DISSERTATION

SYNTHETIC APPROACH TOWARDS CEPHALEZOMINE A AND PHOMOIDRIDE D

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ABSTRACT

SYNTHETIC APPROACH TOWARDS CEPHALEZOMINE A AND PHOMOIDRIDE D

Two synthetic approaches towards cephalezomine A and phomoidride D are described separately.

The first approach towards cephalezomine A invented a new method for the synthesis of 3-butoxy-1-chlorobutenone and successful constructed α-O and β'-N disubstituted dienone for a designed key intermediate of cascade cyclization by Eschenmoser coupling of thiolactam and 3-butoxy-1-chlorobutenone.

The second approach towards phomoidride D systematically studied the electronic effects of different ester substituents for the phenolic oxidation and inverse electron demand Diels-Alder reaction, which resulted in the synthesis of functionalized bicyclic [2.2.1] intermediate. Base on this, a new route for the synthesis of precursor of Grob fragmentation has been established towards the total synthesis of phomoidride D by samarium diiodide mediated radical cascade cyclization.
To my parents and friends
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>AcOH</td>
<td>acetic acid</td>
</tr>
<tr>
<td>aq.</td>
<td>aqueous</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>BTIB</td>
<td>bis(trifluoroacetoxy)-iodobenzene</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>C</td>
<td>carbon</td>
</tr>
<tr>
<td>ºC</td>
<td>degree Celsius</td>
</tr>
<tr>
<td>calcd’</td>
<td>calculated</td>
</tr>
<tr>
<td>CCl₄</td>
<td>chloroform-d</td>
</tr>
<tr>
<td>CH₂N₂</td>
<td>diazomethane</td>
</tr>
<tr>
<td>CH₃CN</td>
<td>acetonitrile</td>
</tr>
<tr>
<td>CHCl₃</td>
<td>chloroform</td>
</tr>
<tr>
<td>m-CPBA</td>
<td>3-chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>δ</td>
<td>chemical shift in ppm downfield from Me₄Si</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>DCE</td>
<td>dichloroethane</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCC</td>
<td>1,3-dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>dd</td>
<td>doublet of doublets</td>
</tr>
<tr>
<td>dddd</td>
<td>doublet of doublets of doublets</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-dichloro-5,6-dicyanobenzoquinone</td>
</tr>
<tr>
<td>DEAD</td>
<td>diethyl azodicarboxylate</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>diisobutylaluminum hydride</td>
</tr>
<tr>
<td>DIEA</td>
<td>N,N-diisopropylethylamine</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-(dimethylamino)pyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethyl formamide</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>dt</td>
<td>doublet of triplets</td>
</tr>
<tr>
<td>equiv.</td>
<td>equivalent</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>Et$_2$O</td>
<td>ethyl ether</td>
</tr>
<tr>
<td>EtOAc</td>
<td>ethyl acetate</td>
</tr>
<tr>
<td>Et$_3$N</td>
<td>triethylamine</td>
</tr>
<tr>
<td>FTIR</td>
<td>Fourier transform infrared</td>
</tr>
<tr>
<td>g</td>
<td>gram(s)</td>
</tr>
<tr>
<td>h</td>
<td>hours</td>
</tr>
<tr>
<td>H</td>
<td>Hydrogen</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>HCl</td>
<td>Hydrochloric acid</td>
</tr>
<tr>
<td>KHMDS</td>
<td>potassium bis(trimethylsilyl) amide</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoric triamide</td>
</tr>
<tr>
<td>HRMS</td>
<td>high-resolution mass spectrum</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant</td>
</tr>
<tr>
<td>L</td>
<td>liter(s)</td>
</tr>
<tr>
<td>LAH</td>
<td>lithium aluminum hydride</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>Lawesson's reagent</td>
<td>2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane2,4-disulfide</td>
</tr>
<tr>
<td>LiOH</td>
<td>lithium hydroxide</td>
</tr>
<tr>
<td>μ</td>
<td>micro</td>
</tr>
<tr>
<td>m</td>
<td>milli, multiplet(NMR)</td>
</tr>
<tr>
<td>M</td>
<td>moles per liter</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MeOH</td>
<td>methanol</td>
</tr>
</tbody>
</table>
mol     moles
MS     mesylate
m/z     mass to charge ratio
NMO     4-methylmorpholine N-oxide
NMR     nuclear magnetic resonance
Ns     nosylate (2-nitrobenzenesulfonate)
O     oxygen
OAC     acetate
PivCl     pivaloyl Chloride
PMB     p-methoxybenzyl
PPh₃     triphenylphosphine
PTSA     p-Toluenesulfonic acid
py.     pyridine
q     quartet
SmI₂     samarium diiodide
t     triplet
td     triplet of doublets
TBAF     tetrabutylammounium fluoride
TBS     tert-butylidemethylsilyl
TBSOTf     tert-butylidemethylsilyl trifluomethylsulfonate
Tf₂O     triflic anyhydride
THF     tertrahydrofuran
TLC     thin layer chromatography
TMS     trimethylbutylsilyl
TMSOTf     trimethylbutylsilyl trifluomethylsulfonate
TPAP     trimethylpropyl ammonium perruthenate
Chapter 1

Cephalezomine A Chemistry and Biology

1.1 Background and Introduction

1.1.1 Cephalezomines: Isolation and Structural Characterization

In 2000, Jun'ichi Kobayashi and co-workers reported the isolation and structural elucidation of cephalezomines A-F (1-6) from the leaves of *Cephalotaxus harringtonine var nana* in Japan (Figure 1.1.1).\(^1\) Additional compounds, cephalezomines G-M (7-12) and bis- cephalezomines A-E (13-17), were isolated and structure elucidated by the same group in 2002 and 2004.\(^2,3\)
Cephalezomines are members of the *Cephalotaxus* alkaloid family found in higher plants of the genus *Cephalotaxus*. Structurally related *Cephalotaxus* alkaloids are known as drupacine (18), cephalotaxine (19), 11-hydroxycephalotaxine (20), harringtonine (21), deoxyharringtonine (22) and homoharringtonine (23) (Figure 1.1.1.2). Some of the latter, such as 21, 22 and 23, display potent antileukemic activity.
upon intraperitoneal injection in mice. \(^8\) Recently, clinical studies of *Cephalotaxus* alkaloids in China have shown that intravenous administration can affect various types of acute leukemia. \(^9,\ 10\)

*Figure 1.1.1.2 Cephalotexus alkaloids*

1.1.2 *Cephalotexus* Alkaloids Biosynthesis

Ronald Parry and co-workers have utilized the method of isotope-labeled precursor incorporation to study the biosynthesis of the *Cephalotexus* Alkaloids in *Cephalotaxus harringtonia*. \(^11\) It had been established that in the early stage of biosynthesis (from 24, 25 to 28), cephalotaxine is biosynthesized from one molecule each of tyrosine (24) and phenylalanine (25) (Scheme 1.1.2.1). The hypothesis predicted that cephalotaxine should come from 24 and 25 via a 1-phenethyltetrahydroisoquinoline derivative (26), oxidative phenol coupling product (27) and dienone (28). This hypothesis is based on results obtained while investigating the biosynthesis of colchicine. \(^12\) In the late stage of biosynthesis (from 28 to 19), loss of one carbon atom from dienone (28) via
a ring contraction formed the D ring of cephalotaxine. It has been suggested that the ring contraction of 28 might result from a benzilic acid rearrangement.\textsuperscript{13}

\textit{Scheme 1.1.2.1 Cephalotaxine Biosynthesis}

The biosynthesis of the acyl side chain of deoxyharringtonine (21) was proposed to involve a pathway that begins with leucine (29) \textbf{(Scheme 1.1.2.2)}.\textsuperscript{14} Diacid (31) should be an intermediate in the biosynthesis of the acyl side chain of deoxyharringtonine (36) and carbon atoms (3-8) of diacid (31) should be derived from leucine. This hypothesis was supported by the isolation of labeled 31 by feeding \textsuperscript{14}C leucine (29) to \textit{Cephalotaxus harringtonia}. The latter \textsuperscript{14}C experiment also indicated that diacid 33 lies on the biosynthetic pathway to 36.
Scheme 1.1.2.2 Acyl Side Chain of Deoxyharringtonine Biosynthesis

The $^{14}$C labeling experiment also clearly established that the acyl side chain of harringtonine is derived in vivo from the acyl side chain of deoxyharringtonine, probably by direct oxidative hydroxylation (Scheme 1.1.2.3). The acyl side chain of homoharringtonine was predicted to be derived by homologation of the acyl side chain of deoxyharringtonine with subsequent oxidative hydroxylation.

Scheme 1.1.2.3 Acyl Side Chains of Harringtonine and Homoharringtonine Biosynthesis
1.1.3 Biological Activity of the Cephalezomines

Several members of cephalezomine family display potent biological activity. The cytotoxicity of cephalezomines A-M and bis-cephalezomines A-E is shown in Table 1.1.3. In general, monomeric cephalezomines display greater potency than the dimeric ones. This study also showed that cephalotaxine-type compounds lacking either the side chain acid or sugar moiety exhibit weak cytotoxicity.1

<table>
<thead>
<tr>
<th>Compound</th>
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<th>Compound</th>
<th>IC_{50} (µg/mL)</th>
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<td></td>
<td>L1210</td>
<td>KB</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>0.067</td>
<td>0.020</td>
<td>K</td>
</tr>
<tr>
<td>B</td>
<td>0.030</td>
<td>0.024</td>
<td>L</td>
</tr>
<tr>
<td>C</td>
<td>0.88</td>
<td>0.078</td>
<td>M</td>
</tr>
<tr>
<td>D</td>
<td>7.6</td>
<td>0.40</td>
<td>Bis-A</td>
</tr>
<tr>
<td>E</td>
<td>0.68</td>
<td>0.18</td>
<td>Bis-B</td>
</tr>
<tr>
<td>F</td>
<td>0.10</td>
<td>0.084</td>
<td>Bis-C</td>
</tr>
<tr>
<td>G</td>
<td>8.0</td>
<td>&gt;30</td>
<td>Bis-D</td>
</tr>
<tr>
<td>H</td>
<td>8.6</td>
<td>&gt;30</td>
<td>Bis-E</td>
</tr>
<tr>
<td>J</td>
<td>12</td>
<td>5.6</td>
<td></td>
</tr>
</tbody>
</table>

1.2 Cephalezomine A: Structure and Synthesis

1.2.1 Structural Features

The structure of cephalezomine A (1) contains a drupacine-type skeleton and an acyl side chain (Figure 1.2.1). It is known that drupacine derives from 11-hydroxycephalotaxine (20). In terms of reported syntheses towards cephalezomine A (1),
the descriptions below will focus on two parts: the acyl side chain and heterocyclic core (11-oxidized-cephalotaxine-type skeleton).

Figure 1.2.1 Cephalozamine A Structure Features

1.2.2 Synthetic Routes to Related Acyl Side Chains

In 1973, Weinreb and co-workers reported the synthesis of the acid side chain of deoxyharringtonine (Scheme 1.2.2.1). First, epoxidation of benzylmethylitaconate 41 by \textit{m-CPBA} gave epoxide 42. Treatment with an organo-copper reagent prepared from isobutyl lithium 43 and cuprous iodide produced tertiary alcohol 44. Finally, hydrogenolysis of benzyl ester 44 using Adams’ catalyst produced acid 45.

Scheme 1.2.2.1 Weinreb’s Procedure for the Synthesis of Acid Side Chain
In 1982, Hudlicky and co-workers reported the synthesis of homoharringtonine (23) commencing with cephalotaxine (19).\textsuperscript{16} During the synthesis, they described the preparation of acyl side chain (Scheme 1.2.2.2). Ozonolysis of methylcyclohexene 46 gave an intermediate ketoaldehyde which was subjected to an intramolecular aldol condensation, followed by oxidation of the resultant aldehyde to acid 47. Ozonolysis of 47 gave the ketopyruvate 48. Generation of the acid chloride from substrate 48, followed by exposure to cephalotaxine formed cephalotaxine ester 49. This ester was difficult to purify by chromatography due to decomposition, therefore no yield was reported. To this crude intermediate was added the zinc reagent derived from methyl bromoacetate, followed by treatment with MeLi or MeMgBr to produce homoharringtonine (23).

Scheme 1.2.2.2 Hudlicky’s Procedure for the Synthesis of Acid Side Chain

1. O\textsubscript{3}, Me\textsubscript{2}S, -78 °C
2. piperidine/ Et\textsubscript{2}O
3. HOAc/ Et\textsubscript{2}O
4. Ag\textsubscript{2}O (four steps: 82% yield)

In 2006, as part of reported total synthesis of (-)-deoxyharringtonine (22), Gin described the preparation of the acyl side chain (Scheme 1.2.2.3).\textsuperscript{17} Commencing with
commercially available D-malic acid 50, acetal 51 was afforded in a two-step procedure. Alkylation of 51 followed by acetal opening gave γ-hydroxy acid 52. Lactone 53 was produced via Yamaguchi lactonization\textsuperscript{18} followed by alkene hydrogenation and removal of benzyl group. Coupling of 53 with cephalotaxine via the Yamaguchi protocol yielded ester 54. Methanolysis concluded the synthesis of (-)-deoxyharringtonine (22).

\textbf{Scheme 1.2.2.3 Gin’s Procedure for the Synthesis of Acid Side Chain}

1.2.3 Synthetic Routes to the Tetracyclic Core of Cephalezomine A

The significant anticancer activities and intriguing chemical structures have made the \textit{Cephalotaxus} alkaloids attractive targets for synthetic chemists. Since the report of the first total synthesis of cephalotaxine by Weinreb and Semmelhack in 1972,\textsuperscript{19,20} a number of innovative synthetic strategies have been developed towards the synthesis of the cephalotaxine core ring system. One of the most commonly employed strategic
approaches involves forming the B-ring of cephalezomine A core ring system (55) from an N-spirocyclic intermediate (56, Scheme 1.2.3.1).

*Scheme 1.2.3.1 B Ring Closure of a N-Spiro Cyclic Precursor*

Typical B ring closure approaches include Friedel-Crafts- and Heck-type cyclization strategies.

*Kuehne’s total synthesis of dl-cephalotaxine:* Lactam 57 was ring-contracted to the spiro C, D ring of 58 in the presence of Pb(OAc)₄ (Scheme 1.2.3.2). Further transformation of 58 furnished acetate 59 which was utilized as substrate in the illustrated palladium mediated coupling to furnish the B-ring of 60.²¹

*Scheme 1.2.3.2 Friedel-Crafts Cyclization for B Ring Closure: Kuehne’s Work*

*Sha’s approach towards total synthesis of dl-cephalotaxine:* An intramolecular cyclization of 61 in the presence of PTSA gave the spiro C, D ring of 62 (Scheme
1.2.3.3). Ozonolysis, followed by deprotection produced 63, which, upon alkylation, provided cyclization precursor 64. Friedel-Crafts cyclization in the presence of polyphosphoric acid completed the construction of 65.22

Scheme 1.2.3.3 Friedel-Crafts Cyclization for B Ring Closure: Sha’s Work

Mori’s total synthesis of (-)-cephalotaxine: Vinyl iodide 66 was cyclized in the presence of Me₃SiSnBu₃ and CsF to form the spirocyclic C, D-ring system in allylic alcohol 67 (Scheme 1.2.3.4). The B-ring of 68 was closed by Friedel-Crafts cyclization in the presence of polyphosphoric acid.23

Scheme 1.2.3.4 Friedel-Crafts Cyclization for B Ring Closure: Mori’s Work
Royer’s total synthesis of (-)-cephalotaxine: Expansion of the cyclobutane ring in 69 under acidic conditions gave ketone 70 which possesses the spirocyclic C, D-ring system (Scheme 1.2.3.5). This substrate was further advance to allylic alcohol 71 which upon exposure to the Lewis acid SnCl₄ underwent B-ring closure to furnish 72.²⁴

**Scheme 1.2.3.5 Friedel-Crafts Cyclization for B Ring Closure: Royer’s Work**

Li’s formal total synthesis of dl-cephalotaxine: The Li group reported that Friedel-Crafts type alkylation occurs upon exposure of 72 to TfOH and forms ketone 73 which, in five steps can be converted to cephalotaxine (Scheme 1.2.3.6).²⁵

**Scheme 1.2.3.6 Friedel-Crafts Cyclization for B Ring Closure: Li’s Work**

Hayes’s first formal total synthesis of (-)-cephalotaxine: Hayes reported that treatment of 74 with deprotonated TMSCHN₂ furnishes carbene intermediate 75, which undergoes intramolecular C-H insertion to give the spirocyclic C, D-ring system in 76
(Scheme 1.2.3.7). Further transformation of 76 produces an allylic alcohol (78) which, upon exposure to Lewis acid SnCl₄ undergoes B-ring closure to produce 68.²⁶

Scheme 1.2.3.7 Friedel-Crafts Cyclization for B Ring Closure: Hayes’s Work

Hayes’s second formal total synthesis of (-)-cephalotaxine: An intramolecular C-H insertion of the vinyl carbene derived from vinyl chloride 78 produced the spirocyclic ring of 79 (Scheme 1.2.3.8). Iodination of 79 provided 80 and set the stage for an intramolecular Heck cyclization that furnished tetracycle 81.²⁷

