

**STEREOSELECTIVE FUNCTIONALIZATION OF MELDRUM'S ACIDS  
AND THE EFFORTS TOWARD  
TOTAL SYNTHESIS OF ECHINOSPORIN**

Dung Tien Do

A dissertation submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Chemistry.

Chapel Hill  
2014

Approved by:

Jeffrey S. Johnson

David A. Nicewicz

Maurice S. Brookhart

Erik J. Alexanian

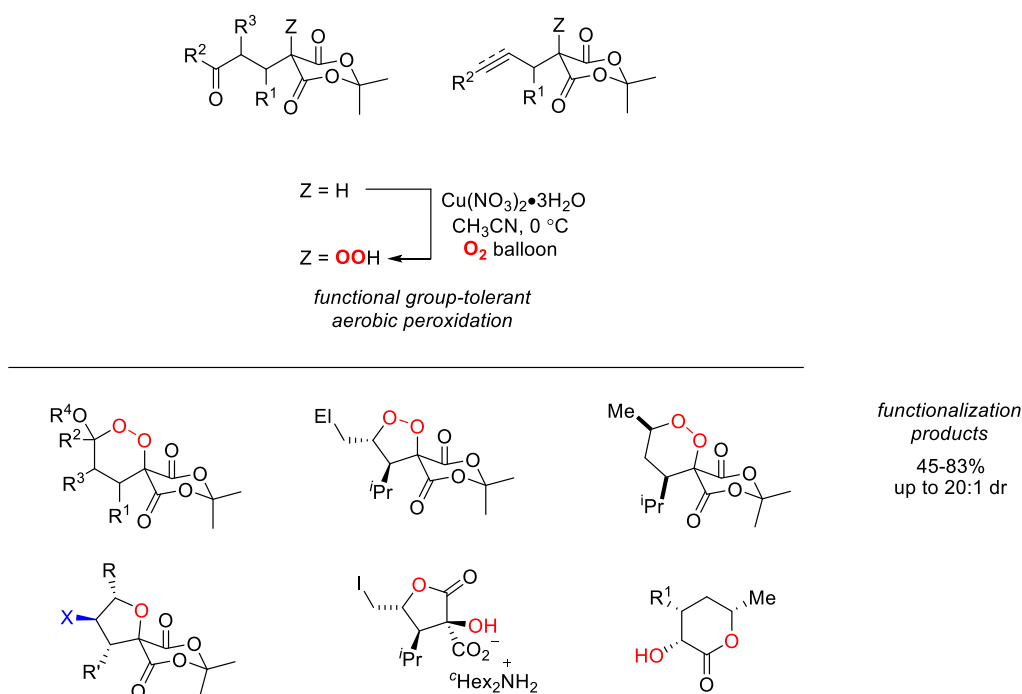
Joseph L. Templeton

© 2014  
Dung Tien Do  
ALL RIGHTS RESERVED

## ABSTRACT

Dung Tien Do: Stereoselective Functionalization of Meldrum's Acids and the Efforts toward Total Synthesis of Echinospurin  
(Under the direction of Jeffrey S. Johnson)

### I. Cu(II)-Catalyzed Aerobic Hydroperoxidation of Meldrum's Acid Derivatives and Application in Intramolecular Functionalization to Access Complex Building Blocks

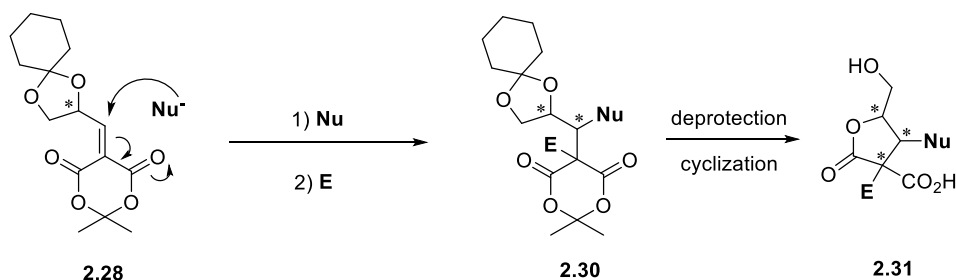


Aerobic hydroperoxidation of Meldrum's acid derivatives via a Cu(II)-catalyzed process is presented. The mild reaction conditions are tolerant to variety of vulnerable functional groups. Au(I)-catalyzed endoperoxidations of hydroperoxyalkynes have been reported for the first time.

Cleavage of the O–O bond provides 1,n-diols with differentiation of the hydroxy groups. A novel research plan centered on the hydroperoxidation of designed Meldrum's acids to generally access fully substituted hemiketal-viable substrates for preparation of complex building blocks is also discussed.

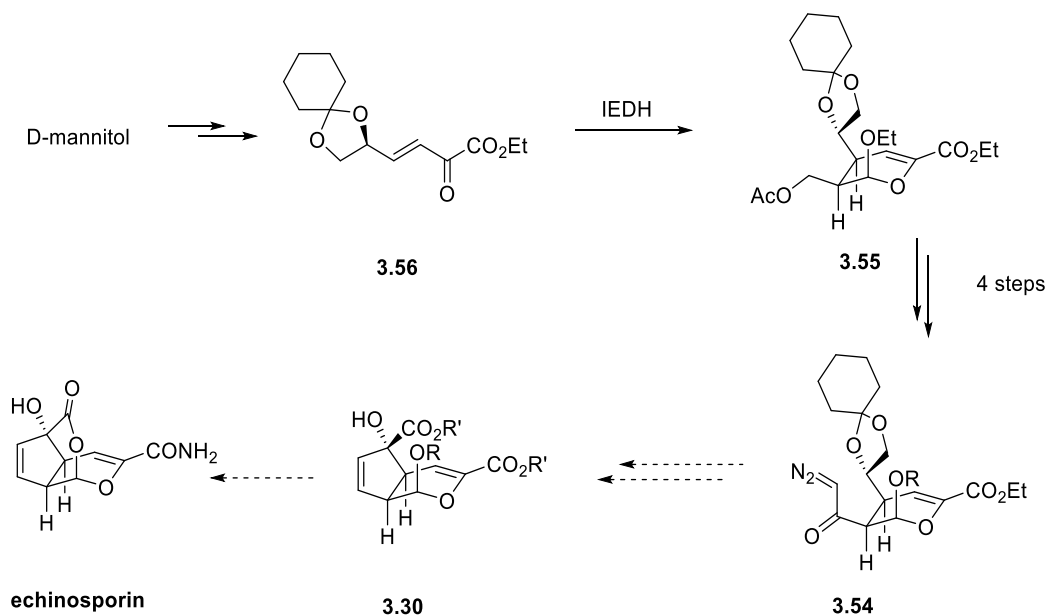
## II. Conceptual Blueprint for a Stereoselective Heterofunctionalization of Carbonyl Compounds

The glamour of a general stereoselective heterofunctionalization of carbonyl compounds encourage us to develop a novel  $\alpha$ -heterofunctionalization of lactone. The strategy based on a highly diastereoselective Michael addition of variety of nucleophiles to readily accessible chiral alkylidene Meldrum's acid and a feasible heterofunctionalization of Meldrum's acids to access difunctionalization adducts. Those compounds have been carried on a symmetry-breaking intramolecular lactonization to reveal a new stereocenter with excellent chirality induction at carbon bearing heterofunctional group. Limited efforts provided a proof of concept for a stereoselective fluorination of lactone.



### III. Efforts Toward The Total Synthesis of Echinospirin

Two approaches for the construction of the echinosporin core are presented. A key strategy includes the rapid formation of the fully substituted-dihydropyran substructure via intermolecular inverse electron demand hetero Diels-Alder reaction of a chiral heterodiene. Highly diastereoselective cyclizations realized by the use of copper(II) triflate and <sup>t</sup>Bu-box ligand, provided access to the dihydropyran core. The stereochemical features of this cycloaddition were previously well established and produced the dihydropyran with high diastereocontrol. An advanced intermediate diazoketone **3.54** was prepared as a single diastereomer in multigram-scale and will provide requisite material for further manipulations.



*To my family  
and  
in honor of my parents,  
Dong Do and Toan Nguyen  
on the celebration of their  
35<sup>th</sup> wedding anniversary*

## ACKNOWLEDGEMENTS

First and foremost, I would like to express my deepest gratitude to my advisor Jeffrey Johnson. It has been a great privilege to work under Jeff's guidance the past five years. Jeff's creative approach to chemistry is very inspiring and it is something that I strive to mimic, although this may not always be evident. I am indebted to Jeff for his incredible level of patience to develop me. Jeff is always willing to listen to any thoughts, concern and most of the time, counterproductive ideas from a student who barely speaks a proper English. I am thankful that Jeff always found the way to make those conversations productively work out and patiently guided me into a right direction of doing research. Additionally, Jeff's support and willingness to let us explore our own idea and plan our own experiments is refreshing and has greatly contributed to my development. The matureness I have developed into during my time in Johnson lab is largely a result of Jeff's constant intellectual and moral support, for which I am truly grateful. To all of the things I have had in UNC, I feel I cannot express enough my sincere gratitude to Jeff.

I would like to thank Professors Maurice Brookhart, Joseph Templeton, Erik J. Alexanian and Prof. David Nicewicz (chair) for serving on my final defense committee and prelim orals. I am especially thankful to Prof. Maurice Brookhart and David Nicewicz for the references and recommendation letters to help me secure my postdoc position.

I feel I am fortunate to be working in Johnson group and have had the privilege to work with an incredible group of people. I would like to thank all of the former members: Steve Greszler,

Andrew Parsons, Chris Tarr, Greg Boyce, Dan Schmitt, Mike Slade, Austin Smith, Kim Steward, Justin Malinowski, my fellow year Michael Corbett, Rani Ulrich, Ryan Carris, Ericka Malow, Steve Wales and Jamie Rogers. Chris Tarr was the mentor who taught me many fundamental stuff starting from how set up reactions. Mike Slade, Austin Smith, Kim Steward all had a major role in my early development. My fellow year “old” Corbett was always there sharing his passion about chemistry mixing with F1 and MotoGP action. His work ethic is also inspiring. I also want to thank all of the contemporary Johnson Group members: Scott Krabbe, Guy Goodman, Robert Sharpe, Sam Bartlett, Will Mackay, John Farrokh, Matt Horwitz, Kendrick Smith, James Giarrusso and Qihai Xu. Scott Krabbe for sharing the Meldrum acid project, Guy Goodman for sharing the DKR chemistry and together with Corbett, giving me “sketchy guy” banter. Scott Krabbe, Guy Goodman, Robert Sharpe, Will Mackay for their help on proofreading my thesis. You guys are all great labmates to me.

Next I would like to thank my friends and people home. I owe a debt of gratitude to my undergraduate advisor Thao Minh Nguyen, who provided me the foundation to continue studying organic chemistry. I also thank Dr. Phong Pham for his academic and spiritual guidance. He always encouraged me to try and come to US for my PhD. My close friends Mon Doan and Son Nguyen for always supporting and encouraging me to pursue my career. My “family” members: Luong Nguyen, Bong Nguyen, Little Trang Nguyen, Duc Tran and Linh Nguyen for the great time we shared over the years at NC. I will miss those weekend-hangouts and the jokes we shared together. My Vietnamese friends that I have met during the years in NC. You guys gave me a family in NC.

Finally, I would like to express my special thankful to my family. I wouldn't be the person I am today if it wasn't for my parents' unconditional love and unwavering support. My parent Dong and Toan always give me all of their resource to provide me the opportunity to success and



never questioned my decision even though, sometimes they might want me to do other things. For so, I think I can never express enough my gratitude to them. I also want to thank my sister Dung Thuy Do for the great time we grew up together, though in fact, most of the time, we were likely to set up some “little fights”. I want to extend my gratitude to all members in my big family back home. They are a source of motivation keeping me going forward.

## TABLE OF CONTENTS

<b>LIST OF TABLES.....</b>	<b>xiii</b>
<b>LIST OF FIGURES AND SCHEMES.....</b>	<b>xiv</b>
<b>LIST OF ABBREVIATIONS AND SYMBOLS.....</b>	<b>xvii</b>
<b>CHAPTER ONE: CU(II)-CATALYZED AEROBIC HYDROPEROXIDATION OF MELDRUM’S ACID DERIVATIVES AND APPLICATION IN INTRAMOLECULAR FUNCTIONALIZATION TO ACCESS COMPLEX BUILDING BLOCKS.....</b>	<b>1</b>
1.1 Introduction.....	1
1.2 Background.....	3
1.2.1 Extant Methods for Enolate Peroxidation.....	3
1.2.2 Diverse Endoperoxides as Candidates for Antimalarial and Anticancer Agents.....	5
1.2.3 Copper-Catalyzed Enolate Oxidation.....	6
1.3 Results and Discussion.....	8
1.3.1 Preliminary Results and Experimental Plan.....	8
1.3.2 Synthesis of Substituted Meldrum’s Acids and Barbituric Acids.....	10
1.3.3 Hydroperoxidation of Meldrum’s Acid Derivatives.....	10
1.3.4 Au(I)-Catalyzed Endoperoxidations of Hydroperoxyalkynes.....	13
1.3.5 The Remote Oxidation of Alkenyl Hydroperoxy Meldrum’s Acid Derivatives.....	18
1.3.6 Secondary Transformation of Endoperoxides.....	19
1.3.7 Application in Stereoselective Access Fully Substituted Building Blocks.....	22
1.4 Conclusion.....	30
1.5 Experimental Details.....	31

1.6	References .....	60
<b>CHAPTER TWO: CONCEPTUAL BLUEPRINT FOR THE STEREOSELECTIVE HETEROFUNCTIONALIZATION OF CARBONYL COMPOUNDS .....</b>		<b>63</b>
2.1	Introduction.....	63
2.2	Background .....	64
2.2.1	The Difunctionalization of $\alpha,\beta$ -Unsaturated Carbonyl Compounds .....	64
2.2.2	The Alkylidene Meldrum's Acids .....	70
2.2.3	Intramolecular Asymmetric Desymmetrization.....	72
2.2.4	Research Proposal .....	74
2.3	Results and Discussion .....	75
2.3.1	Identification of Chiral Alkylidene Meldrum's Acids.....	75
2.3.2	Michael Reaction of The Chiral Alkylidene Meldrum's Acid .....	76
2.3.3	Functionalization of Chiral Meldrum's Acid.....	78
2.3.4	Model One-Pot Procedure for Michael Addition/Fluorination of Alkylidene Meldrum's Acid .....	80
2.3.5	Model Intramolecular Desymmetrization .....	82
2.4	Conclusion .....	84
2.5	Experimental Details.....	85
2.6	References .....	95
<b>CHAPTER THREE: EFFORTS TOWARD THE SYNTHESIS OF ECHINOSPORIN .....</b>		<b>98</b>
3.1	Introduction.....	98
3.2.1	Biological Activity and Biosynthetic Proposal of Echinospurin .....	99
3.2	Prior Synthesis of Echinospurin.....	101
3.2.1	Overview of A. B. Smith Total Synthesis of Echinospurin.....	101
3.2.2	Overview of Weinreb's Approach to The Synthesis of Echinospurin.....	104
3.2.3	Overview of K. J. Hale Formal Total Synthesis of Echinospurin .....	105
3.3	Results and Discussion .....	108
3.3.1	Preliminary Retrosynthetic Analysis .....	108

3.3.2	Synthesis of Pyruvate Alkylidene Dimer.....	<b>110</b>
3.3.3	Reactivity Profile of Pyruvate Alkylidene Dimer.....	<b>116</b>
3.3.4	Revised Retrosynthetic Analysis .....	<b>119</b>
3.3.5	Synthesis of Chiral Building Block-The $\beta,\gamma$ -Unsaturated- $\alpha$ -Ketoester .....	<b>120</b>
3.3.6	Inverse Electron Demand Hetero Diels-Alder Reaction-Construction of Dihydropyran Ring .....	<b>121</b>
3.3.7	Synthesis of $\alpha$ -Diazo Ketone Intermediate .....	<b>124</b>
3.4	Conclusions and Future Direction .....	<b>126</b>
3.5	Experimental Details.....	<b>128</b>
3.6	References .....	<b>136</b>

## LIST OF TABLES

Table 1-1	Cu(II)-Catalyzed Aerobic Oxidation of a Substituted Meldrum's Acid.....	<b>9</b>
Table 1-2	Hydroperoxidation of Meldrum's Acid Derivatives.....	<b>11</b>
Table 1-3	Screen for Acid-Catalyzed Endoperoxidation of Alkynyl Hydroperoxides.....	<b>14</b>
Table 1-4	Illustrative Examples for The Gold(I)-Catalyzed Cyclization.....	<b>16</b>
Table 1-5	Synthesis of Endoperoxide Hemiketals .....	<b>27</b>
Table 2-1	Nucleophilic Additions to Chiral Alkylidene Meldrum's Acid.....	<b>77</b>
Table 2-2	Electrophilic Functionalization of Chiral Meldrum's Acid .....	<b>79</b>
Table 2-3	Representative Substrates for One-Pot Michael Addition/Fluorination .....	<b>82</b>
Table 3-1	1,2-Addition Profile of Pyruvate Alkylidene Dimer.....	<b>117</b>
Table 3-2	Attempts to Selectively Protect Pyruvate Alkylidene Dimer .....	<b>118</b>
Table 3-3	Optimization for The Inverse Electron Demand Hetero Diels-Alder Reaction... ..	<b>122</b>
Table 3-4	Optimization for The Inverse Electron Demand Hetero Diels-Alder Reaction .....	<b>124</b>

## LIST OF FIGURES AND SCHEMES

Scheme 1-1	Methods of Enolate Oxidation .....	2
Scheme 1-2	Photosensitized Hydroperoxidation .....	3
Scheme 1-3	Metal Catalyzed Hydroperoxidation.....	4
Scheme 1-4	Aerobic Hydroperoxidation of Dimedone Derivatives.....	4
Scheme 1-5	Mn(III) Catalyzed Hydroperoxidation of Barbituric Acids .....	5
Figure 1-1	Natural products possessing cyclic peroxides.....	6
Scheme 1-6	Steward Cu(II)-Catalyzed Oxidative Deacylation .....	7
Figure 1-2	Oxidative Deacylation Reaction Proposed Mechanism.....	7
Figure 1-3	Desired Mechanistic Pathway for Meldrum's Acids .....	8
Scheme 1-7	Synthesis of Unsaturated Substituted Meldrum's Acids and Barbituric Acid..	10
Figure 1-4	Limitation of Alkene Substrates. ....	12
Scheme 1-8	Possible Solution of Internal Alkene Substrate.....	13
Scheme 1-9	Control Experiments .....	16
Scheme 1-10	Proposed Mechanism for The Gold(I)-Catalyzed Cyclization.....	17
Scheme 1-11	Iodoendoperoxidation of Homoallylhydroperoxy-Meldrum's Acid and Barbituric Acid Derivatives .....	18
Scheme 1-12	Endoperoxide Cleavage in 1,2-Dioxolane System .....	19
Scheme 1-13	Synthesis of Tetrahydrofuran Derivatives .....	20
Scheme 1-14	Mixed Ketal Endoperoxide Functionalization .....	21
Figure 1-5	Areas of Improvement .....	22
Figure 1-6	Proposed Condition to Access Fully Substituted Endoperoxides.....	23
Figure 1-7	Proposed Approach to Access Fully Substituted Building Blocks.....	25
Scheme 1-15	Preparation of Keto-Meldrum's Acids via Michael Reaction .....	26
Scheme 1-16	Synthesis of Fully Substituted Tetrahydrofurans.....	28

Scheme 1.17	Attempts to The Synthesis of Fully-Substituted Endoperoxide.....	29
Figure 2-1	The Vicinal Difunctionalization of $\alpha,\beta$ -unsaturated Carbonyl Compounds.....	65
Scheme 2-1	Difunctionalization of Enones using Organocopper Reagents .....	67
Scheme 2-2	Stereochemical Issues in Tandem Difunctionalizations .....	68
Figure 2-2	Organo-Cascade Catalysis .....	69
Figure 2-3	MacMillan's Synthesis of Aromadendranediol via Organo-Cascade Catalysis.....	70
Figure 2-4	Electrophilicity Parameter of Alkylidenes.....	71
Scheme 2-3	Intramolecular Desymmetrization .....	72
Scheme 2-4	Chiral Template for The Intramolecular Desymmetrization .....	73
Scheme 2-5	Intramolecular Desymmetrization of Difunctionalized Alkylidene Meldrum's acid.....	75
Scheme 2-6	Synthesis of Chiral Alkylidene Meldrum's Acid.....	76
Scheme 2-7	One-Pot Michael Addition/Fluorination .....	81
Scheme 2-8	Model Intramolecular Desymmetrization .....	83
Scheme 3-1	Silyl Glyoxylate Umpolung Reactivity.....	99
Scheme 2-7	Reagents Evolution .....	99
Figure 3-1	Natural Product Echinospurin.....	100
Scheme 3-3	The Shikimate Biosynthetic Pathway of Echinospurin .....	101
Scheme 3-4	A.B Smith's Echinospurin Retrosynthesis.....	102
Scheme 3-5	Summary of A.B.Smith Total Synthesis of Echinospurin.....	103
Scheme 3-6	Weinreb's Approach to The Synthesis of Echinospurin.....	105
Scheme 3-7	K.J Hale's Echinospurin Retrosynthesis.....	106
Scheme 3-8	Summary of K.J. Hale Formal Total Synthesis of Echinospurin .....	107
Scheme 3-9	First Generation Retrosynthetic Analysis .....	109
Scheme 3-10	The Extant Synthesis of Ethyl Pyruvate Alkylidene Dimer .....	110
Scheme 3-11	Synthesis of Ethyl Pyruvate Alkylidene Dimer-Dimerization of Diazo Precursor.....	111

Scheme 3-12	Approach to the Synthesis of Ethyl Pyruvate Dimer via Homo-Metathesis ...	<b>112</b>
Scheme 3-13	Ramberg-Backlund Approach for Synthesis of Ethyl Pyruvate Alkylidene Dimer.....	<b>112</b>
Scheme 3-14	Attempts to Synthesize Alkyl Pyruvate Dimer .....	<b>114</b>
Scheme 3-15	Second Generation Retrosynthetic Analysis.....	<b>120</b>
Scheme 3-16	Synthesis of Chiral $\beta,\gamma$ -Unsaturated- $\alpha$ -Ketoester .....	<b>121</b>
Scheme 3-17	Synthesis of Precursors of $\alpha$ -Diazo Ketone Intermediate .....	<b>125</b>
Scheme 3-18	Synthesis of $\alpha$ -Diazo Ketone Intermediate .....	<b>125</b>
Scheme 3-19	Echinosporin Summary and Future Direction .....	<b>126</b>



## LIST OF ABBREVIATIONS AND SYMBOLS

2D-NMR	two-dimensional nuclear magnetic resonance
Ac	acetate
Ar	aryl
aq	aqueous
Au	gold
atm	atmospheres
Bn	benzyl
br	broad
bs	broad singlet
<sup>n</sup> Bu	<i>normal</i> -butyl
<sup>t</sup> Bu	<i>tert</i> -butyl
Bz	benzoyl
PTSA	para-toluene sulfonic acid
<sup>13</sup> C NMR	carbon nuclear magnetic resonance spectroscopy
C–C	carbon-carbon single bond
C=C	carbon-carbon double bond
C≡C	carbon-carbon triple bond
cat	catalytic amount or catalyst
Ce(III)	Cesium (III) ion
C-H	carbon-hydrogen bond
conv	conversion

COSY	correlated spectroscopy
<i>m</i> -CPBA	<i>meta</i> -chloroperoxybenzoic acid
Cu(NO <sub>3</sub> ) <sub>2</sub> •3H <sub>2</sub> O	copper(II) nitrate trihydrate
CuCN	copper(I) cyanide
d	doublet or days
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	<i>N,N'</i> -dicyclohexylcarbodiimide
DCM	dichloromethane
dd	doublet of doublet
ddt	doublet of doublet of triplets
DEAD	Diethyl azodicarboxylate
DMP	Dess–Martin periodinane
DIBAL-H	diisobutylaluminum hydride
DIPEA	ethyldiisopropylamine
DTR	dynamic thermodynamic resolution
DKR-ATH	dynamic kinetic resolution asymmetric transfer hydrogenation
dq	doublet of quartet
DMAP	4- <i>N,N</i> -dimethylaminopyridine
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
d.r.	diastereomeric ratio
dt	doublet of triplet
E, El or E <sup>+</sup>	electrophile

e <sup>-</sup>	electron
En	enamine catalysis
eq	equation
equiv	equivalents
e.r.	enantiomeric ratio
ESI	electrospray ionization
Et	ethyl
Et <sub>3</sub> N	triethyl amine
Et <sub>2</sub> O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
EtONa	sodium ethoxide
Et <sub>3</sub> SiH	triethylsilane
EWG	electron withdrawing group
FID	flame ionization detector
G2	Grubbs' second generation catalyst
h	hour
H <sub>2</sub>	hydrogen
HCl	hydrochloric acid
<sup>c</sup> Hex <sub>2</sub> NH	dicyclohexanyl amine
<sup>1</sup> H NMR	proton nuclear magnetic resonance spectroscopy
HOAc	acetic acid
HOMO	highest occupied molecular orbital

HMPA	Hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	hertz
IR	infrared spectroscopy
IEDH	Inverse Electron Demand Hetero
Im	iminium catalysis
<i>J</i>	coupling constant
kcal	kilocalorie
K <sub>2</sub> CO <sub>3</sub>	potassium carbonate
L	liter or ligand
LA	Lewis acid
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LiTMP	Lithium tetramethylpiperidide
LiTFA	lithium trifluoroacetate
LRMS	low resolution mass spectroscopy
LUMO	lowest unoccupied molecular orbital
M	metal or molarity
m	multiplet
MeI	methyl iodide
Mn <sup>III</sup>	Manganese(III) ion
Me	methyl

MeCN	acetonitrile
MeMgBr	Methylmagnesium bromide
MeOH	methanol
MeONa	sodium methoxide
p-MeOPh	para methoxyphenyl
mg	milligram
MgSO <sub>4</sub>	Magnesium sulfate
MHz	megahertz
min	minutes
mL	milliliter
mmol	millimole
mp	melting point
<i>n</i>	number of atoms or counterions
N <sub>2</sub>	nitrogen
NaH	sodium hydride
NaIO <sub>4</sub>	sodium periodate
NaN <sub>3</sub>	sodium azide
NBS	<i>N</i> -bromosuccinimide
NCS	<i>N</i> -chlorosuccinimide
NaBH <sub>4</sub>	Sodium borohydride
nd	not determined
NFSI	N-fluorobenzenesulfonimide
nOe	nuclear Overhauser enhancement

NOESY	nuclear Overhauser enhancement spectroscopy
NR	no reaction
Nu	nucleophile
O <sub>2</sub>	oxygen
O–O	oxygen-oxygen bond
[O]	oxidation
PCC	pyridinium chlorochromate
Pd/C	Palladium on carbon
PG	protecting group
Ph	phenyl
ppm	parts per million
<sup>i</sup> Pr	<i>iso</i> -propyl
psig	pound-force per square inch
Pt/C	platinum on carbon
q	quartet
R	substituent
R <sub>f</sub>	retention factor
rt	room temperature
s	singlet
T	temperature
t	triplet
t <sub>r</sub>	retention time
TBAF	tetrabutylammonium fluoride

TBS	<i>tert</i> -butyldimethylsilyl
TEA	triethylamine
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl
triflate	trifluoromethanesulfonate
triflic	trifluoromethanesulfonic
triflimide	trifluoromethanesulfonimide
UV	ultraviolet
X	halide, substituent, or number
$\delta$	chemical shift or partial charge
$\pi$	pi bond
$\mu\text{L}$	microliter

## CHAPTER ONE: CU(II)-CATALYZED AEROBIC HYDROPEROXIDATION OF MELDRUM'S ACID DERIVATIVES AND APPLICATION IN INTRAMOLECULAR FUNCTIONALIZATION TO ACCESS COMPLEX BUILDING BLOCKS\*

### 1.1 Introduction

Enolate oxidation is an important tool in organic synthesis for the preparation of various  $\alpha$ -functionalized carbonyl compounds.<sup>1</sup> This reaction is often achieved through the application of nonideal reagents such as complex oxygen-based electrophiles--oxaziridines, dioxiranes, and diacyl peroxides (**Scheme 1-1**, equation 1); these reagents are useful for the installation of a hydroxyl group or hydroxyl surrogate but are relatively poor in term of atom economy.<sup>2</sup> When hydroperoxides are generated during the course of enolate functionalization (often as mixtures with the corresponding alcohols), it is common practice to reduce the mixture to the alcohol upon workup (**Scheme 1-1**, equations 2, 4). This reductive workup in essence wastes one oxidation level conferred by the oxidant. In contrast, an enolate oxidation that preserves the elevated product oxidation state could in principle be used to functionalize remote sites (**Scheme 1-1**, equations 3, 5), provided the distal functionality was compatible with the oxidation conditions.

Ideally to achieve such a transformation, oxidation of enolate **1.1** with molecular oxygen would initially provide a hydroperoxide **1.3** which would undergo an intramolecular

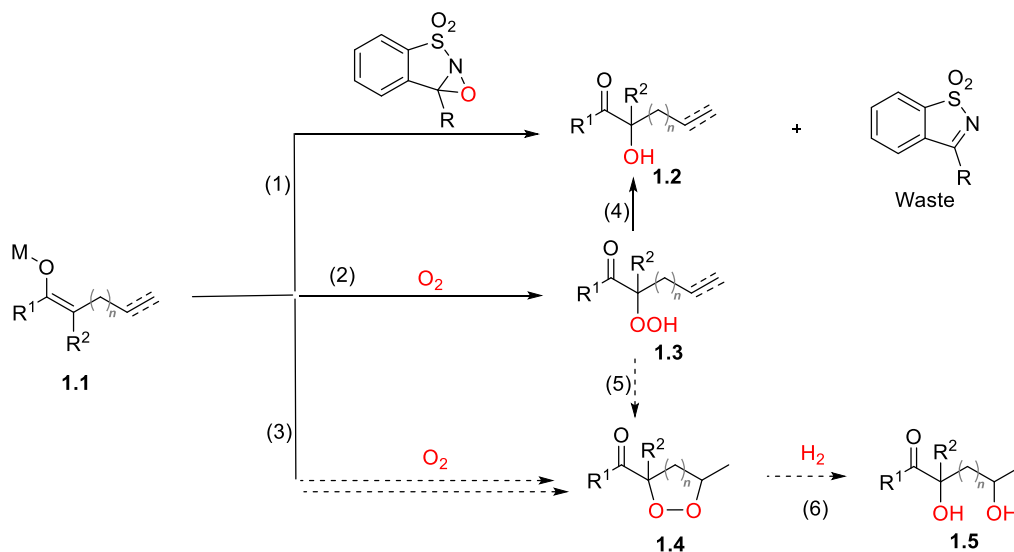
---

\* Reproduced in part by permission from Krabbe, S. W.; Do, D.; Johnson, J. S. *Org. Lett.* **2012**, *14*, 5932



remote oxidation to provide endoperoxide **1.4**. Hydrogenolysis of the O–O bond, would furnish formal dihydroxylation products **1.5** in a redox-economical manner.<sup>3</sup> Moreover, a catalytic enolate oxidation reaction that used O<sub>2</sub> would carry the inherent advantages of complete atom economy through the use of a green oxidant.

**Scheme 1.1** Methods of Enolate Oxidation



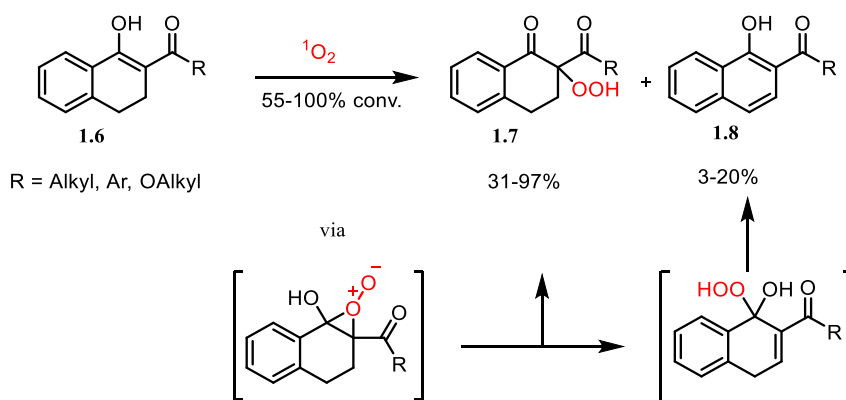
There are two key tasks to be addressed for translating this construct to practice. First, the development of a mild, functional group-tolerant enolate oxidation using O<sub>2</sub>, and second, the development of tools for remote functionalization using the hydroperoxide products. The goal of this study is to develop an efficient, operationally simple method for the catalytic aerobic hydroperoxidation of Meldrum's acid derivatives<sup>4</sup> and the application of these products in intramolecular alkene/alkyne remote oxidation to access structurally unique endoperoxides. Further manipulation of these endoperoxides would provide a variety of synthetically attractive, structurally diverse compounds.

## 1.2 Background

### 1.2.1 Extant Methods for Enolate Peroxidation

While research associated with enolates is widely present in the literature, extant methods for hydroperoxidation of  $\beta$ -dicarbonyls are hardly adequate. These methods often require harsh conditions and/or providing mixtures of hydroperoxides and alcohols. As early as 1933, Hasegawa reported the use of photosensitized  $^1\text{O}_2$  in the hydroperoxidation of  $\beta$ -dicarbonyls. The conditions allow the formal addition of  $\text{O}_2$  into the active methine in **1.6** with retention of the O–O bond.<sup>5</sup>

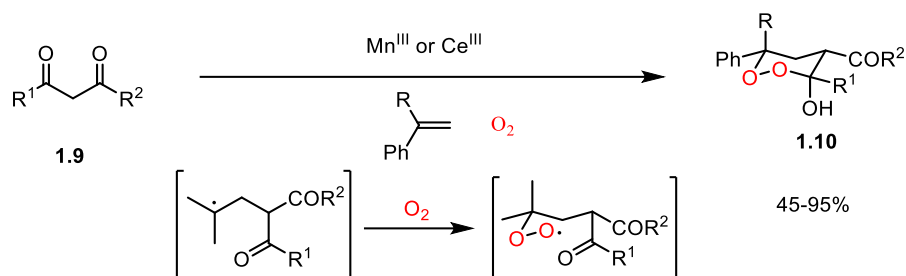
**Scheme 1-2.** Photosensitized Hydroperoxidation



However, the reaction was moderately selective for the formation of the hydroperoxide **1.7**, which was always isolated with a significant amount of the naphtol **1.8** (**Scheme 1-2**).

Metal-catalyzed hydroperoxidations have also been reported.<sup>6</sup>

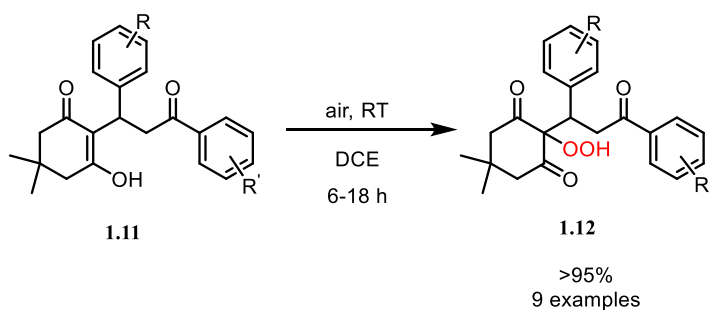
**Scheme 1-3.** Metal Catalyzed Hydroperoxidation



$\beta$ -Dicarbonyl compounds **1.9** can be oxidized to their  $\alpha$ -radicals with Ce(III) or Mn(III). Subsequent trapping of the radical with alkenes and molecular oxygen generated the hemiketal endoperoxides **1.10** in moderate yield (Scheme 1-3).

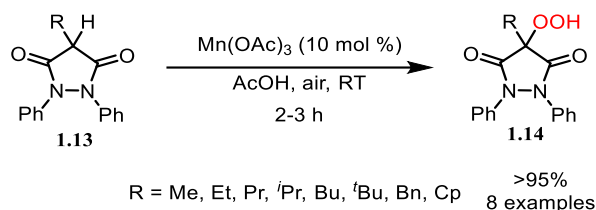
Serendipitously, Xia and coworkers reported a hydroperoxidation under aerobic oxidation of dimedone derivatives<sup>7</sup> (**Scheme 1-4**). Exposing solution of chalcone **1.11** in DCE to air for the indicated time, they isolated the hydroperoxide **1.12** with excellent yield (9 examples with >95% yield). While the aerobic oxidation conditions are quite tempting, this reaction was specific only to dimedone derivatives.

**Scheme 1-4.** Aerobic Hydroperoxidation of Dimedone Derivatives



Nishino demonstrated an efficient autoxidation of heterocyclic 1,3-dicarbonyl compounds employing Mn(III)/O<sub>2</sub> to peroxidize 1,2-diphenylpyrazolidine-3,5-diones and barbituric acid derivatives **1.13** (Scheme 1-5).<sup>8</sup> In all cases, the hydroperoxides **1.14** were isolated with excellent yields (8 examples, >95% yields). However, Mn(III) is well-known to give electrophilic radical intermediates with  $\beta$ -dicarbonyls presumably, rendering this method incompatible with pendant unsaturation due to competitive cyclization.<sup>9</sup> It is not surprising that there are no reported examples of hydroperoxidation of  $\beta$ -dicarbonyls containing alkene or alkyne functionality that would be required for useful subsequent transformations.

**Scheme 1-5.** Mn(III) Catalyzed Hydroperoxidation of Barbituric Acids

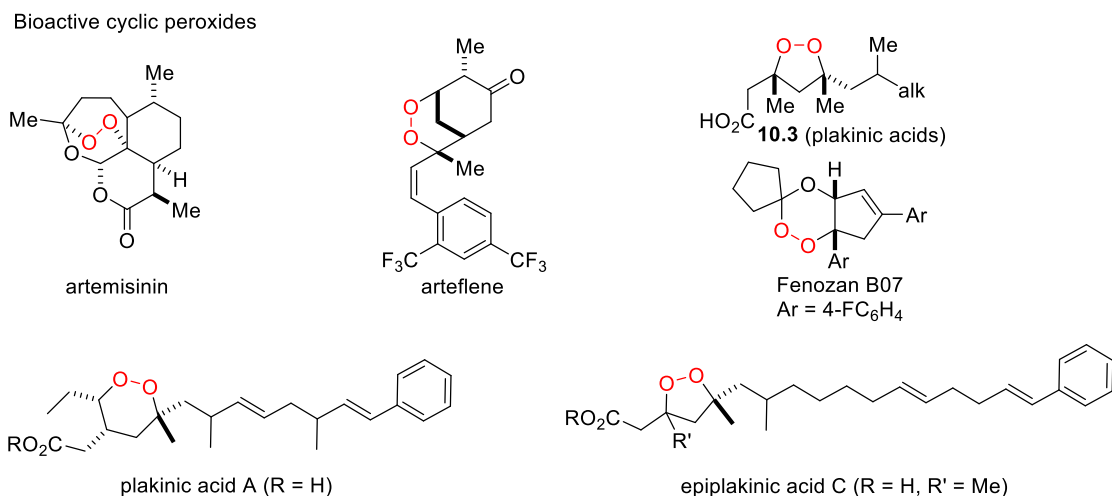


### 1.2.2 Diverse Endoperoxides as Candidates for Antimalarial and Anticancer Agents

Cyclic peroxides exhibit many useful biological activities which provide the potential for application in small molecule therapeutics.<sup>10</sup> The natural product artemisinin and its derivatives are broadly used in antimalarial treatment and cyclic peroxides figure prominently in synthetic artemisinin mimics, as it is believed that the mechanism of action is linked to the peroxide bridge.<sup>11,12</sup> 1,2-Dioxanes and 1,2-dioxolanes are distinguishing features of natural products exhibiting anticancer activity (e.g. plakinic acids),<sup>13,14</sup> but synthetically produced 1,2-dioxolane rings have not been broadly evaluated for antimalarial<sup>15</sup> or anticancer activities. With this knowledge and the findings that many structurally simpler cyclic peroxides can still exhibit useful biological activity, the short and efficient synthesis of new cyclic peroxides has

become a topic of increased effort.<sup>16</sup> Thus, the value of endoperoxides **1.4** is twofold as they are both biologically relevant and potential precursors to ubiquitous 1,*n*-diols **1.5**. This chapter will highlight our work to prepare new unnatural cyclic peroxides and their use in accessing complex building blocks stereoselectively.

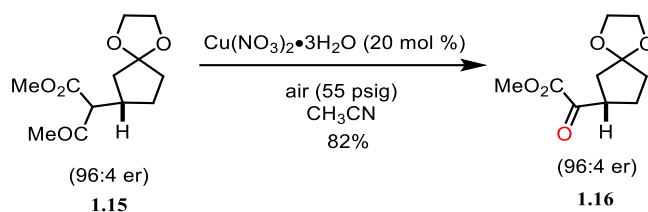
**Figure 1-1** Natural products possessing cyclic peroxides



### 1.2.3 Copper-Catalyzed Enolate Oxidation

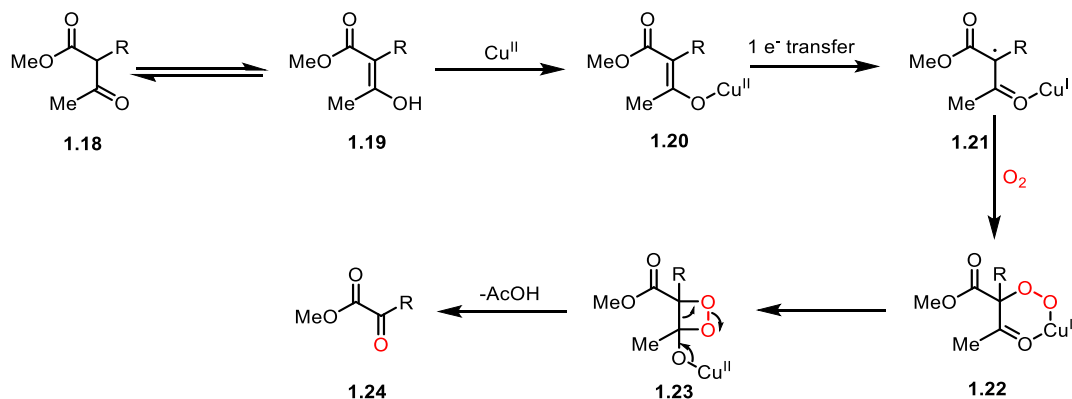
Developed from some early studies,<sup>17,18</sup> Steward reported a simple protocol for the preparation of  $\beta$ -stereogenic  $\alpha$ -keto esters through the aerobic deacylation of substituted acetoacetate derivatives (Scheme 1-6).<sup>19</sup> The acetoacetate derivative **1.15** exposed to Cu(II)/air (55 psig; standard Fisher-Porter bottle) in acetonitrile at ambient temperature provided the  $\beta$ -stereogenic  $\alpha$ -keto esters **1.16**. It is noteworthy that this mild reaction proceeded with good yields and with an excellent chirality transfer.

**Scheme 1-6.** Steward Cu(II)-Catalyzed Oxidative Deacylation



The generation of the reactive enol **1.19** under these mild reaction conditions, by virtue of the low  $\text{pK}_a$  of acetoacetates **1.18**, initiates the series of steps in a proposed mechanism shown in Figure 1-2.

**Figure 1-2.** Oxidative Deacylation Reaction Proposed Mechanism



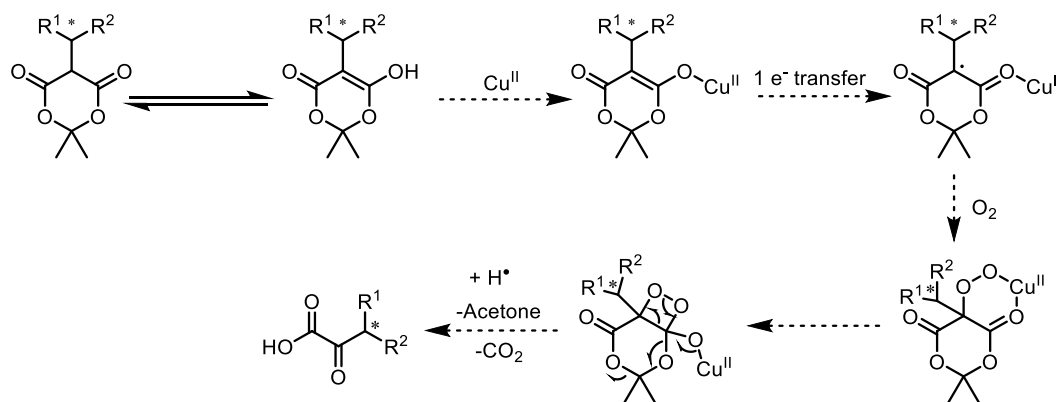
Coordination of  $\text{Cu}(\text{II})$  to the enol **1.19** generates a copper enolate **1.20**, which then undergoes a single electron transfer to form the radical cation **1.21**, thereby reducing  $\text{Cu}(\text{II})$  to  $\text{Cu}(\text{I})$ . A formal [4+2] addition of **1.21** with molecular oxygen to form **1.22** regenerates  $\text{Cu}(\text{II})$ , and a two step rearrangement involving intermediate **1.23** results in expulsion of acetic acid to provide the  $\alpha$ -keto ester **1.24**.

## 1.3 Results and Discussion

### 1.3.1 Preliminary Results and Experimental Plan

In the course of attempting to extend Steward's recently reported aerobic deacylation of acetoacetates to other dicarbonyls,<sup>20</sup> we proposed a pathway to access  $\alpha$ -keto acids. (Figure 1-3). Our point of departure for this study was to examine oxygenation of  $\beta$ -dicarbonyls with the expectation that the unusually high C–H acidity of Meldrum's acids could translate to relatively mild activation conditions.

