluant.



III-2

Benzoic Acid (**III-1a**):

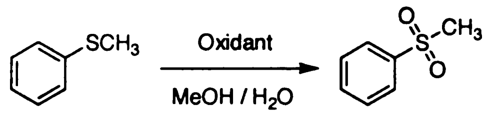
III-2 (100 mg, 0.55 mmol, 1 equiv) was dissolved in DMF (0.1 M), and OsO_4 (0.01 equiv, 2.5% in *t*BuOH) was added and stirred for 5 min. The appropriate HSO_5^- salt (4.4 equiv) was added in one portion and the reaction was stirred at RT for 18 h. Na_2SO_3 (2 equiv) was added and stirred for an hour or until the solution became dark brown/black to reduce the remaining Os(VIII) species. 1N HCl (10 mL) was then added along with Et_2O (20 mL) to extract the products. The organic layer was washed with 1N HCl (10 mL x 3) and brine (10 mL), dried over Na_2SO_4, and the solvent was removed under reduced pressure. Oxidation with Oxone and $KHSO_5{\bullet}H_2O$ yielded **III-1a** in 95% (128 mg), and 97% (131 mg), respectively. The products were analytically pure and did not required additional purification. TBA-OX and $Ph_3PBnHSO_5$ oxidation of **III-2** provided **III-1** in 88% (104 mg) and 25% (29 mg) yield, respectively. The products of the latter two reactions were purified by column chromatography with CH_2Cl_2 as the eluant.



III-3 **III-3a**

Triphenylphosphine oxide (**III-3a**):

III-3 (300 mg, 1.14 mmol, 1 equiv) was dissolved in THF/MeOH (1:1, 0.1 M). The appropriate HSO_5^- salt (1.1 equiv) was added in one portion and the reaction was stirred at RT for 1 h. The solvent was removed under reduced pressure and the products were purified by column chromatography with CH_2Cl_2 as the eluant. Oxidation of **III-3** with $KHSO_5{\bullet}H_2O$, TBA-OX, and $Ph_3PBnHSO_5$ led to the isolation of triphenylphosphine oxide **III-3a** in 99% (325 mg), 97% (318 mg), and 98% (107 mg), respectively.



III-4 **III-4a**

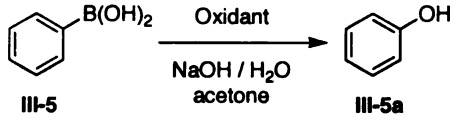
Methyl phenylsulfone (**III-4a**):

Oxidation with $KHSO_5$: **III-4** (347 mg, 2.8 mmol, 1 equiv) was dissolved in $MeOH/H_2O$ (1:1, 0.1 M). $KHSO_5{\bullet}H_2O$ (524 mg, 3.1 mmol, 1.1 equiv) was added in one portion and the reaction was stirred at RT for 4 h. The solvent was diluted with CH_2Cl_2

(20 mL) and water (20 mL). The aqueous fraction was washed with CH_2Cl_2 (20 mL x 3) and the combined organic extract was washed with brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure to obtain methylphenylsulfone (**III-4a**) (90%, 393 mg).

Oxidation with TBA-OX: III-4 (347 mg, 2.8 mmol, 1 equiv) was dissolved in CH_2Cl_2 (0.1 M). TBA-OX (1.1 g, 3.1 mmol, 1.1 equiv) was added in one portion and the reaction was stirred at RT for 3 days. The reaction was absorbed onto silica gel and was purified by column chromatography with CH_2Cl_2 as the eluant to obtain **III-4a** (91%, 398 mg).

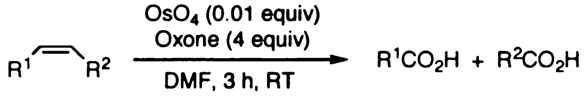
Oxidation with $Ph_3PBnHSO_5$: The procedure outlined above for TBA-OX was used and led to the isolation of **III-4a** (52%, 75 mg).



Phenol (**III-5a**):

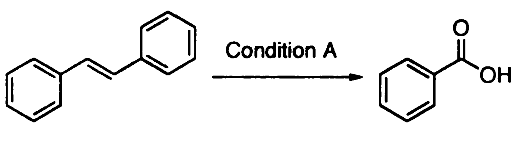
III-5 (100 mg, 0.82 mmol, 1 equiv) and NaOH (50 mg) were stirred for 5 min in H_2O (3 mL). $NaHCO_3$ (8.2 mmol, 10 equiv), the appropriate HSO_5^- salt (1.1 equiv), 400 mM EDTA (4 mL), and acetone (1 mL) were added at 0 °C and stirred for 15 min. The reaction was quenched with sat. sodium bisulfite (10 mL) and extracted with EtOAc (20 mL). The organic extract was washed with 1N HCl (10 mL x 2), H_2O (10 mL), brine (10 mL), and then dried over Na_2SO_4. The solvent was removed under reduced pressure to obtain the crude product, which was purified by column chromatography with CH_2Cl_2 as the eluant. Oxidation with $KHSO_5{\bullet}H_2O$, TBA-OX, and $Ph_3PBnHSO_5$ yielded phenol (**III-5a**) in 80% (62 mg), 40% (31 mg), and 30% (23 mg), respectively.

7.4. Data for Chapter 4



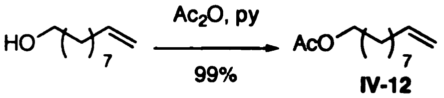
General Procedure for the Oxidative Cleavage of Mono and Disubstituted Olefins (Condition A): The olefin (1 equiv) was dissolved in DMF (0.2 M), and OsO_4 (0.01 equiv, 2.5% in *t*BuOH) was added and stirred for 5 min. Oxone (4 equiv) was added in one portion and the reaction was stirred at RT for 3 h or until the solution becomes colorless. This usually marks the completion of the reaction, which was verified by TLC or GC. Na_2SO_3 (6 equiv w/w) was then added, to reduce the remaining Os(VIII), and stirred for an additional hour or until solution became dark brown / black. 1N HCl was then added along with EtOAc to extract the products. The organic layer was washed with 1N HCl (3x) and brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure to obtain the crude product. Products were purified by silica gel column chromatography.

General Procedure for the Oxidative Cleavage of Tri and Tetrasubstituted Olefins (Condition B): The olefin (1 equiv) was dissolved in DMF (0.2 M), and OsO_4 (0.01 equiv, 2.5% in *t*BuOH) was added and stirred for 5 min. A solid mixture of Oxone (4 equiv) and $NaHCO_3$ (4 equiv) was then added in one portion and the reaction was stirred at RT for 3 h. or until solution becomes colorless. This usually marks the completion of the reaction, which was verified by TLC or GC. Na_2SO_3 (6 equiv w/w) was then added, to reduce the remaining Os(VIII), and stirred for an additional hour or until solution became dark brown / black. 1N HCl was then added along with EtOAc to extract the products. The organic extract was washed with 1N HCl (3x) and brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure to obtain the crude product. Products were purified by silica gel column chromatography.