Scheme 1.2.3.8 Heck Cyclization for B Ring Closure: Hayes’s Work
Tietze's formal total synthesis of (-)-cephalotaxine: Tietze reported that an intramolecular amination of the π-allyl intermediate derived from allylic acetate 83 produces the spirocyclic C, D-ring of 84 (Scheme 1.2.3.9). An intramolecular Heck cyclization was then used to close the B-ring and form 82.²⁸

Scheme 1.2.3.9 Heck Cyclization for B Ring Closure: Tietze’s Work

Stoltz’s total synthesis of (-)-cephalotaxine and (-)-drupacine: Stoltz applied an intramolecular Heck cyclization to advance 85 to intermediate 86. One of the unique features of the Stoltz synthesis is the inclusion of alcohol at C-11 which allows for eventual access to both the cephalotaxine and drupacine ring systems (Scheme 1.2.3.10).²⁹

Scheme 1.2.3.10 Heck Cyclization for B Ring Closure: Stoltz’s Work
Semmelhack’s total synthesis of dl-cephalotaxine: Semmelhack reported that the B-ring in intermediate 87 could be produced upon exposure of 88 to a variety of reaction conditions (Scheme 1.2.3.11). The best yield was achieved by photo-SRN\(^{-1}\) reaction in the presence of base.\(^{31}\)

Scheme 1.2.3.11 Semmelhack’s synthesis

In addition to approaches that assemble the spirocyclic C, D-ring system prior to formation of the B-ring, there are, several reports of strategies leading to the cephalotaxine ring system wherein construction of the spirocycle occurs at a later stage. These include:

Wienreb’s total synthesis of dl-cephalotaxine: In this synthesis, Friedel-Crafts type reaction of aldehyde 90 produced enamine 91 (Scheme 1.2.3.12). In a subsequent 4-steps 91 was converted to diketone 92 which upon exposure to Mg(OMe)\(_2\) underwent Nazarov cyclization to furnish 93.\(^{19,30}\)
**Scheme 1.2.3.12 Weinreb’s Synthesis**

\[
\begin{align*}
\text{90} \xrightarrow{\text{BF}_3\cdot\text{EtO}_2 (85\% \text{ yield})} & \quad \text{91} \\
\text{91} \xrightarrow{\text{4 steps}} & \quad \text{92} \\
\text{Mg}(\text{OMe})_2 & \quad \xrightarrow{(58\% \text{ yield})} \quad \text{93} \\
\text{93} \xrightarrow{\text{2 steps}} & \quad \text{94} \\
\text{94} \xrightarrow{\text{MeO} \cdot \text{N} \cdot \text{O} \cdot \text{C} \cdot \text{H}} & \quad \text{95} \\
\text{95} \xrightarrow{\text{Polyphosphoric acid (74\% \text{ yield})}} & \quad \text{96} \\
\text{96} \xrightarrow{\text{5 steps}} & \quad \text{97} \\
\text{97} \xrightarrow{\text{H}_2\text{SO}_4 (69\% \text{ yield})} & \quad \text{98} \\
\end{align*}
\]

*Hanaoka’s total synthesis of dl-cephalotaxine*: Hanaoka reported that exposure of carboxylic acid 94 to polyphosphoric acid induced a Friedel-Crafts acylation which furnished ketone 95 (**Scheme 1.2.3.13**). Conversion of 95 in 3-steps to vinyl chloride 96 set the stage for acid mediated cyclization to furnish 97.\(^\text{32}\)

**Scheme 1.2.3.13 Hanaoka’s synthesis**

*Fuchs’ total synthesis of dl-cephalotaxine and drupacine*: Oxidation of hydroxamic acid 98 to the corresponding acylnitroso species followed by intramolecular
hetero Diels-Alder reaction formed 99. Intermediate 99 was converted to cephalotaxine and drupacine in 10 and 9 steps respectively. (Scheme 1.2.3.14).\(^{33}\)

**Scheme 1.2.3.14 Fuchs’ Synthesis**

Bryce’s approach towards the total synthesis of dl-cephalotaxine: Lactam-aldehyde 100 was cyclized to hemiaminal 102 by treatment with DIBAL-H. The reaction was believed to occur through an aluminum complex, which is either monocooordinated (to the aldehyde oxygen) or chelated (to both the aldehyde and lactam oxygens). Such a complex (e.g., 101) would activate the carbonyl group of the aldehyde to nucleophilic attack by the lactam nitrogen. (Scheme 1.2.3.15).\(^{34}\)

**Scheme 1.2.3.15 Bryce’s Approach**

Mariano’s total synthesis of dl-cephalotaxine: Macrocyclization of 103 gave intermediate 104 (Scheme 1.2.3.16). Hydrogenolysis to remove the benzyl protecting
group, was followed by transannular conjugate addition of the free amine to provide ketone 93.\textsuperscript{35}

**Scheme 1.2.3.16 Mariano’s Synthesis**

![Scheme 1.2.3.16 Mariano’s Synthesis](image)

**Nagasaki’s formal total synthesis of dl-cephalotaxine:** In Nagasaki’s formal synthesis it was reported that treatment of isoindoquinoline 105 with SO\textsubscript{2}Cl\textsubscript{2} produces ring-expansion product 106 (Scheme 1.2.3.17). Further advancement of 106 furnished β-keto ester 107 which, upon exposure to TiCl\textsubscript{4} and NIS (N-iodosuccinimide) undergoes ring-closure to 108.\textsuperscript{36}

**Scheme 1.2.3.17 Nagasaki’s Synthesis**

![Scheme 1.2.3.17 Nagasaki’s Synthesis](image)
Li’s formal total synthesis of dl-cephalotaxine: In an interesting ring-expansion/contraction approach, Li reported that exposure of intermediate 109 to zinc and acetic acid rearranged product 110 (Scheme 1.2.3.18).37

Scheme 1.2.3.18 Li’s Synthesis

Ishibashi’s total synthesis of (-)-cephalotaxine: In Ishibashi’s total synthesis, a radical cascade cyclization was applied to transform aryl iodide 111 to 112 wherein construction of the B and C rings has occurred via a sequential 7-endo, 5-endo-trig cyclization (Scheme 1.2.3.19).38

Scheme 1.2.3.19 Ishibashi’s Synthesis

Gin’s total synthesis of (-)-cephalotaxine and (-)-dehydroxyharringtonine: Gin reported that the B-ring found in intermediate 113 can be produced from aziridine 114 via [3,3]-rearrangement (Scheme 1.2.3.20). Subsequent alkylation with TMSCH2I sets the stage for a [2+3] cyclization with vinyl sulfonate to complete the construction of the C ring in substrate 115.39
Scheme 1.2.3.20 Gin’s Synthesis

1. $\text{C}_6\text{H}_5\text{CO}_3$ (76% yield)

2. TMSCH$_2$I (75% yield)

$\text{PivCl, AgOTf, TBAT} \xrightarrow{\text{SO}_2\text{Ph}}$ (77% yield)

(-)-Cephalotaxine Acylation$\xrightarrow{(-)-\text{Degydroxharringtonine}}$ (-)-Degydroxharringtonine
1.3 Conclusions

Many research groups have initiated synthetic studies of the *Cephalotaxus* alkaloids due to their significant biological activities and interesting chemical structures. From the investigation of these compact molecular templates, new chemical transformations and methodologies have been developed.
1.4 Notes and References


12. Battersby, A. R.; McDonald, E.; Milner, J. A.; Johns, S. R.; Lamberton, J. A.; Sioumis, A. A., Biosynthesis of schelhammeridine- mode of specific incorporation of 2-


33. (1) Burkholder, T. P.; Fuchs, P. L., Total synthesis of d,l-cephalotaxine- the first example of an intramolecular 4+2 cyclo-addition where the dienophile has been delivered from the face opposite to the tethering moiety. *Journal of the American Chemical Society* **1988**, *110*, (7), 2341-2342;


Chapter 2

Approach Towards the Total Synthesis of Cephalezomine A

Given that cephalezomine A has dramatic biological activities and is isolated in low yield\(^1\) coupled with the fact that it has yet to succumb to total synthesis, led us to target this fascinating and challenging natural product.

2.1 Retrosynthetic Analysis I

The retrosynthetic analysis of cephalezomine A (1) is outlined in Scheme 2.1.1. Retrosynthetic cleavage of the ester bond in cephalezomine A (1) furnishes the acyl side chain (150) and drupacine (18). It is known that drupacine (18) can be prepared from 11-hydroxycephelotaxine (20) in one step.\(^2\) In our retro synthetic analysis, 11-hydroxycephelotaxine (20) derives from the cyclization of substrate 152. In the forward sense, exposure of dienone 152 to Lewis Acid conditions is envisioned to furnish cationic intermediate 151 via a Nazarov cyclization. This intermediate could, in turn, undergo a Friedel- Crafts type cyclization to form 11-hydroxycephelotaxine (20). Disubstituted dienone 152 is seen as arising from 153 by nucleophilic addition of an \(\alpha\)-lithio vinyl ether to Weinreb amide 153 which will derive from the union of epoxide 154 and vinylogous urea 155.
Scheme 2.1.1 Retrosynthetic Analysis I

2.2 Synthesis of Dienone 152

2.2.1 Coupling of an Epoxide and a Vinylogous Amide

One of the coupling precursors, epoxide 154 was prepared from piperonal (156) in good yield by a Johnson-Corey-Chaykovsky reaction (Scheme 2.2.1).3 The remaining coupling partner vinylogous urea 155 was prepared by treatment of 2-methyl-1-pyrroline (157) with LDA, followed by addition of dimethylcarbamic chloride. Attempts to couple epoxide 154 and vinylogous amide 155 were conducted under numerous conditions.
Unfortunately, no desired coupling product 158 was observed and starting material was either recovered or decomposed. The poor nucleophile character of the vinylogous urea nitrogen was not unexpected and similar reactivity was observed upon exposure of pyrrolidin-2-one (159) to epoxide 154. Given that the nucleophile (vinylogous urea 155) was seen as the least variable substrate, we next explored alteration of the electrophile.

**Scheme 2.2.1 Coupling of Epoxide and Vinylogous amide**

![Scheme Diagram]

2.2.2 Coupling of an α-Bromo Ketone and a Vinylogous Urea

In considering other possible electrophiles, we first explored α-bromo ketone 162.

The preparation of 162 began with addition of MeMgBr to piperonal (156) and oxidation of newly formed secondary alcohol to ketone 161 (Scheme 2.2.2). Treatment of ketone 161 with bromine produced α-bromo ketone 162 in excellent yield and the latter could
be readily protected as its ethylene glycol acetal to provide an additional electrophile substrate 163.

**Scheme 2.2.2 Preparation of Bromo Ketone**

As illustrated in Table 2.2.2, our efforts to engage vinylogous urea 155 with the more reactive α-bromo ketone 162 were unsuccessful. Under basic conditions (K₂CO₃, Cs₂CO₃, n-BuLi), bromo ketone 162 decomposed and vinylogous urea 155 was recovered. Under milder conditions (EtOH or Et₃N), both of the starting materials were recovered. Given these results, we turned to another electrophile: bromide 163, which is more stable under harsh conditions; however, only starting material was recovered upon exposure to either mild or strong basic conditions. Although less desirable, at this stage addressing the nucleophilicity of the vinylogous urea 155 became the next step.
Table 2.2.2 Coupling Conditions of Bromo Ketone and Vinylogous Urea

<table>
<thead>
<tr>
<th>conditions</th>
<th>results</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{K}_2\text{CO}_3$, DMF or MeCN, r.t.</td>
<td>162, decomposed; 155, recovered</td>
</tr>
<tr>
<td>$\text{Cs}_2\text{CO}_3$, DMF or MeCN, r.t.</td>
<td>162, decomposed; 155, recovered</td>
</tr>
<tr>
<td>NaH, THF, r.t.</td>
<td>162, decomposed; 155, recovered</td>
</tr>
<tr>
<td>KOH, n-Bu$_3$N, MeCN or THF, r.t</td>
<td>162, decomposed; 155, recovered</td>
</tr>
<tr>
<td>n-BuLi, -78°C, THF</td>
<td>162, decomposed; 155, recovered</td>
</tr>
<tr>
<td>n-BuLi, -78°C to r.t., THF</td>
<td>162, decomposed; 155, decomposed</td>
</tr>
<tr>
<td>EtOH, r.t.</td>
<td>162, recovered; 155, recovered</td>
</tr>
<tr>
<td>Et$_3$N, DCM, r.t.</td>
<td>162, recovered; 155, recovered</td>
</tr>
<tr>
<td>$\text{AgOAc}, \text{AgOTf} \text{ or AgNO}_3, \text{Tol/THF or MeCN, r.t}$</td>
<td>162, decomposed; 155, recovered</td>
</tr>
<tr>
<td>$\text{K}_2\text{CO}_3$, DMF, r.t.</td>
<td>163, recovered; 155, recovered</td>
</tr>
<tr>
<td>n-BuLi, -78°C to r.t., THF</td>
<td>163, recovered; 155, recovered</td>
</tr>
</tbody>
</table>

2.2.3 Coupling of an $\alpha$-Bromo Ketone with an Amide

Since pyrrolidin-2-one (159) has been reported to serve effectively as a nucleophile in coupling reactions with $\alpha$-halogenated ketones at room temperature,$^5$ we decided to explore its coupling with bromo ketone 162. From a retrosynthetic perspective (Scheme 2.2.3.1), this change to a less functionalized nucleophile requires further manipulation of vinylogous urea 153 to produce requisite dienone 152. To this end, it was
envisioned that an Eschenmoser coupling of α-halo amide 166 and thiolactam 167 would deliver intermediate 153 via an addition-elimination process.

Scheme 2.2.3.1 Revised Coupling Retrosynthetic Analysis

In practice, initial studies on the coupling of 162 and pyrrolidin-2-one (159) to yield 168 using NaH were modestly successful (56% yield). Further study revealed that using 2-methoxy-1-pyrroline (169) as nucleophile instead of amide 159 results in a significantly improved yield. Protection of 168 using ethylene glycol gave 170.
**Scheme 2.2.3.2 Coupling of Bromo Ketone with Amide**

![Scheme 2.2.3.2 Coupling of Bromo Ketone with Amide](image)

Having set the stage for the planned coupling (see 170 to 153 in **Scheme 2.2.3.3**), we first explored the use of lactam 171 to establish our ability to effect a coupling of α-halo amide 166.

**Scheme 2.2.3.3 Proposed Model Study on the Coupling of Substrate 170 with 166**

**Proposed Real System:**

![Proposed Real System](image)

**Proposed Model:**

![Proposed Model](image)
In preliminary studies we explored the direct coupling of \textbf{171} to form the vinylogous urea \textbf{172} or amide \textbf{175} (Scheme 2.2.3.4). Different nucleophiles, such as deprotonated $N$-methoxy-$N$-methylacetamide \textbf{173} and silyl enol ether \textbf{174},\textsuperscript{6} were investigated. However, no desired product was observed. Coupling also failed when the corresponding ammonium salt \textbf{176}, which was produced by methylation of amide \textbf{171}.

\textit{Scheme 2.2.3.4 Addition and Elimination for the Coupling Study}

We next turned to the Eschenmoser Coupling\textsuperscript{9} and set the stage for this coupling via the conversion of lactam \textbf{171} to thiolactam \textbf{177} by treatment with Lawesson’s reagent.\textsuperscript{7} Subsequent coupling of \textbf{177} with either an $\alpha$-bromo amide\textsuperscript{8} or ester produced the coupling product (e.g. amide \textbf{179} or ester \textbf{180}, Scheme 2.2.3.5). However, the product \textbf{179} was difficult to separate from triphenyl phosphine sulfide, which was produced in the coupling reaction.
Further optimization of the coupling (Table 2.2.3) identified triethyl phosphite as the best phosphorus source; Eschenmoser coupling under these conditions proceeds in higher yield and purification of the desired product is greatly simplified.

Table 2.2.3 Optimized Eschenmoser Coupling for Model

<table>
<thead>
<tr>
<th>R₃P</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPh₃</td>
<td>S.M. + P.</td>
</tr>
<tr>
<td>(EtO)₂P</td>
<td>yield: 87%</td>
</tr>
<tr>
<td>Et₃P</td>
<td>None P.</td>
</tr>
</tbody>
</table>

As illustrated in Scheme 2.2.3.6, the conditions developed in our model study proceeded effectively in the real system. In the event, conversion of lactam 170 to thiolactam 167, followed by Eschenmoser coupling gave precursor 182 in excellent yield.
Interestingly, purification of this product was easily achieved even when PPh$_3$ was employed.

![Scheme 2.2.3.6 Eschenmoser Coupling for Real System](image)

2.2.4 Efforts to Access Dienone 152 from Weinreb Amide 182

Our exploration into the transformation of Weinreb amide 153 to dienone 152 (as illustrated in the retrosynthetic analysis scheme 2.2.3.1) began with model substrate 179. Exposure of 179 to more than 3 equivalent of lithio vinyl ether$^{10}$ or vinyl magnesium bromide$^{11}$ resulted only in isolation of recovered starting material (Table 2.2.4).
Unfortunately, as illustrated in Scheme 2.2.4, similar results were obtained in the real system. Since the difficult nucleophilic addition was likely due the decreased reactivity of the vinylogous urea, we turned to an alternative wherein the vinyl group would be introduced prior to Eschenmoser coupling.