**Figure 1-3.** Desired Mechanistic Pathway for Meldrum's Acids

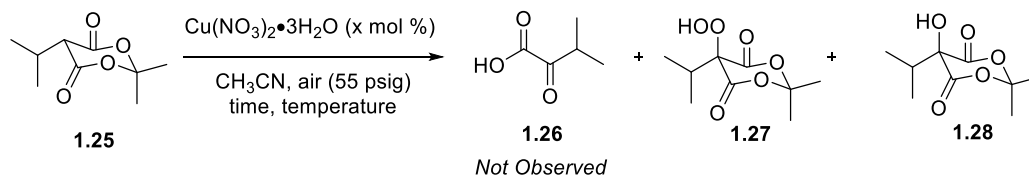


In addition, the use of substituted Meldrum's acids as flexible starting materials for C–H oxidation was attractive, since asymmetric syntheses of these compounds have been developed to a high level of sophistication, simplicity, and scalability.<sup>21,22</sup>

We began by exposing isopropyl Meldrum's acid **1.25** to Cu(II)/air, expecting the formation of the oxidative cleavage product keto acids **1.26**. However, the reduced electrophilicity of the ester carbonyl prevented the formation of  $\alpha$ -keto acid **1.26** and led instead to a mixture of hydroperoxide **1.27** and alcohol **1.28** (Table 1-1). A 2:1 mixture of

hydroperoxide **1.27** and alcohol **1.28** was obtained when reaction was prolonged to 17 h at room temperature (entry 1). The ratio of hydroperoxide to alcohol increased when the reaction was quenched earlier (entries 2-4). Reducing the temperature to 0 °C minimized or eliminated reduction to alcohol **1.28** while still providing good conversion to the hydroperoxide **1.27** (entry 5). Operational simplicity was further enhanced without detriment to yield by using a balloon of O<sub>2</sub>, eliminating the need for a pressure vessel.<sup>22</sup> With the optimized conditions in hand, we aimed to extend this simple, mild and efficient reaction to the hydroperoxidation of a variety of Meldrum's acid derivatives, including those with unsaturation. Possessing a similar property as Meldrum's acids, barbituric acid derivatives will also be investigated for this reaction.

**Table 1-1.** Cu(II)-Catalyzed Aerobic Oxidation of a Substituted Meldrum's Acid



Entry	Catalyst Loading (mol %)	T (°C)	Time (h)	1.27:1.28 <sup>a</sup>
1	20	23	17	2:1
2	20	23	1	10:1
3	10	23	2	10:1 <sup>b</sup>
4	25	23	2	13:1
5	25	0	5	>20:1

<sup>a</sup> Ratio by <sup>1</sup>H NMR comparison of characteristic peaks;

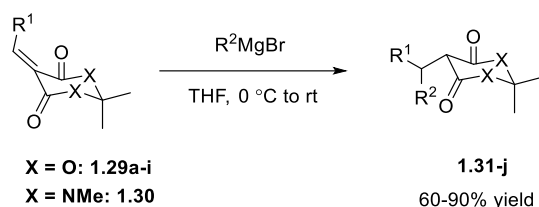
<sup>b</sup> Reaction did not go to completion;



### 1.3.2 Synthesis of Substituted Meldrum's Acids and Barbituric Acids

The conjugate addition of Grignard reagents to alkylidene Meldrum's acids **1.29a-i** or barbituric acid **1.30-j** proved most effective for the rapid generation of substituted Meldrum's acids and barbituric acid library **1.31-j** (Scheme 1-7). In general, the reaction proceeded with complete conversion and both alkylidene Meldrum's acids and barbituric acid provided the desired products with high isolated yields. Both saturated and unsaturated substituted Meldrum's acids were conveniently synthesized via this method.

**Scheme 1-7.** Synthesis of Unsaturated Substituted Meldrum's Acids and Barbituric Acid



### 1.3.3 Hydroperoxidation of Meldrum's Acid Derivatives

With optimized conditions for the hydroperoxidation in hand,<sup>23</sup> various Meldrum's acids **1.31a-j** were subjected to the hydroperoxidation conditions (Table 1-2).

The mild reaction conditions proved tolerant of a variety of potentially vulnerable functional groups including alkenes, terminal and internal alkynes, arenes, tertiary benzylic C–H bonds, and esters. In most cases, the hydroperoxide products **1.32a-h** were obtained in analytically pure form following a simple aqueous work-up. Alkene substrates only provided modest to good yields of the desired hydroperoxides **1.32i-j** following purification.<sup>24</sup> In addition to providing hydroperoxy Meldrum's acid derivatives in good yield, this methodology

also provided the barbituric acid derivative **1.32k** with pendant unsaturation in modest yield, a product that would presumably be unattainable using the Mn(III)-catalyzed conditions.

**Table 1-2.** Hydroperoxidation of Meldrum's Acid Derivatives

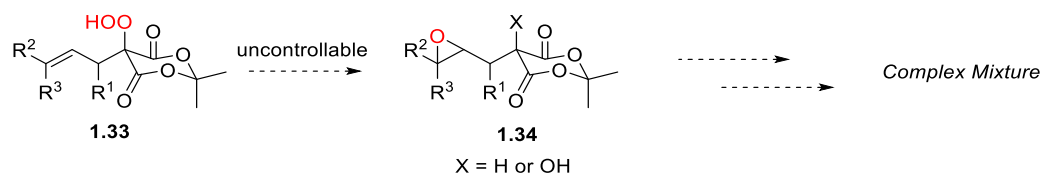
Product			t (h)	Yield (%) <sup>a</sup>
	R' = CH <sub>3</sub>	<b>a</b>	6	>95
	H	<b>b</b>	6	92
	Ph	<b>c</b>	2	>95
	R' = H	<b>d</b>	2	80
	CH <sub>3</sub>	<b>e</b>	2	78
	C <sub>5</sub> H <sub>11</sub>	<b>f</b>	2	80
	CO <sub>2</sub> Et	<b>g</b>	3	>95
	Ph	<b>h</b>	2	>95
	n = 0	<b>i</b>	4	59 <sup>b,c</sup>
	1	<b>j</b>	4.5	86 <sup>b,d</sup>
		<b>k</b>	8	49 <sup>b</sup>

<sup>a</sup> Isolated yield without need for purification (except **1.32i**, **1.32j**, **1.32k**).

<sup>b</sup> Yield following purification on SiO<sub>2</sub>. <sup>c</sup> 10:1 with alcohol. <sup>d</sup> 17:1 with alcohol.

It is noteworthy that the internal alkene substrates are not tolerated with the reaction condition. The reaction of those substrates generally resulted in a messy mixture where the hydroperoxide was not present in the crude mixture. We reasoned that when the hydroperoxides **1.33** were formed, they underwent uncontrollable inter- and/or intramolecular epoxidations to generate epoxides **1.34** which, under the reaction condition, react further to provide a complex mixture of products (Figure 1-4).<sup>18,19</sup>

**Figure 1-4.** Limitation of Alkene Substrates

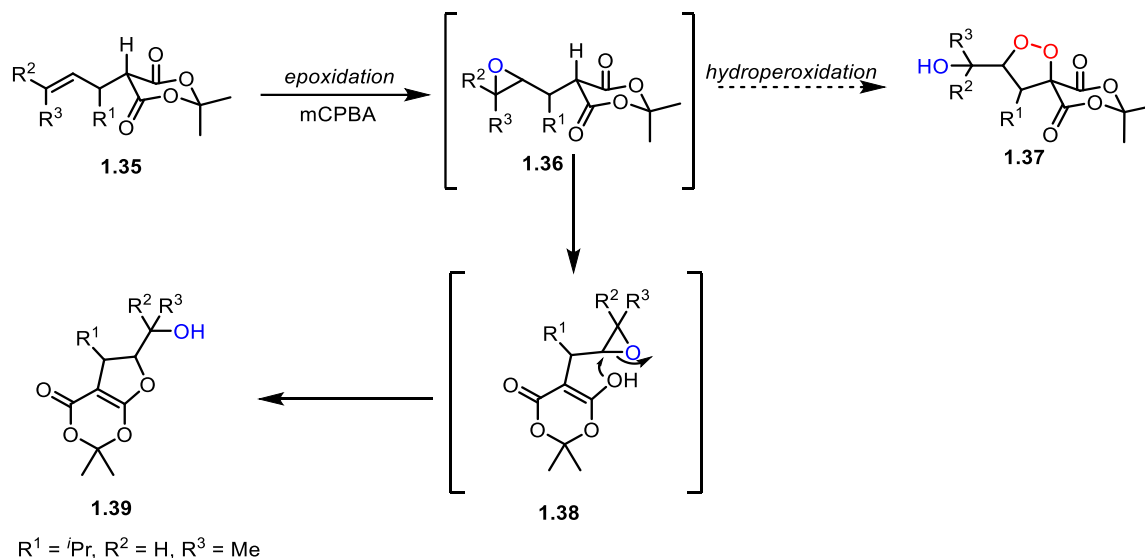


If the proposed scenario in Figure 1-4 were the only complication, we felt that we could potentially control each step of the process. To probe this, we considered pre-forming the epoxide **1.34** and subjecting it to the hydroperoxidation condition. This approach could provide us the endoperoxide **1.37** via an intramolecular epoxide ring-opening reaction of intermediate **1.36**. Since the epoxidation is a stereospecific process and we can expect a regioselective epoxide-ring opening, it seemed reasonable that we could achieve a diastereoselective formation for the endoperoxide **1.37**.

Unfortunately, while we were able to generate the epoxide **1.36** from alkenyl Meldrum's acid **1.35** *in situ*, it readily underwent an intramolecular epoxide ring-opening with the enol **1.38** to form compound **1.39**, relinquishing the opportunity for the hydroperoxidation.

Although we were not successful with the internal alkene substrates, those substrates with the pendant  $\pi_{C=C}$  (**1.32d-h**) and terminal  $\pi_{C=C}$  (**1.32i-k**) functionality would provide us the opportunity to assay the utility of unsaturated hydroperoxide products in intramolecular oxidation via endoperoxide formation.

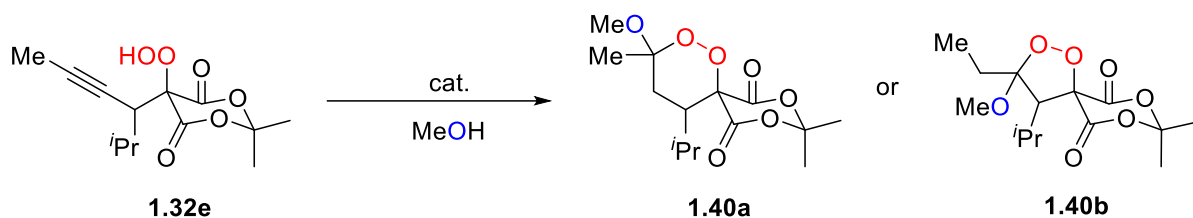
**Scheme 1-8.** Possible Solution of Internal Alkene Substrates



### 1.3.4 Au(I)-Catalyzed Endoperoxidations of Hydroperoxyalkynes

Although metal-catalyzed cycloetherifications have been reported with a variety of catalysts,<sup>25</sup> to the best of our knowledge, the corresponding endoperoxidation was unknown at the time. The primary goal of this endoperoxidation was to find conditions that could tolerate the susceptibility of the O–O bond to metal-mediated cleavage of the hydroperoxide. Drawing an analogy to the alcohol/alkyne etherifications enabled by electrophilic activation, we envisioned that exposure of alkyne **1.32e** to a Brønsted acid or soft late transition metal catalysts in methanol should enable mixed-ketal endoperoxide formation (**1.40a** or **1.40b**).

**Table 1-3.** Screen for Acid-Catalyzed Endoperoxidation of Alkynyl Hydroperoxides



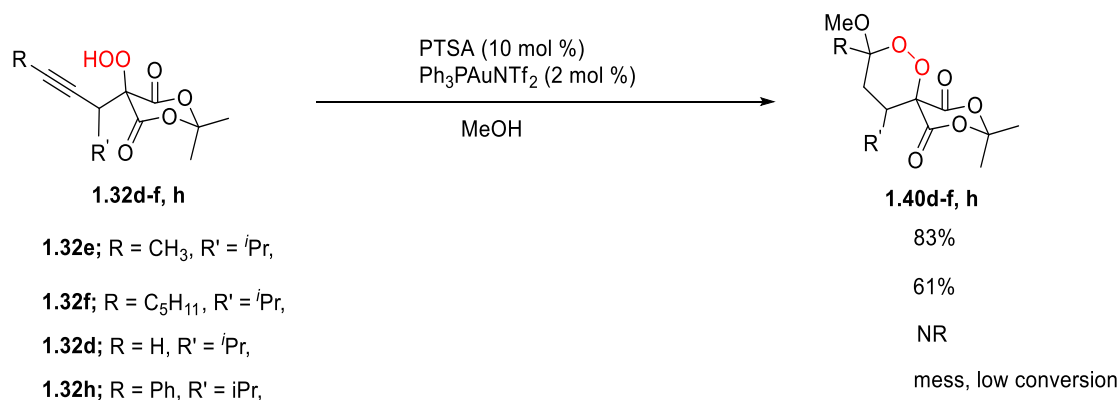
entry	catalyst	result
1	PTSA	NR
2	TfOH	NR
3	Cu(OTf) <sub>2</sub>	NR
4	AgOTf	NR
5	Pd(OAc) <sub>2</sub>	Decomp.
6	Hg(OAc) <sub>2</sub>	Mess
7	PtCl <sub>2</sub>	NR
8	AuCl	NR
9	AuCl <sub>3</sub>	NR
10	Ph <sub>3</sub> PAuCl	NR
11	AuCl/AgPF <sub>6</sub>	NR
12	Ph <sub>3</sub> PAuNTf <sub>2</sub>	Mess
13	Ph <sub>3</sub> PAuCl/AgOTf	56%
14	Ph <sub>3</sub> PAuNTf <sub>2</sub> /PTSA	83%

The five-(**1.40b**) or six-membered ring mixed ketal endoperoxides (**1.40a**) could both be envisioned as potential products (Table 1-3). Initial attempts included a screen of Brønsted acids catalysts. Unfortunately, both strong acids such as PTSA and triflic acid did not promote any reaction (entries 1,2). We next probed the effect of Lewis acids on the transformation. Copper(II) and silver triflate showed no effect (entries 3,4), while mercury(II) acetate gave a mess with low conversion (entry 6). Palladium(II) acetate displayed an unusual effect by destroying the Meldrum's acid under the reaction condition (entry 5). Even catalysts that are well-known to efficiently activate alkynes, such as gold(I), gold(III) and platinum chloride,

were unreactive in our case. The use of triphenylphosphine gold triflate and a 1:1 mixture of combination of gold(I) chloride and silver hexafluorophosphate were also ineffective at promoting the desired transformation (entries 7-11). The use of triphenylphosphine gold(I) triflimide surprisingly gave a messy reaction, given the mild reactivity of the catalyst (entry 12).<sup>26</sup> Gratifyingly, a 1:1 mixture of triphenylphosphine gold(I) chloride and silver triflate provided the mixed ketal endoperoxide **1.40a** with 56% yield (entry 13). It should be noted that no five-membered ring mixed ketal endoperoxide **1.40b** formed in this reaction indicating that a complete regioselective six-endo cyclization occurred under this reaction condition. We were delighted to achieve an increased yield of 83% when a combination of 2 mol % of triphenylphosphine gold(I) triflimide and 10 mol % of PTSA was used (entry 14).<sup>27</sup> The diastereoselectivity for the cyclization was moderate; Nonetheless, the epimerization at the ketal carbon is irrelevant, since the stereochemistry at this position will be erased in the following reduction step, so this highest yielding reaction condition was chosen as the optimal condition.

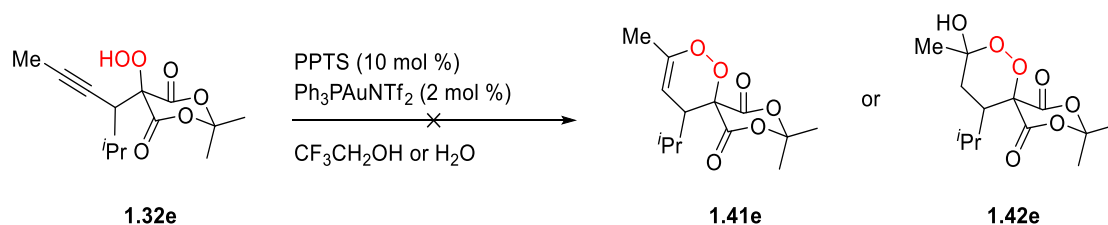
With the optimized conditions in hand, we began to extend this reaction to the alkynyl hydroperoxides (Table 1-4). While the reaction worked moderately well with alkyl alkynyl substrates (when R = alkyl, substrates **1.32e,f**), it gave no reaction when a terminal alkyne was present in molecule (R = H, **1.32d**). The reaction did not tolerate aryl alkynes (R = Ph, **1.32h**). A messy reaction with low conversion was observed in this case.

**Table 1-4.** Illustrative Examples for The Gold(I)-Catalyzed Cyclization



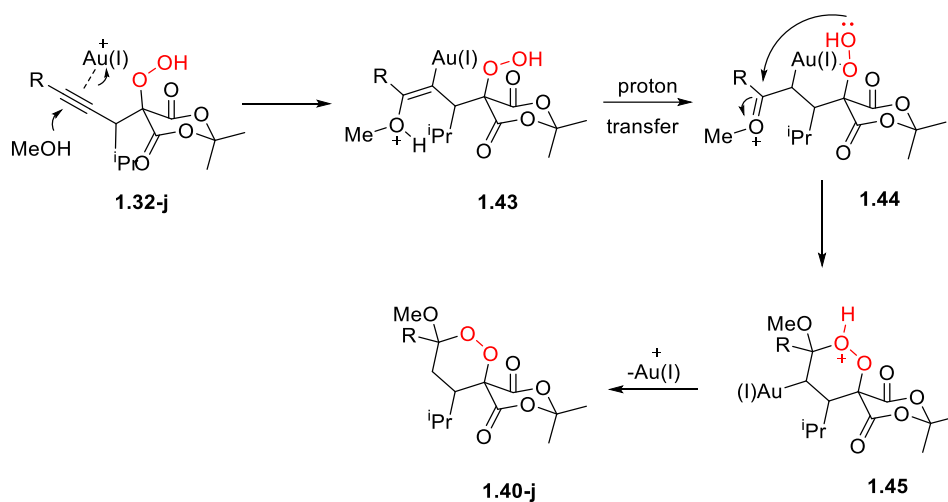
Regarding the mechanism of this novel reaction, control experiments were run to provide insight into the role of methanol in this reaction (Scheme 1-9). We replaced methanol from the reaction with a non-nucleophilic alcohol such as trifluoroethanol. If the role of methanol in the reaction was not necessary as a nucleophile, we would expect the formation of ene-peroxide **1.41e**. However, no reaction was observed when **1.32e** was treated with the combination of 2 mol % of triphenylphosphine gold(I) triflimide and 10 mol % of PTSA in trifluoroethanol. Similarly, replacing methanol by a less nucleophilic solvent such as water, the expected hemiketal **1.42e** was not formed under the reaction condition, and the hydroperoxide **1.32e** was completely recovered.

**Scheme 1-9.** Control Experiments



These two experimental results suggest that a strongly nucleophilic solvent such as methanol is necessary for the reaction to proceed and that it participates in the reaction before the intramolecular action of the hydroperoxide. Given the highly nucleophilic profile of hydroperoxide, it is assumed that two electron withdrawing carboxyl groups in Meldrum's acid reduce the nucleophilicity of the hydroperoxide in this case. The proposed mechanism for this reaction is shown below (Scheme 1-10).

**Scheme 1-10.** Proposed Mechanism for The Gold(I)-Catalyzed Cyclization



Following the coordination and activation of gold(I) to the alkyne **1.32-j**, methanol attacks the less hindered side of the alkyne complex to form the intermediate **1.43**. A proton transfer from the oxygen to the carbon attached to gold generates the oxocarbenium **1.44**, which is susceptible to the attack of the hydroperoxide, forming the protonated mixed ketal **1.45**. Proto-demetalation then releases the endoperoxide mixed ketal **1.40-j** isolated as a 6-*endo* cyclization adduct.

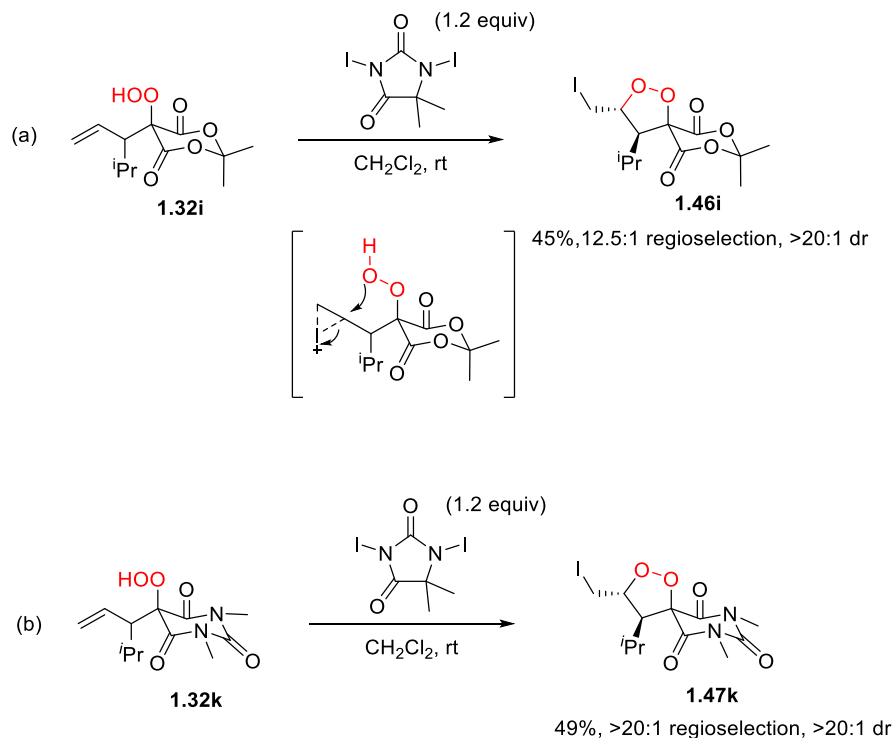


### 1.3.5 The Remote Oxidation of Alkenyl Hydroperoxy Meldrum's Acid Derivatives

While the gold(I)-catalyzed *6-endo* cyclization reaction has demonstrated a formal remote intramolecular oxidation for the alkynes, we sought the complementary cyclization mode through the remote oxidation of alkenyl hydroperoxy Meldrum's acid derivatives.

Homoallyl-hydroperoxy **1.32i** cyclized via electrophilic activation of the alkene with 1,3-diiodo-5,5-dimethyl hydantoin (DIH).<sup>28</sup> This process was highly regio- and stereoselective providing the 1,2-dioxolane **1.46i** with pendant iodide in modest yield. The *N,N*-dimethylbarbituric acid derivative **1.32k** reacted analogously giving the endoperoxide **1.47k** in 49% yield.

**Scheme 1-11.** Iodoendoperoxidation of Homoallylhydroperoxy-Meldrum's Acid and Barbituric Acid Derivatives

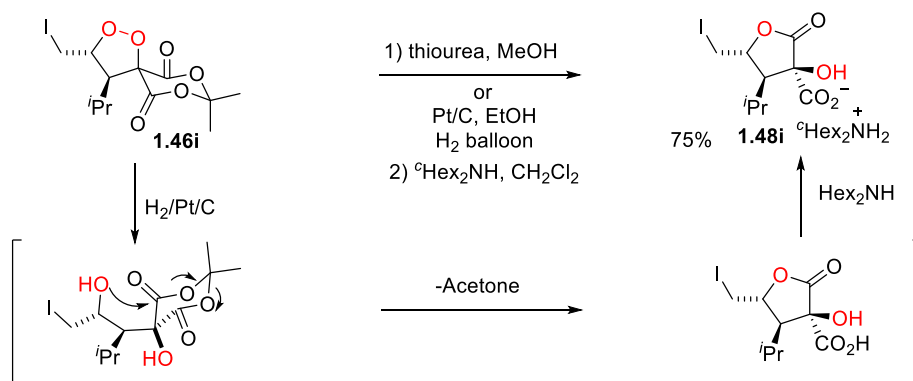


A noteworthy feature of this reaction is that a *5-exo* cyclization mode is dominant in this case. We reasoned that the *6-endo* cyclization in the gold(I)-catalyzed cyclization was dictated by the attack of methanol to the less hindered side of the alkyne and regioselectivity of the cyclization of alkenes was controlled by the preference of *5-exo* over *6-endo* iodonium ring-opening reaction.

### 1.3.6 Secondary Transformation of Endoperoxides

To highlight the synthetic application of the endoperoxides by accessing 1,*n*-diols via formal dihydroxylation with O<sub>2</sub> as the oxidant and H<sub>2</sub> as the reductant, illustrative secondary transformation were pursued. The endoperoxide **1.46i** was the first candidate to test this green chemistry principle. Exposure of **1.46i** to a standard hydrogenolysis condition of hydrogen balloon in the presence of Pt/C in ethanol provided smooth O–O bond cleavage. Concomitant cyclization/ring opening occurred on the Meldrum's acid with complete diastereotopic group discrimination to provide the differentiated 1,3-diol functionality in the form of lactone **1.48i**, which was conveniently isolated in analytically pure form as the dicyclohexylamine salt in good yield as a single diastereomer (Scheme 1-12).

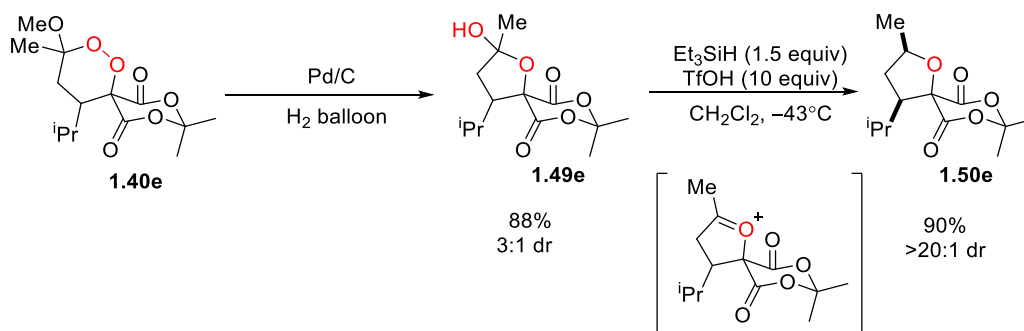
**Scheme 1-12.** Endoperoxide Cleavage in 1,2-Dioxolane System



The relative configuration of **1.48i** was determined by single crystal x-ray diffraction. A similar result was achieved when thiourea/MeOH was used as the reductant for the O–O bond cleavage.<sup>29</sup>

Encouraged by the diastereoselective ring opening of the Meldrum's acid, we investigated the feasibility of performing a similar practice for the mixed ketal endoperoxides and demonstrate an opportunity to access complex building blocks. The mixed ketal endoperoxide **1.40e** was then exposed to the hydrogenolysis condition with a hydrogen balloon and Pd/C in DCM at room temperature for 30 minutes. Subsequent reductive cleavage of the O–O bond of **1.40e** followed by hemiketal formation with the transient ketone provides hemiketal **1.49e** in excellent yield with 3:1 dr (Scheme 1-13).

**Scheme 1-13.** Synthesis of Tetrahydrofuran Derivatives

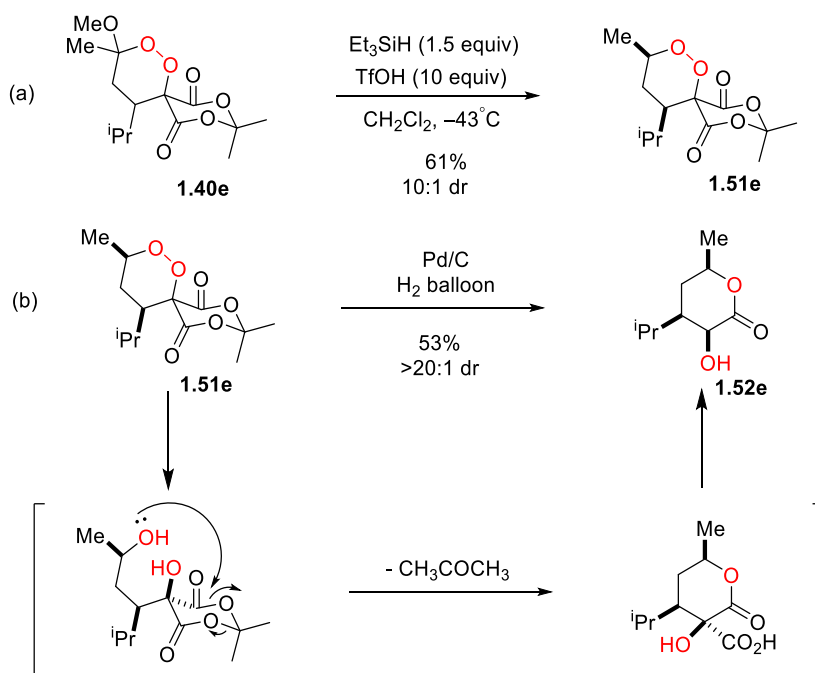


Subjecting the hemiketal **1.49e** to the established ionic hydrogenation with triflic acid and Et<sub>3</sub>SiH afforded tetrahydrofuran **1.50e** in a highly diastereoconvergent process.<sup>30</sup> The oxocarbenium ion intermediate was proposed to explain the diastereoselectivity. Hydride

delivery *anti* to the isopropyl group gave the illustrated diastereomer of **1.50e** providing a unique diastereoselective access to highly-substituted tetrahydrofurans (Scheme 1-13).

Interestingly, by reversing the order of operations, entirely different products can be accessed from the same mixed ketal endoperoxide. Under ionic hydrogenation condition with triflic acid and triethylsilane, **1.40e** provides endoperoxide **1.51e** in modest yield with good diastereoselectivity (Scheme 1-14a). A similar oxocarbenium ion intermediate with delivery of the hydride source *anti* to the isopropyl group could be used to explain the highly diastereoconvergent process. Reductive cleavage of the O–O bond of **1.51e** with concomitant Meldrum's acid opening and decarboxylation gives the desired 1,4-diol functionality as lactone **1.52e** in good yield as a single diastereomer, implying that the decarboxylation/protonation is completely stereoselective (Scheme 1-14b).

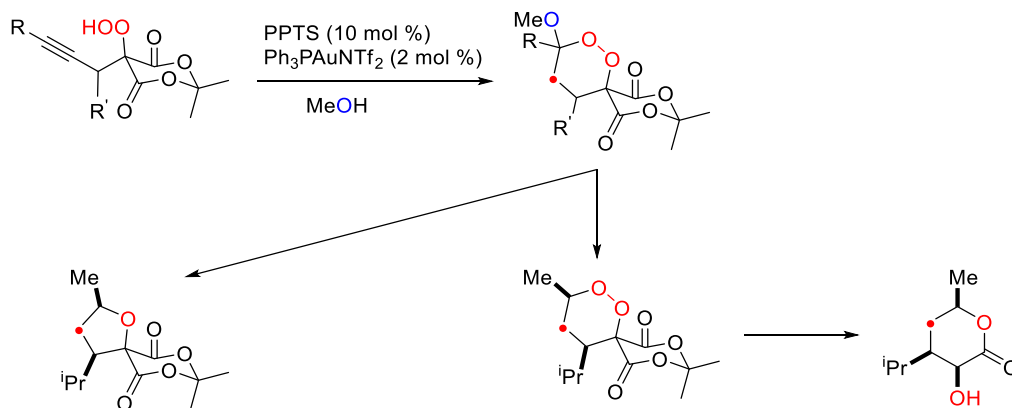
**Scheme 1-14.** Mixed Ketal Endoperoxide Functionalization



### 1.3.7 Application in Stereoselective Access Fully Substituted Building Blocks

From our demonstration of quick access to mixed ketal endoperoxides, endoperoxides, and substituted tetrahydrofurans and the development of atom-efficient  $O_2/H_2$  dihydroxylations, we feel that there are still some areas of improvement for this promising chemistry (Figure 1-5). While the gold(I)-catalyzed cyclization provides unique access to the mixed ketal endoperoxides, the scope for the reaction was very limited. Only substrates with the alkyl substitution on the internal alkyne were the competent partners in the cyclization. And although the reaction proceeds well with a catalyst loading of 2 mol % of the triphenylphosphine gold(I) triflimide, the catalyst itself is not an economic option. It is therefore desirable to seek a more general and economical method to access the endoperoxides.

**Figure 1-5.** Areas of Improvement



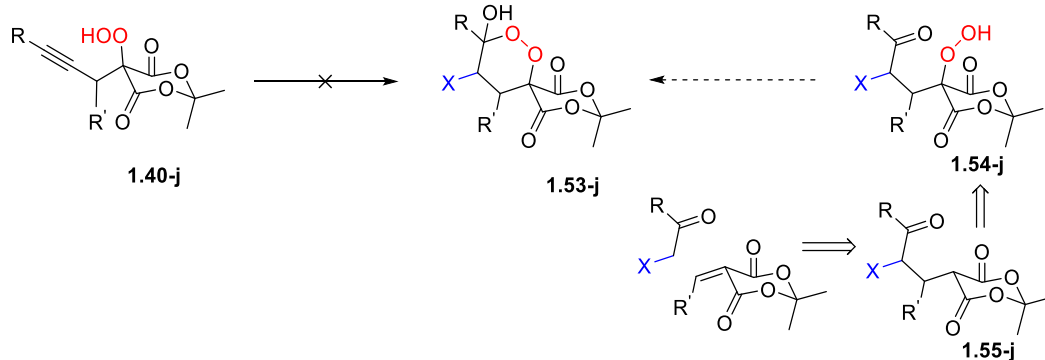
1. More general scope for the synthesis of endoperoxide hemiketal?
2. Can we stereoselectively access fully substituted ones?

As shown in Figure 1-5, the gold(I)-catalyzed cyclization only furnished a mixed ketal endoperoxide with no substitution at the carbons denoted by red dots, thus neglecting an opportunity to access fully-substituted building blocks during the functionalization process.

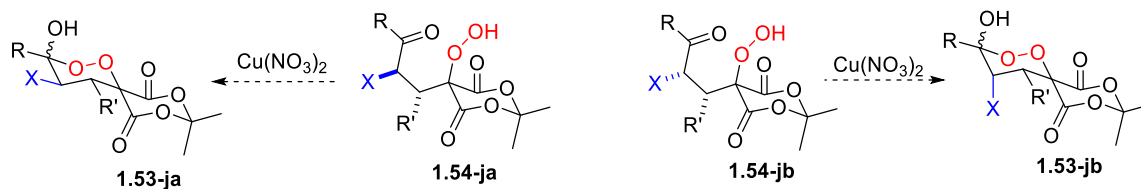
There are two obvious questions to ask at this point: can we access a more general scope for the synthesis of endoperoxide hemiketal? And can we stereoselectively access fully substituted building blocks?

**Figure 1-6.** Proposed Condition to Access Fully Substituted Endoperoxides

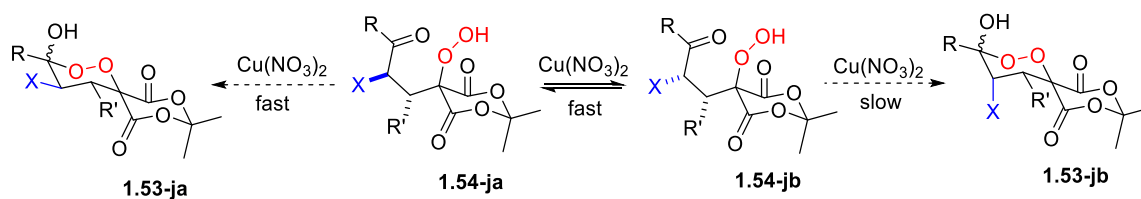
a. Intramolecular Trapping-Synthesis of Hemiketal Endoperoxide



b. Potential Diastereoselectivity Issue



c. Dynamic Thermodynamic Resolution Condition



Regarding the first question, we proposed that while the cyclization of the alkynyl hydroperoxides **1.40-j** could not provide the fully-substituted hemiketal endoperoxides **1.53-j**, these compounds could be prepared by intramolecular trapping of the transient hydroperoxide **1.54-j** with an active ketone functional group present in the molecule (Figure 1-6a). The

transient hydroperoxide itself could be readily access via the standard hydroperoxidation process of the corresponding Meldrum's acid **1.55-j** which presumably accessible via a Michael reaction of the alkylidene or arylidene with the designated ketones (Figure 1-6a).

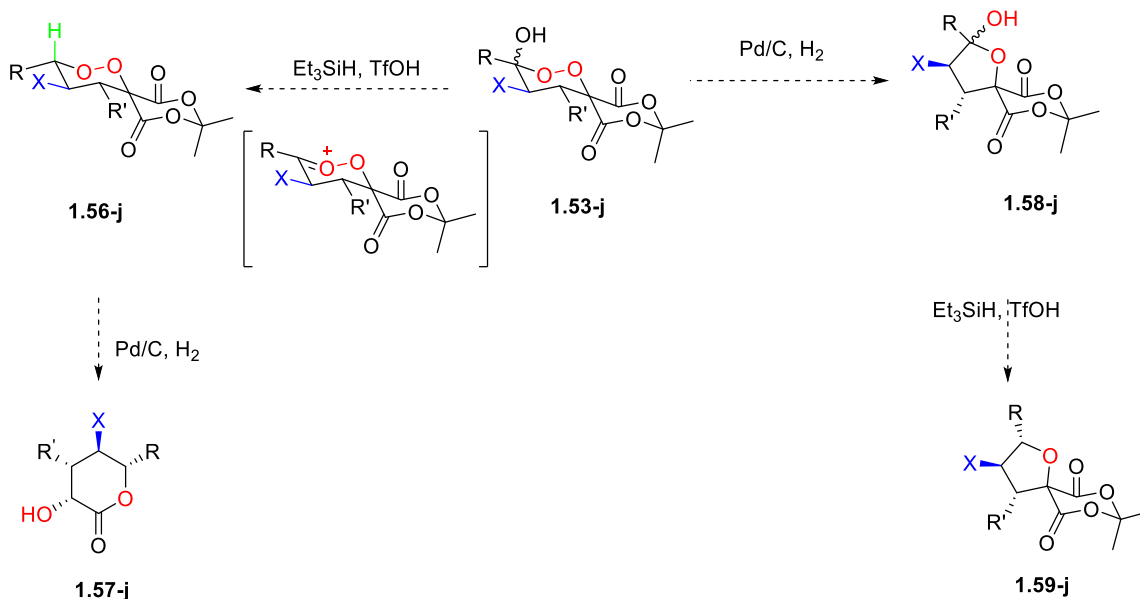
The second question concerning the stereoselectivity appears more challenging. When two preexisting stereocenters are present in molecule, it is expected that the two diastereomeric hydroperoxides **1.54-ja** and **1.54-jb** will undergo a non-diastereoselective cyclization to furnish two sets of diastereomers **1.53-ja** and **1.53-jb** (Figure 1-6b), thereby preventing us from accessing the fully substituted endoperoxide stereoselectively.

To overcome this challenging issue associated with the fully substituted substrates, we hypothesized that if X were an electron withdrawing group, the methine  $\alpha$ -proton of the ketone **1.54-j** would be acidic enough to undergo rapid epimerization under acidic conditions. Standard dynamic thermodynamic resolution (DTR) conditions, with rapid epimerization at the methine stereocenter, where one epimer cyclizes faster relative to the other, should allow us to set the relative stereochemistry at the two tertiary centers (Figure 1-6c).

The newly-established chemistry for the diastereoselective ionic hydrogenation would be an ideal tool to "fix" the stereochemistry at the quaternary hemiketal (Figure 1-7). Exposing the hemiketal endoperoxide **1.53-j** to an ionic hydrogenation with triethylsilane and triflic acid would diastereoselectively provide the endoperoxide **1.56-j**. Upon treatment of **1.56-j** with an established hydrogenation method to undergo a tandem O–O bond cleavage, ring-opening of Meldrum acid following of decarboxylation, would diastereoselectively furnish the fully-substituted  $\alpha$ -hydroxy lactone **1.57-j**. Reversing the order of reactions, the hemiketal endoperoxide would undergo an O–O bond cleavage by hydrogen/Pd/C to provide the

hemiketal tetrahydrofuran derivative **1.58-j**, which would be subjected to the ionic hydrogenation condition with triethylsilane and triflic acid to diastereoselectively access fully-substituted tetrahydrofuran **1.59-j** (Figure 1-7).

**Figure 1-7.** Proposed Approach to Access Fully Substituted Building Blocks

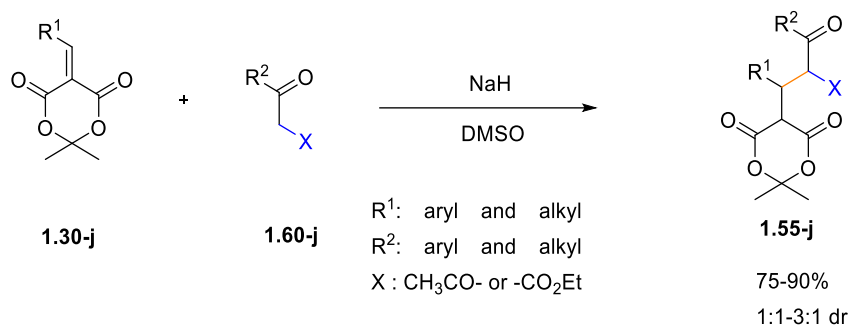


To realize the hypothesis, we started to synthesize the keto-Meldrum's acids, designated substrates for the hydroperoxidation. Michael reaction of the alkylidene or arylidene Meldrum's acids **1.30-j** and the ketones **1.60-j** were elected methods for its simplicity and efficiency. As depicted in Scheme 1-15, representative keto-Meldrum's acids were synthesized via this reaction by treating the 1:1 mixture of ketones and alkylidene or arylidene Meldrum's acids with stoichiometric amount of base ( $\text{NaH}$ ,  $\text{K}_2\text{CO}_3$  or  $\text{MeONa}$ ). Expectedly, the reaction provided these keto-Meldrum's acids with good to excellent yield (75-90%) and poor diastereoselectivity (1:1-3:1 dr). Fortunately, in most case the reaction was clean enough for the next step. Attempts to purify the products by column chromatography resulted in a



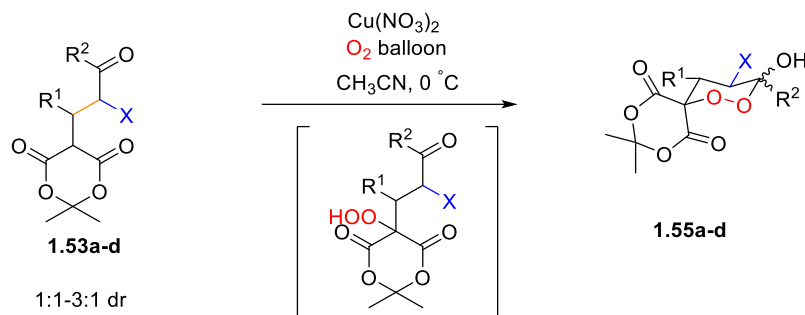
messier mixture due to a retro-Michael reaction of the product over silica gel. Due to these complications during isolation, we decided to use the mixture of two diastereomers for the next oxidation step without further purification.

**Scheme 1-15.** Preparation of Keto-Meldrum's Acids via Michael Reaction



With the keto-Meldrum's acids in hand, we subjected those compounds to the standard hydroperoxidation conditions of 25 mol % of  $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$  in acetonitrile under an oxygen balloon atmosphere. It is necessary that the reaction be set at 0 °C for 3-5 hours before slowly warming to room temperature, since retro-Michael and retro-Knoevenagel condensation were problematic when these reactions were run at room temperature.

**Table 1-5.** Synthesis of Endoperoxide Hemiketals



Entry	R <sup>1</sup>	R <sup>2</sup>	X	Results
1	p-MeOPh-	Me	CH <sub>3</sub> CO-	65%, 3:1 dr
2	p-MeOPh-	Me	-COOEt	85%, 5:1 dr
3	Ph-	Me	-COOEt	65%, 5:1 dr
4	<i>i</i> Pr-	Me	-COOEt	75% 3:1 dr

To our delight, under our hydroperoxidation conditions, hemiketal Meldrum's acids were formed with high efficacy (Table 1-5). Gratifyingly, when X= CH<sub>3</sub>CO or CO<sub>2</sub>Et, the hydroperoxidation reaction provided good to excellent yields of a mixture of only two diastereomers of hemiketal endoperoxides (entries 1-4, Table 1-5).

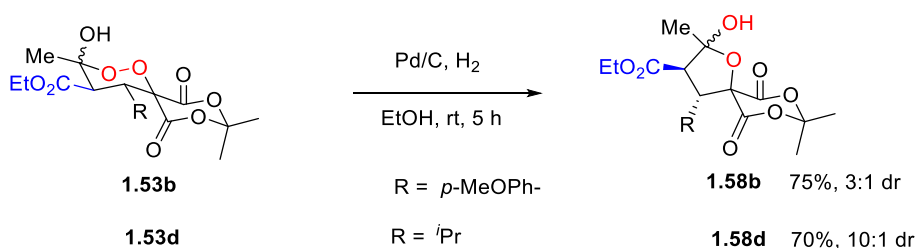
The formation of only two diastereomers in these reactions provided evidence for the existence of DTR conditions, whereas a mixture of four diastereomers would be expected otherwise. The R<sup>1</sup> group did not have strong influence to the outcome of these reactions. Both aryl (Table 1-5, entries 1-3) and isopropyl (Table 1-5, entries 2-6) groups provided a mixture of two diastereomers, with the anticipated moderate diastereoselectivity due to a non-diastereoselective hydroperoxide cyclization.

