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Novel Synthetic Transformations Targeting δ-Valerolactone and Isocoumarin

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NOVEL SYNTHETIC TRANSFORMATIONS
TARGETING δ-VALEROLACTONE AND
ISOCOUMARIN

A Dissertation

Submitted to the Graduate Faculty of the
Louisiana State University and
Agricultural and Mechanical College
in partial fulfillment of the
requirements for the degree of
Doctor of Philosophy

in

The Department of Chemistry

by
Joshua Paul Van Houten
B.S., Southwestern University, 2012
May 2021
I would like to dedicate this work to my loving family. To my 

*Father Jeff, Mother Beth, and Sister Sarah, thank you*

*for always being positive and never doubting me.*
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LIST OF ABBREVIATIONS

1H NMR.................................................................proton nuclear magnetic resonance
13C NMR...............................................................carbon-13 nuclear magnetic resonance
Ar.................................................................aromatic
BPS..........................................................tert-Butyldiphenylsilyl
c-Pr.............................................................cyclopropyl
CDCl3..........................................................deuterated chloroform
CO..............................................................carbon monoxide
CO2.............................................................carbon dioxide
CO3.............................................................carbonate
Conv..........................................................conversion
Cr..........................................................chromium
Cs..........................................................cesium
dba..........................................................Dibenzylideneacetone
DBU......................................................1,8-diazabicyclo[5.4.0]undec-7-ene
DCC..........................................................N,N'-Dicyclohexylcarbodiimide
DCE..........................................................dichloroethane
DCM............................................................methylene chloride
DI..........................................................deionized water
DIPEA..........................................................diisopropylethylamine
DMF..........................................................dimethyl formamide
DMSO..........................................................dimethyl sulfoxide
DMSO-d6..........................................................deuterated dimethyl sulfoxide
dr………………………………………………………………………………..diastereomeric ratio
ESI…………………………………………………………………………..electrospray ionization
$\text{Et}_3\text{N}$…………………………………………………………………………..triethyl amine
Etcage………………………………………………………………………….Trimethylolpropane phosphite
$\text{EtOAc}$…………………………………………………………………………….ethyl acetate
Equiv………………………………………………………………………………..equivalence
F……………………………………………………………………………………………..Faraday
$f_i$………………………………………………………………………………………….frequency
$\text{FeCl}_3$……………………………………………………………………………Iron(III) chloride
g…………………………………………………………………………………………..gram
h……………………………………………………………………………………………hour
$\text{HCl}$…………………………………………………………………………….hydrochloric acid
$\text{HfCl}_4\cdot(\text{THF})_2$…………………………………………………………..Hafnium (IV) chloride tetrahydrofuran
HRMS…………………………………………….high-resolution mass spectrometry
i.e…………………………………………………………………id est (that is)
IR…………………………………………………………………………….infrared spectroscopy
K………………………………………………………………………………………..potassium
k:e…………………………………………………………………..ketone : enol
kg………………………………………………………………………………..kilo gram
$\text{KHSO}_4$…………………………………………………………………..potassium bisulfate
$\text{KMnO}_4$……………………………………………………………….potassium permanganate
L………………………………………………………………………………..laevus
LDA………………………………………………………………………………lithium diisopropylamide
Li$_2$CO$_3$……………………………………………………………………………………lithium carbonate
LiBr…………………………………………………………………………….lithium bromide
M………………………………………………………………………………mass
m…………………………………………………………………………meta
m/z………………………………………………………………………mass-to-charge ratio
m-CPBA…………………………………………………………………meta-chloroperosybenzoic acid
Me…………………………………………………………………………..methyl
MeCN…………………………………………………………………….acetonitrile
MeOH…………………………………………………………………….methanol
mg…………………………………………………………………….milligram
MHz…………………………………………………………………….megahertz
mmol…………………………………………………………………millimole
MnO$_2$…………………………………………………………………manganese oxide
mol…………………………………………………………………….mole
N$_2$O……………………………………………………………………nitrous oxide
NaBH$_4$………………………………………………………………sodium borohydride
NaBr……………………………………………………………………sodium bromide
NaBrO$_2$…………………………………………………………sodium bromite
NaBrO$_3$…………………………………………………………sodium bromate
NaHCO$_3$…………………………………………………………sodium bicarbonate
NaIO$_4$…………………………………………………………sodium periodate
NCS…………………………………………………………………N-Chlorosuccinimide
NH$_4$Cl………………………………………………………………ammonium chloride
NHC..............................................................N-heterocyclic carbene
Ni..............................................................nickel
O_{3(g)}........................................................ozone
OsO_{4}......................................................osmium tetroxide
p..............................................................para
Pb(OAc)$_4$..................................................lead (IV) acetate
Pd..............................................................palladium
Phen......................................................2,2'-bipyridine
pK$_a$.........................................................-log[K$_a$]
PTAB..................................................trimethylphenylammonium tribromide
Rf..............................................................retention factor
RhCl(PPh$_3$)$_3$...........................................Wilkinson’s catalyst/ chlridotrisrhodium(I)
Rh(cod)Cl$_2$..............................................cyclooctadiene rhodium chloride dimer
rt...........................................................room temperature
Ru...........................................................ruthenium
S(2-pyr)...................................................di(pyridine-4-yl)sulfane
SmI$_2$......................................................samarium (II) iodide
SnCl$_4$......................................................tin(IV) chloride
t$_{1/2}$........................................................half life
TBACL..................................................tetrabutylammonium chloride
TBAF......................................................tetra-butyl ammonium fluoride
TBS......................................................tert-butyldimethylsilyl
TEMPO...................................................(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TetMe-IA…………………………………………………………………………3,4,5,6-tetramethyl-2-iodobenzoic acid
TFA……………………………………………………………………………….trifluoroacetic acid
THF………………………………………………………………………………tetrahydrofuran
Ti(Obu)₄………………………………………………………………………….titanium(IV) butoxide
TLC……………………………………………………………………………….thin layer chromatography
TMS………………………………………………………………………………...tri-methyl silyl
TPP……………………………………………………………………………….tetraphenylporphyrin
ABSTRACT

The purpose of this dissertation is to describe the efforts undertaken to develop synthetic methodology targeting δ-valerolactone and isocoumarin. At the onset, an introduction to the δ-valerolactone and isocoumarin is given. Relevant examples of δ-valerolactone being utilized in the production of materials of biological and industrial application are then discussed. Following, current methods for forming δ-valerolactone are presented. After, an introduction to isocoumarin is begun. Current methods for producing isocoumarin are then discussed.

The results and discussion section of this dissertation will focus on two methods that were explored with the goal of producing α-acyl-δ-valerolactone with two different substitution patterns. These patterns are the dihydro-2H-pyran-2-ones and the 3-acetyl tetrahydro-2H-pyran-2-ones. From the effort developing a method for the construction dihydro-2H-pyran-2-ones, valuable information regarding reactivity of acyl Meldrum’s acid with β-hydroxy carbonyls in various solvents was gleaned. Although efforts at dihydro-2H-pyran-2-ones did not produce the desired motif, results from this hypothesis were implemented in optimizing a successful method.

A method was developed that implements a diastereoselective cascade reaction to construct highly functionalized 3-acetyl tetrahydro-2H-pyran-2-ones and isocoumarin. Thermal degradation of acyl Meldrum’s acid derivatives followed by nucleophilic capture with δ-hydroxy yeneone resulted in a malonate ester that was cyclized. Intramolecular Michael addition facilitated furnished highly substituted 3-acetyl tetrahydro-2H-pyran-2-ones. Electronics of the remote δ’-carbonyl carbon was found to highly effect the epimerizability of the α-acyl group. When the described motif’s α’-carbon contained an aromatic substituent, a secondary cyclization occurred under the same conditions resulting in isocoumarin related structures. A proposed reaction mechanism is discussed that accounts for the observed stereochemistry. Further exploration of this
chemistry is centered on developing a method that would allow for isocoumarin formation without specific structural qualifications of the starting material. This reaction is currently being optimized.

In the final chapter, relevant procedures for the production of materials are presented. Additionally, characterization data is discussed, and crude $^1$H NMR data is introduced for material in which crude diastereoselective ratios were determined.
CHAPTER 1. INTRODUCTION TO δ-VALEROLACTONE AND ISOCOUMARIN

1.1. Purpose

The purpose of this section is to introduce the functionalities δ-valerolactone and isocoumarin and discuss applications of these valuable motifs. Additionally, the utilization of these structures in natural products and molecules of biological relevance will be examined. The remainder of the section will focus on the numerous currently available methods and strategies to construct δ-valerolactone. Next, the α-acyl-δ-valerolactone and previous synthetic attempts at this heterocycle will be presented. Finally, the isocoumarin motif will be introduced.

1.2. Introduction to δ-valerolactone

Lactones are heterocyclic molecules that contain an oxygen at the one position and a carbonyl at the two position. Multiple named heterocycles are recognized that can be adopted into this category. Specifically, valerolactone are five carbon heterocycles with oxygen at the one position and carbonyl at the two position. Two five carbon valerolactone are recognized. γ-Valerolactone have methyl at the 5-position of a five membered ring (figure 1.1). The topic being

![Figure 1.1. Structure of common named lactones](image)

introduced here is the δ-valerolactone, a six membered heterocycle with oxygen at the one position and carbonyl at the two position. When describing the positions of the δ-valerolactone a numeric
and Greek method of identification can be implemented. Throughout the document either of these nomenclatures may be utilized to convey necessary positional information. Initially, interest in developing synthetic methodology for δ-valerolactone was triggered from noticing the relevance of this structure in materials isolated from various sources and implementation of this functionality in the production of molecules with biological and industrial relevance.\(^1\) Additionally, δ-valerolactone were recognized as important starting material in polymerization reactions producing material with pharmaceutical application.\(^2\) As an introduction to the δ-valerolactone, some natural products and industrial implementations of this motif are discussed below.

A ubiquitous class of materials isolated from various sources exists that contain δ-valerolactone exists.\(^3\) These natural products differ in the substitution pattern of the heterocyclic core and as a result each offers interesting synthetic challenges that encourage researches to

Figure 1.2. Natural products containing δ-valerolactone
develop novel methodology. Figure 1.2 demonstrates these molecules. A \( \delta \)-valerolactone substituted at the 3,4 and 6 position is found in the structure of Dihydrodictyopyrone C\(^4\) which, due to the enolizable nature of the \( \alpha \)-carbon possesses a unique synthetic challenge. An additional natural product, Salvinorin A, is a kappa-opioid receptor agonist hallucinogen and as a result offers researchers a template for elaboration into novel pharmacotherapeutic agents.\(^5\) The fused ring system of material extracted from \textit{Scutellaria baicalensis} contains the \( \delta \)-valerolactone motif.\(^6\) Rhizoxin was isolated from the \textit{Rhizopus microspores} fungus and has been shown to have anti-tumor activity.\(^7\) Compounds (+)-9-deoxygonioppyrone and 5-Et-parvistone D also contain \( \delta \)-valerolactone and have been shown to possess biological activity.\(^8\) While this list of molecules offers a glimpse at the \( \delta \)-valerolactone containing material discovered thus far, there are thousands of additional known structures containing this motif. After being convinced an abundant class of natural products contains \( \delta \)-valerolactone, a literature search was conducted to uncover how researchers are utilizing the \( \delta \)-valerolactone.

The heterocyclic motif, \( \delta \)-valerolactone, is particularly significant due to its broad relevance in molecules of biomaterial applications. Particularly, \( \delta \)-valerolactone can be subjected to polymerization conditions with various linkers resulting in materials with a range of properties. Figure 1.3 outlines these applications. In 2005 Allen catalyzed the polymerization of \( \delta \)-valerolactone and mPEG with HCl forming methoxy poly(ethylene-glycol)-block-poly(\( \delta \)-valerolactone) copolymer micelles for the formulation of hydrophobic drugs.\(^9\) Vallée-Rehel and co-workers in 2007 prepared pharmaceutical agent binders by copolymerization of \( \varepsilon \)-caprolactone and lactide at high temperatures in the presence of Ti(OBu)\(_4\) initiator.\(^10\) Another application of \( \delta \)-valerolactone was recognized by Chu in 2008 to synthesis molecules with biological activity.\(^11\) \( \delta \)-Valerolactone polymerization was initiated by the hydroxyl group mPEG in the presence of
stannous octoate. Five types of amphiphilic block copolymers were synthesized in this manner. Finally in 2013 Toy, developed a resin bound catalyst \textbf{1.01} capable of inducing ring-opening polymerization of \(\delta\)-valerolactone.\textsuperscript{12} This catalyst resulted in 99% conversion of \(\delta\)-valerolactone into the final product, and was able to be separated from the desired product by simple filtration. These examples demonstrate the value of \(\delta\)-valerolactone as a building block in polymer synthesis.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure13.png}
\caption{Applications of \(\delta\)-valerolactone}
\end{figure}
The natural product structures and the relevance of this motif as a starting reagent in the construction of various materials inspired development of synthetic methodology centered on forming δ-valerolactone. In order to gain an understanding of the existing routes to the motif and how to best add to the already existing literature, a comprehensive review was conducted to decide where targeted research efforts could be most impactful. Discussed next is the result of this search.

1.3. Previous preparations of δ-valerolactone

In the past five years the study of this motif has been of interest to the chemistry community as evidenced by the publication of three review articles focused on lactone formation. After review of the current methods available to researchers for the formation of δ-valerolactone, each method was classified into one of four categories. The four categories adopted for the purpose of better understanding current strategies are outlined in figure 1.4: 1) Intramolecular cyclization strategies are the most abundant class of methods available for δ-valerolactone synthesis. After functional groups on either end of a carbon chain of various lengths have been activated, cyclization produces the desired product. 2) Expanding a pre-existing ring to the δ-valerolactone. This method includes reactions that insert oxygen into a cyclic ketone or install oxygen and

Figure 1.4. Four available strategies for δ-valerolactone synthesis
carbonyl within a cyclic aliphatic system. 3) Oxidizing a pyran at the two position, produces δ-valerolactone and offers additional methods for the construction of the desired motif. Finally, 4) Cleaving 1,2 diols at the requisite position of pyran can result in δ-valerolactone. In the following section relevant strategies that demonstrate each of these four strategies will be discussed.

1.3.1. Intramolecular cyclization

Intramolecular reactions that result in δ-valerolactone formation are discussed in this section reactions (figure 1.5). These sets of reactions rely on activation of one or more functional groups at the terminus of a carbon chain. Within the broader category of intramolecular cyclization reactions, there are four subcategories that each of these reactions can be divided into: acid catalyzed, transition metal catalyzed, carboxylic acid activation, and 1,5-diol oxidation.

1.3.1.1. Brønsted acids

In this brief subcategory, two reactions are discussed that implement strong Brønsted acids to effectuate an intramolecular cyclization resulting in δ-valerolactone that contains no additional functional groups. An early account of Brønsted acids being used to promote intramolecular cyclization was reported by Howard in 1961. In this research, γ-aminovaleric acids were exposed to nitrous acid. Protonation of the amine followed by elimination of the ammonium ion resulted in carbocation intermediate. Intramolecular cyclization yielded 10% of the desired
δ-valerolactone. The inventor Yunhai investigated another acid promoted cyclization. This patent claims the multi-kilogram process begins with the full solvation of 5-hydroxyl butyl cyanide in water. Next, HCl gas is bubbled through the solution and δ-valerolactone was isolated in 95% yield (scheme 1.1). Within the search capabilities available, these examples are the only publications demonstrated utilizing Brønsted acids for δ-valerolactone creation.

**1.3.1.2. Transition metals**

Transition metal catalyzed intramolecular cyclization events that result in δ-valerolactone are described in this section. Some examples are discussed in scheme 1.2 that successfully produce lactones of multiple sizes in addition to the desired δ-valerolactone. Yoshikoshi in 1990 published a δ-valerolactone forming reaction utilizing dirhodium tetraacetate catalyst. Upon exposure of the starting α-diazomalonate to the catalyst, δ-valerolactone was provided in stereoselective fashion. The reaction was perceived to have involved transition state where after initial ring formation, sulfur undergoes intramolecular transfer to the more nucleophilic α'-carbon. δ-Valerolactones were produced in equal diastereomeric portions at the six position. An example by Kapustina in 2004 showcases a solventless approach to transition metal catalyzed...
intramolecular cyclization reactions producing δ-valerolactone. Exposing liquid starting material 1.08 to slow addition of catalytic Pb(OAc)$_4$ and stoichiometric NH$_4$Cl(s) gave the desired δ-valerolactone. Kapustina proposed intermediate 1.09 would undergo intramolecular oxidative

Scheme 1.2. Transition metal implementation for δ-valerolactone synthesis

insertion of [Pd] into the carbon chlorine bond followed by reductive elimination to generate desired δ-valerolactone. Adequately converting dialdehydes to δ-valerolactone via intramolecular cyclization while circumventing polymerization is a non-synthetically trivial task. Ryu in 2009 aptly overcame this challenge via the use of ruthenium catalyst RuHCl(CO)(PPh$_3$)$_3$. The reaction
successfully converts dialdehydes to the desired δ-valerolactone in 70% yield. A reaction mechanism was suggested whereby hydoruthenation product 1.10 underwent intramolecular cyclization via nucleophilic addition of facile oxygen ruthenium bond to electrophilic aldehyde.

Scheme 1.3. Beau’s SmI₂ promoted sugar analog modification

After β-hydride elimination of Ru catalyst from 1.11, δ-valerolactone was generated. Li in 2018 employed Rh(cod)Cl₂ for the macro lactonization of alkynyl alcohols 1.12.¹⁹ Unlike previous methods, this reaction could be conducted without excessively dilute concentrations and minimal polymerization of starting materials. The reaction mechanism was proposed to have proceeded through vinylidene 1.13. After oxidation of the terminal metal allene 1.13 to ketene 1.14, intramolecular capture by alcohol resulted in δ-valerolactone in 52% (scheme 1.2). Other lactones of larger ring size were also produced under these conditions. One additional method published by Beau in 2014 focused on the synthesis of spiro-δ-lactonic-α-C-Sialosides by samarium diiodide mediated cyclization reactions of glycol-syl 2-pyridylsulfides of acetates.²⁰ This method was able to produce the described δ-valerolactone 1.16 in high yield (scheme 1.3). As suggested by Beau, intermediate 1.15 obtained after S(2-pyr) substitution with SmI₂ was crucial to ring formation.
Scheme 1.4. Applications of transition metal produced δ-valerolactone in natural products

A transition metal catalyzed intramolecular cyclization approach to natural product synthesis was developed by Steglich in 2003 to produce (+)-calopin 1.20. At the onset, a highly stereoselective ene reaction was implemented to set two of the three necessary stereocenters. Several functional group interconversion steps followed before material 1.17 was prepared for a stereoselective hydrogenation using RhCl(PPh₃)₃ and hydrogen gas. Researchers were surprised
to discover a mixture of δ-valerolactone 1.18 and 1.19 in the crude reaction mixture. These were easily separated using column chromatography. Another natural product, Artemisinin was produced at 200 kg scale by Burgard in 2014.22 Preparing for the δ-valerolactone forming step, Artemisinic acid 1.21 was diastereoselectively hydrogenated with [Rh] catalyst and hydrogen gas. Carboxylic acid 1.22 was then converted to carbonyl carbamate 1.23. Intramolecular light catalyzed cyclization under a mercury vapor lamp produced the desired product. Across three steps, 55% yield (370 Kg) of the desired product 1.24 was collected. These examples demonstrate how researchers have provided novel transition metal catalysts while forming δ-valerolactone. Reviews highlighting transition metal catalyzed δ-valerolactone forming reactions are available.23

1.3.1.3. Intramolecular esterification

Intramolecular cyclizations resulting in the formation of δ-valerolactone from a free or masked carboxylic acid are described below. These four reactions are not a complete account of the references available in literature that utilize this technique but do highlight important developments in δ-valerolactone forming processes. Scheme 1.5 highlights these results. Removal of the proton from a carboxylic acid produces soft nucleophile that can displace a leaving group at an extended position in the molecule. Kellogg in 1981 released an early report utilizing this technique.24 Exposure of 1.25 to cesium carbonate in DMF produced δ-valerolactone in high yield. In 2001 two reports using different reagents were published by Maruoka. The first report demonstrates a TMS masked carboxylic acid 1.26 being revealed as an acetate anion upon exposure to TBAF.25 A second report by Maruoka in 2001 shows how an alternative set of reaction conditions can activate 1.27.26 Both sets of conditions produce δ-valerolactone in high yields. Finally, Yamamoto in 2002 published an intramolecular cyclization utilizing hydroxyl nucleophile.27 The reaction conditions implemented HfCl₄•(THF)₂ as a Lewis acid to activate
carboxylic acid 1.28 for intramolecular cyclization, forming the δ-valerolactone. An example that utilized intra molecular esterification of carboxylic acid for δ-valerolactone formation is found within the total synthesis of natural product oxandrolone 1.33 reported by Cabaj in 2007.28 Four steps were need to produce this product on kilo-gram scale with no column chromatography. Initial bromination of cyclohexanone 1.29 produced brominated product 1.30 in 82% yield. Several conditions were attempted that selectively eliminated bromine without tandem elimination of the distant alcohol. The conditions LiBr and Li₂CO₃ in DMF at reflux successfully generated product 1.31 with no biproduct formation. Ozonolysis was conducted with O₃(g) in MeOH producing di-
carbonyl material 1.32 in 66%. Reduction of aldehyde 1.32 with NaBH₄ resulted in intramolecular cyclization, forming the δ-valerolactone oxandrolone 1.33 in 97%, with an overall yield of 42%.

1.3.1.4. 1,n-Diol oxidation and cyclization

This section highlights δ-valerolactone forming processes that utilize 1,n-diols as starting material for intramolecular cyclization. Scheme 1.6 and Scheme 1.7 highlights these efforts.

![Scheme 1.6. First set of 1,n-diol reactions](image)

In a publication by Okawara in 1983, NaBrO₂ was employed as an oxidant for the intramolecular cyclization of various diol starting materials 1.34. Utilizing this reagent in aqueous acetic acid resulted in lactones of various sizes isolated in high yields. Specifically, δ-valerolactone was produced in 98% yield. In 1991, work published by Torii implemented electrochemistry and catalytic oxidants to construct δ-valerolactone. Tempo derivative 1.35 was mixed in catalytic
amounts with the starting diol in a NaBr/ NaHCO$_3$ aqueous buffer. Introducing a current of 4.5 F/mol yielded δ-valerolactone in 97%. Borhan in 2003 introduced an interesting approach to generate the desired lactone from alkene alcohols 1.36$^{31}$ Upon exposure of the starting material

![Scheme 1.7. Second set of 1,2-diol reactions](image)

1.36 to OsO$_4$ and oxone in DMF the desired lactone was formed in 68%. The mechanism was suspected to have involved oxone intermediate 1.37, which after removal of geminal hydrogen gave δ-valerolactone. In 2010 Garrell published a method that formed the desired product through the utilization of TEMPO bound to a superparamagnetic nano particle through triazole linker 1.38$^{32}$ After the reaction was complete, δ-valerolactone was isolated in 99% yield, and the catalyst 1.38 was separated from the reaction mixture via simple filtration. Another set of conditions that adequately produced the desired product was presented by Moorthy in 2014.$^{33}$ Using oxone and catalytic TetMe-IA 1.39, δ-valerolactone was formed in 55% yield. In a recent publication by
Makhmutov in 2018 a novel iron oxidant was employed in combination with visible light to initiate the conversion of diol starting material to δ-valerolactone. Application of the diol oxidation method to produce δ-valerolactone was applied to the total synthesis of Dihydrodictyopyrone C as reported by Oshima in 2007. During the lead up to the δ-valerolactone forming reaction, 10% HCl in MeOH was utilized to reveal triol 1.40. The stereoselective lactonization reaction was conducted with TEMPO as an oxidant in accompaniment with TBACl and NCS in a mixture of DCM and water. Desired δ-valerolactone 1.41 was produced in 87% yield. After additional synthetic steps Dihydrodictyopyrone C was produced (scheme 1.8).

1.3.2. Pyran oxidation

Another route to desired δ-valerolactone is available through the installation of a carbonyl at the two position of pyran. In this section, four examples are provided that reflect common strategies adopted by researchers attempting to produce δ-valerolactone via this manner. Two relevant mechanisms of the four methods are discussed.

An early report that described the oxidation of pyrans to the desired δ-valerolactone was published by Wolfe in 1983. Using Zinc (II) permanganate as an oxidant, the starting pyran was
oxidized to the δ-valerolactone using DCM as the solvent. In 2002 Lee employed KMnO₄ as an oxidizing agent at -78 °C in acetone with stoichiometric FeCl₃ to oxidize starting pyran to

![Pyran oxidation](image)

Figure 1.6. Pyran oxidation

δ-valerolactone.³⁶ In 2000 Bittner published a method for construction of δ-valerolactone via use of NaBrO₃ and KHSO₄ in water.³⁷ A mechanism was suggested to have been initiated with bromate ion addition to protonated pyran 1.42. Reductive elimination of the bromate ion from intermediate

Wiolf 1983

\[
\text{Oxidation of pyran} \quad \text{O} = \text{CH}_2\text{Cl}_2, 69\%
\]

Lee 2002

\[
\text{KMnO}_4 (10 \text{ equiv}) \quad \text{FeCl}_3 (6.2 \text{ mmol}) \quad \text{acetone, -78 °C → rt, 83%}
\]

Bittner 2000

\[
\text{NaBrO}_3 (1 \text{ equiv}) \quad \text{KHSO}_4 (1 \text{ equiv}) \quad \text{H}_2\text{O, 69%}
\]

Higuchi 2015

\[
[\text{Ru}] (0.003 \text{ equiv}) \quad \text{2,6-dichloropyridine N-oxide (2.5 equiv)}
\]

Scheme 1.9. Oxidation of pyran
alcohol 1.43 then resulted in an aldehyde which was esterified under oxidative conditions to δ-valerolactone. Methods implementing radical promoting catalysts are also available to synthesize δ-valerolactone. Higuchi in 2015 utilized Ru catalysis to install carbonyl at the two position of pyran producing δ-valerolactone in 56% yield.38 Mechanistic studies suggested hydrogen abstraction generated intermediate 1.44. Oxidation with 2,6-dichloropyridine-N-oxide produced alcohol 1.45 which, after being further oxidized, gave δ-valerolactone. The four methods demonstrated above showcase routes for the production of δ-valerolactone from pyran starting material. In 1988 and 2002, permanganate ion was implemented as an oxidant. Additional conditions of NaBrO₃ and Ru catalysis were implemented by Bittner and Higuchi in 2015.

1.3.3. Ring expansion

Within this section, efforts detailing how δ-valerolactone are created via installation of oxygens within cyclic systems. Five membered aliphatic or cyclic ketones are employed as carbon sources with the addition of transition metals or ionic liquids being utilized to support the desired transformation to δ-valerolactone. Scheme 1.10 details these efforts. While attempting to better understand the reactivity of N₂O toward the Ni complex Hillhouse in 1993 1.46 made an early report dedicated to the formation of δ-valerolactone.39 When exposing 1.46 to N₂O in benzene at isolable 1.47 was obtained. After isolation, the desired δ-valerolactone was produced in 52% yield.
Scheme 1.10. Ring expansion methods for δ-valerolactone formation
The presumed mechanism described by the authors is initiated when CO gas reductive elimination of the Ni catalyst from intermediate 1.48. In 1983 Flood, developed a polystyrene-bound phenylseleninic acid 1.49. A catalytic amount of this polymer in aqueous hydrogen peroxide and DCM was demonstrated to be an effective reagent for converting olefins into trans diols and cyclopentanone into δ-valerolactone. Further developing on Flood’s chemistry, Sheldon in 2001 utilized selenium catalyst 1.50 for the conversion of cycloalkanones to lactones. The reaction was conducted with hydrogen peroxide in 2,2,2-trifluoroethanol. Amongst other substrates, δ-valerolactone was synthesized in 95% yield. In 1996 a report by Anna utilized m-CPBA in the production of δ-valerolactone in good yield from cyclohexanone. An approach to the selective oxidation of hydrocarbons is a challenging subject in fundamental research. In 2019 and 2020 Li introduced two approaches to this challenge via oxidative expansion of cyclopentane and cyclopentanone to δ-valerolactone. In 2019, Li reacted cyclopentane with N-hydroxyphthalimide and two equivalence of benzaldehyde to give δ-valerolactone in 40%. Li’s method in 2020 exposed cyclopentanone to NHPI and cerium ammonium nitrate giving δ-valerolactone in 93%. Li utilized these methods for synthesis of additional substrates. Transition metal free approaches to the synthesis of δ-valerolactone have also been investigated by researcher attempting to expand
the availability NHC catalyzed reactions. Gravel reported one such method in 2009. Upon exposure of aldehyde 1.51 to NHC 1.52 and DBU in DCE, δ-valerolactone was isolated in 78% yield. In the proposed reaction mechanism capture of aldehyde 1.51 with NHC 1.52 generated resonance contributors 1.53 and 1.54. After tautomerization to ketone 1.55, intramolecular nucleophilic addition of anionic oxygen to the carbonyl gave δ-valerolactone while turning around NHC catalyst. Arends in 2011 offered another application of NHC chemistry. Ionic liquid 1.56 was employed as a reactant and solvent in this chemistry. Otanic acids was also added and δ-valerolactone was obtained in 99% yield. Ring expansion approaches for the formation of δ-valerolactone have also been utilized in the total synthesis of (-)-lycojapodine A as demonstrated by Wang in 2012. In the final steps of the synthesis, MnO₂ was implored in DCE for the expansion of α-hydroxy ketone 1.57 to δ-valerolactone 1.58. After additional synthetic operations, the desired product was obtained. Ring expansion methods such as these have demonstrated how researchers advance a variety of reagents via the δ-valerolactone as a synthetic target.