IV-2 **IV-1a**

Benzoic Acid (**IV-1a**), **Large scale preparation**: **IV-2** (9 g) was dissolved in DMF (250 mL), and OsO_4 (0.2 mL, 2.5% in *t*BuOH) was added and stirred for five minutes. Oxone (123 g) was then added slowly *via* a solid addition funnel over 2 h. The reaction was stirred at RT for 6 h followed by addition of Na_2SO_3 (54 g) and stirred for an additional hour. The reaction was diluted with Et_2O (750 mL) and stirred for 10 min. The solid was filtered off and washed with Et_2O (75 mL x 3). The organic extract was washed with 1N HCl (200 mL x 3) and brine (200 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to obtain the **IV-1a** (11.60 g, 95%). The final product was crystallized from hot chloroform to obtain **IV-1a** (10.74 g, 88%). Lit mp = 121-123 °C. obs. mp = 120-122 °C.



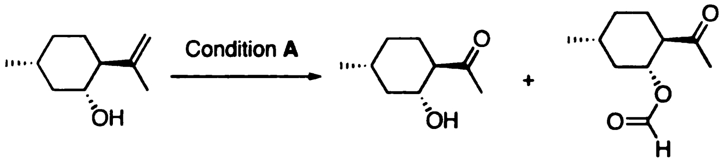
IV-12

9-Decenyl acetate (**IV-12, V-32**):[294] To a solution of 9-decene-1-ol (500 mg, 3.2 mmol) in pyridine (10 mL) was added acetic anhydride (0.91 mL, 9.6 mmol). The mixture was stirred and heated for 3 h at 60 °C. The reaction was then extracted with EtOAc (25 mL) and washed with 1N HCl (25 mL x 5) and brine (25 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to provide a crude, slightly yellow oil. Column chromatography (5% EtOAc/hexanes) provided **IV-12** (630 mg, 99% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.74-5.83 (m, 1H), 4.89-4.99 (m, 2H), 4.03 (t, 2H, J = 6.9

Hz), 2.02 (s, 3H), 2.01-2.07 (m, 2H), 1.56-1.62 (m, 2H), 1.27-1.38 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.2, 139.0, 114.1, 64.6, 33.7, 29.3, 29.1, 28.9, 28.7, 28.5, 25.8, 20.9; IR (neat, NaCl, cm^{-1}) 3077, 2927, 2856, 1741, 1641, 1242; LRMS (70 eV, EI) *m/z* 138 [M-OAc]$^+$.

IV-12 **IV-12a**

9-Acetoxy nonanoic acid (**IV-12a**):[299] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.02 (t, 2H, J = 6.9 Hz), 2.32 (t, 2H, J = 7.4 Hz), 2.02 (s, 3H), 1.56-1.61 (m, 4H), 1.29 (bs, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 179.6, 171.4, 64.5, 33.9, 29.0, 28.9, 28.8, 28.4, 25.7, 24.5, 20.9; IR (neat, NaCl, cm^{-1}) 3455, 2931, 2856 1739, 1737, 1242; LRMS (70 eV, EI) *m/z* 199 (M-H_2O]$^+$, 157 [M-OAc]$^+$.

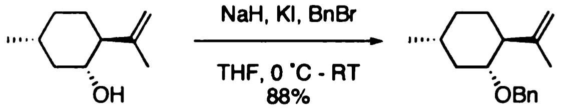


IV-13 **IV-13a, 44%** **IV-13b, 34%**

(1R, 2R, 5R)-2-Acetyl-5-methyl cyclohexanol (**IV-13a**):[320] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.80 (ddd, 1H, J = 4.4, 9.6, 11.1 Hz), 2.27 (ddd, 1H, J = 3.6, 9.6, 12.9 Hz), 2.17 (s, 3H), 1.91-2.00 (m, 2H), 1.68-1.74 (m, 1H), 1.38-1.52 (m, 1H), 1.22-1.27 (m, 1H), 0.91-1.03 (m, 1H), 0.92 (d, 3H, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 212.9, 70.4, 58.5, 42.2, 34.0, 31.1, 29.2, 27.5, 22.0; IR (neat, NaCl, cm^{-1}) 3417, 2952, 2927, 2869, 1705; LRMS (70eV, EI) *m/z* 156 M$^+$, 138 [M-H_2O]$^+$, 95 [M-H_2O-C(O)Me]$^+$.

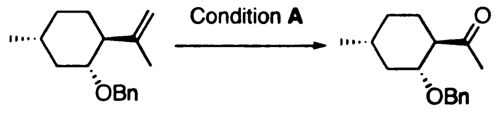
(1R, 2R, 5R)-2-Acetyl-5-methyl cyclohexanyl formate (**IV-13b**): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.95 (s, 1H), 5.06 (ddd, 1H, J = 4.4, 9.6, 11.2 Hz), 2.59 (ddd, 1H, J = 6.9, 8.9, 14.5 Hz), 2.15 (s, 3H), 2.11-2.13 (m, 1H), 1.93 (qd, 1H, J = 3.9, 6.9 Hz), 1.68-1.77 (m,

1H), 1.50-1.62 (m, 1H), 1.27-1.41 (m, 1H), 0.87-1.06 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 209.4, 160.3, 73.1, 55.2, 39.3, 33.3, 30.0, 29.3, 27.8, 21.7; IR (neat, NaCl, cm^{-1}) 2952, 2929, 2869, 1728, 1178; LRMS (70 eV, EI) *m/z* 185 (M+H)$^+$, 149 [M-HCO_2H]$^+$; HRMS [M]$^+$ Calcd for $C_{10}H_{16}O_3$: 184.1099 *m/z*. Observed 184.1095 *m/z*.



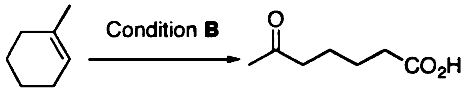
IV-13 **IV-14**

(1R, 2S, 5R)-(2-Isoprenyl-5-methyl-cyclohexyl) benzyl ether (**IV-14**):[295] Sodium hydride (68 mg, 60% dispersion in mineral oil, 1.7 mmol) was suspended in dry THF (9 mL). The reaction was cooled to 0 °C and isopulegol (200 mg, 1.3 mmol) dissolved in dry THF (1 mL) was added and stirred for 30 min. Benzyl bromide (289 mg, 1.7 mmol) and KI (63 mg, 1.7 mmol) were added sequentially at 0 ^{0}C. The reaction mixture was allowed to warm to RT and stirred for an additional 3 h, after which it was quenched with water and sat. NH_4Cl, and then extracted into EtOAc (20 mL x 2). The combined organics were washed with water (40 mL) and brine (40 mL), dried over Na_2SO_4, and the solvent was removed under reduced pressure to obtain a slightly colored oil. Column chromatography (10% EtOAc/hexanes) provided the desired benzyl ether (278 mg, 88%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.25-7.43 (m, 5H), 4.83 (s, 2H), 4.61 (t, 1H, *J*=11.5 Hz), 4.52 (d, 1H, *J*=11.8 Hz), 3.31 (dt, 1H, *J* = 4.1, 10.7 Hz), 2.11 (m, 2H), 1.71 (s, 3H), 1.64 (m, 2H), 1.28-1.45 (m, 2H), 0.95-1.06 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 147.8, 139.1, 128.3, 128.1, 127.7, 127.6, 127.2, 110.9, 79.1, 70.3, 51.7, 40.2, 34.3, 31.5, 31.0, 22.3, 20.0; IR (neat, NaCl, cm^{-1}) 2923, 2867, 1106; LRMS (70 eV, EI) *m/z* 243 [M-H]$^+$, 138 [M-OBn]$^+$.