These promising results have prompted us to explore further functionalization of the hemiketal Meldrum's acids based on our previous established chemistry (Scheme 1-16).

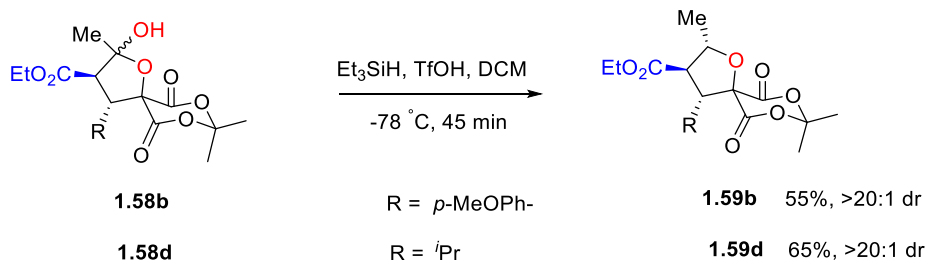
Illustrative secondary transformation were then pursued. Exposure of hemiketal Meldrum's acids **1.53b,d** with R = *p*-methoxyphenyl and isopropyl, to a hydrogenolysis condition with Pd/C under a hydrogen balloon in ethanol provided the corresponding hemiketal tetrahydrofuran derivatives **1.58b,d** in good yields (70-75% yield) and moderate dr (Scheme 1-16a). The hemiketal **1.58b** and **1.58d** were then subjected to the established ionic hydrogenation with triflic acid and triethylsilane in acetonitrile at -78 °C for 45 min. To our delight, the fully substituted tetrahydrofuran **1.59b** and **1.59d** were isolated as a single diastereomer with a promising 55% and 65% corresponding yield. This preliminary result provides an experimental proof for our DTR hypothesis and will open opportunities to extend this promising chemistry.

**Scheme 1-16.** Synthesis of Fully Substituted Tetrahydrofurans

a. Synthesis of hemiketal tetrahydrofuran derivatives

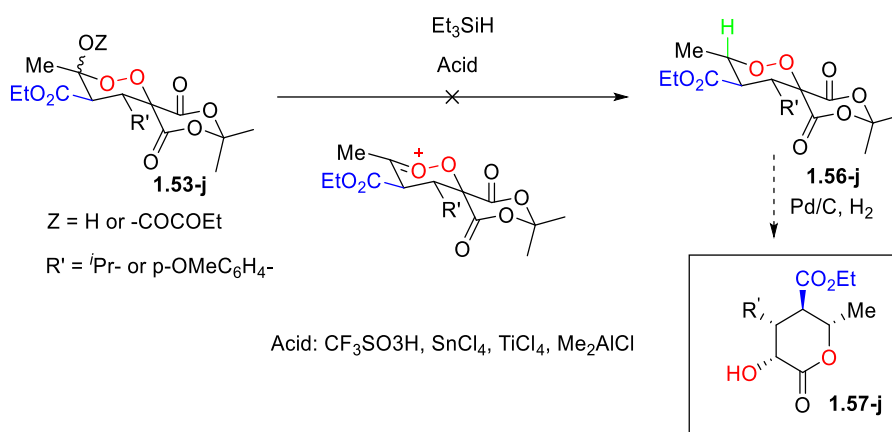


b. Stereoselective synthesis of fully substituted tetrahydrofuran



With the hypothesis experimentally confirmed, we shifted our focus to developing suitable conditions for the diastereoselective ionic hydrogenation for the hemiketal Meldrum's acids **1.53-j** which could pave the way to access fully-substituted endoperoxides **1.56-j** and lactones **1.57-j** (Scheme 1-17).

**Scheme 1-17.** Attempts to The Synthesis of Fully-Substituted Endoperoxide



However, several attempts to reduce the hemiketal endoperoxides **1.53-j** to endoperoxides **1.56-j** were unsuccessful (Scheme 1-17). In this case, the established ionic hydrogenation condition failed to provide the desired endoperoxide. No reaction was observed when the reaction was cooled down to -78 °C, and reaction was messy when slowly warmed up to -20 °C. Having an additional electron withdrawing group in the position of CO<sub>2</sub>Et seems to reduce the reactivity of the ketal to the ionic reduction. We tried to incorporate an oxalate ester in a hope to provide a better leaving group than the hydroxide due to a double-coordination activation with a Lewis acid catalyst. However, a messy reaction with low conversion was generally observed, with no formation of the desired endoperoxide product.

Current efforts in our group will continue to develop suitable conditions for the reduction of these hemiketal endoperoxides and try to develop a broader scope of the hydroperoxidation-cyclization cascade.

#### **1.4 Conclusion**

We have developed a simple, mild and efficient catalytic method for the hydroperoxidation of Meldrum's acid derivatives including those with unsaturation. The hydroperoxide products can be used for intramolecular oxidation via electrophilic activation of the pendant alkyne and alkene functionality. Au(I)-catalyzed endoperoxidations of hydroperoxyalkynes have been reported for the first time. Reductive cleavage of the O–O bond yields 1,*n*-diol functionality with convenient differentiation of the alcohols via lactonization, thereby providing the conceptual blueprint for the development of atom-efficient O<sub>2</sub>/H<sub>2</sub> dihydroxylations. Current efforts in our laboratory are focused on expanding this methodology to a new approaches with select Meldrum's acid derivatives to provide a stereoselective approach to fully-substituted endoperoxides and 1,*n*-diols. This chemistry also provides a method for stereoselective synthesis of highly-substituted tetrahydrofuran derivatives.

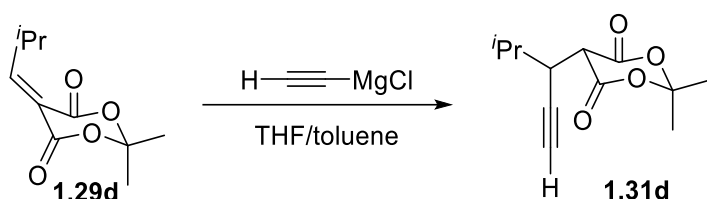
## 1.5 Experimental Details

**Methods: General. Methods.** Infrared (IR) spectra were obtained using a Jasco 260 Plus Fourier transform infrared spectrometer. Proton and carbon nuclear magnetic resonance spectra ( $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR) were recorded on a Bruker DRX 400 or 600 ( $^1\text{H}$  NMR at 400 MHz or 600 MHz and  $^{13}\text{C}$  NMR at 100 or 150 MHz) spectrometer with solvent resonance as the internal standard ( $^1\text{H}$  NMR:  $\text{CDCl}_3$  at 7.26 ppm.  $^{13}\text{C}$  NMR:  $\text{CDCl}_3$  at 77.0 ppm).  $^1\text{H}$  NMR data are reported as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, d = doublet, dd = doublet of doublet, ddd = doublet of doublet of doublets, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. Melting point data was collected on a Thomas Hoover Capillary Melting Point Apparatus and are uncorrected. Thermogravimetric data was collected on a PerkinElmer Pyris 1 Thermogravimetric Analyzer (25 °C initial temperature, 20 °C/min ramp rate, Purge gas:  $\text{N}_2$  at 20 mL/min). Analytical thin layer chromatography (TLC) was performed on Sorbent Technologies Silica G 0.20 mm silica gel plates. Visualization was accomplished with UV light, aqueous basic potassium permanganate solution, or aqueous ceric ammonium molybdate solution followed by heating. Flash chromatography was performed using Silia-P flash silica gel (40-63  $\mu\text{m}$ ) purchased from Silicycle. Yield refers to isolated yield of analytically pure material unless otherwise noted. Yields and diastereomeric ratios (dr) are reported for a specific experiment and as a result may differ slightly from those found in the tables, which are averages of at least two experiments.

**Materials.** Copper(II) nitrate trihydrate, acetonitrile, and thiourea were purchased from Fisher and used as received. Methylmagnesium bromide, vinylmagnesium bromide, ethylmagnesium bromide and ethynylmagnesium chloride were purchased from Sigma Aldrich and used as

received. Dichloromethane, diethyl ether and tetrahydrofuran were passed through a column of neutral alumina under nitrogen prior to use. The following reagents were prepared by literature procedures: 1,3-diiodo-5,5-dimethylhydantoin,<sup>31a</sup> Meldrum's acid<sup>31b</sup>, isopropylidene Meldrum's acid **1.29d**,<sup>32</sup> 3-methylbutylidene Meldrum's acid **1.29j**,<sup>33</sup> *N,N'*-dimethylbarbituric acid **S**,<sup>34</sup> isopropyl Meldrum's acid **1.25**,<sup>35</sup> ethyl Meldrum's acid **1.32b**,<sup>36a</sup> 1-phenethyl Meldrum's acid **1.31c**,<sup>20c</sup> 2,2-dimethyl-5-(2-methylhex-4-yn-3-yl)-1,3-dioxane-4,6-dione **1.31e**,<sup>20d</sup> Ethyl 4-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-5-methylhex-2-ynoate **1.31g**,<sup>20g</sup> arylidene Meldrum's acid **1.30a,c**<sup>36b</sup>

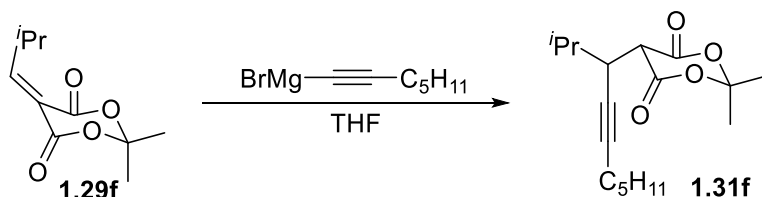
#### Preparation of 2,2-dimethyl-5-(4-methylpent-1-yn-3-yl)-1,3-dioxane-4,6-dione (**1.31d**)



To a flame-dried 150-mL round bottomed flask was added a 0.6 M solution of ethynylmagnesium chloride in THF/toluene (6.0 mmol, 2.0 equiv) under N<sub>2</sub>. A solution of alkylidene Meldrum's acid **1.29d** (594 mg, 3.0 mmol) in dry THF (12 mL) was added over 10 min. The reaction was stirred at rt overnight then was quenched with 1 M citric acid (20 mL) and extracted with Et<sub>2</sub>O (2 x 50 mL). The combined organic extracts were washed with brine (15 mL), dried (MgSO<sub>4</sub>) and concentrated. Flash chromatography with gradient elution (20-30% EtOAc/hexanes) afforded **1.31d** (403 mg, 1.8 mmol, 60% yield) as a white solid. Analytical data for **5d**: mp 92-93 °C; IR (thin film, cm<sup>-1</sup>) 3276, 2970, 2369, 1744, 1473, 1387, 1336, 1307, 1209, 1079, 996; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.67 (d, *J* = 2.6 Hz, 1H), 3.09-3.06 (ddd, *J* = 2.4, 2.6, 10.5 Hz, 1H), 2.48-2.41 (doublet of septets, *J* = 6.6, 10.5 Hz, 1H), 2.18 (d, *J* = 2.4 Hz, 1H), 1.79 (s, 3 H), 1.77 (s, 3H), 1.17 (d, *J* = 6.6 Hz, 3H), 0.98 (d, *J* = 6.6 Hz,

3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  165.1, 163.5, 105.3, 82.4, 72.1, 47.5, 39.4, 29.9, 28.5, 27.8, 21.8, 20.2; **TLC** (30% EtOAc/hexanes)  $R_f$  = 0.35. **HRMS** (ESI) Calcd. for  $\text{C}_{12}\text{H}_{17}\text{O}_4$ : 225.1127, Found: 225.1121.

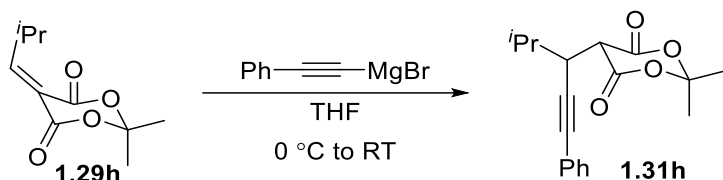
**Preparation of 2,2-dimethyl-5-(2-methyldec-4-yn-3-yl)-1,3-dioxane-4,6-dione (1.31f)**



To a flame-dried 150-mL round bottomed flask containing 1-heptyne (6.0 mmol, 3.0 equiv) in THF (12 mL) was added a 3.0 M solution of methylmagnesium bromide in THF (4.4 mmol, 2.2 equiv) under  $\text{N}_2$ . The reaction was then stirred at rt for 2 h. A solution of alkylidene Meldrum's acid **1.29f** (396 mg, 2.0 mmol) in dry THF (20 mL) was then added over 10 min and the reaction was stirred at rt overnight. The reaction was quenched with 1 M citric acid (20 mL) and extracted with  $\text{Et}_2\text{O}$  (2 x 50 mL). The combined organic extracts were washed with brine (15 mL), dried ( $\text{MgSO}_4$ ) and concentrated. Flash chromatography with gradient elution (20-30% EtOAc/hexanes) afforded **1.31f** (529 mg, 1.8 mmol, 90% yield) as a white solid. Analytical data for **1.31f**: mp 52-53 °C; **IR** (thin film,  $\text{cm}^{-1}$ ) 2961, 2871, 2235, 1785, 1750, 1394, 1335, 1294, 1207, 1075;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.61 (d,  $J$  = 2.9 Hz, 1H), 3.02-2.98 (ddd,  $J$  = 2.3, 2.9, 10.6 Hz, 1H), 2.41-2.37 (doublet of septets,  $J$  = 6.7, 10.6 Hz, 1H), 2.14-2.09 (ddd,  $J$  = 2.3, 6.7, 6.7 Hz, 2H), 1.79 (s, 3H), 1.75 (s, 3H), 1.47-1.41 (m, 2 H), 1.34-1.26 (m, 4H), 1.13 (d,  $J$  = 6.7 Hz, 3H), 0.99 (d,  $J$  = 6.7 Hz, 3H), 0.88 (t,  $J$  = 7.0 Hz, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  166.1, 164.0, 105.1, 84.6, 78.1, 47.7, 40.6, 30.9, 30.4, 28.5, 28.4, 28.1, 22.1, 21.8, 20.3, 18.6, 14.0; **TLC** (20% EtOAc/hexanes)  $R_f$  = 0.30. **HRMS** (ESI) Calcd. for  $\text{C}_{17}\text{H}_{27}\text{O}_4$ : 295.1909, Found: 295.1908.

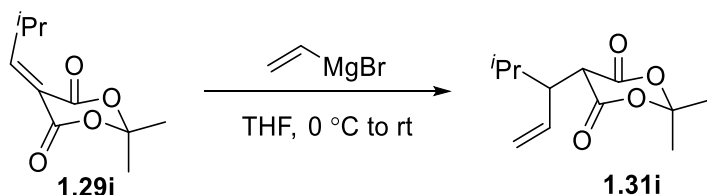


**Preparation of 2,2-dimethyl-5-(4-methyl-1-phenylpent-1-yn-3-yl)-1,3-dioxane-4,6-dione (1.31h)**



To a flame-dried 250-mL round bottomed flask containing phenylacetylene (2.37 g, 23.2 mmol, 2.00 equiv) and dry THF (25 mL) under  $\text{N}_2$  was added a 1.0 M solution of ethylmagnesium bromide in THF (23.2 mL, 23.2 mmol, 2.0 equiv) over 5 min. A solution of alkylidene Meldrum's acid **1.29h** (2.30 g, 11.6 mmol) in dry THF (20 mL) was added via syringe pump over 3 h. After the addition was completed, the reaction was allowed to warm to RT and was stirred for 3 h. The reaction was quenched with 1 M HCl (10 mL) and the resulting mixture was extracted with  $\text{Et}_2\text{O}$  (2 x 50 mL). The combined organic extracts were washed with brine (15 mL), dried ( $\text{MgSO}_4$ ) and concentrated. Flash chromatography (10%  $\text{EtOAc}$ /hexanes) afforded **1.31h** (3.02 g, 10.1 mmol, 87 % yield) as an off-white solid. Analytical data matched that previously reported.<sup>36</sup>

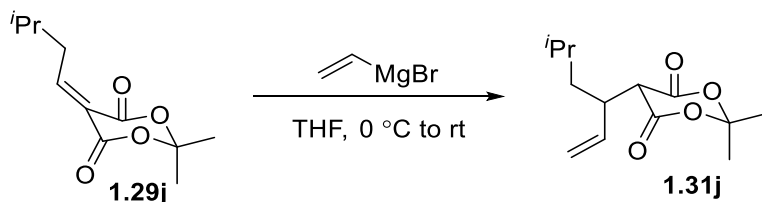
**Preparation of 2,2-dimethyl-5-(4-methylpent-1-en-3-yl)-1,3-dioxane-4,6-dione (1.31i)<sup>37</sup>**



To a flame-dried 250-mL round bottomed flask was added dry THF (50 mL) and 0.7 M vinylmagnesium bromide in THF (33.7 mmol, 1.5 equiv) under  $\text{N}_2$ . The resulting solution was cooled to 0 °C and a solution of alkylidene Meldrum's acid **1.29i** (4.45 g, 22.5 mmol) in dry THF (20 mL) was added via syringe pump (10 mL/h). After the addition was completed, the

reaction was allowed to warm to rt and was stirred for 1.5 h. The reaction was quenched with 1 M HCl (100 mL) and the resulting mixture was extracted with Et<sub>2</sub>O (3 x 150 mL). The combined organic extracts were washed with brine (50 mL), dried (MgSO<sub>4</sub>), and concentrated. Flash chromatography (15% EtOAc/hexanes) afforded **5i** (4.59 g, 20.3 mmol, 90 % yield) as an off-white solid. Analytical data for **1.31i**: mp 55-57 °C; IR (thin film, cm<sup>-1</sup>) 3081, 2963, 2873, 1782, 1748, 1385, 1292, 1207, 1006, 840; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.80-5.70 (m, 1H), 5.18-5.11 (m, 2H), 3.64 (d, *J* = 2.5 Hz, 1H), 2.74 (ddd, *J* = 2.5, 10.0, 10.0 Hz, 1H), 2.27-2.17 (doublet of septets, *J* = 6.7, 10.0 Hz, 1H), 1.72 (s, 3 H), 1.71 (s, 3 H), 0.97 (d, *J* = 6.7 Hz, 3H) 0.91 (d, *J* = 6.7 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 165.8, 164.6, 136.9, 119.4, 104.9, 51.7, 48.1, 28.5, 28.3, 27.8, 21.4, 20.6; TLC (25% EtOAc/hexanes) R<sub>f</sub> = 0.58. HRMS (ESI) Calcd. for C<sub>12</sub>H<sub>18</sub>O<sub>4</sub>Na: 249.1103, Found: 249.1098.

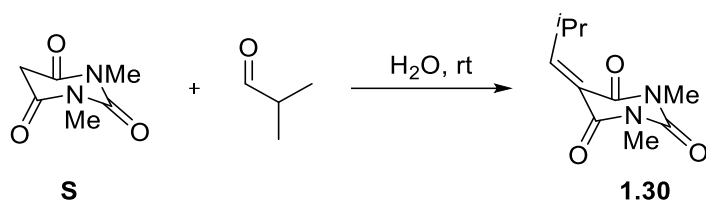
#### Preparation of 2,2-dimethyl-5-(5-methylhex-1-en-3-yl)-1,3-dioxane-4,6-dione (**1.31j**)



To a flame-dried 100-mL round bottomed flask was added a 1.0 M solution of vinylmagnesium bromide in THF (9.43 mmol, 2.0 equiv) under N<sub>2</sub>. The flask was cooled to 0 °C and a solution of alkylidene Meldrum's acid **1.29j** (1.00 g, 4.71 mmol) in dry THF (8 mL) was added over 5 min. After the addition was completed, the reaction was allowed to warm to rt and was stirred for 40 min. The reaction was quenched with 1M HCl (20 mL) and extracted with Et<sub>2</sub>O (2 x 50 mL). The combined organic extracts were washed with brine (15 mL), dried (MgSO<sub>4</sub>) and concentrated. Flash chromatography (5% EtOAc/hexanes) afforded **1.31j** (0.840 g, 3.50 mmol, 74% yield) as a white solid. Analytical data for **1.31j**: mp 62-64 °C; IR (thin film, cm<sup>-1</sup>) 2957,

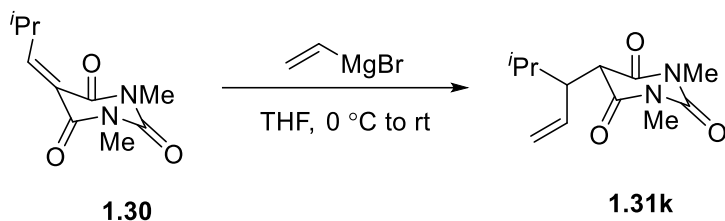
2871, 1783, 1748, 1385, 1295, 1205, 1007, 884; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 5.95-5.86 (ddd, *J* = 10.2, 10.2, 16.5 Hz, 1H), 5.21-5.16 (ddd, *J* = 0.7, 1.6, 16.5 Hz, 1H), 5.13-5.10 (dd, *J* = 1.6, 10.2 Hz, 1H), 3.49 (d *J* = 2.7 Hz, 1H), 3.26-3.19 (m, 1H), 1.83-1.77 (ddd, *J* = 4.8, 10.5, 13.4 Hz, 1H), 1.73 (s, 3H), 1.72 (s, 3H), 1.62-1.53 (s, 3H), 1.26-1.19 (ddd, *J* = 4.4, 9.1, 13.4 Hz, 1H), 0.90 (d, *J* = 6.5 Hz, 3H), 0.88 (d, *J* = 6.3 Hz, 3H); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 164.9, 164.5, 137.8, 118.3, 104.8, 51.1, 41.5, 40.5, 28.3, 27.4, 25.6, 23.4, 21.2; **TLC** (25% EtOAc/hexanes) *R*<sub>f</sub> = 0.39. **HRMS** (ESI) Calcd. for C<sub>13</sub>H<sub>20</sub>O<sub>4</sub>Na: 263.1260, Found: 263.1254.

**Preparation of 1,3-dimethyl-5-(2-methylpropylidene)pyrimidine-2,4,6(1H,3H,5H)-trione (1.30)**



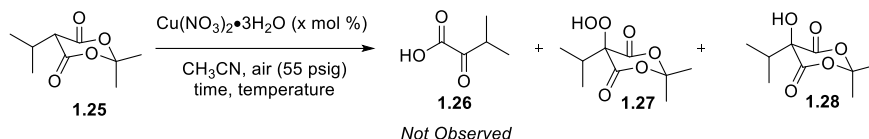
To a stirred mixture of *N,N'*-dimethylbarbituric acid **S** (0.50 g, 3.2 mmol) and H<sub>2</sub>O (30 mL) was added isobutyraldehyde (0.44 mL, 4.8 mmol, 1.5 equiv) at rt in a 100-mL round bottomed flask. After stirring for 18 h, the reaction was extracted with EtOAc (2 x 30 mL). The combined organic extracts were dried (MgSO<sub>4</sub>) and concentrated. Flash chromatography (5% EtOAc/hexanes) afforded **1.30** (393 mg, 1.87 mmol, 58%) as a white solid. Analytical data for **1.30**: mp 50-52 °C; **IR** (thin film, cm<sup>-1</sup>) 2965, 2871, 1737, 1672, 1620, 1378, 1094, 795; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.71 (d, *J* = 10.3 Hz, 1H), 3.98-3.89 (doublet of septets, *J* = 6.6, 10.3 Hz, 1H), 3.31 (s, 3H), 3.30 (s, 3H), 1.11 (d, *J* = 6.6 Hz, 6H); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 173.8, 161.7, 160.8, 151.3, 118.3, 29.1, 28.7, 28.0, 21.3; **TLC** (25% EtOAc/hexanes) *R*<sub>f</sub> = 0.58. **HRMS** (ESI) Calcd. for C<sub>10</sub>H<sub>15</sub>N<sub>2</sub>O<sub>3</sub>: 211.1082, Found: 211.1074.

**Preparation of 1,3-dimethyl-5-(4-methylpent-1-en-3-yl)pyrimidine-2,4,6(1H,3H,5H)-trione (1.31k)**



To a flame-dried 50-mL round bottomed flask was added a 1.0 M solution of vinylmagnesium bromide in THF (3.26 mmol, 2.0 equiv) under N<sub>2</sub>. The flask was cooled to 0 °C and a solution of alkyldene barbituric acid **1.30** (343 mg, 1.63 mmol) in dry THF (7 mL) was added over 5 min. After the addition was completed, the reaction was stirred for 30 min. The reaction was allowed to warm rt and was stirred for an additional 2 h. The reaction was quenched with 1M HCl (10 mL) and extracted with Et<sub>2</sub>O (2 x 30 mL). The combined organic extracts were washed with brine (15 mL), dried (MgSO<sub>4</sub>) and concentrated. Flash chromatography with gradient elution (5-10% EtOAc/hexanes) afforded **1.31k** (303 mg, 1.09 mmol, 67% yield) as a white solid. Analytical data for **1.31k**: mp 44-46 °C; IR (thin film, cm<sup>-1</sup>) 2963, 2360, 1681, 1455, 1377, 1288, 1000, 929; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.43-5.34 (m, 1H), 5.05-4.96 (m, 2H), 3.67 (d, *J* = 3.4 Hz, 1H), 3.22 (s, 3H), 3.20 (s, 3H), 2.44 (ddd, *J* = 3.4, 10.1, 10.1 Hz), 2.00-1.87 (doublet of septets, *J* = 6.6, 10.1 Hz, 1H), 1.08 (d, *J* = 6.6 Hz, 3 H), 0.83 (d, *J* = 6.6 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 169.2, 167.2, 151.7, 135.5, 119.2, 56.8, 51.2, 28.6, 28.2, 28.0, 20.9, 20.7; TLC (25% EtOAc/hexanes) R<sub>f</sub> = 0.42. HRMS (ESI) Calcd. for C<sub>12</sub>H<sub>19</sub>N<sub>2</sub>O<sub>3</sub>: 239.1395, Found: 239.1393.

**Optimization of hydroperoxidation conditions**

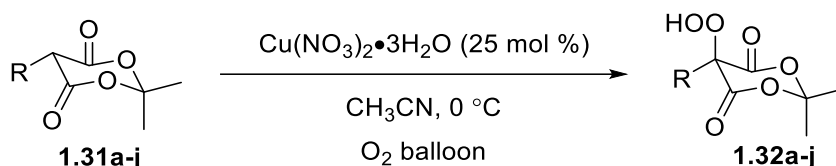


Entry	Catalyst Loading (mol %)	T (°C)	Time (h)	1.27:1.28 <sup>a</sup>
1	20	23	17	2:1
2	20	23	1	10:1
3	10	23	2	10:1 <sup>b</sup>
4	25	23	2	13:1
5	25	0	5	>20:1

<sup>a</sup> Ratio by <sup>1</sup>H NMR comparison of characteristic peaks;

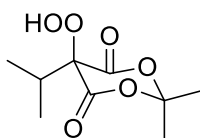
<sup>b</sup> Reaction did not go to completion;

### General Procedure A for hydroperoxidation of Meldrum's acid derivatives

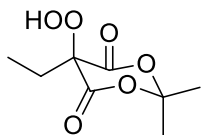


To a solid mixture of Meldrum's acid derivative **1.31a-j** and  $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$  at 0 °C in a round bottomed flask was added cold  $\text{CH}_3\text{CN}$  (0 °C). The flask was capped with a Teflon septum and charged with  $\text{O}_2$  in one of two ways. For small volume reactions (<0.5 mL) the headspace was purged with  $\text{O}_2$  (balloon) for 3-5 min. For larger volume reactions,  $\text{O}_2$  (balloon) was bubbled through the solvent for 5 min. When the starting material was consumed (TLC analysis) the reaction was partitioned between  $\text{H}_2\text{O}$  and EtOAc. The aqueous layer was separated and extracted a second time with EtOAc. The combined organic extracts were dried ( $\text{MgSO}_4$ ) and concentrated to afford hydroperoxy Meldrum's acid derivatives **1.32a-j** as white solids unless otherwise noted. [Note: The hydroperoxide products failed to provide the molecular ion during analysis by mass spectrometry. In addition to several derivatizations that verify the presence of the ROOH functionality, several hydroperoxides were reduced with  $\text{PPh}_3$

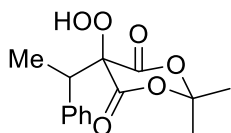
to provide the corresponding alcohols (*vide infra*). The ROOH functionality was inferred from these successful reductions.]



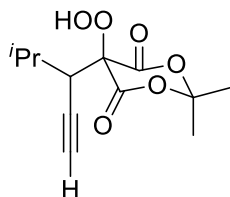
**Analytical data for 5-hydroperoxy-5-isopropyl-2,2-dimethyl-1,3-dioxane-4,6-dione (1.32a):** mp 73-75 °C; **IR** (thin film,  $\text{cm}^{-1}$ ) 3612, 3358, 2979, 2945, 2882, 1790, 1755, 1283, 912, 620;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.40 (s, 1H), 2.46-2.39 (septet,  $J = 6.9$  Hz, 1H), 1.81 (s, 3 H), 1.77 (s, 3H), 1.07 (d,  $J = 6.9$  Hz, 6H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  166.3, 107.0, 89.3, 36.8, 30.2, 27.7, 16.9; **TLC** (25% EtOAc/hexanes)  $R_f = 0.50$ .



**Analytical data for 5-ethyl-5-hydroperoxy-2,2-dimethyl-1,3-dioxane-4,6-dione (1.32b):** mp 91-93 °C; **IR** (thin film,  $\text{cm}^{-1}$ ) 3354, 3006, 2989, 2950, 1791, 1757, 1395, 1079, 914, 693;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.09 (s, 1H), 2.06 (q,  $J = 7.6$  Hz, 2H), 1.82 (s, 3H), 1.77 (s, 3H), 1.00 (t,  $J = 7.6$  Hz, 3H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  166.6, 107.1, 86.3, 30.5, 30.0, 28.0, 7.7; **TLC** (25% EtOAc/hexanes)  $R_f = 0.45$ .

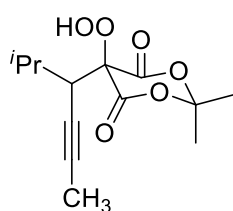


**Analytical data for 5-hydroperoxy-2,2-dimethyl-5-(1-phenylethyl)-1,3-dioxane-4,6-dione (1.32c):** mp 71-73 °C; **IR** (thin film,  $\text{cm}^{-1}$ ) 3362, 1746, 1383, 1294, 1201, 1135, 913, 701;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.52 (bs, 1H), 7.35-7.30 (m, 3H), 7.20-7.18 (m, 2H), 3.61 (q,  $J = 7.2$  Hz, 1H), 1.64 (s, 3H), 1.53 (d,  $J = 7.2$  Hz, 3H), 0.98 (s, 3H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  167.0, 164.7, 136.2, 128.8, 128.7, 128.4, 107.1, 88.6, 47.3, 30.2, 26.8, 14.1; **TLC** (25% EtOAc/hexanes)  $R_f = 0.53$ .



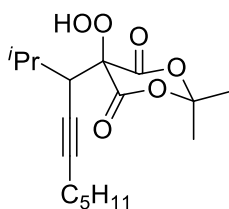
**Analytical data for 5-hydroperoxy-2,2-dimethyl-5-(4-methylpent-1-yn-3-yl)-1,3-dioxane-4,6-dione (1.32d):** mp 96-97 °C; **IR** (thin film,  $\text{cm}^{-1}$ ) 3419, 2970, 2360, 1748, 1647, 1383, 1338, 1286, 1299, 1120, 915;  **$^1\text{H}$**

**NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.11 (s, 1H), 3.09 (dd,  $J$  = 2.8, 3.5 Hz, 1H), 2.41 (d,  $J$  = 2.8, 1H), 2.19-2.11 (doublet of septets,  $J$  = 3.5, 6.6 Hz 1H), 1.81 (s, 3H), 1.80 (s, 3H), 1.06 (d,  $J$  = 6.6 Hz, 3H), 1.02 (d,  $J$  = 6.6 Hz, 3H); **<sup>13</sup>C NMR** (150 MHz, CDCl<sub>3</sub>)  $\delta$  165.3, 164.6, 107.5, 87.0, 76.4, 76.3, 46.1, 30.4, 27.8, 27.5, 23.3, 18.8; **TLC** (30% EtOAc/hexanes)  $R_f$  = 0.32.



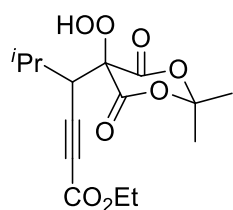
**Analytical data for 5-hydroperoxy-2,2-dimethyl-5-(2-methylhex-4-yn-3-yl)-1,3-dioxane-4,6-dione (7e):** mp 88-89 °C; **IR** (thin film, cm<sup>-1</sup>) 3377, 2970, 2875, 1786, 1744, 1394, 1339, 1286, 1265, 1124, 1022, 917;

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.38 (s, 1H), 3.03-3.01 (m, 1H), 2.16-2.11 (m, 1H), 1.85 (d,  $J$  = 2.5 Hz, 1H), 1.81 (s, 3H), 1.80 (s, 3H), 1.02 (d,  $J$  = 6.7 Hz, 3H), 0.97 (d,  $J$  = 6.6 Hz, 3H); **<sup>13</sup>C NMR** (150 MHz, CDCl<sub>3</sub>)  $\delta$  166.1, 164.9, 107.4, 87.5, 84.2, 71.4, 46.7, 30.3, 27.8, 27.7, 23.4, 19.3, 3.7; **TLC** (30% EtOAc/hexanes)  $R_f$  = 0.34.



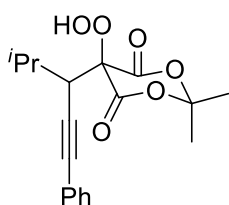
**Analytical data for 5-hydroperoxy-2,2-dimethyl-5-(2-methyldec-4-yn-3-yl)-1,3-dioxane-4,6-dione (1.32f):** mp 70-71 °C; **IR** (thin film, cm<sup>-1</sup>) 3366, 2960, 2933, 2872, 2360, 1791, 1749, 1394, 1264, 1200, 1123, 916;

**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>)  $\delta$  9.44 (s, 1H), 3.05 (m, 1H), 2.21-2.10 (m, 2H), 2.14 (m, 1H), 1.80 (s, 3H), 1.79 (s, 3H), 1.52-1.49 (m, 2 H), 1.35-1.26 (m, 4H), 1.03 (d,  $J$  = 6.6 Hz, 3H), 0.97 (d,  $J$  = 6.0 Hz, 3H), 0.88 (t,  $J$  = 6.6 Hz, 3H); **<sup>13</sup>C NMR** (150 MHz, CDCl<sub>3</sub>)  $\delta$  165.7, 164.7, 107.1, 88.9, 87.7, 72.2, 46.7, 31.0, 30.4, 28.2, 27.8, 27.7, 23.4, 22.1, 19.2, 18.8, 13.9; **TLC** (30% EtOAc/hexanes)  $R_f$  = 0.43.

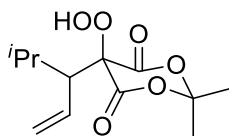


**Analytical data for ethyl 4-(5-hydroperoxy-2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-5-methylhex-2-ynoate (1.32g):** Clear, colorless oil; **IR** (thin film, cm<sup>-1</sup>) 3346, 2972, 2877, 2240, 1792, 1759, 1714, 1467, 1395, 1253, 917; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.87 (bs, 1 H), 4.23 (q,  $J$  = 7.1

Hz, 2H), 3.20 (d,  $J = 4.0$  Hz, 1H), 2.23-2.18 (doublet of septets,  $J = 4.0, 6.7$  Hz, 1H), 1.85 (s, 3H), 1.82 (s, 3H), 1.30 (t,  $J = 7.1$  Hz, 3H), 1.08 (d,  $J = 6.7$  Hz, 3H), 1.03 (d,  $J = 6.7$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  165.1, 164.4, 152.9, 107.9, 85.8, 80.1, 79.6, 62.3, 45.9, 30.2, 27.7, 27.6, 23.3, 19.2, 13.9; **TLC** (25% EtOAc/hexanes)  $R_f = 0.45$ .

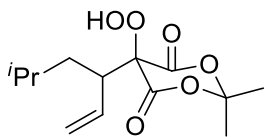


**Analytical data for 5-hydroperoxy-2,2-dimethyl-5-(4-methyl-1-phenylpent-1-yn-3-yl)-1,3-dioxane-4,6-dione (7h):** mp 75-77 °C; **IR** (thin film,  $\text{cm}^{-1}$ ) 3357, 2967, 1791, 1749, 1349, 1270, 1200, 1120, 916;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.69 (bs, 1H), 7.45-7.42 (m, 2 H), 7.33-7.28 (m, 3H), 3.29 (d,  $J = 4.0$  Hz, 1H), 2.31-2.23 (doublet of septets,  $J = 4.0, 6.7$  Hz, 1H), 1.79 (s, 3H), 1.70 (s, 3H), 1.10 (d,  $J = 6.7$  Hz, 3H), 1.07 (d,  $J = 6.7$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  165.7, 164.7, 131.8, 128.7, 128.3, 122.2, 107.5, 88.3, 87.4, 81.8, 47.1, 30.4, 27.9, 27.7, 23.5, 19.4; **TLC** (25% EtOAc/hexanes)  $R_f = 0.53$ .



**Analytical data for 5-hydroperoxy-2,2-dimethyl-5-(4-methylpent-1-en-3-yl)-1,3-dioxane-4,6-dione (1.32i):** mp 74-75 °C; **IR** (thin film,  $\text{cm}^{-1}$ ) 3408, 2966, 1784, 1740, 1385, 1296, 1150, 916;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.57 (bs, 1H), 5.72-5.62 (ddd,  $J = 10.2, 10.2, 16.9$  Hz, 1H), 5.29 (dd,  $J = 1.2, 10.2$  Hz, 1H), 5.13 (dd,  $J = 1.2, 16.9$  Hz, 1H), 2.56 (dd,  $J = 3.5, 10.4$  Hz, 1H), 2.10-2.03 (doublet of septets,  $J = 3.5, 6.8$  Hz, 1H), 1.78 (s, 3H), 1.77 (s, 3H), 0.93 (d,  $J = 6.8$  Hz, 3H), 0.84 (d,  $J = 6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  165.7, 165.6, 129.9, 122.0, 107.1, 89.0, 57.7, 30.3, 27.8, 27.3, 23.0, 18.4; **TLC** (25% EtOAc/hexanes)  $R_f = 0.32$ . The hydroperoxide was purified by flash chromatography on  $\text{SiO}_2$  (10% EtOAc/hexanes) to afford a 10:1 mixture of hydroperoxide and alcohol.

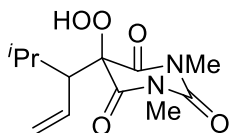




**Analytical data for 5-hydroperoxy-2,2-dimethyl-5-(5-methylhex-1-**

**en-3-yl)-1,3-dioxane-4,6-dione (1.32j):** mp 62-65 °C; **IR** (thin film,  $\text{cm}^{-1}$ ) 3357, 2958, 2871, 1791, 1749, 1287, 1096, 913;  **$^1\text{H}$  NMR** (400

MHz,  $\text{CDCl}_3$ )  $\delta$  9.49 (bs, 1H), 5.50-5.40 (m, 1H), 5.28-5.18 (m, 2H), 2.84 (ddd,  $J = 4.0, 10.0, 10.0$  Hz, 1H), 1.79 (s, 3H), 1.74 (s, 3H), 1.53-1.45 (m, 1H), 1.41-1.29 (m, 2H), 0.89 (d,  $J = 6.6$  Hz, 3H), 0.79 (d,  $J = 6.6$  Hz, 3H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  166.0, 165.3, 132.8, 121.4, 107.1, 88.3, 49.9, 36.6, 30.4, 27.8, 24.8, 23.8, 20.4; **TLC** (25% EtOAc/hexanes)  $R_f = 0.47$ . The hydroperoxide was purified by flash chromatography on  $\text{SiO}_2$  (10% EtOAc/hexanes) to afford a 17:1 mixture of hydroperoxide and alcohol.



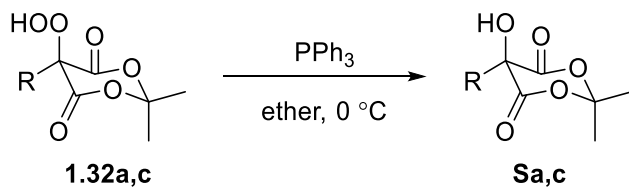
**Analytical data for 5-hydroperoxy-1,3-dimethyl-5-(4-methylpent-1-**

**en-3-yl)pyrimidine-2,4,6(1H,3H,5H)-trione (1.32k):** mp 104-105 °C;

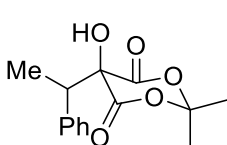
**IR** (thin film,  $\text{cm}^{-1}$ ) 3404, 2963, 1684, 1447, 1377, 1051;  **$^1\text{H}$  NMR** (400

MHz,  $\text{CDCl}_3$ )  $\delta$  10.21 (bs, 1H), 5.51 (ddd,  $J = 10.4, 16.8, 16.8$  Hz 1H), 5.19 (dd,  $J = 1.2, 10.4$  Hz, 1H), 5.05 (dd,  $J = 0.9, 16.8$  Hz, 1H), 3.33 (s, 3H) 3.26 (s, 3H), 2.46 (dd,  $J = 3.9, 10.4$  Hz, 1H), 2.03-1.96 (doublet of septet,  $J = 3.9, 6.7$  Hz, 1H), 0.89 (d,  $J = 6.7$  Hz, 3H), 0.72 (d,  $J = 6.7$  Hz, 3H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  168.1, 167.5, 150.6, 130.1, 121.7, 89.4, 58.1, 29.0, 28.7, 26.9, 22.9, 18.9; **TLC** (25% EtOAc/hexanes)  $R_f = 0.23$ . The hydroperoxide was purified by flash chromatography on  $\text{SiO}_2$  (5-15% EtOAc/hexanes).

#### General Procedure B for reduction of Meldrum's acid hydroperoxides to alcohols

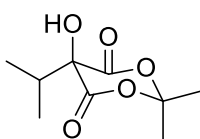


To a solution of hydroperoxide in dry Et<sub>2</sub>O (0.1M) at 0 °C under N<sub>2</sub> atmosphere was added triphenylphosphine (1.0 equiv). After 3 h the reaction was concentrated and flash chromatography on SiO<sub>2</sub> (5-15% EtOAc/hexanes) provided the alcohol product as a white solid.



**Analytical data for 5-hydroxy-2,2-dimethyl-5-(1-phenylethyl)-1,3-dioxane-4,6-dione (Sc):** 61% yield; mp 97-99 °C; IR (thin film, cm<sup>-1</sup>)

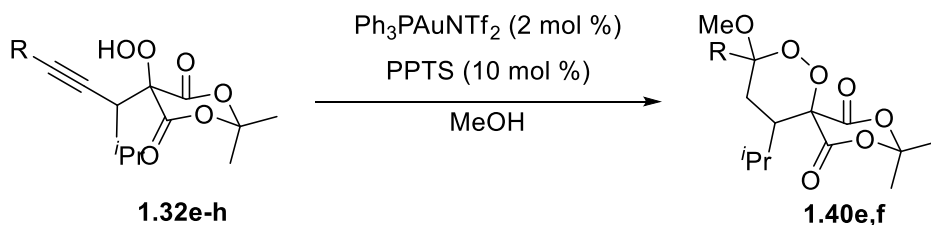
3455, 3000, 1784, 1748, 1384, 1292, 1201, 1139, 908; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.34-7.32 (m, 3H), 7.22-7.20 (m, 2H), 3.46 (q, *J* = 7.2 Hz, 1H), 3.26 (s, 1H), 1.67 (s, 3H), 1.52 (d, *J* = 7.2 Hz, 3H), 1.42 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 167.9, 166.8, 137.0, 128.7, 128.6, 128.2, 106.9, 78.3, 50.1, 30.6, 26.7, 14.2; TLC (25% EtOAc/hexanes) R<sub>f</sub> = 0.35. HRMS (ESI) Calcd. for C<sub>14</sub>H<sub>16</sub>O<sub>5</sub>Na: 287.0896, Found: 287.0894.



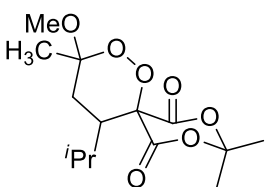
**Analytical data for 5-hydroxy-5-isopropyl-2,2-dimethyl-1,3-dioxane-4,6-dione (Sa):** 89% yield; mp 75-76 °C; IR (thin film, cm<sup>-1</sup>) 3453, 2981,

2945, 1785, 1747, 1466, 1309, 1161, 1089, 1053, 913; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.36 (bs, 1H), 2.26 (septet, *J* = 6.8 Hz, 1H), 1.75 (s, 3 H), 1.71, (s, 3H), 1.01 (d, *J* = 6.8 Hz, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 167.9, 106.8, 78.3, 38.8, 30.6, 27.2, 16.4; TLC (25% EtOAc/hexanes) R<sub>f</sub> = 0.24.

**General Procedure C for gold(I)-catalyzed endoperoxidation of Meldrum's acid hydroperoxides (1.40e,f)**

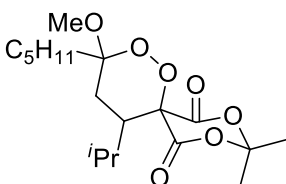


A mixture of the hydroperoxide **1.32d-f,h**, Ph<sub>3</sub>PAuNTf<sub>2</sub> (2 mol %), and PTSA (10 mol %) in methanol (~0.3-1.0 M) was stirred under nitrogen atmosphere at room temperature. After completion of the reaction (TLC analysis), the mixture was filtered through a short pad of Celite (CH<sub>2</sub>Cl<sub>2</sub>), and the solvents were evaporated under reduced pressure to give the crude mixed acetal endoperoxides **1.40e,f**. Flash chromatography (30% EtOAc/hexanes) afforded **1.40e,f** as a mixture of diastereomers.