1.3.4. Cleaving 1,2 Diols

Majorly demonstrated as natural product examples, the oxidative cleavage of 1,2-diols position at the two location of a pyran generates δ-valerolactone in the presences of additional sensitive functionality (figure 1.8). Three relative examples are presented in Scheme 1.12.

![Figure 1.8. 1,2-Diol oxidation introduction](image-url)
In 2008 Das reported an investigation which required the conversion of (L)-(-)-sorbose 1.60 to the resulting δ-valerolactone 1.62. Reaction conditions exposed the sugar to CrO$_2$[phen]·H$_2$O in an aqueous solution of sulfuric acid. The purported rate limiting step was ligand exchange resulting in key intermediate 1.61. Another use full application of δ-valerolactone formation from 1,2 diols for the purposes of stereochemical determination was demonstrated by Kakeya in 2015. This chemistry, exposes verocupetin 1.63 to NaIO$_4$ resulting in δ-valerolactone 1.64.

Scheme 1.12. 1,2-diol oxidation
1.64. Freed from the confusion of the remainder of the molecule, the stereochemistry of 1.64 could be defined. Finally, Wu in 2016 was investigating terpenoids derived from *Flueggea virosa* as treatments for hepatitis.\(^5^0\) While attempting to convert ester 1.65 to carboxylic acid, Wu isolated a δ-valerolactone compound which was easily converted to the desired amide 1.66 with (S)-PGME.

So far, the discussion has focused on a variety of δ-valerolactone forming reactions. There have been four major methods on which researchers have relied for the purposes of δ-valerolactone formation. While conducting this literature review a lack of methods available that produced substituted δ-valerolactones was noticed. Specifically, the majority of currently available methods focused on intramolecular cyclization or manipulation of already cyclic material. An area that was noticed to be particularly lacking in publications was reactions that formed α-acyl-δ-valerolactone. This motif is a specific class of δ-valerolactone with an acyl group at the α-position of a δ-valerolactone. As a result of this gap in the literature it was decided to investigate contributions that would result in the formation of substituted α-acyl-δ-valerolactone.

1.4. α-Acyl-δ-Valerolactone introduction and previous preparations

Prior to beginning our research efforts, another literature search was conducted that unveiled some relevant methods for forming α-acyl-δ-valerolactone (figure 1.9). Currently available methods for the synthesis of α-acyl-δ-valerolactone and the applications of this motif in natural product formation are demonstrated in the following section. In this section, it was decided to discuss early known and modern examples of α-acyl-δ-valerolactone formation.

An early report on the formation of α-acyl-δ-valerolactones was published by Zschocke in 1959.\(^5^1\) Exposing δ-valerolactones 1.67 to sodium hydride in ethyl acetate produced the desired product 1.68 in 50% yield with no control over stereochemistry. Another condensation method for the production of α-acyl-δ-valerolactone was demonstrated by Bury in 1980.\(^5^2\) Reacting δ-
valerolactone and acetyl cyanide with LDA at -78 °C generated α-acyl-δ-valerolactone 1.69 (scheme 1.13). An additional approach α-acyl-δ-valerolactones production was published by Taguchi in 1990. Utilizing the Pd₂(dba)₃ catalyst with Etcage as co-ligand in DMSO, α-acyl-δ-

valerolactones, 1.72 and 1.73, with a variety of different substituents were produced with a mild increase in diastereoselectivity at two of the three stereocenters. No stereo control was reported at the α-acyl/ three position. A mechanism was suggested that began with activation of starting allyl carbonate 1.70. It was suggested, 1,3-diaxial interactions in intermediate 1.71 were responsible for the observed diastereoselectivity. Similar reaction conditions were employed in the synthesis of methyl pederate as reported by Ihara in 1998. Ihara utilized Pd catalysis to cyclize carbonate 1.74 to the necessary α-acyl-δ-valerolactones 1.75 with no observed diastereoselectivity at the three or
four position. After several additional steps, methyl pederate was produced. Another method for the construction of \( \alpha \)-acyl-\( \delta \)-valerolactones was published by Babu in 2015.\(^{54}\) Exposing diarylpropylmalonates 1.76 to allyl bromide and catalytic Zn resulted in the diastereoselective formation of \( \alpha \)-acyl-\( \delta \)-valerolactones while incorporating multiple stereocenters. Mechanistic study suggested a Barbier-type zinc mediated allylation produced intermediate 1.77. Intramolecular lactonization of oxygen anion to malonate ester produced desired lactone with good diastereoselectivity across multiple substrates. The synthesis of \( \alpha \)-acyl-\( \delta \)-valerolactones have also

![Scheme 1.14. Transition metal implementation for \( \alpha \)-acyl-\( \delta \)-valerolactone synthesis](image)

been relevant in natural product synthesis. A multiple step approach was carried out by Krischnamurthy in 1993.\(^{7}\) The synthesis was initiated with malonate installation on alcohol 1.78 using DCC. Ozonolysis of the alkene followed by Witting reaction produced \( \alpha,\beta \)-unsaturated sulfur ester 1.79. Intramolecular cyclization was conducted with \( \text{Cs}_2\text{CO}_3 \) and \( \alpha \)-acyl-\( \delta \)-
valerolactone 1.80 was obtained in a 10:1 diastereomeric ratio. A modern multiple step route to \( \alpha \)-acyl-\( \delta \)-valerolactone 1.83 was presented by Hosokawa in 2018.\textsuperscript{55} A Fischer esterification produced compound 1.81 in 97% yield. Next, \( \text{K}_2\text{CO}_3 \) and 18-crown-6 in toluene was employed in the cyclization step to form the masked ketone enolate 1.82. Treatment of the material with room

Scheme 1.15. Methods for \( \alpha \)-acyl-\( \delta \)-valerolactone synthesis
temperature MeOH gave α-acyl-δ-valerolactone 1.83 in a 2.5:1 diastereomeric ratio (scheme 1.15). The aforementioned reactions are those available to research looking to produce α-acyl-δ-valerolactone. Examination of the literature reveals that a diastereoselective reaction allowing for the formation of a variety of α-acyl-δ-valerolactone would positively impact the resources available to researchers looking to produce this valuable motif.

1.5. Isocoumarin introduction and previous preparations

As the chemistry to produce δ-valerolactones was explored, an opportunity to extend this methodology to the formation of isocoumarin derivatives was realized. These isocoumarin derivatives are nine carbon bicyclic molecules with five carbons composing a δ-valerolactone and the remaining four carbons forming a ring that connects at the alpha and beta position of the lactone ring. An additional carbonyl exists in the enol form at the α-position. The isocoumarin motif has been utilized in a variety of screening processes to test for biological activity. There are

![Figure 1.10. Examples of isocoumarin isolated from various sources](image-url)
two compounds isolated from *Cedrus deodara* and found to possess cytotoxicity against human cancer cell lines HCT-116, A-549, HEP-1, THP-1, and PC-3. Molecules Actinobolin and Bactobolin A were isolated from *Pseudomonas* and have been the target of multiple total synthesis due to their broad-spectrum antibacterial activity. Finally, Peniciisocoumarin A and Peniciisocoumarin B were isolated from *Penicillium*, found to possess biological activity, and been featured in at least one review. The relevance of this molecular motif in biologically active compounds enticed us to discover how researchers are currently producing isocoumarins. Additionally, it was necessary to determine where efforts could be most impactful.

Floreancing in 2011 produced isocoumarin via intramolecular cyclization of oxygen anion. In the final steps of the synthesis of pysmberin 1.84 global deprotection of various silyl ethers with
Bu₄NF unexpectedly resulted in intramolecular cyclization, yielding desired product. Another route to isocoumarins was a method developed by Werz in 2000. Starting from readily available o-diazoacyl-sub-situated arene carboxylates 1.85 the isocoumarin derivative, 5,9-epoxy-cyclohepta[b]pyran-2(3H)-one 1.86 was obtained by co-operative Rh, Lewis and Brønsted acid catalysis. Four new bonds, three new functional groups, and four contiguous stereocenters were formed in a single synthetic step. A variety of substrates were produced via this method with excellent control over diastereoselectivity. Welwistatin in 2007 published two routes to two Isocoumarin derivatives. Upon exposure of substituted carbamate cyclohexanone 1.87 to NaH

![Scheme 1.17. Intramolecular and intermolecular cyclization producing isocoumarin](image)

the desired product 1.88 was isolated. The presumed reaction mechanism was via intramolecular Claisen condensation. In accompaniment with this method, another route by Welwistain made
isocoumarins substituted at the five position. The second route exposes dicarbamate cyclohexanone 1.89 to potassium hydride. Product 1.90 is generated presumably through to intramolecular cyclization reactions.62 In the final example by Watanabe in 2007 diketene was mixed in a single pot reaction with DMAP, K₂CO₃, 18-crown-6, with δ-hydroxyeneal 1.91.63 After mixing until completion of reaction, followed by reflux in benzene 1.92 was produced.

1.6. Conclusion

At the conclusion of our literature review it was decided targeted research efforts focused on the development of a method that selective produced α-acyl-δ-valerolactones and isocoumarin would positively impact the current available literature. Ideally, this method would allow for the selective formation of either functionality with minimal changes to reaction conditions. Additionally, avoiding the implementation of costly catalysts and operational simplicity were desired characteristics of the final methodology. In order for the developed method to be most useful it needed to be stereoselective which, for the α-acyl-δ-valerolactone was particularly challenging due to the acidic nature of the α-hydrogen. The abundance of these structures in materials of biological relevance as well as the non-trivial obstacles associated with developing a method that met our desired criteria compelled our research efforts.
CHAPTER 2. DEVELOPMENT OF A METHOD FOR δ-VALEROLACTONE AND ISOCOUMARIN FORMATION

2.1. Purpose

Within the following section a discussion of the efforts undertaken for the synthesis of α-acyl-δ-valerolactones and isocoumarins is presented. Initially, efforts were focused on the formation of the α-acyl-δ-valerolactones specifically in the form of dihydro-2H-pyran-2-one 2.03. As will be described, attempts at producing this motif resulted in none of the desired product. Instead, three key materials were produced and valuable information regarding the reactivity of the acyl Meldrum’s acid was learned. This information would be implemented when establishing a strategy that successfully produced α-acyl-δ-valerolactone in the form of 3-acetyltetrahydro-2H-pyran-2-ones 2.15. The second route successfully produced the desired product. Optimization of the method was then accomplished, and scope of substrate was tested. A crystal structure led to the application of this method to isocoumarin derivatives. A surprising result was obtained for certain substrates that led to degradation studies being conducted in MeOH.

2.2. Hypothesized method for Dihydro-2H-pyran-2-one synthesis

Initially, attempts to synthesize δ-valerolactones were via the formation of dihydro-2H-pyran-2-ones 2.03. The hypothesis was that formation of these motifs could be conducted via the

![Figure 2.1. Hypothesized method for Dihydro-2H-pyran-2-one synthesis](image-url)
transformation of β-hydroxy carbonyl 2.01 and acyl Meldrum’s acid 2.02 as shown in figure 2.1. A proposed strategy is presented in figure 2.2. Initial thermal degradation of acyl Meldrum’s acid 2.02 releasing acetone and carbon dioxide as the only biproducts produces acylketene 2.04. Nucleophilic capture with β-hydroxy carbonyl 2.01 would result in isolable malonate ester 2.05.

Cooling the reaction to room temperature and adding an activator would then promote intramolecular Knoevenagel condensation via resonance stabilized enol tautomer 2.06. Loss of leaving group from 2.07 produces 2.08, which in our predicted conditions would generate 2.03 via tautomerization of hydrogen on the three carbon and carbonyl at the four carbon. In order to investigate this hypothesis, the starting β-hydroxy carbonyl 2.09 needed to be synthesized. This was easily completed via aldol condensation of phenyl acetate and benzaldehyde, as demonstrated in scheme 2.1. Starting material 2.09 was chosen as it was believed the loss of phenoxide ion as the leaving group would be favorable. Acyl Meldrum’s acid synthesis is discussed in section 2.3.

Attempts to promote the desired cyclization are described in table 2.1. In order to facilitate screening multiple conditions, crude materials were analyzed via NMR for the presence of new
signals potentially indicating interesting reactivity. Conditions with yields represent the first time a new material was obtained. Upon observation of new material via crude NMR, the material was purified, and the structure of the pure compound elucidated. Additionally, to solidify our hypothetical suggestions crystal structures of materials 2.11, 2.12, and 2.13. Unless otherwise noted, the method adopted was as follows, heating the β-hydroxy carbonyl 2.09 and acyl Meldrum’s acid 2.10 to reflux until consumption of both materials was complete as observed via TLC. The mixture was then cooled to room temperature, activator was added, and the reaction was monitored via TLC. At the onset, the barrier to promote cyclization was apparent as evidenced in entries 1-5 where only isolable malonate ester 2.10 was isolated. Attempts to promote cyclization with proton sponge, and potassium tert-butoxide yielded product 2.11. When altering the base to DBU a change in reactivity was observed as shown in entries 6-12. Isolated initially in 50%, product 2.12 was observed when DBU was employed in toluene (entry 6). Altering the solvent, via gradually increasing the polarity from toluene to dioxane produced only product 2.12 (entry 7-11). A surprising result was observed when employing the reaction conditions utilizing MgBr$_2$•OEt$_2$ as the activator (entry 12). This activator initially resulted in bromination product 2.13 and elimination product 2.12 in a 1:1 mixture as observed when analyzing the crude reaction mixtures. Demonstrated in entry 13, attempting to further understand this transformation, material 2.11 was exposed to the MgBr$_2$•OEt$_2$ conditions and bromination product 2.13 was obtained in

Scheme 2.1. Phenyl 3-hydroxy-3-phenylpropanoate synthesis
high yield. Entry 14 attempts to ensure that observed product 2.12 and 2.13 were a result of the altered reaction conditions and not an unexpected result obtained from high temperature heating.

Although the desired material was not obtained, interesting reactivity was still induced. Several important conclusions can be drawn from the attempts to create dihydro-2H-pyran-2-ones

Table 2.1. Products obtained from attempts to optimize Dihydro-2H-pyran-2-one method

<table>
<thead>
<tr>
<th>entry</th>
<th>activator (# equiv)</th>
<th>solvent (M)</th>
<th>producta</th>
<th>yieldb</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>proton sponge (1.1)</td>
<td>THF</td>
<td>2.11</td>
<td>74%</td>
</tr>
<tr>
<td>2</td>
<td>KO-tBu (1.1)</td>
<td>Toluene</td>
<td>2.11</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>KO-tBu (1.1)c</td>
<td>Toluene</td>
<td>2.11</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>MgCl₂ (1.1)</td>
<td>Toluene</td>
<td>2.11</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>La(OTf)₃ (1.1)</td>
<td>Toluene</td>
<td>2.11</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>DBU (1.1)</td>
<td>THF</td>
<td>2.12</td>
<td>50%</td>
</tr>
<tr>
<td>7</td>
<td>DBU (1.0)</td>
<td>THF</td>
<td>2.12</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>DBU (1.1)</td>
<td>Hexanes</td>
<td>2.12</td>
<td>–</td>
</tr>
<tr>
<td>9</td>
<td>DBU (1.1)</td>
<td>DCE</td>
<td>2.12</td>
<td>–</td>
</tr>
<tr>
<td>10</td>
<td>DBU (1.1)</td>
<td>THF</td>
<td>2.12</td>
<td>–</td>
</tr>
<tr>
<td>11</td>
<td>DBU (1.1)</td>
<td>dioxane</td>
<td>2.12</td>
<td>–</td>
</tr>
<tr>
<td>12</td>
<td>MgBr₂·OEt₂ (1.1)</td>
<td>Toluene</td>
<td>2.12/2.13d</td>
<td>75%</td>
</tr>
<tr>
<td>13a</td>
<td>MgBr₂·OEt₂ (1.1)</td>
<td>Toluene</td>
<td>2.13</td>
<td>quant</td>
</tr>
<tr>
<td>14</td>
<td>–</td>
<td>Toluene</td>
<td>2.11</td>
<td>71%</td>
</tr>
</tbody>
</table>

[a] Major product was determined by analysis of crude reaction mixture with ¹H NMR
[b] Upon observation of new signals in the crude NMR, the material was isolated and the structure elucidated [c] 18-crown-6 (1.1 equiv) was added with KO-tBu [d] crude ¹H NMR revealed a 1:1 mixture of products 2.12 and 2.13 [e] starting material 2.09 was substituted for material 2.11.

2.03. Primarily, the formation of the malonate was observed via TLC in all solvents tested. This implies, moving forward, the reaction necessary to optimize is the cyclization step, as the malonate ester is readily obtainable in a variety of conditions. Second, the product observed from the reaction can be selected for based on the activator added to the mixture. Testing various activators
revealed the ester 2.11 formed as a result of nucleophilic addition of the β-hydroxy carbonyl to the acyl ketene intermediate, was not reversible in the present of Brønsted acids, Lewis Acids, and refluxing temperature. Finally, an interesting application of MgBr$_2$•OEt$_2$ was uncovered, and future investigation of this reactivity could produce promising results.

Despite key information gleaned from the investigations thus far, the successful production of δ-valerolactone had not yet been accomplished. Moving forward, altering the starting material and shifting the target structure to 3-acetyl tetrahydro-2H-pyran-2-ones 2.15 proved to be a successful adjustment. Efforts on this second path, starting material development, and scope of substrates is described in the following section.

2.3. Method for forming highly substituted 3-acetyl tetrahydro-2H-pyran-2-ones

The relevance of the δ-valerolactone and the associated synthetic challenges inspired us to develop a one-pot protocol for the formation of 3-acetyl tetrahydro-2H-pyran-2-ones 2.15 and isocoumarin 2.16. With the information gleaned from the previous section, a strategy demonstrated in figure was adopted. A bimolecular cascade process was envisioned by bond disconnection 2.15 that was initiated with the coupling of δ-hydroxyenone 2.14 and acylketene 2.04. An acylketene would be generated *in situ* via thermal degradation of acyl Meldrum’s acid...
Intramolecular Michael-addition of the malonate to the α,β-unsaturated ketone would enclose the δ-valerolactone core 2.15. In order to facilitate isocoumarin 2.16 an intramolecular aldol cyclizations was purposed. A second ring formation could be accomplished through enolates at the less acidic α'-position, which was achieved via a sequence of proton transfer (figure 2.3).

To commence our efforts, routes to the δ-hydroxyenone 2.14 and acyl Meldrum’s acid 2.02 needed to be developed. So that these routes could be most accommodating to a set of substrates, the routes required minimum steps and tolerance to a broad range of functionality. Examination of three different locations for modification required three routes to starting material. The routes are labeled in accordance with the position on the final δ-valerolactone. Efforts for the formation of starting materials are outlined below. Starting materials with modifications to the Rₐ position were assembled via a two-step procedure. Aldehydes 2.17.1 were readily converted to allyl alcohols 2.17.2 in a single step using vinyl magnesium bromide. Alkenes alcohols 2.17.2 were treated with methyl vinyl ketone and Grubb’s II, producing δ-hydroxyenones 2.18 in good yield.

Modifications at the Rₐ position required producing a material that could be easily synthesized but also contains functionality that can be converted to the desired product with
minimal interference from reagents. After much thought, it was decided to produce Weinreb amide 2.20. This material would allow for transformation of the Weinreb amide to the desired ketone via implementation different Grignard reagents. Initially efforts to synthesize 2.20 were attempted via a direct route of alkene metathesis with TBS protected alcohol-alkene 2.19 and methylacrylamide 2.21. However, attempts at optimizing this route were hindered by two major obstacles. Primarily, the alkene metathesis reaction between 2.19 and methylacrylamide 2.21 failed under a variety of conditions. Secondly, formation of methylacrylamide 2.21 from acryloyl chloride was low yielding and difficult to purify. Due to the failure of the metathesis reaction and the low yielding formation of the starting material, a secondary route to the desired Weinreb amide 2.20 was attempted. During the secondary route, acrylic acid underwent low yielding metathesis with alkene 2.19. To our surprise, a variety of conditions were then unable to promote the transformation of carboxylic acid 2.22 to desired Weinreb’s amide 2.20. With the strategies learned in the primary and secondary attempts to synthesize the desired material, a tertiary route to the Weinreb amide 2.20 was adopted. The leading step in this route was high yielding metathesis of allyl alcohol 2.17.2 with methyl acrylate. Protection of alcohol 2.23 with TBSCl in DCM gave quantitative yield of ester 2.24. After removal of TBSOH via column chromatography and 12 hours on high vacuum, ester 2.24 was prepared for α,β- unsaturated Weinreb’s amide formation. This
transformation was conducted at 0 °C in THF utilizing two equivalence of \( i\text{PrMgBr} \) as a base. Desired material 2.20 was obtained after purification with column chromatography in 60% yield.

Now the convince of material 2.20 can be utilized. Creating acyl Meldrum’s acid starting materials was done so via a two-step procedure. In the first, step a Grignard reagent was employed in order to effectivity transform the amide to the desired ketone 2.26. In the following step, the alcohol was
revealed via removal of the TBS group with BF₃OEt₂ giving 2.14. All eight of the necessary substrates with variation at the Rᵦ position were synthesized in this manner. The final material that needed to be created was acyl Meldrum’s acid derivative 2.02. Routes to this material had already been published. Two of these methods were adopted. In the first route, the necessary acyl chloride could be easily captured with Meldrum’s acid in the presence of excess DMAP. Secondly, a

![Scheme 2.5. Synthesis of acyl Meldrum’s acid derivatives](image)

carboxylic acid could be employed with activating reagent DCC for capture of Meldrum’s acid. These two methods allowed for easy creation of necessary materials 2.02. After the robustness of the formation of the β-ketone ester was realized in section 2.2 we decided to move forward with optimizing the cyclization reaction in combination with acylation reaction. The optimization studies were initiated with the use of δ-hydroxyenone 2.26 and acyl Meldrum’s acid 2.27 as model substrates (table 2.2). These materials were easily prepared from starting materials in the manner described in scheme 2.4 and scheme 2.5. Compounds were initially refluxed in solvent to promote
acylation of alcohol 2.26 by acylketene generated in situ with decomposition of 2.27. After consumption of material 2.26 via TLC analysis the mixture was cooled to room temperature

Table 2.2. Optimization of method

<table>
<thead>
<tr>
<th>entry</th>
<th>base</th>
<th>equiv</th>
<th>solvent</th>
<th>yield (%)</th>
<th>time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DIPEA</td>
<td>2.0</td>
<td>MeCN</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>pyridine</td>
<td>2.0</td>
<td>MeCN</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>imidazole</td>
<td>2.0</td>
<td>MeCN</td>
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<td>DCE</td>
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<td>DCE</td>
<td>69</td>
<td>24</td>
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</table>

and base was added to induce lactonization. At the beginning, the use of organic bases DIPEA, pyridine, imidazole, and proton sponge were not effectively able to induce cyclization (entries 1 - 4). Changing to inorganic carbonate bases K₂CO₃ and Cs₂CO₃, afforded the desired δ-valerolactone 2.28 in 57% yield. An increase in reactivity was noted with Cs₂CO₃ as the desired δ-valerolactone was obtained in 67% yield (entry 6). Next, solvent effects were investigated. In entries 6-10, MeCN, toluene, 1,4-dioxane, THF, and DCE were tested and DCE was found to be the most effective solvent. Evaluation of the molar amount of Cs₂CO₃ revealed δ-valerolactone was produced in 88% yield using 2.5 equivalence of the base (entry 13). Excesses Cs₂CO₃ did not
decreases the selectivity of the reaction, δ-valerolactone was isolated as a single diastereomer as determined by "H NMR. Relative stereochemistry was assigned via X-ray crystallographic analysis in accompaniment with 1D NOSY, and COSY experiments.

After revealing optimized conditions, it was decided to examine the scope of the reaction’s tolerance to multiple functionalities. For each substrate, not only was the diastereomeric ratio measured via "H NMR analysis of crude material, but the ketone to enol ratio of the α’ carbon was measured of the purified material. As the scope of substrate examination commenced it was noted the ketone-enol ratio of the α’ carbon varied with each substrate. As a result, purified compound that contained a mixture of the ketone and enol was exposed to two separate NMR conditions, one

Table 2.3. Scope of Rα position

<table>
<thead>
<tr>
<th>Rα</th>
<th>Structure</th>
<th>Yield (%)</th>
<th>α’ Carbon Ratio</th>
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</thead>
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<tr>
<td>2.30.1</td>
<td><img src="image" alt="Structure" /></td>
<td>57% (8 h)</td>
<td>k:e = 9.1:1</td>
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<tr>
<td>2.30.2</td>
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<td>83% (21 h)</td>
<td>k:e = 7.1:1</td>
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<tr>
<td>2.30.3</td>
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<td>79% (25 h)</td>
<td>k:e = 20:1</td>
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<tr>
<td>2.30.4</td>
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<td>77% (5 h)</td>
<td>k:e = 20:1</td>
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<td>79% (24 h)</td>
<td>k:e = 20:1</td>
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<tr>
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<td><img src="image" alt="Structure" /></td>
<td>64% (8 h)</td>
<td>k:e = 20:1</td>
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<tr>
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<td><img src="image" alt="Structure" /></td>
<td>69% (25 h)</td>
<td>k:e = 20:1</td>
</tr>
<tr>
<td>2.30.8</td>
<td><img src="image" alt="Structure" /></td>
<td>72% (5 h)</td>
<td>k:e = 20:1</td>
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in CDCl$_3$ and one in $d_6$-DMSO. Our scope of substrate effort was commenced with $\delta$-hydroxyenone 2.29 that was varied at the $\delta$-position (table 2.3). Two substrates were tested that complemented the phenyl group in substrate 2.28. Effects of electronically opposite $p$-methoxy

![Chemical structure](image)

Table 2.4. Scope of R$_b$ position

and $m$-trifluoromethyl substituents were investigated. Corresponding $\delta$-valerolactones 2.30.1 and 2.30.2 were isolated as single diastereomers, however, a higher yield was observed with electron deficient substrate 2.30.2. Ketone to enol ratios of these substrates in CDCl$_3$ were found to be 9.1:1 and 7.1:1, respectively. When conducting $^1$H NMR analysis of 2.30.1 and 2.30.2 in $d_6$-DMSO the ketone-enol ratio shifted to 5.6:1 and 20:1, respectively. Next, a series of substrates containing aliphatic functionalities, benzyl, octyl, $t$-butyl and bromoethyl, were subjected to these conditions,
producing δ-valerolactone 2.30.4 – 2.30.6 in 64 – 79% yields. Also, common alcohol protecting groups primary benzyl ether, and BPS ether, were subjected to these studies and afforded 2.307 and 2.30.8 in 69% and 72% yields. When primary TBS ether was tested in these conditions, degradation of the product was observed, none of the δ-valerolactone was isolated. In opposition to the δ-aryl containing counterparts, products 2.30.3 – 2.30.8 were isolated as the keto form.