Scheme 2.2.4 Nucleophilic Addition Failure in Real System for Synthesis of Dienone
2.2.5 Changing the Order of Events: Eschenmoser Coupling of Enones

Since Eschenmoser Coupling with α-halogenated amides or esters has been reported, we were optimistic about coupling the α-halogenated enone 187 with thiolactam 167 to form dienone 152 (Scheme 2.2.5.1).

Scheme 2.2.5.1 Revised Coupling Retrosynthetic Analysis

Implementation of this idea required preparation of the α-halo ketone 187. To this end, our first approach was to attempt the nucleophilic addition of a lithium, magnesium or zinc, vinyl metal species to bromoacetyl bromide (188, Scheme 2.2.5.2). Unfortunately, no desired product (190) was obtained.

Scheme 2.2.5.2 Approach to Bromo Enone by Vinyl Nucleophile Addition

Turning to an alternative approach involving bromination of an intact enone system we were delighted to find several examples of in the literature describing the bromination of methyl vinyl ketones. For example, Li demonstrated that vinyl ketone 191 furnished
bromide 193 upon treatment with tri[pyrrolidine-2-one] hydrobromide (192) at -78 °C (Scheme 2.2.5.3).\textsuperscript{12} Given our need for a terminal alkenyl ketone, we explored Li’s conditions on methyl vinyl ketone 194; however, the undesired dibromide 196 was the only observed product.

\textit{Scheme 2.2.5.3 Approach to Bromo Enone via Bromination Process I}

In a different report, Herman described that treatment of TMS silyl enol ether 197 with NBS produced bromination product 193 (Scheme 2.2.5.4).\textsuperscript{13} Exploring these conditions on TMS silyl enol ether 194, we observed only starting material decomposition and no desired product.
A more relevant example was found in the work of Danishefsky who reported that addition of ethylene (198) to chloroacetyl chloride (199) followed by elimination produced product 200 in good yield (Scheme 2.2.5.5). In repeating this experiments, we did obtain some of the desired product 200. However, the yield was poor.

In a more recent report, Ram described that the treatment of allylic alcohol 201 with cuprous chloride to give α-chloro enone 202 in good yield (Scheme 2.2.5.6). The mechanism is believed to involve a copper(I) carbenoid mediated 1,2-H shift process. Since our coupling target was α-chloro alkoxy-enone 209 or 210, the exploration of
Ram’s procedure requires the preparation of alkoxy-allylic alcohol 205 or 206 as illustrated in Scheme 2.2.5.6. Addition of litho vinyl ether 204 to DMF (203) produced aldehyde 205 or 206, which upon exposure to chloroform under basic conditions furnished the corresponding allylic alcohol 207 or 208 in good yield. At this point we were delighted to find that the application of Ram’s procedure to 207 or 208 furnished the desired α-Chloro alkoxy-enone 209 or 210 in good yield. Since ethoxyl enone 209 is volatile at room temperature, we employed butoxyl enone 210 in subsequent studies.

**Scheme 2.2.5.6 Synthesis of Chloro Enone via Copper(I) Carbenoid 1,2 H Shift Process**

![Scheme 2.2.5.6 Synthesis of Chloro Enone via Copper(I) Carbenoid 1,2 H Shift Process](image)

Impressively, Eschenmoser coupling of 167 with 210 gave the desired key precursor 211 and set the stage for investigation of the Nazarov cyclization (Scheme 2.2.5.7).
2.3 Nazarov Cyclization of Dienone 211

Recent reports by West\textsuperscript{16} describing the successful tandem Nazarov cyclization/Friedel-Crafts reaction of heavily substituted dienone 213 left us encouraged at prospects of employing dienone 211 in a similar reaction (Scheme 2.3.1). We were additionally encouraged by recent studies from Frontier describing the benefits of electron donating substituents.\textsuperscript{17} Unfortunately, despite similarity to West’s system and presence of additional electron donating substituent’s, the Nazarov cyclization failed for our substrate 211 under standard Lewis acid conditions (TiCl\textsubscript{4} or BF\textsubscript{3}•OEt\textsubscript{2} at room temperature). At lower temperature, only starting material was observed and when the temperature was increased to 0 °C, NMR monitoring indicated only decomposition. Given that West’s substrates lack both alkoxy and N-substituted functional groups, we decided to investigate the Nazarov cyclization on model systems wherein these two dienone substituents are present individually.
To explore the effects of an alkoxy substituent, model system dienone 217 was prepared by addition of lithio vinyl ether to the Weinreb amide derived from benzoyl chloride (Scheme 2.3.2). Additionally, model system 220 was prepared by addition of lithiated vinyl ether to piperine (219). Interestingly, both model dienone 217 and 220 underwent smooth cyclization under Lewis acid conditions. These results indicated that alkoxy substituents in the α-position were not deleterious to Nazarov cyclization. Noteworthy was the decrease in yield for the cyclization of 220 compared to 217. Based on studies by Sharpen this was expected.18
To investigate the effect of the vinylogous amide substituent on Nazarov cyclization, we prepared model 175 (Scheme 2.3.3). In a first attempt to this end, treatment of acryloyl chloride with lithiated 2-methyl-1-pyrroline (157) gave undesired product amide 224 via N-acylation. In a second attempt, acryloyl chloride (225) was pretreated with N, O-dimethylhydroxylamine hydrochloride (226) to yield Weinreb amide 227. With this substrate, addition of lithiated 2-methyl-1-pyrroline furnished the desired vinylogous amide 223 which, upon, methylation delivered dienone 175.
With the model substrate dienone 175 in hand, a variety of conditions were explored in order to produce spiro ketone 228 by Nazarov cyclization. Conditions include Lewis acid: SiO$_2$, AlCl$_3$, Et$_2$AlCl or Me$_3$Al, TiCl$_4$ or BF$_3$•OEt$_2$, PdCl$_2$(MeCN)$_2$ or Pd(OAc)$_2$, Sc(OTf)$_3$, FeCl$_3$, Cu(OTf)$_2$, Yb(OTf)$_3$, TBSOTf; TFA and HCOOH/H$_3$PO$_4$. Unfortunately, under all of the conditions no desired product was observed. Starting material was recovered or decomposed (Table 2.3). This result led us to believe that the vinylogous amide substituent was the culprit in our failed Nazarov cyclization.
Table 2.3 Nazarov Cyclization Test with N-Substituted Model 175

![Diagram showing Nazarov cyclization]

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>SiO₂, r.t.</td>
<td>S.M. recovered</td>
</tr>
<tr>
<td>AlCl₃, 0° or r.t. or reflux</td>
<td>S.M. recovered; decomposed (reflux)</td>
</tr>
<tr>
<td>Et₂AlCl or Me₃Al, -78 °C to r.t.</td>
<td>S.M. recovered</td>
</tr>
<tr>
<td>TiCl₄ or BF₃·OEt₂, -78°C to r.t.</td>
<td>decomposed</td>
</tr>
<tr>
<td>PdCl₂(MeCN)₂ or Pd(OAc)₂, r.t.</td>
<td>S.M. recovered</td>
</tr>
<tr>
<td>Sc(OTf)₃</td>
<td>decomposed</td>
</tr>
<tr>
<td>FeCl₃</td>
<td>decomposed</td>
</tr>
<tr>
<td>Cu(OTf)₂, r.t. or 50°</td>
<td>S.M. recovered</td>
</tr>
<tr>
<td>Yb(OTf)₃</td>
<td>S.M. recovered</td>
</tr>
<tr>
<td>TBSOTf, -78° to r.t.</td>
<td>S.M. recovered</td>
</tr>
<tr>
<td>TFA, r.t.</td>
<td>S.M. recovered</td>
</tr>
<tr>
<td>HCOOH, H₃PO₄</td>
<td>decomposed</td>
</tr>
</tbody>
</table>

As a third model system we prepared a dienone containing both of the alkoxy and vinylogous amide substituents. To prepare dienone 231, dimethyl carbamic chloride (229) was treated with lithiated vinyl ether, followed by addition of lithiated 2-methyl-1-pyrroline. Methylation of intermediate 230 gave desired dienone 231 (scheme 2.3.4). Nazarov cyclization was only conducted under the TiCl₄ conditions that proved successful for dienone 217. Unfortunately, only the diketone 233 was produced and none of the spiro product 232 was observed.
Results from the above studies indicated that altering the electronic nature of the amine might impact the Nazarov cyclization. To investigate this possibility, it was decided to attempt converting the vinylogous amide to a vinylogous imide prior to Nazarov cyclization. Access to this new Nazarov substrate (235) was gained simple through a simple peptide coupling of 234 and 230 (Scheme 2.3.5). \(^{21}\)

**Scheme 2.3.5 Preparation of Deactivated N-Substituted Dienone**

\[ \begin{align*}
156 & \xrightarrow{\text{1. CHBr}_3, \text{KOH}} 234 + 230 \\
& \xrightarrow{\text{2. AcCl, py}} \text{(3 steps: 80\% yield)} \\
& \xrightarrow{\text{3. SOCl}_2} \\
& \xrightarrow{\text{KO}^\text{tBu}} \text{MeCN, r.t.} \quad \text{(37\% yield)} \\
\end{align*} \]
Unfortunately, under Lewis acid promoted Nazarov cyclization conditions \textbf{235} was found to deliver none of the desired product \textbf{236}. Only decomposition of the starting material was observed (\textit{Scheme 2.3.6}). Based on these results the Nazarov cyclization route was abandoned and alternatives were considered.

\textit{Scheme 2.3.6 Nazarov Cyclization Test with Deactivated N-Substituted Dienone 235}

\begin{center}
\includegraphics[width=\textwidth]{Scheme2.3.6.png}
\end{center}

\textbf{2.4 Considering an Alternative Strategy}

The failure of the Nazarov cyclization approach coupled with recent success with tandem radical reactions in the Wood group\textsuperscript{22} led us to consider an alternative approach (\textit{Scheme 2.4.1}). As illustrated in retrosynthetic fashion, this approach relies on the same bond construction as the Nazarov cyclization strategy; however in this radical based approach one can view bond formation as moving from the aromatic moiety to the vinylogous amide system (substrate \textbf{239} to \textbf{238} to \textbf{237}). Importantly, although the underlying chemistry is quite different, the substrates required for the radical approach are fairly similar to those employed in our studies of the Nazarov cyclization. Thus great advantage could be taken of previously developed chemistry.
In the forward sense, preparation of the radical cyclization substrate began with bromination of piperonal (Scheme 2.4.2). The desired bromide 240 was taken through a 7-step sequence similar to that employed for substrate 211. In the end, substrate 247 and 248 were accessed in good yield.
Scheme 2.4.2 Preparation for Radical Cyclization

With radical cyclization substrates 247 and 248 in hand, we were disappointed to find that in the presence of Bu₃SnH/ AIBN or SmI₂ neither gave the desired product 249 (Scheme 2.4.2). Under the Bu₃SnH/AIBN conditions,²²,²³ reductive debromination products were observed whereas under the SmI₂ conditions,²²,²⁴ the starting materials were found to decompose.

Scheme 2.4.2 Radical Cyclization Approach
2.5 Conclusions

Efforts to assemble the core structure found in 11-hydroxycepalotaxine (20) using either a tandem Nazarov/Friedel-Crafts cyclization or radical cascade sequence failed. Despite the failure of the key steps, considerable chemistry was developed in the course of the assembling the requisite intermediates.
2.6 Experimental Section

2.6.1 Materials and Methods

General. Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran (THF) was dried either by distillation from sodium/benzophenone or by passing through activated alumina columns. Methylene chloride (DCM), diethyl ether (Et₂O), benzene (PhH), toluene (Tol) and acetonitrile (MeCN) were dried by passing through activated alumina columns. Dimethylformamide (DMF) was dried over activated molecular sieves or by passing through activated alumina columns. MeOH was distilled over magnesium oxide. All other commercially obtained reagents were used as received. All reactions were monitored by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm). Flash chromatography was performed with indicated solvents using silica gel (particle size 0.032-0.063) purchased from Silicycle. Microwave experiments were performed using a Biotage Initiator® or CEM Discover microwave reactor. ¹H NMR spectra were recorded at 500 MHz, 400 MHz or 300 MHz using a Bruker AM-500, Bruker Avance DPX-500, Bruker AM-400, Varian Inova 400, Varian Inova 300 or Varian Mercury Inova 300 instrument. ¹³C NMR spectra were recorded at 125 MHz, 100 or 75 MHz using a Bruker AM-500, Bruker Avance DPX-500, Bruker AM-400, Varian Inova 400, Varian Inova 300 or Varian Mercury Inova 300 instrument. Chemical shifts are reported relative to internal chloroform (¹H, δ = 7.26, ¹³C, δ = 77.1) as indicated. Splitting patterns are reported as such, app = apparent, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet. Infrared spectra were recorded on a
Nicolet Avatar 320 FT-IR. High-resolution mass spectra were acquired at the Colorado State University CIF using an Agilent 6210 TOF LCMS.

2.6.2 Preparative Procedures

Preparation of vinylogous amide 155

![Chemical structure](image)

To a solution of diisopropylamine (280 µL, 2 mmol, 2.0 equiv.) in THF (1mL) at 0 °C was added n-BuLi (1.25 mL, 2 mmol, 2.0 equiv., 1.6 M hexanes solution) dropwise over 5 minutes. The resultant mixture was stirred at 0 °C for 10 minutes and then cooled to -78 °C. To this LDA solution was added 2-methyl-pyrroline (157) (95 µL, 1.00 mmol, 1 equiv.). The solution was stirred for 1 hour. To this mixture was added dimethylcarbamic chloride (180 µL, 2 mmol, 2 equiv.). The reaction was stirred for three hours at -78 °C and quenched by H₂O (2 mL). The layers were separated and aqueous layer was washed with EtOAc (2 × 2 mL). The combined organic layers were washed with brine (4 mL) and dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%-50% EtOAc/Hexanes) to yield 155 (101mg, 65%) as brown oil.

Vinylogous amide 155: FTIR(NaCl/ thin film) 3343, 2925, 2877, 2361, 2339, 1624, 1567, 1516, 1369, 1310, 1294, 1144,1059, 762, 685 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.62-8.49 (m, 1H), 4.66 (s, 1H), 3.43 (t, J=6.8 Hz, 2H), 2.90 (s, 6H), 2.53 (t,
\( J=7.7 \text{ Hz}, 2\text{H})\), 1.89 (dd, \( J=7.3, 14.5 \text{ Hz}, 2\text{H})\); \(^{13}\text{C} \text{ NMR} (100 \text{ MHz, CDCl}_3) \delta \ 171.3, 164.1, 76.0, 46.8, 36.4, 32.5, 22.1; \ \text{HRMS (TOF LCMS)} \text{ calc'd for } C_8H_{14}N_2O [M+H]^{+} 155.1184, \text{ found } 155.1178.

**Preparation of amide 168**

\[
\begin{array}{c}
\text{O} \\
\text{O} \\
Br \\
N \text{O} \\
\text{Me} \\
M \\
C \text{N} \\
60 ^\circ \text{C} \\
(\text{quant. yield}) \\
\end{array}
\]

To a solution of 162 (18.8 g, 49.1 mmol, 1 equiv.) in MeCN (45 mL) was added 2-Methoxy-1-pyrrole (169) (7.3 g, 73.7 mmol, 1.5 equiv.). The mixture was heated to 60 \(^\circ\text{C}\) and stirred for 2 days. The reaction was cooled to room temperature and concentrated by reducing pressure to yield pure 168 (12.5g) as brown oil.

**Amide 168:** FTIR (NaCl/ thin film) 2911, 1677, 1604, 1445, 1365, 1289, 1255, 1141, 1110, 1036, 931, 886 cm\(^{-1}\); \(^1\text{H} \text{ NMR} (400 \text{ MHz, CDCl}_3) \delta 7.56 (dd, \( J=1.8, 8.2 \text{ Hz}, 1\text{H}), 7.41 (d, \( J=1.6 \text{ Hz}, 1\text{H}), 6.85 (d, \( J=8.2 \text{ Hz}, 1\text{H}), 6.05 (s, 2\text{H}), 6.64 (s, 2\text{H}), 3.49 (t, \( J=6.9 \text{ Hz}, 2\text{H}), 2.47 (t, \( J=7.8 \text{ Hz}, 2\text{H}), 2.19-2.01 (m, 2\text{H}); \(^{13}\text{C} \text{ NMR} (100 \text{ MHz, CDCl}_3) \delta 191.9, 175.9, 152.4, 148.4, 129.8, 124.6, 108.2, 107.8, 102.1, 48.9, 48.0, 30.5, 18.2; \ \text{HRMS (TOF LCMS)} \text{ calc'd for } C_{13}H_{14}NO_4 [M+H]^{+} 248.0923, \text{ found } 248.0922.
Preparation of amide 170

To a solution of 168 (1.8 g, 7.28 mmol, 1 equiv.) in Benzene (125 mL) was added ethyl glycol (4.1 mL, 73.3 mmol, 10 equiv.) and p-Toluenesulfonic acid (180mg, 1.05 mmol, 0.14 equiv.). The mixture was heated to reflux and stirred for overnight. The mixture was cooled to room temperature and washed by saturated aqueous NaHCO₃ (2 × 20 mL). The organic layer was dried by Na₂SO₄, filtered through Celite and concentrated by reducing pressure to yield pure 170 (2.2g) as brown solid.