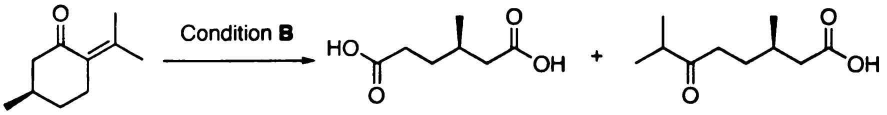
IV-14 **IV-14a**

(1R, 2R, 5R)-(2-Acetyl-5-methylcyclohexyl) benzyl ether (**IV-14a**): ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.21-7.32 (m, 5H), 4.56 (d, 1H, J = 11.3 Hz), 4.37 (d, 1H, J=11.3 Hz), 3.6 (dt, 1H, J = 6, 10.4 Hz), 2.53 (ddd, 1H, J = 3.8, 10.1, 12.6 Hz), 2.16 (s, 3H), 2.12-2.19 (m, 1H), 1.75 (qd, 1H, J = 3.6, 10.2 Hz), 1.64-1.70 (m, 1H), 1.25-1.52 (m, 2H), 0.93 (d, 2H, J = 3.3 Hz); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 212.3, 138.5, 128.2, 127.6, 127.4, 79.1, 70.9, 56.6, 39.4, 33.5, 30.9, 30.8, 27.7, 22.1; IR (neat, NaCl, cm^{-1}) 2950, 2927, 2867, 1739, 1712; LRMS (70 eV, EI) *m/z* 228 [M-H$_2$O]$^+$, 140 [M-OBn]$^+$; HRMS [M+H]$^+$ Calcd. for $C_{16}H_{22}O_2$: 246.1620 *m/z* . Observed 246.1631 *m/z* .



IV-19 **IV-19a**

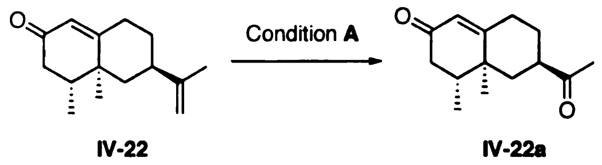
6-Oxyheptanoic acid (**IV-19a**):[321] ^{1}H NMR (CDCl$_3$, 300 MHz): δ 2.41-2.45 (m, 2H), 2.31-2.36 (m, 2H), 2.11 (s, 3H), 1.56-1.62 (m, 4H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 208.8, 179.1, 43.2, 33.7, 29.9, 24.0, 22.9; IR (neat, NaCl, cm^{-1}) 3455, 2939, 1714; LRMS (70 eV, EI) *m/z* 144 M$^+$, 126 [M-H$_2$O]$^+$.



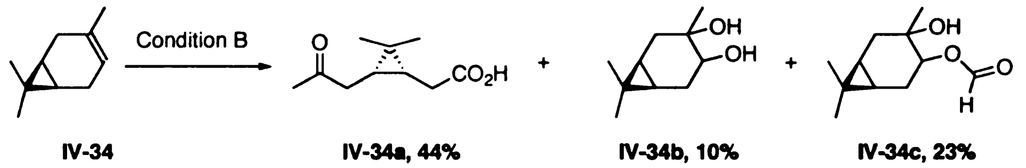
IV-21 **IV-21a, 67%** **IV-21b, 16%**

(R)-3,7-Dimethyl-6-oxo-octanoic acid (**IV-21b**):[322] ^{1}H NMR (CDCl$_3$, 500 MHz): δ 2.57 (p, 1H, J = 7.0 Hz), 2.46 (dt, 1H, J = 6.2, 9.1 Hz), 2.32 (dd, 1H, J = 6.0, 15.3 Hz), 2.16 (dd, 1H, J = 6.9, 15.3 Hz), 1.93 (sept, 1H, J = 6.6 Hz), 1.63 (m, 1H), 1.48 (m, 1H), 1.07 (d, 6H, J = 6.8 Hz), 0.95 (d, 3H, J = 6.7 Hz); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 214.5,

178.3, 41.2, 40.9, 37.8, 30.2, 29.8, 19.5, 18.3; IR (neat, NaCl, cm^{-1}) 3164, 2964, 2933, 1706, 1384, 1465; LRMS (70 eV, EI) *m/z* 186 M$^+$, 168 [M-H$_2$O]$^+$, 143 [M-C$_3$H$_7$]$^+$.

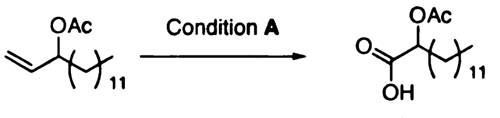


(4S, 4aR, 6R)-6-Acetyl-4,4a-dimethyl-4,4a,5,6,7,8-hexahydro-3H-naphthalen-2-one (**IV-22a**):[323] ^{1}H NMR (CDCl$_3$, 300 MHz): δ 5.72 (s, 1H), 2.71 (m, 1H), 2.33-2.48 (m, 2H), 2.20-2.25 (m, 2H), 2.1 (s, 2H). 1.94-2.06 (m, 4H), 1.40 (m, 1H), 1.21 (t, 1H, J = 12.5 Hz), 1.06 (s, 3H), 0.93 (dd, 3H, J = 6.6, 1.9 Hz); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 10.4, 199.2, 168.5, 125.1, 46.6, 41.9, 40.1, 39.8, 38.8, 31.9, 28.4, 28.1, 16.6, 14.8; IR (neat, NaCl, cm^{-1}) 2966, 2939, 2883, 1708, 1668, 1617; LRMS (70 eV, EI) *m/z* 220 M$^+$, 177 [M-COMe]$^+$.



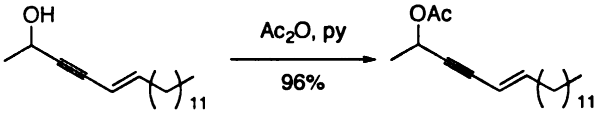
2-((1R,3S)-2,2-Dimethyl-3-(2-oxopropyl)cyclopropyl)acetic acid (**IV-34a**): [324,325] ^{1}H NMR (CDCl$_3$, 300 MHz): δ 2.38-2.34 (m, 2H), 2.28-2.23 (m, 2H), 2.15 (s, 3H), 1.1 (s, 3H), 0.90-0.92 (m, 2H) 0.90 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 208.7, 178.9, 39.3, 30.0, 29.6, 28.4, 21.4, 21.1, 17.2, 14.9; IR (neat, NaCl, cm^{-1}) 3164, 2948, 1714, 1168; LRMS (70 eV, EI) *m/z* 184 (M)$^+$, 166 (M-H$_2$O)$^+$.

(1R,6S)-4-Hydroxy-4,7,7-trimethylbicyclo[4.1.0]heptan-3-yl formate (**IV-34c**): ^{1}H NMR (CDCl$_3$, 300 MHz): δ 8.08 (s, 1H), 4.59 (t, 1H, J = 9.1 Hz), 2.15 (br, 1H), 1.71-1.99 (m, 2H), 0.07-1.68 (m, 13H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 161.3, 77.8, 71.5, 34.0, 28.4, 25.5, 20.5, 20.2, 19.6, 17.8, 15.8.