Table 2.5. Scope of R<sub>c</sub> position

Substituent effects of functionality changes on the δ'-carbon were then investigated using starting material 2.31 as our initial motif. Table 2.4 outlines this examination. With the aromatic substituents, phenyl, p-methoxyphenyl, p-chlorophenyl, and naphthyl, this reaction produced δ-
valerolactone 2.32.1-2.32.4 in decent yield. The ketone-enol ratio of the phenyl substituent 2.32.1 in $^1$H NMR was observed at 9.1:1 in CDCl$_3$ and 20:1 in $d_6$-DMSO. Ketone-enol ratio of 2.32.2 in CDCl$_3$ was observed at 10:1 and 13:1 in $d_6$-DMSO. Substituent containing p-chlorophenyl 2.32.3 was observed with ketone-enol rations of 10:1 in CDCl$_3$ and 20:1 in $d_6$-DMSO. Naphthyl containing 2.32.4 had observable ketone-enol ratios of 7.2:1 in CDCl$_3$ and 17:1 in $d_6$-DMSO. Alkyne functionality generated δ-valerolactone 2.32.5 in 41% yield with a 6.3:1 k:e ratio in CDCl$_3$ and a 7.1:1 k:e in $d_6$-DMSO. In an interesting change to k:e ratio, alkene δ-valerolactone was isolated in 65% with a 20:1 k: e. Aliphatic and benzyl functionality when subjected to these reaction conditions generated the desired products 2.32.7 and 2.32.8 in 64% with 20:1 k:e and 61% with 10:1 k:e in CDCl$_3$, respectfully. When subjected to $^1$H NMR in $d_6$-DMSO the ketone-enol ratio of 2.32.8 shifted to 17:1. It was interesting to note all of these α-acyl-δ-valerolactone were isolated as single diastereomers, however ranges of k:e ratios from 6.7:1 to 20:1 were observed in CDCl$_3$ and in $d_6$-DMSO. Additional information on ketone-enol ratios is in the supporting information.

The scope of acyl Meldrum’s acid 2.02 was also surveyed under the designed reaction conditions (table 2.5). Replacing the methyl group of our original substrate 2.02 with phenyl and furyl generated the desired α-acyl-δ-valerolactone 2.33.1 and 2.33.2. Using this strategy, the incorporation of 1-butenyl group into 2.33.3 was easily accomplished in 67%. Other heterocycle motifs were also easily incorporated into α-acyl-δ-valerolactone products. Tetrahydropyran containing material 2.33.4 and N-Boc piperidine containing 2.33.5 were successfully synthesized using these conditions in 72% and 78% yield, respectfully. Notably, materials 2.33.1 – 2.33.5 were generated in 20:1 diastereomeric ratios as indicated by analysis of crude material with $^1$H NMR. Additionally, ketone-enol ratios of 20:1 were observed with these materials.
As previously suggested in figure 2.3 an opportunity to extend the method toward isocoumarin structures via tandem Michael-aldol reactions, was envisioned. Inspiration for this premise was gleaned by a discovery made when efforts were employed to promote the crystallization of δ-valerolactone 2.30.1. Crystallization from an oily residue was attempted via slow evaporative method from hexanes and DCM across seven months. As a result of this process a mixture of two distinct sets of crystalline materials were found, as observable under microscope. X-ray analysis of the major crystals confirmed α-acyl-δ-valerolactone 2.30.1 as the desired product. However, x-ray analysis of the secondary set of crystals revealed isocoumarin 2.35. These results, while unexpected, supported our original notion that partial enolization of less acidic α’-hydrogen of the α-acyl-δ-valerolactone core was possible. Should this enolization occur (viz 2.34), it could result in a key intramolecular aldol event, generating isocoumarin core. Adapting this annulation chemistry for practical synthesis would require predisposing the α’-carbon to enolization at greater extent under equilibrium. Achieving this equilibrium shift could be done via implementation of enolate stabilizing substituents in the corresponding acyl Meldrum’s acid precursors. This would decrease the pKa of the α’-hydrogen and increase enolization chances at the necessary position thus providing opportunity for secondary cyclization to isocoumarin.

Scheme 2.6. Discovery of cascade cyclization
To test this hypothesis, aryl-substituted acyl Meldrum’s acid 2.36 was prepared and subjected to our typical reaction conditions, i.e., acylation at reflux and then cyclization in the presence of Cs$_2$CO$_3$ at room temperature (table 2.6), with δ-hydroxyenone 2.31. In a single synthetic operation, this strategy, gratifyingly, furnished highly substituted isocoumarin adduct 2.37. Variation of 2.31 to contain hydrogen and methyl were conducted under these conditions and 2.37.1 and 2.37.2 were produced in 51% and 62%, respectively. Increasing the steric bulk of the variation at the R$_c$ to an ethyl group resulted in a complex mixture of materials, 2.37.3. Electronically different 4-bromo and 4-methoxy substrates were tested and resulted in modest yield (32% – 56%) of desired isocoumarin as exemplified in compounds 2.37.4 – 2.37.6. Finally, electronically withdrawing 4-trifluoromethyl gave isocoumarin 2.37.6 in 37%. These collective
results revealed four truths that can be deduced: 1) Varying the electronics of the phenyl substituent at the α’-carbon did not have a pronounced effect on yield or diastereomeric ratio. 2) Steric influence of the substituent on the δ’-carbon readily influenced the result of the cyclization; introduction of an ethyl group at this position led to complex mixtures. 3) Modest diastereomeric ratio of the isolate isocoumarin was noted, but in comparison, δ-hydroxyenone (R = Me) had higher diastereomeric selectivity when compared to δ-hydroxyenal (R = H). Efforts for a diastereoselective method are being conducted and will be discussed further in section 2.4.

This chemistry yielded α-acyl-δ-valerolactone 2.30, 2.32, and 2.33, from their respective δ-hydroxyenone with excellent diastereocontrol. When this method was applied to analogous δ-

![Scheme 2.7. Probing degrading stereochemistry](image)

d-hydroxyacrylate ester 2.38, product 2.39 was surprisingly, isolated in as a 1:1 mixture of diastereomers (scheme 2.7). In order to investigate further the underlying factor behind the loss of diastereoselectivity, three experiments were conducted to examine the δ’ position’s effect on the system. Primarily, δ-hydroxyenone 2.40 with acrylic amide functionality was subjected to these reaction conditions. Remarkably, these conditions with δ-hydroxyenone 2.40 failed produce δ-
valerolactone, instead 2.41 was isolated. This result suggests reduced Michael reactivity with increased electron donation from the NMe₂ functionality. To gain further insight into the underlying factor behind the loss of diastereoselectivity, the propensity of α-acyl-δ-valerolactone 2.39 and 2.42 to undergo proton-deuterium exchange in CD₃OD was examined. It was discovered, deuteriation of the α-carbon in methyl ester 2.39 underwent proton-deuterium exchange faster than that of methyl ketone 2.30.3. Figure 2.4 and figure 2.5 demonstrates these experimental results.

![Diagram showing proton-deuterium exchange](image)

Figure 2.4. Examination of α-carbon methyl ester proton deuterium exchange
In each of these experiments, equal concentrations of 2.39 and 2.30.3 were prepared in CD$_3$OD with the solvent being added to each compound directly prior to initial NMR experiments. At equal intervals $^1$H NMR was conducted and the integration value of the hydrogen at the $\alpha$-carbon was measured. Figure 2.4 shows the exchange with compound 2.39. As represented by the labeled signals, hydrogen/deuterium exchange had been completed after 48 hours. When applying the

Figure 2.5. Examination of $\alpha$-carbon methyl ketone proton deuterium exchange
same assessment to compound 2.30.3 in figure 2.5 hydrogen/deuterium exchange had not been fully completed after the 48-hour mark. In fact, proton-deuterium exchange of 2.39 was 5 times faster with a $t_{1/2} = 21$ hours in comparison to the exchange in 2.30.3 with a $t_{1/2} = 107$ hours. The implication of this result is that the observed mixture of diastereomers in 2.39 could have come from facile epimerization of the $\alpha$-carbon that occurred independently after the diastereoselective cyclization event. This epimerization, under the described reaction conditions, could have been heightened by the methyl ester moiety. A 6-membered intramolecular enolization with incorporated cesium chelation to $\beta$-ketoester viz 2.39.1 could be envisioned to account for the
difference in $t_{1/2}$. Due to the lack of electronic donating ability of the methyl group versus that of the methoxy functionality, a similar electronic effect in 2.42 would be much less pronounced.

The results obtained thus far led to the proposition of a plausible reaction mechanism (scheme 2.8). Thermal decomposition of acyl Meldrum’s acid 2.43.1 revealed acyl ketene 2.43.2 that was directly captured by nucleophilic hydroxyenone 2.14.66 Isolable intermediate 2.43.3 was retained in solution while the mixture was cooled to room temperature and Cs$_2$CO$_3$ base was added. Enolization of the $\beta$-ketoester moiety in 2.43.3 then led to intramolecular Michael addition to form the $\delta$-valerolactone core 2.43.5. Stereochemistry of 2.43.5 could be accounted for via implication of the Zimmerman-Traxler model 2.43.4.67 When $\delta$-valerolactone 2.43.5 contains an enolizable $\alpha'$-carbon ($R = Ar$), excess Cs$_2$CO$_3$ generated a second cesium intermediate. Another cyclization event via intramolecular aldol condensation then furnished isocoumarin 2.43.7. Again, observed stereochemistry could be induced via chair like transition state 2.43.6.

2.3.1. Conclusion of section 2.3

In conclusion, a method for the diastereomeric construction of $\alpha$-acyl-$\delta$-valerolactone was developed. A variety of substrates and functional groups were tolerated under the discovered reaction conditions. Further extending this bi-molecular process into a cascade cyclization event allowed for the construction of a variety of isocoumarin substrates. Proton – deuterium exchange experiments were then conducted to explain a decrease in diastereoselectivity observed when a methyl ester was implemented at the $\delta'$ carbonyl carbon. A purposed reaction mechanism was then discussed. Attempts to further develop this method are discussed in section 2.4.
2.4. Non-selective method for Isocoumarin formation

After concluding our in-depth studies on the method forming δ-valerolactone, transformations targeting potential industrial applications of this motif were attempted. With inspiration from studies on polymerization explained in figure 1.3 detailing how polymers from δ-valerolactone were created under a variety of conditions, similar transformations were desired with the molecules produced in the method developed in section 2.3. A transformation was envisioned whereby δ-hydroxyenone 2.26 could be reacted with acyl Meldrum’s acid 2.02 in a solvent at reflux (figure 2.6). After full consumption of 2.26 as measured by TLC, a different set of regents could then be added that promote cyclization to the δ-valerolactone 2.15. Presumably,

![Figure 2.6. Hypothesized polymerization method](image)

...in situ polymerization could follow after addition of an initiator that promotes the polymerization of 2.15 to polymer 2.44. Ideally, the stereochemistry set at the α, β, and γ carbons would be retained in polymer 2.44. Therefore, this method would allow for the construction of polymers with set stereochemical substitutions along the backbone figure 2.6. Various polymers could then be synthesized and the difference in the compounds could be reported.

As the formation of δ-valerolactone had already been deeply explored, efforts were focused on the transformation described in scheme 2.9. After optimization of the polymerization the, two
methods could then be combined and further optimized. It was decided to begin with δ-valerolactone 2.28 as an initial case study. When attempting the polymerization with 2.5 equivalents of Cs₂CO₃ and 2.5 equivalents of phenol as an initiator, it was surprising to see no evidence of polymerization in the crude ¹H NMR of the reaction mixture. Instead, evidence of a single diastereomer of isocoumarin derivative 2.45 was discovered. Isolation and characterization of the material provided further support for the formation of isocoumarin 2.45 as a single diastereomer. Before further exploring this transformation, ensuring isocoumarin production from δ-hydroxyenone and δ-valerolactone was necessary. The reaction described in scheme 2.9 was attempted. Heating acyl Meldrum’s acid 2.27 in the presence of δ-hydroxyenone 2.26 followed by

Scheme 2.9. Current method for diastereoselective isocoumarin formation

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cooling to room temperature and adding 2.5 equivalents of Cs₂CO₃ and 2.5 equivalents of phenol resulted in a single diastereomer of 2.45. This initial result does not support the evidence that polymerization of the δ-valerolactone would be possible under the attempted conditions. Instead, this important result fills a gap of the method developed in section 2.3. No longer does isocoumarin formation rely on a specific class of acyl Meldrum’s acid. Upon further development of this approach, a diastereoselective method for isocoumarin formation could be explored.

2.5. Conclusion of chapter 2

In conclusion, while attempting to produce δ-valerolactone in the form dihydro-2H-pyran-2-ones key information was gained in the acylation of β-hydroxy carbonyl alcohols. This information was used in the development of a method for the construction δ-valerolactone in the form of 3-acetyltetrahydro-2H-pyran-2-ones. A method producing 3-acetyltetrahydro-2H-pyran-2-ones substituted at the 3,4, and 6 positions was successfully developed and tested with a variety of functionalities. These unique functionalities produced the desired motif in 20:1 diastereomeric ratio in all instances. Variations at the extended δ’-carbonyl resulted in a change of ketone: enol ratio which was measured in CDCl₃ and DMSO-d₆. A serendipitous discovery of crystalized isocoumarin material resulted in exploration of isocoumarin substrates. These substrates resulted in diminished stereo control. Degradation studies in MeOD of δ-valerolactone were then conducted to gain understanding of the epimerizable nature of the acyl group at the α-carbon when an ester was present at the δ’-position. Attempts at developing a polymer application of the δ-valerolactone motif uncovered a diastereoselective isocoumarin forming reaction that produces the motif in a 20:1 diastereomeric ratio. Upon optimizing the yield of this reaction, further exploration of additional functionality will be undertaken.
CHAPTER 3. EXPERIMENTAL PROCEDURES AND CHARACTERIZATION

3.1. General information

Unless otherwise noted, all materials were used as received from commercials suppliers without further purification. All anhydrous reactions were performed using oven-dried or flame-dried glassware, which was then cooled under vacuum and purged with nitrogen gas. Tetrahydrofuran (THF), dichloromethane (DCM), acetonitrile (MeCN), and toluene were filtered through activated 3Å molecular sieves under Argon contained in a Pure Process Technology solvent purification system. 1,2- Dichloroethane was purchased from Oakwood Chemical and used as purchased. All reactions were monitored by EMD analytical thin layer chromatography (TLC Silica 60 F254, Glass Plates) and analyzed with 254 nm UV light and/or anisaldehyde – sulfuric acid or potassium permanganate treatment. Silica gel for column chromatography was purchased from Dynamic Absorbents, Inc. or Sigma Aldrich (Flash Silica Gel 32-63μ).

Unless otherwise noted, all 1H and 13C NMR spectra were recorded in CDCl3 or DMSO-d6 using a Bruker Ascend 400 spectrometer operating at 400 MHz for 1H and 100 MHz for 13C or Bruker Ascend 500 spectrometer operating at 500 MHz for 1H and 125 MHz for 13C. Chemical shifts (δ) are reported in ppm relative to residual CHCl3 as an internal reverence (1H: 7.26 ppm, 13C: 77.00 ppm) or residual DMSO (1H: 2.54 ppm, 13C: 39.52 ppm). Coupling constants (J) are reported in Hertz (Hz). Peak multiplicity is indicated as follows: s (singlet), d (doublet) t (triplet), q (quartet), p (pentet), se (septet), h (heptet), b (broad), and m (multiplet). FT-IR spectra were recorded on a Bruker Tensor 27 spectrometer with OPUS 6.5 Data Collection Program, and absorption frequencies were reported in reciprocal centimeters (cm⁻¹). High Resolution Mass Spectrometry – Electron Spray Ionization (HRMS-ESI) analyses were performed by the Louisiana State University Mass Spectrometry Facility using an Agilent 6210.
3.2. Experimental procedures

Phenyl 3-hydroxy-3-phenylpropanoate (2.09)

**Procedure:** Benzaldehyde (313 μL, 3.1 mmol) and MgBr₂•OEt₂ (948 mg, 3.7 mmol) were dissolved in DCM (15 mL, 0.2 M), with vigorous stirring and phenyl acetate (467 μL, 3.7 mmol) was added in a single portion. Hunig’s base (693 μL, 4.0 mmol) was added portion wise across 10 minutes and the mixture was allowed to stir at room temperature. Upon completions as monitored by TLC the reaction was quenched with 2M HCl (15 mL) and diluted with water (15 mL). The aqueous layer was extracted with DCM (3 x 25 mL) before being washed with brine (15 mL). The organic layer was dried over Na₂SO₄ and reduced under vacuum. Crude reaction materials were purified with column chromatography using 100% hexanes to 60:40 (hexanes : EtOAc) to give (2.09) in 63% yield as a white solid (469 mg, 1.9 mmol).⁶⁹

**Rf:** 0.44 in 80:20 (Hexanes : EtOAc)

**¹H NMR:** (400 MHz, CDCl₃) δ = 7.46 – 7.31 (m, 8H), 7.07 – 7.04 (m, 2H), 5.27 (dt, J = 4.0, 8.7 Hz, 1H), 3.09 – 2.96 (m, 2H).

3-oxo-3-phenoxy-1-phenylpropyl 3-oxo-3-phenylpropanoate (2.11)
**Procedure**: β-hydroxy ester 2.09 (15 mg, 0.06 mmol) was dissolved in THF (300 μL) and acly Meldrum’s acid (16 mg, 0.07 mmol) was added. The reaction mixture was stirred at reflux for 1 hour. Once β-hydroxy ester 2.09 was consumed, as monitored by TLC, the reaction was cooled to room temperature and proton sponge (14 mg, 0.07 mmol) was added. The reaction was stirred at room temperature for 24 hours and no progress was noted as determined by TLC. The reaction was quenched with a mixture of brine (2 mL) and DI H2O (2 mL). The aqueous layer was extracted with DCM (5 x 2 mL). The combined organic layers were dried over Na2SO4 and reduced under vacuum. Crude material was purified with column chromatography using 100% hexanes to 40:60 (hexanes : EtOAc) to give 2.11 and 2.11.1 in 74 % yield (17 mg, 0.044 mmol) as a white solid.

**Rf**: 0.47 in 50:50 (Hexanes : EtOAc)

**1H NMR**: (500 MHz, CDCl3) δ = 7.29 – 7.90 (m, 2H), 7.50 – 7.29 (m, 11H), 7.01 – 6.98 (m, 2H), 6.37 (dd, J = 4.4, 6.7 Hz, 1H), 4.07 – 4.00 (m, 2H), 3.24 (dd, J = 7.0, 12.7 Hz, 1H), 3.03 (dd, J = 4.4, 12.7 Hz, 1H).

**13C NMR**: (125 MHz, CDCl3) δ = 191.99, 168.00, 166.31, 150.35, 138.23, 135.89, 133.71, 129.38, 128.75, 128.70, 128.66, 128.51, 126.58, 125.95, 121.41, 73.16, 47.87, 38.63.

**X-ray Structure:**

![X-ray structure image]
Phenyl cinnamate (2.12)

**Procedure:** β-hydroxy ester 2.09 (15 mg, 0.06 mmol) was dissolved in THF (300 μL) and acyl Meldrum’s acid (16 mg, 0.07 mmol) was added. The reaction mixture was stirred at reflux for 1 hour. Once β-hydroxy ester xx was consumed, as monitored by TLC, the reaction was cooled to room temperature and DBU (10 μL, 0.07 mmol) was added. The reaction was stirred at room temperature for 24 hours until completion as monitored via TLC. The reaction was quenched with a mixture of brine (2 mL) and DI H₂O (2 mL). The aqueous layer was extracted with DCM (5 x 2 mL). The combined organic layers were dried over Na₂SO₄ and reduced under vacuum. The crude material was purified with column chromatography using 100% hexanes to 80:20 (hexanes : EtOAc) to give 2.12 in 50% yield (8 mg, 0.035 mmol) as a white solid.

**Rf:** 0.81 in 80:20 (Hexanes : EtOAc)

**¹H NMR:** (400 MHz, CDCl₃) δ = 7.89 (d, J = 12.8 Hz, 1H), 7.61 - 7.59 (m, 2H), 7.44 - 7.50 (m, 5H), 7.26 (m 1H), 7.19 - 7.17 (m, 1H), 6.65 (d, J = 12.7 Hz, 1H).

**X-ray Structure:**
Phenyl 3-bromo-3-phenylpropanoate (2.13)

![Chemical structure]

**Procedure:** β-hydroxy ester 2.09 (15 mg, 0.06 mmol) was dissolved in toluene and acyl Meldrum’s acid (16 mg, 0.07 mmol) was added. The reaction mixture was stirred at reflux for 1 hour. Once β-hydroxy ester 2.09 was consumed, as monitored by TLC, the reaction was cooled to room temperature and MgBr$_2$•OEt$_2$ (17 mg, 0.07 mmol) was added. The reaction was stirred at room temperature for 24 hours and no progress was noted as determined by TLC. The reaction was quenched with a mixture of brine (2 mL) and DI H$_2$O (2 mL). The aqueous layer was extracted with DCM (5 x 2 mL). The combined organic layers were dried over Na$_2$SO$_4$ and reduced under vacuum. Crude materials were analyzed via $^1$H NMR to reveal a 1:1 mixture of 2.13 and 2.12. The crude material was purified with column chromatography using 100% hexanes to 40:60 (hexanes : EtOAc) to give 2.13 in 38 % yield (10 mg, 0.023 mmol) as a white solid in a separate fraction giving 2.12 in 37% (10 mg, 0.23 mmol) as a white solid. For a combined yield of 75%.

**Rf:** 0.77 in 80:20 (Hexanes : EtOAc)

**2.13: $^1$H NMR:** (500 MHz, CDCl$_3$) δ = 7.50 – 7.49 (m, 2H), 7.44 – 7.33 (m, 5H), 7.24 – 7.22 (m, 1H), 7.01 – 6.99 (m, 2H), 5.51 (dd, $J = 6.4, 9.0$ Hz, 1H), 3.59 (dd, $J = 9.0, 16$ Hz, 1H), 3.47 (dd, $J = 6.4, 16$ Hz, 1H)

**X-ray Structure:**

![X-ray Structure Image]
(E)-6-hydroxy-6-phenylhex-3-en-2-one (2.26)

Procedure: The starting alkene (5.0 g, 33.70 mmol) was dissolved in DCM (67 mL, 0.5 M). Methyl vinyl ketone (13.7 mL, 168.50 mmol) was added followed by Grubb’s II (72 mg, 0.08 mmol). The reaction mixture was stirred at reflux for 12 hours. Once the starting alkene was fully consumed as monitored by TLC, the reaction mixture was cooled to room temperature and concentrated under vacuum. Crude reaction materials were purified with column chromatography using 100% hexanes to 60:40 (hexanes : EtOAc) to give 2.26 in 88% yield (5.63 g, 29.70 mmol) as a brown oil.

Rf: 0.32 in 80:20 (Hexanes : EtOAc)

1H NMR: (400 MHz, CDCl3) δ = 7.31 – 7.19 (m, 5H), 6.74 (dt, J = 7.2, 14.7 Hz, 1H), 6.03 (d, J = 16.0 Hz, 1H), 4.75 (t, J = 6.1 Hz, 1H), 2.65 – 2.53 (m, 2H), 2.43 (bs, 1H), 2.13 (s, 3H).

13C NMR: (125 MHz, CDCl3) δ = 198.59, 143.94, 143.43, 133.42, 128.56, 127.88, 125.62, 73.07, 41.98, 26.78.

IR: f (cm⁻¹) = 3409, 3030, 2904, 1666, 1624, 1493, 1453, 1423, 1361, 1255, 1196, 1046, 974, 889, 755, 603, 535.

5-(1-hydroxyethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (2.27)
**Procedure:** A round bottom flask was charged with Meldrum acid (5.00 g, 35.0 mmol) and DMAP (8.30 g, 68.0 mmol). The solid materials were dissolved in DCM (14 mL, 0.5 M) and cooled to -10 °C. A solution of acyl chloride (2.85 mL, 40.0 mmol) in DCM (3 mL) was added dropwise to the round bottom flask. The reaction was stirred at -10 °C for 1 hour then warmed to room temperature. Once Meldrum’s acid was fully consumed as monitored by TLC, the reaction was diluted with DCM (15 mL). The crude reaction was washed with KHSO₄ (2%, 80 mL), HCl (10%, 80 mL), DI H₂O (160 mL), and brine (160 mL). The combined aqueous layers were extracted once with DCM (40 mL) and the combined organic layers were dried over Na₂SO₄. Crude yellow solid was recrystallized from acetone to give 2.27 in 95% yield (6.18 g, 33.3 mmol) as a yellow solid.

**Rf:** 0.09 in 60:40 (Hexanes : EtOAc)

**¹H NMR:** (400 MHz, CDCl₃) δ = 15.12 (s, 1H), 2.68 (s, 3H), 1.74 (s, 6H).

**¹³C NMR:** (125 MHz, CDCl₃) δ = 194.46, 170.05, 160.29, 104.77, 91.72, 26.69, 23.34.

**IR:** υ (cm⁻¹) = 3063, 3029, 2925, 1789, 1728, 1603, 1244, 1176, 1026, 909, 729, 701, 605.

**X-ray Structure:**

3-acetyl-4-(2-oxopropyl)-6-phenyltetrahydro-2H-pyran-2-one (2.28)
Procedure: δ-hydroxyenone 2.26 (200 mg, 1.05 mmol), was dissolved in DCE (10.5 mL, 0.1M) and acyl Meldrum acid 2.27 (216 mg, 1.2 mmol) was added. The reaction mixture was stirred at reflux for 1 hour. Once δ-hydroxyenone 2.26 was consumed, as monitored by TLC, the reaction was cooled to room temperature and Cs$_2$CO$_3$ (857 mg, 2.63 mmol) was added. The reaction was stirred at room temperature for 23 hours. Upon completion as monitored by TLC, the reaction was quenched with a mixture of brine (12 mL) and DI H$_2$O (12 mL). The aqueous layer was extracted with DCM (5 x 25 mL). The combined organic layers were dried over Na$_2$SO$_4$ and reduced under vacuum. The crude material was purified with column chromatography using 100% hexanes to 40:60 (hexanes : EtOAc) to give 2.28 in 88 % yield (252 mg, 0.93 mmol) as a white solid.

Rf: 0.3 in 50:50 (Hexanes : EtOAc)

$^1$H NMR: (400 MHz, CDCl$_3$) δ = 7.39 – 7.31 (m, 5H), 5.39 (dd, $J = 2.2$, 9.5 Hz, 1H), 3.58 (d, $J = 7.9$ Hz, 1H), 3.13 (m, 1H), 2.54 (d, $J = 6.6$ Hz, 2H), 2.45 (s, 3H), 2.30 (ddd, $J = 2.6$, 5.1, 10.2 Hz, 1H), 2.14 (s, 3H), 1.64 (dt, $J = 11.9$, 14.2 Hz, 1H).

$^{13}$C NMR: (100 MHz, CDCl$_3$) δ = 206.21, 202.45, 166.99, 137.74, 128.67, 128.64, 125.78, 83.76, 63.55, 46.40, 39.90, 30.25, 30.19, 29.38.

IR: $\nu$(cm$^{-1}$) = 2923, 1706, 1638, 1600, 1497, 1454, 1417, 1356, 1243, 1174, 1086, 1052, 1029, 874, 845, 547.

HRMS (ESI-TOF) $m/z$: (M + H)$^+$ = 275.1278 calculated for C$_{16}$H$_{19}$O$_4$; Found 275.1289

X-ray Structure:
Procedure: The starting alkene (1.30 g, 7.29 mmol) was dissolved in DCM (14.6 mL, 0.5 M). Methyl vinyl ketone (2.95 mL, 36.50 mmol) was added followed by Grubb’s II (20 mg, 0.04 mmol). The solution was heated to reflux and stirred for 3 hours. Once the starting alkene was fully consumed as monitored by TLC, the reaction mixture was cooled to room temperature and concentrated under vacuum. Crude reaction materials were purified with column chromatography using 100% hexanes to 60:40 (hexanes : EtOAc) to yield 2.29.1 in 74% yield (1.2 g, 5.39 mmol) as a brown oil.

Rf: 0.1 in 80:20 (Hexanes : EtOAc)

$^1$H NMR: (400 MHz, CDCl$_3$) $\delta = 7.27$ (d, $J = 12.0$ Hz, 2H), 6.89 (d, $J = 12.0$ Hz, 2H), 6.79 (dt, $J = 7.2, 16.0$ Hz, 1H), 6.10 (d, $J = 16.0$ Hz, 1H), 4.78 (dd, $J = 5.2, 7.8$ Hz, 1H), 3.81 (s, 3H), 2.72 – 2.57 (m, 2H), 2.51 (bs, 1H), 2.22 (s, 3H).