**Amide 170:** FTIR (NaCl/ thin film) 2892, 1686, 1437, 1248, 1175, 1103, 1036, 1000, 932, 812 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.98 (dd, J=1.2, 7.2 Hz, 1H), 6.97 (d, J=0.7 Hz, 1H), 6.76 (d, J=7.4 Hz, 1H), 5.95 (s, 2H), 4.02 (t, J=6.9 Hz, 2H), 3.80 (t, J=6.5 Hz, 2H), 3.62 (s, 2H), 3.45 (t, J=6.9 Hz, 2H), 2.29 (t, J=8.0, 2H), 1.98-1.87 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 175.5, 147.8, 147.7, 134.3, 119.7, 109.4, 108.0, 106.8, 101.2, 64.8, 49.8, 49.0, 30.8, 18.6; HRMS (TOF LCMS) calc’d for C₁₅H₁₈NO₅ [M+H] 292.1185, found 292.1178.
Preparation of vinylogous amide 180

To a solution of 177 (230 mg, 2 mmol, 1 equiv.) in MeCN (800 µL) was added methyl 2-bromoacetate (178b) (38 µL, 4 mmol, 2 equiv.) at room temperature. The mixture was stirred for 1 day and was concentrated by reducing pressure. The residue was dissolved in DCM (800 µL) and was added Et₃N (340 µL, 2.4 mmol, 1.2 equiv.), PPh₃ (630mg, 2.4 mmol, 1.2 equiv.). The mixture was stirred for overnight and filtered through Celite, concentrated by reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%-50% EtOAc/ Hexanes) to yield 180 (150 mg, 48%) as yellow oil.

Vinylogous Amide 180: FTIR (NaCl/ thin film) 2969, 2947, 2883, 1675, 1582, 1456, 1456, 1412, 1375, 1298, 1243, 1135, 1108, 1054, 980, 908, 778 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.46 (s, 1H), 3.61 (d, J=2.4 Hz, 3H), 3.37 (td, J=1.8, 7.8 Hz, 2H), 3.13 (td, J=1.8, 7.8 Hz, 2H), 3.79 (d, J=1.9 Hz, 3H), 1.99-1.89 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 169.8, 165.8, 77.2, 54.5, 50.0, 33.2, 32.5, 21.0; HRMS (TOF LCMS) calc’d for C₈H₁₄NO₂ [M+H] 156.1025, found 156.1020.
Preparation of thiolactam 167

To a solution of 170 (675.4 mg, 2.32 mmol, 1 equiv.) in THF (2 mL) was added Lawesson’s reagent (562.8 mg, 11.6 mmol, 0.5 equiv.) at room temperature. The mixture was stirred for overnight. The reaction was concentrated under reduced pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%-50% EtOAc/Hexanes) to yield 167 (580 mg, 81.4%) as orange solid.

**Thiol lactam 167:** FTIR (NaCl/ thin film) 2892, 1687, 1503, 1488, 1363, 1250, 1119, 1036, 934, 993, 812 cm\(^{-1}\); ¹H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 6.95 (dd, \(J=1.6, 8.4, 1H\)), 6.95 (d, \(J=1.7\) Hz, 1H), 6.70 (d, \(J=8.4\) Hz, 1H), 5.89 (s, 2H), 4.14 (s, 2H), 3.98 (t, \(J=7.2\) Hz, 2H), 3.75 (t, \(J=7.1\) Hz, 4H), 2.89 (t, \(J=7.8\) Hz, 2H), 1.97-1.84 (m, 2H); ¹³C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 203.2, 147.7, 147.5, 133.5, 119.4, 108.8, 107.8, 106.6, 101.1, 64.5, 55.9, 53.7, 44.6, 20.0; HRMS (TOF LCMS) calc’d for C\(_{15}\)H\(_{18}\)NO\(_4\)S [M+H] \(308.0957\), found 308.0959.

Preparation of vinylogous amide 182

Preparation of thiolactam 167

![Diagram](image)

Preparation of vinylogous amide 182

![Diagram](image)
To a solution of 167 (190 mg, 0.62 mmol, 1 equiv.) in MeCN (250 µL) was added 2-bromo-N-methoxy-N-methylacetamide (181) (95 µL, 1 mmol, 1.62 equiv.) at room temperature. The mixture was stirred for 1 day and concentrated by reducing pressure. The residue was dissolved in DCM (250 µL) and was added Et₃N (100 µL mL, 0.74 mmol, 1.2 equiv.), PPh₃ (295 mg, 0.74 mmol, 1.2 equiv.). The mixture was stirred for overnight and filtered by Celite, concentrated by reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%–50% EtOAc/Hexanes) to yield 182 (100 mg, 43%) as yellow oil.

**Vinylogous Amide 182:** FTIR (NaCl/thin film) 2890, 1634, 1573, 1487, 1435, 1387, 1246, 1168, 1099, 1035, 990 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.94–6.88 (m, 2H), 6.72 (d, J=8.6 Hz, 1H), 5.91 (s, 2H), 5.23 (s, 1H), 3.99–3.93 (m, 2H), 3.79–3.73 (m, 2H), 3.64 (s, 3H), 3.48 (s, 2H), 3.27 (t, J=7.0 Hz, 2H), 3.12–3.05 (m, 5H), 1.83–1.74 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 172.1, 165.3, 147.7, 147.6, 134.5, 119.3, 109.8, 108.0, 106.5, 101.1, 77.9, 64.9, 61.0, 55.2, 54.1, 33.1, 32.2, 21.8; HRMS (TOF LCMS) calc’d for C₁₉H₂₅N₂O₆ [M+H] 377.1713, found 377.1705.

**Preparation of chloro ketone 210**

![Diagram of reaction](image)

To a solution of 208 (644 mg, 2.60 mmol, 1 equiv.) in DCM (7 mL) was added CuCl (522 mg, 5.25 mmol, 2.02 equiv.) and 2,2’-bipyridine (785 mg, 5.03 mmol, 1.93 equiv.). The mixture was heated to reflux and stirred for 3 hours. Then the reaction was
cooled to room temperature and filtered through Celite by Et$_2$O (2 × 20mL). The solution was washed by H$_2$O (40 mL) and dried by Na$_2$SO$_4$, concentrated by reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 10%-20% EtOAc/Hexanes) to yield 210 (380 mg, 90%) as brown oil.

**Chloro ketone 210:** FTIR (NaCl/thin film) 2960, 2936, 2874, 1732, 1614, 1465, 1398, 1368, 1313, 1264, 1062 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.29 (d, $J$=2.6 Hz, 1H), 4.51 (s, 2H), 4.46 (d, $J$=2.5 Hz, 1H), 3.76 (t, $J$=7.4 Hz, 2H), 1.82-1.59 (m, 2H), 1.56-1.37 (m, 2H), 0.96 (t, $J$=7.4 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 189.0, 156.3, 92.1, 68.4, 47.3, 30.9, 19.5, 14.0; HRMS (TOF LCMS) calc’d for C$_8$H$_{14}$ClO$_2$ [M+H] 176.0682, found 177.0676.

**Preparation of dienone 211**

To a solution of 167 (224 mg, 0.73 mmol, 1 equiv.) in MeCN (1.6 mL) was added 210 (257 mg, 2.03 mmol, 2.8 equiv.) and NaI (240 mg, 1.60 mmol, 2.2 equiv.) at room temperature. The mixture was stirred for 1 day and concentrated by reducing pressure. The residue was dissolved in DCM (5 mL) and was added Et$_3$N (122 µL, 0.90 mmol, 1.2 equiv.), PPh$_3$ (230 mg, 0.90 mmol, 1.2 equiv.). The mixture was stirred for overnight and filtered by Celite, concentrated by reducing pressure. The residue was loaded onto silica
and purified by column chromatography (gradient elution, 50%:1% - 50% :10% EtOAc/Hexanes: MeOH) to yield 211 (84 mg, 28%) as brown oil.

**Dienone 211 (rotamer):** FTIR (NaCl/ thin film) 2957, 2890, 1705, 1544, 1487, 1436, 1287, 1247, 1036, 939, 812 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.96 (d, J=1.6 Hz, 1H), 6.95 (s, 1H), 6.75 (dd, J=1.7, 8.7 Hz, 1H), 5.95 (d, J=2.5 Hz, 2H), 5.83 (d, J=45.0 Hz, 1H), 5.09 (d, J=1.4 Hz, 1H), 4.19 (d, J=1.3 Hz, 1H), 4.05- 3.93 (m, 2H), 3.86- 3.78 (m, 2H), 3.57 (s, 1H), 3.42- 3.38 (m, 2H), 3.24 (t, J=7.7 Hz, 2H), 1.99- 1.82 (m, 2H), 1.81- 1.70 (m, 2H), 1.63- 1.43 (m, 2H), 0.99 (t, J=7.5 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 183.6, 182.9, 171.1, 169.2, 161.0, 148.1, 148.0, 134.4, 133.9, 119.7, 119.5, 109.8, 109.4, 108.2, 108.2, 106.7, 101.4, 101.3, 86.7, 86.1, 83.5, 67.5, 65.1, 65.0, 55.0, 55.1, 54.7, 34.0, 33.8, 31.4, 21.6, 21.3, 19.7, 14.1; HRMS (TOF LCMS) calc’d for C₂₃H₃₀NO₆ [M+H] 416.2073, found 417.2066.

**Preparation of dienone 220**

To a solution of vinyl ether (216) (1.60 mL, 16.5 mmol, 6.0 equiv.) in THF (20mL) at -78 °C was added 'BuLi (4.85 ml, 8.25 mmol, 3.0 equiv., 1.7 M hexanes solution) dropwise over 5 minutes. The resultant mixture was stirred at -78 °C for 30 minutes, and then warmed to 0 °C and stirred for 2 hours. To a solution of piperine (219) (784 mg, 2.75 mmol, 1 equiv.) in THF (1 mL) was added lithio vinyl ether solution at -78
ºC and stirred for 15 minutes. The mixture was warmed to room temperature and stirred for overnight. The reaction was quenched by H₂O (5 mL). The layers were separated and aqueous layer was washed with EtOAc (2 × 30 mL). The combined organic layers were washed with brine (60 mL) and dried over Na₂SO₄, filtered through Celite and concentrated under reduced pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 10%- 20% EtOAc/ Hexanes) to yield 220 (1 g, 100%) as brown solid.

**Dienone 220**: FTIR(NaCl/ thin film) 2980, 2900, 1667, 1607, 1575, 1503, 1489, 1447, 1372, 1329, 1296, 1254, 1217, 1080, 1038, 930, 853 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.53 (dd, J=10.8, 15.1 Hz, 1H), 7.01 (s, 1H), 6.99 - 6.71 (m, 5H), 6.00 (s, 2H), 5.25 (d, J=2.2 Hz, 1H), 4.49 (d, J=2.2 Hz, 1H), 3.85 (q, J=6.9 Hz, 2H), 1.42 (t, J=6.9 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 186.6, 158.5, 148.9, 148.5, 145.0, 142.0, 130.9, 125.6, 123.6, 123.4, 108.7, 106.0, 101.6, 91.4, 64.0, 14.6; HRMS (TOF LCMS) calc’d for C₁₆H₁₇O₄ [M+H] 273.1127, found 273.1125.

**Preparation of unsaturated ketone 221**

![Chemical Structure](image)

To a solution of 220 (272.3 mg, 1 mmol, 1 equiv.) in DCM (27 mL) was added AlCl₃ (13.4 mg, 0.1 mmol, 0.1 equiv.) at room temperature. The mixture was stirred for 4 days, filtered through Celite and concentrated under reduced pressure. The residue was
loaded onto silica and purified by column chromatography (gradient elution, 10%-25% EtOAc/Hexanes) to yield 221 (120 mg, 44%) as orange oil.

**Ketone 221:** FTIR(NaCl/ thin film) 2980, 2895, 17616, 1621, 1503, 1489, 1446, 1250, 1119, 1037, 965, 927 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 6.88 (s, 1H), 6.81-6.67 (m, 2H), 6.39 (d, \(J=15.7\) Hz, 1H), 6.26 (d, \(J=3.0\) Hz, 1H), 5.94 (s, 2H), 5.87 (dd, \(J=8.4, 15.7\) Hz, 1H), 4.01-3.85 (m, 2H), 3.61-3.45 (m, 1H), 2.77 (dd, \(J=6.5, 19.3\) Hz, 1H), 2.24 (dd, \(J=2.0, 9.2\) Hz, 1H), 1.41 (t, \(J=7.0\) Hz, 3H); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 201.9, 156.6, 148.3, 147.4, 131.3, 130.3, 129.6, 129.5, 121.0, 108.5, 105.7, 101.3, 66.0, 40.7, 37.8, 14.5; HRMS (TOF LCMS) calc’d for C\(_{16}\)H\(_{17}\)O\(_4\) [M+H] 273.1127, found 273.1122.

**Preparation of amine 233**

![Reaction diagram](image)

To a solution of diisopropylamine (179 \(\mu\)L, 1.20 mmol, 5.3 equiv.) in THF (1mL) at 0 °C was added \(n\)-BuLi (750 \(\mu\)L, 1.20 mmol, 5.3 equiv., 1.6 M hexanes solution) dropwise over 5 minutes. The resultant mixture was stirred at 0 °C for 10 minutes, and then cooled to -78 °C. To this LDA solution was added 2-methyl-pyrroline (157) (100 \(\mu\)L, 1.05 mmol, 4.6 equiv.). The mixture was stirred at -78 °C for 1 hour. To this mixture was added to 227 (57.5 mg, 0.23 mmol, 1 equiv.) and the mixture was stirred for three hours at -78 °C. The reaction was quenched by H\(_2\)O (2 mL). The layers were separated and aqueous layer was washed with EtOAc (2 x 2 mL). The combined organic layers
were washed with brine (4 mL) and dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 50-67% EtOAc/Hexanes) to yield 223 (30 mg, 44%) as brown oil.

**Vinylogous amide 223:** FTIR (NaCl/thin film) 3278, 1607, 1540, 1505, 1396, 1330, 1298, 1257, 1144, 1046, 987, 939, 806, 774, 739 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 10.30-10.10 (m, 1H), 6.27 (dd, J=1.2, 17.3 Hz, 1H), 6.05 (dd, J=1.7, 17.1 Hz, 1H), 5.39 (d, J=10.4 Hz, 1H), 5.16 (s, 1H), 3.55 (t, J=8.1 Hz, 2H), 2.60 (t, J=7.8 Hz, 2H), 1.95 (dd, J=7.9, 15.4 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 186.0, 169.4, 137.9, 122.3, 89.6, 47.4, 32.5, 21.2; HRMS (TOF LCMS) calc'd for C₈H₁₁NO [M+H] 138.0919, found 138.0910.

**Preparation of vinylogous amide 230**

![Chemical reaction diagram]

To a solution of diisopropylamine (340 µL, 2.43 mmol, 1.15 equiv.) in THF (2mL) at 0 °C was added n-BuLi (1.5 ml, 2.32 mmol, 1.1 equiv., 1.6 M hexanes solution) dropwise over 5 minutes. The resultant mixture was stirred at 0 °C for 10 minutes, and then cooled to -78 °C. To this LDA solution was added 2-methyl-pyrrolidine (157) (200 µL, 2.11 mmol, 1 equiv.) The mixture was stirred at -78 °C for 1 hour. To this mixture was added 251 (304 mg, 2.11 mmol, 1 equiv.) and the solution was warmed to room
temperature and stirred for overnight. The reaction was quenched by H₂O (2 mL). The layers were separated and aqueous layer was washed with EtOAc (2 × 2 mL). The combined organic layers were washed with brine (4 mL) and dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%-50% EtOAc/Hexanes) to yield 230 (240 mg, 62.7%) as brown solid.

**Vinylogous amide 230:** FTIR(NaCl/ thin film) 2978, 1700, 1600, 1534, 1507, 1377, 1282, 1225, 1127, 1061, 977, 794 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 10.3-10.1 (m, 1H), 5.71 (s, 1H), 5.11 (s, 1H), 4.24 (s, 1H), 3.79 (q, J=6.9 Hz, 2H), 3.61 (t, J=6.9 Hz, 2H), 2.00 (t, J =7.7 Hz, 2H), 2.05-1.93 (m, 2H), 1.36 (t, J=6.9 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 183.6, 170.2, 159.6, 87.1, 85.4, 63.5, 47.9, 33.0, 21.4, 14.6; HRMS (TOF LCMS) calc’d for C₁₀H₁₅NO₂ [M+H] 182.1181, found 182.1176.

**Preparation of vinylogous amide 231**

To a solution of 230 (100mg, 0.55 mmol, 1 equiv.) in THF (3 mL) was added KO'Bu (68mg, 0.61 mmol, 1.1 equiv.) and Me₂SO₄ (60 µL, 0.63 mmol, 1.1 equiv.) at room temperature. The mixture was stirred for 2 days ad quenched by H₂O (1mL). The layers were separated and aqueous layer was washed with EtOAc (2 × 5 mL). The combined organic layers were washed with brine (10 mL) and dried over Na₂SO₄, filtered through Celite and concentrated under reduced pressure. The residue was loaded onto
silica and purified by column chromatography (gradient elution, 33%-67% EtOAc/Hexanes) to yield 231 (75 mg, 69.6%) as orange solid.