**Analytical data for 5-isopropyl-3-methoxy-3,9,9-trimethyl-1,2,8,10-tetraoxaspiro[5.5]undecane-7,11-dione (1.40e):** mp 94-95 °C; IR (thin film, cm<sup>-1</sup>) 2964, 2878, 1787, 1753, 1295, 1240, 1202, 1102, 1085,

928; <sup>1</sup>H NMR of major diastereomer (400 MHz, CDCl<sub>3</sub>) δ 3.33 (s, 3H), 2.89-2.83 (ddd, *J* = 5.8, 9.1, 12.1 Hz, 1H), 2.21-2.14 (dd, *J* = 12.1, 13.4 Hz, 1H), 2.10-2.05 (dd, *J* = 5.8, 13.4 Hz, 1H), 1.95 (s, 3H), 1.76 (s, 3H), 1.64-1.58 (doublet of septets, *J* = 6.6, 9.1 Hz, 1H), 1.33 (s, 3H), 0.99 (d, *J* = 6.6 Hz, 3H), 0.80 (d, *J* = 6.6 Hz, 3H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 162.5, 161.6, 161.1, 106.9, 106.7, 102.8, 79.4, 49.8, 49.2, 43.4, 38.5, 34.2, 33.3, 29.6, 29.4, 28.7, 28.6, 28.2, 21.5, 21.1, 20.9, 20.5, 20.4; TLC (10% EtOAc/hexanes) R<sub>f1</sub>(major) = 0.26, R<sub>f2</sub> (minor) = 0.30.



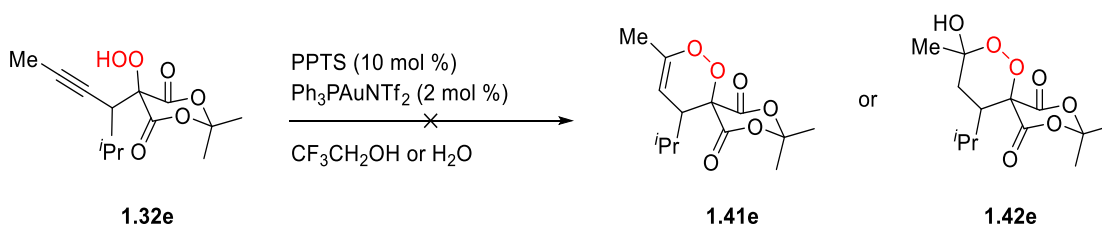
**Analytical data for 5-isopropyl-3-methoxy-9,9-dimethyl-3-pentyl-1,2,8,10-tetraoxaspiro[5.5]undecane-7,11-dione (1.40f):** mp 63-64°C; IR (thin film, cm<sup>-1</sup>) 2957, 2873, 1788, 1756, 1464, 1394, 1290,

1203, 1085, 925; <sup>1</sup>H NMR of major diastereomer (600 MHz, CDCl<sub>3</sub>) δ 3.26 (s, 1H), 2.82-2.80 (m, 1H), 2.09-2.05 (t, *J* = 13.2 Hz, 1H), 2.04-2.00 (dd, *J* = 6.0, 13.2 Hz, 1H), 1.95 (s, 3H), 1.76 (s, 3H), 1.66-1.59 (m, 1H), 1.41-1.29 (m, 8H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.90 (t, *J* = 7.2 Hz,

3H), 0.80-0.79 (d,  $J = 6.6$  Hz, 3H);  $^1\text{H}$  NMR of minor diastereomer (600MHz,  $\text{CDCl}_3$ )  $\delta$  3.31 (s, 1H), 2.50-2.60 (m, 1H), 2.30-2.10 (m, 2H), 1.88 (s, 3H), 1.75 (s, 3H), 1.66-1.59 (m, 1H), 1.41-1.29 (m, 8H), 1.0 (d,  $J = 6.0$  Hz, 3H), 0.90 (t,  $J = 7.2$  Hz, 3H), 0.80-0.79 (d,  $J = 6.6$  Hz, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  162.5, 161.1, 106.8, 106.6, 104.3, 79.7, 49.5, 48.7, 43.4, 38.3, 32.3, 31.9, 31.9, 31.8, 30.0, 29.5, 28.7, 28.6, 28.2, 22.5, 22.4, 22.3, 22.1, 21.5, 21.1, 20.8, 20.5, 14.0, 13.9; TLC (10% EtOAc/hexanes)  $R_{f1} = 0.32$ ,  $R_{f2} = 0.34$ . HRMS (ESI) Calcd. for  $\text{C}_{18}\text{H}_{20}\text{O}_7\text{Na}$ : 381.1889, Found: 381.1890.

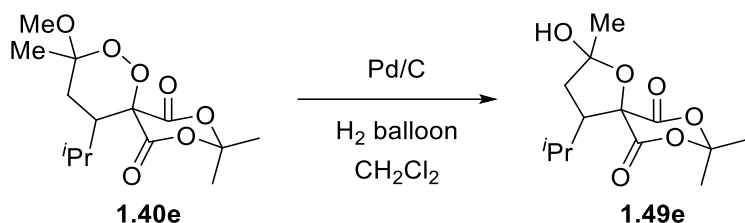
### Control Experiments for gold(I)-catalyzed endoperoxidation of Meldrum's acid

#### hydroperoxides



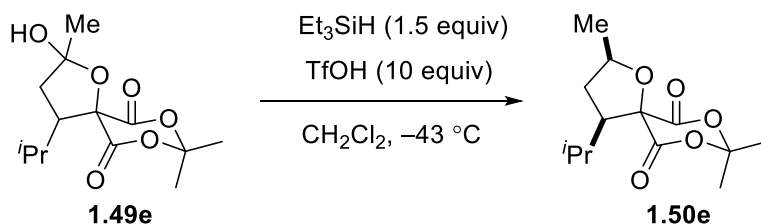
A mixture of the hydroperoxide **1.32e**,  $\text{Ph}_3\text{PAuNTf}_2$  (2 mol %), and PTSA (10 mol %) in trifluoroethanol or water (~0.3-1.0 M) was stirred under nitrogen atmosphere at room temperature overnight. The mixture was then filtered through a short pad of Celite, extracted with dichloromethane (when the reaction was run in water) and the solvents were evaporated under reduced pressure. Only starting material was recovered from the reaction.

### Preparation of 2-hydroxy-4-isopropyl-2,8,8-trimethyl-1,7,9-trioxaspiro[4.5]decane-6,10-dione (**11**) by palladium-catalyzed hydrogenolysis



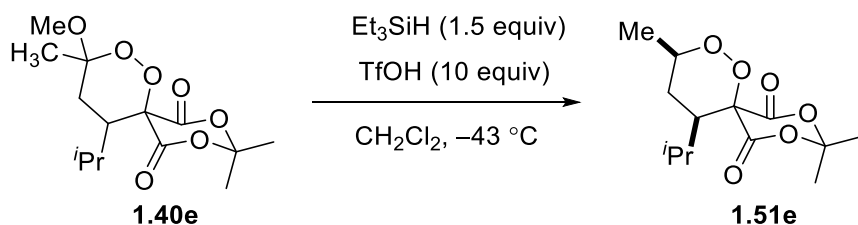
To a solution of mixed acetal endoperoxide **1.40e** (131 mg, 0.43 mmol) in dichloromethane (2 mL) was added 10% Pd/C (44 mg, 100mg/mmol). The reaction was then stirred under H<sub>2</sub> (balloon) atmosphere at room temperature for 30 minutes. The mixture was filtered through a short pad of Celite (CH<sub>2</sub>Cl<sub>2</sub>), and the solvents were evaporated under reduced pressure. Flash chromatography (30% EtOAc/hexane) afforded **1.49e** (104 mg, 0.38 mmol, 88 %) as a 3:1 mixture of diastereomers. Analytical data for **1.49e**: mp 108-109 °C; **IR** (thin film, cm<sup>-1</sup>) 3525, 2965, 2876, 1784, 1751, 1394, 1309, 1289, 1201, 1073, 916; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>, major diastereomer) δ 3.16-3.10 (m, 2H), 2.33-2.22 (m, 3H), 1.82 (s, 3H), 1.76 (s, 3H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.4 Hz, 3H); characteristic peaks of minor diastereomer: δ 3.70-3.56 (m, 1H), 2.96-2.88 (m, 1H), 2.57-2.51 (dd, *J* = 8.0, 13.2 Hz, 1H), 1.86 (s, 3H), 1.77 (s, 3H); **<sup>13</sup>C NMR** (150 MHz, CDCl<sub>3</sub>) δ 170.5, 168.1, 166.8, 110.7, 109.4, 106.3, 106.1, 81.8, 81.3, 58.8, 58.5, 45.4, 44.0, 30.2, 28.9, 28.6, 27.4, 27.2, 27.2, 26.3, 22.3, 22.2, 21.7, 21.3; **TLC** (30% EtOAc/hexanes) R<sub>f</sub> = 0.35. **HRMS** (ESI) Calcd. for C<sub>13</sub>H<sub>20</sub>O<sub>6</sub>Na: 295.1158, Found: 295.1164.

**Preparation of 4-isopropyl-2,8,8-trimethyl-1,7,9-trioxaspiro[4.5]decane-6,10-dione (1.50e) by ionic hydrogenation**



To a solution hemiacetal **1.49e** (68 mg, 0.25 mmol) and triethylsilane (43.5 mg, 0.375 mmol, 1.5 equiv) in dichloromethane (2 mL) at -43 °C was slowly added triflic acid (~10 equiv). The reaction was maintained at -43 °C and monitored (TLC analysis) until the starting material was consumed. The reaction was quenched with water and extracted with dichloromethane (2 x 15 mL). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. Flash chromatography (10% EtOAc/hexanes) afforded **12** (58 mg, 0.23 mmol, 90%). Analytical data for **1.50e**: mp 108-109 °C; IR (thin film, cm<sup>-1</sup>) 2973, 2911, 1785, 1750, 1396, 1302, 1207, 1110, 1069, 1001, 918; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.53-4.48 (m, 1H), 2.98-2.90 (ddd, *J* = 6.4, 10.9, 12.7 Hz, 1H), 2.32-2.25 (m, 1H), 2.04-1.91 (m, 1H), 1.87-1.75 (m, 1H), 1.85 (s, 3H), 1.74 (s, 3H), 1.32 (d, *J* = 6.1 Hz, 3H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.83 (d, *J* = 6.6 Hz); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 169.9, 167.6, 105.7, 80.9, 80.4, 60.0, 39.6, 29.9, 28.5, 27.5, 22.4, 21.7, 20.4; TLC (10% EtOAc/hexanes) R<sub>f</sub> = 0.32. HRMS (ESI) Calcd. for C<sub>13</sub>H<sub>20</sub>O<sub>5</sub>Na: 279.1209, Found: 279.1205.

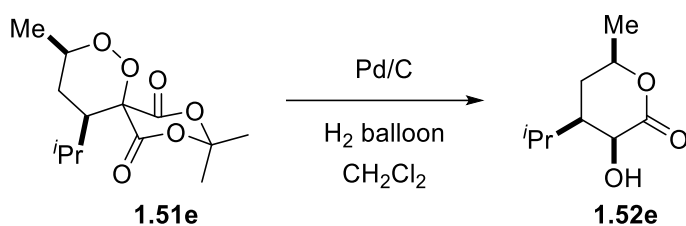
**Preparation of 5-isopropyl-3,9,9-trimethyl-1,2,8,10-tetraoxaspiro[5.5]undecane-7,11-dione (1.51e) by ionic hydrogenation**



To a solution of mixed acetal endoperoxide **1.40e** (35 mg, 0.116 mmol) and triethylsilane (20 mg, 0.174 mmol, 1.5 equiv) in dichloromethane (1.5 mL) at -43 °C was slowly added triflic acid (~10 equiv). The reaction was maintained at -43 °C and monitored by TLC until the starting material was consumed. The reaction was quenched with water and extracted with

dichloromethane (2 x 10 mL). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. Flash chromatography (10% EtOAc/hexane) afforded **13** (20 mg, 61 %). Analytical data for **1.51e**: mp 114-115°C; IR (thin film, cm<sup>-1</sup>) 2953, 1779, 1749, 1396, 1289, 1203, 1020, 947, 925; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 4.46-4.42 (m, 1H), 2.63-2.58 (m, 1H), 2.01-1.94 (m, 2H), 1.93 (s, 3H), 1.76 (s, 3H) 1.73-1.66 (m, 1H), 1.21 (d, *J* = 6.4 Hz, 3H), 0.99 (d, *J* = 6.6 Hz, 3H), 0.80 (d, *J* = 6.6 Hz, 3H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 162.8, 160.9, 107.0, 80.3, 78.2, 42.4, 32.5, 29.7, 28.7, 28.6, 21.0, 20.7, 18.6; TLC (10% EtOAc/hexanes) R<sub>f</sub> = 0.31. HRMS (ESI) Calcd. for C<sub>13</sub>H<sub>20</sub>O<sub>6</sub>Na: 295.1158, Found: 295.1164.

**Preparation of 3-hydroxy-4-isopropyl-6-methyltetrahydro-2H-pyran-2-one (1.52e) by palladium-catalyzed hydrogenolysis**

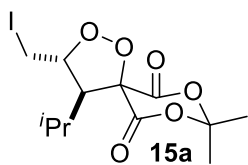


To a solution of endoperoxide **1.51e** (60 mg, 0.22 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was added 10% Pd/C catalyst (88 mg, 400mg/mmol). The reaction was stirred under H<sub>2</sub> (balloon) atmosphere at room temperature overnight. The mixture was filtered through a short pad of Celite (CH<sub>2</sub>Cl<sub>2</sub>), and the solvents were evaporated under reduced pressure. Flash chromatography (30% EtOAc/hexane) afforded **1.52e** (20 mg, 0.12 mmol, 53% yield). Analytical data for **1.52e**: mp 95-96°C; IR (thin film, cm<sup>-1</sup>) 3419, 2956, 2872, 1729, 1540, 1472, 1226, 1210, 1130, 1091, 967; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 4.51-4.45 (m, 1H), 4.45-4.41 (dd, *J* = 2.6, 9.2 Hz, 1H), 3.08 (d, 2.6 Hz, 1H), 2.49-2.43 (m, 1H), 2.26-2.21 (m, 1H), 1.94-1.89 (ddd, *J* = 2.7, 6.4, 14.6 Hz, 1H), 1.56- 1.50 (ddd, *J* = 8.5, 11.9, 14.6 Hz, 1H), 1.41 (d, *J* = 6.1 Hz, 3H), 0.88 (d, *J* = 7.0

Hz), 0.75 (d,  $J = 6.8$  Hz);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  176.4, 73.2, 67.1, 39.4, 29.5, 26.0, 21.2, 20.5, 16.1; **TLC** (30% EtOAc/hexanes)  $R_f = 0.20$ . **HRMS** (ESI) Calcd. for  $\text{C}_9\text{H}_{16}\text{O}_3\text{Na}$ : 195.0997, Found: 195.0990.

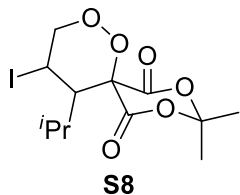
**General Procedure D for iodoendoperoxidation of alkenyl Meldrum's acid and barbituric acid hydroperoxides (1.46i) and (1.47k)**

To a stirred solution of hydroperoxy Meldrum's acid or barbituric acid derivative **1.32i** or **1.32k** in dry  $\text{CH}_2\text{Cl}_2$  in a vial wrapped in aluminum foil was added 1,3-diiodo-5,5-dimethyl hydantoin (1.2 equiv). The vial was capped and stirred for 16 h. The reaction was quenched with aqueous saturated sodium thiosulfate (until pink color dissipates) and the resulting mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (3x). The combined organic extracts were dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. Flash chromatography on  $\text{SiO}_2$  (5% EtOAc/hexanes) provided the iodoendoperoxide as a white, solid mixture of regioisomers as indicated.



**Analytical data for 3-(iodomethyl)-4-isopropyl-8,8-dimethyl-1,2,7,9-tetraoxaspiro[4.5]decane-6,10-dione (1.46i):** mp 114-116 °C

(decomp); **IR** (thin film,  $\text{cm}^{-1}$ ) 2962, 1779, 1754, 1396, 1296, 1200,



1023, 923;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  4.59-4.56 (ddd,  $J = 2.6, 5.8,$

8.4 Hz, 1H), 3.50 (dd,  $J = 8.4, 11.2$  Hz, 1H), 3.41 (dd,  $J = 2.6, 11.2$  Hz,

1H), 3.38 (dd,  $J = 5.8, 11.0$  Hz, 1H), 2.39-2.32 (m, 1H), 1.86 (s, 3H),

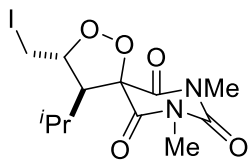
1.78 (s, 3H), 1.04 (d,  $J = 6.7$  Hz, 3H), 0.83 (d,  $J = 6.7$  Hz, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )

$\delta$  162.6, 161.5, 106.9, 86.3, 83.5, 71.4, 29.3, 27.8, 27.5, 22.2, 21.8, 5.9; **TLC** (15%

EtOAc/hexanes)  $R_f = 0.39$ . **HRMS** (ESI) Calcd. for  $\text{C}_{12}\text{H}_{17}\text{IO}_6\text{Na}$ : 406.9968, Found: 406.9974.

14:1 mixture with regioisomer **S8** (at left).



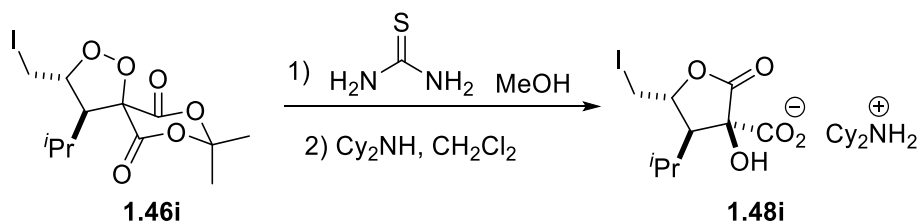


**Analytical data for 3-(iodomethyl)-4-isopropyl-7,9-dimethyl-1,2-dioxo-7,9-diazaspiro[4.5]decane-6,8,10-trione (1.47k):** mp 100-103

°C (decomp); **IR** (thin film,  $\text{cm}^{-1}$ ) 2964, 2874, 1688, 14442, 1422, 1379,

1110, 1041, 752;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.58-4.54 (ddd,  $J = 3.9, 5.6, 7.5$  Hz, 1H), 3.52-3.47 (dd,  $J = 7.5, 11.1$  Hz, 1H), 3.46-3.43 (dd,  $J = 3.9, 11.1$  Hz, 1H), 3.33 (s, 3H), 3.32 (s, 3H), 3.26 (dd,  $J = 5.6, 10.6$  Hz, 1H), 2.30-2.21 (m, 1H), 1.01 (d,  $J = 6.6$  Hz, 3H), 0.72 (d,  $J = 6.6$  Hz, 3H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  164.4, 164.2, 149.9, 85.9, 83.8, 70.7, 29.8, 28.9, 27.1, 22.1, 22.0, 5.6; **TLC** (15% EtOAc/hexanes)  $R_f = 0.24$ . **HRMS** (ESI) Calcd. for  $\text{C}_{12}\text{H}_{17}\text{IN}_2\text{O}_5\text{Na}$ : 419.0080, Found: 419.0086.

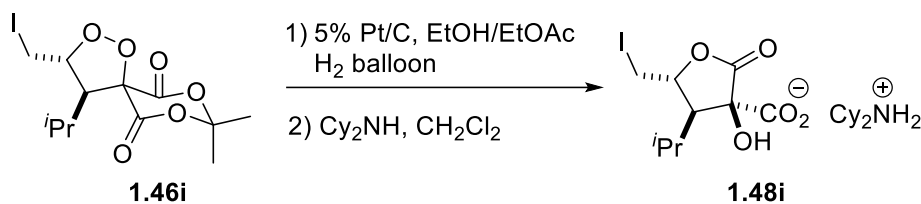
#### O-O bond cleavage of iodoendoperoxide (1.48i) by thiourea



To a stirred solution of iodoendoperoxide (50 mg, 0.130 mmol, 10:1 mixture of **1.46i** to **S7**) in dry MeOH (3.0 mL) in an aluminum foil wrapped vial was added thiourea (10 mg, 0.130 mmol, 1.0 equiv). After 4 h, the reaction was concentrated to dryness, the residue was taken up in  $\text{CH}_2\text{Cl}_2$  (10 mL) and washed with  $\text{H}_2\text{O}$  (5 mL). The aqueous layer was separated and extracted with  $\text{CH}_2\text{Cl}_2$  (10 mL). The combined organic extracts were dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and a solution of freshly distilled dicyclohexylamine (21.2 mg, 0.90 equiv) in  $\text{CH}_2\text{Cl}_2$  was added and stirred for 5 min. The solution was concentrated to dryness, and the residue triturated with hexanes. The precipitate was isolated by suction filtration to give 43 mg (72%) of the dicyclohexylamine salt as cream colored solid (dr >20:1). Analytical data for dicyclohexylamine ( $\pm$ )-3-hydroxy-5-(iodomethyl)-4-isopropyl-2-oxotetrahydrofuran-3-

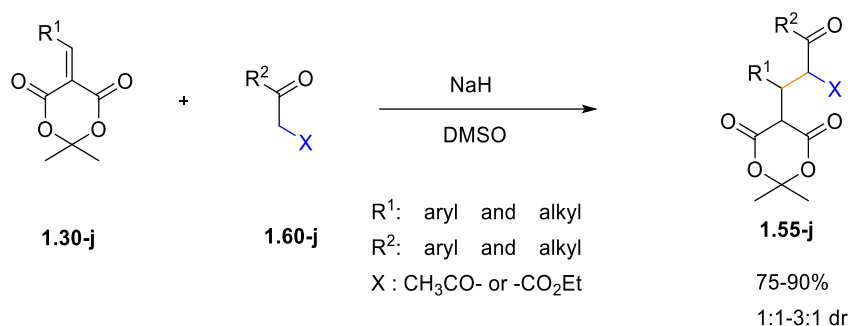
carboxylate **1.48i**:  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.95 (bs, 2H), 4.91 (bs, 1H), 4.33 (m, 1H), 3.82 (dd,  $J = 4.8, 10.6$  Hz, 1H), 3.56 (dd,  $J = 6.3, 10.6$  Hz, 1H), 3.02-2.96 (m, 2H), 2.47 (app. t,  $J = 6.8$  Hz, 1H), 2.21-2.12 (m, 1H), 2.02-1.99 (m, 4H), 1.83-1.81 (m, 4H), 1.66 (m, 2H), 1.48-1.39 (m, 4H), 1.30-1.21 (m, 6H), 0.97 (d,  $J = 6.8$  Hz, 3H) 0.96 (d,  $J = 6.8$  Hz, 3H);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  175.8, 173.8, 79.9, 78.6, 53.4, 52.9, 28.9, 26.2, 24.9, 24.7, 21.2, 19.2, 8.2.

#### Hydrogenolysis of iodoendoperoxide (**1.46i**) by Pt/C

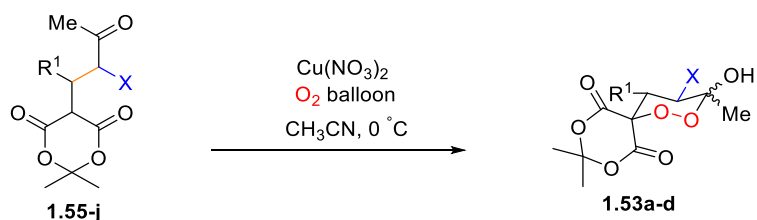


A degassed soln of iodoendoperoxide **1.46i** (20 mg, 0.052 mmol, 10:1 mixture of **1.46i** to **S7**) in EtOAc/EtOH (1:10, 2.2 mL) was added to a suspension of 5% Pt/C (10.4 mg, 200 mg/mmol) in EtOH (1 mL) under  $\text{N}_2$ . The vial was purged with  $\text{H}_2$  (balloon) and stirred vigorously. After 5 h the reaction was filtered through a plug of Celite (EtOAc) and a soln of dicyclohexylamine (8.5 mg, 0.047 mmol, 0.90 equiv) in dry  $\text{CH}_2\text{Cl}_2$  was added. After 15 min, the reaction was concentrated to dryness and triturated with hexanes (4 mL). The precipitate was isolated by suction filtration to give 18.3 mg (77%) of the dicyclohexylamine salt as cream colored solid (dr >20:1).

#### General Procedure for the Preparation of Keto-Meldrum's Acids via Michael Reaction

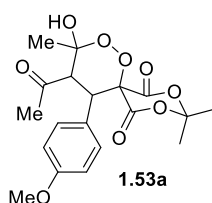


To a solution of ketone in 0.2 M in DMSO at rt was added a stoichiometric amount of base. The mixture was stirred at rt for 1 h before a solution of alkylidene (or arylidene) was then added and the reaction was stirred for 20h. The reaction was then quenched with 1 M HCl and extracted three times with ethyl acetate. The combined organic solution was washed five times with water (in the case reaction was run in DMSO) to remove DMSO. The organic extracts were dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. The crude product was used for the next step without further purification.



To a solid mixture of Meldrum's acid derivative **1.55a-d** and  $\text{Cu(NO}_3)_2 \cdot 3\text{H}_2\text{O}$  at  $0^\circ\text{C}$  in a round bottomed flask was added cold  $\text{CH}_3\text{CN}$  ( $0^\circ\text{C}$ ). The flask was capped with a Teflon septum and charged with  $\text{O}_2$ . The reaction was stirred at  $0^\circ\text{C}$  for three more hours before

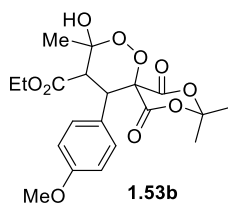
slowly warmed up to rt. The reaction was then quenched with H<sub>2</sub>O and partitioned between H<sub>2</sub>O and EtOAc. The aqueous layer was separated and extracted a second time with EtOAc. The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. Flash chromatography (25% EtOAc/hexanes) afforded hemiketal endoperoxide Meldrum's acid derivatives **1.53a-d**



**Analytical data for 4-acetyl-3-hydroxy-5-(4-methoxyphenyl)-3,9,9-trimethyl-1,2,8,10-tetraoxaspiro[5.5]undecane-7,11-dione (1.53a):** 65%

yield; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, major diastereomer) δ 7.29-7.26 (d, *J* = 8.8 Hz, 2H), 6.81-6.79 (d, *J* = 8.8 Hz, 2H), 4.54-4.50 (d, *J* = 12.8 Hz, 1H), 4.48 (s, 1H), 4.39-4.35 (d, *J* = 12.8 Hz, 1H) 3.77 (s, 3H), 2.05 (s, 3H), 1.85 (s, 3H), 1.54 (s, 3H), 1.46 (s, 3H);

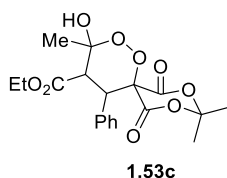
**TLC** (25% EtOAc/hexanes) *R*<sub>f</sub> = 0.3.



**Analytical data for ethyl 3-hydroxy-5-(4-methoxyphenyl)-3,9,9-trimethyl-7,11-dioxo-1,2,8,10-tetraoxaspiro[5.5]undecane-4-**

**carboxylate (1.53b):** 85% yield; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, major

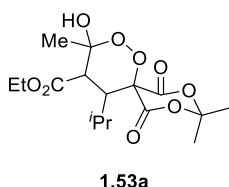
diastereomer) δ 7.30-7.28 (d, *J* = 8.8 Hz, 2H), 6.81-6.78 (d, *J* = 8.8 Hz, 2H), 4.58-4.54 (d, *J* = 12.8 Hz, 1H), 4.26-4.23 (d, *J* = 12.8 Hz, 1H), 4.10-3.90 (m, 2H), 3.76 (s, 3H), 1.86 (s, 3H), 1.62 (s, 3H), 1.47 (s, 3H), 1.03-0.99 (t, *J* = 7.0 Hz, 3H); **TLC** (25% EtOAc/hexanes) *R*<sub>f</sub> = 0.3.



**Analytical data for ethyl 3-hydroxy-3,9,9-trimethyl-7,11-dioxo-5-phenyl-1,2,8,10-tetraoxaspiro[5.5]undecane-4-carboxylate (1.53c):**

65% yield; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, major diastereomer) δ 7.39-7.26 (m, 5H), 4.64-4.60 (d, *J* = 13.2 Hz, 1H), 4.31-4.28 (d, *J* = 13.2 Hz, 1H), 4.10-3.95 (m, 2H),

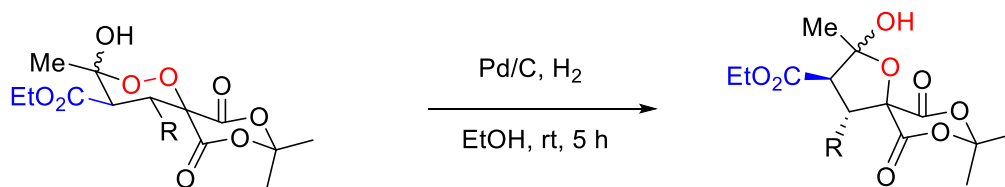
1.85 (s, 3H), 1.63 (s, 3H), 1.43 (s, 3H), 0.99-0.95 (t,  $J = 7.2$  Hz, 3H); **TLC** (25% EtOAc/hexanes)  $R_f = 0.3$ .



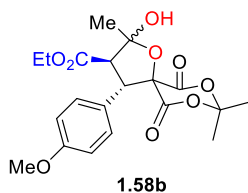
**Analytical data for 5-hydroxy-5-isopropyl-2,2-dimethyl-1,3-dioxane-4,6-dione (Sa):** 75% yield;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , major diastereomer)  $\delta$  4.29-4.23 (m, 2H), 4.09 (bs, 1H), 3.56-3.53 (d,  $J = 11.6$

Hz, 1H), 3.35-3.30 (dd, (d,  $J = 11.6$  Hz,  $J = 5.6$  Hz, 1H), 1.96 (s, 3 H), 1.78, (s, 3H), 1.60-1.57 (m, 1H), 1.50 (s, 3H), 1.35-1.31 (t,  $J = 7.2$  Hz, 3H), 0.92-0.91 (d,  $J = 6.8$  Hz, 3H), 0.92-0.90 (d,  $J = 6.8$  Hz, 3H); **TLC** (25% EtOAc/hexanes)  $R_f = 0.25$ .

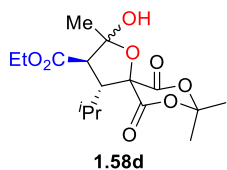
General procedure for Synthesis of hemiketal tetrahydrofuan derivatives:



To a solution of hemiketal endoperoxide **1.53b,d** in EtOH was added 10% Pd/C catalyst (200mg/mmol). The reaction was stirred under  $\text{H}_2$  (balloon) atmosphere at room temperature overnight. The mixture was filtered through a short pad of Celite ( $\text{CH}_2\text{Cl}_2$ ), and the solvents were evaporated under reduced pressure. Flash chromatography (25% EtOAc/hexanes) afforded **1.58b,d**.

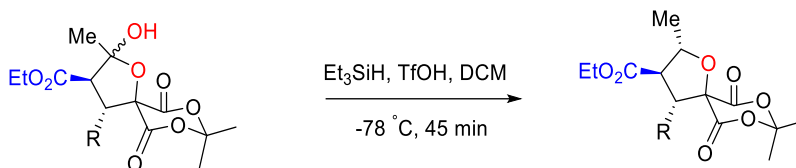


**Analytical data for ethyl (3R,4S)-2-hydroxy-4-(4-methoxyphenyl)-2,8,8-trimethyl-6,10-dioxo-1,7,9-trioxaspiro[4.5]decane-3-carboxylate (1.58b):** 75% yield;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , major diastereomer)  $\delta$  7.14-7.12 (m, 2H), (d,  $J = 8.8$  Hz, 2H), 6.86-6.84 (d,  $J = 8.8$  Hz, 2H), 4.70-4.67 (d,  $J = 12.8$  Hz, 1H), 4.18-4.09 (m, 2H), 3.99-3.96 (d,  $J = 12.8$  Hz, 1H) 3.78 (s, 3H), 3.60 (s, 1H), 1.87 (s, 3H), 1.66 (s, 3H), 1.31 (s, 3H), 1.22-1.85 (t,  $J = 7.0$  Hz, 3H); **TLC** (25% EtOAc/hexanes)  $R_f = 0.3$ .



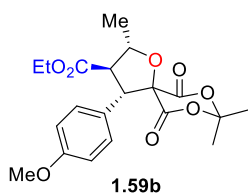
**Analytical data for ethyl (3R,4R)-2-hydroxy-4-isopropyl-2,8,8-trimethyl-6,10-dioxo-1,7,9-trioxaspiro[4.5]decane-3-carboxylate (1.58d):** 70% yield;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , major diastereomer)  $\delta$  4.29-4.21 (m, 2H), 3.55-3.38 (m, 2H), 1.89-1.86 (m, 1H), 1.85 (s, 3 H), 1.77, (s, 3H), 1.65 (s, 3H), 1.30-1.29 (t,  $J = 7.2$  Hz, 3H), 0.89-0.87 (d,  $J = 6.4$  Hz, 3H), 0.88-0.86 (d,  $J = 6.4$  Hz, 3H); **TLC** (25% EtOAc/hexanes)  $R_f = 0.30$ .

### General Procedure for synthesis of fully substituted tetrahydrofuran



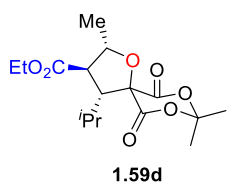
To a solution hemiketal **1.58b,d** and triethylsilane (1.5 equiv) in dichloromethane (0.2M) at -78 °C was slowly added triflic acid (~10 equiv). The reaction was maintained at -78 °C and monitored (TLC analysis) until the starting material was consumed. The reaction was

quenched with water and extracted with dichloromethane (2 x 15 mL). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. Flash chromatography (25% EtOAc/hexanes) afforded **1.59b,d**.



**Analytical data for ethyl (2S,3R,4S)-4-(4-methoxyphenyl)-2,8,8-trimethyl-6,10-dioxo-1,7,9-trioxaspiro[4.5]decane-3-carboxylate**

**(1.59b)**: 55% yield, single diastereomer; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.17-7.14 (m, 2H), (d, *J* = 8.8 Hz, 2H), 6.86-6.83 (d, *J* = 8.8 Hz, 2H), 4.76-4.73 (m, 1H), 4.54-4.51 (d, *J* = 12.4 Hz, 1H), 4.11-4.05 (m, 2H), 3.99-3.96 (d, *J* = 12.8 Hz, 1H) 3.78 (s, 3H), 3.76-3.74 (dd, *J* = 12.8 Hz, *J* = 2.8 Hz 1H), 1.67 (s, 3H), 1.57-1.55 (d *J* = 6.0 Hz, 3H), 1.28 (s, 3H), 1.16-1.12 (t, *J* = 7.2 Hz, 3H); **TLC** (25% EtOAc/hexanes) R<sub>f</sub> = 0.35.



**Analytical data for ethyl (2S,3R,4R)-4-isopropyl-2,8,8-trimethyl-6,10-dioxo-1,7,9-trioxaspiro[4.5]decane-3-carboxylate (1.59d)**: 65% yield,

single diastereomer; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.53-4.47 (m, 1H), 4.22-4.17 (m, 2H), 3.52-3.46 (t, *J* = 11.6 Hz, 1H), 3.17-3.11 (dd, *J* = 11.6 Hz, *J* = 9.6 Hz, 1H), 1.85 (s, 3 H), 1.75, (s, 3H), 1.35-1.34 (d, *J* = 6.0 Hz, 3H), 1.29-1.26 (t, *J* = 7.2 Hz, 3H); **TLC** (25% EtOAc/hexanes) R<sub>f</sub> = 0.30.

### Crystal Structure Determination of (1.48i)

Single crystals of **1.48i** (C<sub>21</sub>H<sub>36</sub>INO<sub>5</sub>) were prepared via recrystallization from CH<sub>2</sub>Cl<sub>2</sub>/hexanes. A suitable crystal was selected and placed on a MiteGen mylar tip with paratone oil on a Bruker-AXS SMART APEX-II diffractometer. The crystal was kept at 100

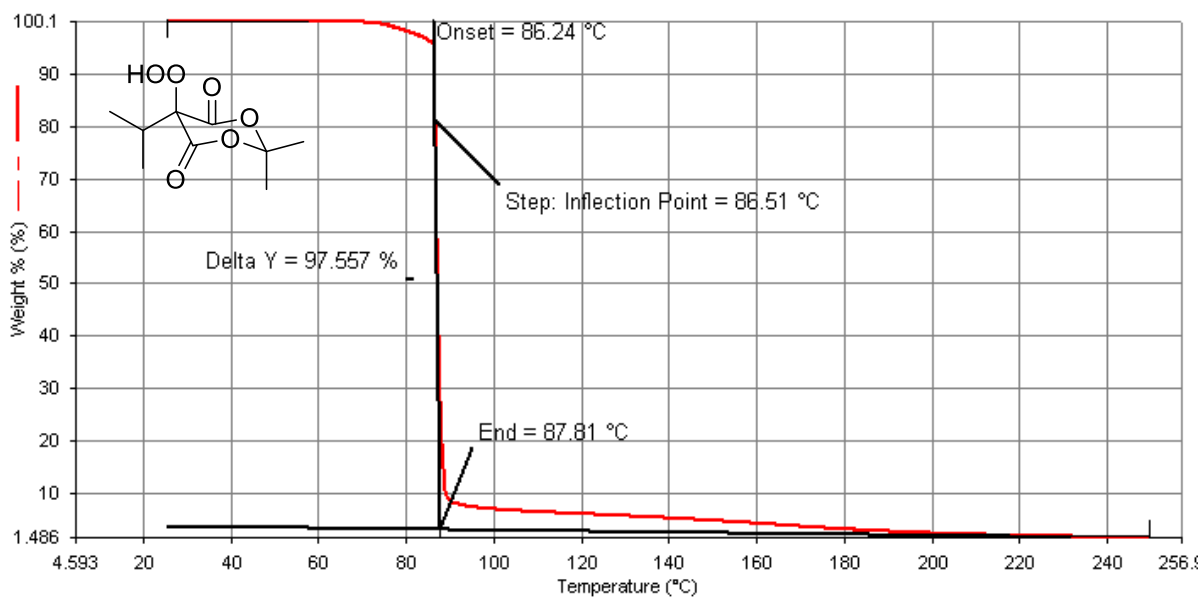
K during data collection. Using Olex2,<sup>38</sup> the structure was solved with the olex2.solve<sup>39</sup> structure solution program using Charge Flipping and refined with the XL<sup>40</sup> refinement package using Least Squares minimization.

**Crystal Data.** C<sub>21</sub>H<sub>36</sub>INO<sub>5</sub>,  $M = 509.41$ , monoclinic,  $a = 13.3142(2) \text{ \AA}$ ,  $b = 16.8691(3) \text{ \AA}$ ,  $c = 10.6959(2) \text{ \AA}$ ,  $\beta = 104.1800(10)^\circ$ ,  $V = 2329.09(7) \text{ \AA}^3$ ,  $T = 100$ , space group P2<sub>1</sub>/c (no. 14),  $Z = 4$ ,  $\mu(\text{CuK}\alpha) = 11.044$ , 11077 reflections measured, 4334 unique ( $R_{\text{int}} = 0.0526$ ) which were used in all calculations. The final  $wR_2$  was 0.1110 (all data) and  $R_1$  was 0.0433 ( $>2\sigma(I)$ ).



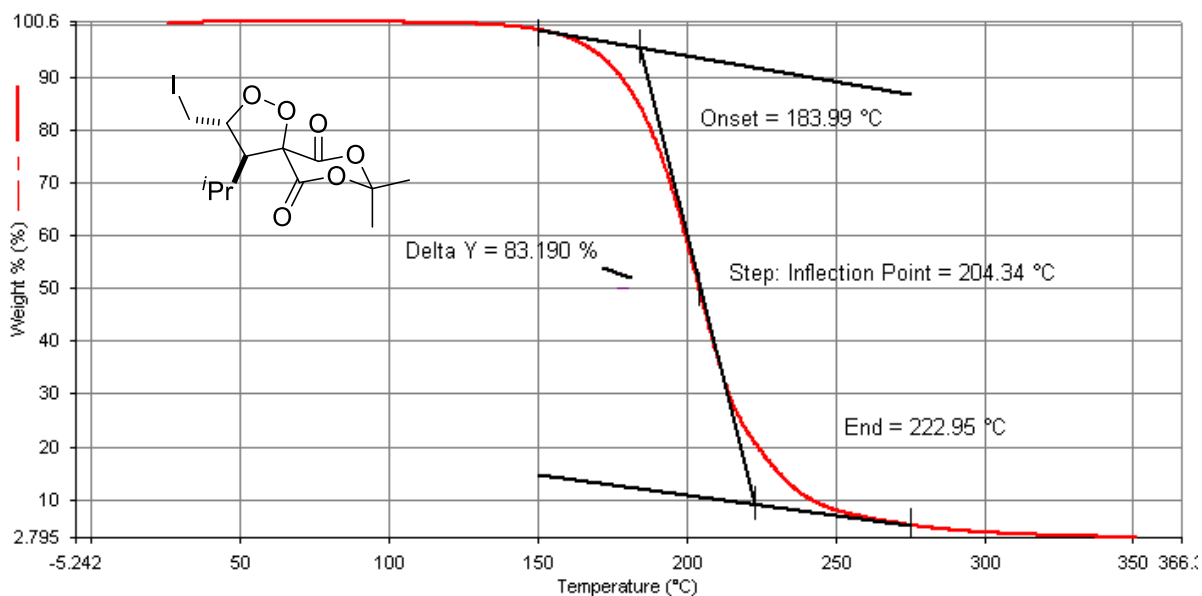
## Thermogravimetric Analysis

### 5-ethyl-5-hydroperoxy-2,2-dimethyl-1,3-dioxane-4,6-dione (1.40a)

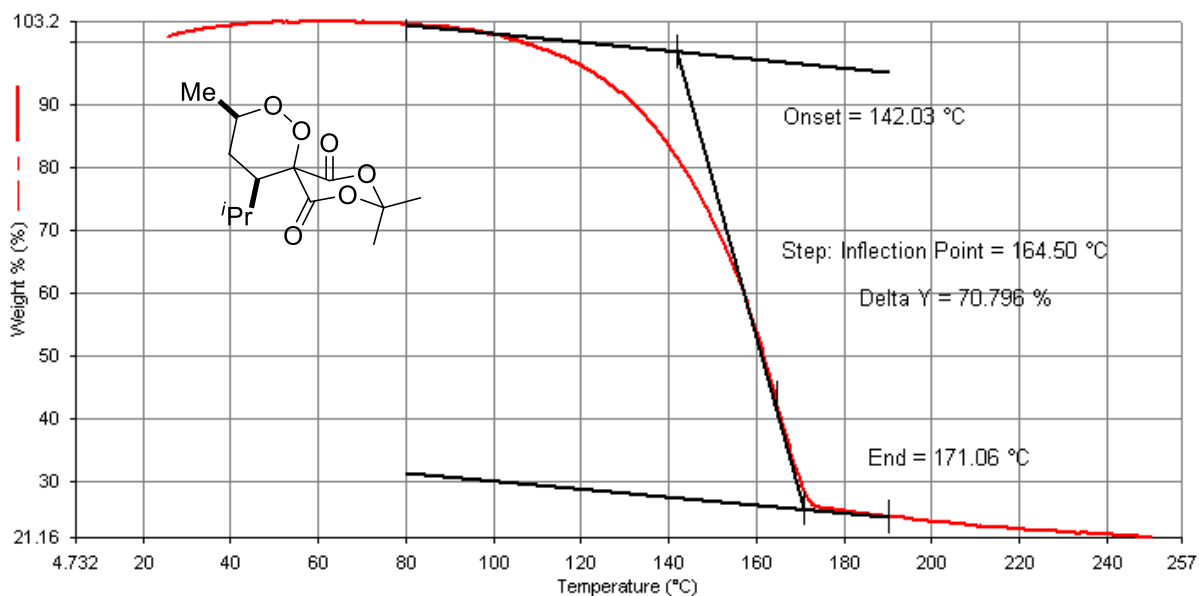


### 3-(iodomethyl)-4-isopropyl-8,8-dimethyl-1,2,7,9-tetraoxaspiro[4.5]decane-6,10-dione

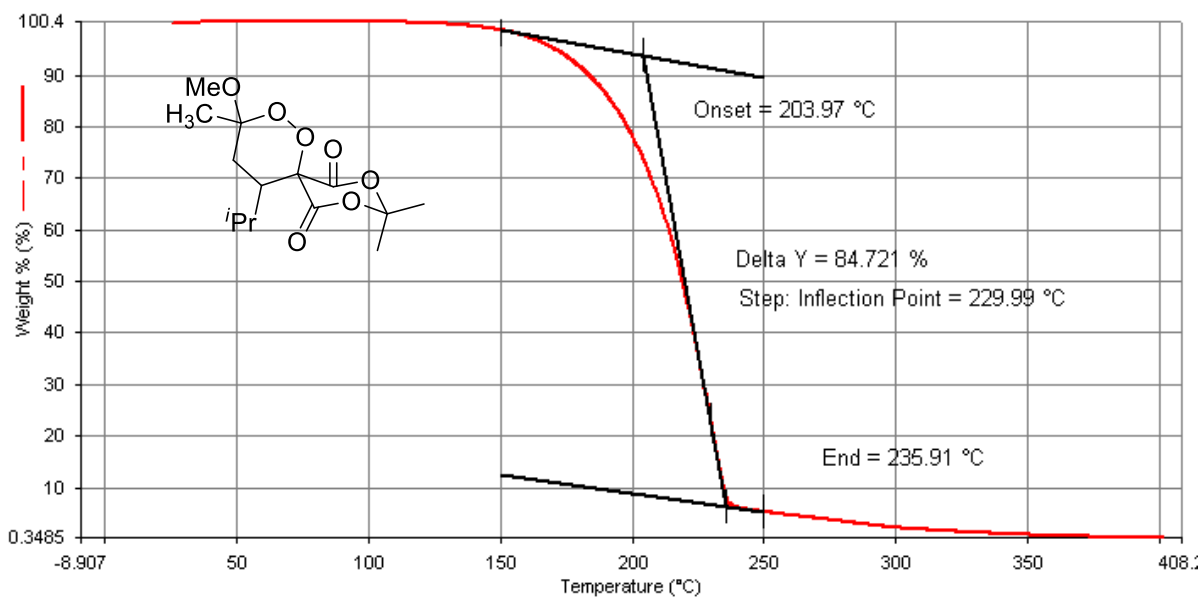
#### (1.46i)



**5-isopropyl-3,9,9-trimethyl-1,2,8,10-tetraoxaspiro[5.5]undecane-7,11-dione (1.51e)**



**5-isopropyl-3-methoxy-3,9,9-trimethyl-1,2,8,10-tetraoxaspiro[5.5]undecane-7,11-dione (1.40e)**



## 1.6 References

1. Smith, A. M. R.; Hii, K. K. *Chem. Rev.* **2011**, *111*, 1637-1656.
2. (a) Chen, B.-C.; Zhou, P.; Davis, F. A.; Ciganek, E. *Org. React. (N.Y.)* **2003**, *62*, 1-356 (b) For direct hydroxylation of active methines using Pd(II)/O<sub>2</sub>, see: Chuang, G. J.; Wang, W.; Lee, E.; Ritter, T. *J. Am. Chem. Soc.* **2011**, *133*, 1760-1762.
3. Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. *Angew. Chem. Int. Ed.* **2009**, *48*, 2854-2867.
4. (a) Meldrum, A. N. *J. Chem. Soc.* **1908**, *93*, 598-601. (b) Davidson, D.; Bernhard, S. A. *J. Am. Chem. Soc.* **1948**, *70*, 3426-3428. For recent reviews of Meldrum's acid in organic synthesis: (c) Dumas, A. M.; Fillion, E. *Acc. Chem. Res.* **2010**, *43*, 440-454. (d) Lipson, V. V.; Gorobets, N. Y. *Mol. Diversity* **2009**, *13*, 399-419. (e) Ivanov, A. S. *Chem. Soc. Rev.* **2008**, *37*, 789-811. (f) Chen, B.-C. *Heterocycles* **1991**, *32*, 529-597.
5. Yoshioka, M.; Nishioka, T.; Hasegawa, T. *J. Org. Chem.* **1993**, *58*, 278-281.
6. Christoffers, J.; Werner, T.; Frey, W.; Baro, A. *Eur. J. Org. Chem.* **2003**, 4879-4886.
7. (a) Wang, G.-W.; Lu, Q.-Q.; Xia, J.-J. *Eur. J. Org. Chem.* **2011**, 4429-4438. For autoxidation of dienols, please see: (b) Fuson, R. C.; Hatchard, W. R.; Kottke, R. H.; Fedrich, J. L. *J. Am. Chem. Soc.* **1960**, *82*, 4330-4333. (c) Triquigneaux, M.; Charles, L.; André-Barrès, C.; Tuccio, B. *Org. Biomol. Chem.* **2010**, *8*, 1361-1367.
8. (a) Rahman, T.; Nishino, H. *Org. Lett.* **2003**, *5*, 2887-2890. (b) Rahman, T.; Haque, A.; Igarashi, H.; Nishino, H. *Molecules* **2011**, *16*, 9562-9581. (c) Haque, A.; Nishino, H. *Synth. Commun.* **2012**, *42*, 608-619.
9. (a) Snider, B. B. *Chem. Rev.* **1996**, *96*, 339-364. (b) Snider, B. B. *Transition Metals for Organic Synthesis*; Beller, M.; Bolm, C.; Eds.; Wiley-VCH: Weinheim, **2004**; Vol 1; 481-490.
10. Hencken, C. P.; Kalinda, A. S.; D'Angelo, J. G. *Annu. Rep. Med. Chem.* **2009**, *44*, 359-378.
11. Tang, Y.; Dong, Y.; Vennerstrom, J. L. *Med. Res. Rev.* **2004**, *24*, 425-448.
12. Keiser, J.; Utzinger, J. *Curr. Opin. Infect. Diseases* **2007**, *20*, 605-612.
13. Davidson, B. S. *J. Org. Chem.* **1991**, *56*, 6722-6724.