$^{13}$C NMR: (125 MHz, CDCl$_3$) $\delta = 198.60, 159.19, 144.14, 135.60, 133.30, 126.89, 113.90, 72.66, 55.21, 41.93, 26.74.$

IR: $f$(cm$^{-1}$) = 3422, 3001, 2935, 2836, 1665, 1611, 1585, 1511, 1461, 1423, 1360, 1300, 1243, 1174, 1031, 811, 760, 544.
(E)-6-hydroxy-6-(3-(trifluoromethyl)phenyl)hex-3-en-2-one (2.29.2)

**Procedure:** The starting alkene (1.05 g, 4.86 mmol) was dissolved in DCM (9.7 mL, 0.5 M). Methyl vinyl ketone (1.9 mL, 24.0 mmol) was added followed by Grubb’s II (20 mg, 0.024 mmol). The solution was heated to reflux and stirred for 3 hours. Once the starting alkene was fully consumed as monitored by TLC, the reaction mixture was cooled to room temperature and concentrated under vacuum. Crude reaction materials were purified with column chromatography using 100% hexanes to 60:40 (hexanes : EtOAc) to yield 2.29.2 in 78% yield (987 mg, 3.79 mmol) as a brown oil.

**Rf:** 0.26 in 80:20 (Hexanes : EtOAc)

**1H NMR:** (400 MHz, CDCl₃) δ = 7.63 (s, 1H), 7.55 (m, 2H), 7.49 (m, 1H), 6.79 (dt, J = 7.2, 14.6 1H), 6.13 (d, J = 16.0 Hz, 1H), 4.93 (m, 1H), 2.67 – 2.64 (m, 2H), 2.48 (bs, 1H), 2.23 (s, 3H).

**13C NMR:** (125 MHz, CDCl₃) δ = 198.39, 144.43, 142.91, 133.83, 131.10, 129.01, 125.08, 124.70, 122.91, 122.47, 72.48, 42.07, 26.99.

**IR:** f(cm⁻¹) = 3413, 2896, 1667, 1627, 1491, 1426, 1326, 1161, 1119, 977, 804, 704, 672, 462.

(2.29.3)

(E)-6-hydroxy-7-phenylhept-3-en-2-one (2.29.3)
**Procedure:** The alkene (1.0 g, 7.90 mmol) was dissolved in DCM (16 mL, 0.5 M). Methyl vinyl ketone (3.2 mL, 40 mmol) was added followed by Grubb’s II (33 mg, 0.04 mmol). The solution was heated to reflux and stirred for 14 hours. Once the starting alkene was fully consumed as monitored by TLC, the reaction mixture was cooled to room temperature and concentrated under vacuum. Crude reaction materials were purified with column chromatography using 100% hexanes to 60:40 (hexanes : EtOAc) to give 2.93.3 in 60 % yield (968 mg, 4.74 mmol) as a brown oil.

**Rf:** 0.33 in 60:40 (Hexanes : EtOAc)

**$^1$H NMR:** (400 MHz, CDCl$_3$) $\delta$ = 7.36 – 7.21 (m, 5H), 6.897 (dt, $J = 7.2, 14.8$ Hz, 1H), 6.16 (d, $J = 16.0$ Hz, 1H), 4.01 (m, 1H), 2.85 (m, 1H), 2.76 (m, 1H), 2.52 – 2.41 (m, 2H), 2.26 (s, 3H), 1.88 (bs, 1H).

**$^{13}$C NMR:** (125 MHz, CDCl$_3$) $\delta$ = 198.48, 144.22, 137.61, 133.44, 129.36, 128.70, 126.77, 71.39, 43.82, 39.58, 26.92.

**IR:** $f(\text{cm}^{-1}) = 3422, 3027, 2920, 1667, 1625, 1495, 1453, 1424, 161, 1184, 977, 604, 503.$

**(E)-6-hydroxytridec-3-en-2-one (2.29.4)**

![chemical structure](image)

**Procedure:** The alkene (829 mg, 4.90 mmol) was dissolved in DCM (9.7 mL, 0.5 M). Methyl vinyl ketone (2.0 mL, 24.4 mmol) was added followed by Grubb’s II (20 mg, 0.02 mmol). The solution was heated to reflux and stirred for 1 hour. Once the starting alkene was fully consumed as monitored by TLC, the reaction mixture was cooled to room temperature and concentrated under...
vacuum. Crude reaction materials were purified with column chromatography using 100% hexanes to 60:40 (hexanes: EtOAc) to give 2.29.4 in 71% yield (728 mg, 3.50 mmol) as a brown oil.

Rf: 0.5 in 60:40 (Hexanes : EtOAc)

$^1$H NMR: (500 MHz, CDCl$_3$) $\delta = 6.85$ (dt, $J = 7.4$, 16.1 Hz, 1H), 6.15 (d, $J = 16.0$ Hz, 1H), 3.78 (m, 1H), 2.45 (m, 1H), 2.35 (m, 1H), 2.27 (s, 3H), 1.64 (s, 1H), 1.50 – 1.45 (m, 3H), 1.35 – 1.23 (m, 9H), 0.88 (t, $J = 5.6$ Hz, 3H).

$^{13}$C NMR: (125 MHz, CDCl$_3$) $\delta = 198.46$, 144.42, 133.40, 70.67, 40.35, 37.32, 31.76, 29.47, 29.21, 26.95, 25.56, 22.61, 14.06.

IR: $\tilde{v}$ (cm$^{-1}$) = 3438, 2924, 2854, 1670, 1626, 1426, 1425, 1361, 1255, 979, 524.

$(E)$-6-hydroxy-7,7-dimethyloct-3-en-2-one (2.29.5)

Procedure: The alkene (995 mg, 7.76 mmol) was dissolved in DCM (16 mL, 0.5 M). Methyl vinyl ketone (3.1 mL, 39.0 mmol) was added followed by Grubb’s II (33 mg, 0.039 mmol). The solution was heated to reflux and stirred for 8 hours. Once the starting alkene was fully consumed as monitored by TLC, the reaction mixture was cooled to room temperature and concentrated under vacuum. Crude reaction materials were purified with column chromatography using 100% hexanes to 60:40 (hexanes : EtOAc) to yield 2.29.5 in 67% yield (884 mg, 5.20 mmol) as a brown oil.

Rf: 0.3 in 80:20 (Hexanes : EtOAc)

$^1$H NMR: (500 MHz, CDCl$_3$) $\delta = 6.90$ (dt, $J = 7.9$, 15.4 Hz, 1H), 6.15 (d, $J = 16.0$ Hz, 1H), 3.38 (d, $J = 10.4$ Hz, 1H), 2.46 (m, 1H), 2.25 (s, 3H), 2.20 (m, 1H), 1.66 (s, 1H), 0.94 (s, 9H).
**C NMR**: (125 MHz, CDCl$_3$) $\delta =$ 198.50, 146.46, 133.00, 78.55, 35.06, 35.01, 26.86, 25.55.

**IR**: $f$(cm$^{-1}$) = 3446, 2955, 2870, 1666, 1624, 1478, 1362, 1256, 1067, 975, 917.

(E)-8-bromo-6-hydroxyoct-3-en-2-one (2.29.6)

![Chemical Reaction Diagram]

**Procedure**: The starting alkene (1.0 g, 5.70 mmol) was dissolved in DCM (11.4 mL, 0.5 M). Methyl vinyl ketone (2.3 mL, 28.0 mmol) was added followed by Grubb’s II (24 mg, 0.028 mmol). The solution was heated to reflux and stirred for 3 hours. Once the starting alkene was fully consumed as monitored by TLC, the reaction mixture was cooled to room temperature and concentrated under vacuum. Crude reaction materials were purified with column chromatography using 100% hexanes to 60:40 (hexanes : EtOAc) to yield 2.29.6 in 63% yield (797 mg, 3.60 mmol) as a brown oil.

**Rf**: 0.21 in 80:20 (Hexanes : EtOAc)

**H NMR**: (400 MHz, CDCl$_3$) $\delta =$ 6.82 (dt, $J = 7.3$, 16.0 Hz, 1H), 6.16 (d, $J = 15.9$ Hz, 1H), 4.03 (m, 1H), 3.60 – 3.50 (m, 2H), 2.48 – 2.35 (m, 2H), 2.26 (s, 3H), 2.01 (m, 2H), 1.75 (bs, 1H).

**C NMR**: (125 MHz, CDCl$_3$) $\delta =$ 198.39, 143.35, 133.71, 68.34, 40.27, 39.45, 29.99, 27.08.

**IR**, $f$(cm$^{-1}$) = 3419, 1667, 1424, 1361, 1257, 1049, 977, 914, 562.

**HRMS (ESI-TOF)** m/z: (M + H)$^+$ = 221.01717 calculated for C$_8$H$_{14}$BrO$_2$; Found 221.01719.
(E)-7-(benzyloxy)-6-hydroxyhept-3-en-2-one (2.29.7)

**Procedure:** The alkene (840 mg, 4.40 mmol) was dissolved in DCM (9.0 mL, 0.5 M). Methyl vinyl ketone (1.8 mL, 21.9 mmol) was added followed by Grubb’s II (19 mg, 0.02 mmol). The solution was heated to reflux and stirred for 3 hours. Once the starting alkene was fully consumed as monitored by TLC, the reaction mixture was cooled to room temperature and concentrated under vacuum. Crude reaction materials were purified with column chromatography using 100% hexanes to 60:40 (hexanes : EtOAc) to yield 2.29.7 in 83% yield (844 mg, 3.60 mmol) as a brown oil.

**Rf:** 0.17 in 80:20 (Hexanes : EtOAc)

**1H NMR:** (500 MHz, CDCl₃) δ = 7.37 – 7.29 (m, 5H), 6.82 (dt, J = 7.2, 14.4 Hz, 1H), 6.13 (d, J = 15.8 Hz, 1H), 4.55 (s, 2H), 3.95 (m, 1H), 3.52 (dd, J = 2.8, 9.5 Hz, 1H), 3.38 (dd, J = 7.1, 9.5 Hz, 1H), 2.51 (bs, 1H), 2.41 (t, J = 7.3 Hz, 2H), 2.24 (s, 3H).

**13C NMR:** (125 MHz, CDCl₃) δ = 198.41, 143.65, 137.62, 133.37, 128.49, 127.91, 127.76, 73.66, 73.44, 69.22, 36.40, 26.84.

**IR:** f (cm⁻¹) = 3437, 3030, 2860, 1668, 1626, 1496, 1361, 1255, 1203, 1092, 912, 739, 699, 464.

(E)-6-hydroxy-8-(((thioxoboraneyl)-l²-phosphaneyl)oxy)oct-3-en-2-one (2.29.8)
Procedure: The alkene (1.57 g, 4.61 mmol) was dissolved in DCM (9.0 mL, 0.5 M). Methyl vinyl ketone (1.9 mL, 23.10 mmol) was added followed by Grubb’s II (19 mg, 0.023 mmol). The solution was heated to reflux and stirred for 6.5 hours. Once the starting alkene was fully consumed as monitored by TLC, the reaction mixture was cooled to room temperature and concentrated under vacuum. Crude reaction materials were purified with column chromatography using 100% hexanes to 60:40 (hexanes : EtOAc) to yield 2.29.8 in 53% yield (961 mg, 2.40 mmol) as a brown oil.

Rf: 0.24 in 80:20 (Hexanes : EtOAc)

^1H NMR: (400 MHz, CDCl₃) δ = 7.67 (d, J = 7.8 Hz, 4H), 7.47 – 7.39 (m, 6H), 6.87 (dt, J = 7.2, 15.9 Hz, 1H), 6.13 (d, J = 16.0 Hz, 1H), 4.08 (m, 1H), 3.91 – 3.84 (m, 2H), 3.45 (s, 1H), 2.48 – 2.36 (m, 2H), 2.27 (s, 3H), 1.77 (m, 1H), 1.64 (m, 1H), 1.06 (s, 9H).

^13C NMR: (125 MHz, CDCl₃) δ = 198.52, 144.46, 135.49, 133.31, 132.73, 132.65, 129.91, 127.82, 70.76, 63.35, 40.43, 37.93, 26.77, 18.98.

IR: f (cm⁻¹) = 3453, 3070, 2930, 2856, 1671, 1626, 1589, 1472, 1389, 1360, 1254, 1105, 1083, 980, 938, 822, 737, 687, 503, 433.

3-acetyl-6-(4-methoxyphenyl)-4-(2-oxopropyl)tetrahydro-2H-pyran-2-one (2.30.1)

Procedure: δ-hydroxyenone 2.29.1 (200 mg, 0.91 mmol) was dissolved in DCE (9.1 mL, 0.1 M) and acyl Meldrum acid 2.27 (186 mg, 1.00 mmol) was added. The reaction mixture was stirred at reflux for 1 hour. Once δ-hydroxyenone 2.29.1 was fully consumed as monitored by TLC, the reaction was cooled to room temperature and Cs₂CO₃ (739 mg, 1.93 mmol) was added. The
reaction was stirred at room temperature for 7 hours. Upon completion as monitored by TLC, the reaction was quenched with a mixture of brine (20 mL) and DI H2O (20 mL). The aqueous layer was extracted with DCM (5 x 25 mL). The combined organic layers were dried over Na2SO4 and reduced under vacuum. The crude material was purified with column chromatography using 100% hexanes to 40:60 (hexanes : EtOAc) to give product 2.30.1 in 57 % yield (158 mg, 0.52 mmol) as a brown powder.

Rf: 0.46 in 50:50 (Hexanes : EtOAc)

CDCl3: Ketone : Enol = 9.1:1, DMSO: Ketone : Enol = 5.6:1

1H NMR: (400 MHz, CDCl3) δ = 7.28 – 7.26 (m, 2H), 6.90 (d, J = 8.9 Hz, 2H), 5.35 (dd J = 2.4, 11.9 Hz, 1H), 3.82 (s, 3H), 3.58 (d, J = 7.8 Hz, 1H), 3.11 (m, 1H), 2.55 (d, J = 6.6 Hz, 2H), 2.45 (s, 3H), 2.27 (ddd J = 3.5, 6.2, 15.3 Hz, 1H), 2.15 (s, 3H), 1.66 (dt J = 11.8, 14.0 Hz, 1H).

13C NMR: (125 MHz, CDCl3) δ = 206.25, 202.52, 167.10, 159.85, 130.69 127.35, 114.01, 80.90, 60.58, 55.32, 48.19, 36.45, 30.25, 30.19, 29.37.

1H NMR: (500 MHz, DMSO-d6) δ = 7.32 (d, J = 10.9 Hz, 2H), 6.95 (d, J = 10.9 Hz, 2H), 5.40 (dd, J = 3.4, 15.0 Hz, 1H), 3.76 (s, 3H), 3.68 (d, J = 12.1 Hz, 1H), 2.86 (m, 1H), 2.55 – 2.53 (m, 2H), 2.30 (s, 3H), 2.10 – 2.01 (m, 4H), 1.74 (m, 1H).

13C NMR: (125 MHz, DMSO-d6) δ = 207.05, 203.89, 167.60, 159.31, 131.48, 127.76, 113.86, 80.68, 59.66, 55.15, 47.20, 35.06, 30.06, 30.03, 29.58.

IR: f (cm⁻¹) = 2961, 2927, 1711, 1641, 1613, 1588, 1516, 1461, 1407, 1358, 1248, 1174, 1084, 1054, 1031, 548.

HRMS (ESI-TOF) m/z: (M + H)+ = 305.13835 calculated for C17H21O5; Found 305.13910
X-ray Structure:

3-acetyl-4-(2-oxopropyl)-6-(3-(trifluoromethyl)phenyl)tetrahydro-2H-pyran-2-one (2.30.2)

**Procedure:** δ-hydroxyenone 2.29.2 (200 mg, 0.77 mmol), was dissolved in DCE (7.7 mL, 0.1M) and acyl Meldrum acid 2.27 (158 mg, 0.85 mmol) was added. The reaction mixture was stirred at reflux for 1 hour. Once δ-hydroxyenone 2.29.2 was consumed as monitored by TLC, the reaction was cooled to room temperature and Cs₂CO₃ (628 mg, 0.19 mmol) was added. The reaction was stirred at room temperature for 20 hours. Upon completion as monitored by TLC, the reaction was quenched with a mixture of brine (15 mL) and DI H₂O (15 mL). The aqueous layer was extracted with DCM (5 x 25 mL). The combined organic layers were dried over Na₂SO₄ and reduced under vacuum. The crude material was purified with column chromatography using 100% hexanes to 30:70 (hexanes : EtOAc) to give 2.30.2 in 83 % yield (217 mg, 0.64 mmol) as a yellow oil.

**Rf:** 0.43 in 50:50 (Hexanes : EtOAc)

**CDCl₃:** Ketone : Enol = 7.1:1, **DMSO:** Ketone : Enol = 20:1
**1H NMR:** (400 MHz, CDCl₃) δ = 7.62 – 7.27 (m, 4H), 5.46 (dd, J = 2.4, 11.8 Hz, 1H), 3.63 (d, J = 7.7 Hz, 1H), 3.15 (m, 1H), 2.57 (d, J = 6.6 Hz, 2H), 2.47 (s, 3H), 2.35 (m, 1H), 2.16 (s, 3H), 1.64 (m, 1H).

**13C NMR:** (125 MHz, CDCl₃) δ = 206.20, 202.33, 166.61, 139.63, 129.23, 129.17, 125.43, 125.39, 122.57, 122.53, 80.00, 60.38, 47.97, 36.54, 30.28, 30.19, 29.25.

**1H NMR:** (400 MHz, DMSO-d₆) δ = 7.79 – 7.64 (m, 4H), 5.61 (m, 1H), 3.74 (d, J = 7.8 Hz, 1H), 2.90 (m, 1H), 2.54 (d, J = 4.1 Hz, 2H), 2.31 (s, 3H), 2.15 (m, 1H), 2.07 (s, 3H), 1.73 (q, J = 9.8 Hz, 1H).

**13C NMR:** (125 MHz, DMSO-d₆) δ = 206.59, 203.75, 167.33, 141.04, 130.39, 129.74, 125.12, 125.09, 122.76, 122.73, 80.70, 57.51, 47.67, 34.32, 30.11, 30.06, 29.52.

**IR:** $f$(cm⁻¹) = 2926, 1710, 1614, 1600, 1358, 1328, 1271, 1073, 703, 544, 494, 407.

**HRMS (ESI-TOF) m/z:** (M + H)⁺ = 343.11517 calculated for C₁₇H₁₈F₃O₄; Found 343.11558

3-acetyl-6-benzyl-4-(2-oxopropyl)tetrahydro-2H-pyran-2-one (2.30.3)

**Procedure:** δ-hydroxyenone 2.29.3 (200 mg, 0.98 mmol), was dissolved in DCE (9.8 mL, 0.1M) and acyl Meldrum acid 2.27 (201 mg, 1.10 mmol) was added. The reaction mixture was stirred at reflux for 1 hour. Once δ-hydroxyenone 2.29.3 was consumed, as monitored by TLC, the reaction was cooled to room temperature and Cs₂CO₃ (798 mg, 2.45 mmol) was added. The reaction was stirred at room temperature for 24 hours. Upon completion as monitored by TLC, the reaction was quenched with a mixture of brine (12 mL) and DI H₂O (12 mL). The aqueous layer was extracted
with DCM (5 x 25 mL). The combined organic layers were dried over Na₂SO₄ and reduced under
vacuum. The crude material was purified with column chromatography using 100% hexanes to
40:60 (hexanes : EtOAc) to give 2.30.3 in 79 % yield (224 mg, 0.77 mmol) as a white solid.

Rf: 0.32 in 60:40 (Hexanes : EtOAc)

^1H NMR: (400 MHz, CDCl₃) δ = 7.32 – 7.19 (m, 5H), 4.58 (m 1H), 3.42 (d, J = 8.2 Hz, 1H), 3.03
(m, 1H), 2.91 – 2.84 (m, 2H), 2.44 (d, J = 6.5 Hz, 2H), 2.36 (s, 3H), 2.09 (s, 3H), 2.01 (m, 1H),
1.22 (m, 1H).

^13C NMR: (125 MHz, CDCl₃) δ = 206.31, 202.50, 167.12, 135.69, 129.60, 128.59, 126.96, 80.14,
60.54, 48.14, 41.68, 33.15, 30.23, 30.07, 29.03.

IR: \( f(\text{cm}^{-1}) = 2924, 1705, 1496, 1357, 1247, 1175, 1087, 756, 703, 483. \)

HRMS (ESI-TOF) m/z: (M + H)^+ = 289.14344 calculated for C₁₇H₂₁O₄; Found 289.14463

3-acetyl-6-heptyl-4-(2-oxopropyl)tetrahydro-2H-pyran-2-one (2.30.4)

**Procedure:** δ-hydroxyenone 2.29.4 (200 mg, 0.94 mmol) was dissolved in DCE (9.4 mL, 0.1M)
and acyl Meldrum acid 2.27 (194 mg, 1.04 mmol) was added. The reaction mixture was stirred at
reflux for 1.5 hours. Once δ-hydroxyenone 2.29.4 was consumed as monitored by TLC, the
reaction was cooled to room temperature and Cs₂CO₃ (769 mg, 2.36 mmol) was added. The
reaction was stirred at room temperature for 3.5 hours. Upon completion as monitored by TLC,
the reaction was quenched with a mixture of brine (15 mL) and DI H₂O (15 mL). The aqueous
layer was extracted with DCM (5 x 25 mL). The combined organic layers were dried over Na₂SO₄
and reduced under vacuum. The crude material was purified with column chromatography using 100% hexanes to 40:60 (hexanes : EtOAc) to give 2.30.4 in 77 % yield (214 mg, 0.73 mmol) as a yellow oil.

**Rf:** 0.51 in 50:50 (Hexanes : EtOAc)

**1H NMR:** (400 MHz, CDCl₃) δ = 4.33 (m, 1H), 3.41 (d, J = 8.2 Hz, 1H), 2.91 (m, 1H), 2.48 (d, J = 6.6 Hz, 2H), 2.38 (s, 3H), 2.13 (s, 3H), 2.05 (m, 1H), 1.67 – 1.43 (m, 4H), 1.28 – 1.22 (m, 9H), 0.88 – 0.85 (m, 3H).

**13C NMR:** (125 MHz, CDCl₃) δ = 206.35, 202.57, 167.46, 80.06, 60.66, 48.27, 35.55, 33.97, 31.69, 30.24, 30.02, 29.28, 29.10, 29.08, 24.62, 22.59, 14.05.

**IR:** f/cm⁻¹ = 2926, 2856, 1710, 1643, 1604, 1357, 1253, 1195, 1115, 1091.

**HRMS (ESI-TOF) m/z:** (M + H)+ = 297.2064 calculated for C₁₇H₂₉O₄; Found 297.2090

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**3-acetyl-6-(tert-butyl)-4-(2-oxopropyl)tetrahydro-2H-pyran-2-one (2.30.5)**

**Procedure:** δ-hydroxyenone 2.29.5 (200 mg, 1.17 mmol), was dissolved in DCE (8.5 mL, 0.1M) and acyl Meldrum acid 2.27 (240 mg, 1.30 mmol) was added. The reaction mixture was stirred at reflux for 1 hour. Once δ-hydroxyenone 13e was consumed, as monitored by TLC, the reaction was cooled to room temperature and Cs₂CO₃ (954 mg, 2.93 mmol) was added. The reaction was stirred at room temperature for 23 hours. Upon completion as monitored by TLC, the reaction was quenched with a mixture of brine (12 mL) and DI H₂O (12 mL). The aqueous layer was extracted with DCM (5 x 25 mL). The combined organic layers were dried over Na₂SO₄ and reduced under
vacuum. The crude material was purified with column chromatography using 100% hexanes to 40:70 (hexanes : EtOAc ) to give 2.30.5 in 79 % yield (235 mg, 0.92 mmol) as light yellow oil.

**Rf:** 0.32 in 60:40 (Hexanes : EtOAc)

**1H NMR:** (400 MHz, CDCl3) δ = 4.02 (dd, J = 2.3, 11.7 Hz, 1H), 3.41 (d, J = 8.3 Hz, 1H), 2.89 (m, 1H), 2.49 (d, J = 6.4 Hz, 2H), 2.38 (s, 3H), 2.13 (s, 3H), 2.03 (m, 1H), 1.26 (dt, J = 11.7, 13.7 Hz, 1H), 0.94 (s, 9H).

**13C NMR:** (125 MHz, CDCl3) δ = 206.37, 202.61, 167.55, 87.20, 60.76, 48.42, 34.12, 30.23, 30.02, 29.13, 28.90, 25.30.

**IR:** f ´ (cm⁻¹) = 2962, 1708, 1639, 1480, 1399, 1357, 1275, 1246, 1200, 1095, 999, 934.

**HRMS (ESI-TOF) m/z:** (M + H)⁺ = 255.15909 calculated for C₁₄H₂₃O₄; Found 255.15991

3-acetyl-6-(2-bromoethyl)-4-(2-oxopropyl)tetrahydro-2H-pyran-2-one (2.29.6)

**Procedure:** δ-hydroxyenone 2.29.6 (200 mg, 0.90 mmol), was dissolved in DCE (9.0 mL, 0.1M) and acyl Meldrum acid 2.27 (184 mg, 0.99 mmol) was added. The reaction mixture was stirred at reflux for 1 hour. Once δ-hydroxyenone 2.30.6 was consumed as monitored by TLC, the reaction was cooled to room temperature and Cs₂CO₃ (733 mg, 2.25 mmol) was added. The reaction was stirred at room temperature for 7 hours. Upon completion as monitored by TLC, the reaction was quenched with a mixture of brine (12 mL) and DI H₂O (12 mL). The aqueous layer was extracted with DCM (5 x 25 mL). The combined organic layers were dried over Na₂SO₄ and reduced under
vacuum. The crude material was purified with column chromatography using 100% hexanes to 30:70 (hexanes : EtOAc) to give \(2.30.6\) in 64 % yield (175 mg, 0.58 mmol) as a white solid.

**Rf:** 0.25 in 50:50 (Hexanes : EtOAc)

**\(^1\)H NMR:** (400 MHz, CDCl\(_3\)) \(\delta = 4.57\) (tt, \(J = 2.4, 11.6\) Hz, 1H), 3.58 – 3.48 (m, 2H), 3.46 (d, \(J = 8.2\) Hz, 1H), 2.97 (m, 1H), 2.50 (d, \(J = 6.6\) Hz, 2H), 2.39 (s, 3H), 2.23 – 2.14 (m, 5H), 2.08 (m, 1H), 1.38 (dt, \(J = 11.7, 13.9\) Hz, 1H).

**\(^{13}\)C NMR:** (125 MHz, CDCl\(_3\)) \(\delta = 206.18, 202.15, 166.83, 77.39, 60.37, 47.95, 38.43, 33.59, 30.20, 30.01, 29.02, 27.78.

**IR:** \(f(\text{cm}^{-1}) = 2925, 1709, 1597, 1419, 1419, 1246, 1204, 1158, 1097, 1049, 868, 607.

**HRMS (ESI-TOF) m/z:** (M + H)\(^+\) = 305.0383 calculated for C\(_{12}\)H\(_{18}\)BrO\(_4\); Found 305.03917

3-acetyl-6-((benzylxoy)methyl)-4-(2-oxopropyl)tetrahydro-2\(H\)-pyran-2-one (2.30.7)

**Procedure:** \(\delta\)-hydroxyenone 2.29.7 (200 mg, 0.85 mmol), was dissolved in DCE (8.5 mL, 0.1M) and acyl Meldrum acid 2.27 (175 mg, 0.93 mmol) was added. The reaction mixture was stirred at reflux for 1 hour. Once \(\delta\)-hydroxyenone 2.30.7 was consumed, as monitored by TLC, the reaction was cooled to room temperature and Cs\(_2\)CO\(_3\) (697 mg, 2.14 mmol) was added. The reaction was stirred at room temperature for 24 hours. Upon completion as monitored by TLC, the reaction was quenched with mixture of brine (15 mL) and DI H\(_2\)O (15 mL). The aqueous layer was extracted with DCM (5 x 25 mL). The combined organic layers were dried over Na\(_2\)SO\(_4\) and reduced under
vacuum. The crude material was purified with column chromatography using 100% hexanes to 40:70 (hexanes : EtOAc) to give 2.30.7 in 69 % yield (178 mg, 0.59 mmol) as light yellow oil.