**Vinylogous amide 231:** FTIR (NaCl/thin film) 2976, 2919, 1637, 1594, 1493, 1443, 1376, 1269, 1060, 984, 858, 802 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\) \(\delta\) 5.63 (s, 1H), 5.12 (s, 1H), 4.21 (s, 1H), 3.80 (q, \(J=6.9\) Hz, 2H), 3.46-3.35 (m, 2H), 3.30 (t, \(J=7.6\) Hz, 2H), 2.92 (s, 3H), 2.03-1.89 (m, 2H), 1.37 (t, \(J=6.9\) Hz, 3H); \(^13\)C NMR (100 MHz, CDCl\(_3\) \(\delta\) 183.1, 168.8, 160.8, 87.0, 84.7, 63.5, 54.8, 33.9, 33.5, 20.9, 14.6; HRMS (TOF LCMS) calc’d for C\(_{11}\)H\(_{18}\)NO\(_2\) [M+H] 196.1338, found 196.1336.

**Preparation of diaketone 233**

\[
\begin{array}{c}
\text{231} \\
\text{\xrightarrow{TiCl}_4, -78 \degree C to r.t.} \\
\text{(88% yield)} \\
\text{233}
\end{array}
\]

To a solution of 231 (28 mg, 0.14 mmol, 1 equiv.) in DCM (15 mL) at -78\(^\circ\)C was added TiCl\(_4\) (140 \(\mu\)L, 0.14 mmol, 1 equiv.) dropwise. Then the mixture was warmed to room temperature and stirred for overnight. The reaction was quenched by H\(_2\)O (15 mL). The organic was dried by Na\(_2\)SO\(_4\) and concentrated by reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 50%-75% EtOAc/Hexanes) to yield 233 (21 mg, 88%) as orange oil.

**Diaketone 233:** FTIR (NaCl/thin film) 2924, 1701, 1653, 1559, 1457, 1419, 1301 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\) \(\delta\) 5.69 (s, 1H), 3.51 (t, \(J=6.4\) Hz, 2H), 3.31 (t, \(J=7.8\) Hz, 2H), 2.98 (s, 3H), 2.38 (s, 3H), 3.31 (dd, \(J=7.7, 15.4\) Hz, 2H); \(^13\)C NMR (100
Preparation of dienone 235

To a solution of 230 (87mg, 0.48 mmol, 1 equiv.) in THF (5 mL) was added KHMDS (1.05 mL, 0.53 mmol, 1.1 equiv.) at -78 °C and the mixture was stirred for 10 min. To the mixture was added 234 (186.2mg, 0.73 mmol, 1.5 equiv.) at -78 °C dropwise over 5 min. Then the mixture was warmed to room temperature and stirred for overnight. The reaction was quenched by H₂O (1 mL). The layers were separated and aqueous layer was washed with EtOAc (2 × 5 mL). The combined organic layers were washed with brine (10 mL) and dried over Na₂SO₄, filtered through Celite and concentrated under reduced pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%-50% EtOAc/Hexanes) to yield 235 (70 mg, 36.3%) as yellow oil.

Dienone 235: FTIR(NaCl/ thin film) 2979, 2895, 1742, 1697, 1666, 1568, 1504, 1490, 1446, 1393, 1371, 1309, 1232, 1104, 1039, 935, 864, 810 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.00 (s, 1H), 6.95 (d, J=1.5 Hz, 1H), 6.90 (dd, J=1.5, 7.9 Hz, 1H), 6.81 (d, J=7.9 Hz, 1H), 5.99 (s, 2H), 5.98 (s, 1H), 5.16 (d, J=2.3 Hz, 1H), 4.42 (d, J=2.3 Hz, 1H), 3.90- 3.87 (m, 1H), 3.81 (q, J=7.0 Hz, 2H), 3.54- 3.45 (m, 1H), 3.24- 3.05 (m, 2H), 2.47, 2.07; HRMS (TOF LCMS) calc’d for C₉H₁₄NO₂ [M+H] 168.1025, found 168.1020.
2.17 (s, 3H), 2.04- 1.78 (m, 2H), 1.4 (t, \(J=7.0 \text{ Hz}\), 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 188.1, 170.7, 168.1, 159.4, 158.6, 149.1, 148.6, 125.9, 123.3, 109.1, 108.8, 103.9, 101.7, 90.4, 75.0, 63.8, 49.0, 31.9, 22.0, 20.9, 14.4; HRMS (TOF LCMS) calc’d for C\(_{21}\)H\(_{24}\)NO\(_7\) [M+H] 402.1553, found 402.1553.

**Preparation of ketone 242**

![Chemical reaction diagram](image)

To a solution of 241 (1.75 g, 5.43 mmol, 1 equiv.) in MeCN (3 mL) was added 2-Methoxy-1-pyrroline (169) (708 mg, 7.15 mmol, 1.3 equiv.). The mixture was heated to 60 °C and stirred for 1 day. The mixture was cooled to room temperature and concentrated by reducing pressure to yield pure 242 (1.6g, 90.6%) as orange solid.

**Ketone 242:** FTIR (NaCl/ thin film) 2918, 1680, 1612, 1503, 1480, 1442, 1408, 1385, 1350, 1243, 1122, 1035, 932 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.05 (s, 1H), 7.04 (s, 1H), 6.05 (s, 2H), 4.59 (s, 2H), 3.50 (t, \(J=6.9 \text{ Hz}\), 2H), 2.45 (t, \(J=7.0 \text{ Hz}\), 2H), 2.16-2.04 (m, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 196.2, 175.9, 151.0, 147.7, 131.8, 114.1, 112.2, 109.3, 102.7, 51.7, 47.9, 30.4, 18.2; HRMS (TOF LCMS) calc’d for C\(_{13}\)H\(_{13}\)BrNO\(_4\) [M+H] 326.0028, found 302.0024.
Preparation of amide 243

To a solution of 242 (580 mg, 1.78 mmol, 1 equiv.) in Benzene (40 mL) was added ethyl glycol (1.1 mL, 19.7 mmol, 11 equiv.) and \( p \)-Toluenesulfonic acid (44 mg, 0.257 mmol, 0.14 equiv.). The mixture was heated to reflux and stirred for overnight. The mixture was cooled to room temperature and washed by saturated aqueous NaHCO\(_3\) (2 × 10 mL). The organic layer was dried by Na\(_2\)SO\(_4\), filtered through Celite and concentrated by reducing pressure to yield pure 243 (565 mg, 86.0%) as brown solid.

**Amide 243:** FTIR (NaCl/ thin film) 2893, 1690, 1477, 1286, 1238, 1196, 1114, 1039, 1009, 931 \text{ cm}^{-1}; \( ^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.17 (s, 1H), 7.03 (s, 1H), 5.97 (s, 2H), 4.03 (t, \( J=6.9 \) Hz, 2H), 3.87 (s, 2H), 3.80 (t, \( J=6.7 \) Hz, 2H), 3.48 (t, \( J=7.0 \) Hz, 2H), 2.31 (t, \( J=8.0 \) Hz, 2H), 2.02-1.83 (m, 2H); \( ^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 175.7, 148.5, 147.3, 132.2, 114.9, 111.9, 109.4, 108.8, 102.1, 64.7, 49.2, 47.6, 30.8, 18.7; HRMS (TOF LCMS) calc’d for C\(_{15}\)H\(_{17}\)BrNO\(_5\) [M+H] 370.0290, found 370.0281.

Preparation of alcohol 252
To a solution of 242 (510 mg, 1.56 mmol, 1 equiv.) in EtOH (5 ml) was added NaBH4 (660 mg, 15.6, 10 equiv.) and the mixture was stirred for overnight at room temperature. The reaction was quenched by H2O (10 mL) and washed by EtOAc 2 x 10 mL. The combined organic layers was dried by Na2SO4, filtered through Celite and concentrated by reducing pressure to yield pure 252 (492 mg, 96.5%)

**Alcohol 252:** FTIR (NaCl/ thin film) 3338, 2906, 1664, 1501, 1475, 1421, 1288, 1237, 1111, 1036, 931, 876 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.17 (s, 1H), 6.03 (s, 1H), 5.97 (s, 2H), 5.13 (t, J=5.1 Hz, 1H), 4.90- 4.62 (m, 1H), 3.67- 3.36 (m, 3H), 3.26- 3.10 (m, 1H), 2.43 (t, J=7.4 Hz, 2H), 2.11-1.86 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 178.1, 147.9, 147.8, 134.3, 112.5, 111.5, 108.0, 101.9, 72.9, 50.7, 49.6, 30.9, 18.6; HRMS (TOF LCMS) calc’d for C₁₃H₁₄BrNO₄Na [M+Na] 350.0004, found 349.9994.

**Preparation of amide 244**

To a solution of 252 (700 mg, 2.27 mmol, 1 equiv.) in DCM (10 mL) was added TBSCl (772 mg, 5.44 mmol, 2.4 equiv.) and imidazole (2.98 g, 45.4 mmol, 20 equiv.) at room temperature. The mixture was stirred for 2 days and concentrated by reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 10%- 33% EtOAc/ Hexanes) to yield 244 (735 mg, 78.0%) as white solid.
Amide 244: FTIR (NaCl/ thin film) 2954, 2928, 2895, 2856, 1692, 1503, 1475, 1411, 1286, 1237, 1110, 1090, 1035, 940, 836 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.03 (s, 1H), 6.91 (s, 1H), 5.96 (dd, \(J=1.2\) Hz, 2H), 5.19 (dd, \(J=4.3, 7.6\) Hz, 1H), 3.56- 3.30 (m, 3H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 175.2, 147.8, 147.7, 135.2, 112.2, 111.9, 108.0, 101.8, 71.6, 50.2, 48.8, 31.0, 25.8, 18.3, 18.1, -4.76, -5.02; HRMS (TOF LCMS) calc’d for C\(_{19}\)H\(_{29}\)BrNO\(_4\)Si \([M+H]\) 442.1049, found 442.1044.

Preparation of thiol lactam 245

![Chemical structure]

To a solution of 243 (2.90 g, 8.98 mmol, 1 equiv.) in THF (10 mL) was added Lawesson’s reagent (1.90 g, 5.34 mmol, 0.6 equiv.) at room temperature. The mixture was stirred for overnight. The reaction was concentrated under reduced pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%- 50% EtOAc/ Hexanes) to yield 245 (2 g, 58.2%) as orange solid.

Thiol lactam 245: FTIR (NaCl/ thin film) 2892, 1501, 1477, 1238, 1201, 1223, 1033, 951 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.20 (s, 1H), 7.04 (s, 1H), 5.99 (s, 2H), 4.44 (s, 2H), 4.11- 3.99 (m, 2H), 3.88- 3.77 (m, 4H), 3.0 (t, \(J=7.6\) Hz, 2H), 2.05- 1.91 (m, 2H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 203.9, 148.7, 147.5, 131.8, 114.9, 112.0, 109.0, 103.8, 94.0, 83.6 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.03 (s, 1H), 6.91 (s, 1H), 5.96 (dd, \(J=1.2\) Hz, 2H), 5.19 (dd, \(J=4.3, 7.6\) Hz, 1H), 3.56- 3.30 (m, 3H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 175.2, 147.8, 147.7, 135.2, 112.2, 111.9, 108.0, 101.8, 71.6, 50.2, 48.8, 31.0, 25.8, 18.3, 18.1, -4.76, -5.02; HRMS (TOF LCMS) calc’d for C\(_{19}\)H\(_{29}\)BrNO\(_4\)Si \([M+H]\) 442.1049, found 442.1044.

Preparation of thiol lactam 245

To a solution of 243 (2.90 g, 8.98 mmol, 1 equiv.) in THF (10 mL) was added Lawesson’s reagent (1.90 g, 5.34 mmol, 0.6 equiv.) at room temperature. The mixture was stirred for overnight. The reaction was concentrated under reduced pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%- 50% EtOAc/ Hexanes) to yield 245 (2 g, 58.2%) as orange solid.

Thiol lactam 245: FTIR (NaCl/ thin film) 2892, 1501, 1477, 1238, 1201, 1223, 1033, 951 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.20 (s, 1H), 7.04 (s, 1H), 5.99 (s, 2H), 4.44 (s, 2H), 4.11- 3.99 (m, 2H), 3.88- 3.77 (m, 4H), 3.0 (t, \(J=7.6\) Hz, 2H), 2.05- 1.91 (m, 2H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 203.9, 148.7, 147.5, 131.8, 114.9, 112.0, 109.0,
108.8, 102.1, 64.6, 56.6, 52.1, 45.0, 20.4; HRMS (TOF LCMS) calc’d for C\textsubscript{15}H\textsubscript{17}BrNO\textsubscript{4}S [M+H] 386.0062, found 386.0057.

**Preparation of thiol lactam 246**

![Reaction diagram]

To a solution of 244 (52 mg, 0.12 mmol, 1 equiv.) in THF (0.2 mL) was added Lawesson’s reagent (28.5 g, 0.07 mmol, 0.6 equiv.) at room temperature. The mixture was stirred for overnight. The reaction was concentrated under reduced pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%- 50% EtOAc/ Hexanes) to yield 246 (25 mg, 48.0%) as yellow oil.

**Thiol lactam 246**: FTIR (NaCl/ thin film) 2954, 2928, 2886, 2856, 1503, 1475, 1409, 1326, 1235, 1110, 1085, 1038, 936, 837 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.03 (s, 1H), 6.93 (s, 1H), 5.98 (dd, \(J=1.4, 10.4 \text{ Hz}, 2\text{H}\)), 5.50 (dd, \(J=5.2, 7.5 \text{ Hz}, 1\text{H}\)), 3.91 (dd, \(J=7.6, 13.0 \text{ Hz}, 1\text{H}\)), 3.84- 3.76 (m, 1H), 3.70 (dd, \(J=5.2, 10.8 \text{ Hz}, 1\text{H}\)), 3.56- 3.48 (m, 1H), 3.0 (t, \(J=7.9 \text{ Hz}, 2\text{H}\)), 2.04- 1.95 (m, 2H), 0.87 (s, 9H), 0.06 (s, 3H), 0.11(s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 202.3, 148.1, 147.9, 135.1, 112.4, 112.3, 108.0, 101.9, 70.4, 57.2, 55.2, 45.1, 25.9, 20.1, 18.0, -4.8; HRMS (TOF LCMS) calc’d for C\textsubscript{19}H\textsubscript{19}BrNO\textsubscript{3}SSi [M+H] 458.0821, found 458.0812.
Preparation of dienone 247

To a solution of 245 (191 mg, 0.50 mmol, 1 equiv.) in MeCN (4 mL) was added 3-butoxy-1-chlorobut-3-en-2-one (210) (131 mg, 0.75 mmol, 1.5 equiv.) and NaI (93 mg, 0.70 mmol, 1.4 equiv.) at room temperature. The mixture was stirred for 1 day and concentrated by reducing pressure. The residue was dissolved in DCM (2 mL) and was added Et$_3$N (170 µL, 0.60 mmol, 1.2 equiv.), PPh$_3$ (157 mg, 0.60 mmol, 1.2 equiv.). The mixture was stirred for overnight and filtered by Celite, concentrated by reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 50%:1% - 50% :10% EtOAc/ Hexanes: MeOH) to yield 247 (100 mg, 49.7%) as brown oil.

**Dienone 247**: FTIR (NaCl/ thin film) 2957, 1709, 1593, 1537, 1502, 1477, 1305, 1238, 1198, 1119, 1004, 934, 847 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.14 (s, 1H), 7.02 (s, 1H), 6.05 (s, 1H), 5.97 (s, 2H), 5.09 (d, $J$=1.5 Hz, 1H), 4.19 (d, $J$=1.4 Hz, 1H), 4.02-3.95 (m, 2H), 3.84 (s, 2H), 3.82- 3.76 (m, 2H), 3.73 (t, $J$=6.5 Hz, 2H), 3.51 (t, $J$=7.3 Hz, 2H), 3.25 (t, $J$=7.6 Hz, 2H), 1.95- 1.84 (m, 2H), 1.79- 1.69 (m, 2H), 1.56– 1.44 (m, 2H), 0.96 (t, $J$=7.4 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 183.8, 169.3, 161.0, 148.7, 147.5, 132.2, 114.8, 111.7, 110.0, 108.6, 102.1, 86.7, 86.3, 67.6, 64.9, 54.9, 52.4, 33.8, 31.3,
21.6, 19.6, 14.0; HRMS (TOF LCMS) calc’d for C_{23}\text{H}_{29}\text{BrNO}_6 [M+H] 494.1178, found 494.1176.

**Preparation of dienone 248**

![Reaction Scheme](attachment:image.png)

To a solution of 246 (60 mg, 0.13 mmol, 1 equiv.) in MeCN (1 mL) was added 3-butoxy-1-chlorobut-3-en-2-one (210) (46 mg, 0.20 mmol, 1.5 equiv.) and NaI (47 mg, 0.18 mmol, 1.4 equiv.) at room temperature. The mixture was stirred for 1 day and concentrated by reducing pressure. The residue was dissolved in DCM (1 mL) and was added Et$_3$N (33 µL, 0.16 mmol, 1.2 equiv.), PPh$_3$ (62 mg, 0.16 mmol, 1.2 equiv.). The mixture was stirred for overnight and filtered by Celite, concentrated by reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 50%:1% - 50%:10% EtOAc/ Hexanes: MeOH) to yield 248 (40 mg, 54.0%) as brown oil.