IV-36 → **IV-36a**

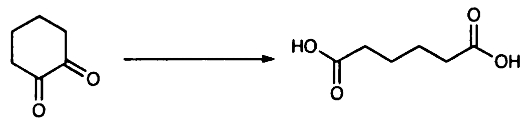
2-Acetoxytetradecanoic acid (**IV-36a**):[333] ^{1}H NMR (CDCl$_3$, 300 MHz): δ 8.5-8.2 (br, 1H), 4.97 (t, 1H, *J* = 6.3 Hz), 2.11 (s, 3H), 1.85 (m, 2H), 1.40 (m, 1H), 1.23 (b, 20H), 0.85 (t, 3H, *J* = 6.0 Hz); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 176.3, 170.9, 72.1, 32.1, 31.2, 29.9, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 25.3, 22.9, 20.7, 14.3.



IV-38 → **IV-39**

(E)-Octadec-5-en-3-yn-2-yl acetate (**IV-39**): To a solution of IV-38 (132 mg, 0.5 mmol) in pyridine (5 mL) was added acetic anhydride (102 mg, 1 mmol). The mixture was stirred and heated for 3 h at 60 °C. The reaction was then extracted with EtOAc (25 mL) and washed with 1N HCl (15 mL x 5) and brine (25 mL). The organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure to provide a crude, slightly yellow oil. Column chromatography (5% EtOAc/hexanes) provided the desired acetate (630 mg, 96% yield). ^{1}H NMR (CDCl$_3$, 300 MHz): δ 6.15 (dt, 1H, *J* = 15.9, 7.1 Hz), 5.45 (m, 1H), 2.08 (m, 2H), 1.47 (d, 3H, *J* = 6.6 Hz), 1.49-1.23 (b, 20H), 0.85 (t, 3H, *J* = 6.0 Hz).

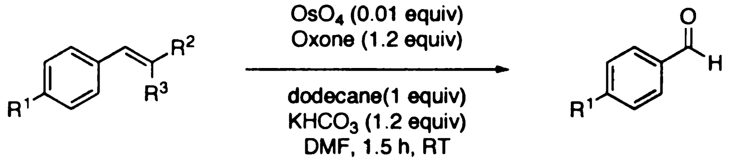
7.4.1. Additional data related to Chapter 4



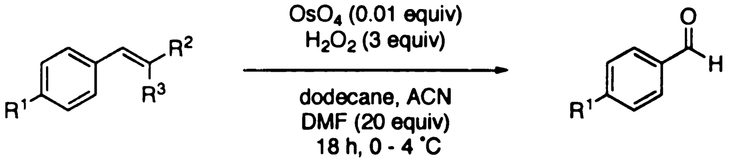
Oxidation of 1,2-Cyclohexanedione to Adipic acid

1,2-Cyclohexanedione (1 equiv) was dissolved in DMF (0.2 M), and Oxone (4 equiv) was added in one portion. The reaction was stirred at RT for 3 h and an aliquot was removed and diluted with EtOAc for GC analysis. This showed an 80% conversion to adipic acid.

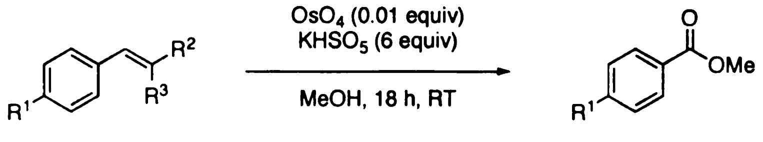
7.5. Data for Chapter 5



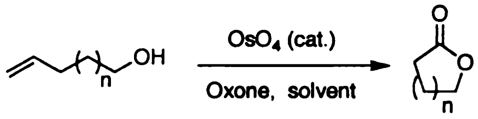
General Procedure for the Oxidative Cleavage to Aldehydes with $KHCO_3$ (Condition A): The olefin (1 equiv) was dissolved in DMF (0.2 M) followed by the addition of dodecane (1equiv), the internal standard, and OsO_4 (0.01 equiv, 2.5% in *t*BuOH). After 5 min. $KHCO_3$ (1.2 equiv) and Oxone (1.2 equiv) were added sequentially and the reaction was stirred at RT for 1.5 h. Reaction progress was monitored by GC and the data analyzed against a standard curve.



General Procedure for the Oxidative Cleavage to Aldehydes with H_2O_2 (Condition B): The olefin (1 equiv) was dissolved in ACN (0.2 M) followed by the addition of DMF (20 equiv), dodecane (1 equiv) and OsO_4 (0.01 equiv, 2.5% in *t*BuOH). The reaction was cooled to 0 °C and then H_2O_2 (3 equiv) was added and the reaction was stirred at 4 °C for 18 h. or until the solution becomes colorless. Reaction progress was then monitored by GC and the data analyzed against a standard curve.

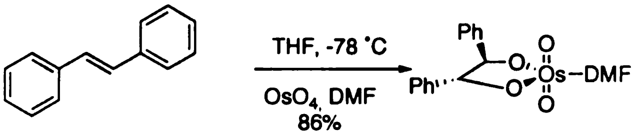


General Procedure for the Oxidative Cleavage to Esters in MeOH (Condition C): The olefin (1 equiv) was dissolved in MeOH (0.2 M), and OsO_4 (0.01 equiv, 2.5% in *t*BuOH) was added and stirred for 5 min. $KHSO_5$ (6 equiv) was added in one portion and the reaction was stirred at RT for 18 h. Na_2SO_3 (6 equiv w/w) was then added, to reduce the remaining Os(VIII), and stirred for an additional hour or until solution became dark brown / black. 1N HCl was then added along with EtOAc to extract the products. The organic layer was washed with 1N HCl (3x) and brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure to obtain the crude product. Products were purified by silica gel column chromatography.



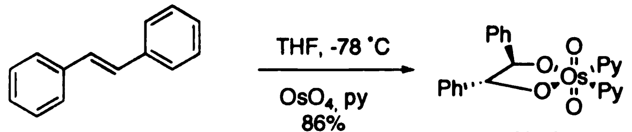
General Procedure for the Oxidative Cyclization Yielding Water-Soluble Products (Condition D): A 0.1 M solution of the appropriate alkenol was prepared in dimethylformamide that had been dried over calcium sulfate. Oxone (4.0 equiv) was added in one portion, followed by 1.0 mol% of OsO4 as a 0.2 M solution in *t*BuOH or dichloromethane. An internal standard could be added either prior to or immediately following reaction to determine the in-pot yield. Both 1,2,3,4-tetramethylbenzene and dodecane were used in this capacity. The reaction was stirred at room temperature, and progress monitored by either TLC or GC. In a few cases, the reactions were also performed in deuterated DMF and the NMR was compared to that of an authentic sample of the lactone in deuterated DMF prior to isolation using benzene as an internal standard.

General Procedure for the Oxidative Cyclization Yielding Water-Insoluble Products (Condition E): A 0.1 M solution of the appropriate alkenol was prepared in dimethylformamide that had been dried over calcium sulfate. Oxone (4.0 equiv) was added in one portion, followed by 1.0 mol% of OsO_4 as a 0.2 M solution in *t*BuOH or dichloromethane. The reaction was stirred at room temperature, and progress monitored by either TLC or GC. After completion of the reaction, an equal volume of water was added and the solution was saturated with NaCl. It was then extracted with 3x portions of ethyl acetate. The combined organics were washed 1x with $NaHCO_3$, dried over Na_2SO_4 and evaporated under reduced pressure. The resultant lactones could be purified by column chromatography using 1:1 petroleum ether/diethyl ether.