**Rf:** 0.27 in 50:50 (Hexanes : EtOAc)

**¹H NMR:** (400 MHz, CDCl₃) δ = 7.37 – 7.29 (m, 5H), 4.58 – 4.55 (m, 2H), 4.52 (m, 1H), 3.61 – 3.58 (m, 2H), 3.43 (d, J = 8.3 Hz, 1H), 2.93 (m, 1H), 2.48 (d, J = 6.6 Hz, 2H), 2.37 (s, 3H), 2.12 - 2.06 (m, 4H), 1.50 (dt, J = 11.8, 13.9 Hz, 1H).

**¹³C NMR:** (125 MHz, CDCl₃) δ = 206.24, 202.45, 166.94, 137.55, 128.41, 127.81, 127.68, 78.59, 73.55, 71.24, 60.40, 48.06, 30.27, 30.19, 30.09, 28.86.

**IR:** ε(cm⁻¹) = 2922, 2865, 1707, 1637, 1496, 1452, 1410, 1208, 1027, 912, 1068, 466.

**HRMS (ESI-TOF) m/z:** (M + H)⁺ = 319.1540 calculated for C₁₈H₂₃O₅; Found 319.15542

3-acetyl-6-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-4-(2-oxopropyl)tetrahydro-2H-pyran-2-one (2.30.8)

**Procedure:** δ-hydroxyenone 2.29.8 (200 mg, 0.50 mmol), was dissolved in DCE (5.0 mL, 0.1M) and acyl Meldrum acid 2.27 (103 mg, 0.55 mmol) was added. The reaction mixture was stirred at reflux for 1 hour. Once δ-hydroxyenone 2.30.8 was consumed, as monitored by TLC, the reaction was cooled to room temperature and Cs₂CO₃ (410 mg, 1.26 mmol) was added. The reaction was stirred at room temperature for 4 hours. Upon completion as monitored by TLC, the reaction was quenched with a mixture of brine (12 mL) and DI H₂O (12 mL). The aqueous layer was extracted with DCM (5 x 25 mL). The combined organic layers were dried over Na₂SO₄ and reduced under
vacuum. The crude material was purified with column chromatography using 100% hexanes to 50:50 (hexanes : EtOAc) to give **2.30.8** in 72 % yield (174 mg, 0.36 mmol) as a yellow oil.

**Rf**: 0.68 in 50:50 (Hexanes : EtOAc)

**1H NMR**: (400 MHz, CDCl₃) δ = 7.65 – 7.63 (m, 5H), 7.43 – 7.37 (m, 5H), 4.60 (m, 1H), 3.85 (m, 1H), 3.75 (m, 1H), 3.42 (d, J = 7.9 Hz, 1H), 2.94 (m, 1H), 2.47 (d, J = 6.6 Hz, 2H), 2.37 (s, 3H), 2.12 (s, 3H), 1.92 – 1.76 (m, 3H), 1.31 (m, 1H), 1.05 (s, 9H).

**13C NMR**: (100 MHz, CDCl₃) δ = 206.27, 202.28, 167.35, 135.53, 133.56, 133.39, 129.74, 127.74, 60.71, 59.26, 48.29, 38.30, 34.21, 30.25, 29.90, 29.14, 26.85, 19.17.

**IR**: f(cm⁻¹) = 2931, 2888, 2857, 1711, 1469, 1426, 1251, 1179, 1105, 998, 912, 822, 736, 502.

**HRMS (ESI-TOF) m/z**: (M + Na)⁺ = 503.22242 calculated for C₂₈H₃₆NaO₅Si; Found 503.22438

**General Procedure (A) for the formation of δ-hydroxyenones: 2.31.1 – 2.31.8**

![Chemical structure](image)

**Procedure**: Weinreb amide was dissolved in THF (0.2 M) and cooled to 0 ℃. A Grignard reagent (2.0 equiv) was added dropwise across 15 minutes. The reaction was stirred at 0 ℃ and monitored using TLC (80:20 hexanes : EtOAc). Upon completion, the reaction was quenched with a saturated aqueous solution of NH₄Cl (20 mL) and DI H₂O (20 mL). The solution was then warmed to room temperature for 20 minutes and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na₂SO₄ and reduced under vacuum. Crude reaction materials were purified using column chromatography to give the desired TBS protected eneone.

The eneone was dissolved in MeCN (0.2 M) and cooled to -10 ℃. BF₃·OEt₂ (1.20 equiv) was added in a single portion and the reaction was stirred at -10 ℃. Upon completion, as monitored
by TLC, (80:20 hexanes : EtOAc), the reaction was quenched with equal portions of 2M HCl (5 mL) and DI H₂O (5 mL). The aqueous layer was extracted with DCM (3 x 15 mL) and the combined organic layers were reduced under vacuum. Crude reaction materials were purified by column chromatography to give δ-hydroxyenones 2.32.1 – 2.32.8.

(E)-5-hydroxy-1,5-diphenylpent-2-en-1-one (2.31.1)

![Structure of 2.31.1]

**Procedure:** Compound 15a was synthesized in accordance to general procedure A to give 15a in 42 % yield across two steps (184 mg, 0.73 mmol).

**Rf:** 0.35 in 80:20 (Hexanes : EtOAc)

**¹H NMR:** (500 MHz, CDCl₃) δ = 7.89 – 7.87 (m, 2H), 7.55 (tt, J = 1.4, 6.9 Hz, 1H), 7.47 – 7.44 (m, 2H), 7.40 – 7.36 (m, 4H), 7.32 – 7.29 (m, 1H), 7.03 (m, 1H), 6.92 (m, 1H), 4.91 (t, J = 5.6 Hz, 1H), 2.83 – 2.72 (m, 2H), 2.12 (bs, 1H).

**¹³C NMR:** (125 MHz, CDCl₃) δ = 190.61, 144.83, 143.44, 137.67, 132.73, 128.65, 128.61, 128.59, 128.50, 127.95, 125.75, 73.22, 42.46.

**IR:** ν(cm⁻¹) = 3422, 3060, 2924, 1665, 1618, 1597, 1577, 1493, 1447, 1342, 1225, 1179, 1020, 966, 697, 541.

(E)-5-hydroxy-1-(4-methoxyphenyl)-5-phenylpent-2-en-1-one (2.31.2)

![Structure of 2.31.2]
Procedure: Compound 2.31.2 was synthesized in accordance to general procedure A to give 2.31.2 in 58 % yield across two steps (199 mg, 0.70 mmol).

Rf: 0.24 in 80:20 (Hexanes : EtOAc)

$^1$H NMR: (400 MHz, CDCl$_3$) $\delta = 7.90$ (d, $J = 8.9$ Hz, 2H), 7.39 – 7.34 (m, 4H), 7.30 (m, 1H), 7.01 (m, 1H), 6.93 (m, 1H), 6.95 – 6.91 (m, 3H), 4.90 (t, $J = 5.4$ Hz, 1H), 3.86 (s, 3H), 2.82 – 2.69 (m, 2H), 2.33 (bs, 1H).

$^{13}$C NMR: (125 MHz, CDCl$_3$) $\delta =$ 187.35, 162.74, 145.66, 130.90, 130.04, 128.60, 128.37, 127.86, 125.77, 121.42, 116.31, 73.21, 54.18, 42.91.

IR: $f$(cm$^{-1}$) = 3415, 2933, 2839, 1661, 1593, 1571, 1509, 1493, 1454, 1419, 1341, 1251, 1168, 1114, 1021, 968, 803, 757, 700, 678, 633, 605, 510.

HRMS (ESI-TOF) m/z: (M + H)$^+$ = 283.13287 calculated for C$_{18}$H$_{19}$O$_3$; Found 283.13263.

(E)-1-(4-chlorophenyl)-5-hydroxy-5-phenylpent-2-en-1-one (2.31.3)

Procedure: Compound 2.31.3 was synthesized in accordance to general procedure A to give 2.31.3 in 47 % yield across two steps (219 mg, 0.76 mmol).

Rf: 0.39 in 80:20 (Hexanes : EtOAc)

$^1$H NMR: (400 MHz, CDCl$_3$) $\delta = 7.83 – 7.80$ (m, 2H), 7.43 – 7.41 (m, 2H), 7.39 – 7.37 (m, 4H), 7.31 (m, 1H), 7.04 (dt, $J = 7.2$, 14.4 Hz, 1H), 6.88 (dt, $J = 1.2$, 15.4 Hz, 1H), 4.92 (m, 1H), 2.84 – 2.71 (m, 2H), 2.07 (bs, 1H).

$^{13}$C NMR: (125 MHz, CDCl$_3$) $\delta =$ 189.26, 145.42, 143.38, 139.18, 135.94, 130.00, 128.83, 128.68, 128.11, 128.01, 125.73, 73.20, 42.41.
IR: $f \,(\text{cm}^{-1}) = 3430, 3029, 1739, 1666, 1618, 1587, 1490, 1092, 1027, 669.$

\((E)\)-5-hydroxy-1-(naphthalen-1-yl)-5-phenylpent-2-en-1-one (2.31.4)

![2.31.4]

Procedure: Compound 2.31.4 was synthesized in accordance to general procedure A to give 2.31.4 in 9 % yield across two steps (62 mg, 0.20 mmol).

Rf: 0.35 in 80:20 (Hexanes : EtOAc)

$^1$H NMR: (400 MHz, CDCl$_3$) $\delta = 8.24$ (m, 1H), 7.95 (d, $J = 8.3$ Hz, 1H), 7.88 (m, 1H), 7.60 (m, 1H), 7.54 – 7.52 (m, 2H), 7.46 (m, 1H), 7.38 – 7.28 (m, 5H), 6.83 (dt, $J = 7.1, 14.2$ Hz, 1H), 6.68 (d, $J = 15.8$ Hz, 1H), 4.85 (m,1H), 2.81 – 2.67 (m, 2H) 2.19 (bs, 1H).

$^{13}$C NMR: (125 MHz, CDCl$_3$) $\delta = 195.71, 146.46, 143.38, 136.02, 133.77, 133.99, 131.15, 130.47, 128.64, 128.53, 127.93, 127.33, 126.36, 125.79, 125.71, 125.62, 124.33, 73.22, 40.42.

IR: 3422, 3059, 2926, 1721, 1664, 1644, 1614, 1591, 1508, 1493, 1453, 1435, 1396, 1287, 1198, 1110, 1045, 1026, 979, 802, 778, 700, 656, 602.

HRMS (ESI-TOF) $m/z$: (M - OH)$^+$ = 285.12739 calculated for C$_{21}$H$_{17}$O; Found 285.12701

\((E)\)-8-hydroxy-8-phenyloct-5-en-2-yn-4-one (2.31.5)

![2.31.5]

Procedure: Compound 2.31.5 was synthesized in accordance to general procedure A to give 2.31.5 in 79 % yield across two steps (290 mg, 1.36 mmol).
Rf: 0.32 in 80:20 (Hexanes : EtOAc)

$^1$H NMR: (500 MHz, CDCl$_3$) δ = 7.39 – 7.35 (m, 4H), 7.31 (m, 1H), 7.16 (dt, $J = 7.2$, 15.9 Hz, 1H) 6.19 (d, $J = 15.8$ Hz, 1H), 4.88 (m, 1H), 2.78 – 2.66 (m, 2H), 2.08 (bs, 1H), 2.04 (s, 3H).

$^{13}$C NMR: (125 MHz, CDCl$_3$) δ = 178.50, 149.10, 143.34, 134.43, 128.66, 128.05, 125.66, 90.71, 78.32, 73.14, 42.01, 4.10.

IR: $f$ (cm$^{-1}$) = 3424, 2219, 1640, 1616, 1493, 1453, 1268, 1026, 972, 759, 700, 543.

HRMS (ESI-TOF) m/z: (M + H)$^+$ = 215.10666 calculated for C$_{14}$H$_{15}$O$_2$; Found 215.1065.

(E)-8-hydroxy-2-methyl-8-phenylocta-2,5-dien-4-one (2.31.6)

Procedure: Compound 2.31.6 was synthesized in accordance to general procedure A to give 2.31.6 in 40 % yield across two steps (110 mg, 0.48 mmol).

Rf: 0.34 in 80:20 (Hexanes : EtOAc)

$^1$H NMR: (500 MHz, CDCl$_3$) δ = 7.36 – 7.35 (m, 4 H), 7.30 (m, 1H), 6.81 (dt, $J = 7.2$, 14.6 Hz, 1H), 6.22 – 6.18 (m, 2H), 4.83 (t, $J = 5.4$ Hz, 1H), 2.71 – 2.60 (m, 2H), 2.15 – 2.13 (m, 4H), 1.91 (s, 3H).

$^{13}$C NMR: (125 MHz, CDCl$_3$) δ = 190.09, 156.27, 143.54, 141.66, 134.49, 128.58, 127.86, 125.70, 122.73, 73.24, 42.18. 27.82, 20.96.

IR: $f$ (cm$^{-1}$) = 3405, 2910, 1653, 1629, 1602, 1493, 1447, 1356, 1243, 1123, 1043, 759, 700, 543.

HRMS (ESI-TOF) m/z: (M + H)$^+$ = 231.13796 calculated for C$_{15}$H$_{19}$O$_2$; Found 231.13684.
(E)-1-hydroxy-1-phenyltridec-3-en-5-one (2.31.7)

![Chemical Structure](image)

Procedure: Compound 2.31.7 was synthesized in accordance to general procedure A to give 2.31.7 in 25 % yield across two steps (123 mg, 0.43 mmol).

Rf: 0.43 in 80:20 hexanes : EtOAc

1H NMR: (400 MHz, CDCl3) δ = 7.38 – 7.34 (m, 4H), 7.32 – 7.28 (m, 1H), 6.81 (dt, J = 5.8, 12.7 Hz, 1H), 6.15 (dt, J = 1.1, 12.7 Hz, 1H), 4.85 (m, 1H), 2.72 – 2.61 (m, 2H), 2.51 (t, J = 5.9 Hz, 2H), 1.99 (bs, 1H), 1.61 – 1.55 (m, 2H), 1.31 – 1.23 (m, 10H), 0.88 (t, J = 5.5 Hz, 3H).

13C NMR: (125 MHz, CDCl3) δ = 200.63, 143.41, 142.27, 132.77, 128.65, 127.99, 125.68, 73.26, 42.06, 40.21, 31.83, 29.38, 29.30, 29.14, 24.24, 22.65, 14.09.

IR: f (cm⁻¹) = 3421, 2924, 2854, 1663, 1628, 1493, 1454, 1375, 1205, 1048, 976, 757, 544.

HRMS (ESI-TOF) m/z: (M – OH)⁺ = 271.20565 calculated for C₁₉H₂₇O; Found 271.20645.

(E)-6-hydroxy-1,6-diphenylhex-3-en-2-one (2.31.8)

![Chemical Structure](image)

Procedure: Compound 2.31.8 was synthesized in accordance to general procedure A to give 2.31.8 in 31 % yield across two steps (85 mg, 0.37 mmol).

Rf: 0.29 in 50:50 (Hexanes : EtOAc)

1H NMR: (400 MHz, CDCl3) δ = 7.37 – 7.27 (m, 8H), 7.19 – 7.17 (m, 2H), 6.90 (dt, J = 7.2, 14.4 Hz, 1H), 6.19 (dt, J = 1.4, 15.8 Hz, 1H), 4.82 (m, 1H), 3.81 (s, 2H), 2.71 – 2.59 (m, 2H), 1.92 (bs, 1H).
$^{13}$C NMR: (125 MHz, CDCl$_3$) $\delta = 197.23, 143.67, 143.2, 134.35, 131.79, 129.41, 128.68, 128.64, 127.99, 126.90, 125.66, 73.16, 47.54, 42.06.$

IR: $f$ (cm$^{-1}$) = 3433, 3029, 1663, 1625, 1494, 1339, 1047, 755, 700, 539.

HRMS (ESI-TOF) $m/z$: (M – OH)$^+$ 249.12739 calculated for C$_{18}$H$_{17}$O; Found 249.12738.

$(E)$-5-hydroxy-5-phenylpent-2-enal (2.31.9)

![Chemical Structure](image)

**Procedure:** 1-phenylbut-3-en-1-ol (3.71 g, 25.0 mmol) was dissolved in DCM (50.0 mL, 0.5 M). Freshly distilled acrolein (3.34 mL, 50.0 mmol) was added followed by Grubb’s II (106 mg, 0.13 mmol). The reaction mixture was stirred at 25 °C for 5.5 hours. Once the benzyl alcohol was fully consumed as monitored by TLC, the reaction mixture was cooled to room temperature and concentrated under vacuum. Crude reaction materials were purified with column chromatography using 100% hexanes to 60:40 (hexanes : EtOAc) to give 2.31.9 in 70% yield (3.10 g, 17.5 mmol) as a brown oil.

**Rf:** 0.17 in 80:20 (Hexanes : EtOAc)

$^1$H NMR: (400 MHz, CDCl$_3$) $\delta = 9.47$ (d, $J = 8.0$ Hz, 1H), 7.40 – 7.30 (m, 5H), 6.86 (dt, $J = 7.2$, 14.5 Hz, 1H), 6.16 (dd, $J = 8.0$, 15.8 HZ, 1H), 4.88 (t, $J = 7.2$ Hz, 1H), 2.85 – 2.71 (m, 2H), 2.38 (bs, 1H).

$^{13}$C NMR: (100 MHz, CDCl$_3$) $\delta = 194.05, 153.48, 145.79, 134.00, 128.62, 128.01, 126.25, 73.44, 43.82.$

IR: $f$ (cm$^{-1}$) = 3410, 3030, 2823, 1672, 1493, 1453, 1307, 1174, 1129, 1024, 970, 915, 699, 545.
3-acetyl-4-(2-oxo-2-phenylethyl)-6-phenyltetrahydro-2H-pyran-2-one (2.32.1)

**Procedure:** δ-hydroxyenone 2.31.1 (184 mg, 0.73 mmol) was dissolved in DCE (7.3 mL, 0.1 M) and acyl Meldrum acid 2.27 (149 mg, 0.80 mmol) was added. The reaction mixture was stirred at reflux for 1 hour. Once δ-hydroxyenone 2.31.1 was fully consumed as monitored by TLC, the reaction was cooled to room temperature and Cs₂CO₃ (593 mg, 1.82 mmol) was added. The reaction was stirred at room temperature for 5 hours. Upon completion as monitored by TLC, the reaction was quenched with a mixture of brine (15 mL) and DI H₂O (15 mL). The aqueous layer was extracted with DCM (5 x 25 mL). The combined organic layers were dried over Na₂SO₄ and reduced under vacuum. The crude material was purified with column chromatography using 100% hexanes to 40:60 (hexanes : EtOAc) to give product 2.32.1 in 59 % yield (145 mg, 0.43 mmol) as yellow oil.

**Rf:** 0.85 in 50:50 (Hexanes : EtOAc)

**CDCl₃** Ketone : Enol = 9.1:1, **DMSO:** Ketone : Enol = 20:1

**¹H NMR:** (500 MHz, CDCl₃) δ = 7.93 – 7.91 (m, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.47 (t, J = 7.9 Hz, 2H), 7.41 – 7.31 (m, 5H), 5.43 (dd, J = 2.3, 11.8 Hz, 1H), 3.72 (d, J = 7.7 Hz, 1H), 3.34 (m, 1H), 3.14 – 3.02 (m, 2H), 2.49 (s, 3H), 2.39 (ddd, J = 2.4, 5.2, 14.0 Hz, 1H), 1.73 (dt, J = 14.9, 17.6 HZ, 1H).

**¹³C NMR:** (125 MHz, CDCl₃) δ = 202.63, 197.63, 167.11, 138.56, 136.15, 133.68, 128.77, 128.64, 128.62, 127.95, 125.81, 81.01, 60.78, 43.35, 36.77, 30.38, 29.75.
\[ ^1H\ NMR: \ (500\ MHz,\ DMSO-d_6) \ \delta = 7.94 \ (d,\ J = 7.4\ Hz,\ 2H),\ 7.64 \ (t,\ J = 7.5\ Hz,\ 1H),\ 7.53 \ (t,\ J = 7.7\ Hz,\ 2H),\ 7.41 - 7.34 \ (m,\ 5H),\ 5.52 \ (m,\ 1H),\ 3.86 \ (d,\ J = 9.2\ Hz,\ 1H),\ 3.22 - 3.14 \ (m,\ 2H),\ 3.09 \ (m,\ 1H),\ 2.36 \ (s,\ 3H),\ 2.18 \ (dt,\ J = 4.2,\ 13.9\ Hz,\ 1H),\ 1.82 \ (q,\ J = 11.9\ Hz,\ 1H). \]

\[ ^{13}C\ NMR: \ (125\ MHz,\ DMSO-d_6) \ \delta = 203.87,\ 198.48,\ 167.50,\ 139.53,\ 136.49,\ 133.39,\ 128.73,\ 128.55,\ 128.42,\ 127.94,\ 126.16,\ 80.75,\ 59.82,\ 42.79,\ 35.47,\ 30.29,\ 30.07. \]

\[ IR: f (\text{cm}^{-1}) = 3063,\ 2923,\ 1708,\ 1679,\ 1329,\ 1026,\ 981,\ 911,\ 847,\ 753,\ 732,\ 690,\ 600,\ 516. \]

\[ HRMS\ (ESI-TOF)\ m/z: \ (M + H)^+ = 337.14344\ calculated\ for\ C_{21}H_{21}O_4;\ Found\ 337.14186. \]

(Z)-3-(1-hydroxyethylidene)-4-(2-(4-methoxyphenyl)-2-oxoethyl)-6-phenyltetrahydro-2H-pyran-2-one (2.32.2)

**Procedure:** \( \delta \)-hydroxyenone \( 2.31.2 \) (163 mg, 0.58 mmol) was dissolved in DCE (5.8 mL, 0.1 M) and acyl Meldrum acid \( 2.27 \) (118 mg, 1.20 mmol) was added. The reaction mixture was stirred at reflux for 1 hour. Once \( \delta \)-hydroxyenone \( 2.31.2 \) was fully consumed as monitored by TLC, the reaction was cooled to room temperature and \( \text{Cs}_2\text{CO}_3 \) (469 mg, 1.44 mmol) was added. The reaction was stirred at room temperature for 8 hours. Upon completion as monitored by TLC, the reaction was quenched with a mixture of brine (15 mL) and DI H\textsubscript{2}O (15 mL). The aqueous layer was extracted with DCM (5 x 25 mL). Combined organic layers were dried over Na\textsubscript{2}SO\textsubscript{4} and reduced under vacuum. The crude material was purified with column chromatography using 100% hexanes to 40:60 (hexanes : EtOAc) to give product \( 2.32.2 \) in 40 % yield (75 mg, 0.20 mmol) as a white powder.
Rf: 0.60 in 50:50 (Hexanes : EtOAc)

**CDCl₃:** Ketone : Enol = 10:1, **DMSO:** Ketone : Enol = 13:1

**¹H NMR:** (400 MHz, CDCl₃) δ = 7.90 (d, J = 8.9 Hz, 2H), 7.41 – 7.32 (m, 5H), 6.94 (d, J = 8.9 Hz, 2H), 5.43 (dd, J = 2.4, 11.9 Hz, 1H), 3.87 (s, 3H), 3.72 (d, J = 7.7 Hz, 1H), 3.31 (m, 1H), 3.01 (ddd, J = 6.4, 17.2, 26.1 Hz, 2H), 2.49 (s, 3H), 2.38 (m, 1H), 1.73 (dt, J = 11.8, 14.2 HZ, 1H).

**¹³C NMR:** (125 MHz, CDCl₃) δ = 202.46, 196.42, 166.97, 140.22, 138.57, 134.56, 129.40, 129.13, 128.68, 128.67, 125.82, 80.97, 60.79, 43.37, 36.76, 30.30, 29.74.

**¹H NMR:** (400 MHz, DMSO-d₆) δ = 7.92 (d, J = 8.8 Hz, 2H), 7.42 – 7.33 (m, 5H), 7.04 (d, J = 8.9 Hz, 2H), 5.50 (dd, J = 2.7, 11.9 Hz, 1H), 3.86 – 3.82 (m, 4H), 3.13 – 3.03 (m, 3H), 2.35 (s, 3H), 2.15 (dt, J = 3.8, 13.9 Hz, 1H), 1.82 (m, 1H).

**¹³C NMR:** (125 MHz, DMSO-d₆) δ = 203.85, 197.51, 167.44, 139.50, 138.28, 135.17, 129.86, 128.83, 128.54, 128.41, 126.14, 80.70, 59.73, 42.80, 35.42, 30.28, 29.96.

**IR:** f (cm⁻¹) = 2931, 2840, 1734, 1670, 1632, 1597, 1510, 1455, 1400, 1359, 1245, 12015, 1168, 1112, 1094, 964, 9′5, 831, 759, 735, 701, 489.

**HRMS (ESI-TOF) m/z:** (M + H)⁺ = 367.1540 calculated for C₂₂H₂₃O₅; Found 367.15394

3-acetyl-4-(2-(4-chlorophenyl)-2-oxoethyl)-6-phenyltetrahydro-2H-pyran-2-one (2.32.3)

** Procedure:** δ-hydroxyenone 2.31.3 (189 mg, 0.66 mmol) was dissolved in DCE (6.6 mL, 0.1 M) and acyl Meldrum acid 2.27 (135 mg, 0.73 mmol) was added. The reaction mixture was stirred at
reflux for 1 hour. Once δ-hydroxyenone 2.31.3 was fully consumed as monitored by TLC, the reaction was cooled to room temperature and Cs₂CO₃ (538 mg, 1.65 mmol) was added. The reaction was stirred at room temperature for 2 hours. Upon completion as monitored by TLC, the reaction was quenched with a mixture of brine (15 mL) and DI H₂O (15 mL). The aqueous layer was extracted with DCM (5 x 25 mL). Combined organic layers were dried over Na₂SO₄ and reduced under vacuum. The crude material was purified with column chromatography using 100% hexanes to 40:60 (hexanes : EtOAc) to give product 2.32.3 in 61 % yield (149 mg, 0.40 mmol) as a white solid.

Rf: 0.78 in 50:50 (Hexanes : EtOAc)

CDCl₃: Ketone : Enol = 10:1, DMSO: Ketone : Enol = 20:1

¹H NMR: (500 MHz, CDCl₃) δ = 7.86 (d, J = 8.7 Hz, 2H), 7.45 (d, J = 8.6 Hz, 2H), 7.39 – 7.30 (m, 5H), 5.42 (dd, J = 2.2, 11.8 Hz, 1H), 3.71 (d, J = 7.7 Hz, 1H), 3.32 (m, 1H), 3.09 – 2.99 (m, 2H), 2.49 (s, 3H), 2.37 (ddd, J = 2.4, 5.2, 14.2 Hz, 1H), 1.73 (dt, J = 11.9, 14.0 Hz, 1H).

¹³C NMR: (125 MHz, CDCl₃) δ = 202.46, 196.42, 166.97, 140.22, 138.19, 134.56, 129.40, 129.13, 128.68, 128.67, 125.82, 80.97, 60.79, 43.37, 36.76, 30.30, 29.74.

¹H NMR: (400 MHz, DMSO-d₆) δ = 7.94 (d, J = 8.7 Hz, 2H), 7.60 (d, J = 8.5 Hz, 2H), 7.41 – 7.35 (m, 5H), 5.50 (dd, J = 2.6, 11.8 Hz, 1H), 3.85 (d, J = 8.9 Hz, 1H), 3.22 – 3.13 (m, 2H), 3.07 (m, 1H), 2.36 (s, 3H), 2.18 (dt, J = 4.2, 13.8, Hz, 1H), 1.81 (q, J = 14 Hz, 1H).

¹³C NMR: (125 MHz, DMSO-d₆) δ = 204.20, 197.51, 167.44, 139.50, 138.27, 135.17, 129.86, 128.83, 128.54, 128.41, 126.14, 80.70, 59.73, 42.80, 34.99, 30.28, 29.97.

IR: f (cm⁻¹) = 3035, 2901, 1710, 1682, 1589, 1247, 1027, 700, 527.