**Dienone 248**: FTIR (NaCl/ thin film) 2956, 2931, 2859, 1547, 1504, 1475, 1400, 1390, 1288, 1237, 1111, 1094, 1035, 930, 837, 779 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.03 (s, 1H), 6.93 (s, 1H), 5.97 (dd, $J$=1.4, 15.9 Hz, 2H), 5.91 (s, 1H), 5.29 (dd, $J$=3.7, 8.5 Hz, 1H), 5.11 (d, $J$=1.6 Hz, 1H), 4.20 (d, $J$=1.6 Hz, 1H), 3.73 (td, $J$=1.2, 6.6 Hz, 2H), 3.65- 3.57 (m, 1H), 3.48- 3.25 (m, 5H), 2.00- 1.91 (m, 2H), 1.79- 1.71 (m, 2H), 1.53-
1.42 (m, 2H), 0.96 (t, J=7.4 Hz, 3H), 0.84 (s, 9H), 0.02 (s, 3H), 0.15 (s, 3H); $^13$C NMR (100 MHz, CDCl$_3$) δ 183.4, 168.3, 161.0, 148.1, 148.0, 134.8, 112.3, 111.6, 107.8, 101.9, 86.8, 85.7, 71.2, 67.7, 54.9, 53.9, 34.2, 31.2, 25.8, 21.1, 19.7, 18.0, 14.1, -4.91, -4.99; HRMS (TOF LCMS) calc’d for C$_{27}$H$_{41}$BrNO$_5$Si [M+H] 566.1937, found 566.1924.
2.7 Notes and References


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Appendix I: Spectra Relevant to Chapter 2
Figure A.2.1 1H NMR (400MHz, CDCl₃) of compound 155
Figure A.2.2 Infrared Spectrum (thin film/NaCl) of compound 155.

Figure A.2.3 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 155.
Figure A.2.4 1H NMR (400MHz, CDCl₃) of compound 168
Figure A.2.5 Infrared Spectrum (thin film/NaCl) of compound 168

Figure A.2.6 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 168
Figure A.2.7 1H NMR (400MHz, CDCl₃) of compound 170
Figure A.2.8 Infrared Spectrum (thin film/NaCl) of compound 170

Figure A.2.9 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 170
Figure A.2.10 1H NMR (400MHz, CDCl₃) of compound 180
Figure A.2.11 Infrared Spectrum (thin film/NaCl) of compound 180

Figure A.2.12 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 180
Figure A.2.13 1H NMR (400MHz, CDCl$_3$) of compound 167
Figure A.2.14 Infrared Spectrum (thin film/NaCl) of compound 167

Figure A.2.15 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 167
Figure A.2.16 1H NMR (400MHz, CDCl₃) of compound 182
Figure A.2.17 Infrared Spectrum (thin film/NaCl) of compound 182

Figure A.2.18 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 182
Figure A.2.19 1H NMR (400MHz, CDCl₃) of compound 210
Figure A.2.20 Infrared Spectrum (thin film/NaCl) of compound 210

Figure A.2.21 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 210
Figure A.2.22 1H NMR (400MHz, CDCl₃) of compound 211
Figure A.2.23 Infrared Spectrum (thin film/NaCl) of compound 211

Figure A.2.24 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 211
Figure A.2.25 1H NMR (400MHz, CDCl₃) of compound 220
Figure A.2.26 Infrared Spectrum (thin film/NaCl) of compound 220

Figure A.2.27 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 220
Figure A.2.28 1H NMR (400MHz, CDCl₃) of compound 221
Figure A.2.29 Infrared Spectrum (thin film/NaCl) of compound 221

Figure A.2.30 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 221
Figure A.2.31 1H NMR (400MHz, CDCl₃) of compound 223
Figure A.2.32 Infrared Spectrum (thin film/NaCl) of compound 223

Figure A.2.33 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 223
Figure A.2.34 1H NMR (400MHz, CDCl₃) of compound 230
Figure A.2.35 Infrared Spectrum (thin film/NaCl) of compound 230

Figure A.2.36 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 230
Figure A.2.37 1H NMR (400MHz, CDCl₃) of compound 231
Figure A.2.38 Infrared Spectrum (thin film/NaCl) of compound 231

Figure A.2.39 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 231
Figure A.2.40 1H NMR (400MHz, CDCl₃) of compound 233
Figure A.2.41 Infrared Spectrum (thin film/NaCl) of compound 233

Figure A.2.42 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 233
Figure A.2.43 1H NMR (400MHz, CDCl₃) of compound 235
Figure A.2.44 Infrared Spectrum (thin film/NaCl) of compound 235

Figure A.2.45 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 235
Figure A.2.46 1H NMR (400MHz, CDCl₃) of compound 242
Figure A.2.47 Infrared Spectrum (thin film/NaCl) of compound 242

Figure A.2.48 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 242
Figure A.2.49 1H NMR (400MHz, CDCl₃) of compound 243
Figure A.2.50 Infrared Spectrum (thin film/NaCl) of compound 243

Figure A.2.51a $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 243
Figure A.2.52 1H NMR (400MHz, CDCl₃) of compound 252
Figure A.2.53 Infrared Spectrum (thin film/NaCl) of compound 252

Figure A.2.54 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 252
Figure A.2.55 1H NMR (400MHz, CDCl₃) of compound 244
Figure A.2.56 Infrared Spectrum (thin film/NaCl) of compound 244

Figure A.2.57 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 244
Figure A.2.58 $^1$H NMR (400MHz, CDCl$_3$) of compound 245

![Chemical Structure](image)
Figure A.2.59 Infrared Spectrum (thin film/NaCl) of compound 245

Figure A.2.60 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 245
Figure A.2.61 1H NMR (400MHz, CDCl₃) of compound 246
Figure A.2.62 Infrared Spectrum (thin film/NaCl) of compound 246

Figure A.2.63 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 246
Figure A.2.64 1H NMR (400MHz, CDCl₃) of compound 247
Figure A.2.65 Infrared Spectrum (thin film/NaCl) of compound 247

Figure A.2.66 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 247
Figure A.2.67 1H NMR (400MHz, CDCl₃) of compound 248
Figure A.2.68 Infrared Spectrum (thin film/NaCl) of compound 248

Figure A.2.69 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 248
Chapter 3

Phomoidride Chemistry and Biology

3.1 Background and Introduction

3.1.1 Phomoidrides: Isolation and Structural Characterization

In 1995, researchers at Pfizer in Groton, Connecticut reported the isolation and characterization of phomoidride A (300) and phomoidride B (301) (Figure 3.1.1) from an unidentified fungus discovered on the twigs of Juniperus ashei trees in Dripping Springs, Texas.¹ In 1999, two additional compounds, phomoidride C (302) and phomoidride D (303) were found in the fungal broth.²³
The phomoidrides are the members of the nonadride family of natural products. The name phomoidride derives from the name of the *phoma* genus, which exhibits characteristics of the phomoidride producing fungus. In addition, the name also reflects the classification of these fungal metabolites as nonadrides, a name given by Barton based on the observation that these compounds derive from dimerization of two nine-carbon natural products (nona-), containing bisanhydride rings (-dride). Other members of the nonadride family have been found that are postulated to arise from a similar biosynthetic pathways (Figure 3.1.2).
Figure 3.1.2 Nonadride Family

304: Glaucanic acid  
305: Cordyanhydride A  
306: Cornexisitin

307: Rubratoxin A  
308: Byssochlamic acid

3.1.2 Phomoidride Biosynthesis

In Sulikowski's biosynthesis study of the phomoidride,\textsuperscript{11-15} decarboxylative homodimerization of an unsaturated anhydride 313 is a key step (Scheme 3.1.2). Anhydride 313 could be derived from the condensation of oxaloacetyl-CoA (310, derived from succinic acid (309)) and diene 312 (derived from acetyl-CoA (311)). Dimerization of 313 followed by oxidation would afford the core of phomoidrides (314). Subsequent ether formation and thioester hydrolysis would furnish phomoidride B (301).
3.1.3 Biological Activity of the Phomoidrides

The phomoidrides display modest activity against the enzyme squalene synthase (phomoidride A $IC_{50} = 43 \, \mu M$, phomoidride B $IC_{50} = 160 \, \mu M$),\(^{16}\) an enzyme that catalyzes the synthesis of squalene (317) from farnesyl pyrophosphate (316) (Scheme 3.1.3). From a chemotherapy perspective, the inhibition of squalene synthase may serve to decrease the level of cholesterol (318) since squalene is a precursor in the biosynthesis of cholesterol.\(^{17-19}\)
The phomoidrides also have shown biological activity against \textit{ras} farnesyl transferase (phomoidride A \textit{IC}_{50} = 6 \, \mu\text{M}, phomoidride B \textit{IC}_{50} = 20 \, \mu\text{M}). Mutated forms of cellular \textit{ras} genes are among the most common genetic abnormalities in human cancers, occurring in 90\% of pancreatic carcinomas, 50\% of colon carcinomas, and 20-30\% of acute leukemias. Thus, inhibition of oncogenic \textit{ras} activity is thought to be useful for anticancer treatment. One promising pharmacological approach against oncogenic \textit{ras} activity would be interference of \textit{ras} membrane localization. The crucial modification required for \textit{ras} membrane association and transformation is the addition of a farnesyl moiety to the cysteine residue of a C-terminal CAAX motif in a reaction catalyzed by protein farnesyltransferase. Therefore, phomoidrides may have chemotherapeutic potential for inhibiting farnesyltransferase.\textsuperscript{20-21}

3.2 Phomoidrides: Structure and Synthesis

3.2.1 Structural Features
In addition to their intriguing biological activity, the phomoidrides possess interesting structural features. For example, phomoidride D (303) contains a bicyclo[4.3.1] decadiene moiety with a maleic anhydride, bridgehead olefin, all-carbon quaternary center, bridging lactone ketal, an epimerizable stereocenter and two olefinic side chains (Figure 3.2.1). The complicated structure makes phomoidrides challenging targets for synthetic chemists.

Figure 3.2.1 Phomoidride D Structural Features

Dabrah and co-workers reported the conversion of phomoidride A (300) to phomoidride B (301) by treatment with catalytic methanesulfonic acid (scheme 3.2.2.1).\textsuperscript{1} Correspondingly, Nicolaou’s group found that phomoidride B (301) can be converted to phomoidride A (300) upon exposure to LiOH.\textsuperscript{2,22}
In an epimerization study, Danishefsky and co-workers reported that phomoidride B could be epimerized to phomoidride D and phomoidride A can be epimerized to phomoidride C (Scheme 3.2.2.2). The reverse epimerization, from phomoidride D to phomoidride B or phomoidride C to phomoidride A, does not occur. However, Danishefsky did demonstrate that Phomoidride D can be converted to phomoidride A in seven steps (see section 3.2.3.4 for details).  

Scheme 3.2.2.2 Phomoidrides Epimerization
3.2.3 Synthetic Routes to the Phomoidrides

Numerous synthetic efforts have been made towards the total synthesis of the phomoidrides. To date, only four groups (Nicolaou, Fukuyama, Shair and Danishefsky) have reported completion of the total syntheses. In this dissertation, only the four completed total synthesis will be discussed since the other synthetic efforts have been summarized in a review article.24

3.2.3.1 K. C. Nicolaou’s Route

K. C. Nicolaou reported the first total synthesis of phomoidride A and B in 1999.22,29-44 Nicolaou’s synthesis started with dimethyl malonate 320 (Scheme 3.2.3.1.1). Bis-alkylation, reduction of the diester and acetal formation gave acetonide 321. Ozonolysis of alkene 321 produced an intermediate aldehyde, which underwent a modified aldol condensation with aldehyde 322 to yield enal 323. The diene 324 for intramolecular Diels-Alder reaction was prepared from aldehyde 323 via PMB ether formation, deprotection of the primary alcohol and Parikh-Doering-oxidation.

Scheme 3.2.3.1.1 Nicolaou Diene’s Synthesis
Diels-Alder product 327 was obtained from 325 via aldol addition of the vinyl lithium reagent derived from vinyl iodide 326, Dess-Martin oxidation, and aluminum Lewis acid catalyzed [4+2] cycloaddition (Scheme 3.2.3.2). Removal of the bis TBS ethers revealed an intermediate diol which underwent oxidative cleavage in the presence of NaIO₄ to yield an aldehyde intermediate. Addition of the lithio dithiane reagent 328 to this aldehyde gave secondary alcohol 329.

Scheme 3.2.3.2 Nicolaou’s Intramolecular Diels-Alder Reaction

Installation of the maleic anhydride moiety commenced with alcohol 329 (Scheme 3.2.3.3). TES ether protection, vinyl triflate formation using Comins reagent, and Pd-mediated CO insertion, gave methyl ester 330. Protecting group exchanged in the presence of BTIB and MeOH, followed by ester reduction, directed epoxidation and cyanide addition with Nagata’s reagent opened the newly formed epoxide to yield diol 331. Treatment of diol 331 with MsCl, K₂CO₃ and oxalic acid furnished the maleic
anhydride moiety. Nicolaou believed that the anhydride was formed via the following transformations: (1) selective protection of primary alcohol by mesylation; (2) epoxide formation under the basic conditions; (3) epoxide opening via β-elimination; (4) 5-exo-dig cyclization on cyanide in the presence of acid; (5) double oxidation by exposure to air (6) hydrolysis to lose ammonia. After removal of dimethyl ketal and reprotcion of the secondary alcohol as TBS ether, they prepared ketone 332.

**Scheme 3.2.3.1.3 Nicolaou’s Maleic Anhydride Synthesis**

Treatment of ketone 332 with DDQ to remove the PMB protecting group was followed by PDC oxidation and removal of the acetonide in the presence of acetic acid to
give a diol which, underwent cyclization to form a hemiacetal. Protection of the remaining alcohol as a TES ether provided hemiacetal 333 (Scheme 3.2.3.1.4). Bis hemiacetal 334 was obtained by exposing 333 to the Dess-Martin reagent followed by removal of the TES protecting group and MeSO$_3$H-mediated removal of the TBS ether.

Scheme 3.2.3.1.4 Nicolaou’s Bridging Ketel Synthesis

At this stage, oxidation of the primary alcohol, protection of the hemiacetal alcohol and Pinnick oxidation yield an intermediate carboxylic acid which underwent Arndt-Eistert homologation to furnish carboxylic acid 335 (Scheme 3.2.3.1.5). Protection of carboxylic acid 335 as its indoline amide, removal of the TBS group, oxidation of the hemiacetal to the corresponding lactone, oxidation of the indoline amide to its indole derivative and hydrolysis of the derived indole amide to the acid gave the natural product phomoidride A (300). In the presence of MeSO$_3$H, phomoidride A (300) was converted to phomoidride B (301).
3.2.3.2 Fukuyama’s Route

The second total synthesis of phomoidride B was reported by Fukuyama in 2000.\textsuperscript{45-47} Fukuyama’s synthesis commenced with the conversion of progargylic thioether 340 to the corresponding allene which was followed by nucleophilic addition of vinyl cuprate 341, ester alkylation with Mander’s reagent and Michael addition with a chiral oxazolidinone to give 342 (Scheme 3.2.3.2.1). Adol reaction between this intermediate and aldehyde 343 was followed by oxidation and intramolecular Diels-Alder reaction in the presence of ZnCl\textsubscript{2}•OEt\textsubscript{2} to afford cycloaddition product 344.
Proceeding forward with Diels–Alder product 344, the chiral oxazolidinone functionality is displaced by allyl thioglycolate, followed by intramolecular adol addition, decarboxylation catalyzed by Pd(OAc)$_2$ and elimination of the tertiary alcohol to give thio lactone 345 (Scheme 3.2.3.2.2). Maleic anhydride formation was achieved by the formation of the TBS silyl enolether and treatment with NIS in the presence of AgNO$_3$. Selective hydrolysis of the less hindered methyl ester, produced carboxylate 346.
As in the Nicolau’s synthesis, an Arndt-Eistert homologation protocol was utilized to install the neopentyl carboxylic acid (Scheme 3.2.3.3). To this end, carboxylic acid 346 was converted to the corresponding diazoketone by treatment with (COCl)₂ and CH₂N₂. In the presence of the silver (I) salt PhCO₂Ag, the diazoketone was converted to the ketene, which formed the tert-Butyl ester in the presence of ²BuOH. Turning to the lactones, a Pummerer rearrangement converted the sulfide to its corresponding ketone which, upon treatment with acid, produced ketal 347. Jones oxidation and deprotection of the tert-butyl ester gave the natural product phomoidride B (301).
### Scheme 3.2.3.2.3 Fukuyam’s Phomoidride B Synthesis

![Scheme 3.2.3.2.3 Fukuyam’s Phomoidride B Synthesis](image)

**3.2.3.3 Shair’s Route**

In 2000, Shair published the third total synthesis of phomoidride B. Shair’s synthesis started with a Stille coupling between vinyl iodide 350 and vinyl stannane 351 which was followed by cuprate addition and alkylation with Mander’s reagent to give ketone 352 (Scheme 3.2.3.1). Enantiomerically pure ketone 352 was provided by an efficient kinetic resolution using Corey’s oxazaborolidine catalyst and catecholborane. The resolved ketone, upon addition of Grignard reagent 353, underwent oxy-Cope rearrangement and subsequent transannular Dieckmann cyclization to furnish the [4.3.1] core of phomoidride B (354).
Scheme 3.2.3.1 Shair’s Oxy-Cope Rearrangement/Transannular Dieckmann Cascade

Treatment of ketone 354 with Mander’s reagent, removal of the PMB group and oxidation yielded carboxylic acid 355. The acid was converted to a MOM ester which, upon treatment with Mander’s reagent yielded enol carbonate 356. Exposure of 356 to TMSOTf and HC(OMe)3 initiated a Fries-like rearrangement to furnish lactone 357.
Scheme 3.2.3.3.2 Shair’s Fries Rearrangement

Similar to the previous two total syntheses, homologation of carboxylic acid 358 by mesylation, diazoketone formation and Wolf rearrangement gave tert-butyl ester 359. Phomoidride B (301) was completed via enol triflate formation, palladium catalyzed CO insertion and deprotection of the tert-butyl ester.