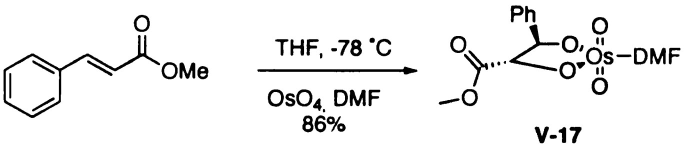
V-15

(**V-15**): THF (1 mL) and DMF (17 mg, 0.236 mmol) were cooled to –78 °C. OsO_4 (20 mg, 0.078 mmol) was then added and stirred for 5 min. followed by the addition of *t*-stilbene (14 mg, 0.078 mmol) in THF (0.5 mL). The reaction was warmed to 0 °C and stored in the freezer overnight. The precipitate was filtered, washed with Et_2O and dried under vacuum to provide **VII-15** (25 mg, 64%). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.99 (s, 1H), 7.46-7.11 (m, 10H), 5.98-5.56 (m, 2H), 2.94 (s, 3H), 2.87 (s, 3H).



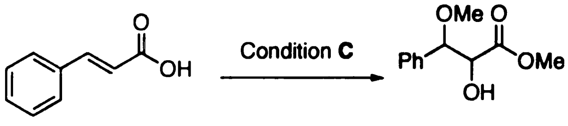
V-16

3-195(**V-16**): THF (1 mL) and pyridine (18 mg, 0.236 mmol) were cooled to –78 °C. OsO_4 (20 mg, 0.078 mmol) was then added and stirred for 5 min. followed by the addition of *t*-stilbene (14 mg, 0.078 mmol) in THF (0.5 mL). The reaction was warmed to 0 °C and stored in the freezer overnight. The precipitate was filtered, washed with Et_2O and dried under vacuum to provide **VII-16** (40 mg, 86%).



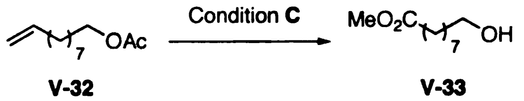
V-17

(**V-17**): Toluene (1 mL) and DMF (15 mg, 0.2 mmol) were cooled to –78 °C. OsO_4 (25 mg, 0.1 mmol) was then added and stirred for 5 min. followed by the addition of methyl cinnimate (16 mg, 0.1 mmol) in toluene (0.5 mL). The reaction was warmed to –0 °C and then stored in the freezer overnight. The precipitate was filtered, washed with Et_2O and dried under vacuum to provide **VI-17** (25 mg, 64%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.02 (s, 1H), 7.43-7.41 (m, 5H), 6.28-6.01 (m^{*1}, 1H) [^{*1} eight doublets 6.28 (d, J = 4.9), 6.25 (d, J = 5.3), 6.24 (d, J = 5.9), 6.18 (d, J = 7.1), 6.07 (d, J = 5.3), 6.05 (d, J = 6.6), 6.02 (d, J = 4.9), 6.01 (d, J = 4.6)], 5.65-5.43 (m^{*2}, 1H) [^{*2} eight doublets 5.64 (d, J = 4.6), 5.63 (d, J = 5.5), 5.59 (d, J = 5.9), 5.52 (d, J = 7.1), 5.47 (d, J = 5.3), 5.46 (d, J = 6.6), 5.45 (d, J = 5.6), 5.44 (d, J = 5.3)], 3.86-3.78 (m^{*3}, 3H)[^{*3} eight singlets 3.86. 3.85, 3.83, 3.82, 3.81, 3.80. 3.78, 3.78], 2.95 (s, 3H), 2.88 (s, 3H).

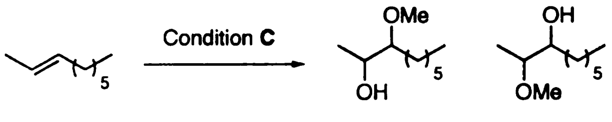


V-8 **V-31**

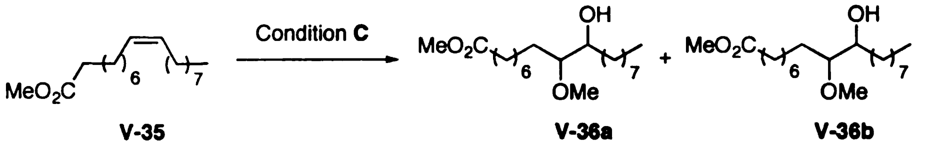
Methyl 2-hydroxy-3-methoxy-3-phenylpropanoate (**V-31**):[334] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.34 (b, 5H), 4.53 (d, 1H, J = 3.2 Hz), 4.25 (dd, 1H, J = 6.6, 3.2 Hz), 3.77 (s, 3H), 3.26 (s, 3H) 2.97 (d, 1H, J = 6.6); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.2, 136.9, 128.6, 126.7, 113.9, 83.1, 74.5, 57.0. 52.2.



Methyl 3-hydroxypropanoate (**V-33**):[335] ^{1}H NMR (CDCl$_3$, 300 MHz): δ 3.64 (s, 3H), 3.60 (t, 2H, J = 6.6 Hz), 2.27 (t, 2H, J = 7.5 Hz), 1.65-1.41 (m, 4H), 1.36-1.16 (b, 8H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 174.3, 62.8, 51.4, 34.0, 32.6, 29.1, 28.9, 25.6, 24.7.



3-Methoxynonan-2-ol (**V-34a**) and *2-Methoxynonan-3-ol* (**V-34b**): ^{1}H NMR (CDCl$_3$, 500 MHz): δ 3.35 (s, 3H), 3.34 (s, 1H), 3.10 (p, 1H, J = 6.4 Hz), 2.56 (br, 1H), 1.51-1.42 (m, 2H), 1.36-1.24 (br, 8H), 1.09 (t, 3H, J = 6.3 Hz), 0.86 (t, 3H, J = 6.3 Hz); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 80.5, 74.9, 56.6, 32.8, 31.8, 29.4, 2.5, 22.6, 14.8, 14.0.



Name (**V-34a**) and *Name* (**V-34b**): ^{1}H NMR (CDCl$_3$, 300 MHz): δ 3.61 (s, 3H), 3.42 (m, 1H), 3.35 (s, 3H), 2.94 (q, 1H, J = 5.4 Hz), 2.25 (t, 2H, J = 7.4 Hz), 1.63-1.17 (br, 26H), 0.83 (t, 3H, J = 6.8 Hz); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 174.2, 84.3, 72.5, 58.0, 51.3, 34.0, 33.3, 31.8, 29.9, 29.7, 29.5, 29.4, 29.2, 29.1, 29.0, 25.6, 25.0, 24.8, 22.6, 13.98.

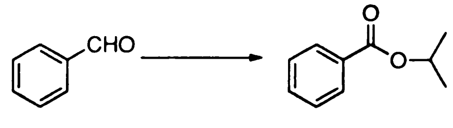
For data regarding the oxidative cleavage / lactonization please refer to the original reference.[5]

7.6. Data for Chapter 6

General Procedure for Oxidation of Aldehydes to Carboxylic Acids (Condition A): The aldehyde (1 equiv) was dissolved in DMF (0.1 M). Oxone (1 equiv) was added in one portion and stirred at RT for 3 h. The reactions were monitored by TLC and GC analysis. 1N HCl was used to dissolve the salts and EtOAc was added to extract the products. The organic extract was washed with 1N HCl (3 x) and brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure to obtain the crude product. Products were purified by silica gel column chromatography.