HRMS (ESI-TOF) m/z: (M + H)⁺ = 371.10446 calculated for C₂₁H₂₀ClO₄; Found 371.10382
3-acetyl-4-(2-(naphthalen-1-yl)-2-oxoethyl)-6-phenyltetrahydro-2H-pyran-2-one (2.32.4)

**Procedure:** δ-hydroxyenone 2.31.4 (62 mg, 0.21 mmol) was dissolved in DCE (2.1 mL, 0.1 M) and acyl Meldrum acid 2.27 (42 mg, 0.23 mmol) was added. The reaction mixture was stirred at reflux for 1 hour. Once δ-hydroxyenone 2.31.4 was fully consumed as monitored by TLC, the reaction was cooled to room temperature and Cs₂CO₃ (167 mg, 0.51 mmol) was added. The reaction was stirred at room temperature for 17 hours. Upon completion as monitored by TLC, the reaction was quenched with a mixture of brine (15 mL) and DI H₂O (15 mL). The aqueous layer was extracted with DCM (5 x 25 mL). Combined organic layers were dried over Na₂SO₄ and reduced under vacuum. Crude material was purified with column chromatography using 100% hexanes to 40:60 (hexanes : EtOAc) to give product 2.32.4 in 52 % yield (41 mg, 0.11 mmol) as clear oil.

**Rf:** 0.69 in 50:50 (Hexanes : EtOAc)

**CDCl₃:** Ketone : Enol = 7.2:1, **DMSO:** Ketone : Enol 17:1

**¹H NMR:** (500 MHz, CDCl₃) δ = 8.62 (d, J = 8.5 Hz, 1H), 8.02 (d, J = 8.3 Hz, 1H), 7.88 (t, J = 8.7 Hz, 2H), 7.55 (tt, J = 6.9, 28.7 Hz, 3H), 7.42 – 7.29 (m, 5H), 5.46 (m, 1H), 3.78 (d, J = 7.8 Hz, 1H), 3.41 (m, 1H), 3.22 (dd, J = 6.4, 17.4 Hz, 1H), 3.13 (dd, J = 6.4, 17.4 Hz, 1H), 2.52 (s, 3H), 2.44 (m, 1H), 1.80 (q, J = 11.9 Hz, 1H).
\(^{13}\text{C NMR}\): (125 MHz, CDCl\(_3\)) \(\delta = 202.51, 201.52, 167.06, 138.28, 134.75, 134.03, 133.47, 130.06, 128.68, 128.63, 128.57, 128.32, 128.09, 126.66, 125.71, 125.52, 124.96, 124.30, 81.04, 58.63, 46.52, 36.88, 30.29.

\(^{1}\text{H NMR}\): (500 MHz, DMSO-d\(_6\)) \(\delta = 8.46 (d, J = 8.4 \text{ Hz}, 1\text{H}), 8.14 (d, J = 8.3 \text{ Hz}, 1\text{H}), 8.07 (d, J = 7.3 \text{ Hz}, 1\text{H}), 8.01 (d, J = 7.8 \text{ Hz}, 1\text{H}), 7.63 - 7.56 (m, 3\text{H}), 7.42 - 7.31 (m, 5\text{H}), 5.56 (dd, J = 2.8, 11.9 \text{ Hz}, 1\text{H}), 3.90 (d, J = 9.3 \text{ Hz}, 1\text{H}), 3.27 (m, 2\text{H}), 3.18 (m, 1\text{H}), 2.39 (s, 3\text{H}), 2.25 (m, 1\text{H}), 1.88 (q, J = 11.9 \text{ Hz}, 1\text{H}).

\(^{13}\text{C NMR}\): (125 MHz, DMSO-d\(_6\)) \(\delta = 203.88, 202.49, 167.53, 139.55, 135.05, 133.48, 129.31, 128.62, 128.57, 128.52, 128.44, 128.36, 127.86, 126.45, 126.18, 125.29, 124.79, 79.82, 60.90, 45.55, 34.92, 30.32, 30.17.

\(\text{IR} \): \(f (\text{cm}^{-1}) = 3060, 2922, 1708, 1675, 1593, 1507, 1454, 1435, 1395, 1356, 1323, 1243, 1085, 947, 909, 802, 775, 699, 647, 547, 477.

\(\text{HRMS (ESI-TOF)} \): \(m/z\): (M + H\(^+\)) = 387.1590 calculated for C\(_{25}\)H\(_{23}\)O\(_4\); Found 387.15893

3-acetyl-4-(2-oxopent-3-yn-1-yl)-6-phenyltetrahydro-2H-pyran-2-one (2.32.5)

\[ \text{Procedure: } \delta\text{-hydroxyenone 2.31.5 (145 mg, 0.67 mmol) was dissolved in DCE (6.8 mL, 0.1 M) and acyl Meldrum acid 2.27 (139 mg, 0.74 mmol) was added. The reaction mixture was stirred at reflux for 1 hour. Once } \delta\text{-hydroxyenone 2.31.5 was fully consumed as monitored by TLC, the reaction was cooled to room temperature and Cs}_2\text{CO}_3 (551 mg, 1.69 mmol) was added. The} \]
reaction was stirred at room temperature for 6 hours. Upon completion as monitored by TLC, the reaction was quenched with a mixture of brine (15 mL) and DI H$_2$O (15 mL). The aqueous layer was extracted with DCM (5 x 25 mL). Combined organic layers were dried over Na$_2$SO$_4$ and reduced under vacuum. The crude material was purified with column chromatography using 100% hexanes to 40:60 (hexanes : EtOAc) to give product 2.32.5 in 41 % yield (83 mg, 0.28 mmol) as yellow oil.

**Rf:** 0.72 in 50:50 (Hexanes : EtOAc)

**CDCl$_3$:** Ketone : Enol = 6.3:1, **DMSO:** Ketone : Enol = 7.1:1

$^1$H NMR: (400 MHz, CDCl$_3$) $\delta$ = 7.38 – 7.30 (m, 5H), 5.36 (dd, $J$ = 2.1, 11.8 Hz, 1H), 3.61 (d, $J$ = 7.9 Hz, 1H), 3.19 (m, 1H), 2.64 – 2.62 (m, 2H), 2.44 (s, 3H), 2.29 (ddd, $J$ = 2.4, 5.1, 14.2 Hz, 1H), 2.01 (s, 3H), 1.65 (m, 1H).

$^{13}$C NMR: (125 MHz, CDCl$_3$) $\delta$ = 200.71, 194.28, 167.85, 153.12, 138.11, 130.06, 128.99, 128.81, 125.57, 82.21, 66.04, 39.59, 36.03, 33.74, 27.87, 23.28.

$^1$H NMR: (500 MHz, DMSO-d$_6$) $\delta$ = 7.43 – 7.34 (m, 5H), 5.48 (dd, $J$ = 2.8, 11.9 Hz, 1H), 3.76 (d, $J$ = 9.6 Hz, 1H), 2.97 (m, 1H), 2.69 (dd, $J$ = 2.8, 6.7 Hz, 2H), 2.32 (s, 3H), 2.11 (m, 1H), 2.06 (s, 3H), 1.77 (q, $J$ = 11.9 Hz, 1H).

$^{13}$C NMR: (125 MHz, DMSO-d$_6$) $\delta$ = 203.65, 185.36, 167.29, 139.43, 128.58, 126.16, 91.63, 80.68, 80.10, 59.33, 49.33, 39.52, 35.07, 30.19, 29.69.

**IR:** $f$(cm$^{-1}$) = 2922, 2217, 1712, 1669, 1606, 1401, 1358, 1247, 1182, 1080, 1027, 971, 762, 701.

**HRMS (ESI-TOF) $m/z$:** (M + H)$^+$ = 299.12816 calculated for C$_{18}$H$_{19}$O$_4$; Found 299.12816
3-acetyl-4-(4-methyl-2-oxopent-3-en-1-yl)-6-phenyltetrahydro-2H-pyran-2-one (2.32.6)

**Procedure:** δ-hydroxyenone 2.31.6 (110 mg, 0.48 mmol) was dissolved in DCE (5 mL, 0.1 M) and acyl Meldrum acid 2.27 (98 mg, 0.53 mmol) was added. The reaction mixture was stirred at reflux for 1 hour. Once δ-hydroxyenone 2.31.6 was fully consumed as monitored by TLC, the reaction was cooled to room temperature and Cs$_2$CO$_3$ (391 mg, 1.20 mmol) was added. The reaction was stirred at room temperature for 2 hours. Upon completion as monitored by TLC, the reaction was quenched with a mixture of brine (10 mL) and DI H$_2$O (10 mL). The aqueous layer was extracted with DCM (5 x 25 mL). The combined organic layers were dried over Na$_2$SO$_4$ and reduced under vacuum. Crude material was purified via column chromatography using 100% hexanes to 40:60 (hexanes : EtOAc) to give product 2.32.6 in 65 % yield (98 mg, 0.31 mmol) as yellow oil.

**Rf:** 0.52 in 50:50 (Hexanes : EtOAc)

**$^1$H NMR:** (400 MHz, CDCl$_3$) δ = 7.38 – 7.31 (m, 5H), 6.00 (m, 1H), 5.39 (dd, $J = 2.3$, 11.8 Hz, 1H), 3.62, (d, $J = 7.9$ Hz, 1H), 3.13 (m, 1H), 2.50 (dd, $J = 3.6$, 6.4 Hz, 2H), 2.44 (s, 3H), 2.29 (ddd, $J = 2.3$, 5.0, 14.1 Hz, 1H), 2.13 (s, 3H), 1.88 (s, 3H), 1.65 (dt, $J = 11.9$, 14.2 Hz, 1H).

**$^{13}$C NMR:** (125 MHz, CDCl$_3$) δ = 202.64, 197.71, 167.23, 157.39, 138.78, 128.63, 128.57, 128.53, 123.17, 81.12, 60.63, 48.60, 36.78, 30.34, 29.85, 27.77, 21.32.

**IR:** $f$(cm$^{-1}$) = 2916, 1711, 1683, 1444, 1358, 1245, 1171, 1078, 1026, 984, 701.

**HRMS (ESI-TOF) m/z:** (M + H)$^+$ = 315.15909 calculated for C$_{19}$H$_{23}$O$_4$; Found 315.15968
**Procedure:** δ-hydroxyenone 2.31.7 (123 mg, 0.43 mmol) was dissolved in DCE (4.3 mL, 0.1 M) and acyl Meldrum acid 2.27 (87 mg, 1.20 mmol) was added. The reaction mixture was stirred at reflux for 1 hour. Once δ-hydroxyenone 2.31.7 was fully consumed as monitored by TLC, the reaction was cooled to room temperature and Cs$_2$CO$_3$ (349 mg, 1.07 mmol) was added. The reaction was stirred at room temperature for 5 hours. Upon completion as monitored by TLC, the reaction was quenched with a mixture of brine (15 mL) and DI H$_2$O (15 mL). The aqueous layer was extracted with DCM (5 x 25 mL). The combined organic layers were dried over Na$_2$SO$_4$ and reduced under vacuum. The crude material was purified with column chromatography using 100% hexanes to 40:60 (hexanes : EtOAc) to give product 2.32.7 in 64 % yield (89 mg, 0.38 mmol) as a yellow oil.

**Rf:** 0.77 in 50:50 (Hexanes : EtOAc)

**$^1$H NMR:** (400 MHz, CDCl$_3$) δ =7.40 – 7.31 (m, 5H), 5.38 (dd, $J = 2.4$, 11.7 Hz, 1H), 5.59 (d, $J = 7.9$ Hz, 1H), 3.13 (m, 1H), 2.50 (d, $J = 6.6$ Hz, 2H), 2.45 (s, 3H), 2.39 – 2.35 (m, 2H), 2.29 (ddd, $J = 2.5$, 5.1, 14.1 Hz, 1H), 1.63 (m, 1H), 1.28 – 1.22 (m, 12H), 0.87 (t, $J = 6.6$ Hz, 3H).

**$^{13}$C NMR:** (125 MHz, CDCl$_3$) δ = 208.78, 197.54, 168.76, 138.69, 128.62, 128.56, 128.57, 125.75, 82.02, 60.62, 47.15, 42.24, 36.70, 31.72, 30.12, 29.47, 29.42, 29.09, 29.01, 23.63, 22.55, 14.48.

**IR:** $\tilde{f}$ (cm$^{-1}$) = 2924, 2854, 1710, 1638, 1604, 1456, 1408, 1026, 760, 700.

**HRMS (ESI-TOF) m/z:** (M + H)$^+$ = 373.2373 calculated for C$_{23}$H$_{35}$O$_4$; Found 373.2370
3-acetyl-4-(2-oxo-3-phenylpropyl)-6-phenyltetrahydro-2H-pyran-2-one (2.32.8)

**Procedure:** δ-hydroxyenone 2.31.8 (85 mg, 0.31 mmol) was dissolved in DCE (3.0 mL, 0.1 M) and acyl Meldrum acid 2.27 (65 mg, 1.20 mmol) was added. The reaction mixture was stirred at reflux for 1 hour. Once δ-hydroxyenone 2.31.8 was fully consumed as monitored by TLC, the reaction was cooled to room temperature and Cs$_2$CO$_3$ (260 mg, 2.63 mmol) was added. The reaction was stirred at room temperature for 2 hours. Upon completion as monitored by TLC, the reaction was quenched with a mixture of brine (10 mL) and DI H$_2$O (10 mL). The aqueous layer was extracted with DCM (5 x 20 mL). The combined organic layers were dried over Na$_2$SO$_4$ and reduced under vacuum. The crude material was purified with column chromatography using 100% hexanes to 40:60 (hexanes : EtOAc) to give product 2.32.8 in 61 % yield (68 mg, 0.19 mmol) as a white solid.

**Rf:** 0.65 in 50:50 (Hexanes : EtOAc)

**CDCl$_3$:** Ketone : Enol = 10:1, **DMSO:** Ketone : Enol = 17:1

**$^1$H NMR:** (400 MHz, CDCl$_3$) $\delta = 7.40 – 7.28$ (m, 8H), $7.17$ (m, 2H), $5.33$ (dd, $J = 2.3, 11.7$ Hz, 1H), $3.66$ (s, 3H), $3.54$ (d, $J = 7.8$ Hz, 1H), $3.09$ (m, 1H), $2.54$ (d, $J = 6.4$ Hz, 1H), $2.40$ (s, 3H), $2.20$ (ddd, $J = 2.6, 5.2, 14.2$ Hz, 1H), $1.55$ (m, 1H).

**$^{13}$C NMR:** (125 MHz, CDCl$_3$) $\delta = 206.61, 203.16, 167.47, 139.50, 134.48, 129.64, 128.52, 128.40, 128.28, 126.57, 126.13, 80.75, 59.63, 48.96, 46.03, 35.24, 29.97, 29.61.
\textbf{H NMR:} (500 MHz, DMSO-\textit{d}_6) \( \delta = 7.41 - 7.08 \) (m, 10H), 5.44 (m, 1H), 3.72 (m, 2H), 3.07 (s, 1H), 2.89 (m, 1H), 2.61 (m, 1H), 2.27 (s, 3H), 2.04 (m, 1H), 1.68 (m, 1H), 1.16 (m, 1H).

\textbf{C NMR:} (125 MHz, DMSO-\textit{d}_6) \( \delta = 206.63, 207.79, 167.48, 139.05, 134.49, 129.65, 128.53, 128.37, 128.29, 126.58, 126.14, 82.13, 58.64, 49.76, 46.04, 35.25, 29.98, 29.62.

\textbf{IR:} \( \nu (\text{cm}^{-1}) = 3031, 2922, 1707, 1601, 1496, 1453, 1357, 1245, 1028, 757, 700.

\textbf{HRMS (ESI-TOF) \( m/z: \)} \((M + H)^+ = 337.14344\) calculated for C_{21}H_{21}O_4; Found 337.14493

5-(hydroxy(phenyl)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (2.02.1)

![Chemical structure](image)

**Procedure:** A round bottom flask was charged with Meldrum’s acid (1.8 g, 12.50 mmol) and DMAP (3.00 g, 24.40 mmol). The solid materials were dissolved in DCM (28 mL, 0.5 M) and cooled to -10 °C. A solution of benzoyl chloride (1.65 mL, 14.20 mmol) in DCM (2.0 mL) was added dropwise to the round bottom flask. The reaction was stirred at -10 °C for 1 hour and warmed to room temperature. Once Meldrum acid was fully consumed as monitored by TLC, the reaction was diluted with DCM (20 mL). The crude reaction was washed with KH\textsubscript{2}SO\textsubscript{4} (2%, 60 mL), HCl (10%, 60.0 mL), DI H\textsubscript{2}O (80.0 mL), and brine (80.0 mL). The combined aqueous layers were extracted once with DCM (50.0 mL) and the combined organic layers were dried over Na\textsubscript{2}SO\textsubscript{4}. The crude yellow solid was recrystallized from acetone to give 2.02.1 in 48 % yield (1.70 g, 6.83 mmol) as a yellow solid.

**Rf:** 0.14 in 50:50 (Hexanes : EtOAc)

\textbf{H NMR:} (500 MHz, CDCl\textsubscript{3}) \( \delta = 15.46 \) (bs, 1H), 7.69 - 7.67 (m, 2H), 7.60 (tt, \( J = 1.2, 7.5 \) Hz, 1H), 7.47 (t, \( J = 8.1 \) Hz, 2H), 1.85 (s, 6H).
\( ^{13} \text{C NMR} \): (125 MHz, CDCl\(_3\)) \( \delta = 188.81, 170.65, 159.40, 132.92, 132.42, 121.16, 127.69, 104.68, 90.71, 26.37. \)

\( \text{IR:} \ f(\text{cm}^{-1}) = 3063, 2998, 2942, 1787, 1739, 1656, 1603, 1551, 1489, 1394, 1379, 1201, 1136, 1075, 1023, 934, 896, 865, 774, 724, 643, 616, 572, 503, 411. \)

**X-ray Structure:**

![X-ray Structure Image]

\( 5\text{-}(\text{furan-2-yl(hydroxy)methylene})\text{-2,2-dimethyl-1,3-dioxane-4,6-dione (2.02.2)} \)

**Procedure:** A round bottom flask was charged with Meldrum acid (977 mg, 6.78 mmol) and DMAP (1.61 g 13.2 mmol). The solid materials were dissolved in DCM (14 mL, 0.5 M) and cooled to -10 °C. A solution of 2-furoyl chloride (755 \( \mu \)L, 7.66 mmol) in DCM (5 mL) was added dropwise to the round bottom flask. The reaction was stirred at -10 °C for 1 hour and warmed to room temperature. Once Meldrum acid was fully consumed as monitored by TLC, the reaction was diluted with DCM (15 mL). The crude reaction was washed with KHSO\(_4\) (2%, 20 mL), HCl (10%, 20 mL), DI H\(_2\)O (40 mL), and brine (40 mL). The combined aqueous layers were extracted once with DCM (30 mL) and the combined organic layers were dried over Na\(_2\)SO\(_4\). The crude purple solid **2.02.2** was given in quantitative yield (1.61 g, 6.78 mmol) and used without further purification as a 3.6:1.0 mixture of enol: ketone.
Rf: 0.03 in 50:50 (Hexanes : EtOAc)

\(^1\)H NMR: (400 MHz, CDCl\(_3\)) \(\delta = 15.78\) (s, 1H), 8.12 (d, \(J = 3.9\) Hz, 1H), 7.77 (m, 1H), 6.67 (m, 1H), 1.80 (s, 6H).

\(^1\)C NMR: (125 MHz, CDCl\(_3\)) \(\delta = 173.60, 171.63, 159.41, 148.75, 146.05, 126.15, 113.40, 104.93, 88.43, 26.62\).

IR: \(f(\text{cm}^{-1}) = 2929, 2788, 1781, 1729, 1653, 1599, 1550, 1459, 1395, 1378, 1304, 1204, 1156, 1139, 1091, 1022, 926, 907, 885, 826, 800, 770, 727, 652\).

5-(1-hydroxypent-4-en-1-ylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (2.02.3)

![Chemical structure](image)

**Procedure:** To a solution of DCM (100 mL, 0.1 M), 4-pentenoic acid (1.02 mL, 10.0 mmol) and Meldrum’s acid (1.4g, 10 mmol) was added DCC (N,N'-dicyclohexylcarbodiimide, 2.27 g, 11.0 mmol) and DMAP (1.28 g, 10.5 mmol). The reaction was stirred for 18 hours. Upon completion as monitored by TLC, the reaction was diluted with DCM (20.0 mL). The crude reaction was washed with KH\(_2\)SO\(_4\) (2%, 40mL), HCl (10%, 40 mL), DI H\(_2\)O (60.0 mL), and brine (60.0 mL). The combined aqueous layers were extracted once with DCM (35.0 mL) and dried over Na\(_2\)SO\(_4\). After the combined organic layers were reduced under vacuum the crude reaction material was filtered through celite and washed several times with hexanes. The combined organic layers were reduced under vacuum. The filtered material was purified with column chromatography using 100 % DCM to 90:10 DCM : MeOH to give 2.02.3 in 87 % yield (1.97 g, 8.70 mmol).

Rf: 0.12 in 60:40 (Hexanes : EtOAc)
\textbf{1H NMR:} (400 MHz, CDCl$_3$) $\delta = 15.33$ (s, 1H), 5.85 (m, 1H), 5.11 – 5.01 (m, 2H), 3.23 – 3.17 (m, 2H), 2.51 – 2.45 (m, 2H), 1.74 (s, 6H).

\textbf{13C NMR:} (100 MHz, CDCl$_3$) $\delta = 197.00, 170.49, 160.16, 136.02, 116.17, 104.85, 91.61, 34.93, 29.80, 26.78.$

\textbf{IR:} $f (\text{cm}^{-1}) = 3080, 3000, 2944, 1737, 1661, 1569, 1405, 1381, 1336, 1279, 1202, 1153, 1027, 995, 644, 461.$

\textbf{5-(hydroxy(tetrahydro-2H-pyran-4-yl)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (2.02.4)}

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\textbf{2.02.4}};
\end{tikzpicture}
\end{center}

\textbf{Procedure:} To a solution of DCM (100 mL, 0.1 M) and 4-pentenoic acid (1.02 mL, 10.0 mmol) was added DCC (N,N’- dicyclohexylcarbodiimide, 2.27 g, 11 mmol) and DMAP (1.28 g, 10.5 mmol). The reaction was stirred for 18 hours. Upon completion as monitored by TLC, the reaction was diluted with DCM (20.0 mL). The crude reaction was washed with KHSO$_4$ (2%, 40 mL), HCl (10%, 40 mL), DI H$_2$O (60.0 mL), and brine (60.0 mL). The combined aqueous layers were extracted once with DCM (35.0 mL) and dried over Na$_2$SO$_4$. After the combined organic layers were reduced under vacuum the crude reaction material was filtered through celite and washed several times with hexanes. The combined organic layers were reduced under vacuum. The filtered material was purified with column chromatography using 100 % DCM to 90:10 DCM : MeOH to give \textbf{2.02.4} in 37 % yield (647 mg, 2.52 mmol).

\textbf{Rf:} 0.4 in 25:75 (Hexanes : EtOAc)

\textbf{1H NMR:} (500 MHz, CDCl$_3$) $\delta = 15.61$ (s, 1H), 4.09 – 4.03 (m, 3H), 3.52 (td, $J = 1.8, 12$ Hz, 2H), 1.91 (qd, $J = 4.4, 12.9$ Hz, 2H), 1.75 – 1.72 (m, 8H).
**C NMR:** (100 MHz, CDCl$_3$) $\delta =$ 198.88, 170.89, 159.99, 104.91, 90.54, 67.12, 40.27, 28.54, 26.79.

**IR:** $f$(cm$^{-1}$) = 2956, 2845, 1734, 1657, 1569, 1415, 1383, 1360, 1321, 1293, 1202, 1153, 1115, 1052, 1017, 986, 865, 801, 649, 553, 505, 470.

**tert-butyl 4-((2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)(hydroxy)methyl)piperidine-1-carboxylate (2.02.5)**

![Chemical structure](image)

**Procedure:** To a solution of DCM (7.3 mL, 0.4 M), the desired carboxylic acid (666 mg, 2.9 mmol), and DMAP (562 mg, 4.60 mmol) was added a solution of DCC (N,N'-dicyclohexylcarbodiimide, 722 mg, 3.50 mmol) in DCM (3.50 mL). The reaction was stirred at room temperature for 6.5 hours. Upon completion as monitored by TLC, the crude reaction material was filtered directly through celite. The filtrate as washed with 1M HCl (100 ml) and brine (100 ml). The organic layer was dried over Na$_2$SO$_4$ and reduced under vacuum to give 2.02.5 in 78 % (818 mg, 2.30 mmol) and used without further purification.

**Rf:** 0.25 in 100% EtOAc

**H NMR:** (500 MHz, CDCl$_3$) $\delta =$ 15.58 (s, 1H), 4.32 – 4.14 (m, 2H), 3.95 (tt, $J =$ 4.0, 11.9 Hz, 1H), 2.88 – 2.76 (m, 2H), 1.85 – 1.79 (m, 2H), 1.74 (s, 6H), 1.73 – 1.67 (m, 2H), 1.47 (s, 9H).

**C NMR:** (100 MHz, CDCl$_3$) $\delta =$ 199.81, 168.79, 161.55, 153.65, 101.00, 91.15, 79.72, 38.13, 30.60, 27.54, 26.05.

**IR:** $f$(cm$^{-1}$) = 3133, 2923, 2853, 1712, 1665, 156, 1497, 1462, 1393, 1357, 1198, 969, 911 833.
3-benzoyl-4-(2-oxopropyl)-6-phenyltetrahydro-2H-pyran-2-one (2.33.1)

**Procedure:** δ-hydroxyenone 2.26 (200 mg, 1.05 mmol) was dissolved in DCE (10.5 mL, 0.1 M) and acyl Meldrum acid 2.02.1 (288 mg, 1.2 mmol) was added. The reaction mixture was stirred at reflux for 1 hour. Once δ-hydroxyenone 2.26 was fully consumed as monitored by TLC, the reaction was cooled to room temperature and Cs₂CO₃ (857 mg, 2.63 mmol) was added. The reaction was stirred at room temperature for 10 hours. Upon completion as monitored by TLC, the reaction was quenched with a mixture of brine (15 mL) and DI H₂O (15 mL). The aqueous layer was extracted with DCM (5 x 25 mL). The combined organic layers were dried over Na₂SO₄ and reduced under vacuum. The crude material was purified with column chromatography using 100% hexanes to 40:60 (hexanes : EtOAc) to give product 2.33.1 in 76 % yield (267 mg, 0.80 mmol) as a white solid.

**Rf:** 0.53 in 50:50 (Hexanes : EtOAc)

**¹H NMR:** (400 MHz, CDCl₃) δ = 8.09 – 8.07 (m, 2H), 7.62 (tt, J = 1.4, 6.7 Hz, 1H), 7.52 (t, J = 7.9 Hz, 2H), 7.39 – 7.32 (m, 5H), 5.60 (dd, J = 2.7, 11.8 Hz, 1H), 4.52 (d, J = 8.6 Hz, 1H), 3.29 (m, 1H), 2.54 (dd, J = 5.4, 7.4 Hz, 2H), 2.42 (ddd, J = 2.8, 4.7, 14.1 Hz, 1H). 2.08 (s, 3H), 1.80 (m, 1H).

**¹³C NMR:** (125 MHz, CDCl₃) δ = 206.06, 195.60, 167.32, 138.82, 136.28, 133.84, 129.24, 128.71, 128.54 128.47, 125.78, 81.32, 54.26, 47.36, 36.33, 31.14, 30.21.

**IR:** $\nu$ (cm⁻¹) = 3063, 3034, 2932, 1714, 1677, 1596, 1580, 1496, 1448, 1409, 1086, 1052, 1028, 881, 858, 629, 487.
HRMS (ESI-TOF) \(m/z\): \((M + H)^+ = 337.14344\) calculated for \(C_{21}H_{21}O_4\); Found 337.14284

3-(furan-2-carbonyl)-4-(2-oxopropyl)-6-phenyltetrahydro-2H-pyran-2-one (2.33.2)

![Chemical Structure](image)

**Procedure**: \(\delta\)-hydroxyenone 2.26 (150 mg, 0.80 mmol) was dissolved in DCE (8.0 mL, 0.1 M) and acyl Meldrum acid 2.02.2 (207 mg, 0.87 mmol) was added. The reaction mixture was stirred at reflux for 1 hour. Once \(\delta\)-hydroxyenone 2.26 was fully consumed as monitored by TLC, the reaction was cooled to room temperature and \(Cs_2CO_3\) (642 mg, 2.63 mmol) was added. The reaction was stirred at room temperature for 8 hours. Upon completion as monitored by TLC, the reaction was quenched with a mixture of brine (15 mL) and DI H\(_2\)O (15 mL). The aqueous layer was extracted with DCM (5 x 25 mL). The combined organic layers were dried over Na\(_2\)SO\(_4\) and reduced under vacuum. Crude materials were purified with column chromatography using 100% hexanes to 50:50 (hexanes : EtOAc) to give product 2.33.2 in 62% yield (160 mg, 0.49 mmol) as a brown solid.