Scheme 3.2.3.3.3 Shair’s Phomoidride B Synthesis
3.2.3.4 Danishesky’s Route

The fourth total synthesis of the phomoidrides was reported by Danishefsky in 2000.\textsuperscript{51-54} Danishefsky began by silylation of furan 360 at the 2-position followed by iodinating at the 4-position and mesylation of the alcohol (Scheme 3.2.3.4.1). The derived mesylate 361 was converted to the corresponding furanoaldehyde, which was in turn subjected to an aldol reaction with 362. Protection of the newly formed alcohol as the TBS ether provided 364 which, upon Heck cyclization, ketone reduction and TBS protection provided key intermediate 364. A two-step allylic oxidation/ iodination applied to the olefin gave vinyl iodide 365. Palladium mediated coupling of 365 with trialkyl borane 366, followed by selective removal of the TBS protecting group and Michael addition with allytrimethylsilane yielded olefin 367.
Reduction of ketone 367 with LAH, oxidation of the less hindered alcohol, mesylation, and elimination with DBU gave bridgehead olefin 368 (Scheme 3.2.3.4.2). Using Tebbe’s reagent, the ketone was converted to the corresponding exo-methylene, which upon [2+2] cycloaddition with 2,2- dichloroketene, reductive removal of the chlorine atoms and removal of TBS protecting group produced alcohol 369. The unsymmetrical all-carbon quaternary center was constructed via a sequence that began with treatment of cyclobutanone 369 with diphenyl disulfide. This was followed by oxidation of the allylic secondary alcohol to the corresponding ketone, Baeyer-Villiger oxidation of the cyclobutanone with H$_2$O$_2$ and concomitant oxidation of the phenylsulfide to its sulfoxide. The terminal olefin in the resultant intermediate was then oxidized with
OsO₄ and NMO to yield an intermediate diol the cyclized to the corresponding hemiacetal \textbf{370}. The lactone \textbf{371} was formed \textit{via} base-mediated rearrangement and subsequent Swern oxidation.

\textit{Scheme 3.2.3.4.2 Danishefsky Ketal synthesis}

Danishefsky next turned toward installing the side chains. To this end aldehyde \textbf{371} was exposed to Grignard reagent \textbf{372} to furnish an alcohol which, upon oxidation, oxidative removal of benzyl protecting group, oxidation of resultant primary alcohol and finally olefin formation by treatment with 1,1-diiodomethane in the presence of CrCl₂, gave olefin \textbf{373} (\textit{Scheme 3.2.3.4.3}). Singlet oxygen oxidation of the furan ring, followed by TPAP oxidation, hydrolysis of the methyl ester and subsequent reclosure of the acetal
with MeSO$_3$H furnished the natural product phomoidride D (303). As illustrated, in another seven steps, phomoidride D (303) was converted to phomoidride A (300).

**Scheme 3.2.3.4.3 Danishefsky Phomoidride A and D synthesis**
3.3 Conclusions

To date numerous synthetic efforts have been directed toward the phomoidrides and four total syntheses have been completed. While in part, these investigations were motivated by an interesting biological profile, the fascinating structures innovative strategies and tactics they inspire are likely the true driving force behind these synthetic efforts. Further synthetic studies will likely provide more efficient access to these compounds, new structural analogs, and additional advances in both the strategies and tactics available to synthetic chemists.
3.4 Notes and References


bicyclic core of CP-225,917 and CP-263,114 by an intramolecular Diels-Alder reaction. 


Chapter 4

Phomoidride Synthetic Studies from the Wood Group

4.1 Introduction

In the Wood Group, a total synthesis of the Phomoidrides has been ongoing for about ten years. Graduate students Jón Njardarson, David Spiegel, Ivar McDonald, and Barry Twenter, as well as several post-doctoral fellows and undergraduate students have worked on this project. This chapter will first introduce their pioneering research and then discuss our current progress towards a total synthesis of the phomoidrides.

4.2 Previous Studies Towards the Total Synthesis of Phomoidrides

4.2.1 Synthetic Approach I: Diester Model

Illustrated in Scheme 4.2.1 is a retrosynthetic analysis for phomoidride D (303) that was under investigation just prior to my joining the project. As indicated, phomoidride D (303) was expected to derive from diester 400. Grob fragmentation of intermediate 401 would give the [4.3.1] bicyclic core and install the bridgehead olefin. Opening the acetal in 402 and subsequent dithiane formation, followed by installation of a leaving group would yield the fragmentation precursor 401. Intermediate 402 was expected to arise from radical cascade cyclization of bromide 403. The latter would be produced from ketone 404 via aldol-type introduction of the carbons needed for
exomethylene lactone formation. Finally, the [2.2.2] bicyclic core found in 404 would be delivered through a tandem phenolic oxidation/Diels-Alder sequence applied to phenol 405 which, in turn, would be available from the coupling of phenol 406 and bromide 407.

Scheme 4.2.1 Retrosynthetic Analysis I of Total synthesis of Phomoidride D
4.2.2 Development of Phenolic Oxidation/Diels-Alder Cascade Reaction

To investigate the planned synthetic route to the phomoidrides, a model system was employed wherein primary alcohol 408 replaced the more elaborate side-chain component 407. Mitsunobu coupling of catechol 410 with 408 gave the corresponding mono alkylation product, phenol 411 (Scheme 4.2.2.1). Oxidation of 411 with Pb(OAc)_4 gave the intermediate diene 412 which underwent intramolecular [4+2] cycloaddition to yield ketone 413.\(^{12-18}\) To maintain compatibility in subsequent transformations, the acetyl group was replaced by TMS to yield 414.

**Scheme 4.2.2.1 Phenolic Oxidation and Diels- Alder Cycloaddition**

Aldol addition of enolate 415\(^{36-39}\) to ketone 414 gave tertiary alcohol 416 (Scheme 4.2.2.2). Introduction of the required exomethylene followed by N-oxidation (m-CPBA) and Cope elimination. The derived ester (417) was converted to lactone 418 following removal of the TMS protecting group and exposure to mild acid.
Scheme 4.2.2.2 Exo-Methylene Lactone Construction

Alkylation of lactone 418 with Stork’s bromoacetal (419)\(^{20-23}\) gave radical cascade cyclization precursor 420 (Scheme 4.2.2.3). Treatment of 420 with SmI\(_2\) yielded a cyclization product 423 resulting from a sequential 5-\textit{endo-trig}, 5-\textit{exo-tet} cyclization.\(^{24-31}\) The cascade cyclization is highly efficient and is believed to occur via initial reduction of the maleate followed by addition to the exomethylene and substitution of the bromine.\(^3\)
Opening of acetal 423 in the presence of BF$_3$•OEt$_2$ and propane-1,3-dithiol gave tertiary alcohol 424 (Scheme 4.2.2.4). Reduction of lactone 424 to the corresponding hemiacetal (425), followed by methylation gave acetal 426. Treatment of 426 with KH, CS$_2$ and MeI furnished xanthate 427.
After considerable experimentation it was found that treatment of xanthate 427 with SmI₂ and HMPA produces the desired Grob fragmentation product 428a, as well as the byproduct 428b resulting from reductive removal of the xanthate (Scheme 4.2.2.5).³²-³³ Although the derived fragmentation product is the result of a two electron reduction, the exact nature of the intermediate undergoing fragmentation (radical or anionic) is not known.

Scheme 4.2.2.5 Grob Fragmentation
Numerous attempts were made to convert diester 428a to olefin 429 (Scheme 4.2.2.6). Unfortunately, all efforts to effect this transformation were unsuccessful.

**Scheme 4.2.2.6 Maleic Anhydride Synthesis Approach**

4.2.3 Synthetic Approach II: Ester and Benzyl Ether Model

Since attempts to install the maleic anhydride moiety were unsuccessful from substrate 428a, an alternative approach targeting β-keto ester 432 as substrate was explored. In this approach it was envisioned that the maleic anhydride moiety in 430 would arise via a Pd(0)-catalyzed CO-insertion applied to the corresponding enol triflate 431 (Scheme 4.2.3.1). The requisite β-Keto ester 432 would derive from a Wharton fragmentation of tertiary alcohol 433. Using similar procedures as the previous diester approach, 433 would be prepared from phenol 434 wherein the aromatic core possesses a single methyl ester and a benzyl ether. Alkylation of phenol 435 with iodide 436 would yield oxidation precursor 434.
This approach commenced with 2,4-dihydroxy benzaldehyde (440, Scheme 4.2.3.2). Selective bis protection of the diphenol followed by Baeyer-Villiger oxidation and formate hydrolysis yielded phenol 441. Regioselective bromination$^{34}$ and phenol alkylation with iodide 436$^{35}$ gave aryl bromide 442. Lithium-bromide exchange and trapping of the resulting aryl lithium species with methyl chloroformate was followed by removal of the allyl protecting group to provide 443.$^{40}$ Phenolic oxidation and Diels-Alder cycloaddition was performed using Pb(OAc)$_4$ as the oxidant and produced bicycle 445 in excellent yield.
**Scheme 4.2.3.2 Phenolic Oxidation and Diels-Alder Cycloaddition**

1. BnBr, K$_2$CO$_3$
2. m-CPBA; K$_2$CO$_3$, MeOH
3. m-CPBA; K$_2$CO$_3$, MeOH

**Scheme 4.2.3.3 Bu$_3$SnH Radical Cascade Cyclization**

Using procedures similar to those employed in the diester approach, ketone 445 was converted to the corresponding lactone (446) wherein the Stork bromoacetal was poised for radical cascade cyclization. In contrast to the diester system, exposure of 446 to SmI$_2$ resulted in decomposition of the starting material (**Scheme 4.2.3.3**); however, treatment 446 with Bu$_3$SnH and AIBN furnished a 1:1 mixture of the desired 5-exo-trig, 5-exo-trig product 448 and an undesired 6-endo-trig, 4-exo-trig byproduct 447.
Following previously-established procedures, acetal 448 was converted to fragmentation precursor 449 (Scheme 4.2.3.3). However, efforts to fragment intermediate 449 led only to epimerization product 452, the structure of which was confirmed by X-ray structure analysis.\(^4\) The lack of fragmentation coupled with the observed epimerization product 452, suggested the intermediacy of a retro-aldol process. Based on this unanticipated retro-aldol epimerization pathway, we reasoned that the ester group, although necessary for eventual installation of the maleic anhydride moiety, could not be present in the fragmentation substrate.

**Scheme 4.2.3.3 Approach to Wharton Fragmentation**

\[
\text{BnO} \quad \overset{1. BF_3\cdot OEt_2, \text{HS(CH}_2)_2\text{SH}}{\text{DCM, r.t.}} \quad \overset{2. \text{MsCl, Et}_3\text{N, DMAP, DCM, r.t.}}{\text{(3 steps: 32\% yield)}} \quad \overset{3. \text{BBr}_3, \text{DCM, r.t.}}{\text{retro-aldol}} \quad \overset{\text{E=CO}_2\text{Me}}{\text{449}} \quad \overset{\text{450}}{\xrightarrow{\text{E=CO}_2\text{Me}}} \quad \text{E=CO}_2\text{Me} \quad \overset{\text{451}}{\xrightarrow{\text{E=CO}_2\text{Me}}} \quad \text{452}
\]

In an effort to remove the ester groups deleterious influence on the Wharton fragmentation, it was found that treatment of 452 with LAH selectively reduces the ester without affecting the lactone (Scheme 4.2.3.4). Importantly, the derived alcohol (453) undergoes smooth fragmentation to desired product 454 in good yield upon exposure KOH.
At this stage, completing the synthesis in the model system required oxidation of the primary alcohol 454 to the corresponding acid or aldehyde 455 (Scheme 4.2.3.5). Unfortunately, all conditions attempted resulted in recovery or decomposition of starting materials. The difficulty in manipulating 454 was further illustrated by several failed attempts to simply install a protecting group.
4.3 Current Approach Towards the Total Synthesis of the Phomoidrides

4.3.1 Proposed Solution for Removal Carboxylate

Given that our prior studies had established the need to remove the ester in 449 prior to fragmentation (see Scheme 4.2.3.3) and that removing the ester by reduction was a dead-end, a more dramatic modification of the synthetic plan was needed. Thus began my involvement with the project and as a first solution the complete removal of the ester group was proposed.

As illustrated in Scheme 4.3.1, it was envisioned that the proposed decarboxylated intermediate 462 could be accessed in two ways. One approach involved the decarboxylation of an intermediate similar to that already prepared in previous studies (i.e., 460 to 462). Alternatively, we had the option of leaving out the CO₂ unit from the outset and bringing the synthesis through a more simplified intermediate 461.

Scheme 4.3.1 Proposed Solution to Remove of Carboxylate
4.3.2 Decarboxylation Attempts

To determine whether the decarboxylation approach would be viable, we attempted to prepare substrate 464 (Scheme 4.3.2); however, hydrolysis of ester 463 to carboxylic acid 464 led only to decomposition of the starting material. As an alternative, we attempted to prepare acid 464 via an oxidation of the corresponding aldehyde (465). To this end, preparation of the 465 began with previously prepared aryl bromide 442. Removal of the allyl protecting group, followed by exposure to n-BuLi and trapping of the derived dianion with DMF furnished benzaldehyde 466. Oxidation of 466 and intramolecular Diels-Alder cycloaddition, yielded aldehyde 465. Unfortunately, attempts to oxidize aldehyde 465 to carboxylic acid 464 under Pinnick conditions failed and only starting material was recovered.

Scheme 4.3.2 Proposed Solution to Remove Carboxylate
4.3.3 Initial Studies with Simplified Substrates

Given the difficulty of converting aldehyde 465 to carboxylic acid 464, we began to consider [2.2.2] bicyclic core structures that were devoid of a carboxylate moiety, such as substrate 468. In fact, efforts to prepare this intermediate are illustrative of the inherent difficulties associated with this design change. As can be seen in Scheme 4.3.3, phenol 467 is readily available from deallylation of 442; however, when 467 is exposed to conditions expected to result in the tandem phenolic oxidation/Diels-Alder reaction, the only observed product is 469. Thus, the electronic demands of the intramolecular Diels-Alder reaction are not met by this substrate.

Scheme 4.3.3 Phenolic Oxidation and Diels- Alder reaction of bromide phenol 467

4.3.4 Tuning of the Diels-Alder Substrate

When one considers the successful phenolic oxidation/ Diels-Alder reactions of di- and mono-ester substrates 411 and 443 in conjunction with the unsuccessful phenolic oxidation/Diels-Alder of 467 (Scheme 4.3.4.1, inset), it becomes clear that an electron withdrawing group must be present on the diene to enable the inverse electron demand Diels-Alder process. Therefore, we began to develop an alternative route wherein an electron withdrawing group replaces the benzyl ether at the 3- position (e.g., 470, Scheme 4.3.4.1). In contrast to 443, the C-4 functionalized monoester substrate, the
newly envisioned intermediate manifests an aldehyde as the electron withdrawing group. The change in oxidation level was made in anticipation of employing a Baeyer-Villiger oxidation to cleave the aldehyde and deliver the hydroxyl group required for Wharton fragmentation (see 473 to 462 in Scheme 4.3.4.1). In addition to incorporation of the aldehyde, substrate 470 is unfunctionalized at C-4; this change was made to circumvent complications akin to those encountered when trying to manipulate the C-4 hydroxymethyl group in 454 (vide supra, Scheme 4.2.3.5). Overall, exposure of 470 to the tandem penolic oxidation/ Diels-Alder was expected to deliver the [4+2] product 472 via the intermediacy of acetate 471. Paralleling our previous routes, 472 would be advanced to 473 via radical cascade chemistry applied to an exomethylene lactone. Baeyer-Villiger oxidation, thioacetal formation and introduction of a mesylate group would deliver 462 and set the stage for the Wharton fragmentation.

Scheme 4.3.4.1 Synthetic Plan Using EWG for Diels- Alder Reaction

![Scheme 4.3.4.1 Synthetic Plan Using EWG for Diels-Alder Reaction](image-url)
To investigate this plan, we set out to prepare phenol 470. In an initial approach 3,4-dihydroxy benzaldehyde (437) was used as the starting material and selectively converted to the corresponding monoacetate (474) upon exposure to AcCl in the presence of NaOH (Scheme 4.3.4.2). Unfortunately, efforts to alkylate the derived phenol (474) with iodide 436 only yielded an undesired bis alkylation product 475. Eventually we discovered that, in contrast to acylation, alkylation of 3,4-dihydroxy benzaldehyde proceeds selectively at the C-4 phenolic oxygen; thus, simply treating with K$_2$CO$_3$ and iodide 436, furnishes desired phenol 470 in reasonable yield.