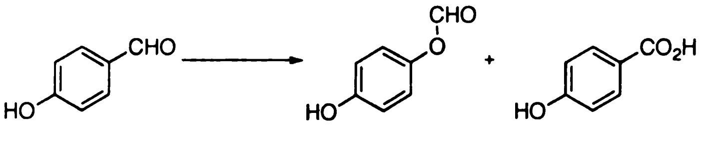
General Procedure for Oxidation of Aldehydes to Esters (Conditon B): The aldehyde (1 equiv) was dissolved in the appropriate alcoholic solvent (0.1 M). Oxone (1 equiv) was added and stirred at RT for 18 h. The reaction was monitored by TLC and GC analysis. 1N HCl was used to dissolve the salts and EtOAc was added to extract the products. The organic extract was washed with 1N HCl (3x) and brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure to obtain the crude product. Products were purified by silica gel column chromatography.

General Procedure for Oxidation of α- or β-Diones and α-Ketoalcohols with Oxone (Conditon C): The substrate (1 equiv) was dissolved in the appropriate solvent (methanol, ethanol, or isopropanol (0.2 M)). Dry $KHSO_5$ (95% pure, 4 equiv) was added to the solution in one portion and stirred at room temperature for 18 h. The reactions were monitored by TLC, GC or NMR analysis. After the substrate had been consumed the reaction was diluted with Et_2O and 10% (v/v) HCl solution. The layers were separated and the aqueous layer was extracted with Et_2O (x 3). The combined organic layers were collected and dried over anhydrous Na_2SO_4 or $MgSO_4$. After filtration of the drying agents, the solvent was removed under reduced pressure to yield the crude product. Products were purified by silica gel column chromatography.



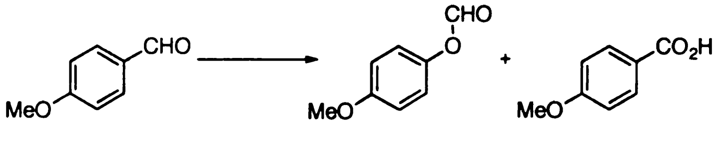
VI-7 **VI-7e**

Iso-propyl benzoate (**VI-7e**):[336] ^{1}H NMR (CDCl$_3$, 300 MHz): δ 8.02 (m, 2H), 7.43 (m, 3H), 5.24 (sept, 1H, J = 6.3 Hz), 1.34 (d, 6H, J = 6.3 Hz); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 175.2, 132.2, 130.4, 129.0, 127.8, 67.9, 21.5; IR (neat, NaCl, cm^{-1}) 2981, 2938, 1716, 1276, 1103, 711; LRMS (70 eV, EI) *m/z* 164 [M]$^+$, 122 [M-C$_3$H$_6$]$^+$, 105 [M-OC$_3$H$_7$]$^+$.



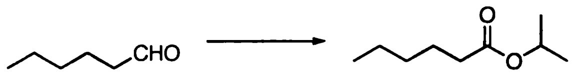
VI-13 **VI-13b, 62%** **VI-13a, 19%**

4-Hydroxyphenyl formate (**VI-13b**):[337] ^{1}H NMR (CDCl$_3$, 300 MHz): δ 8.27 (s, 1H), 6.98 (d, 2H, J = 9.0 Hz), 6.78 (d, 2H, J = 8.9 Hz), 5.35 (bs, 1H); mp = 56-58 °C, [lit. 57 °C].[337]



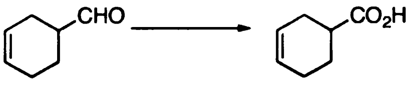
VI-15 **VI-15b, 58%** **VI-15a, 31%**

4-Methoxyphenyl formate (**VI-15b**):[95,338,339] ^{1}H NMR (CDCl$_3$, 300 MHz): δ 8.26 (s, 1H), 7.03 (d, 2H, J = 9.0 Hz), 6.89 (d, 2H, J = 8.9 Hz), 3.78 (s, 3H); mp = 31-33 °C, [lit. 32-34 °C].[338]



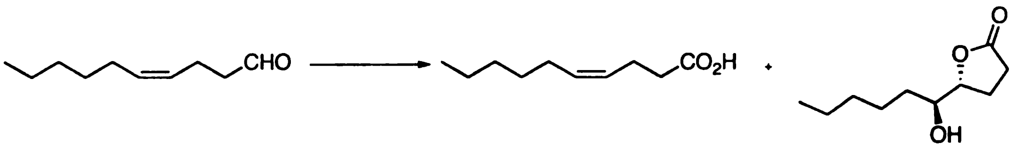
VI-20 **VI-20e**

i-Propyl hexanoate (**VI-20e**):[340] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.04 (m, 1H), 2.30 (m, 2H), 1.12-1.54 (m, 12H), 0.86 (bs, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 186.6,50.9, 34.7, 31.7, 29.8, 22.6, 21.8, 14.0, 13.9; IR (neat, NaCl, cm^{-1}) 2956, 2930, 1729, 1457, 1375, 1176, 1108; LRMS (70 eV, EI) *m/z* 158 $[M]^+$, 116 $[M-C_3H_6]^+$, 99 $[M-OC_3H_7]^+$.



VI-26 **VI-26a**

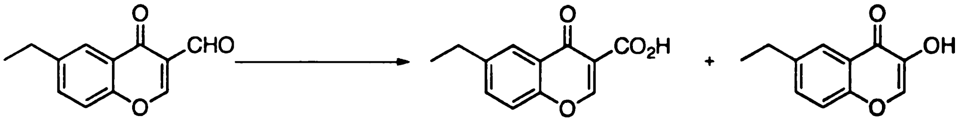
1,2,3,6-Tetrahydrobenzoic acid (**VI-26a**):[341,342] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.63-5.7 (m, 2H), 2.54-2.64 (m, 1H), 2.24-2.27 (m, 2H), 1.98-2.15 (m, 3H), 1.62-1.76 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 182.6, 126.7, 124.9, 39.1, 27.1, 24.8, 24.3; IR (neat, NaCl, cm^{-1}) 3027, 2926, 1705, 1438, 1306, 1238; LRMS (70 eV, EI) *m/z* 126 $[M]^+$, 108 $[M-H_2O]^+$, 81 $[M-CO_2H]^+$.



VI-27 **VI-27a, 53%** **VI-28, 32%**

Cis-4-decanoic acid (**VI-27a**):[343] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.28-5.45 (m, 2H), 2.30-2.40 (m, 4H), 1.99 (bs, 2H), 1.26 (bs, 6H), 0.85 (bs, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 179.4, 131.9, 126.9, 34.1, 31.4, 29.2, 27.1, 22.5, 14.0; IR (neat, NaCl, cm^{-1}) 3139, 2958, 2930, 2872, 1711, 909, 734; LRMS (70 eV, EI) *m/z* 170 $[M]^+$.