**Rf**: 0.35 in 50:50 (Hexanes : EtOAc)

**\(^1\)H NMR**: (400 MHz, CDCl\(_3\)) \(\delta = 7.65\) (s, 1H), 7.40 – 7.35 (m, 6H), 6.60 (dd, \(J = 1.7, 3.7\) Hz, 1H), 5.59 (dd, \(J = 2.7, 11.8\) Hz, 1H), 4.06 (d, \(J = 9.8\) Hz, 1H), 3.18 (m, 1H), 2.63 (dd, \(J = 4.5, 18.0\) Hz, 1H), 2.51 (dd, \(J = 8.1, 18.2\) Hz, 1H), 2.40 (m, 1H), 2.09 (s, 3H), 1.74 (dt, \(J = 11.9, 14.1\) Hz, 1H).

**\(^{13}\)C NMR**: (100 MHz, CDCl\(_3\)) \(\delta = 205.95, 183.43, 167.13, 151.74, 147.43, 138.81, 128.63, 128.57, 125.79, 119.73, 113.06, 81.49, 55.74, 47.29, 36.54, 30.82, 30.34.
IR: \( f (\text{cm}^{-1}) = 3133, 2923, 2853, 1717, 1665, 1566, 1497, 1462, 1393, 1357, 1275, 1227, 1198, 1084, 1054, 911, 850, 699 \).

HRMS (ESI-TOF) \( m/z \): \((M + H)^+ = 327.1227 \) calculated for \( \text{C}_{19}\text{H}_{19}\text{O}_5 \); Found 372.12197

4-(2-oxopropyl)-3-(pent-4-enoyl)-6-phenyltetrahydro-2H-pyran-2-one (2.33.3)

\[
\begin{align*}
\text{OH} & \quad \text{O} \\
\text{Me} & \quad \text{O} \\
\text{Me} & \quad \text{O} \\
\end{align*}
\]

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
2.26 & \quad 2.02.3 & \quad 2.33.3 \\
\end{align*}
\]

\text{Procedure:} \ \delta\text{-hydroxyenone 2.26 (200 mg, 1.05 mmol), was dissolved in DCE (10.5 mL, 0.1M) and Meldrum acid derivative 2.02.3 (262 mg, 1.20 mmol) was added. The reaction mixture was stirred at reflux for 1 hour. Once \( \delta\text{-hydroxyenone 2.26} \) was consumed, as monitored by TLC, the reaction was cooled to room temperature and \( \text{Cs}_2\text{CO}_3 \) (857 mg, 2.63 mmol) was added. The reaction was stirred at room temperature for 5 hours. Upon completion as monitored by TLC, the reaction was quenched with a solution of brine (15 mL) and DI H\(_2\)O (15 mL). Aqueous layer was extracted with DCM (5 x 25 mL). Combined organic layers were dried over \( \text{Na}_2\text{SO}_4 \) and reduced under vacuum. Crude material was purified with column chromatography using 100% hexanes to 40:60 (hexanes : EtOAc) to give 2.33.3 in 67% yield (220 mg, 0.70 mmol) as yellow oil.

\text{Rf:} \ 0.67 \text{ in 50:50 (Hexanes : EtOAc)}

\(^1\text{H NMR:} \ (400 \text{ MHz, CDCl}_3) \ \delta = 7.40 – 7.31 \ (m, 5H), 5.84 \ (ddt, J = 6.4, 10.7, 17.1 \text{ Hz, 1H}), 5.40 \ (dd, J = 2.6, 11.7 \text{ Hz, 1H}), 5.07 \ (dd, J = 1.7, 17.2 \text{ Hz, 1H}), 5.01 \ (m, 1H), 3.60 \ (d, J = 7.7 \text{ Hz, 1H}), 3.13 \ (m, 1H), 3.04 \ (m, 1H), 2.76 \ (dt, J = 7.7, 18.2 \text{ Hz, 1H}), 2.52 \ (d, J = 6.6 \text{ Hz, 2H}), 2.41 \ (m, 2H), 2.29 \ (ddd, J = 2.3, 5.1, 14.2 \text{ Hz, 1H}), 2.13 \ (s, 3H), 1.62 \ (dt, J = 11.8, 14.3 \text{ Hz, 1H}).
$^{13}\text{C NMR}$: (125 MHz, CDCl$_3$) $\delta =$ 206.17, 203.97, 167.01, 138.66, 136.62, 128.62, 128.58, 125.78, 115.48, 80.94, 59.24, 48.13, 42.08, 36.20, 30.16, 29.49, 27.35.

IR: $f$ (cm$^{-1}$) = 2920, 1710, 1640, 1601, 1497, 1437, 1403, 1358, 1240, 1174, 1000, 916, 759, 700, 658, 478.

HRMS (ESI-TOF) $m/z$: (M + H)$^+$ = 315.15909 calculated for C$_{19}$H$_{23}$O$_4$; Found 315.15982.

4-(2-oxopropyl)-6-phenyl-3-(tetrahydro-$2H$-pyran-4-carbonyl)tetrahydro-$2H$-pyran-2-one (2.33.4)

![Chemical structure](attachment:image.png)

**Procedure:** $\delta$-hydroxyenone 2.26 (200 mg, 1.05 mmol) was dissolved in DCE (10.5 mL, 0.1 M) and acyl Meldrum acid 2.02.4 (297 mg, 1.20 mmol) was added. The reaction mixture was stirred at reflux for 1 hour. Once $\delta$-hydroxyenone 2.26 was fully consumed as monitored by TLC, the reaction was cooled to room temperature and Cs$_2$CO$_3$ (857 mg, 2.63 mmol) was added. The reaction was stirred at room temperature for 5 hours. Upon completion as monitored by TLC, the reaction was quenched with a mixture of brine (15 mL) and DI H$_2$O (15 mL). The aqueous layer was extracted with DCM (5 x 25 mL). The combined organic layers were dried over Na$_2$SO$_4$ and reduced under vacuum. The crude material was purified with column chromatography using 100% hexanes to 40:60 (hexanes : EtOAc) to give product 2.33.4 in 72 % yield (261 mg, 0.76 mmol) as a yellow oil.

**Rf:** 0.33 in 50:50 (Hexanes : EtOAc)
$^1$H NMR: (400 MHz, CDCl$_3$) $\delta$ = 7.41 – 7.32 (m, 5H), 5.41 (dd, $J$ = 2.7, 11.7 Hz, 1H), 4.06 – 4.00 (m, 2H), 3.82 (d, $J$ = 7.8 Hz, 1H), 3.51 – 3.41 (m, 2H), 3.17 – 3.11 (m, 2H), 2.49 (d, $J$ = 6.4 Hz, 2H), 2.29 (m, 1H), 2.13 (s, 3H), 1.92 – 1.79 (m, 3H), 1.72 – 1.60 (m, 2H).

$^{13}$C NMR: (125 MHz, CDCl$_3$) $\delta$ = 206.18, 167.03, 138.59, 128.66, 128.64, 81.12, 67.20, 66.93, 57.62, 47.72, 47.64, 36.44, 30.29, 29.26, 28.58, 27.67.

IR: $\tilde{f}$ (cm$^{-1}$) = 2954, 2848, 1704, 1629, 1444, 1357, 1239, 1203, 1166, 1111, 1087, 1019, 731, 700.

HRMS (ESI-TOF) m/z: (M – OH)$^+$ = 327.15909 calculated for C$_{20}$H$_{23}$O$_4$; Found 327.15974.

**tert-buty l 4-(2-oxo-4-(2-oxopropyl)-6-phenyltetrahydro-2H-pyran-3-carbonyl)piperidine-1-carboxylate (2.33.5)**

![Chemical structure](image)

**Procedure:** $\delta$-hydroxyenone 2.26 (197 mg, 1.04 mmol) was dissolved in DCE (10.4 mL, 0.1 M) and acyl Meldrum acid 2.02.5 (406 mg, 1.10 mmol) was added. The reaction mixture was stirred at reflux for 1 hour. Once $\delta$-hydroxyenone 2.26 was fully consumed as monitored by TLC, the reaction was cooled to room temperature and Cs$_2$CO$_3$ (847 mg, 2.60 mmol) was added. The reaction was stirred at room temperature for 5 hours. Upon completion as monitored by TLC, the reaction was quenched with a mixture of brine (15 mL) and DI H$_2$O (15 mL). The aqueous layer was extracted with DCM (5 x 25 mL). The combined organic layers were dried over Na$_2$SO$_4$ and reduced under vacuum. The crude material was purified with column chromatography using 100% hexanes to 40:60 (hexanes : EtOAc) to give product 2.33.5 in 78 % yield (358 mg, 0.81 mmol) as a white powder.
Rf: 0.35 in 50:50 (hexanes : EtOAc)

$^1$H NMR: (400 MHz, CDCl$_3$) $\delta = 7.39 - 7.32$ (m, 5H), 5.40 (dd, $J = 2.6$, 11.9 Hz, 1H), 4.24 – 4.05 (m, 2H), 3.83 (d, $J = 8.0$ Hz, 1H), 3.14 (m, 1H), 3.03 (m, 1H), 2.89 – 2.68 (m, 3H), 2.49 (d, $J = 6.2$ Hz, 2H), 2.31 (ddd, $J = 1.9$, 4.8, 13.8 Hz, 1H), 2.13 (s, 3H), 1.97 (m, 1H), 1.82 (m, 1H), 1.72 – 1.61 (m, 2H), 1.46 (s, 9H).

$^{13}$C NMR: (125 MHz, CDCl$_3$) $\delta = 206.43$, 206.09, 168.48, 152.18, 138.57, 128.60, 125.86, 125.74, 81.11, 79.54, 48.66, 47.62, 42.89, 36.34, 30.22, 29.28, 28.35, 27.85, 27.04.

IR: $\nu$ (cm$^{-1}$) = 2973, 2929, 2858, 1688, 1450, 1423, 1365, 1276, 1238, 1128, 1089, 1017, 972, 700.

HRMS (ESI-TOF) $m/z$: (M + H)$^+$ = 344.18618 calculated for C$_{20}$H$_{26}$O$_4$; Found 344.18696; Loss of BOC group: (M + Na)$^+$ = 466.22001 calculated for C$_{25}$H$_{33}$NNaO$_6$; Found 466.22055.

6,8-dihydroxy-3-(4-methoxyphenyl)-6-methyl-3,4,4a,5,6,7-hexahydro-1H-isochromen-1-one (2.35)

Procedure: Compound 2.30.1 was dissolved in an equal mixture of hexanes and DCM. The solvent was allowed to evaporate in a place free from vibration. Upon full evaporation of the solvent from the sample, it was analyzed for crystals. If no crystals were present, an equal portion of hexanes and DCM was again used to dissolve the material. This process was repeated for 7 months, until crystalline material was observed. The majority of the crystalize material was compound 2.30.1 with only trace crystals of 2.35 present in the sample.
X-ray Structure:

5-(1-hydroxy-2-phenylethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (2.36.1)

Procedure: A round bottom flask was charged with Meldrum acid (1.00 g, 7.0 mmol) and DMAP (1.66 g, 13.6 mmol). The solid materials were dissolved in DCM (14 mL, 0.5 M) and cooled to -10 °C. A solution of phenylacetyl chloride (1.1 mL, 8.0 mmol) in DCM (1.0 mL) was added dropwise to the round bottom flask. The reaction was stirred at -10 °C for 1 hour then warmed to room temperature. Once Meldrum’s acid was fully consumed as monitored by TLC, the reaction was diluted with DCM (5.0 mL). The crude reaction was washed with KHSO$_4$ (2%, 20.0 mL), HCl (10%, 20 mL), DI H$_2$O (25.0 mL), and brine (25.0 mL). The combined aqueous layers were extracted once with DCM (15.0 mL) and the combined organic layers were dried over Na$_2$SO$_4$. The crude yellow solid was recrystallized from acetone to give 2.36.1 in 50% yield (918 mg, 3.50 mmol) as a light yellow solid.

R$_f$: 0.12 in 50:50 (Hexanes : EtOAc)

$^1$H NMR: (400 MHz, CDCl$_3$) $\delta = 15.32$ (s 1H), 7.40 – 7.28 (m, 5H), 4.43 (s, 2H), 1.72 (s, 6H).
$^{13}$C NMR: (125 MHz, CDCl$_3$) $\delta$ = 194.46, 170.36, 160.14, 134.00, 129.46, 128.55, 127.35, 104.81, 91.34, 40.64, 26.66.

IR: $f$(cm$^{-1}$) = 3063, 3037, 2999, 2942, 1739, 1647, 1571, 1495, 1452, 1417, 1373, 1329, 1201, 1074, 994, 957, 897, 832, 735, 711, 692, 619, 604, 563, 536, 504, 457, 411.

X-ray Structure:

5-(2-(4-bromophenyl)-1-hydroxyethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (2.36.2)

Procedure: A round bottom flask was charged with Meldrum’s acid (546 mg, 3.79 mmol) and DMAP (898 mg, 7.35 mmol). The solid materials were dissolved in DCM (8.0 mL, 0.5 M) and cooled to -10 °C. A solution of 4-(bromophenyl) acetylchloride (636 μL, 40.0 mmol) in DCM (4.0 mL) was added dropwise to the round bottom flask. The reaction was stirred at -10 °C for 1 hour and warmed to room temperature. Once Meldrum acid was fully consumed as monitored by TLC, the reaction was diluted with DCM (10 mL). The crude reaction was washed with KHSO$_4$ (2%, 15 mL), HCl (10%, 15 mL), DI H$_2$O (20 mL), and brine (20 mL). The combined aqueous layers were extracted once with DCM (30 mL) and the combined organic layers were dried over Na$_2$SO$_4$ and reduced under vacuum. The crude yellow solid was recrystallized from acetone to give 2.36.2 in 84 % yield (1.08 g, 3.16 mmol) as a yellow solid.

Rf: 0.05 in 50:50 (Hexanes : EtOAc)
**H NMR:** (400 MHz, CDCl₃) δ = 15.34 (s, 1H), 7.45 (d, J = 8.4 Hz, 2H), 7.26–7.28 (m, 2H), 4.36 (s, 2H), 1.72 (s, 6H).

**C NMR:** (125 MHz, CDCl₃) δ = 193.68, 170.36, 160.12, 132.95, 131.73, 131.25, 121.58, 105.03, 91.46, 40.10, 26.79.

**IR:** f (cm⁻¹) = 3000, 2942, 1735, 1658, 1564, 1487, 1404, 1380, 1299, 1269, 1203, 1151, 1111, 1071, 1027, 960, 640. 543, 505, 484, 413.

**X-ray Structure:**

**5-(1-hydroxy-2-(4-methoxyphenyl)ethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (2.36.3)**

**Procedure:** A round bottom flask was charged with Meldrum’s acid (346 mg, 2.40 mmol) and DMAP (569 mg, 4.66 mmol). The solid materials were dissolved in DCM (14 mL, 0.5 M) and cooled to -10 °C. A solution of 4-methoxy phenylacetylchloride (414 µL, 2.71 mmol) in DCM (3.0 mL) was added dropwise to the round bottom flask. The reaction was stirred at -10 °C for 1 hour and warmed to room temperature. Once Meldrum acid was fully consumed as monitored by TLC, the reaction was diluted with DCM (15.0 mL). The crude reaction was washed with KHSO₄ (2%, 10.0 mL), HCl (10%, 10.0 mL), DI H₂O (20.0 mL), and brine (20.0 mL). The combined aqueous layers were extracted once with DCM (20.0 mL) and the combined organic layers were dried over
Na₂SO₄. The crude yellow solid was recrystallized from acetone to give 2.36.3 in 50% yield (396 mg, 1.36 mmol) as a yellow solid.

Rf: 0.19 in 50:50 (Hexanes : EtOAc)

**¹H NMR:** (500 MHz, CDCl₃) δ = 15.32 (bs, 1H), 7.32 – 7.30 (d, J = 8.8 Hz, 2H), 6.87 – 6.85 (m, 2H), 4.35 (s, 2H), 3.79 (s, 3H), 1.72 (s, 6H).

**¹³C NMR:** (125 MHz, CDCl₃) δ = 195.08, 159.01, 130.71, 130.38, 126.12, 114.10, 104.86, 91.13, 55.24, 39.75, 30.91, 26.83.

**IR:** ν (cm⁻¹) = 2999, 2939, 2837, 1734, 1662, 1609, 1562, 1510, 1402, 1296, 1201, 1177, 1150, 1107, 1028, 961, 920, 855, 818, 802, 699, 504, 408.

**5-(1-hydroxy-2-(4-(trifluoromethyl)phenyl)ethyldene)-2,2-dimethyl-1,3-dioxane-4,6-dione (2.36.4)**

**Procedure:** A round bottom flask was charged with Meldrum’s acid (287 mg, 1.99 mmol) and DMAP (472 mg, 3.86 mmol). The solid materials were dissolved in DCM (4 mL, 0.5 M) and cooled to -10 °C. A 4-trifluoromethyl phenylacetylchloride (369 μL, 2.25 mmol) in DCM (2.5 mL) was added dropwise to the round bottom flask. The reaction was stirred at -10 °C for 1 hour and warmed to room temperature. Once Meldrum acid was fully consumed as monitored by TLC, the reaction was diluted with DCM (10.0 mL). The crude reaction was washed with KHSO₄ (2%, 15.0 mL), HCl (10%, 15.0 mL), DI H₂O (20.0 mL), and brine (20.0 mL). The combined aqueous layers were extracted once with DCM (20.0 mL) and the combined organic layers were dried over
Na₂SO₄. The crude yellow solid was recrystallized from acetone to give 2.36.4 in 83 % yield (547 mg, 1.65 mmol) as a yellow solid.

**Rf:** 0.13 in 50:50 hexanes : EtOAc

**¹H NMR:** (500 MHz, CDCl₃) δ = 15.39 (s, 1H), 7.59 (d, J = 8.2 Hz, 2H), 7.52 (d, J = 8.1 Hz, 2H), 4.48 (s, 2H), 1.73 (s, 6H).

**¹³C NMR:** (125 MHz, CDCl₃) δ = 193.31, 137.98, 130.00, 129.84, 129.77, 125.64, 125.61, 105.24, 91.74, 48.96, 40.58, 26.90.

**IR:** ν (cm⁻¹) = 3063, 3038, 2999, 2942, 1739, 1647, 1571, 1495, 1452, 1417, 1373, 1329, 1201, 1065, 994, 957, 897, 832, 738, 711, 692, 619, 603, 563, 536, 504, 457, 411

**6,8-dihydroxy-3,7-diphenyl-3,4,4a,5,6,7-hexahydro-1H-isochromen-1-one (2.37.1)**

**Procedure:** δ-hydroxyenanal 2.31.9 (123 mg, 0.70 mmol) was dissolved in DCE (7.0 mL, 0.1 M) and acyl Meldrum acid 2.36.1 (202 mg, 0.77 mmol) was added. The reaction mixture was stirred at reflux for 1 hour. Once δ-hydroxyenanal 2.31.9 was fully consumed as monitored by TLC, the reaction was cooled to room temperature and Cs₂CO₃ (570 mg, 1.75 mmol) was added. The reaction was stirred at room temperature for 6 hours. Upon completion as monitored by TLC, the reaction was quenched with a mixture of brine (15 mL) and DI H₂O (15 mL). The aqueous layer was extracted with DCM (5 x 25 mL). The combined organic layers were dried over Na₂SO₄ and reduced under vacuum. The crude material was analyzed to show a diastereomeric ratio of 2.5:1.
(2.37.1: major : minor). Crude materials were then purified with column chromatography using 100% hexanes to 50:50 (hexanes : EtOAc) to give product 2.37.1 in 51 % overall yield (major = 81 mg, 0.24 mmol, minor = 40 mg, 0.12 mmol) as yellow solids.

**Major Rf:** 0.73 in 50:50 (Hexanes : EtOAc)

**Minor Rf:** 0.52 in 50:50 (Hexanes : EtOAc)

**Major $^1$H NMR:** (400 MHz, CDCl$_3$) $\delta = 13.45$ (s, 1H), 7.43 – 7.34 (m, 8H), 7.27 – 7.24 (m, 2H), 5.46 (dd, $J = 2.4$, 11.7 Hz, 1H), 4.20 (m, 1H), 3.97 (m, 1H), 3.29 (m, 1H), 2.24 (dt, $J = 3.9$, 12.8 Hz, 1H), 2.18 (dq $J = 2.44$, 13.6 Hz, 1H), 1.76 (q, $J = 13.2$ Hz, 1H), 1.56 (s, 2H).

**Major $^{13}$C NMR:** (125 MHz, CDCl$_3$) $\delta = 173.33$, 169.90, 141.12, 136.37, 129.59, 128.97, 128.63, 128.45, 127.74, 125.83, 97.19, 82.42, 64.68, 53.71, 42.30, 35.89, 27.32.

**Minor $^1$H NMR:** (400 MHz, CDCl$_3$) $\delta = 13.14$ (s, 1H), 7.42 – 7.33 (m, 5H), 7.29 – 7.26 (m, 3H), 7.23 – 7.20 (m, 2H), 5.48 (dd, $J = 2.7$, 11.9 Hz, 1H), 4.15 (s, 1H), 3.76 (s, 1H), 3.20 (t, $J = 11.9$ Hz, 1H), 2.23 (d, $J = 13.4$ Hz, 1H), 2.03 (m, 1H), 1.83 (m, 2H), 1.57 (t, $J = 11.8$ Hz, 1H).

**Minor $^{13}$C NMR:** (125 MHz, CDCl$_3$) $\delta = 206.75$, 172.34, 171.03, 140.03, 139.20, 128.81, 128.64, 128.33, 127.28, 125.84, 98.58, 82.07, 70.89, 53.65, 37.97, 30.79, 27.38.

**Major IR:** $f$ (cm$^{-1}$) = 3451, 2938, 2914, 1635, 1592, 1497, 1454, 1439, 1393, 1357, 1325, 1273, 1169, 1109, 1078, 752, 731, 700, 677, 608, 560.

**Minor IR:** $f$ (cm$^{-1}$) = 3445, 3030, 2922, 1640, 1597, 1494, 1453, 1393, 1355, 1326, 1271, 1216, 1156, 1095, 1041, 1002, 975, 754, 732, 698, 673, 640, 505.

**Major HRMS (ESI-TOF) m/z:** (M + H)$^+$ = 337.14344 calculated for C$_{21}$H$_{21}$O$_4$; Found 337.14353.

**Minor HRMS (ESI-TOF) m/z:** (M + H)$^+$ = 337.14344 calculated for C$_{21}$H$_{21}$O$_4$; Found 337.14405
**6,8-dihydroxy-6-methyl-3,7-diphenyl-3,4,4a,5,6,7-hexahydro-1H-isochromen-1-one (2.37.2)**

**Procedure:** δ-hydroxyenone 2.26 (200 mg, 1.05 mmol) was dissolved in DCE (10.5 mL, 0.1 M) and acyl Meldrum acid 2.36.1 (304 mg, 1.20 mmol) was added. The reaction mixture was stirred at reflux for 1 hour. Once δ-hydroxyenone 2.26 was fully consumed as monitored by TLC, the reaction was cooled to room temperature and Cs₂CO₃ (857 mg, 2.63 mmol) was added. The reaction was stirred at room temperature for 5 hours. Upon completion as monitored by TLC, the reaction was quenched with a mixture of brine (15 mL) and DI H₂O (15 mL). The aqueous layer was extracted with DCM (5 x 25 mL). The combined organic layers were dried over Na₂SO₄ and reduced under vacuum. The crude material was analyzed to show a diastereomeric ratio of 3.6:1 (2.37.2: major : minor). The crude material was purified with column chromatography using 100% hexanes to 40:60 (hexanes: EtOAc) to give product 2.37.2 in 62 % yield (228 mg, 0.65 mmol) as a white crystalline solid.

**Rf:** 0.74 in 50:50 (Hexanes : EtOAc)

**¹H NMR:** (400 MHz, CDCl₃) δ = 13.37 (s, 0.21H, minor) 13.33 (s, 0.78 H, major) 7.43 – 7.19 (m, 12H, major and minor), 5.80 (m, 0.22H, minor) 5.46 (dd, J = 2.4, 11.7 Hz, 0.83H, major), 3.71 (d, J = 2.2 Hz, 0.78H, major), 3.68 (d, J = 2.3 Hz, 0.22H, minor) 3.28 (m, 0.83H, major), 2.85 (m, 0.29H, minor), 2.19 (dq, J = 2.4, 13.6 Hz, 1H, major), 2.10 (dd, J = 4.0, 12.9 Hz, 1H, major), 2.04 (m, 0.26H, minor), 1.92 (m, 0.34H, minor), 1.73 (q, J = 12.7 Hz, 1H, major and minor), 1.52 (t, J = 11.6 Hz, 2H, major and minor), 1.25 (s, 2.83H, major), 1.18 (s, 0.80H, minor).
$^{13}$C NMR: (125 MHz, CDCl$_3$) $\delta =$ 173.71, 171.38, 139.45, 135.27, 130.74, 128.57, 128.44, 127.80, 125.84, 124.93, 98.25, 81.65, 69.22, 56.87, 42.42, 37.84, 29.43, 28.66.

IR: $f'(\text{cm}^{-1}) =$ 3526, 3032, 2926, 1712, 1636, 1597, 1495, 1393, 1334, 1294, 1219, 1164, 1064, 1002, 952, 902, 856, 829, 829, 745, 648.

HRMS (ESI-TOF) $m/z$: (M + H)$^+$ = 351.15909 calculated for C$_{22}$H$_{23}$O$_4$; Found 351.15983.

X-ray Structure 2.37.2 major:

7-(4-bromophenyl)-6,8-dihydroxy-3-phenyl-3,4,4a,5,6,7-hexahydro-1H-isochroman-1-one (2.37.4)

**Procedure:** $\delta$-hydroxyenanal 2.31.9 (200 mg, 1.13 mmol) was dissolved in DCE (11.0 mL, 0.1 M) and acyl Meldrum acid 2.36.2 (423 mg, 1.20 mmol) was added. The reaction mixture was stirred at reflux for 1.5 hours. Once $\delta$-hydroxyenanal 2.31.9 was fully consumed as monitored by TLC, the reaction was cooled to room temperature and Cs$_2$CO$_3$ (922 mg, 2.63 mmol) was added. The reaction was stirred at room temperature for 21.5 hours. Upon completion as monitored by TLC, the reaction was quenched with a mixture of brine (20 mL) and DI H$_2$O (20 mL). The
aqueous layer was extracted with DCM (5 x 25 mL). The combined organic layers were dried over Na₂SO₄ and reduced under vacuum. The crude material was analyzed to show a diastereomeric ratio of 2.0:1 (21d: major : minor). The crude material was purified with column chromatography using 100% hexanes to 40:60 (hexanes: EtOAc) to give product 2.37.4 in 32% overall yield (major = 100 mg, 0.24 mmol, minor = 51 mg, 0.123 mmol) as yellow oils.

**Major Rf:** 0.76 in 50:50 (Hexanes : EtOAc)

**Minor Rf:** 0.52 in 50:50 (Hexanes : EtOAc)

**Major ¹H NMR:** (500 MHz, CDCl₃) δ = 13.43 (s, 1H), 7.55 – 7.52 (m, 2H), 7.39 – 7.33 (m, 5H), 7.15 – 7.12 (m, 2H), 5.45 (dd, J = 3.1, 10.3 Hz, 1H), 4.19 (s, 1H), 3.91 (s, 1H), 3.28 (m, 1H), 2.21 (m, 2H), 1.75 (qd, J = 5.4, 12.8 Hz, 1H), 1.58 (t, J = 13.1 Hz, 1H), 1.45 (m, 1H).

**Major ¹³C NMR:** (125 MHz, CDCl₃) δ = 172.03, 171.34, 139.26, 135.59, 131.90, 131.38, 128.62, 128.47, 125.80, 121.66, 98.77, 81.86, 67.40, 51.90, 37.75, 35.45, 27.23.