14. Dembitsky, V. M. *Eur. J. Med. Chem.* **2008**, *43*, 223-251.
15. (a) Helesbeux, J.-J.; Peyronnet, D.; Labaïed, M.; Grellier, P.; Frappier, F.; Seraphin, D.; Richomme, P.; Duval, O. "Synthesis and Antimalarial Activity of Some New 1,2-Dioxolane Derivatives." *J. Enz. Inhib. Med. Chem.* **2002**, *17*, 431-437. (b) Jefford, C. W. *Drug Disc. Today* **2007**, *12*, 487-495.
16. (a) Ghorai, P.; Dussault, P. H.; Hu, C. *Org. Lett.* **2008**, *10*, 2401-2404. (b) Gemma, S.; Martí, F.; Gabellieri, E.; Campiani, G.; Novellino, E.; Butini, S. *Tetrahedron Lett.* **2009**, *50*, 5719-5722. (c) Parrish, J. D.; Ischay, M. A.; Lu, Z.; Guo, S.; Peters, N. R.; Yoon, T. P. *Org. Lett.* **2012**, *14*, 1640-1643.
17. Cossy, J.; Belotti, D.; Bellosta, V.; Brocca, D. *Tetrahedron Lett.* **1994**, *35*, 6089-6092.
18. Vallejos, J.-C.; Capelle, N.; Arzoumanian, H. U. S. Patent 6,057,474, 2000.
19. Steward, K. M.; Johnson, J. S. *Org. Lett.* **2011**, *13*, 2426-2429.
20. (a) Ref. 4e. (b) Allen, J. C.; Kociok-Köhn, G.; Frost, C. G. *Org. Biomol. Chem.*, **2012**, *10*, 32-35. (c) Cui, S.; Walker, S. D.; Woo, J. C. S.; Borths, C. J.; Mukherjee, H.; Chen, M. J.; Faul, M. M. *J. Am. Chem. Soc.* **2010**, *132*, 436-437. (d) Fujimori, S.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 4964-4967. (e) Fujimori, S.; Knöpfel, T. F.; Zarotti, P.; Ichikawa, T.; Boyall, D.; Carreira, E. M. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1635-1657. (f) Knöpfel, T. F.; Zarotti, P.; Ichikawa, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 9682-9683. (g) Knöpfel, T. F.; Boyall, D.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 2281-2283. (h) Knöpfel, T. F.; Carreira, E. M. *J. Am. Chem. Soc.* **2003**, *125*, 6054-6055.
21. (a) Kimmel, K. L.; Weaver, J. D.; Ellman, J. A. *Chem. Sci.* **2012**, *3*, 121-125. (b) Hong, B.-C.; Dange, N. S.; Ding, C.-F.; Liao, J.-H. *Org. Lett.* **2012**, *14*, 448-451. (c) Trost, B. M.; Osipov, M.; Kaib, P. S. J.; Sorum, M. T. *Org. Lett.* **2011**, *13*, 3222-3225.
22. For representative thermogravimetric analyses of the peroxide products, please see the Experimental details. While we encountered no hazardous decomposition during the course of this work, anyone working with peroxides should be aware that spontaneous and exothermic decomposition is possible. For some references on peroxide properties and safety, see: (a) Zabicky, J. In *The Chemistry of the Peroxide Group*; Rappoport, Z., Ed.; John Wiley and Sons: Chichester, 2006; Vol. 2, pp 597-773. pt 2. (b) Medard, L. A. *Accidental Explosions: Types of Explosive Substances*; Ellis Horwood Limited: Chichester, 1989; Vol. 2. (c) Patnaik, P. A. *Comprehensive Guide to the Hazardous Properties of Chemical Substances*, 2nd ed.; John Wiley & Sons: New York, 1999. (d) Shanley, E. S. In *Organic Peroxides*; Swern, D., Ed., Wiley-Interscience: New York, 1970; Vol. 3, p 341.

23. The experiment section describes additional optimization studies.
24. Alcohol formation in variable amounts was observed upon purification on SiO<sub>2</sub>. The necessity for purification of alkene substrates may be attributable to epoxidation of the alkene which was observed in the oxidative deacylation.
25. (a) Corma, A.; Leyva-Pérez, A.; Sabater, M. J. *Chem. Rev.* **2011**, *111*, 1657-1712.  
(b) Muzart, J. *Tetrahedron* **2008**, *64*, 5815-5849.
26. Mézailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133-4136.
27. a) Liu, B.; De Brabander, J. K. *Org. Lett.* **2006**, *8*, 4907-4910. (b) Antoniotti, S.; Genin, E.; Michelet, V.; Genêt, J.-P. *J. Am. Chem. Soc.* **2005**, *127*, 9976-9977.
28. (a) Ref. 11 (b) Orazi, O. O.; Corral, R. A.; Bertorello, H. E. *J. Org. Chem.* **1965**, *30*, 1101-1104.
29. Schenk G. O.; Dunlap, D. E. *Angew. Chem.* **1956**, *68*, 248-249.
30. (a) Kursanov, D. N.; Parnes, Z. N.; Loim, N. M. *Synthesis* **1974**, 633-651. (b) Bullock, R. M. *Chem. Eur. J.* **2004**, *10*, 2366-2374.
31. (a) Orazi, O. O.; Corral, R. A.; Bertorello, H. E. *J. Org. Chem.* **1965**, *30*, 1101-1104. (b) Davison, D.; Bernhard, S. A. *J. Am. Chem. Soc.*, **1948**, *70*, 3426-3428.
32. Bigi, F.; Carloni, S.; Ferrari, L.; Maggi, R.; Mazzacani, A.; Sartori, G. *Tet. Lett.* **2001**, *42*, 5203-5205.
33. Chhabra, B. R.; Bolte, M. L.; Crow, W. D. *Aust. J. Chem.* **1984**, *37*, 1795-1797.
34. Clark-Lewis, J. W.; Thompson, M. J. *J. Chem. Soc.* **1959**, 1628-1629.
35. Hrubowchak, D. M.; Smith, F. X. *Tet. Lett.* **1983**, *24*, 4951-4954.
36. (a) Fillion, E.; Wilsily, A.; Fishlock, D. *J. Org. Chem.* **2009**, *74*, 1259-1267. (b) Kaumanns, O.; Mayr, H. *J. Org. Chem.* **2008**, *73*, 2738-2745.
37. Haslego, M. L.; Smith, F. X. *Synth. Commun.* **1980**, *10*, 421-427.
38. Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H. *J. Appl. Cryst.* **2009**, *42*, 339-241.
39. Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H. *olex2.solve*, in preparation, **2011**.
40. Sheldrick, G. M. *Acta Cryst.* **2008**, *A64*, 112-122.

## CHAPTER TWO: CONCEPTUAL BLUEPRINT FOR THE STEREOSELECTIVE HETEROFUNCTIONALIZATION OF CARBONYL COMPOUNDS

### 2.1 Introduction

Identification of new chemical strategies that can rapidly assemble complex small molecules remains an important synthetic goal. Multi-component coupling reactions have been widely used to achieve this goal due to their ability to construct multiple carbon-carbon bonds in a single synthetic step.<sup>1</sup> A primary challenge associated with these reactions is the control of stereoselectivity. Multi-component coupling strategies that generally deliver products with high chemo and stereoselectivity are highly desirable.

While catalyst controlled for C-C bond construction have received more attention over the past decade, use of substrate control via starting material taken from the chiral pool remains an important strategy to stereo-controlled bond construction in complex organic systems.<sup>2</sup> These enantiomeric scaffolds present fundamental templates with tactically versatile functionality enabling asymmetric elaboration of additional functional groups.

Heterofunctionalization of carbonyl compounds is an efficient method for the synthesis of a large number of interesting molecules and synthetic building blocks, such as amino acids (by amination), hydroxy acids (by hydroxylation), and fluorinated products. These methods have been widely developed using strategies ranging from chiral auxiliaries<sup>3,4</sup> or stoichiometric chiral electrophilic reagents<sup>5,6</sup> to enantioselective processes achieved by the use of chiral

transition metal catalysts.<sup>7</sup> Although they are well-developed, an obvious limitation for these methods is that each system can only promote one type of transformation for a specific substrate class.

In this chapter, we will discuss a strategy using chiral alkylidene Meldrum's acid, derived from inexpensive starting materials, serving as a linchpin for stereoselective multifunctional array manipulations. Preliminary results in desymmetrization will provide a conceptual blueprint for a general method promoting stereoselective heterofunctionalization of carbonyl compounds.

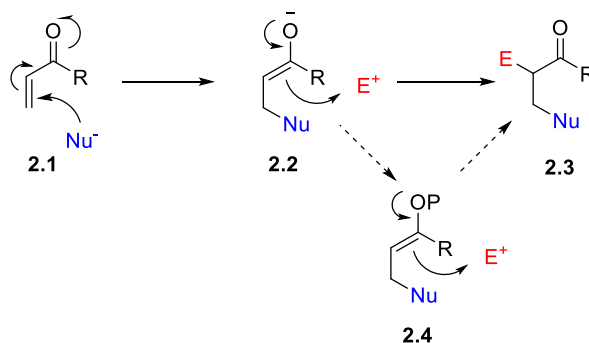
## 2.2 Background

### 2.2.1 The Difunctionalization of $\alpha,\beta$ -Unsaturated Carbonyl Compounds

#### *Introduction*

The vicinal difunctionalization of  $\alpha,\beta$ -unsaturated carbonyl compounds plays a pivotal role in organic synthesis. Although there are exhaustive examples of this transformation in the literature, in this section we will limit the discussion to the tandem reactivity of nucleophiles and electrophiles to  $\alpha,\beta$ -unsaturated carbonyl compounds. The usual embodiment of this transformation is initiated by the conjugate addition of a nucleophile to  $\alpha,\beta$ -unsaturated carbonyl compound **2.1** to generate enolate **2.2**. The resulting enolate can then be trapped with an appropriate electrophile at the  $\alpha$ -position to furnish the vicinal difunctionalized carbonyl compound **2.3** (Figure 2-1).

**Figure 2-1.** The Vicinal Difunctionalization of  $\alpha,\beta$ -unsaturated Carbonyl Compounds



In these reactions, the two carbons of a double bond act as a "relay," mediating electron flow from the nucleophile to the electrophile with the formation of two new chemical bonds at adjacent carbons.<sup>8</sup> In cases where the one-pot procedure is not feasible, the transformation may also be carried out as distinct experimental operations, if the initially formed enolate is protected as vinyl ether **2.4** (i.e.  $\text{P} = \text{SiMe}_3$ ) or quenched by proton to generate a Michael adduct ( $\text{E}^+ = \text{H}^+$ ). Subsequent  $\alpha$ -functionalization would then produce the difunctionalized carbonyl compound **2.3**. In either case, these reactions are highly tunable, whereby the counterion of the enolate or the protecting group imparts a strong influence upon the reactivity of the enolate.<sup>9</sup> Cyclic  $\alpha,\beta$ -unsaturated ketones are the most commonly employed substrates for such vicinal difunctionalization, due to their higher reactivity than their acyclic counterparts, and their diminished susceptibility to direct 1,2-additions, relative to aldehydes.<sup>2</sup>

#### *Scope and Limitation*

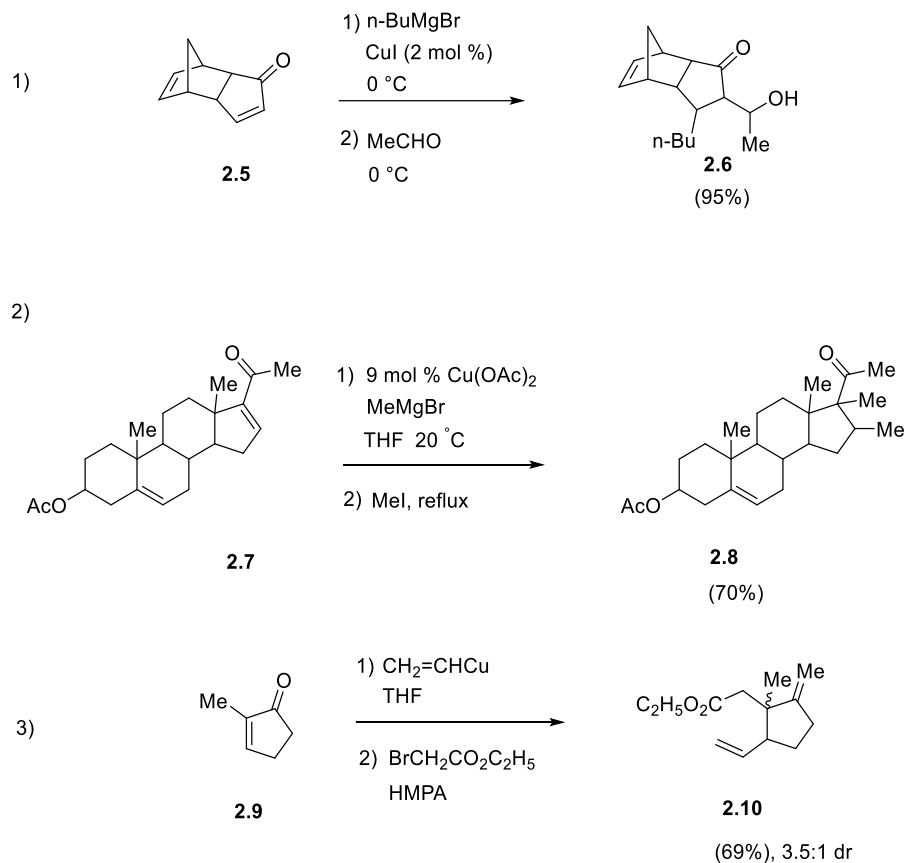
The conjugate addition of nucleophiles to  $\alpha,\beta$ -unsaturated carbonyl compounds have been reported with a wide range of Michael acceptors including enals, enones and enoates. The 1,4-nucleophilic addition to  $\alpha,\beta$ -unsaturated aldehydes, ketones and esters are quite often limited by the use of organocopper (Gilman) reagents, due to their propensity to participate in



1,4-addition as opposed to 1,2-addition.<sup>10-12</sup> In these nucleophilic additions, Gilman reagents can either be generated *in situ* from stoichiometric Grignard reagent and catalytic amount of copper(I) or (II) salts or by preforming the organocuprate stoichiometrically.<sup>13</sup> In the case where organocuprates were used in the first step of the tandem difunctionalization, the enolates resulting from the addition of cuprates are often relatively unreactive, limiting the scope of potential electrophiles.

For example, Rouessac reported a Michael/aldol cascade reaction for the difunctionalization of cyclic ketones. Treatment of cyclopentenone **2.5** with a mixture of stoichiometric amount of *n*-BuMgBr and 2 mol % of copper(I) iodide at 0 °C, followed by trapping of the resultant enolate with acetaldehyde, produced the  $\beta$ -hydroxyketone **2.6** with a 95% yield as a mixture of diastereomers (Scheme 2-1, eq 1).<sup>14</sup> Conjugate addition of methylmagnesium bromide to the steroid **2.7** catalyzed by copper(II) acetate, followed by  $\alpha$ -methylation produced steroid **2.8** in good yield (Scheme 2-1, eq 2).<sup>15</sup> Unfortunately, no diastereoselectivity was reported in either case. Tandem reactions of cyclopentenone **2.9** with stoichiometric vinylcuprate and ethyl bromoacetate furnished the difunctionalization adduct **2.10** in 69% yield, albeit poor diastereoselectivity (3.5:1 trans:cis) (Scheme 2-1, eq 3).<sup>16</sup>

**Scheme 2-1.** Difunctionalization of Enones using Organocopper Reagents

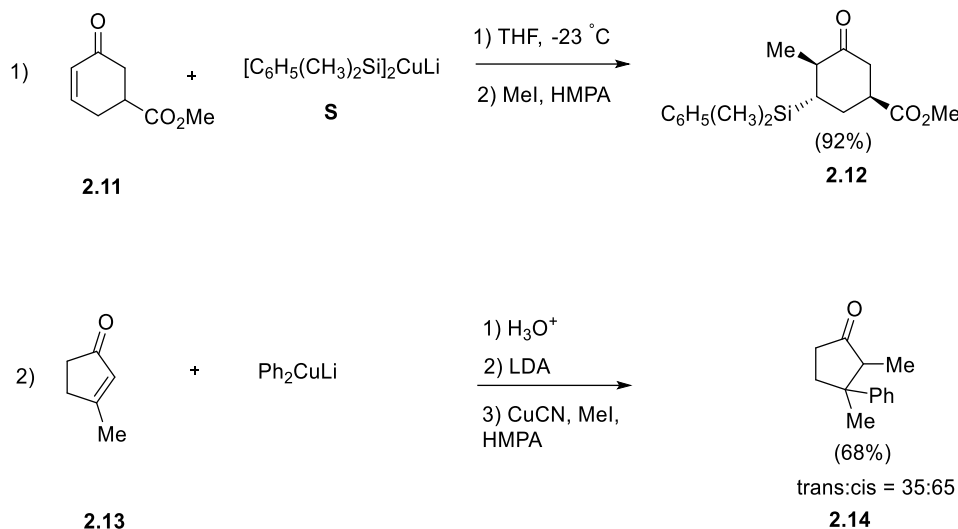


*Stereochemistry*

Though there is a broad scope for the difunctionalization of  $\alpha,\beta$ -unsaturated carbonyl compounds, control over the stereochemistry of these processes is far from ideal. The conjugate addition is highly sensitive to the steric environment of Michael acceptor. Although the more thermodynamically stable *trans* products after  $\alpha$ -functionalization usually prevails, a combination of complex factors such as the nature of enolate, the counterion, the nature of

electrophiles and the reaction conditions, make it difficult to predict the stereochemical outcome.<sup>17,18</sup>

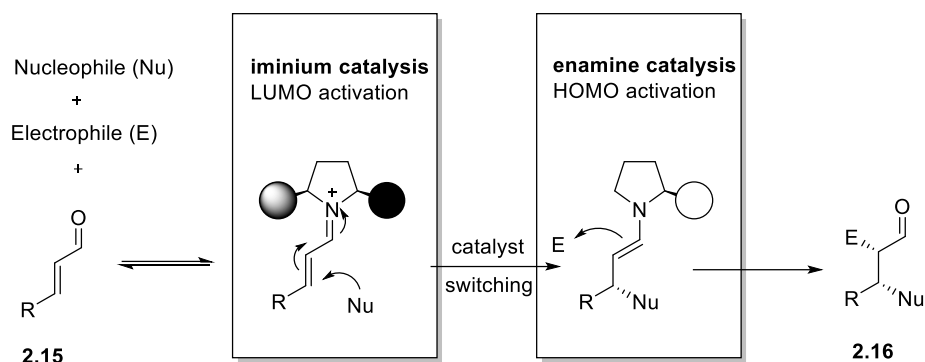
**Scheme 2-2.** Stereochemical Issues in Tandem Difunctionalizations



For example, Patel and coworkers employed the difunctionalization of cyclohexenone **2.11** in route to synthesis of carvone. The *trans*-difunctionalized adduct **2.12** was isolated in 92% yield when **2.11** was successively treated with the silylcuprate **S** and methyl iodide in THF (Scheme 2-2, eq 1).<sup>17</sup> However, when cyclopentenone **2.13** was treated with diphenylcopper lithium, and methyl iodide in a step-wise functionalization (Scheme 2-2, eq 2),<sup>18</sup> the functionalized cyclopentanone **2.14** was produced with only a slight preference for *cis*-isomer. These two examples highlight some of the stereochemical challenges associated with difunctionalization.

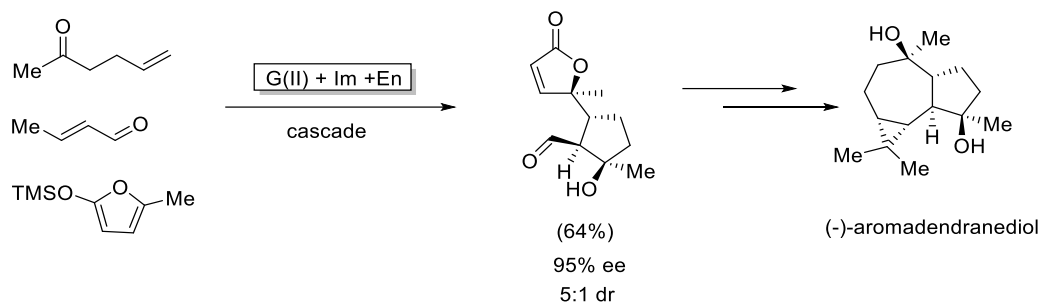
Recently, the MacMillan group has disclosed the concept of organocascade catalysis in attempts to develop a general method for the asymmetric difunctionalization of  $\alpha,\beta$ -unsaturated aldehydes.<sup>19,20</sup>

**Figure 2-2.** Organo-Cascade Catalysis



Through their design,  $\alpha,\beta$ -unsaturated aldehydes **2.15** tactically enter into cascade catalysis cycles to enantioselectively furnish the difunctionalized **2.16**. Condensation of the chiral amine catalyst with the aldehyde enables the enantioselective addition of nucleophiles via LUMO activation. The resultant enamine promotes the stereoselective addition of an electrophile, furnishing **2.16** (Figure 2-3). By exploiting the orthogonal dual reactivity profiles of imidazolidinones (well-established in iminium catalysis) and prolines (standard catalysts for the enamine catalysis, but generally ineffective as an iminium catalyst with enals or enones), MacMillan and coworkers have succeeded in vicinal difunctionalization of various  $\alpha,\beta$ -unsaturated aldehydes with good to excellent diastereoselection and excellent enantioselectivity. The scope for the nucleophiles include hydride from Hantzsch esters and heteroaromatics, while the electrophiles included electrophilic halogens, imines, and nitrogen- and oxygen-based examples. An enantioselective total synthesis of natural product aromadendranediol then showcased the practicability of this chemistry (Figure 2-3).<sup>20</sup>

**Figure 2-3.** MacMillan's Synthesis of Aromadendranediol via Organo-Cascade Catalysis



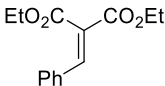

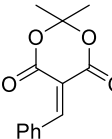
MacMillan's organocascade catalysis was excellent in term of efficiency and stereoselectivity, however, the niche activation mode requires the use  $\alpha,\beta$ -unsaturated aldehydes as Michael acceptors, which limits the functional array for the final products. With the power of this reaction manifold highlighted through the work of MacMillan, there is an impetus for exploring other Michael acceptors to determine if such control can be relayed to more diverse systems than  $\alpha,\beta$ -unsaturated aldehydes.

### 2.2.2 The Alkylidene Meldrum's Acids

Alkylidene Meldrum's acids occasionally termed as "neutral organic Lewis acid" possess unusual, highly electrophilic properties originating from the special structure of its parent motif: Meldrum acid.<sup>21</sup>

Based on the measurement of the rate of addition of nucleophiles to alkylidenes, Mayr has been able to quantify the relative electrophilicity of several classes of alkylidenes (Figure 2-4).<sup>22</sup>

**Figure 2-4.** Electrophilicity Parameter of Alkylidenes

			
<b>2.17</b>	<b>2.18</b>	<b>2.19</b>	
Electrophilicity parameter:	-20.55	-9.42	-9.15

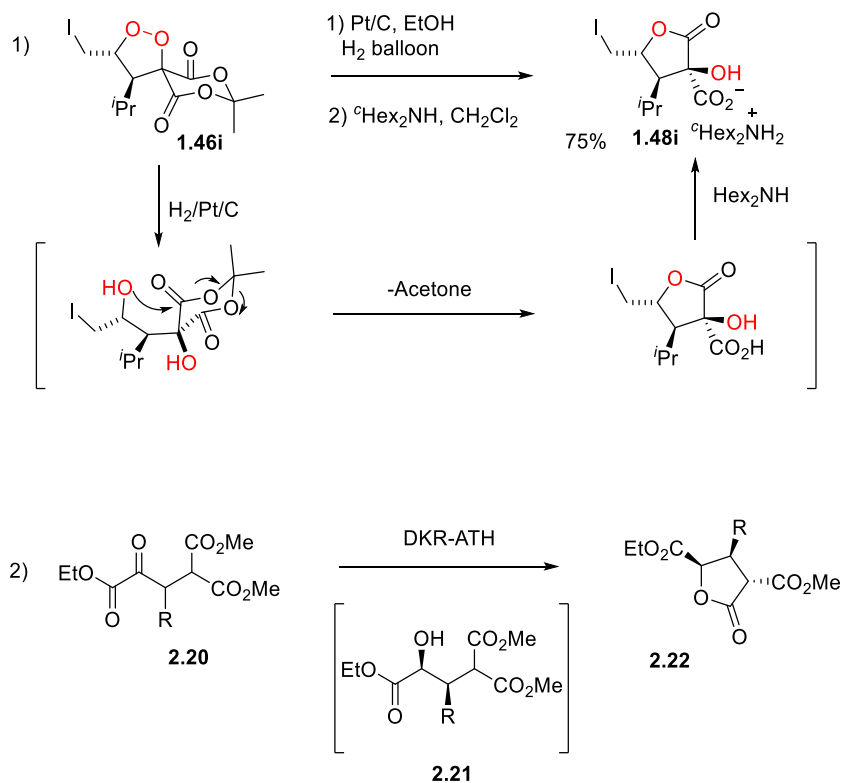
As depicted in Figure 2-5, Mayr's scale of electrophilicity is presented as negative values. The more negative value of the parameter, the less electrophilic the reagent. The difference in electrophilicity value between malonate **2.17** and Meldrum's acid **2.19** alkylidenes indicates a significantly higher electrophilicity of alkylidene Meldrum's acids compared to their malonate counterparts. As a result, this class of molecules has demonstrated exceptional utility for the development of new reactions, which might not be readily accessible from other unsaturated carbonyl electrophiles.

Due to its unusually high electrophilicity, alkylidene Meldrum's acids can effectively react with a wide range of nucleophile including carbon nucleophiles such as aromatic compounds, enolates, organozinc, organotin reagents, and heteroatomic nucleophiles.<sup>23</sup> Several enantioselective Michael additions to alkylidene Meldrum's acids have also developed.<sup>24</sup> While reports using alkylidene Meldrum's acids as Michael acceptors are numerous, it is surprising that there are only a few attempts at further functionalization, analogous to the tandem nucleophile/electrophile additions of  $\alpha,\beta$ -unsaturated aldehydes.

### 2.2.3 Intramolecular Asymmetric Desymmetrization

The desymmetrization is a unique way to create a new chiral building block via a symmetry-breaking operation on heterotopic functional groups under the action of chiral catalyst or reagent.<sup>25</sup>

**Scheme 2-3.** Intramolecular Desymmetrization

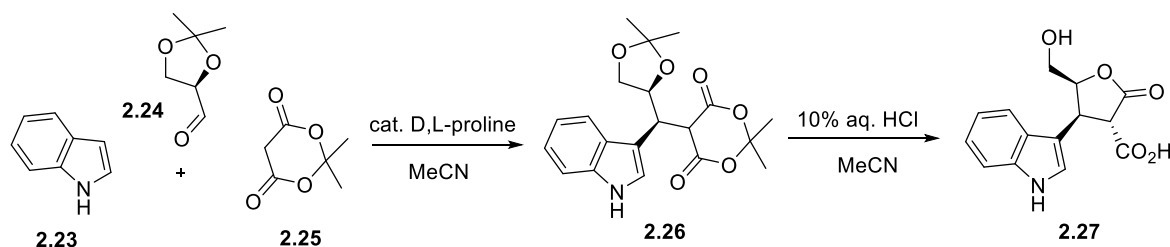


In organic synthesis, in the case there is a preexisting chiral stereocenter in molecule, the intramolecular desymmetrization is usually employed to take advantage of a diastereoselective symmetry-breaking reaction to define a distant center.<sup>26,27</sup> In Chapter 1, we discussed the strategy using the tandem O–O bond cleavage/diastereoselective ring-opening of Meldrum's acid endoperoxides **1.46i** to create  $\alpha$ -hydroxylactones **1.48i** (Scheme 2-3, eq 1).<sup>26</sup> This tactic was also previously employed by Steward when she developed a diastereoselective

dynamic reduction of  $\alpha$ -keto ester **2.20** to create the  $\alpha$ - and  $\beta$ -stereocenters of the *in situ* formed hydroxyester **2.21** via the DTR reduction.<sup>27</sup> The third stereocenter in lactone **2.22** was established by concomitant lactonization of the nascent hydroxyl group with one of the diastereotopic methyl esters to generate a single diastereomer **2.22** (Scheme 2-3, eq 2).

Using a similar idea, Laronze and coworkers reported an interesting example using a preexisting stereocenter of a chiral template to establish two new stereocenters (Scheme 2-4).<sup>28,29</sup>

**Scheme 2-4.** Chiral Template for The Intramolecular Desymmetrization



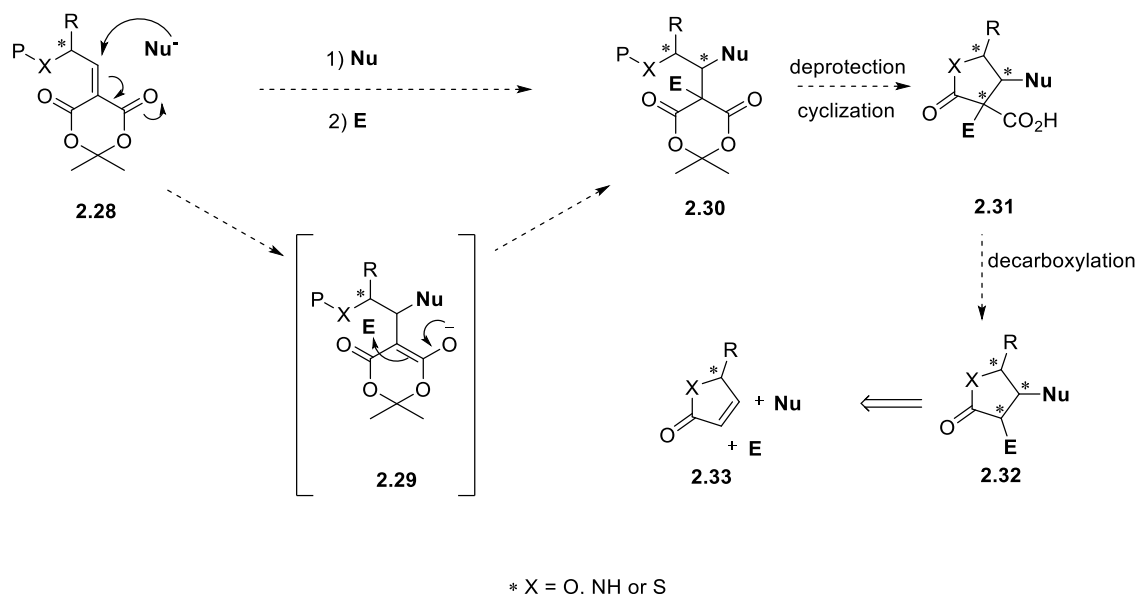
In their work, chiral template 2,3-*O*-isopropylidene-D-glyceraldehyde **2.24** was reacted with Meldrum's acid **2.25** and indole **2.23** in an one-pot procedure, to effectively produce Michael adduct **2.26** as a single diastereomer. Hydrolytic deprotection followed by spontaneous diastereoselective cyclisation eventually revealed the third stereocenter of the lactone **2.27**. In fact, the lactone was isolated as a single diastereomer, demonstrating a complete diastereoselective lactonization process. This method was conceptually attractive by obtaining stereochemical information from the chiral pool (2,3-*O*-isopropylidene-D-glyceraldehyde) to construct a complex building block with multiple consecutive stereocenters.



#### 2.2.4 Research Proposal

Taking lessons from Laronze's work and seeking to expand the number of products available via difunctionalization, we proposed a new approach to multisubstituted cyclic carbonyl compounds (Scheme 2-5). We hypothesize that readily available chiral alkylidene Meldrum's acid **2.28** would be an ideal Michael acceptor for various nucleophiles. In chapter one, we experienced a propensity for 1,4-addition of variety of nucleophiles to alkylidene Meldrum's acid and we hope that the preexisting stereocenter in the chiral alkylidene Meldrum's acid would bias the Michael adduct **2.29** towards high diastereoselectivity. Treatment of the resulting Meldrum acid enolate **2.29** with variety of electrophiles **E** would produce the difunctionalized adduct **2.30**. In order to facilitate an intramolecular desymmetrization, we plan to use a chiral alkylidene Meldrum's acid with a protected functional group that would be able to participate in a downstream ring-opening of Meldrum's acid upon deprotection generating carboxylic acid **2.31**.

**Scheme 2-5.** Intramolecular Desymmetrization of Difunctionalized Alkylidene Meldrum's Acid



Based on our lab's previous successes on the intramolecular desymmetrization to create a new stereocenter and the seminal work of Laronze, we envisioned that the third stereocenter in carboxylic acid **2.31** would be revealed with a high degree of chirality induction. Decarboxylation of **2.31** would produce the trifunctionalized carbonyl compound **2.32**, which is analogous to the product of a highly stereoselective difunctionalization of **2.33**.

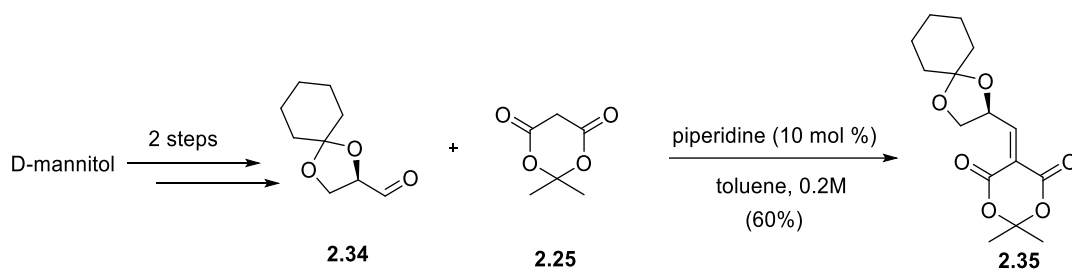
## 2.3 Results and Discussion

### 2.3.1 Identification of Chiral Alkylidene Meldrum's Acids

Our efforts began with the synthesis of a readily available chiral alkylidene Meldrum's acid, which would be able to serve as a chiral template for the installation of the functional array. Laronze's success of achieving high level of diastereoselectivity for one-pot cascade

Knoevenagel condensation/Michael addition using a cheap and readily available chiral template<sup>23,24</sup> (Scheme 2-4) encouraged us to choose protected D-glyceraldehyde to synthesize our requisite chiral alkylidene Meldrum's acid (Scheme 2-6).<sup>30</sup> 2,3-O-cyclohexylidene-D-glyceraldehyde **2.34** was readily prepared via two steps from D-mannitol on multigram scale. The aldehyde was then condensed with Meldrum's acid **2.24** in the presence of 10 mol % piperidine in toluene to furnish the chiral alkylidene **2.35** with 60% yield.

**Scheme 2-6.** Synthesis of Chiral Alkylidene Meldrum's Acid



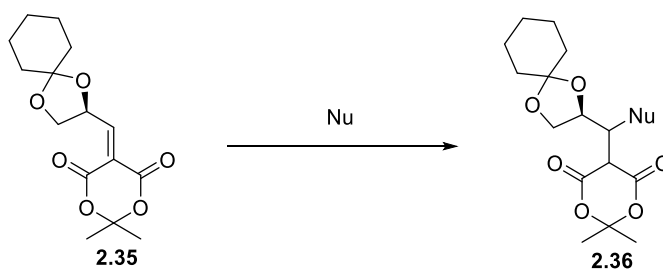
### 2.3.2 Michael Reaction of The Chiral Alkylidene Meldrum's Acid

One crucial requirement of our proposal is that the Michael reaction produces necessary chiral substrates for the intramolecular desymmetrization. With the chiral alkylidene Meldrum's acid **2.35** in hand, we investigated the diastereoselective Michael addition of various nucleophiles (Table 2-1).

We were delighted to observe that many nucleophiles gave the Michael adducts with high diastereoselectivity. Neutral nucleophiles such as indoles (Table 2-1, entries 1-2) provided the Michael adducts in quantitative yield as a single diastereomer. Organometallic reagents,

such as MeMgBr, also gave desired product with high diastereoselectivity (Table 2-1, entries 3). Sodium phenylthiolate also furnished the desired product with 90% conversion and >20:1 dr (Table 2-1, entry 4). Unfortunately, sodium ethoxide did not promote the Michael reaction (Table 2-1, entry 5) and sodium azide gave a messy mixture of unidentified products (Table 2-1, entry 6). These initial results indicated that this template would be suitable for our proposed chemistry, as it reacts with variety of nucleophiles in a highly diastereoselective fashion

**Table 2-1.** Nucleophilic Additions to Chiral Alkylidene Meldrum's Acid

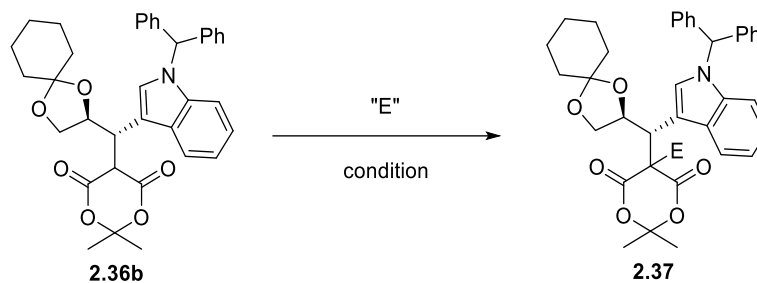


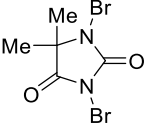
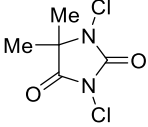
Entry	Nucleophile/Nu	Condition	Result
1		MeCN/ rt, 20 h	Quant. >20:1dr
2		MeCN/rt, 20 h	Quant. >20:1dr
3	MeMgBr	THF/-78 °C	90% yield, >20:1dr
4	PhSNa	DMSO/rt, 20 h	90% conversion, >20:1dr
5	EtONa	DMSO/rt, 20 h	No reaction
6	NaN <sub>3</sub>	DMSO/rt, 20 h	Messy

### 2.3.3. Functionalization of Chiral Meldrum's Acid

With the Michael reaction of alkylidene **2.35** shown to be successful with a variety of nucleophiles--and importantly, with high diastereoselection--we began investigation of the subsequent  $\alpha$ -functionalization to variety of electrophiles (Table 2-2). The fluorination of **2.36b** with *N*-fluorobenzenesulfonimide in the presence of a stoichiometric amount of Hünig's base (ethyl diisopropylamine) in acetonitrile delivered the desired product **2.37b** with 80% yield and >20:1 dr (Table 2-2, entry 1). Attempts to promote the bromination using NBS, Br<sub>2</sub> or 1,3-dibromo-3,3-dimethyl hydantoin and chlorination using NCS or 1,3-dichloro-3,3-dimethyl hydantoin in DCM were not successful (Table 2-2, entries 2,3). Messy reactions were observed in both cases and no desired product was obtained. Standard hydroperoxidation conditions for Meldrum's acid with 25 mol % of copper nitrate in acetonitrile at 0 °C were also applied. Unfortunately, only a messy mixture with no desired product was observed (Table 2-2, entry 4). A sulfenylation condition was tested but no reliable data was collected as a result of messy reactions (Table 2-2, entry 5).<sup>31</sup>

**Table 2-2.** Electrophilic Functionalization of Chiral Meldrum's Acid



Entry	Condition	"E"	Result
1	NFSI/Hünig's base/MeCN	-F	80% yield, >20:1dr
2	 or NBS or Br <sub>2</sub> / Hünig's base/DCM	-Br	Mess
3	 or NCS/ Hünig's base/DCM	-Cl	Mess
4	Cu(NO <sub>3</sub> ) <sub>2</sub> •2H <sub>2</sub> O/O <sub>2</sub> /MeCN/0 °C	-OOH(-OH)	Mess
5	PhSH/NCS/ Hünig's base/DCM	PhS-	Mess
6	PhN=O/ Hünig's base/THF	PhN-O-/PhN(OH)-	NR
7	EtO <sub>2</sub> CN=NCO <sub>2</sub> Et/ Hünig's base/THF	EtO <sub>2</sub> CNHN(CO <sub>2</sub> Et)-	NR
8	BnBr/ Hünig's base/THF	Bn-	NR
9	CH <sub>2</sub> =CH-CH <sub>2</sub> Br/ Hünig's base/THF	CH <sub>2</sub> =CH-CH <sub>2</sub> -	NR

No *N*- or *O*-aldol reaction of nitrosobenzene with the Meldrum's acid was observed, even with stoichiometric amount of Hünig's base (Table 2-2, entry 6).<sup>32</sup> Similarly, ethyl azidocarboxylate showed no reactivity for the amination reaction (Table 2-2, entry 7).<sup>33</sup> Since asymmetric fluorination is an important reaction, especially for biologically relevant compounds,<sup>34</sup> we decided to establish a protocol for the stereoselective fluorination reaction via intramolecular desymmetrization.