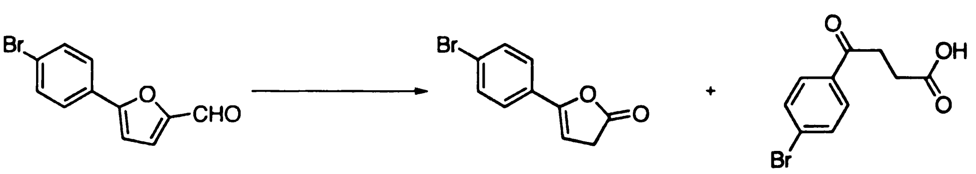
5,6-trans-5-(1-hydroxyhexyl)-dihydrofuran-2-one (**VI-28**):[344] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.36-4.42 (m, 1H), 3.50-3.56 (m, 1H), 2.49-2.62 (m, 2H), 2.05-2.27 (m, 3H), 1.49 (bs, 3H), 1.28 (bs, 5H), 0.84 (bs, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 177.3, 83.0, 73.6, 32.8, 31.6, 28.7, 25.1, 24.0, 22.5, 13.9; mp = 40-42 °C, [lit 42-44 °C].[344]



VI-29 **VI-29a, 34%** **VI-30, 52%**

6-ethyl-4-oxo-4H-chromene-3-carboxylic acid (**VI-29a**): ^{1}H NMR (CDCl$_3$, 300 MHz): δ 13.50 (bs, 1H), 8.98 (s, 1H), 8.11 (s, 1H), 7.68 (dd, 1H, J = 2.2, 8.5 Hz), 7.55 (d, 1H, J = 8.8 Hz), 6.80 (bs, 1H), 2.72 (q, 2H, J = 7.7 Hz), 1.24 (t, 3H, J = 7.7 Hz); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 179.4, 164.3, 163.6, 155.1, 144.0, 136.3, 124.2, 122.7, 118.6, 112.7, 28.4, 15.3; IR (neat, NaCl, cm^{-1}) 3073, 2961, 2924, 2869, 1734, 1616, 1478, 1436, 1310; LRMS (70 eV, EI) *m/z* 218 [M]$^+$; HRMS (CI) calcd for $C_{12}H_{10}O_4$: 218.0579 *m/z* [M]$^+$, observed 218.0580 *m/z;* mp = 133-135 °C.

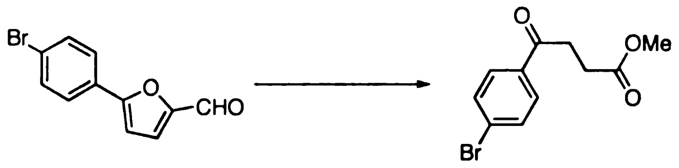
6-ethyl-3-hydroxychromene-4-one (**VI-30**): ^{1}H NMR (CDCl$_3$, 300 MHz): δ 8.03 (d, 1H, J=2.2), 7.97 (s, 1H), 7.47 (dd, 1H, J=2.2, 8.8), 7.36 (d, 1H, J=8.8), 6.80 (bs, 1H), 2.72 (q, 2H, J=3.4), 1.24 (t, 3H, J=3.6); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 173.4, 154.7, 141.7, 140.8, 138.7, 133.9, 123.3, 121.7, 118.2, 28.2, 15.4; IR (neat, NaCl, cm^{-1}) 3276, 2959, 1610, 1408, 1204, 1170; LRMS (70 eV, EI) *m/z* 190 [M]$^+$; HRMS (CI) calcd for $C_{11}H_{10}O_3$: 190.0630 *m/z* [M]$^+$, observed 190.0627 *m/z*; mp = 119-121 °C.



VI-31 **VI-32, 42%** **VI-33, 30%**

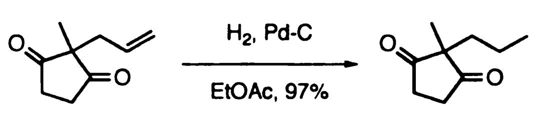
5-(p-Bromophenyl)-2(3H)-furanone (**VI-32**):[345] ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.51 (d, 2H, J = 8.5 Hz), 7.49 (d, 2H, J = 8.2 Hz), 5.78 (t, 1H, J = 2.7 Hz), 3.49 (d, 2H, J = 2.7 Hz); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 175.4, 153.0, 131.9, 131.6, 127.2, 126.2, 123.7, 98.3, 34.7, 14.2; IR (neat, NaCl, cm^{-1}) 2916, 2848, 1780, 1673; LRMS (70 eV, EI) *m/z* 238 $[M]^+$, 240 $[M+2]^+$; HRMS (CI) calcd for $C_{10}H_7O_2Br$: 237.9630 *m/z* $[M]^+$, observed 237.9631 *m/z*; mp = 124-127 °C, [lit. 126-130 °C].[345]

4-(p-Bromophenyl)-4-oxobutanoic acid (**VI-33**):[346] ^1H NMR ($CDCl_3$, 300MHz): δ 7.83 (d, 2H, *J* = 8.5 Hz), 7.59 (d, 2H, *J* = 8.7 Hz), 3.26 (t, 1H, *J* = 6.4 Hz), 2.81 (d, 2H, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 196.8, 178.5, 132.0, 131.9, 131.7, 130.3, 129.6, 33.1, 27.9; IR (neat, NaCl, cm^{-1}) 3425, 3091, 2958, 2925, 1694, 1678, 1585, 1339, 1229; LRMS (70 eV, EI) *m/z* 256 $[M]^+$, 183 $[M-C_3H_5O_2]^+$; mp = 144-146 °C, [lit 148-150 °C].[346]



VI-31 VI-34

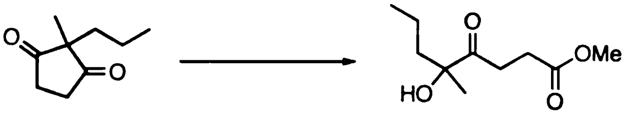
Methyl 4-(p-bromophenyl)-4-oxobutanoate (**VI-34**):[347-349] ^1H NMR ($CDCl_3$, 300MHz): δ 7.80 (d, 2H, *J* = 2.2 Hz), 7.77 (d, 2H, *J* = 2.0 Hz), 3.65 (s, 3H), 3.22 (t, 2H, *J* = 6.6 Hz), 2.49 (t, 2H, *J* = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 197.0, 173.2, 135.1, 131.9, 129.5, 128.4, 51.8, 33.2, 27.8; IR (neat, NaCl, cm^{-1}) 3024, 2952, 2916, 2848, 1736, 1688, 1586, 1218, 1171, 1070, 757; LRMS (70 eV, EI) *m/z* 270 $[M]^+$, 183 $[M-C_4H_7O_2]^+$; HRMS (CI) calcd for $C_{11}H_{11}O_3Br$: 269.9892 *m/z* $[M]^+$, observed 269.9896 *m/z*; mp = 48-50°C.