**Minor ¹H NMR:** (500 MHz, CDCl₃) δ = 13.13 (s, 1H), 7.48 (d, J = 8.6 Hz, 2H), 7.42 – 7.39 (m, 4H), 7.36 (m, 1H), 7.10 (d, J = 8.4 Hz, 2H), 5.48 (dd, J = 2.6, 11.8 Hz, 1H), 4.12 (s, 1H), 3.71 (s, 1H), 3.20 (tt, J = 4.0, 11.9 Hz, 1H), 2.23 (dt, J = 3.7, 13.6 Hz, 1H), 1.90 – 1.76 (m, 2H), 0.87 (m, 1H).

**Minor ¹³C NMR:** (125 MHz, CDCl₃) δ = 171.09, 170.99, 139.22, 138.15, 131.96, 130.03, 128.67, 128.56, 125.83, 121.32, 99.46, 82.12, 71.16, 52.28, 37.84, 30.78, 27.28.

**Major IR:** λ (cm⁻¹) = 3454, 3032, 2919, 2250, 1716, 1636, 1600, 1487, 1454, 1390, 1357, 1322, 1267, 1231, 1163, 1057, 1010, 1002, 907, 849, 758, 698, 647, 579, 500.

**Minor IR:** λ (cm⁻¹) = 3436, 2921, 1639, 1487, 1390, 1356, 1270, 1216, 1155, 1114, 1059, 1009, 907, 812, 728, 698, 647, 507.
**Major HRMS (ESI-TOF) m/z:** \((M+H)^+ = 415.05395\) calculated for \(C_{21}H_{20}BrO_4\); Found 415.05421

**Minor HRMS (ESI-TOF) m/z:** \((M+H)^+ = 415.05395\) calculated for \(C_{21}H_{20}BrO_4\); Found 415.05369

7-(4-bromophenyl)-6,8-dihydroxy-6-methyl-3-phenyl-3,4,4a,5,6,7-hexahydro-1H-isochromen-1-one (2.37.5)

![Chemical structure diagram]

**Procedure:** 8-hydroxyenone 2.26 (127 mg, 0.67 mmol) was dissolved in DCE (6.7 mL, 0.1 M) and acyl Meldrum’s acid 2.36.2 (250 mg, 0.73 mmol) was added. The reaction mixture was stirred at reflux for 1 hour. Once 8-hydroxyenone 2.26 was fully consumed as monitored by TLC, the reaction was cooled to room temperature and \(Cs_2CO_3\) (544 mg, 1.67 mmol) was added. The reaction was stirred at room temperature for 4 hours. Upon completion as monitored by TLC, the reaction was quenched with a mixture of brine (15 mL) and DI H\(_2\)O (15 mL). The aqueous layer was extracted with DCM (5 x 25 mL). The combined organic layers were dried over Na\(_2\)SO\(_4\) and reduced under vacuum. The crude material was analyzed with \(^1\)HNMR to show a diastereomeric ratio of 3.9:1. The crude material was purified with column chromatography using 100% hexanes to 40:60 (hexanes : EtOAc) to give product 2.37.5 as an inseparable 3.9:1 mixture of diastereomers in 55 % yield (174 mg, 0.40 mmol) as a white solid.

**Rf:** 0.61 in 50:50 (Hexanes : EtOAc)
\textbf{\textsuperscript{1}H NMR:} (400 MHz, CDCl\textsubscript{3}) \( \delta = 13.35 \) (s, 0.21H, minor), 13.31 (s, 0.78H, major) 7.53 (d, \( J = 8.4 \) Hz, 2H, major and minor), 7.40 – 7.32 (m, 5H, major and minor), 7.13 (d, \( J = 8.4 \) Hz, 2H, major and minor), 5.80 (m, 0.21H, minor) 5.45 (dd, \( J = 2.3 \), 11.7 Hz, 0.81H, major), 3.66 (d, \( J = 2.3 \), 0.82H, major), 3.63 (d, \( J = 2.3 \), 0.20H, minor), 3.25 (m, 0.83H, major), 2.83 (m, 0.26H, minor), 2.19 (dq, \( J = 2.4 \), 13.6 Hz, 1H, major and minor), 2.09 (dd, \( J = 4.0 \), 13.0 Hz, 0.85H, major), 1.91 (dd, \( J = 4.3 \), 13.1 Hz, 0.29H, minor) 1.72 (q, \( J = 12.7 \) Hz, 1H, major and minor), 1.55 – 1.49 (m, 2H, major and minor), 1.24 (s, 2.31H, major), 1.17 (s, 0.69H, minor).

\textbf{\textsuperscript{13}C NMR:} (125 MHz, CDCl\textsubscript{3}) \( \delta = 172.95, 171.30, 139.30, 134.45, 132.47, 131.51, 128.61, 128.46, 125.80, 124.88, 98.31, 81.68, 69.18, 56.30 42.44, 37.69, 29.27, 28.59.

\textbf{IR:} \( f (\text{cm}^{-1}) = 3466, 2927, 1739, 1639, 1602, 1488, 1453, 1393, 1274, 1166, 1125, 1067, 1036, 1011, 908, 853, 805, 777, 731, 649, 586.

\textbf{HRMS (ESI-TOF) m/z:} (M + H)\(^{+}\) = 429.0696 calculated for C\textsubscript{22}H\textsubscript{22}BrO\textsubscript{4}; Found 429.07036.

\textbf{6,8-dihydroxy-7-(4-methoxyphenyl)-6-methyl-3-phenyl-3,4,4a,5,6,7-hexahydro-1\textit{H}-isochromen-1-one (2.37.6)}

\begin{center}
\includegraphics[width=0.8\textwidth]{structure.png}
\end{center}

\textbf{Procedure:} \( \delta \)-hydroxyenone 2.26 (147 mg, 0.77 mmol) was dissolved in DCE (7.7 mL, 0.1 M) and acyl Meldrum acid 2.36.6 (147 mg, 0.85 mmol) was added. The reaction mixture was stirred at reflux for 1 hour. Once \( \delta \)-hydroxyenone 2.26 was fully consumed as monitored by TLC, the reaction was cooled to room temperature and Cs\textsubscript{2}CO\textsubscript{3} (629 mg, 1.93 mmol) was added. The reaction was stirred at room temperature for 5 hours. Upon completion as monitored by TLC, the
reaction was quenched with a mixture of brine (20 mL) and DI H₂O (20 mL). The aqueous layer was extracted with DCM (5 x 25 mL). The combined organic layers were dried over Na₂SO₄ and reduced under vacuum. The crude material was analyzed with ¹H NMR to show a diastereomeric ratio of 3.6:1. Crude materials were then purified with column chromatography using 100% hexanes to 40:60 hexanes : EtOAc to give product **2.37.6** as an inseparable 3.6:1 mixture of diastereomers in overall yield of 56 % (164 mg, 0.43 mmol) as a white powder.

**Rf:** 0.44 in 50:50 (Hexanes : EtOAc)

**¹H NMR:** (400 MHz, CDCl₃) δ = 13.39 (s, 0.22H, minor), 13.35 (s, 0.76H, major), 7.42 – 7.33 (m, 5H, major and minor), 7.16 (d, J = 8.6 Hz, 1.67H, major), 7.11 (d, J = 8.8 Hz, 0.50H, minor), 6.94 (d, J = 8.7 Hz, 1.84H, major), 6.86 (d, J = 8.8 Hz, 0.27H, minor), 5.79 (m, 0.22H, minor), 5.45 (dd, J = 2.2, 11.7 Hz, 0.79H major), 3.82 (s, 2.30H, major), 3.81 (s, 0.71H, minor), 3.66 (m, 0.85H, major), 3.62 (m, 0.21H, minor) 3.25 (m, 0.81H, major), 2.83 (m, 0.23H, minor), 2.18 (dq, J = 2.4, 13.6 Hz, 1H, major and minor), 2.10 (m, 1H, major and minor), 1.71 (q, J = 12.7 Hz, 1H, major and minor), 1.50 (t, J = 12 HZ, 1H, major and minor), 1.40 (s, 1H, major and minor), 1.24 (s, 2.52H, major), 1.17 (s, 0.64H, minor).

**¹³C NMR:** (125 MHz, CDCl₃) δ = 174.02, 171.34, 158.99, 139.37, 131.65, 128.50, 128.30, 127.06, 125.75, 113.89, 98.00, 81.53, 69.13, 55.92, 55.15, 42.22, 37.67, 29.23, 28.49.

**IR:** f (cm⁻¹) = 3492, 2924, 2836, 1712, 1633, 1595, 1510, 1451, 1390, 1352, 1323, 1302, 1276, 1116, 1067, 937, 858, 809, 756, 734, 614, 527, 500.

**HRMS (ESI-TOF) m/z:** (m + H)⁺ = 381.16965 calculated for C₂₃H₂₅O₅; Found 381.16897.
**Procedure:** δ-hydroxyenone 2.26 (96 mg, 0.50 mmol) was dissolved in DCE (5 mL, 0.1 M) and acyl Meldrum acid 2.36.4 (183 mg, 0.55 mmol) was added. The reaction mixture was stirred at reflux for 1 hour. Once δ-hydroxyenone 2.26 was fully consumed as monitored by TLC, the reaction was cooled to room temperature and Cs$_2$CO$_3$ (411 mg, 1.26 mmol) was added. The reaction was stirred at room temperature for 4 hours. Upon completion as monitored by TLC, the reaction was quenched with a mixture of brine (20 mL) and DI H$_2$O (15 mL). The aqueous layer was extracted with DCM (5 x 25 mL). The combined organic layers were dried over Na$_2$SO$_4$ and reduced under vacuum. The crude material was analyzed with $^1$HNMR to show a diastereomeric ratio of 5.6:1. Crude materials were then purified with column chromatography using 100% hexanes to 40:60 (hexanes : EtOAc) to give product 2.37.7 as an inseparable 5.6:1 mixture of diastereomers in an overall yield of 37 % (79 mg, 0.40 mmol) as a white powder.

**Rf:** 0.45 in 50:50 (Hexanes : EtOAc)

$^1$H NMR: (400 MHz, CDCl$_3$) δ = 13.37 (s, 0.14H, minor), 13.33 (s, 0.84H, major), 7.66 (d, J = 8.0 Hz, 2H, major and minor), 7.41 – 7.33 (m, 7H, major and minor), 5.81 (m, 0.15H, minor), 5.46 (dd, J = 2.4, 11.2 Hz, 0.87H, major), 3.76 (m, 0.87H, major), 3.73 (m, 0.15H, minor), 3.28 (m, 0.89H, major), 2.85 (m, 0.14H, minor) 2.20 (m, 1H, major and minor), 2.10 (dd, J = 4.0, 13.0 Hz, 0.91H, major), 1.92 (dd, J = 4.2, 13.1 Hz, 0.21H, minor), 1.76 (q, J = 12.7 Hz, 1H, major and minor), 1.58 – 1.52 (m, 2H, major and minor), 1.26 (s, 2.84H, major), 1.19 (s, 0.33H, minor).
\(^{13}\)C NMR: \((125 \text{ MHz, CDCl}_3\) \(\delta = 172.61, 171.31, 139.72, 139.65, 139.26, 131.27, 128.64, 128.50, 125.82, 125.17, 124.89, 98.43, 81.74, 69.36, 56.67, 42.58, 37.68, 29.28, 28.63.\)

IR: \(f (\text{cm}^{-1}) = 3461, 2926, 2252, 1713, 1638, 1602, 1497, 1454, 1419, 1393, 1378, 1322, 1275, 1236, 907, 854, 786, 767, 754, 698, 681, 569.\)

HRMS (ESI-TOF) \(m/\text{z}: (M + H)^+ = 419.14647 \) calculated for \(\text{C}_{23}\text{H}_{22}\text{F}_3\text{O}_4; \) Found 419.14687

**Methyl 2-(3-acetyl-2-oxo-6-phenyltetrahydro-2H-pyran-4-yl)acetate (2.39)**

\[
\begin{align*}
\text{Bn} & \quad \text{OH} \quad \text{O} \quad \text{Me} \\
\text{Me} & \quad \text{H} \quad \text{O} \quad \text{Me} \\
\text{Bn} & \quad \text{O} \quad \text{Me} \\
\text{O} & \quad \text{Me} \\
\end{align*}
\]

**Procedure:** \(\delta\)-hydroxyenone 2.38 (200 mg, 0.91 mmol) was dissolved in DCE (9.1 mL, 0.1 M) and acyl Meldrum acid 2.27 (186 mg, 1.00 mmol) was added. The reaction mixture was stirred at reflux for 1 hour. Once \(\delta\)-hydroxyenone 2.38 was fully consumed as monitored by TLC, the reaction was cooled to room temperature and Cs\(_2\)CO\(_3\) (739 mg, 2.27 mmol) was added. The reaction was stirred at room temperature for 5 hours. Upon completion as monitored by TLC, the reaction was quenched with a mixture of brine (15 mL) and DI H\(_2\)O (15 mL). The aqueous layer was extracted with DCM (5 x 25 mL). The combined organic layers were dried over Na\(_2\)SO\(_4\) and reduced under vacuum. The crude material was purified with column chromatography using 100% hexanes to 40:60 (hexanes : EtOAc) to give product 2.39 as a 1:1 mixture of diastereomers in 62 % yield (228 mg, 0.651 mmol) as a yellow oil.

**Rf:** 0.35 in 50:50 (Hexanes : EtOAc)
$^1$H NMR: (400 MHz, CDCl$_3$) $\delta$ = 7.31 – 7.26 (m, 10 H), 4.51 (m, 2H), 3.73 (s, 3H), 3.71 (s, 3H), 3.35 (m, 2H), 3.00 (dd, $J$ = 5.9, 12.2 Hz, 2H), 2.89 (m, 2H), 2.78 – 2.65 (m, 4H), 2.21 (s, 3H), 2.20 (s, 3H) 2.13 (m, 2H), 1.91 (m, 2H), 1.25 (m, 2H).

$^{13}$C NMR: (125 MHz, CDCl$_3$) $\delta$ = 200.65, 169.73, 168.09, 135.96, 129.51, 128.51, 126.88, 79.96, 63.87, 52.69, 41.86, 33.73, 31.98, 30.58, 29.91.

IR: $\nu$(cm$^{-1}$) = 3029, 2924, 1715, 1496, 1454, 1435, 1360, 1242, 1161, 1078, 993, 755, 702, 505.

HRMS (ESI-TOF) $m/z$: (M + H)$^+$ = 291.1227 calculated for C$_{16}$H$_{19}$O$_5$; Found 291.12337

6,8-dihydroxy-6-methyl-3-phenyl-3,4,4a,5,6,7-hexahydro-1H-isochromen-1-one (2.45)

![Chemical Structure](image)

Procedure: $\delta$-hydroxyenone 2.26 (200 mg, 1.05 mmol) was dissolved in DCE (11 mL, 0.1 M) and acyl Meldrum acid 2.27 (216 mg, 1.2 mmol) was added. The reaction mixture was stirred at reflux for 1 hour. Once $\delta$-hydroxyenone 2.26 was fully consumed as monitored by TLC, the reaction was cooled to room temperature and Cs$_2$CO$_3$ (857 mg, 2.6 mmol) and phenol (200 mg, 2.6 mmol) was added. The reaction was stirred at room temperature for 2 hours. Upon completion as monitored by TLC, the reaction was quenched with a mixture of brine (15 mL) and DI H$_2$O (15 mL). The aqueous layer was extracted with DCM (5 x 25 mL). The combined organic layers were dried over Na$_2$SO$_4$ and reduced under vacuum. The crude material was analyzed with $^1$HNMR to show a diastereomeric ratio of 20:1. Crude materials were then purified with column
chromatography using 100% hexanes to 40:60 hexanes : EtOAc to give product 2.45 in a 20:1 diastereomeric ratio with an overall yield of 32 % (92 mg, 0.34 mmol) as a white powder.

**1H NMR:** (400 MHz, CDCl₃) δ = 13.12 (s, 1H), 7.40 – 7.31 (m, 5H), 5.40 (dd, J = 2.1 Hz, 1H), 3.09 (m, 1H), 2.53 (dd, J = 2.0, 15.4 Hz, 1H), 2.45 (m, 1H), 2.15 (dq, J = 2.0, 10.9 Hz, 1H), 1.89 (ddd, J = 1.4, 3.5, 10.5 Hz, 1H), 1.70 (q, J = 9.4 Hz, 1H), 1.40 (m, 1H), 1.39 (s, 3H), 1.33 (t, J = 9.4 Hz, 1H).

**13C NMR:** (125 MHz, CDCl₃) δ = 172.57, 171.13, 139.46 128.43, 125.85, 96.02, 81.63, 68.12, 43.13, 41.92, 37.71, 30.84, 29.15.

**IR:** f (cm⁻¹) = 3436, 2964, 2922, 1639, 1605, 1497, 1454, 1405, 1374, 1325, 1280, 1228, 1168, 1122, 1065, 1038, 1004, 850, 812, 650.

**HRMS (ESI-TOF) m/z:** (M + H)⁺ = 275.12779 calculated for C₁₆H₁₉O₄; Found 275.12708

**X-ray structure:**
3.3. NMR spectra

\[ \text{OH} \text{O} \]

2.09
2.28 

k:e = 20:1
Ph

Me

2.28

Me

k:e = 20:1
Crude material

\[
\begin{align*}
\text{Ph} & \quad \text{H}_a \\
\text{Me} & \quad \text{H}_b \\
\text{O} & \quad \text{O} \\
\text{2.28} & \quad \text{dr = 20:1}
\end{align*}
\]
2.29.1
\begin{align*}
\text{OH} & \quad \text{Me} \\
2.29.3 & \quad \text{(structure)}
\end{align*}
Me\_2\_O
\[\text{Me} \]
\[\text{Me} \]
\[\text{Me} \]
\[\text{OH} \]
\[\text{=C} \]
\[\text{Me} \]
2.29.5

![Chemical structure diagram](image)

![NMR spectrum graph](image)
2.30.1

k:e = 9.1:1 (CDCl₃)
k:e = 9.1:1 (CDCl₃)
2.30.1

$k:e = 5.6:1$ (DMSO-d$_6$)

enol OH

H$_a$ (enol)  H$_a$ (ketone)

H$_2$O
$2.30.1$

$k:e = 5.6:1$ (DMSO-$d_6$)
3) Crude $^1$H NMR of reaction mixture; 2) $^1$H NMR of purified isolated; 14a 1) After 7 months of slow evaporation cycle
3) Crude $^1$HNMR of reaction mixture; 2) $^1$HNMR of purified isolated; 14a 1) After 7 months of slow evaporation cycle
3) Crude $^1$HNMR of reaction mixture; 2) $^1$HNMR of purified isolated; 14a 1) After 7 months of slow evaporation cycle
Crude material

2.30.1

dr = 20:1
$k:e = 7.1:1 \text{ (CDCl}_3\text{)}$
2.30.2
k:e = 7.1:1 (CDCl₃)
2.30.2
k:e = 20:1 (DMSO-d$_6$)
2.30.2

k:e = 20:1 (DMSO-d$_6$)
Crude material

2.30.2

\( \text{F}_3\text{C} \)

\( \text{H}_a \) (ketone)

\( \text{H}_b \) (enol)

\( \text{H}_a \) (ketone)

\( \text{H}_b \) (ketone)

\( \text{dr} = 20:1 \)
2.30.3

Chemical shift (ppm): 
-206.31, -202.50
-187.12
139.69, 139.69
128.69
128.69
-80.14, -77.00
-60.54
-48.14
-41.68
-33.15
-30.23
-29.07
-29.03

k:e = 20:1

Chemical structure:

![Chemical structure image]
Crude material

[Chemical structure image]

2.30.3

dr = 20:1

[1H NMR spectrum image with peaks labeled H_a, H_b, H_c, H_s (ketone), H_b]
2.30.4
k:e = 20:1
Crude material

\[
\begin{align*}
2.30.4 \\
\text{dr} = 20:1.0
\end{align*}
\]
2.30.5

k:e = 20:1
Crude material

\[
\begin{align*}
O & \quad O \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
2.30.5 \\
dr = 20:1
\end{align*}
\]
2.30.6
k:e = 20:1
2.30.6
k:e = 20:1
Crude material

[Chemical Structure Image]

2.30.6

$dr = 20:1$
\[ k:e = 20:1 \]
Crude material

\[
\begin{align*}
&\text{BnO} \\
&\text{Me} \\
&\text{2.30.7} \\
&\text{dr} = 20:1
\end{align*}
\]
2.30 \text{ ppm} \\
\text{k:e} = 20:1
$k:e = 20:1$

BPSO
Crude material

BPSO

$\text{dr} = 20:1$

$2.30.8$

$H_a$

$H_b$

$\delta$ values:

- $H_a$: 4.63
- $H_b$: 2.30.8
2.31.1
OH

OMe

2.31.2
OH

Me

2.31.5
2.31.8
2.32.1

k:e = 9.1:1 (CDCl₃)
$\text{2.32.1}$

$k:e = 9:1$ (CDCl$_3$)
2.32.1

k:e = 20:1 (DMSO-d6)

H2O
2.32.1

k:e = 20:1 (DMSO-d₆)
Crude material

2.32.1

$\text{dr} = 20:1$
2.32.2

$k:a = 10:1$ (CDCl$_3$)

enol OH

H$_a$ (enol)

H$_b$ (ketone)

H$_a$ (ketone)

$OCH_3$ (b)
2.32.2

k:e = 10:1 (CDCl₃)
2.32.2

k:e = 13:1 (DMSO-d$_6$)
\[ \text{\textit{2.32.2}} \]

\[ k:e = 13:1 \quad (\text{DMSO-d}_6) \]
Crude material

\[
\text{dr} = 20:1
\]
$k:e = 10:1 \ (CDCl_3)$
2.32.3

$k:e = 10:1$ (CDCl$_3$)
2.32.3

k:ε = 20:1 (DMSO-d$_6$)
2.32.3
κ:ε = 20:1 (DMSO-d$_6$)
Crude material

2.32.3

$\text{dr} = 20:1$

$7.87$
$7.85$
$7.47$
$7.44$
$7.38$
$7.31$
$7.26$
$3.44$
$3.39$
$3.35$
$3.29$
$3.04$
$2.98$
$2.49$
$2.36$
$2.10$
$2.07$
$1.78$
k:e = 7.2:1 (CDCl₃)
2.32.4

k:e = 7.2:1 (CDCl₃)
$\text{enol OH}$

$k:e = 17:1$ (DMSO-$d_6$)

2.32.4

$\text{H}_b$ (ketone) $\text{H}_a$ (enol) $\text{H}_b$ (enol) $\text{H}_a$ (ketone)
2.32.4
k:e = 17:1 (DMSO-d$_6$)
Crude material

2.32.4
dr = 20:1
k.e = 6.3:1 (CDCl₃)
$k/e = 6.3:1$ (CDCl$_3$)
2.32.5

k:e = 7.1:1 (DMSO-d$_6$)
$k:e = 7.3:1$ (DMSO-d$_6$)
Crude material

\[
\begin{align*}
&\text{H}_a \\
&\text{H}_b
\end{align*}
\]

\[\text{dr} = 20:1\]
2.32.6
k:e = 7.3:1
Crude material

2.32.6

dr = 20:1
2.32.7
k:e = 20:1
k:e = 20:1
Crude material

![Chemical structure and NMR spectrum](image-url)


2.32.8

k:e = 10:1 (CDCl₃)
2.32.8
k:e = 10:1 (CDCl₃)
2.32.8

$k:e = 17:1$ (DMSO-d$_6$)
2.32.8
k:e = 17:1 (DMSO-d$_6$)
Crude material

2.32.8
dr: 20:1
2.33.1
κ:ε = 20:1
Crude material

\[
\begin{align*}
 & H_a \quad H_b \\
 & \text{dr} = 20:1
\end{align*}
\]
2.33.2

k:e = 20:1
Crude material

$$\begin{align*}
\text{H}_a & \quad 5.61 \\
\text{H}_b & \quad 5.68 \\
\text{H}_a & \quad 5.57
\end{align*}$$

$$\begin{align*}
\text{H}_a & \quad 3.21 \\
\text{H}_b & \quad 2.67 \\
\text{H}_a & \quad 2.66 \\
\text{H}_a & \quad 2.43 \\
\text{H}_b & \quad 2.17 \\
\text{H}_a & \quad 1.98
\end{align*}$$

$2.33.2$

$\text{dr} = 20:1$
2.33.3

k:e = 20:1
2.33.3
k:e = 20:1
Crude material

\[
\begin{align*}
\text{Ph} & \quad \text{H}_a \\
\text{H}_a & \quad \text{H}_b \\
\text{Me} & \quad \text{O} \\
\end{align*}
\]

\[\text{dr} = 20:1\]
2.33.4
κ:ε = 20:1
k:e = 20:1
Crude material

\[
\begin{align*}
\text{Ph} & \to ^{\text{H}_a} \\
\text{H}_a & \to ^{\text{Me}} \\
\end{align*}
\]

**2.33.4**

dr = 20:1
2.335
k:e = 20:1
The diagram shows a chemical structure labeled as 2.33.5 with the measurement $\delta = 20:1$. The spectrum is labeled with peak values such as 206.43, -168.48, -152.18, -138.57, 128.60, 125.86, 125.74, 79.54, 77.00, 48.66, 47.62, 42.89, 36.34, 30.22, 29.28, 28.35, and 13.01.
Crude material

\[
\begin{align*}
\text{Ph} & \quad \text{H}_a \\
\text{=} & \quad \text{H}_b \\
\text{O} & \quad \text{O} \\
\text{Me} & \quad \text{NBoc}
\end{align*}
\]

2.33.5

\[\text{dr} = 20:1\]
2.37.1 minor

Chemical shifts:
- 206.75
- 172.34
- 171.03
- 140.03
- 139.20
- 128.81
- 128.64
- 128.33
- 127.28
- 127.58
- 98.58
- 82.07
- 77.00
- 70.89
- 53.65
- 37.97
- 30.79
- 27.38
Crude material

2.37.1 major
dr = 2.5:1

2.37.1 minor
dr = 2.5:1
2.37.2 major  3.6:1  2.37.2 minor
Crude material

2.37.2 major
dr = 3.6:1

2.37.2 minor
dr = 3.6:1
Crude material

2.37.3
complex mixture
2.37.4 major
2.37.4 major
2.37.4 minor
Crude material

2.37.4 major
\( \text{dr} = 2.0:1 \)

2.37.4 minor
\( \text{dr} = 2.0:1 \)

\( \text{HO} \rightarrow \text{O} \text{H} \)

\( \text{Ph} \rightarrow \text{Br} \)

\( \text{Ha}, \text{Hb}, \text{Hc}, \text{Hd}, \text{He} \)

\( f_1 \text{ (ppm)} \)

\( 7.53, 7.45, 7.37, 7.15, 7.06 \)

\( 4.19, 4.10, 3.90, 3.31, 2.16 \)

\( 2.33, 2.25, 2.16, 1.85, 1.72, 1.57, 1.52 \)
Crude Material

\[ \text{O}_2 \text{Ha} \text{Hb} \text{Hc} \text{Hd} \text{O}_2 \text{Ph} \text{Br} \]

2.37.5 major
\[ \text{dr} = 3.4:1 \]

2.37.5 minor
\[ \text{dr} = 3.4:1 \]
Crude material

2.37.6 major
dr = 3.6:1

2.37.6 minor
dr = 3.6:1

f1 (ppm)
2.37.7 major 5.8:1

2.37.7 minor
Crude material

2.37.7 major
dr = 5.9:1

2.37.7 minor
dr = 5.9:1
2.39

1:1

2.39
\[
\begin{align*}
\text{Bn} & \quad \text{O} \\
\text{Me} & \quad \text{OMe}
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{Me} & \quad \text{OMe}
\end{align*}
\]

\[
\begin{align*}
2.39 & \quad + \\
2.39 & \quad 1:1
\end{align*}
\]

\[
\begin{align*}
\text{f1 (ppm)} & : 210, 200, 190, 180, 170, 160, 150, 140, 130, 120, 110, 100, 90, 80, 70, 60, 50, 40, 30, 20, 10, 0, -10
\end{align*}
\]
\[
\text{dr} = 20:1
\]
dr = 20:1
Crude material

2.45

dr = 20:1
REFERENCES


VITA

Joshua Paul Van Houten was born in New Braunfels, Texas, but grew up in, and considers home, Mandeville, Louisiana. In this growing town, he attended Mandeville High School. Joshua attended college at Southwestern University in Georgetown, Texas. In August of 2016 he joined the organic chemistry research lab of Dr. Rendy Kartika. During his time as a graduate student, Joshua studied organic synthesis and methodological development. Upon completion of his doctorate Joshua will begin his career as a Senior Scientist at PPD in Middleton, Wisconsin.