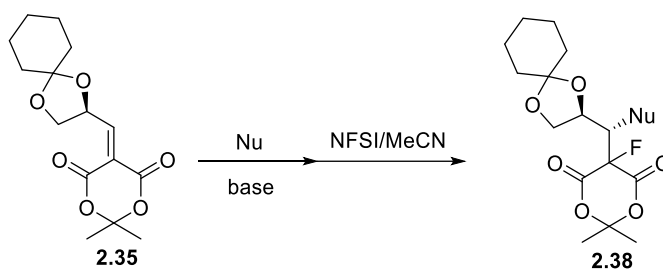
### **2.3.5. Model One-Pot Procedure for Michael Addition/Fluorination of Alkylidene Meldrum's Acid**

We next sought to develop a one-pot procedure for the tandem Michael addition/fluorination. We started first with organometallic nucleophiles as the metallic Meldrum's acid enolates produced in these reactions would be effectively ready for the subsequent fluorination, without addition of further base. Grignard reagents such as methyl-, vinyl-, allyl-, phenylmagnesium bromide were separately added to solution of the alkylidene Meldrum's acid **2.35** in THF at -78 °C, followed by addition of NFSI after 3 h at the same temperature. The reaction was then slowly warmed to rt overnight and quenched with aqueous solution of 10% HCl.

Disappointingly, the reaction mixtures from this procedure were always messy. Attempts to purify the crude product via column chromatography with silica gel using 20% ethyl acetate/hexanes resulted solely in loss of material on the column. We were never able to cleanly isolate a desired fluorinated Meldrum's acid **2.39** using this procedure. Given the presence of vulnerable groups such as the ketal and fully substituted Meldrum acid, we

envisioned that the acidic work up procedure could be the source of the complications. Therefore, modified work up conditions were then devised. Specifically, instead of quenching the reaction with 10% HCl solution, the reaction was concentrated to remove most of the acetonitrile and triturated with diethyl ether to remove most of the inorganic salts from the mixture. Significant improvements in yield were observed using this new protocol. Results for some representative nucleophiles for the new procedure are presented in Table 2-3.

**Scheme 2-7.** One-Pot Michael Addition/Fluorination

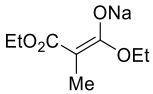
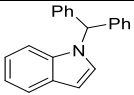
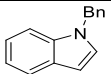


With the organometallic nucleophiles the crude  $^1\text{H}$  NMR and  $^{19}\text{F}$ -NMR showed complete conversion to desired product with only a single diastereomer (Table 2-3, entries 1-4). In the case of neutral nucleophile such as *N*-diphenylmethyl indole, a stoichiometric amount of additional base was needed for an efficient fluorination (Table 2-3, entry 5).

Attempts to purify these fluorinated products via column chromatography with silica gel were ineffective. Poor mass recovery after column chromatography indicated that these compounds were not stable on the silica gel column. Therefore, these substrates were carried on the next step without further purification.



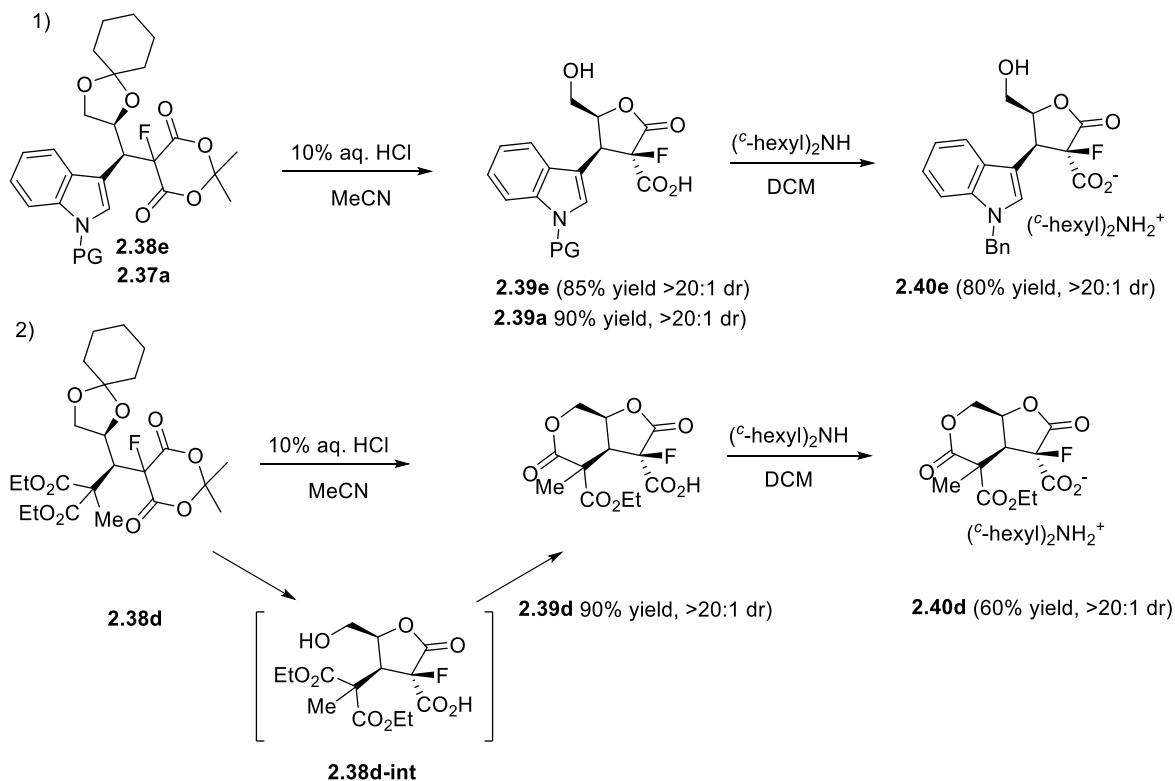
**Table 2-3.** Representative Substrates for One-Pot Michael Addition/Fluorination

Entry	Nucleophile/Nu	Base	Result
1	MeMgBr	None	100% conversion, >20:1 dr <b>2.38a</b>
2	PhMgBr	None	100% conversion, >20:1 dr <b>2.38b</b>
3	CH <sub>2</sub> =CHMgBr	None	100% conversion, >20:1 dr <b>2.38c</b>
4		None	100% conversion, >20:1 dr <b>2.38d</b>
5		MeONa	100% conversion, >20:1 dr <b>2.37a</b>
6		MeONa	100% conversion, >20:1 dr <b>2.38e</b>

### 2.3.5. Model Intramolecular Desymmetrization

With the fluorinated Meldrum's acids in hand, we next investigated the intramolecular desymmetrization. We hoped that when the difunctionalized ketals were deprotected under acidic conditions, one of the two hydroxyl groups would spontaneously cyclize to open the Meldrum's acid.

**Scheme 2-8.** Model Intramolecular Desymmetrization



Gratifyingly, when subjecting the ketal **2.38e** and **2.37a** to a mixture of 10% aqueous HCl and acetonitrile, five-membered ring lactones **2.39e** and **2.39a** were revealed with a high diastereoselection and high yield. This indicates complete enantiofacial discrimination during the lactonization (Scheme 2-8, eq 1). Cumulatively, this method sets three stereocenters with high diastereoselection in each case. The stereochemistry of these products was tentatively assigned based on the similar works from Laronze and coworkers.<sup>28,29</sup>

Interestingly, under the deprotection condition, Meldrum's acid **2.38d** provided bislactone **2.39d** as a single diastereomer. The product is formed via intramolecular lactonization of the secondary alcohol with Meldrum's acid revealed the third stereocenter, followed by enantiofacially selective lactonization of the remaining hydroxy group with one

of the pendant esters. For convenient usage, the corresponding carboxylic acids, **2.39d** and **2.39e** were converted into ammonium salts with dicyclohexylamine (Scheme 2-8). All attempts to develop a one-pot procedure for the three successive steps--Michael addition/fluorination/desymmetrization--have proven unsuccessful so far.

## 2.4 Conclusion

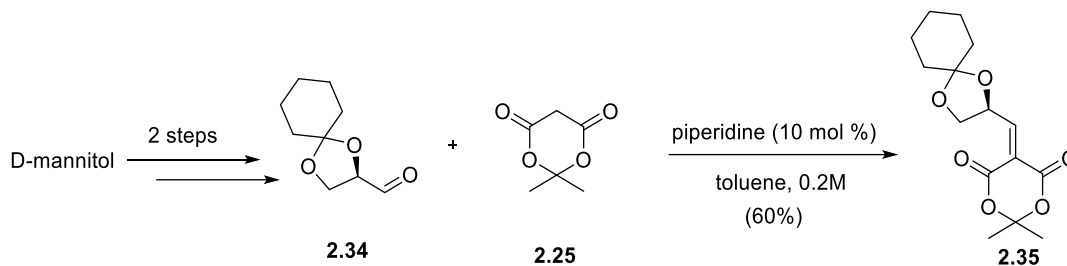
When we embarked upon this project, we sought to develop a general method for a highly diastereoselective difunctionalization of unsaturated carbonyl compounds, via substrate-controlled Michael addition to a chiral alkylidene Meldrum's acid followed by an intramolecular desymmetrization via lactonization. Promising proof-of-concept for this manifold has been established for tandem Michael addition/fluorination, followed by desymmetrization by ring-opening of the Meldrum's acid moiety. However, at this stage, limited efforts to establish conditions for the functionalization of monosubstituted Meldrum's acid were only successful in the case of fluorination. Continued efforts will be needed to investigate conditions for other functionalization of monosubstituted Meldrum's acids to expand the application of this chemistry. Other chiral alkylidene Meldrum's acids will also be investigated, and broader scope for the diastereoselective Michael addition will also bring added value to this already-promising reaction.

## 2.5 Experimental Details

**Methods: General.** Proton, and fluorine magnetic resonance spectra ( $^1\text{H}$  NMR and  $^{19}\text{F}$  NMR) were recorded on a Bruker model Avance 400 ( $^1\text{H}$  NMR at 400 and  $^{19}\text{F}$  NMR at 376 MHz), Bruker model Avance 500 ( $^1\text{H}$  NMR at 500 MHz), or a Bruker Avance III 600 ( $^1\text{H}$  NMR at 600 MHz and  $^{19}\text{F}$  NMR at 564 MHz) spectrometer with solvent resonance as the internal standard ( $^1\text{H}$  NMR:  $\text{CDCl}_3$  at 7.26 ppm).  $^1\text{H}$  NMR data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, br d = broad doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. Analytical thin layer chromatography (TLC) was performed on Sorbent Technologies 0.20 mm Silica G TLC plates. Visualization was accomplished with UV light,  $\text{KMnO}_4$ , and/or aqueous ceric ammonium nitrate solution followed by heating. Purification of the reaction products was carried out by flash chromatography using Siliaflash-P60 silica gel (40-63 $\mu\text{m}$ ) purchased from Silicycle. Unless otherwise noted, all reactions were carried out under an atmosphere of dry nitrogen in oven-dried glassware with magnetic stirring. Yield refers to isolated yield of analytically pure material unless otherwise noted. Yields are reported for a specific experiment and as a result may differ slightly from those found in the tables, which are averages of at least two experiments.

**Materials: General.** Tetrahydrofuran, diethyl ether, dichloromethane, and toluene were dried by passage through a column of neutral alumina under nitrogen prior to use. All other reagents were purchased from commercial sources and were used as received unless otherwise noted.

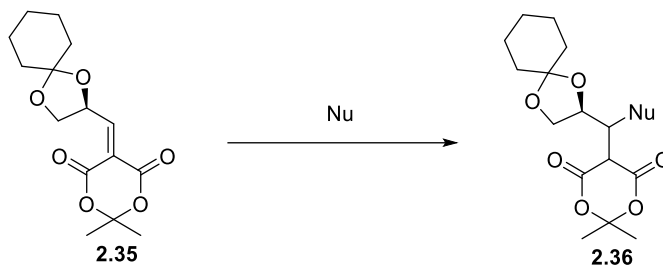
## Experimental Procedures:



### S)-5-((1,4-dioxaspiro[4.5]decan-2-yl)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione

**(2.35):** A mixture of D-mannitol (10.0 g, 54 mmol), cyclohexanone (16.8 mL, 162 mmol), triethyl orthoformate (9 mL, 54 mmol),  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  (0.6 mL, 5.4 mmol) and dry DMSO (25 mL) was stirred for 13 h at rt. The mixture was then poured into 20 mL of 10% ice-cooled  $\text{NaHCO}_3$  solution and was extracted with ether (15 mL x 3). The organic layer was dried over  $\text{MgSO}_4$  and concentrated *in vacuo*. To a solution of the residue obtained in 100 mL of ether was added a solution of  $\text{NaIO}_4$  (14.6 g, 68 mmol) and  $\text{Bu}_4\text{NF}$  (0.22 mL, 0.7 mmol) in 60 mL of water, and the mixture was stirred for 3 h at rt. The mixture was separated and aqueous layer was extracted with ether (15 mL x 3). The combined organic layers were dried over  $\text{MgSO}_4$  and concentrated *in vacuo* to give 8.6 g of 2,3-O-cyclohexylidene-D-glyceraldehyde as an oil. To a stirred solution of this aldehyde in toluene was added 7.3 g of Meldrum acid (1 equiv), 10 g sodium sulfate ( $\text{Na}_2\text{SO}_4$ ) and 43 mg of piperidine (10 mol%). The mixture was stirred at rt for 20h. The mixture was then filtered and the filtrate was concentrated *in vacuo*. The product was purified via flash chromatography (70:30 hexane/ethyl acetate) to give the desired product as a white solid (9.0 g, 60%). Analytical data:  $^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.96-7.95 (d,  $J$  = 5.4 Hz, 1H), 5.56-5.52 (q,  $J$  = 6.6 Hz, 1H), 4.53-4.50 (t,  $J$  = 7.8 Hz, 1H), 3.77-3.75 (m, 1H) 1.76 (s, 6H), 1.75-1.42 (m, 10H); **TLC** (70:30 hexane/ethyl acetate):  $R_f$  = 0.30.

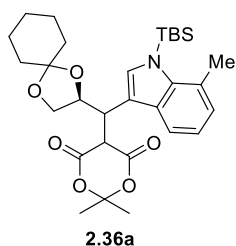
## Nucleophilic Additions to Chiral Alkylidene Meldrum's Acid



General procedure A: A 1:1 mixture of the alkylidene **3.5** and nucleophile in acetonitrile was stirred at rt for 20h. The solvent was then evaporated *in vacuo* to provide desired product. No purification was needed.

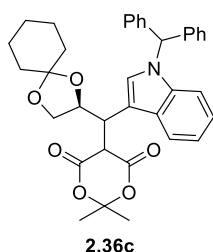
Procedure B: To a solution of 170 mg of the alkylidene **3.5** in THF (0.5 M) at  $-78^{\circ}\text{C}$  was slowly added 0.4 ml (3 M) solution of MeMgBr in THF (1.2 equiv). The resulting solution was stirred at  $-78^{\circ}\text{C}$  for 2 h and quenched with 1 M HCl (5 ml). The organic layer was separated and the aqueous layer was extracted with diethyl ether ( $\text{Et}_2\text{O}$ ). The combined organic extracts were washed with brine (15 mL), dried ( $\text{MgSO}_4$ ) and concentrated.

Procedure C: A 1:1 mixture of 170 mg of the alkylidene **3.5** and 132 mg PhSNa in DMSO was stirred at rt for 20 h. The reaction was quenched by 5 ml solution of HCl 1 M. The organic layer was separated and the aqueous layer was extracted with diethyl ether ( $\text{Et}_2\text{O}$ ). The combined organic extracts were washed five times with brine (15 mL), dried ( $\text{MgSO}_4$ ) and concentrated.



**Analytical data for 5-((1-(tert-butyldimethylsilyl)-7-methyl-1H-indol-3-yl))((S)-1,4-dioxaspiro[4.5]decan-2-yl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**2.36a**):**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.52-7.49 (m,

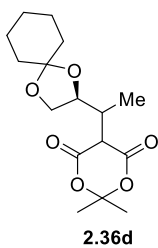
1H), 7.41 (s, 1H), 7.08-7.05 (m, 1H), 6.96-6.95 (m, 1H), 4.91-4.88 (m, 1H), 4.42-4.41 (m, 1H), 4.11-4.10 (m, 1H), 3.99-3.95 (m, 1H), 3.72-3.71 (d,  $J = 2.8$  Hz, 1H), 2.6 (s, 3H), 1.64 (s, 3H), 1.60-1.49 (m, 10H), 1.31 (s, 3H), 0.88 (s, 9H), 0.62 (s, 6H).



**Analytical data for 5-((1-benzhydryl-1H-indol-3-yl)((S)-1,4-dioxaspiro[4.5]decan-2-yl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione**

**(2.36c):**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.64-7.63 (m, 1H), 7.33-7.08 (m, 13H), 6.97 (s, 1H), 6.80 (s, 1H), 4.83-4.78 (m, 1H), 4.36-4.34 (m, 1H), 4.08-

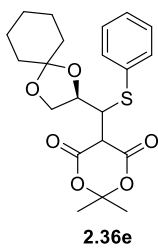
4.05 (m, 1H), 3.83-3.79 (t,  $J = 8$  Hz, 3.67-3.66 (s, 3.2 Hz, 1H), 1.62 (s, 3H), 1.55-1.31 (m, 10H), 1.23 (s, 3H).



**Analytical data for 5-(1-((S)-1,4-dioxaspiro[4.5]decan-2-yl)ethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (2.36d):**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.47-

4.41 (m, 1H), 4.08-4.05 (dd,  $J = 8$  Hz,  $J = 6$  Hz, 1H), 3.78-3.74 (t,  $J = 7.6$  Hz, 1H), 3.38-3.37 (d,  $J = 3.2$  Hz, 1H), 2.82-2.78 (m, 1H), 1.77 (s, 3H), 1.75 (s, 3H),

1.61-1.59 (m, 8H), 1.39-1.38 (m, 2H), 1.21-1.19 (d,  $J = 6.8$  Hz, 1H).

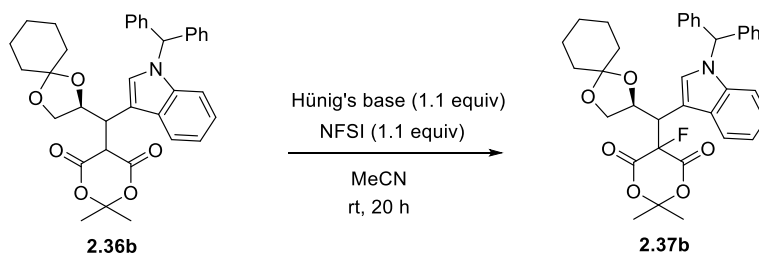


**Analytical data for 2,2-dimethyl-5-((phenylthio)((R)-1,4-**

**dioxaspiro[4.5]decan-2-yl)methyl)-1,3-dioxane-4,6-dione (2.36e):**  $^1\text{H}$  NMR

(400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.50-7.47 (m, 2H), 7.30-7.22 (m, 3H), 4.72-4.67 (m, 1H), 4.29-4.28 (m, 1H), 4.10-4.05 (m, 1H), 3.97-3.94 (dd,  $J = 10.8$  Hz,  $J = 1.6$  Hz,

1H), 3.71-3.68 (dd,  $J = 8.8$  Hz,  $J = 4.4$  Hz, 1H), 1.77 (s, 3H), 1.76 (s, 3H), 1.53-1.50 (m, 10H);



**5-((1-benzyl-1H-indol-3-yl)((S)-1,4-dioxaspiro[4.5]decan-2-yl)methyl)-5-fluoro-2,2-**

**dimethyl-1,3-dioxane-4,6-dione (2.37a):** To a solution of **2.36b** (201 mg, 0.4 mmol, 1.00

equiv) in 5 ml of acetonitrile was added a solution of 57 mg (0.44 mmol) *N,N*-

Diisopropylethylamine (Hünig's base) in acetonitrile. The reaction was stirred at rt for 1 h

then NFSI (143 mg) was added. The mixture was stirred at rt for 20 h. The reaction was

quenched with 1 M HCl (5 mL) and extracted with EtOAc (2 x 10 mL). The combined

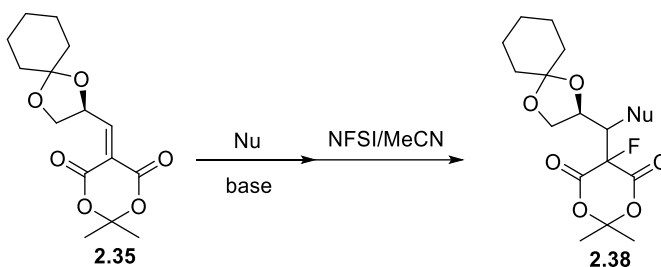
organic extracts were washed with brine, dried with magnesium sulfate, and concentrated *in*

*vacuo* to give product **2.37a** as a brown-red solid (167 mg, 80%). Analytical data: **<sup>1</sup>H NMR**

(400 MHz, CDCl<sub>3</sub>):  $\delta$  7.34-7.13 (m, 14H), 7.01 (s, 1H), 6.83 (s, 1H), 4.83-4.78 (m, 1H),

4.19-4.11 (m, 2H), 3.59-3.55 (t,  $J = 8.0$  Hz, 1H), 1.62 (s, 3H), 1.54 (s, 3H), 1.46-1.24 (m,

10H), 1.14 (s, 3H); **<sup>19</sup>F NMR** (376 MHz, CDCl<sub>3</sub>):  $\delta$  -158.0;



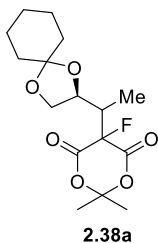
**General Method for One-Pot Michael Addition/Fluorination**



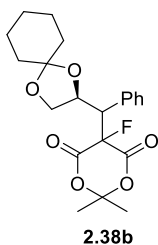
**Method A:** To a solution of 170 mg of the alkylidene **3.5** in THF (0.5 M) at  $-78^{\circ}\text{C}$  was slowly added solution of Grignard reagent in THF (1.2 equiv). The resulting solution was stirred at  $-78^{\circ}\text{C}$  for 2 h and 390 mg NFSI (1.2 mmol) was added at once. The reaction was then slowly warmed to rt and stirred for 20 h. Solvent was evaporated *in vacuo* and the residue was triturated with 10 ml of  $\text{Et}_2\text{O}$ . The solid was removed by filtration and the filtrate was concentrated *in vacuo*.

**Method B:** A 1:1 mixture of the alkylidene **3.5** and the protected indole in acetonitrile was stirred at rt for 20h. The solvent was then evaporated *in vacuo*. THF (10 ml) was then added followed by an addition of 82 mg (1.2 mmol) of EtONa. The reaction was stirred at rt for 2 h before 390 mg NFSI (1.2 mmol) was added at once. The suspension was stirred at rt for additional 20 h. Solvent was evaporated and the residue was triturated with 10 mL of  $\text{Et}_2\text{O}$ . The solid was removed by filtration and the filtrate was concentrated *in vacuo*.

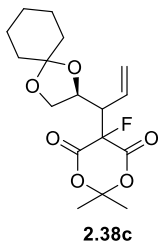
**Method C:** To a solution of 1 mmol diethyl methylmalonate in THF was added 60 mg sodium hydride (60% dispersion in mineral oil). The mixture was stirred at rt for 1 h then 170 mg alkylidene Meldrum's acid was added. The reaction was stirred for 4 h at rt and then cooled down to  $-78^{\circ}\text{C}$ . 390 mg NFSI was added at once. The suspension was then stirred at rt for additional 20 h. Solvent was evaporated by rotavap and the residue was triturated with 10 ml of  $\text{Et}_2\text{O}$ . Filtration to remove the solid and the filtrate was concentrated *in vacuo*.



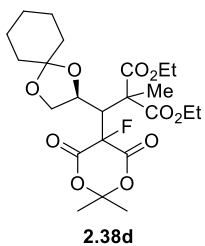
**Analytical data for 5-(1-((S)-1,4-dioxaspiro[4.5]decan-2-yl)ethyl)-5-fluoro-2,2-dimethyl-1,3-dioxane-4,6-dione (2.38a):** (Method A):  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  4.22-4.19 (m, 1H), 4.16-4.12 (m, 1H), 3.76-3.72 (t,  $J = 7.6$  Hz, 1H), 2.67-2.61 (m, 1H), 1.80 (s, 3H), 1.78 (s, 3H), 1.59-1.39 (m, 10H), 1.19-1.18 (d,  $J = 6.8$  Hz, 3H);  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ ):  $\delta$  -162.9.



**Analytical data for 5-fluoro-2,2-dimethyl-5-(phenyl((S)-1,4-dioxaspiro[4.5]decan-2-yl)methyl)-1,3-dioxane-4,6-dione (2.38b):**  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.29-7.28 (m, 5H), 5.20-5.17 (dd,  $J = 8.4$  Hz,  $J = 6.0$  Hz, 1H), 3.98-3.95 (m, 2H), 1.76 (s, 3H), 1.59-1.25 (m, 10H), 1.14 (s, 3H;  $^{19}\text{F}$  NMR (565 MHz,  $\text{CDCl}_3$ ):  $\delta$  -157.7;

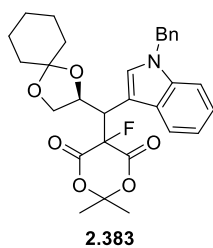


**Analytical data 5-(1-((S)-1,4-dioxaspiro[4.5]decan-2-yl)allyl)-5-fluoro-2,2-dimethyl-1,3-dioxane-4,6-dione (2.38c):** (Method A):  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.88-5.78 (m, 1H), 5.47-5.44 (d,  $J = 10.4$  Hz, 1H), 5.35-5.31 (d,  $J = 18.4$  Hz, 1H), 4.37-4.34 (m, 1H), 4.11-4.04 (m, 1H), 3.74-3.70 (t,  $J = 7.6$  Hz, 1H), 3.18-3.10 (m, 1H), 1.78 (s, 6H), 1.59-1.39 (m, 10H);  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ ):  $\delta$  -159.7;



**Analytical data for diethyl 2-((5-fluoro-2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)((S)-1,4-dioxaspiro[4.5]decan-2-yl)methyl)-2-methylmalonate (2.38d)** (Method A) Analytical data:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  4.93-4.89 (m, 1H), 4.37-4.33 (dd,  $J = 10.4$  Hz,  $J = 5.6$  Hz, 1H),

4.26-4.05 (m, 7H), 3.64-3.59 (dt,  $J = 8.4$  Hz,  $J = 2.4$  Hz, 1H), 1.86 (s, 3H), 1.84 (s, 3H), 1.77 (s, 3H), 1.33-1.29 (t,  $J = 6.8$  Hz), 3H), 1.24-1.19 (t,  $J = 6.8$  Hz), 3H);  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ ):  $\delta$  -146.0;

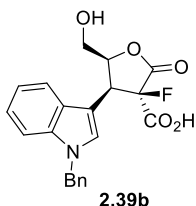


**Analytical data for 5-((1-benzyl-1H-indol-3-yl))((S)-1,4-dioxaspiro[4.5]decan-2-yl)methyl)-5-fluoro-2,2-dimethyl-1,3-dioxane-4,6-dione (2.383):**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.29-7.10 (m, 9H), 7.11 (s, 1H), 5.28 (s, 2H), 4.93-4.89 (m, 1H), 4.22-4.15 (m, 2H), 3.67-3.63 (t,  $J = 8.0$  Hz, 1H), 3.06-3.00 (m, 1H), 1.61 (s, 3H), 1.60-1.20 (m, 10H), 1.06 (s, 3H);

### General Procedure for Intramolecular Desymmetrization

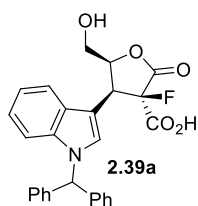
To a solution of 1 mmol fluorinated Meldrum's acid in 10 ml acetonitrile was added 2 ml 10% HCl solution and the reaction was stirred at rt for 20 h. The solution was then extracted with ethyl acetate (3x10 ml). The combined organic extracts were washed with brine, dried with sodium sulfate, and concentrated *in vacuo*.

To a solution of 0.5 mmol of the carboxylic acid **3.39d,e** a soln of dicyclohexylamine (91 mg, 0.5 mmol, 1 equiv) in dry  $\text{CH}_2\text{Cl}_2$  was added. After 1 h, the reaction was concentrated to dryness and triturated with hexanes (10 mL). The precipitate was isolated by suction filtration to give the dicyclohexylamine salt as cream colored solid (dr >20:1).



**Analytical data for (3R,4S,5S)-3-fluoro-5-(hydroxymethyl)-2-oxo-4-phenyltetrahydrofuran-3-carboxylic acid (2.39b):**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.28-7.13 (m, 9H), 7.06 (s, 1H), 5.30-5.29 (d,  $J = 16$  Hz, 2H), 5.22-

5.18 (m, 1H), 4.78-4.69 (dd,  $J = 26.0$  Hz,  $J = 7.6$  Hz, 1H), 3.75-3.70 (dd,  $J = 13.2$  Hz,  $J = 8.0$  Hz, 1H); 3.60-3.56 (dd,  $J = 12.8$  Hz,  $J = 3.6$  Hz, 1H);

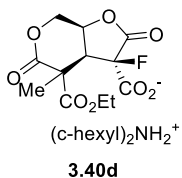


**2.39a**

**Analytical data for (3R,4S,5S)-4-(1-benzhydryl-1H-indol-3-yl)-3-fluoro-5-(hydroxymethyl)-2-oxotetrahydrofuran-3-carboxylic acid (2.39a):  $^1\text{H}$**

**NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.40-7.05 (m, 14H), 6.89 (s, 1H), 6.80 (s, 1H),

5.18-5.13 (m, 1H), 4.71-4.63 (dd,  $J = 24.0$  Hz,  $J = 8.0$  Hz, 1H), 3.73-3.65 (m, 1H), 3.56-3.52 (dd,  $J = 12.8$  Hz,  $J = 4.0$  Hz, 1H);  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ ):  $\delta$  -167.5;

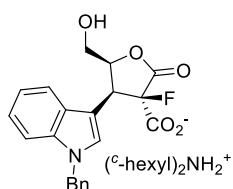


**3.40d**

**Analytical data for (3R,3aS,4S,7aS)-4-(ethoxycarbonyl)-3-fluoro-4-methyl-2,5-dioxohexahydro-2H-furo[2,3-c]pyran-3-carboxylate (2.40d):**

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.13-5.10 (m, 1H), 4.61-4.57 (d,  $J = 14.4$  Hz,

1H), 4.48-4.40 (dd,  $J = 18.0$  Hz,  $J = 9.2$  Hz, 1H), 4.29-4.26 (m, 2H), 4.18-4.13 (dd,  $J = 14.8$  Hz,  $J = 3.6$  Hz, 1H), 3.05-3.02 (m, 2H), 2.05-1.99 (m, 4H), 1.83-1.80 (m, 4H), 1.66 (m, 2H), 1.45-1.43 (m, 4H), 1.30-1.21 (m, 6H), 1.32-1.29 (t,  $J = 6.8$  Hz, 3H);  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ ):  $\delta$  -157.1;



**3.40e**

**Analytical data for (3R,3aS,4S,7aS)-4-(ethoxycarbonyl)-3-fluoro-4-methyl-**

**2,5-dioxohexahydro-2H-furo[2,3-c]pyran-3-carboxylate(3R,4S,5S)-4-(1-**

**benzyl-1H-indol-3-yl)-3-fluoro-5-(hydroxymethyl)-2-oxotetrahydrofuran-3-carboxylate (2.40f):  $^1\text{H}$  NMR** (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.51 (m, 1H), 7.27-7.04

(m, 8H), 7.17 (s, 1H), 5.29-5.28 (d,  $J = 16.8$  Hz, 2H), 5.27-5.24 (m, 1H), 4.68-4.64 (dd,  $J =$

14.4 Hz,  $J = 7.2$  Hz, 1H), 3.64-3.62 (m, 1H), 3.51-3.49 (dd,  $J = 12.6$  Hz,  $J = 4.2$  Hz, 1H), 2.74 (bs, 4H), 1.89-1.87 (m, 4H), 1.69(m, 2H), 1.57-1.55 (m, 4H), 1.30-1.21 (m, 6H);

## 2.6 References

1. Tietze, L. F. *Chem. Rev.* **1996**, 96, 115-136. (b) Tietze, F. L.; Kinzel T.; Brazel, C. *C. Acc. Chem. Res.* **2009**, 42, 367-378. (c) Oikawa, M. *Kagaku Kogyo* **2007**, 58, 377-385.
2. Hanessian, S. *Pure Appl. Chem.* **1993**, 65, 1189-204.
3. Chassaing, C.; Haudrechy, A.; Langlois, Y. *Tetrahedron Lett.* **1999**, 40, 8805.
4. Haudrechy, A.; Chassaing, C.; Riche, C.; Langlois, Y. *Tetrahedron.* **2000**, 56, 3181.
5. Davis, F. A.; Liu, H.; Chen, B. C.; Zhou, P. *Tetrahedron* **1998**, 54, 10481.
6. Differding, E.; Lang, R. W. *Tetrahedron Lett.* **1988**, 29, 6087.
7. Alexander M. R. Smith. A. M. R.; Hii. K. K. *Chem. Rev.* **2011**, 111, 1637–1656.
8. Chapdelaine, M. J.; Hulce, M. *Organic Reactions.* **2004**, 38:2, 225–653.
9. (a) Ashby, C.; Argyropoulos, N. *Tetrahedron Lett.* **1984**, 7. (b) Hannah, J.; Smith, J. *Tetrahedron Lett.* **1975**, 187.
10. Taylor. R. J. K. *Synthesis*, **1985**, 364.
11. Normant. J. F. *J. Organomet. Chem.* **1976**, 1, 219.
12. Posner. G. H. *Org. React.* **1972**, 19, 1.
13. (a) Kharasch. M. S.; Tawney. P. O. *J. Am. Chem. Soc.*, **1982**, 104, 2308. (b) Alexakis. A.; Chapdelaine. M. J.; Posner. G. H.; Runquist. A. W. *tetrahedron Lett*, **1978**, 4205.
14. J.-B. Wiel, F. Rouessac, *Bull. Soc. Chim. Fr. II* **1979**, 273.
15. Cairns. J.; Hewett. C. L.; Logan. R. T.; McGarry. G.; Steveson. D. F. M.; Wppds. G. F. *J. Chem. Soc., Perkin Trans. I.* **1976**, 1558.
16. Nicolaou. K. C.; Barnette. W. E.; Ma. P. *J. Org. Chem.*, **1980**, 45, 1463–1470.
17. Ager. D. J.; Fleming. I.; Patel. S. K. *J. Chem. Soc., Perkin Trans. I.* **1981**, 2520.

18. Posner. G. H.; Lentz. C. M. *J. Am. Chem. Soc.*, **1979**, *101*, 934.
19. Huang. Y.; Walji. A. M.; Larsen. C. H.; MacMillan. D. W. C. *J. Am. Chem. Soc.*, **2005**, *127*, 15051-15053.
20. Simmons. B.; Walji. A.; MacMillan. D. W. C.; *Angew. Chem. Int. Ed.* **2009**, *48*, 4349–4353.
21. (a) Swoboda, G. Swoboda, J.; Wessely, F. *Monatsch. Chem.* **1964**, *95*, 1283-1304.  
(b) Bernasconi, C. F.; Ketner, R. J.; Ragains, M. L.; Chen, X.; Rappoport, Z. *J. Am. Chem. Soc.* **2001**, *123*, 2155-2164.
22. (a) Lemek, T.; Mayr, H. *J. Org. Chem.* **2003**, *68*, 6880-6886. (b) Berger, S. T. A.; Seeliger, F. H.; Hofbauer, F.; Mayr, H. *Org. Biol. Chem.* **2007**, *5*, 3020-3026. (c) Seeliger, F.; Berger, S. T. A.; Remennikov, G. Y.; Polborn, K.; Mayr, H. *J. Org. Chem.* **2007**, *73*, 9170-9180. (d) Kaumanns, O.; Lucius, R.; Mayr, H. *Chem. Eur. J.* **2008**, *14*, 9675-9682. (e) Mayr, H.; Bug, T.; Gotta, M. F.; Hering, N.; Irrgang, B.; Janker, B.; Kempf, B.; Loos, R.; Ofial, A. R.; Remennikov, G.; Schimmel, H. *J. Am. Chem. Soc.* **2001**, *123*, 9500-9512. For an overview of the development of quantitative determination of reactivity parameters see: (f) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* 2003, *36*, 66-77. (g) Kaumanns, O.; Mayr, H. *J. Org. Chem.* **2008**, *73*, 2738-2745.
23. Dumas. A. M.; Fillion. E. *Acc. Chem. Res.*, **2010**, *43*, 440–454.
24. (a) Watanabe, T.; Knöpfel, T. F.; Carreira, E. M. *Org. Lett.* **2003**, *5*, 4557–4558.  
(b) Knöpfel, T. F.; Zarotti, P.; Takashi, Y.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 9682–9683. (c) Wilsily, A.; Fillion, E. *J. Org. Chem.* **2009**, *74*, 8583-8594. (d) Fillion, E.; Wilsily, A. *J. Am. Chem. Soc.* **2006**, *128*, 2774–2775. (e) Fillion, E.; Wilsily, A.; Liao, E.-T. *Tetrahedron: Asymmetry* **2006**, *17*, 2957–2959.
25. (a) Ward, R. S. *Chem. Soc. Rev.* **1990**, *19*, 1–19; (b) Willis, M. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1765–1784.
26. Krabbe, S. W.; Do, D.; Johnson, J. S. *Org. Lett.* **2012**, *14*, 5932
27. Steward, K. M.; Gentry, E. C.; Johnson, J. S. *J. Am. Chem. Soc.* **2012**, *134*, 7329
28. Boisbrun. M, Kova'cs-Kulyassa. A.; Jeannin. L.; Sapi. J.; Toupetb. L.; Laronze. J. Y. *Tetrahedron Letters*, **2000**, *41*, 9771–9775.
29. Dardennes. E.; Kova'cs-Kulyassa. A.; Boisbrun. M.; Petermann. C.; Laronze J. Y.; Sapi. J., *Tetrahedron: Asymmetry*, **2005** *16*, 1329–1339.

30. Fujimori. S.; Carreira, E. M. *Angew. Chem. Int. Ed.*, **2007**, *46*, 4964 – 4967.
31. Hopkins. P. B.; Fuchs. P. L. *J. Org. Chem.*, **1978**, *43*, 1208-1217.
32. Momiyama. N.; Yamamoto. H, *J. Am. Chem. Soc* **2005**, 1080-81.
33. Nandakumar, M. V.; Ghosh, S.; Schneider, C. *Eur. J. Org. Chem.* **2009**, 6393
34. Filler. R.; Shaha. R. *Future Med. Chem.* **2009**, *5*, 777-791.

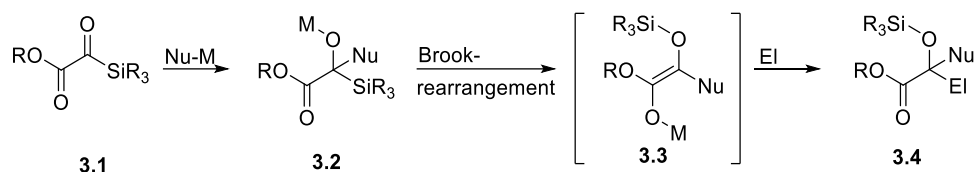


## CHAPTER THREE: EFFORTS TOWARD THE SYNTHESIS OF ECHINOSPORIN

### 3.1 Introduction

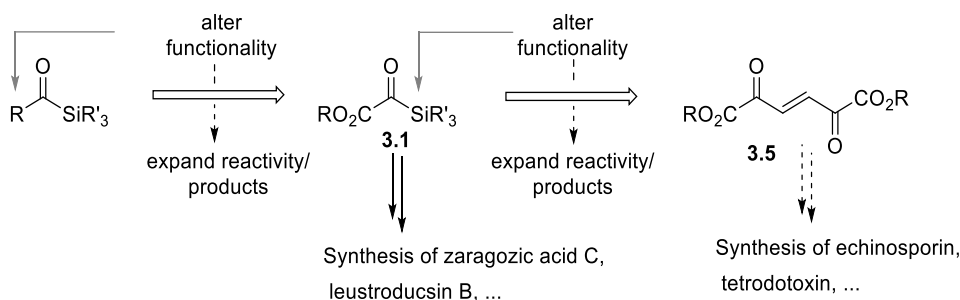
A crucial aspect of complex synthesis studies is the opportunity for discovering new methods in tandem with the development of new useful building blocks for rapid complexity assembly. Identifying simple compounds that manifest unique reactivity to allow quick access to complex molecules is a primary goal of modern synthetic chemistry.<sup>1</sup> Our group's development of silyl glyoxylate, is a prototypical example of this reaction class. Addition of a nucleophile to these unique reagents triggers a [1,2]-Brook rearrangement (**3.2**  $\rightarrow$  **3.3**) to achieve an acyl anion equivalent (**Scheme 3-1**). Subsequent trapping of the nascent carbanion (enolate, **3.3**) with an electrophile provides the 2,2-difunctionalized product **3.4**. Thus, the silyl glyoxylate serves as a linchpin for multi-component reactions to access to a glycolic acid framework. Several natural products have been prepared based on the conjunctive reagent utilizing silyl glyoxylate in various cascade reactions exploring its valuable umpolung reactivity.<sup>2</sup>

### Scheme 3-1. Silyl Glyoxylate Umpolung Reactivity



In this chapter, we extend the idea of reagent evolution through the exploration of “pyruvate alkylidene dimers” (**3.5**) as simple reagents for complexity-building operations (**Scheme 3-2**). We envision that the three distinct and chemo-orthogonal functional groups in this six-atom building block will offer a new range of novel product class.

### Scheme 3-2. Reagents Evolution



The capacity of **3.5** and its equivalents to act as a multifunctional reagent for the rapid assembly of molecular complexity will be demonstrated in the preparation of an advanced intermediate toward the synthesis of echinosporin.

#### 3.1.1 Biological Activity and Biosynthetic Proposal of Echinospurin

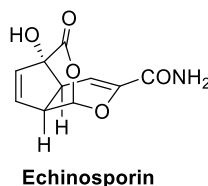
Echinospurin was first isolated in 1981 from *Streptomyces echinosporur* culture broth.<sup>3</sup> The natural product exhibits weak antibacterial activities against Gram-positive and Gram-

negative bacteria as it is presented by the MICs 100  $\mu$ /ml against *Proteus vulgaris*, *Salmonella typhosa*, *Shigella sonnei* and higher than 200  $\mu$ /ml against *Escherichia coli* and *Bacillus subtilis*.<sup>4</sup> Echinospirin also showed promising antitumor activity against rodent tumor models such as leukemia P388, P388/VCR, and fibrosarcoma Meth 1. *In vitro* studies indicate the pharmacokinetic pathway of action which is inhibition of DNA, RNA, and protein synthesis.

4

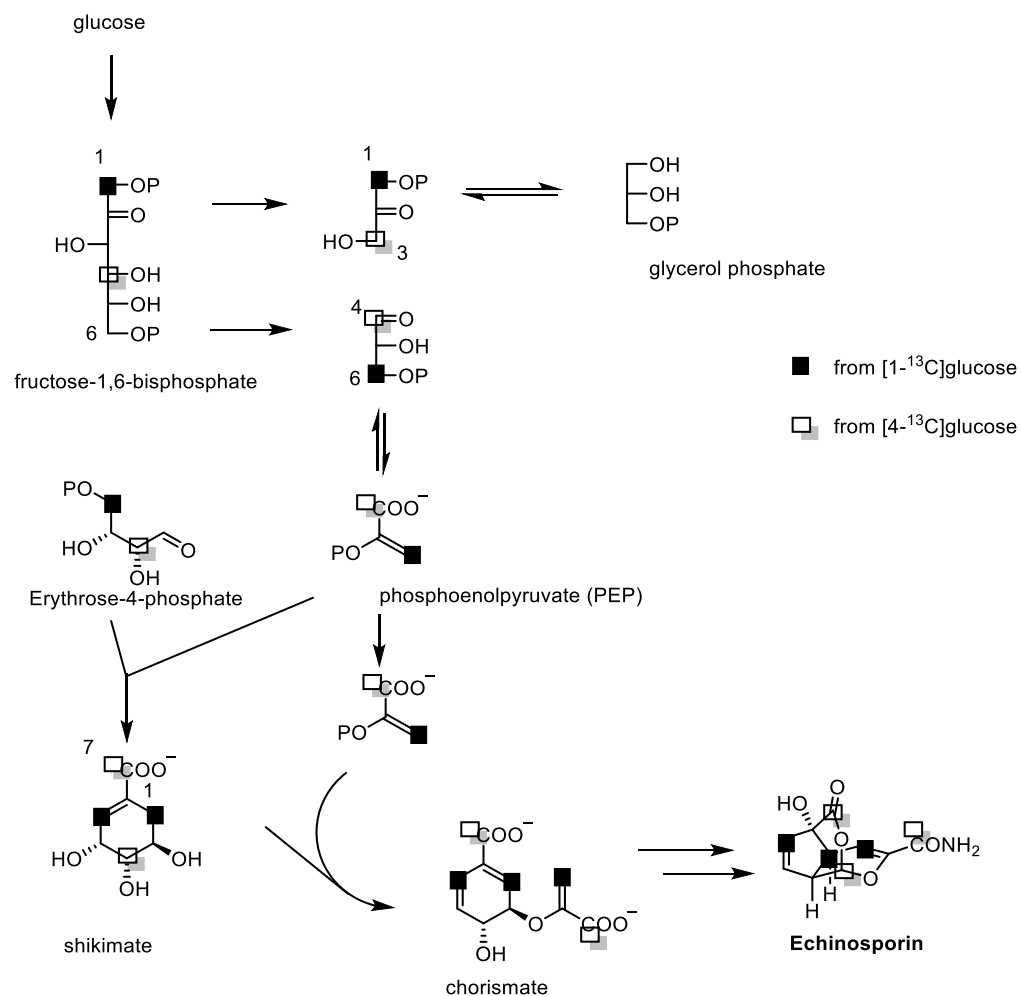
In addition to useful biological activity, echinosporin possesses an intriguing molecular architecture. Initially deduced by a combination of chemical and spectroscopic studies, the structure of echinosporin was later confirmed via a single-crystal X-ray analysis (**Figure 3-1**).<sup>5</sup>

**Figure 3-1.** Natural Product Echinospirin



The highly strained tricyclic ring system presents a compact but densely functionalised structure and poses a significant challenges to the synthetic community. Significant bond angle distortions due to the tricyclic framework are primary challenge in assembling this molecule. Although echinosporin's biosynthetic pathway is not evident from its structure, some experiments have shed some light on the process.<sup>6</sup> In 2002, Axel Zeeck and coworkers, revealed an unexpected branch of the shikimate pathway for the biosynthesis of echinosporin via <sup>13</sup>C labeling experiment. As shown in **Scheme 3-3**, echinosporin is produced via a shikimate pathway where shikimate and chorismate are biosynthetic intermediates.