VI-41

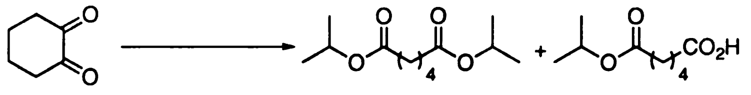
2-methyl-2-propylcyclopentane-1,3-dione (**VI-41**):[318] To a RT solution of 2-allyl-2-methyl-1,3-cyclopentadione (89 mL, 0.6 mmol) in EtOAc (6 mL) was added 10% Pd-C

(4.6 mg, 5% by wt). A hydrogen filled balloon was attached and the system was purged under vacuum and replaced with hydrogen gas. The reaction was stirred at RT for 15 h. The Pd-C was then filtered and washed with EtOAc. The solvent was removed under reduced pressure providing **VI-41** (90 mg, 97% yield) and did not require additional purification. **VI-41**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.68 (s, 4H), 1.54-1.49 (m, 2H), 1.12-1.04 (m, 2H), 1.02 (s, 3H), 0.76 (t, 3H, *J*= 7.1 Hz).



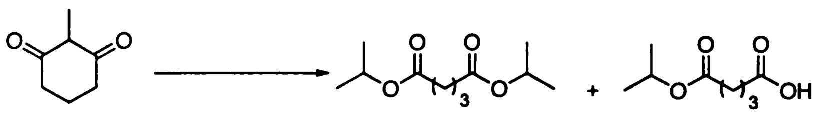
VI-41 **VI-41a**

Methyl 5-hydroxy-5-methyl-4-oxooctanoate (**VI-41a**): $KHSO_5$ (547 mg, 3.6 mmol) was added in one portion to a solution of diketone **VI-41** (145 mg, 0.9 mmol) in methyl alcohol (8 mL) at RT. The reaction was stirred at RT for 18 h, after which it was diluted with Et_2O and 10% (v/v) HCl (15 mL). The layers were separated and the aqueous layer was extracted with Et_2O (10 mL x 3). The combined organic layers were dried over anhydrous $MgSO_4$, the salt was filtered and the organics were concentrated under reduced pressure. The product was purified by silica gel column chromatography (20% EtOAc / hexanes) to furnish ester **VI-41a** as a colorless oil (58 mg, 65% yield). **VI-41a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.63 (s, 3H), 2.87-2.72 (m, 2H), 2.61-2.56 (m, 2H), 1.66-1.60 (m, 2H), 1.32 (s, 3H), 1.09-0.97 (m, 2H), 0.85 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.8, 172.9, 78.7, 51.8, 41.8, 30.8, 27.6, 25.5, 16.5, 14.2; IR (thin film) 3400, 2961, 1741, 1713, 1441, 1373, 1242, 1173, 1047 cm^{-1}; LRMS (70 ev, EI) m/z 202 $[M]^+$, 184 $[M-H_2O]^+$, 171 $[M-CH_3O]^+$; HRMS (CI) calcd for $C_{10}H_{19}O_4$: 203.1283 *m/z* $[M+H]^+$, observed 203.1283 *m/z*.



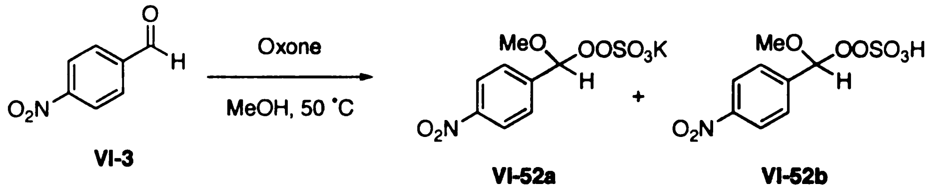
VI-37 **VI-35d, 34%** **VI-35e, 45%**

6-Isopropoxy-6-oxohexanoic acid (**VI-35e**): $KHSO_5$ (608 mg, 4 mmol) was added in one portion to a solution of diketone **VI-37** (112 mg, 1 mmol) in isopropanol (10 mL) at RT. The reaction was stirred at RT for 18 h, after which it was diluted with Et_2O and 10% (v/v) HCl (15 mL). The layers were separated and the aqueous layer was extracted with Et_2O (10 mL x 3). The combined organic layers were dried over anhydrous $MgSO_4$, the salt was filtered and the organics were concentrated under reduced pressure. The product was purified by silica gel column chromatography (20% EtOAc / hexanes) to furnish esters **VI-35d** (70 mg, 33%) and **VI-35e** (32 mg, 18%) as colorless oils. **VI-35e**: ^1H NMR (300 MHz, $CDCl_3$): δ 11.05 (br, 1H), 4.95 (sept, 1H, $J = 6.32$ Hz), 2.32 (t, 2H, $J = 6.87$ Hz), 2.25 (t, 2H, $J = 7.14$ Hz), 1.67-1.57 (m, 4H), 1.17 (d, 6H, $J = 6.04$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.6, 172.9, 67.6, 34.2, 33.6, 24.3, 23.9, 21.7; IR (thin film) 3210, 2982, 2939, 1730, 1729, 1375, 1242, 1182, 1109, 1047, 939, 822 cm^{-1}; LRMS (70 ev, EI) m/z 170 $[M-H_2O]^+$, 129 $[M-OCH(CH_3)_2]^+$; HRMS (CI) calcd for $C_9H_{17}O_4$: 189.1127 *m/z* $[M+H]^+$, observed 189.1128 *m/z*.



VI-44 **VI-42d, 24%** **VI-42e, 45%**

Diisopropyl glutarate (**VI-42d**): $KHSO_5$ (608 mg, 4 mmol) was added in one portion to a solution of diketone **VI-44** (126 mg, 1 mmol) in isopropanol (10 mL) at RT. The reaction was stirred at RT for 18 h after which it was diluted with Et_2O and 10% (v/v) HCl (15 mL). The layers were separated and the aqueous layer was extracted with Et_2O (10 mL x 3). The combined organic layers were dried over anhydrous $MgSO_4$, the salt was filtered and the organics were concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (20% EtOAc / hexanes) to furnish esters **VI-42d** (51 mg, 24%) and **VI-42e** (77 mg, 45%) as colorless oils. **VI-42d**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.96 (sept, 2H, *J* = 6.32 Hz), 2.27 (t, 4H, *J* = 7.14 Hz), 1.88 (p, 2H, *J* = 7.14 Hz), 1.18 (d, 12H, *J* = 6.32 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.5, 67.6, 33.6, 21.8, 20.2; IR (thin film) 2982, 2934, 1732, 1375, 1256, 1202, 1181, 1109, 1057, 1011, 970, 933 cm^{-1}; LRMS (70 ev, EI) m/z 216 $[M]^+$, 157 $[M-OCH(CH_3)_2]^+$; HRMS (CI) calcd for $C_{11}H_{21}O_4$: 217.1440 *m/z* $[M+H]^+$, observed 217.1440 *m/z*.



4-Nitrobenzaldehyde-methyl-potassiumperoxysulfate acetal (**VI-52a**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.22 (d, 2H, *J* = 9.1 Hz), 7.66 (d, 2H, *J* = 9.0 Hz), 5.76 (s, 1H), 3.65 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.2, 142.7, 127.9, 123.3, 105.6, 56.7; IR (thin film) 3117, 2939, 1510, 1353, 1315, 1200, 1097, 980, 854.

4-Nitrobenzaldehyde-methyl-peroxysulfate acetal (**VI-52b**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.22 (d, 2H, *J* = 8.4 Hz), 7.66 (d, 2H, *J* = 7.14 Hz), 5.80 (s, 1H), 3.70 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.5, 131.0, 128.1, 123.5, 106.2, 56.5; IR (thin film) 3420, 3115, 3082, 2940, 2842, 1523, 1349, 1205, 1097, 1013, 854.

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