**Scheme 3-3.** The Shikimate Biosynthetic Pathway of Echinospurin



## 3.2 Prior Synthesis of Echinospurin

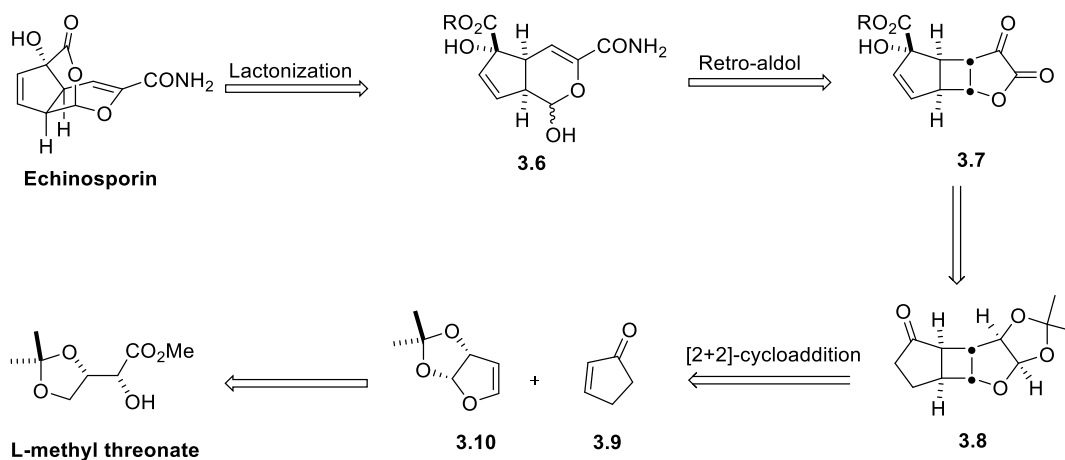
### 3.2.1 Overview of A. B. Smith Total Synthesis of Echinospurin

Until 2012, the landmark strategy by A.B. Smith and coworkers in 1989 remained the only report for the successful total synthesis of echinosporin.<sup>7</sup>

In their approach, Smith proposed that the lactol **3.6** would be a logical penultimate intermediate. To address the two fused stereocenters, lactol **3.6** would be accessed via a retro-aldol reaction from lactone **3.7** which could be achieved via elaboration of cyclobutane **3.8**. This cyclobutane would be assembled via a [2+2]-cycloaddition of cyclopentenone **3.9** and dihydrofuran **3.10**. The dextrorotary enantiomer of **3.10** would be prepared from L-methyl threonate. A general retrosynthetic analysis is shown in **Scheme 3-4**.

The forward synthesis of echinosporin is depicted in **Scheme 3-5**. Dihydrofuran **3.10** was prepared in seven steps from L-methyl threonate in multigram-scale which set the stage for their proposed [2+2] cycloaddition. In the event, the union of **3.9** and **3.10** was accomplished under standard photolytic conditions and provided the desired cis-anti-cis cyclobutane **3.8** in ca. 50% yield together with two diastereomers.

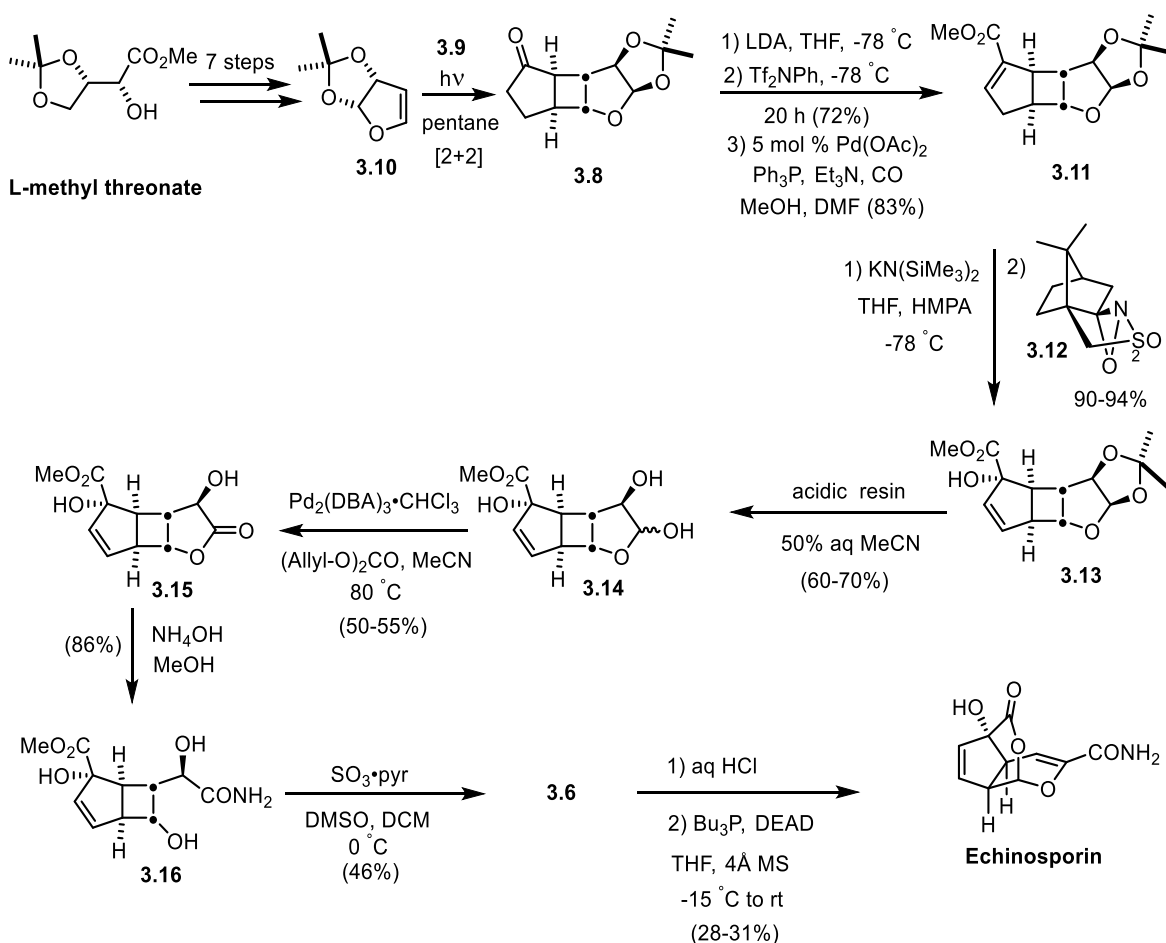
**Scheme 3-4.** A.B Smith's Echinospurin Retrosynthesis



A three-step manipulation of **3.8** furnished cyclopentene **3.11** with the introduction of the carbomethoxy moiety at the carbonyl carbon. The following enolate oxidation with the Davis (+)-(camphorsulfonyl) oxaziridine **3.12** furnished carbinol **3.13**. The lactol **3.14** was

then revealed via treatment of the protected carbinol **3.13** with acidic resin in 50% aq acetonitrile. Oxidation of lactol **3.14** generated lactone **3.15** which was then ammonolyzed to provide the cyclobutanol **3.16**. Subsequent oxidation of **3.16** with  $\text{SO}_3 \cdot \text{pyridine}$  led to a fragmentation product which was recrystallized as a 20:1 anomeric mixture **3.6**. Hydrolysis of the methyl ester followed by a Mitsunobu reaction of the hydroxyl acid to provide (-)-echinosporin.

**Scheme 3-5.** Summary of A.B.Smith Total Synthesis of Echinospirin



With this 19 steps total synthesis, echinosporin's absolute configuration was unambiguously defined. At 19 steps, this landmark synthesis is probably too lengthy to be used

in the preparation of analogs for a structure–activity relationship study. Consequently concise synthetic approach for this molecule remained highly desirable.

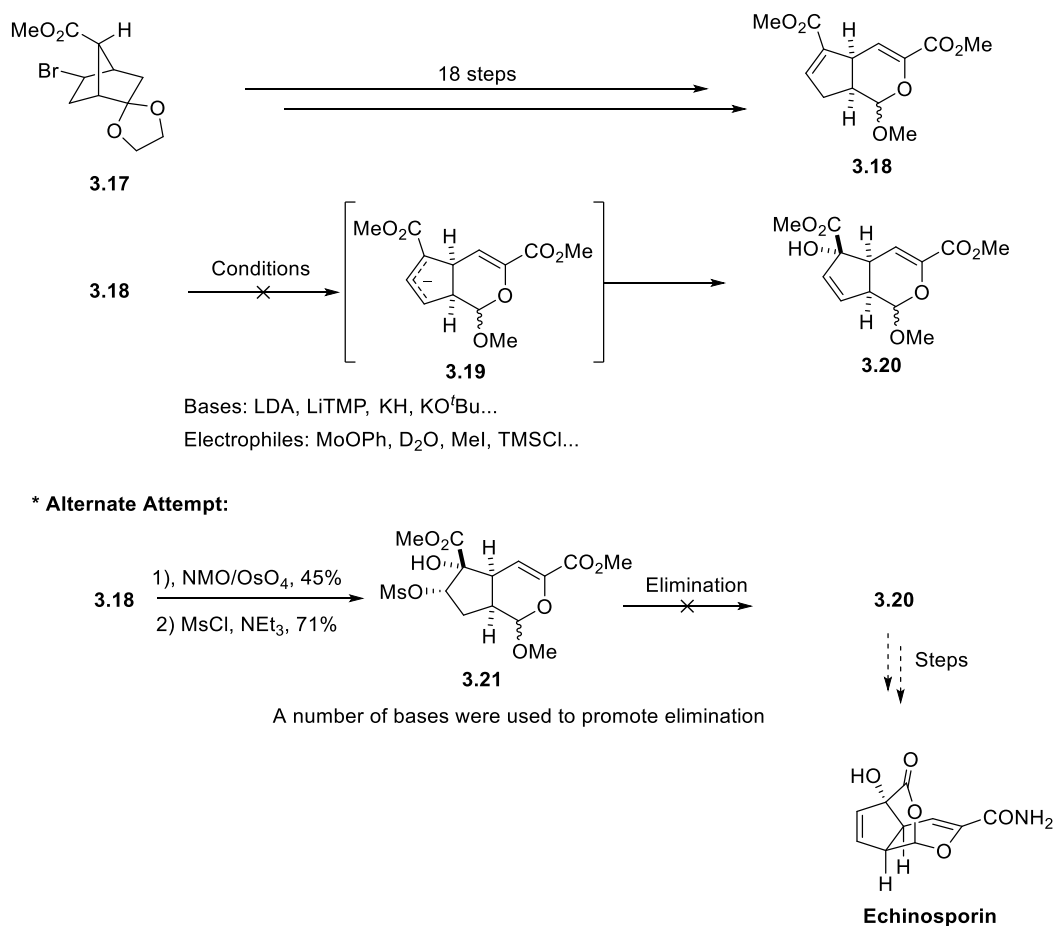
### 3.2.2 Overview of Weinreb's Approach to The Synthesis of Echinospurin

Independently of the Smith group, Weinreb and coworkers reported an approach providing access to an advanced intermediate toward the synthesis of echinospurin.<sup>8</sup> The approach is presented in **Scheme 3-6**.

Weinreb's plan centered on accessing intermediate **3.20** which is only two synthetic steps away from the natural product. They envisaged that this intermediate could be prepared in an efficient manner from readily available bromoester **3.17**. Their strategy to reveal the cyclopentenyl hydroxyl group in **3.20** via an enolate oxidation of **3.19** was never achieved. The desired enolate **3.19** was never efficiently produced under various basic conditions. An alternative approach was then devised when they successfully accomplished selective dihydroxylation of the bis-unsaturated ester **3.18** to afford a diol which was then converted to the mono-mesylate **3.21** with ca. 30% overall yield. Unfortunately, their attempts to promote the elimination were never met with desirable reactivity.

This synthesis did not deliver echinospurin but did help to establish the methodological boundaries for the molecule.

**Scheme 3-6.** Weinreb's Approach to The Synthesis of Echinospirin

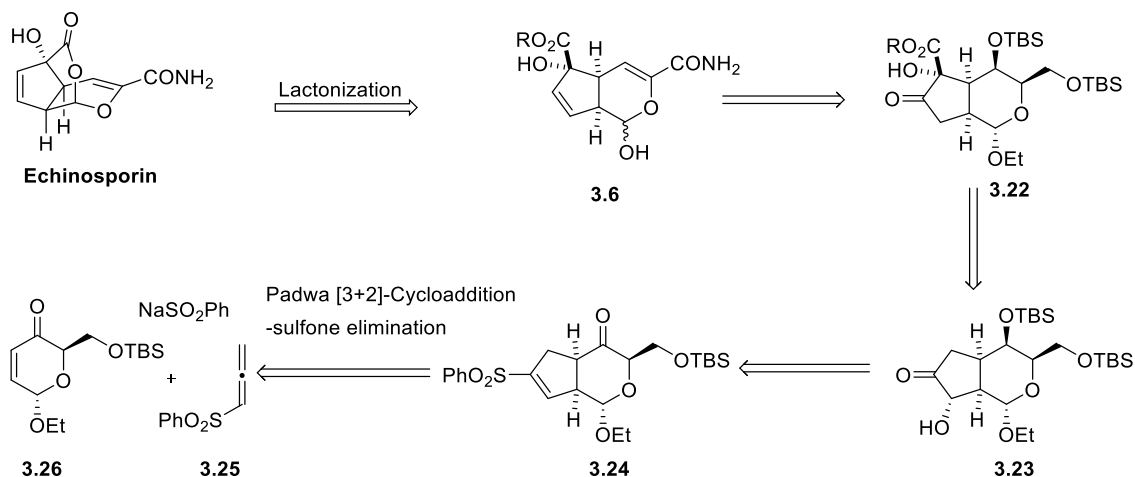


### 3.2.3 Overview of K. J. Hale Formal Total Synthesis of Echinospirin

Twenty-three years after the initial synthesis, Hale and coworkers at Queen University provided a formal synthesis of Smith's penultimate intermediate in a 26 steps synthesis.<sup>9</sup> In this formal total synthesis, a novel Padwa [3+2]-cycloadditive elimination reaction was developed for chiral cyclopentane ring assembly along with devised an efficient method for the acylation of ketone enolate under mild, non-basic, conditions.

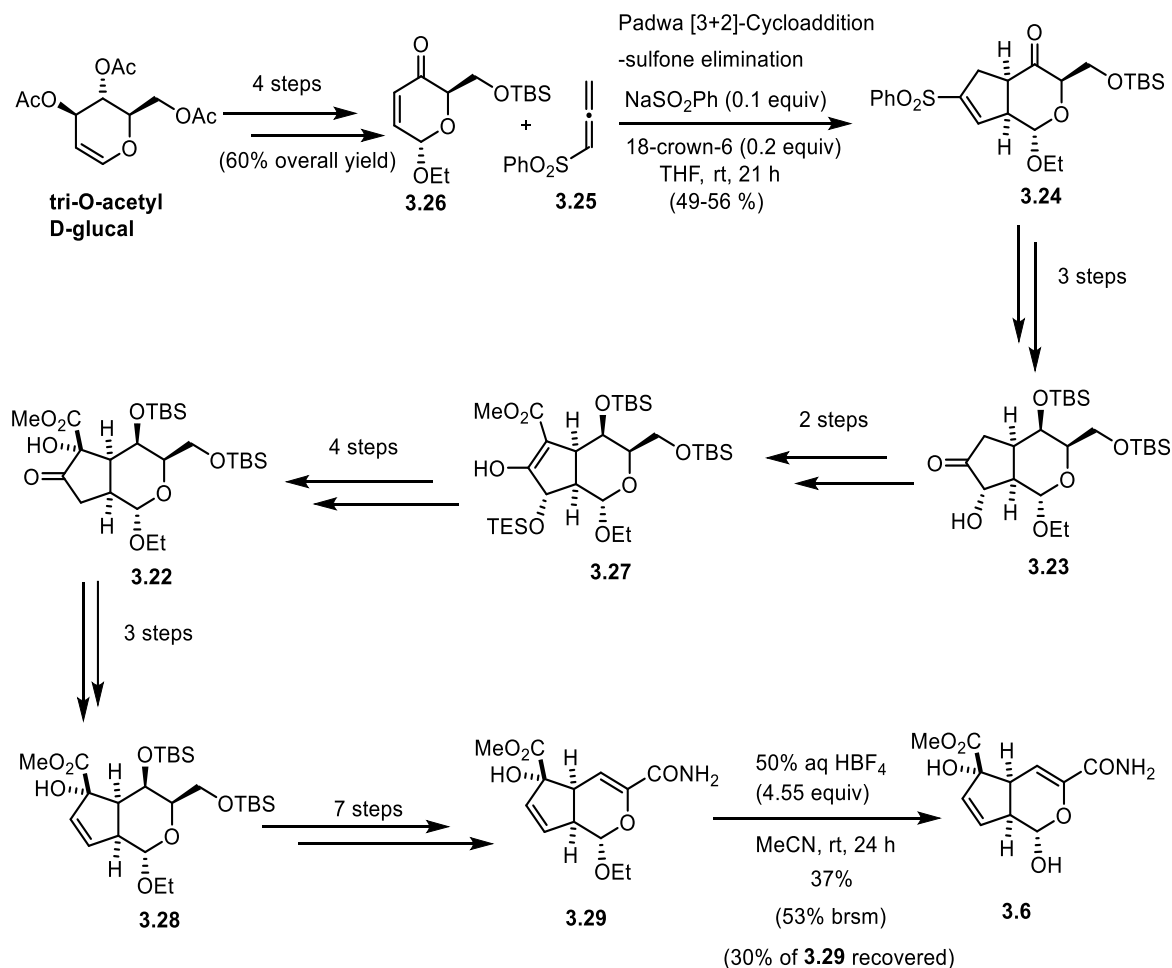


**Scheme 3-7.** K.J Hale's Echinospurin Retrosynthesis



Hale's approach is depicted in **Scheme 3-7**. Hale and coworkers planned to synthesize intermediate **3.6** via the manipulation of cyclopentanone **3.22** which in turn could be achieved from  $\alpha$ -hydroxyketone **3.23**. A simpler building block **3.24** was proposed to make the highly functionalized intermediate **3.23**. Finally, a novel Padwa [3+2]-cycloaddition-sulfone elimination reaction was proposed to yield **3.24** from allene **3.25** and mixed-ketal **3.26**.

**Scheme 3-8.** Summary of K.J. Hale Formal Total Synthesis of Echinospurin



The forward synthesis of echinosporin is depicted in **Scheme 3-9** starting from a commercially available chiral compound tri-O-acetyl D-glucal. Enone **3.26** was prepared with 60% overall yield via a 4-step synthesis comprising a Ferrier glycosidation on tri-O-acetyl D-glucal and a Swern oxidation. They then developed a novel anionic Padwa [3+2]-cycloaddition elimination of enone **3.26** and allenyne **3.25** to stereoselectively furnish ketone **3.24** with 56% yield on a 60 g scale. A three-step manipulation of **3.24** involving a stereoselective reduction and *syn*-dihydroxylation gave the  $\alpha$ -hydroxy ketone **3.24** as the sole product. Two subsequent steps including alcohol protection and kinetic enolate C-acylation provided enol

**3.27** which was then transformed into cyclopentanone **3.22** via a four-step functionalization including enol dihydroxylation and Barton deoxygenation to reveal the. From there, the cyclopentene **3.28** to set up the two fused rings of echinosporin framework. 7 steps of further functionalization of the hydroxyl ester **3.28** constructed the dihydropyran **3.29-a** compound possessing most of the functionality of Smith's penultimate intermediate **3.6**. Lactol **3.6** was then revealed via an acid-catalyzed chemoselective deprotection of ketal **3.29**. The <sup>1</sup>H-NMR spectrum of this compound showed a perfect match to the data reported for Smith's intermediate.

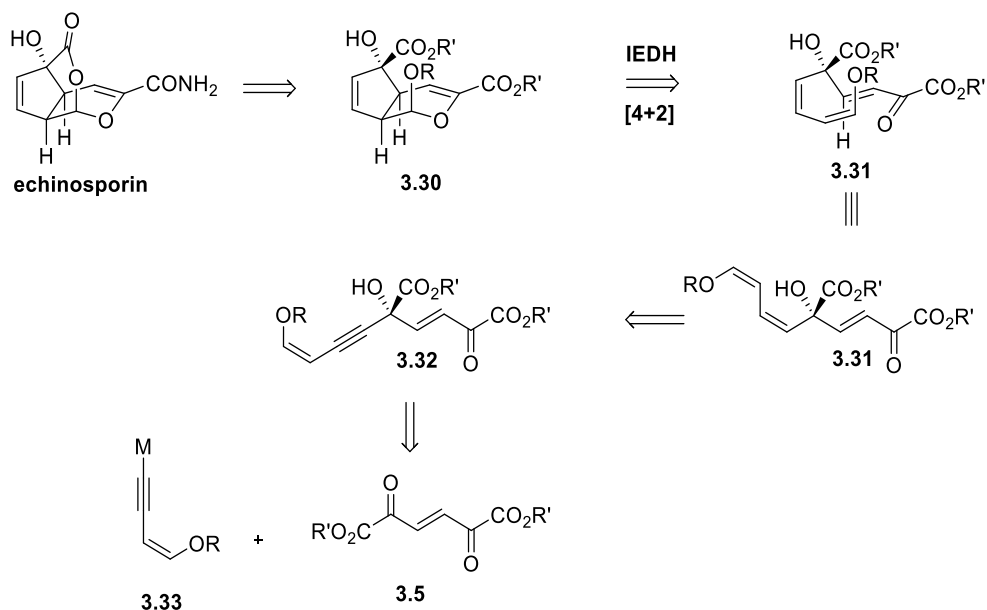
This new enantioselective synthesis of A.B Smith's penultimate intermediate provided echinosporin in a 26 steps route. While it provides a new approach to stereoselectively construct the molecule, it remains impractical as a method for preparation of the natural product analogs. In this chapter, we will discuss on our efforts to provide a synthetic route suited for preparation of echinosporin analogues.

### **3.3 Results and Discussion**

#### **3.3.1 Preliminary Retrosynthetic Analysis**

The synthesis of echinosporin was a target we sought to achieve in a developing program derived from the use of unique yet simple building block for rapid molecular assembly. Our ultimate goal for the synthesis of echinosporin was to discover a concise route that could quickly achieve the core structure via simple manipulation and which will provide an opportunity to access other analogs via a modular approach. The first generation of retrosynthetic analysis for the molecule is presented in **Scheme 3-9**.

**Scheme 3-9.** First Generation Retrosynthetic Analysis

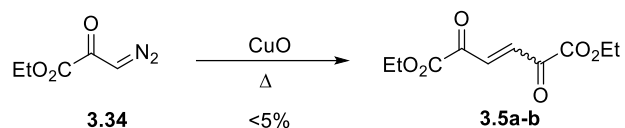


Similar to previous approaches, we chose the dihydropyran-2-carboxylate **3.30** as the ultimate precursor for the synthesis of echinosporin. We identified that intermediate as a retron for an intramolecular inverse electron demand hetero (IEDH) Diels-Alder reaction of **3.31**.<sup>10</sup> This unsaturated  $\alpha$ -ketoester would be prepared via a Lindlar reduction of the alkyne **3.32**. Enantioselective metal acetylide addition of the readily available enyne **3.33** to the designated pyruvate alkylidene dimer **3.5** would be the desirable reaction to construct the chiral alkyne **3.32**.<sup>11</sup> Much of our early work has been focused on the preparation of **3.5** and its use in asymmetric synthesis.

### 3.3.2. Synthesis of Pyruvate Alkylidene Dimer

The extant synthesis of **3.5** involved Cu-catalyzed dimerization of diazo-oxopropionate **3.34** providing the product in low yield (**Scheme 3-10**).<sup>12</sup> Therefore our early efforts were directed at the development of a practical, scalable preparation of **3.5**

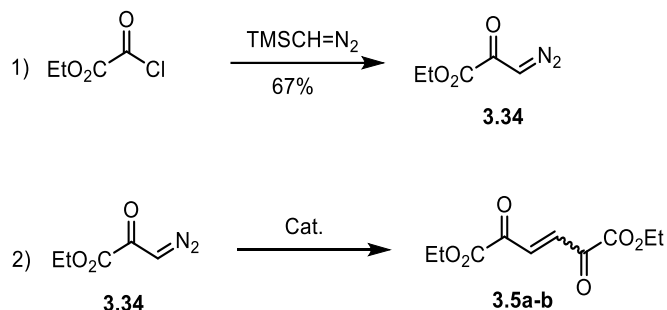
**Scheme 3-10.** The Extant Synthesis of Ethyl Pyruvate Alkylidene Dimer



The diazo-oxopropionate **3.34** was prepared via an acylation of commercially available trimethylsilyl diazomethane by ethyl oxalylchloride (equation 1, **Scheme 3-11**).<sup>13</sup> With the diazo compound **3.34** in hand, we screened various copper- and rhodium-based catalysts for catalyzing the dimerization of diazo compounds.<sup>14</sup> However, no catalyst provided practical reactivity (reaction 2, **Scheme 3-11**). Copper-based catalysts showed no reactivity, and most of the rhodium-based catalysts gave a messy mixture of unknown products. Only rhodium(I) acetate produced *E* and *Z*-mixture of the desired dimer and a large amount of unknown byproduct.

**Scheme 3-11.** Synthesis of Ethyl Pyruvate Alkylidene Dimer-Dimerization of Diazo

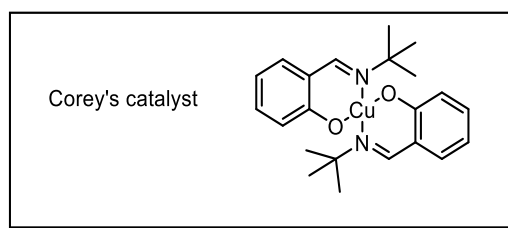
Precursor.



Cat: 3 equiv: CuO, Cu<sub>2</sub>O, Corey's catalyst: No reaction

1 mol %: Rh<sub>2</sub>(esp)<sub>4</sub>, Rh(TFA)<sub>2</sub>, Rh<sub>2</sub>(S-DOSP)<sub>4</sub>, Rh<sub>2</sub>(acac)<sub>4</sub>,...: Messy mixture

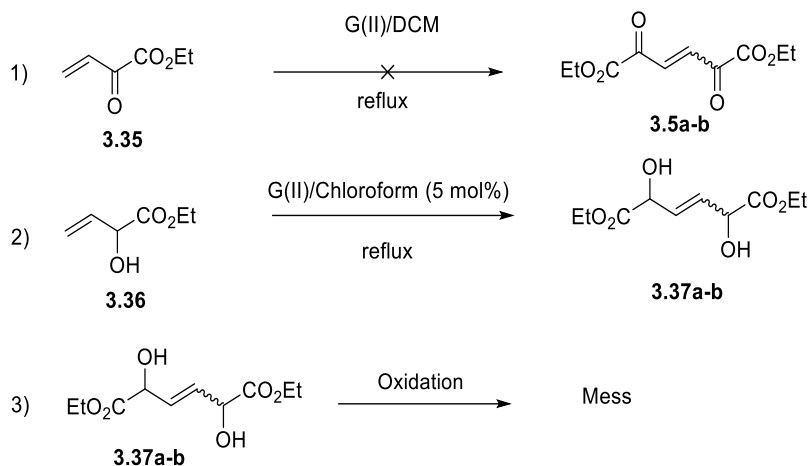
1 mol %: Rh<sub>2</sub>(OAc)<sub>4</sub>: mixture of E, Z desired product and unknown components.



Due to the high cost of both the precursor diazomethane and the catalyst coupled with the lack of desired reactivity of the reaction, we decided to not pursue this reaction further for the preparation of pyruvate alkylidene dimer **3.5**.

The next approach was to pursue a homo-metathesis of ethyl 2-oxobut-3-enoate **3.35** (Scheme 3-12).<sup>15</sup> Unfortunately, refluxing **3.35** with 10 mol% of Grubbs second generation catalyst (G(II)-catalyst) in dichloromethane or chloroform only resulted in decomposition of starting material and not the generation of desired product **3.5a-b**. Using related compound  $\alpha$ -hydroxy ester **3.36** we observed a full conversion to an E-and Z-mixture of the homo-metathesis compound **3.37a-b** (Scheme 3-12, equation 2)

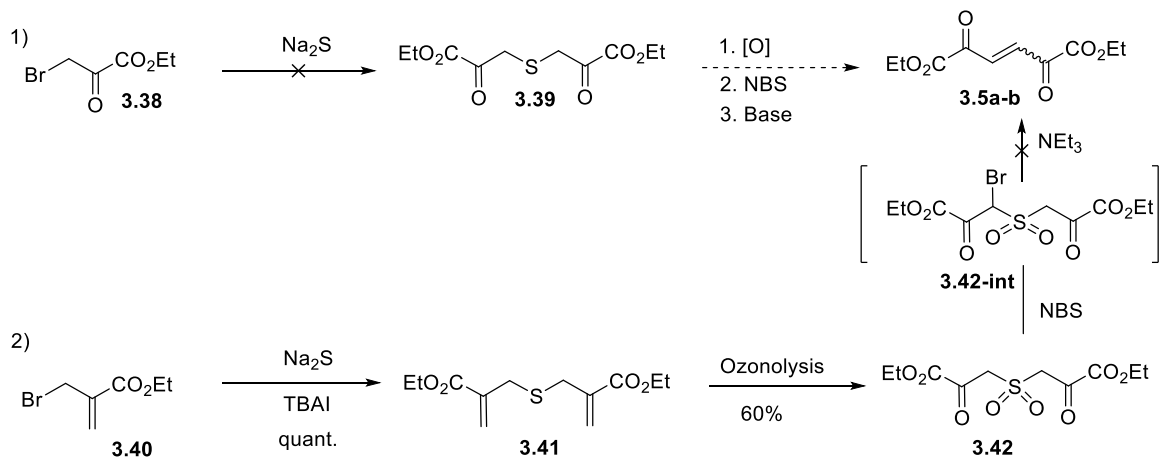
**Scheme 3-12.** Approach to the Synthesis of Ethyl Pyruvate Dimer via Homo-Metathesis.



However, attempts to oxidize the E-and Z-mixture of diol **3.37a-b** with various oxidizing agents failed to furnish the desired pyruvate alkylidene dimer **3.5a-b**. Messy mixture was generally observed from these oxidation reactions (**Scheme 3-12**, equation 3).

We then approached the synthesis of **3.5** via a Ramberg-Bäcklund elimination reaction (**Scheme 3-13**, equation 1,2).<sup>16</sup>

**Scheme 3-13.** Ramberg-Bäcklund Approach for Synthesis of Ethyl Pyruvate Alkylidene Dimer



Precursor **3.39** would be an ideal substrate for the oxidative-elimination process. However, we were never able to prepare **3.39** from reaction of ethyl bromopyruvate **3.38** (Scheme 3-13, equation 1) probably due to the non selective reactivity of **3.38** under reaction condition. A different approach was then pursued by making sulfide **3.41** from the reaction of **3.40** and sodium sulfide under phase-transfer catalysis condition.<sup>17</sup> The diketoe ester **3.42** was then revealed via an ozonolysis. However, attempts to access dimer **3.5a-b** via the intermediate **3.42-int** of the Ramberg-Bäcklund elimination were not successful. Complex mixture were observed in all cases.

We attempted to access the pyruvate dimer **3.43m** which could potentially produce the alkylidene pyruvate dimer **3.5m** via a one-pot two step halogenation-elimination (Scheme 3-14, reaction 1).<sup>18</sup>

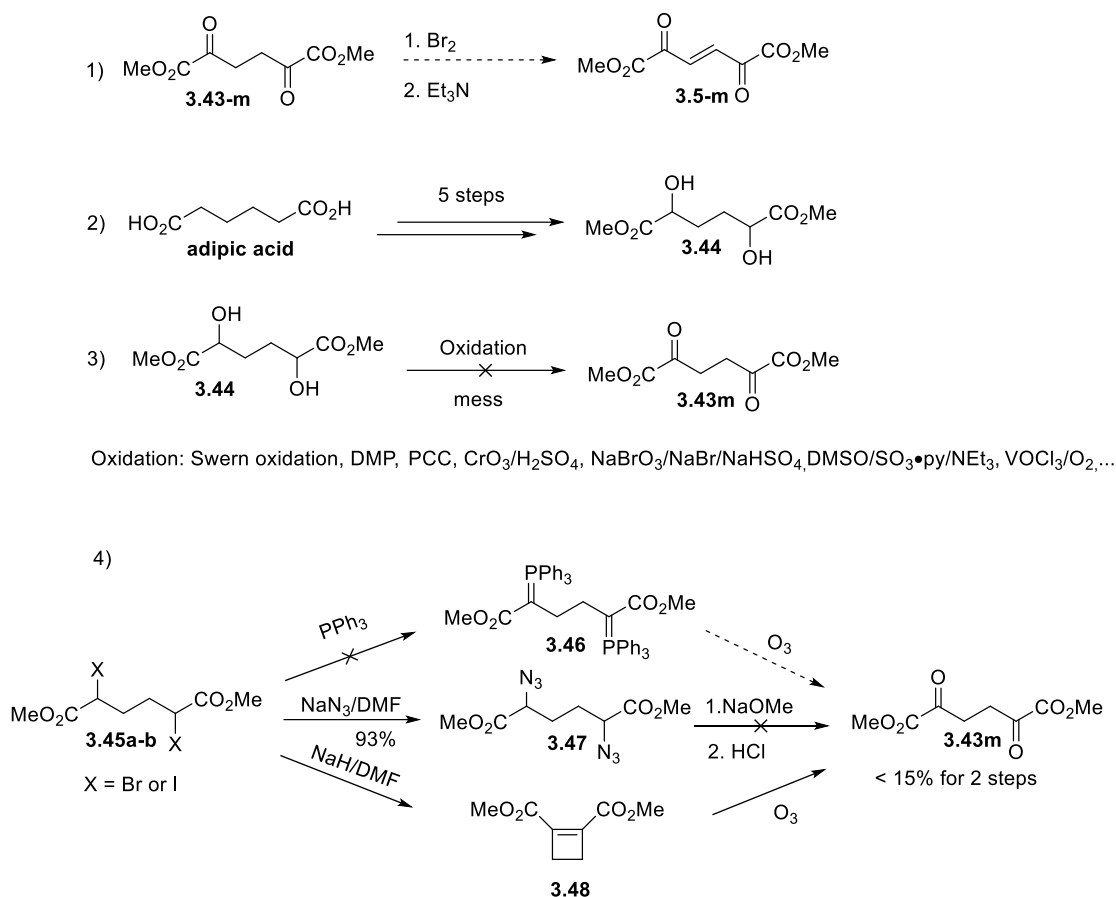
The most logical substrate to access pyruvate dimer **3.43m** would be the bis( $\alpha$ -hydroxy ester) **3.44** which was readily prepared via a 5 steps manipulation of adipic acid on multigram-scale.<sup>19</sup> Unfortunately, attempts to oxidize the diol under various conditions including Swern oxidation, DMP, DCC oxidation were never fruitful (Scheme 3-14, reaction 3). These reactions were either complex including products of the dehydration, intramolecular cyclization *etc* or unreactive due to the less reactive  $\alpha$ -hydroxy ester alcohol.

In similar fashion, the reaction of  $\alpha$ -halogeno esters **3.45a-b** with triphenylphosphine never delivered diphosphorane **3.46a** compound potentially one step from pyruvate dimer **3.43m** while the functionalization of diazido ester **3.47** failed to provide **3.43m** even though the reaction is reported for the monoazido ester analogs.<sup>20</sup> We did obtain **3.43m** via a two steps consequence including cyclization of dibromo ester **3.45a** and ozonolysis of cyclized adduct



**3.47.**<sup>21</sup> However, reaction was low yielding due to a non-selective intramolecular cyclization of **3.45a** resulting in a < 15% total yield of **3.43** from the two steps (**Scheme 3-14**, reaction 4).

**Scheme 3-14.** Attempts to Synthesize Alkyl Pyruvate Dimer

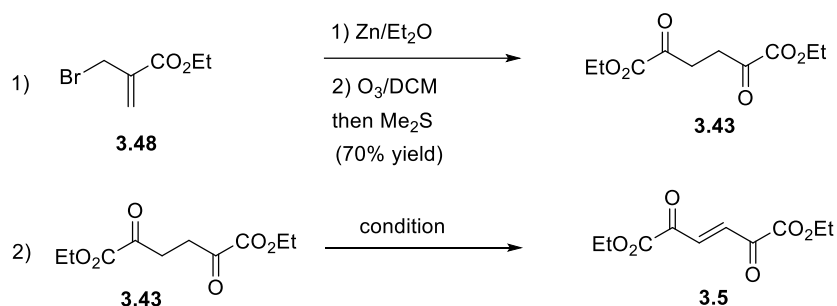


Ultimately, this low yielding reaction was not viable pathway towards a scalable method of making the pyruvate alkylidene dimer **3.5**.

Gratifyingly, we were able to prepare the ketoester **3.43** on multigram scale via (**Scheme 3-14**, equation 1) zinc-mediated dimerization of **3.48** followed by ozonolysis dialkene **3.49**, revealing the diketone **3.43** in 70% isolated yield over two steps.<sup>22</sup> With the

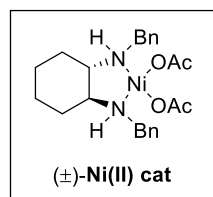
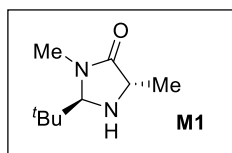
diketoester **3.43** readily prepared in multigram-scale, we next investigated the oxidative dehydrogenation to reveal the alkene **3.5** (**Scheme 3-14**, equation 2).<sup>23</sup>

**Scheme 3-14.** Synthesis of Pyruvate Alkylidene Dimer



Condition:  $\text{Br}_2/\text{DCM}$ ;  $\text{NCS}/\text{Et}_3\text{N}/\text{DCM}$ ;  $\text{Br}_2/\text{DCM}/\text{Et}_3\text{N}$ ;  $\text{CuBr}_2/\text{CHCl}_3$   
 $\text{NCS}/\text{Sodeoka's } (\pm)\text{-Ni(II) cat}/\text{THF}$ , etc...

Best condition:  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$  (1.1 equiv),  $\text{LiTFA}$  (2.2 equiv),  $\text{Na}_2\text{S}_2\text{O}_8$  (2.5 equiv), 20 mol % **cat M1**, MeCN. (35% yield)

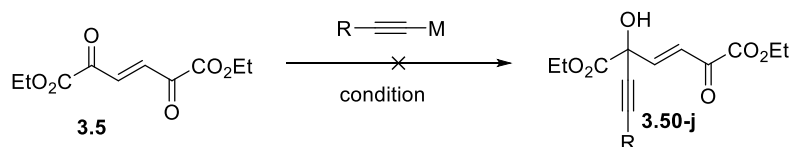


Many conditions were pursued with the goal of monohalogenation of the bis(ketoester) **3.43** followed by elimination of  $\text{HX}$ . However, using various electrophiles for the halogenation, we only obtained the desired pyruvate alkylidene dimer **3.5** with low yield from these messy reactions (**Scheme 3-14**, equation 2). Fortunately, when we employed a slightly modified MacMillan's reported chlorination condition<sup>23</sup> using 1.1 equiv of  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ , 2.2 equiv of  $\text{LiTFA}$ , 2.5 equiv of  $\text{Na}_2\text{S}_2\text{O}_8$  and 20 mol% of MacMillan catalyst **M1**, the desired diethyl pyruvate alkylidene dimer **3.5** was isolated in 35% yield. This condition allowed the preparation of **3.5** in multigram-scale so we decided to move forward to next steps of the synthesis.

### 3.3.3 Reactivity Profile of Pyruvate Alkylidene Dimer

Though we were excited to finally have the pyruvate alkylidene dimer in hand, its reactivity profile remained unknown. In the literature,  $\beta,\gamma$ -unsaturated- $\alpha$ -keto esters were shown to have a propensity for 1,2-addition over 1,4-addition.<sup>24</sup> Our proposed synthesis relies on the observation at similar reactivity.

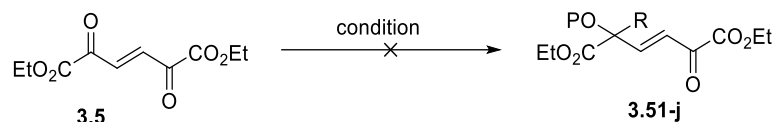
To investigate the reactivity profile for pyruvate alkylidene dimer **3.5**, we subjected the dimer into various Mg- or Li-acetylides addition conditions.<sup>24</sup> Unfortunately, the desired tertiary alcohol **3.50-j** was never obtained. (**Table 3-1**) Li-phenylacetylide quickly gave decomposition even at -78 °C (**Table 3-1**, entry 1) and the magnesium chloride analogs promoted an incomplete and messy reaction (**Table 3-1**, entry 2). A similar result was observed with ethynyl magnesium chloride. Several attempts to promote asymmetric alkynyl addition were also unsuccessful (**Table 3-1**, entries 4-6).<sup>25,26</sup> Though there are myriad methods available for enantioselective alkyne addition to carbonyl electrophiles,<sup>11</sup> we postulated that this unique structure of **3.5** bearing two conjugated  $\alpha$ -ketoester groups renders the pyruvate alkylidene dimer **3.5** in very reactive. As a result, it failed to react cleanly under all conditions examined. We proposed that if one of the ketone functional group could be selectively protected to remove the conjugation of one of the two ketoester groups, we could be able to functionalize the remaining  $\alpha$ -ketoester group in an efficient manner.

**Table 3-1.** 1,2-Addition Profile of Pyruvate Alkylidene Dimer

Entry	R	M	Cat./ligand	Temp/time	Solvent	Result
1	Ph	Li	No	-78 °C/1 h	THF	Mess
2	Ph	MgCl	No	-78 °C-rt/1 h	THF	Mess and incomplete
3	H	MgCl	No	-78 °C-rt/20 h	THF	Mess and incomplete
4	Ph	Zn	Ti(O <sup>i</sup> Pr) <sub>4</sub> /(R)-BINOL	rt/20 h	Et <sub>2</sub> O	Mess
5	Ph	Zn	Prophenol ligand	5 °C/48 h	Toluene	Mess and incomplete

A number of conditions for the protection of ketone were pursued.<sup>27</sup> However, the experiments were met with failure. **Table 3-2** highlights a summary of these results. Disappointingly, efforts to form a 1,2-diketal with ethylene glycol derivatives were unsuccessful (**Table 3-2**, entries 1-2). Protecting methods using cyanide addition to the α-ketoester also showed no promise (**Table 3-2**, entries 3-4). Attempts to selectively reduce one of the ketone functional group by NaBH<sub>4</sub>/EtOH or Noyori's reduction using ruthenium-diamine catalyst and formic acid failed to deliver the desired monohydroxy ester (**Table 3-2**, entry 5).<sup>27c</sup>

**Table 3-2.** Attempts to Selectively Protect Pyruvate Alkylidene Dimer



Entry	Condition	Results
1	HOCH <sub>2</sub> CH <sub>2</sub> OH / (EtO) <sub>3</sub> CH / PTSA cat. / Benzene / overnight	Incomplete and messy
2	TMSOCH <sub>2</sub> CH <sub>2</sub> OTMS / TMSOTf (10 mol%) / DCM / 20 h	Messy and incomplete
3	NaCN / Ac <sub>2</sub> O / toluene:H <sub>2</sub> O / -20 °C-rt / 20 h	Mess
4	NaCN / TMSCl / DMSO / rt / 30 min	Mess
5	NaBH <sub>4</sub> / EtOH or Noyori's reduction	Mess

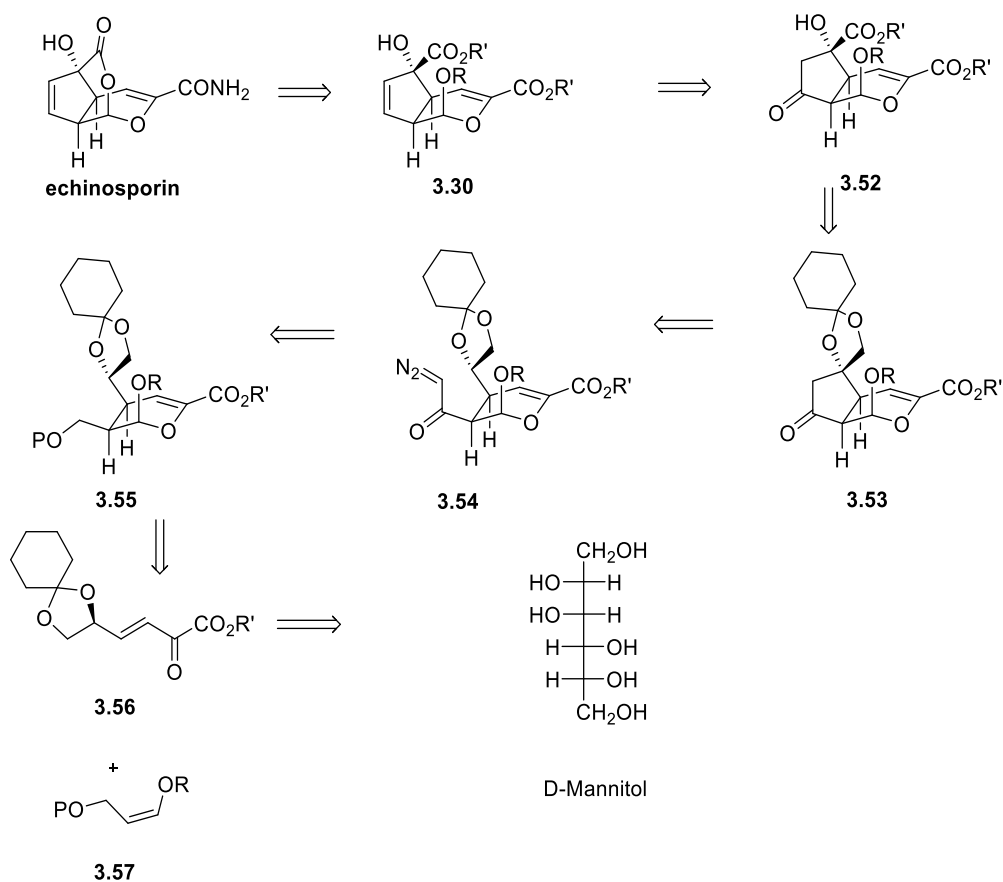
This results illustrate the problematic reactivity pattern of **3.5** which prompted us to revise our strategy.

While the pyruvate alkylidene provides an opportunity potentially access echinosporin in a rapid fashion, the inability to functionalize **3.5** prevented us from exploring this approach directly. A new route to the molecule was necessary.

### 3.3.4 Revised Retrosynthetic Analysis

Our revised retrosynthetic plan is shown in **Scheme 3-15**. In this strategy, cyclopentene **3.30** remained the key precursor for echinosporin synthesis. Cyclopentanone **3.52** would provide the necessary functionality to access **3.30**. We planned to reveal the  $\alpha$ -hydroxyester would be revealed from the protected diol **3.53** which itself could be prepared via a stereoselective C-H insertion of diazo compound **3.54**.<sup>28</sup> The diazoketone **3.54** was proposed to be synthesized via manipulation of protected alcohol **3.55** which in turn would be accessed by Lewis acid-catalyzed intermolecular inverse electron demand hetero Diels-Alder reaction of vinyl ether **3.57** and  $\beta,\gamma$ -unsaturated- $\alpha$ -ketoester **3.56**.<sup>29</sup> It is important to note that this chiral building block in our second generation retrosynthetic analysis is a close derivative of the pyruvate alkylidene dimer **3.5** where one of the two ketoester groups is masked in the form of protected diol. The chiral protected diol **3.56** could be readily prepared in multigram-scale from *D*-mannitol.<sup>30a</sup>

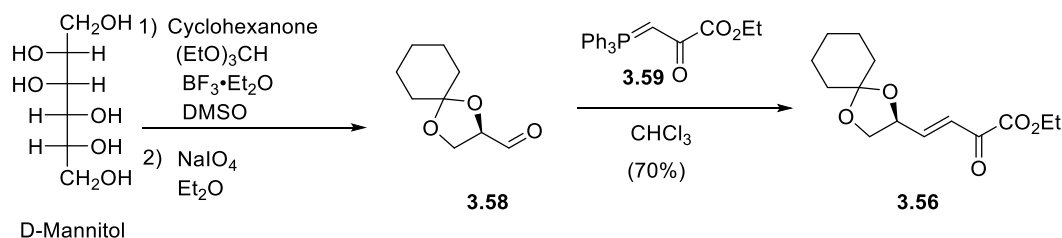
**Scheme 3-15.** Second Generation Retrosynthetic Analysis



### 3.3.5 Synthesis of Chiral Building Block-The $\beta,\gamma$ -Unsaturated- $\alpha$ -Ketoester

We began to pursue the next route to echinosporin with the preparation of the chiral  $\beta,\gamma$ -unsaturated- $\alpha$ -ketoester **3.56**. While the synthesis of acetonide protected version of **3.56** has been reported<sup>30b</sup> we chose to use the cyclohexylidene protecting group since it provided a more robust protecting group for subsequent manipulation. The synthesis of **3.56** is depicted in **Scheme 3-16**.

**Scheme 3-16.** Synthesis of Chiral  $\beta,\gamma$ -Unsaturated- $\alpha$ -Ketoester



The protected chiral glyceraldehyde **3.58** prepared in two steps from D-mannitol, was subjected into a Wittig reaction with the phosphorane **3.59** effectively producing **3.56** with 70% yield. This synthesis was scalable allowing for the preparation of **3.56** on multigram-scale.

### 3.3.6 Inverse Electron Demand Hetero Diels-Alder Reaction-Construction of Dihydropyran Ring

Precedent from Evans and Jorgensen groups have established an excellent method for highly stereoselective construction of dihydropyran rings via a C2-symmetric bis(oxazoline)-Cu(II)-catalyzed inverse electron demand hetero Diels-Alder reaction of  $\beta,\gamma$ -unsaturated carbonyl compounds (heterodiene) with electron-rich olefins (heterodienophile).<sup>29</sup> With the  $\alpha$ -ketoester **3.56** in hand, we began to investigate on using this work as a guide and with this reaction as a method to construct the dihydropyrane. We utilized active copper-catalysts highly in conjunction with vinyl ether envisioning that the cyclization adducts would provide suitable functional groups for further manipulation to the diazoketone **3.54**. The results are presented in **Table 3-3**



**Table 3-3.** Optimization for The Inverse Electron Demand Hetero Diels-Alder Reaction

3.56 + 3.60  $\xrightarrow[\text{10 mol \% cat.}]{\text{condition}}$  3.61

1, X=OTf; 2, X=SbF<sub>6</sub>  
a, R=<sup>t</sup>Bu; b, R=Ph

Entry	R <sup>1</sup>	R <sup>2</sup>	Cat.	Temp	Time	Result
1	Et	COOEt	<b>1a</b>	rt	4 days	NR
2	Et	CH <sub>2</sub> OH	<b>1a</b>	rt	2 days	NR
3	Et	CH <sub>2</sub> OH	<b>1b</b>	rt	3 days	NR
4	Et	CH <sub>2</sub> OTMS	<b>1a</b>	-50 °C	2 days	NR
5	Et	CH <sub>2</sub> OAc	<b>1a</b>	-30 °C	2 days	50% conversion, >20:1dr
6	Bn	MeCH(OAc)	<b>1a</b>	-78 °C	2 days	NR
7	Bn	CH(OAc)CO <sub>2</sub> <sup>t</sup> Bu	<b>2a</b>	-78 °C	2 days	NR

It came as no surprise that electron poor alkene bearing a conjugated electron withdrawing group did not participate in the cyclization under the condition (**Table 3-3**, entry 1). Alkene bearing a free hydroxyl group also displayed no reactivity (**Table 3-3**, entries 2-3). We proposed that competitive coordination of the free hydroxyl group with the catalyst might interrupt the necessary bidentate coordination of  $\alpha$ -ketonester shutting down the reaction. An acetate-protected primary alcohol vinyl ether showed promising reactivity at -30 °C (**Table 3-3**, entry 5). However, more encumbering group such as trimethyl silyl at R<sup>2</sup> completely shut down the reaction (**Table 3-3**, entries 4). Unfortunately, more functionalized

vinyl ethers also showed no reactivity at  $-78^{\circ}\text{C}$  (**Table 3-3**, entries 6-7) and decomposition was observed upon warming. Upon completing this screen, we proceeded with the vinyl ether **3.60** as our substrate of choice.

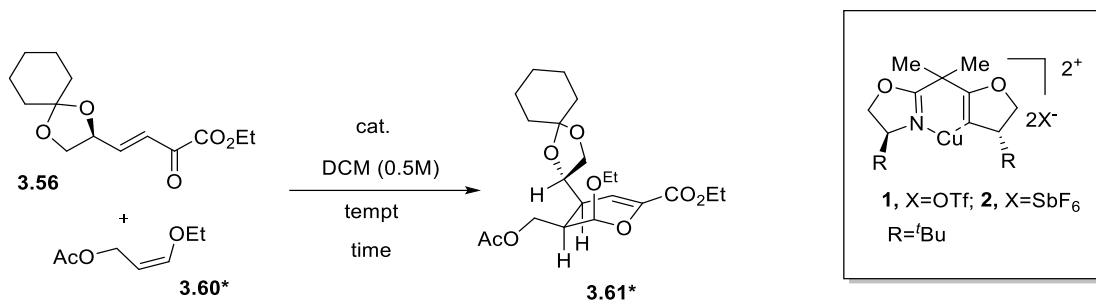
We then moved forward to the IEDH reaction. Catalyst identity, loading, and reaction temperature were among the parameters investigated. The results are presented in **Table 3-4**.

Attempts to decrease the reaction temperature below  $-30^{\circ}\text{C}$  with the hope of increasing selectivity were met with low conversion (less than 10% conversion after 48 h at  $-50^{\circ}\text{C}$ ) (**Table 3-4**, entry 1).

Increasing the temperature to  $-10^{\circ}\text{C}$  resulted in 50% conversion to **3.61\*** even with 5 mol% catalyst loading (**Table 3-4**, entry 3). The desired dihydropyran **3.61\*** was isolated in 65% yield when the reaction was carried out at  $0^{\circ}\text{C}$  for 48 h, with a slight drop in dr observed (10:1) (**Table 3-4**, entry 4).

The change in catalyst counter ion gave no positive results (**Table 3-4**, entries 5-7) and we were pleased to obtain a yield of 85% when increasing the catalyst loading to 10 mol% (**Table 3-4**, entry 8). An expected only 20% conversion to **3.61\*** was observed when we decreased the catalyst loading to 2.5 mol% (**Table 3-4**, entry 9). With the condition in hand, we prepared the dihydropyran **3.61\*** in multi-gram scale and moved forward in our synthetic proposal.

**Table 3-4.** Optimization for The Inverse Electron Demand Hetero Diels-Alder Reaction



Entry	Cat.(mol %)	Tempt	Time	Result
1	<b>1</b> (10)	-50 °C	48 h	<10% conversion
2	<b>1</b> (10)	-30 °C	48 h	50% conversion, >20:1 dr
3	<b>1</b> (5)	-10 °C	48 h	50% conversion
4	<b>1</b> (5)	0 °C	48 h	65% yield, 10:1 dr
5	<b>2</b> (5)	-10 °C	48 h	Low conversion
6	<b>2</b> (5)	0 °C	24 h	Low conversion
7	<b>2</b> (5)	rt	48 h	Mess
8	<b>1</b> (10)	0 °C	48 h	85% yield, 10:1 dr
9	<b>1</b> (2.5)	0 °C	48 h	<20% conversion

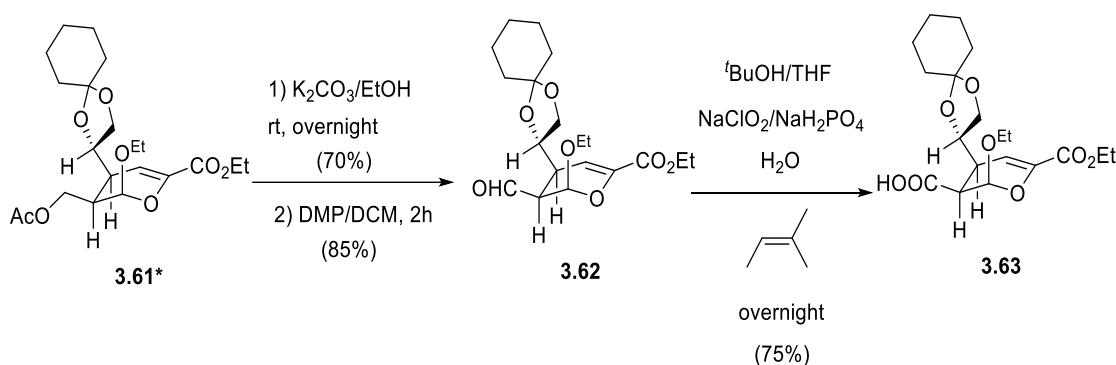
### 3.3.7 Synthesis of $\alpha$ -Diazo Ketone Intermediate

The simplest way to access the diazoketone **3.54** would be the acylation of the carboxylic acid **3.63** to diazomethane. Alternatively, we felt that diazo transfer followed by deacylation of the diketone **3.64** accessed via aldehyde **3.62** was a secondary option.<sup>31</sup>

Both aldehyde **3.62** and carboxylic acid **3.63** could be readily synthesized from the dihydropyran **3.61\*** as presented in **Scheme 3-17**.<sup>32,33</sup>

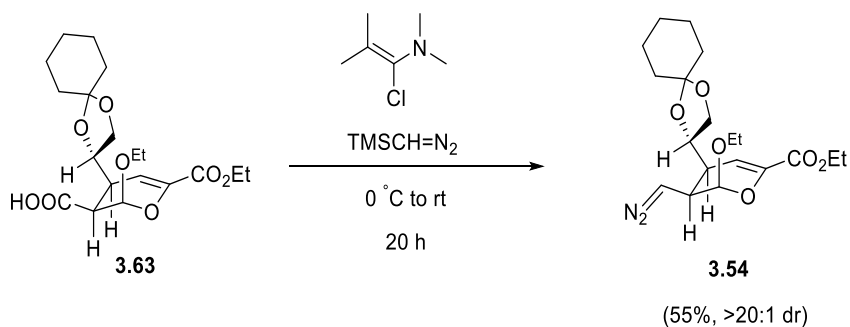
From a 10:1 diastereomers mixture of **3.61\***, a two-step sequence involving deprotection of the primary alcohol with  $\text{K}_2\text{CO}_3/\text{EtOH}$  (70% yield) and Dess-Martin oxidation (85% yield) furnished the aldehyde **3.62** with no observed change in diastereoselectivity. Pinnick oxidation of **3.62** revealed the carboxylic acid **3.63** in 75% yield. Both precursors were readily prepared in multi-gram scale.

**Scheme 3-17.** Synthesis of Precursors of  $\alpha$ -Diazo Ketone Intermediate



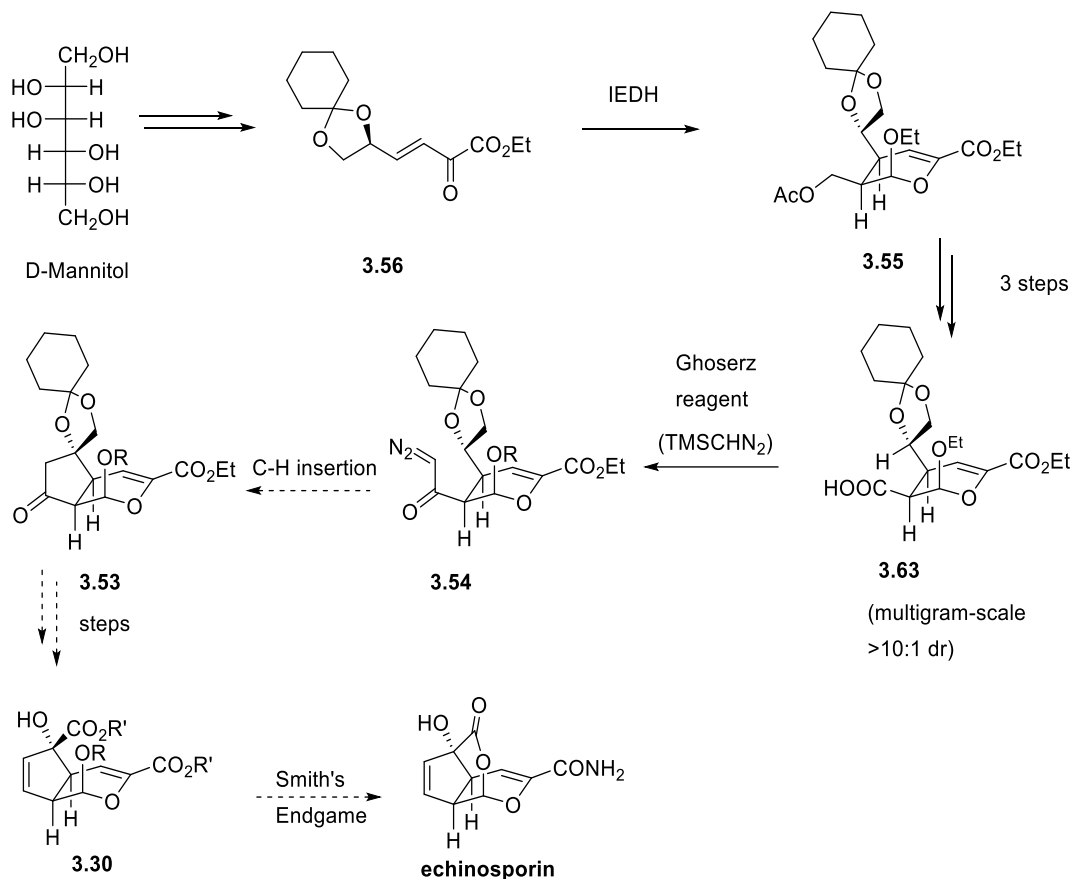
To our delight, the diazo **3.54** was readily synthesized as a single diastereomer from carboxylic acid **3.63** via an acylation of trimethylsilyl diazomethane using Ghosez reagent (Scheme 3-18)

**Scheme 3-18.** Synthesis of  $\alpha$ -Diazo Ketone Intermediate



### 3.4 Conclusions and Future Direction

**Scheme 3-19.** Echinospirin Summary and Future Direction



In conclusion, we have developed a method to access a unique building block of pyruvate alkylidene dimer in multigram-scale and investigated its use toward the synthesis of echinosporin. Though the pyruvate alkylidene itself showed uncontrollable reactivity, which led us to second generation retrosynthetic analysis, its derivative  $\beta,\gamma$ -unsaturated- $\alpha$ -ketoester has provided a suitable alternative. We were able to use this building block construct the dihydropyran core of echinosporin in high yielding and good diastereoselection (10:1 dr). Diazoketone **3.54** was prepared as a single diastereomer. Our group's next step will be

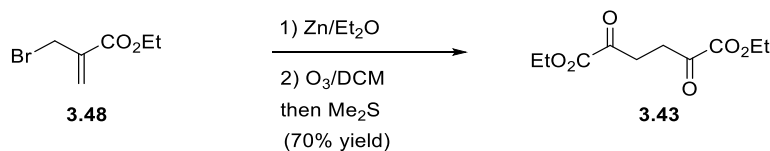
screening large number of known methods for C-H insertion to identify suitable condition for insertion of the carbene to the tertiary C-H bond forming the five-membered ring cyclopentanone **3.53**.<sup>34</sup> From there, several steps functional groups manipulation would generate cyclopentene **3.30** and present a formal synthesis of echinosporin.<sup>35</sup>

The highlight of this work are the development of a simple synthetic building block which enabled us to construct the dihydropyran core of echinosporin with desired stereochemistry and functionality. Multigram-scale preparation of advanced intermediate has provided requisite material for further manipulations which we are optimistic will lead to the natural product in due time.

### 3.5 Experimental Details

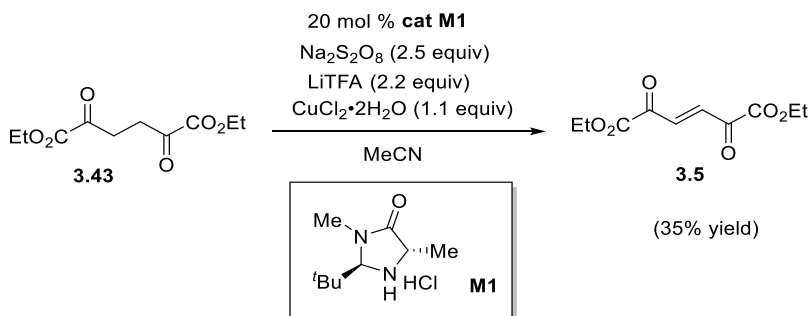
**Methods: General.** Proton and carbon magnetic resonance spectra ( $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR) were recorded on a Bruker model Avance 400 ( $^1\text{H}$  NMR at 400 MHz and  $^{13}\text{C}$  at 100 MHz) or a Bruker model Avance 600 ( $^1\text{H}$  NMR at 600 MHz and  $^{13}\text{C}$  NMR at 150 MHz) spectrometer with solvent resonance as the internal standard ( $^1\text{H}$  NMR:  $\text{CDCl}_3$  at 7.26 ppm;  $^{13}\text{C}$  NMR:  $\text{CDCl}_3$  at 77.0 ppm).  $^1\text{H}$  NMR data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, br t = broad triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. Analytical thin layer chromatography (TLC) was performed on Sorbent Technologies 0.20 mm Silica G TLC plates. Visualization was accomplished with UV light and/or aqueous ceric ammonium nitrate solution followed by heating. Purification of the reaction products was carried out by flash chromatography using Siliaflash-P60 silica gel (40-63 $\mu\text{m}$ ) purchased from Silicycle. Unless otherwise noted, all reactions were carried out under an atmosphere of dry nitrogen in oven-dried glassware with magnetic stirring. Yield refers to isolated yield of analytically pure material unless otherwise noted. Yields are reported for a specific experiment and as a result may differ slightly from those found in the tables, which are averages of at least two experiments.

**Materials: General.** Dichloromethane was dried by passage through a column of neutral alumina under nitrogen prior to use. Triethylamine was freshly distilled from calcium hydride prior to use. All other reagents were purchased from commercial sources and were used as received unless otherwise noted.



An oven-dried 100-mL round-bottomed flask equipped with a magnetic stir bar was charged with zinc dust (1.30 g, 20.0 mmol, 1 equiv) and diethyl ether (25 mL). The flask was fitted with a condenser and purged with nitrogen. Br<sub>2</sub> (0.07 mL, 1.4 mmol, 0.14 equiv) was added dropwise over 5 min with stirring (exotherm observed). The suspension was heated to reflux, and ethyl 2-(bromomethyl)acrylate (7.72 g, 40 mmol, 2.0 equiv) was added dropwise over 15 min. The solution was stirred at this temperature for 4 h then cooled to RT. The reaction was cooled to 23 °C and quenched by 1M HCl. Two time extraction with Et<sub>2</sub>O (2x20 ml) and the combined organic layer was separated and washed with brine. Volatiles were removed in rotavap. The crude product was charged into a 250-mL round-bottomed flask with CH<sub>2</sub>Cl<sub>2</sub> (60 mL). The resulting solution was cooled to -78 °C, and a stream of O<sub>3</sub> was bubbled through the solution until a blue color was observed, typically 5 min. The mixture was sparged with O<sub>2</sub> for 5 min, and Me<sub>2</sub>S (5 mL) was added. The resulting mixture was warmed to rt and stirred for 12 h and concentrated in vacuo. The crude product was purified via flash chromatography (80:20 hexane: ethyl acetate) afforded the pyruvate dimer **3.43** (3.22 g, 70%).

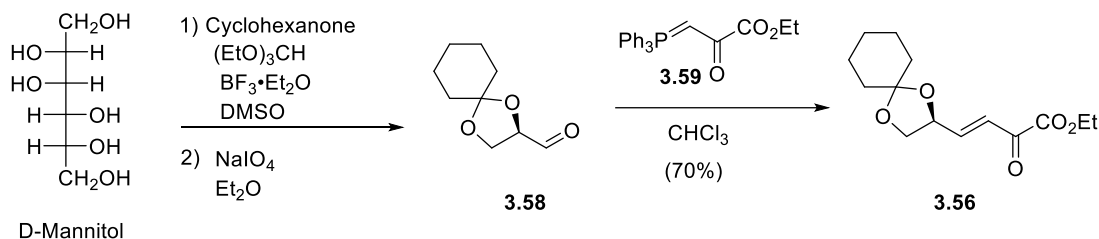
**Diethyl 2,5-dioxohexanedioate (3.24):** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 4.37-4.31 (q, *J* = 7.2 Hz, 4H), 3.21 (s, 4H), 1.39-1.36 (t, *J* = 7.2 Hz, 6H); **TLC** (80:20 hexane/EtOAc): R<sub>f</sub> = 0.40





Round bottom flask (at 0 °C) equipped with a magnetic stir bar and charged with (2R,5S)-2-tert-butyl-3,5-dimethylimidazolidin-4-one hydrochloride salt (20 mol%, 340 mg, 2 mmol), lithium trifluoroacetate (2.2 equiv., 2.64 g, 2.2 mmol), copper(II) chloride hydrate (1.1 equiv, 1.88 g, 1.1 mmol) and sodium persulfate (2.5 equiv., 5.95 g, 2.5 mmol) was added acetonitrile (80 mL, 0.125 M) The medium was stirred at 0 °C for five minutes, before the pyruvate dimer **3.43** (2.3 g, 10.0 mmol) was added and the reaction mixture stirred vigorously for 10 hours at 0 °C. Upon completion, the reaction was quenched with H<sub>2</sub>O and extracted with EtOAc (3x 20 ml). The combined extracts were dried over sodium sulfate and volatiles were removed *in vacuo*. The crude product was purified via flash chromatography (80:20 hexane: ethyl acetate) afforded the pyruvate alkylidene dimer **3.5** (798 mg, 35%).

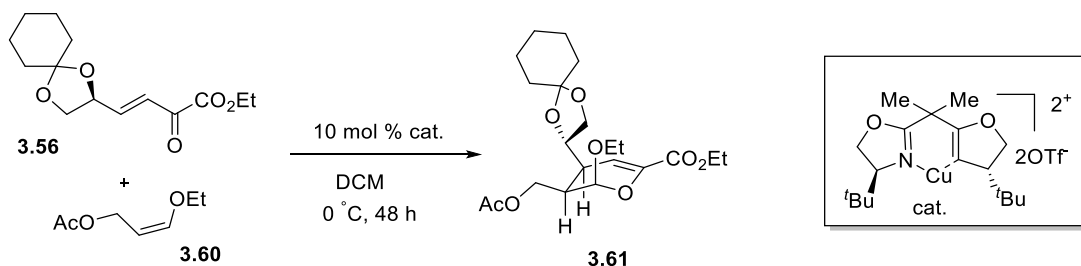
**Diethyl (E)-2,5-dioxohex-3-enedioate:** <sup>1</sup>H NMR (MHz, CDCl<sub>3</sub>): δ 7.73 (s, 2H), 4.44-4.38 (q, *J* = 7.2 Hz, 4H), 1.43-1.39 (t, *J* = 7.2 Hz, 6H); **TLC** (80:20 hexane/EtOAc): R<sub>f</sub> = 0.35.



A mixture of D-mannitol (10.0 g, 54 mmol), cyclohexanone (16.8mL, 162 mmol), triethyl orthoformate (9 mL, 54 mmol), BF<sub>3</sub>·Et<sub>2</sub>O (0.6 mL, 5.4 mmol) and dry DMSO (25 mL) was stirred for 13 h at rt. The mixture was then poured into 20 mL of 10% ice-cooled NaHCO<sub>3</sub> solution and was extracted with ether (15 mL x 3). The organic layer was dried over MgSO<sub>4</sub> and concentrated in vacuo. To a solution of the residue obtained in 100 mL of ether was added

a solution of NaIO<sub>4</sub> (14.6 g, 68 mmol) and Bu<sub>4</sub>NF (0.22 mL, 0.7 mmol) in 60 mL of water, and the mixture was stirred for 3 h at rt. The mixture was separated and aqueous layer was extracted with ether (15 mL x 3). The combined organic layers were dried over MgSO<sub>4</sub> and concentrated in vacuo to give 15 g (82%) of 2,3-O-cyclohexylidene-D-glyceraldehyde as an oil. To a stirred solution of this aldehyde in 60 ml chloroform was added 40 g (1.2 equiv) of the phosphorane **3.59** and the reaction was stirred at rt for 20 h. The solution was then concentrated and the residue was purified by trituration with Et<sub>2</sub>O to remove the phosphine oxide to the desired product (16.6 g, 70%). Flash chromatography (80:20 hexanes/ethyl acetate) to provide product for characterization.

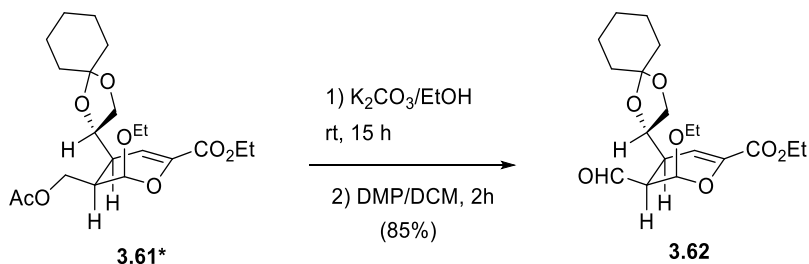
**Ethyl (S,E)-2-oxo-4-(1,4-dioxaspiro[4.5]decan-2-yl)but-3-enoate (3.56):** Analytical data: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.12-7.08 (dd, *J* = 16.0 Hz, 1H, *J* = 5.0 Hz, 1H), 6.97-6.94 (dd, *J* = 16.0 Hz, 1H, *J* = 1.5 Hz, 1H), 4.77-4.73 (m, 1H), 4.37-4.33 (q, *J* = 7.0 Hz, 2H), 4.23-4.20 (dd, *J* = 8.5 Hz, *J* = 7.0 Hz, 1H), 3.72-3.69 (dd, *J* = 8.5 Hz, *J* = 7.0 Hz, 1H), 1.66-1.40 (m, 10H), 1.39-1.36 (t, *J* = 7.0 Hz, 3H); **TLC** (80:20 hexane/EtOAc): R<sub>f</sub> = 0.4.



To an flame-dried round-bottom flask containing a magnetic stir bar was added, in an inert-atmosphere glove box, 2,2-bis{2-[4(S)-tert-butyl-1,3-oxazoliny]}propane (163 mg, 0.554 mmol) and copper(ii) trifluoromethanesulfonate (200 mg, 0.554 mmol). The flask was fitted with a serum cap, removed from the glove box, and charged with CH<sub>2</sub>Cl<sub>2</sub> (20 mL). The reaction

mixture was stirred under nitrogen for 3 h and cooled to 0 °C. The mixture was treated sequentially with ketoester **3.56** (1.49 g, 5.54 mmol) and vinyl ether **3.60** (1.44 g, 10 mmol) at this temperature and stirred for 48 h. The reaction solution was applied to a silica gel column and eluted with EtOAc/hexanes (20:80) to afford the dihydropyran **3.61** (1.98 g, 85%, 10:1 dr).

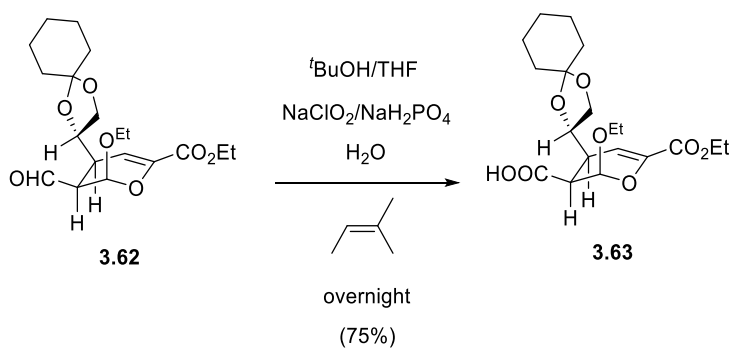
**Ethyl 3-(acetoxymethyl)-2-ethoxy-4-((S)-1,4-dioxaspiro[4.5]decan-2-yl)-3,4-dihydro-2H-pyran-6-carboxylate (3.61):** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 5.94 (d, *J* = 5.2 Hz, 1H), 5.24-5.23 (d, *J* = 2.0 Hz, 1H), 4.52-4.48 (dd, *J* = 14.0 Hz, 1H, *J* = 7.0 Hz, 1H), 4.4-4.35 (m, 1H), 4.29-4.23 (m, 4H), 4.09-4.01 (m, 1H), 3.87-3.83 (m, 1H), 3.65-3.61 (t, *J* = 10 Hz, 1H), 3.60-3.55 (m, 1H), 2.62-2.60 (m, 1H), 2.05 (s, 3H), 1.61-1.55 (m, 10H), 1.34-1.31 (t, *J* = 7.5 Hz, 3H), 1.21-1.17 (t, *J* = 8.0 Hz, 3H); **TLC** (70:30 hexanes/ethyl acetate): *R*<sub>f</sub> = 0.35.



To a solution of the dihydropyran **3.61\*** (1.98 g, 4.8 mmol) in 10 ml ethanol was added K<sub>2</sub>CO<sub>3</sub> (100 mg) and the reaction was stirred at rt for 15 h. 10 ml H<sub>2</sub>O was then added and the mixture was extracted with EtOAc (2x10 ml). The combined organic extracts was washed with brine and dried over sodium sulfate. Solvents were removed *in vacuo* and the product was charged in to a round-bottomed flask with 20 ml of CH<sub>2</sub>Cl<sub>2</sub>. The flask was cooled to 0 °C and 3.43 g (14.54 mmol) of Dess–Martin periodinane was then added. The reaction was warmed up and stirred at rt for 1.5 h. Upon completion, volatiles were removed *in vacuo* and the crude product

was purified via flash chromatography (80:20 hexane/EtOAc) to provide the desired product as a pale yellow oil (1.50 g, 85%, 10:1 dr).

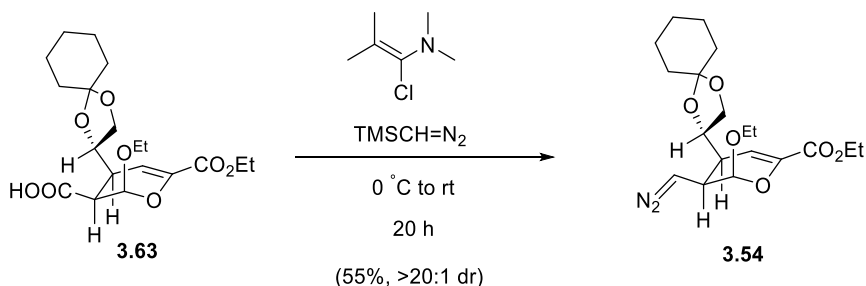
**Ethyl (2R,3R,4R)-2-ethoxy-3-formyl-4-((S)-1,4-dioxaspiro[4.5]decan-2-yl)-3,4-dihydro-2H-pyran-6-carboxylate (3.62):**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.88 (s, 1H), 5.34-5.92 (d,  $J = 4.4$  Hz, 1H), 5.48-5.47 (d,  $J = 2.0$  Hz, 1H), 4.55-4.48 (m, 1H), 4.30-4.26 (m, 2H), 4.13-4.07 (m, 1H), 3.95-3.91 (m, 1H), 3.74-3.67 (m, 2H), 2.88-2.82 (m, 2H), 1.61-1.51 (m, 10H), 1.35-1.31 (t,  $J = 7.2$  Hz, 3H), 1.24-1.20 (t,  $J = 7.2$  Hz, 3H); **TLC** (80:20 hexanes/ethyl acetate):  $R_f = 0.30$ .



The aldehyde **3.62** (1.5 g, 4.1 mmol) was dissolved in 40 ml of tert-butyl alcohol and 10 ml of 2-methyl-2-butene. A solution of sodium chlorite (3.0 g, 33 mmol) and sodium dihydrogenphosphates (3.0 g, 25 mmol) in 20 ml of  $\text{H}_2\text{O}$  was added dropwise over a 20 minute. The pale yellow reaction mixture was stirred at room temperature overnight. Volatile components were then removed under vacuum, the residue was dissolved in 30 ml of water and extracted with two 15 ml portions of ethyl acetate. The aqueous layer was acidified to pH 3 with  $\text{HCl}$  and extracted with three 20 ml portions of ethyl acetate. The combined organic layers was dried over sodium sulfate and concentrated *in vacuo*. The crude was then purified

via flash chromatography (50:50 hexane/EtOAc) to provide the desired product (1.18 g, 75%, 10:1 dr).

**(2R,3S,4R)-2-ethoxy-6-(ethoxycarbonyl)-4-((S)-1,4-dioxaspiro[4.5]decan-2-yl)-3,4-dihydro-2H-pyran-3-carboxylic acid (3.63):**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ): (Major Diastereomer)  $\delta$  6.03-6.02 (d,  $J$  = 5.5 Hz, 1H), 5.41-5.5.40 (d, 2.0 Hz, 1H), 4.49-4.45 (q,  $J$  = 6.5 Hz, 1H), 4.31-4.23 (m, 2H), 4.07-4.04 (m, 1H), 3.96-3.93 (m, 1H), 3.77-3.74 (dd,  $J$  = 8.5 Hz,  $J$  = 6.5 Hz, 1H), 3.72-3.68 (m, 1H), 3.15-3.13 (dd,  $J$  = 7.0 Hz,  $J$  = 2.5 Hz, 1H) 3.03-3.00 (m, 1H), 1.63-1.56 (m, 8H), 1.33 (m, 2H), 1.34-1.31 (t,  $J$  = 7.5 Hz, 3H), 1.25-1.22 (t,  $J$  = 7.0 Hz, 3H); **TLC** (50:50 hexanes/ethyl acetate):  $R_f$  = 0.20.



To a solution of 384 mg (1 mmol) carboxylic acid **3.63** in 5 ml  $\text{CH}_2\text{Cl}_2$  was added 0.3 ml (2.25 mmol) 1-Chloro-*N,N*,2-trimethyl-1-propenylamine via syringe and the reaction was stirred at rt for 1 h. The reaction was cooled to 0  $^\circ\text{C}$  and solution of (trimethylsilyl) diazomethane (5 ml, 2M sol. in  $\text{Et}_2\text{O}$ ) was then added dropwise via syringe. Reaction was slowly warmed up and stirred for 20 h at rt. Volatiles were removed *in vacuo* and the residue was purified via flash chromatography (70:30 hexane/EtOAc) to provide the desired product as a single diastereomer (209 mg, 55%, >20:1 dr).

**Ethyl (2R,3R,4R)-3-(diazomethyl)-2-ethoxy-4-((S)-1,4-dioxaspiro[4.5]decan-2-yl)-3,4-dihydro-2H-pyran-6-carboxylate (3.54)** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.28-6.26 (d, *J* = 8.8 Hz, 1H), 5.58-5.57 (d, 4.0 Hz, 1H), 4.65 (bs, 1H), 4.60-4.58 (m, 1H), 4.31-4.27 (m, 2H), 3.91-3.90 (m, 1H), 3.78-3.75 (m, 1H), 3.65-3.61 (m, 1H), 3.16-3.15 (m, 1H), 3.00-2.96 (dd, *J* = 9.6 Hz, 1H, *J* = 4.4 Hz, 1H), 2.08-2.04 (m, 4H), 1.68-1.66 (m, 2H), 1.56-1.53 (m, 4H), 1.35-1.32 (t, *J* = 7.2 Hz, 3H), 1.18-1.14 (t, *J* = 7.2 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 173.3, 161.8, 154.1, 140.2, 109.0, 94.6, 94.1, 81.9, 65.2, 64.6, 61.3, 60.2, 41.9, 33.1, 27.3, 23.2, 22.6, 22.4, 14.6, 14.0; TLC (70:30 hexanes/ethyl acetate): R<sub>f</sub> = 0.30.

### 3.6 References

1. Nicewicz, D.A.; Satterfield, A.D.; Schmitt, D.S.; Johnson, J.S. *J. Am. Chem. Soc.* **2008**, *130*, 17281-17283. (b) Malinowski, J.T.; Sharpe, R.J.; Johnson, J.S. *Science.*, **2013**, *340*, 180.
2. Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77-84.
3. (a) Iida, T. N.; Hirayama, N.; Shirahata, K. *Abstr. Papers, 44th Annu. Meeting Jpn. Chem. Soc.*, **1981**, 1E-18, 403. Kyowa Hakko Kogyo Co., Ltd. *Jpn. K. Tokkyo Koho* **1981**, 59, 777. (b) Sato, T.; Kawamoto, I.; Oka, T.; Okachhi, R. *J. Antibior.* **1982**, *35*, 266.
4. Morimoto, M.; Imai, R. *J. Antibior.* **1985**, *38*, 490.
5. Hirayama, N.; Iida, T.; Shirahata, K.; Ohashi, Y.; Sasada, Y. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 287.
6. Dubeler, A.; Krastel, P.; Floss, H. G.; Zeeck, A. *Eur. J. Org. Chem.* **2002**, 983
7. Smith, A. B., III; Sulikowski, G. A.; Fujimoto, K. *J. Am. Chem. Soc.* **1989**, *111*, 8039. (b) Smith, A. B., III; Sulikowski, G. A.; Sulikowski, M. M.; Fujimoto, K. *J. Am. Chem. Soc.* **1992**, *114*, 2567.
8. Kinsella, M. A.; Kalish, V. J.; Weinreb, S. M. *J. Org. Chem.* **1990**, *55*, 105.
9. Flasz, J. T.; Hale, K. J. *Organic Letters* **2012**, *14*, 3024-3027.
10. Jiang, X.; Wang, J. *Chem. Rev.*, **2013**, *113* (7), pp 5515–5546.
11. Lu, G.; Li, Y. M.; Li, X. S.; Chan, A. S. C. *Coord. Chem. Rev.* **2005**, *249*, 1736-1744.
12. Ernest, I. *Coll. Czech. Chem. Commun.* **1954**, *19*, 1179-1190.
13. M. Paul.; C., Sabrina. *Helvetica Chimica Acta*, **2005**, *88*, 1010 – 1021.
14. Hansen, J. H.; Parr, B. T.; Pelphrey, P.; Jin, Q.; Autschbach, J.; Davies, H. M. L. *Angew. Chem. Int. Ed.* **2011**, *50*, 2544 –2548.
15. Schnermann, M. J.; Romero, F. A.; Hwang, I.; Nakamaru-Ogiso, E.; Yagi, T.; Boger, D. L. *J. Am. Chem. Soc.* **2006**, *128*, 11799-11807.
16. Taylor, R. J. K.; Casy, G. *Org. React. (N.Y.)* **2003**, *62*, 357-476.

17. Saltigo GMBH. *Patent: US2009/163736 A1*, **2009**.
18. Corey, E. J.; Tramontano, A. *J. Am. Chem. Soc.* **1981**, *103*, 5599-5600.
19. McDonald, R. N.; Reitz, R. R. *J. Org. Chem.*, **1972**, *37*, 2418 – 2423.
20. B. Stephane.; O. Francis; P. Claude. *Tetrahedron*, **1997**, *53*, 16767 – 16782.
21. Manis, P. A.; Rathke, M. W. *J. Org. Chem.*, **1980**, *45*, 4952 – 4954.
22. Knochel, P.; Normant, J. F. *J. Org. Chem.*, **1986**, *309*, 1 – 24.
23. (a) Tsuboi, S.; Furutani, H.; Utaka, M.; Takeda, A. *Tetrahedron Lett.* **1987**, *28*, 2709-2712; (b) Tsuboi, S.; Furutani, H.; Ansari, M. H.; Sakai, T.; Utaka, M.; Takeda, A. *J. Org. Chem.* **1993**, *58*, 486–492; (c) Rodrigues, J. A. R.; Milagre, H. M. S.; Milagre, C. D. F.; Moran, P. J. S. *Tetrahedron: Asymmetry* **2005**, *16*, 3099–3106. (c) Takeda, A.; Wada, S.; Fujii, M.; Nakasima, I.; Hirata, S. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1342–1345; (d) Okonya, J. F.; Johnson, M. C.; Hoffman, R. V. *J. Org. Chem.* **1998**, *63*, 6409–6413; (e) Okonya, J. F.; Hoffman, R. V.; Johnson, M. C. *J. Org. Chem.* **2002**, *67*, 1102–1108; Nakamura, A.; Lectard, S.; Hashizume, D.; Hamashima, Y.; Sodeoka, M. *J. Am. Chem. Soc.* **2010**, *132*, 4036–4037. (f) Amatore, M.; Beeson, T. D.; Brown, S. P.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* **2009**, *48*, 5121 –5124.
24. Satake, T.; Nakatsuji, S.; Iyoda, M.; Akiyama, S.; Nakagawa, M. *Tetrahedron Lett.* **1976**, *17*, 1881-1884.
25. G. Lu.; X. Li.; W.L. Chan.; A.S.C. Chan. *Chem. Commun.* **2002**, 172.
26. Trost, B. M.; Bartlett, M. J.; Weiss, A. H.; von Wangelin, A. J.; Chan, V. S. *Chem. Eur. J.* **2012**, *18*, 16498 – 16509.
27. (a) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357. (b) F. Effenberger.; A. Kremser.; U. Stelzer. *Tetrahedron: Asymmetry*. **1996**, *7*, 607-618. (c) F. Effenberger.; U. Stelzer. *Tetrahedron: Asymmetry*. **1995**, *6*, 283-286. (d) Steward, K. M.; Corbett, M. T.; Goodman, G.; Johnson, J. S. *J. Am. Chem. Soc.* **2012**, *134*, 20197.
28. (a) Taber, D. F.; You, K. K.; Rheingold, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 547. (b) Davies, H. M. L.; Beckwith, R. E. *J. Chem. Rev.* **2003**, *103*, 2861.
29. (a) Evans, D. A.; Johnson, J. S.; Olhava, E. J. *JACS.* **2000**, *122*, 1635-1649. (b) Thorhauge, J.; Johannsen, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 2404-2406.
30. (a) Fruh, T.; Chemla, P.; Ehrler, J.; Farooq, S. *Pestic. Sci.* **1996**, *46*, 37-47. (b) Dvořáková, H.; Hrabal, R.; Kniežo, L. *Magn. Reson. Chem.* **2000**, *38*, 738–746.



31. Regitz. M. *Angew. Chem. Int. Ed. Engl.* **1966**, 5, 681–682.
32. Dess. D. B.; Martin. J. C. *J. Org. Chem.* **1983**, 48, 4155.
33. Bal. B. S.; Childers. W. E.; Pinnick. H. W. *Tetrahedron*. **1981**, 37, 2091–2096.
34. Cacchi. S.; Morera. E.; Ortar. G. *Org. Synth.* **1990**, 68, 138.