**Scheme 4.3.4.2 Preparation of Phenol 470**

![Scheme 4.3.4.2](image)

Proceeding with phenol 470, we observed that the tandem phenolic oxidation/Diels-Alder reaction behaves differently at varied temperatures (Table 4.3.4). The highest yield for the desired [4+2] product 480 was observed in reactions performed at 90 °C; however, efforts to improve the yield by running the reaction at warmer temperatures resulted in increasing amounts of rearomatized byproduct 481; at 140 °C 481 was the only observed product.
**Table 4.3.4 Phenolic Oxidation and Diels-Alder Cycloaddition of Phenol 470**

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 °C</td>
<td>480: 52%</td>
</tr>
<tr>
<td>90 °C</td>
<td>480: 54%</td>
</tr>
<tr>
<td>140 °C</td>
<td>481: 47%</td>
</tr>
</tbody>
</table>

4.3.5 Chemoselectivity Issues in Advancing 480

Although introduction of the aldehyde in 470 had served to meet the electronic demands of the Diels-Alder reaction, advancing the cycloadduct 480 required differentiation of the aldehyde and newly formed ketone moieties. This differentiation was important given that aldol addition to the ketone with methyl 3-(dimethylamino)propanoate enolate was the next step. 36-39 Given the potential difficulties associated with eventual removal of many carbonyl protecting groups, we chose to first explore differentiation of the aldehyde and ketone by nucleophilic addition. As illustrated in **Scheme 4.3.5.1**, this effort began by removal of the acetate and exposure of the derived hemiacetal (482) to either TMSCl followed by MeLi or NaH/MeLi. Given somewhat improved efficiency, the latter sequence was employed for material advancement and the derived diol 485 was protected as the corresponding bis silyl ether 486. Unfortunately, 486 failed to undergo subsequent aldol addition to produce 487.
After the unsuccessful intermolecular aldol reaction to ketone 486, we decided to attempt an intramolecular variant and explored the conversion of hemiacetyl 482, to ester 488 by exposure to 2-bromoacryloyl chloride; unfortunately this acylation reaction failed (Scheme 4.3.5.2).

Scheme 4.3.5.2 Attempted Intramolecular Addition of a Vinyl Bromide
In a second attempt at intramolecular addition we explored the use of different lead salts such as Pb(O₂CCH₂CH₃)₄ 494⁴³⁻⁴⁵ as oxidants in the tandem phenolic oxidation/Diels-Alder reaction. Although this approach allowed quick access to the desired ester (490), subsequent intramolecular aldol reaction to the lactone (491) failed under a variety of different conditions (Scheme 4.3.3).

Scheme 4.3.3 Intramolecular Addition for Differentiation of Enol 480 by Lead Salt

In a final attempt at intramolecular lactone formation we exposed hemiacetal 482 to ylide 497 and were delighted to find that butenolide 492 was produced in modest yield (Scheme 4.3.4)⁴⁷. Mechanistically this transformation is believed to begin with alcohol addition to ketene 497 to furnish 493 which, in turn, undergoes intramolecular Wittig olefination via intermediate 494⁴⁶. Lactone 492 was produced after elimination of triphenylphosphine oxide. Encouraged by this success we set out to explore preparation of a more functionalized lactone system via treatment of 482 with cumulene 495. It was hoped that the in situ generated cumulene would acylate hemiacetyl 482 and that the derived intermediate would undergo intramolecular addition to directly furnish the desired exomethylene lactone 489. Unfortunately, these efforts resulted only in decomposition of the starting material.
Experiencing only limited success with nucleophilic addition and intramolecular additions we next attempted to differentiate the aldehyde and ketone moieties in 480 via oxidation (Scheme 4.3.5). Attempt to transform the aldehyde to ketone 500 via a Baeyer-Villiger reaction using \textit{m}-CPBA, \textit{H}_2\textit{O}_2, \textit{or} \textit{CF}_3\textit{CO}_2\textit{H} resulted in either recovery or decomposition of starting material.\textsuperscript{48,49} Attempts to convert aldehyde 480 to its
corresponding carboxylic acid using the Pinnick oxidation resulted only in recovery of starting material.

Scheme 4.3.5.5 Attempted Differentiation of Enol 480 via Oxidation

In a last approach to differentiate the carbonyl groups, an effort was made to effect conjugate reduction. To this end, it was hoped that conversion of 482 to the corresponding aldehyde 502 would provide a substrate suitable for subsequent Baeyer-Villiger oxidation and thus a variety of conditions for conjugate reduction were explored that included: L-selectride;\(^{50}\) \([(\text{PPh}_3\text{CuH})_6];^{51}\) (Ph\(_3\text{P})\text{RhCl}, \text{Et}_3\text{SiH};^{52}\) NaBH\(_6\), NiCl\(_2;^{53}\) Mg or Zn/MeOH;\(^{54}\) \text{Et}_3\text{SiH}, \text{CuCl}; \text{Al}(\text{O}(2,5-\text{Ph})\text{Ph})_3, \text{DIBAL}, \text{nBuLi};^{55}\) Morpholine, Hantz reagent;\(^{56}\) 9-BBN; pyridine, and; Pd/C, H\(_2\) (Table 4.3.5). As illustrated in Table 4.3.5 reduction using Pd/C and H\(_2\) was the only successful result. Although, this condition provided a high yield of the desired product, potential lack of compatibility with the olefins present in the side chains in the real system led us to abandon this approach.
4.3.6 Diels- Alder Reaction of a Triflate-Containing Substrate

Efforts thus far have demonstrated the necessity of an electron withdrawing group (EWG) on the phenol for success in the phenolic oxidation/inverse electron demand Diels-Alder reaction. In addition, deleterious retro-aldol chemistry in attempted fragmentation reactions led us toward temporarily placing the EWG at C-3 of the aryl substrate. Although this latter maneuver worked with regard to the electronic demands of the Diels-Alder reaction, transforming the EWG (i.e., aldehyde) to a ketone-containing substrate (e.g., 513) suite for a subsequent radical cascade cyclization proved unworkable. Based on this growing body of results we decided to explore the affect of electron withdrawing substituents attach to the aryl oxygen. If these “OEWGs” proved
capable of meeting the electronic demands of the Diels-Alder reaction, we could avoid many of the deleterious issues encountered in our previous studies. As illustrated retrosynthetically in Scheme 4.3.6.1, model system 430 was envisioned to derive from \( \beta \) keto ester 510 via Pd(0) catalyzed CO insertion. Wharton fragmentation would deliver 510 from 512 which, in turn, would be produced by application of a radical cascade reaction to bromo acetyl 513. Following the previous established procedures, bromo acetal 513 would be derived from Diels-Alder product 514 which we hoped could be produced from phenol 515 wherein an OEWG substituent would meet the electronic demands of the tandem phenolic oxidation/Diels-Alder sequence.

Scheme 4.3.6.1 Retrosynthetic Analysis III: Model with OEWG Substitution

In accord with the above synthetic plan we began our studies by exploring the effectiveness of OEWG substituents on the Diels-Alder reaction. To this end we first
explored the affect of incorporating a triflate group. As illustrated in Scheme 4.3.6.2, we exposed the previously prepared phenol 470 to allylbromide to furnish benzaldehyde 516. Baeyer-Villiger oxidation of 516 in the presence of PhSeSePh and H₂O₂ produced a mixture of the desired phenol 518 and byproduct epoxide 517. Isolation of 518 followed by exposure to triflic anhydride furnished the corresponding triflate 519 which, upon exposure to Pd(0) and NaBH₄ underwent smooth deallylation to afford 520, the substrate needed for the proposed tandem phenolic oxidation/Diels-Alder reaction. To our delight, treatment of 520 with Pb(OAc)₄ produced desired [4+2] cycloaddition products 521 and 522 in good yield. This result provided solid evidence that use of OEWG substitution on the phenol ring was a suitable strategy in this inverse electronic demand Diels-Alder reaction. Moreover, this substrate afforded better yields than previous model systems.

_Scheme 4.3.6.2 Preparation 1: Precursor for Phenolic Oxidation and Diels-Alder Reaction_

Although we were excited by this initial success, the observed over oxidation in the Baeyer-Villiger oxidation of 516 left us a bit concerned about compatibility issues.
with the olefins that would be present in the side chains of the real system (Scheme 4.3.6.2, inset). Thus, rather than forge ahead with the model system we opted to explore an alternative route to 518. As illustrated in Scheme 4.3.6.3, we chose to explore a route emanating from 2,4-dihydroxy benzaldehyde (440) which, upon exposure to BOM-Cl can be selectively protected at the least hindered phenol to give aldehyde 525. Subsequent allylation and Baeyer-Villiger oxidation delivers phenol 526. Coupling of 526 with iodide 436 delivers phenol ether 527 and removal of the BOM protecting group then completes the construction of 518. Importantly, this approach to 518 is very short, proceeds in excellent yield and can be readily adapted to the phomoidride D (303) synthesis by simply incorporating a fully functionalized side-chain unit (i.e., 407) in place of 436.

Having developed an alternative preparation of 518, we turned toward completing the model study and advanced the Diels-Alder adduct (521) to the corresponding hemiacetyl (522) by exposure to silica gel.
As illustrated in Scheme 4.3.6.4, intermediate 522 was advanced by protecting the free alcohol as its TMS ether (528), followed by aldol addition and Cope elimination to yield olefin 529 (Scheme 4.3.6.4). Removal of the TMS protecting group with TBAF and AcOH was followed by spontaneous cyclization to provide lactone 530.

Unfortunately, efforts to remove the triflate and deliver ketone 531 failed. The undesired seco acid 532 was the only product observed.
Scheme 4.3.6.4 Lactone Synthesis

Somewhat surprised by the resiliency of the enol triflate we decided to explore this transformation in a simplified system. To this end model enol triflate 535 was prepared and the conditions that were explored for its conversion to ketone 536 included: A) attempts to saponify under basic conditions (LiOH or KOH); B) initial transformation to the corresponding enamine via by Pd (0) or Cu (I) catalysis; C) addition of amine nucleophiles such as DBU or NaNH₂, and; D) reductive cleavage of the O-S bond (Table 4.3.6.1). Although several of these conditions produced some of the desired ketone, a combination of Pd(OAc)₂, BINAP, morpholine, and Cs₂CO₃ proved the most effective.
Having had some success with the conversion of 535 to 536, we applied a few of the more promising conditions to 528, including: LiOH; Pd(OAc)$_2$, BINAP, morpholine, NaO$_2$Bu;$^{59}$ Pd(OAc)$_2$, BINAP, morpholine, Cs$_2$CO$_3$;$^{61}$ DBU;$^{63}$ Na(NH$_3$)$_2$;$^{65}$ Pyridine; NaNH$_2$;$^{64}$ CuI, proline, morpholine, K$_3$PO$_4$ $^{62}$ (Table 4.3.6.2). Unfortunately, no desired product (537) was produced and starting material was either recovered or decomposed in all cases except the last, wherein an unexpected heterocyclic product (538) was observed.

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>LiOH, r.t.</td>
<td>decomposition</td>
</tr>
<tr>
<td>Pd(OAc)$_2$, BINAP, morpholine, NaO$_2$Bu, Tol, reflux</td>
<td>decomposition</td>
</tr>
<tr>
<td>Pd(OAc)$_2$, BINAP, Cs$_2$CO$_3$, Tol, reflux</td>
<td>26%</td>
</tr>
<tr>
<td>Pd(OAc)$_2$, BINAP, morpholine, Cs$_2$CO$_3$, Tol, reflux</td>
<td>46%</td>
</tr>
<tr>
<td>DBU, THF, r.t.</td>
<td>decomposition</td>
</tr>
<tr>
<td>NaNH$_2$, DMF, r.t.</td>
<td>25%</td>
</tr>
<tr>
<td>Na(NH$_3$)$_2$, -78 °C</td>
<td>trace</td>
</tr>
</tbody>
</table>
Table 4.3.6.2 Removal Triflate in the Real System 522

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>LiOH, THF r.t to reflux</td>
<td>decomposition</td>
</tr>
<tr>
<td>Pd(OAc)$_2$, BINAP, morpholine, NaO'Bu, Tol, reflux</td>
<td>decomposition</td>
</tr>
<tr>
<td>Pd(OAc)$_2$, BINAP, morpholine, Cs$_2$CO$_3$, Tol, reflux</td>
<td>decomposition</td>
</tr>
<tr>
<td>DBU, THF, r.t.</td>
<td>decomposition</td>
</tr>
<tr>
<td>Na(NH$_3$)$_3$, -78 °C</td>
<td>decomposition</td>
</tr>
<tr>
<td>Py. r.t. to reflux</td>
<td>S.M. recovered</td>
</tr>
<tr>
<td>NaNH$_2$, DMF, r.t.</td>
<td>decomposition</td>
</tr>
<tr>
<td>CuI, (-)-proline, morpholine, K$_3$PO$_4$, MeCN, reflux</td>
<td>538: 39% yield</td>
</tr>
</tbody>
</table>

4.3.7 Investigation of Other OEWG Substituents

Due to the difficulties encountered while attempting to remove the triflate group, we decided to investigate other OEWG groups. To this end phenol 518 was acylated with different electron withdrawing groups, including: acetate, benzoylate, trifluoroacetate, phosphate, mesylate and nosylate to give the corresponding products 540 to 545, respectively (Table 4.3.7.1).
**Table 4.3.7.1 Preparation of Substrate for Diels- Alder Reaction: Acylation**

As illustrated in **Table 4.3.7.2**, derivatives **540-545**, could be deallylated to the corresponding phenols (**547-552**) using Pd(0) and either NaBH₄/EtOH or K₂CO₃/MeOH.⁴⁰,⁶⁶
With a series of substrates in hand (i.e., 546-552) the subsequent tandem phenolic oxidation/Diels-Alder addition was investigated. The first step, phenolic oxidation was found to work well for all substrates; however, the subsequent [4+2] cycloaddition was observed to proceeded with only three: phenol 550 (phosphate EWG), 551 (mesylate EWG), and 552 (nosylate EWG) (Table 4.3.7.3). Of these successful substrates, the yield for 552 was best at 77% (combined).
Table 4.3.7.3 Substrates 553 for Phenolic oxidation and Diels-Alder Reaction

Our next challenge was to convert enolether 555 to the corresponding ketone 560.

To this end we chose to explore three conditions: LiOH; KOH; PhSH/KOH. In the event, exposure of 521 (the enoltriflate) and 556-559 to the first two conditions resulted in no desired product (Table 4.3.7.4). However, for substrate 558, exposure to PhSH/KOH furnished the desired ketone in excellent yield.
Proceeding with ketone 560, our next goal was differentiation of the two ketone moieties. To this end, we began advancing 560 by removal of the acetate to provide hemiacetal 537. Reprotection of 537 as the TMS ether (561) was followed by exposure to TBSOTf to produce silyl enolether 563. With the two carbonyls effectively differentiated, the stage was set for the aldol addition/Cope elimination sequence. To our delight, 563 proved to be a superb substrate and furnished the desired ester 564 in 85% overall yield. Conversion of 564 to the corresponding exomethylene lactone (531) was followed by alkylation with Stork’s bromo acetyl to provide radical cyclization precursor 513 (Scheme 4.3.7.1)
Scheme 4.3.7.1 Synthesis of Lactone 531

Treatment of 513 with SmI₂ gave tertiary alcohol 512. Having accessed cyclization product 512, our next goal was to conduct the Wharton fragmentation. To this end, the acetal in 512 was opened and converted to the corresponding dithiane (566) upon exposure to BF₃•OEt₂ and 1,3-propanethiol. Unfortunately mesylation of 566 furnished bis mesylate 567, an intermediate which has to date proven unadvancable (Scheme 4.3.7.2).
Given that selective alcohol functionalization had now presented itself as a problem we recognized that oxidation of the ethyl ketal to the corresponding lactone might provide an intermediate suited for fragmentation. Unfortunately, although conversion of acetal 512 to the corresponding hemiacetyl 570 was successful subsequent oxidation to 571 failed under numerous conditions (Scheme 4.3.7.3). As an alternative approach to delivering lactone 571, we explored introduction of an alpha halo ester replacement for the bromo acetal. The derived ester (585) was seen as a potential precursor to 571 for via a radical cyclization akin to that initiated with the corresponding bromo acetal. However, efforts to prepare 585 by treatment of lactone 531 with 2-chloroacetic anhydride (497) gave undesired product 586, from the product of an apparent [3,3] sigmatropic rearrangement of 585.
The final approach to prepare a substrate for Wharton fragmentation involved differentiating the two tertiary alcohols that would result following acetal opening of substrate 512 (Scheme 4.3.7.4). Thus, acylation of the tertiary alcohol in 512 was followed by acetal opening/ dithiane formation, mesylation, and deacylation to furnish 572.
4.4 Future Plans

Future studies will focus on the fragmentation of mesylate 572 to the corresponding ketone 568. Subsequent completion of the model system begin with homologation of 568 using Mander’s reagent. Conversion of the intermediate β-keto ester to the corresponding enol triflate followed by palladium catalyzed CO insertion, will set the stage for dithane removal and oxidation using the Jones Reagent.

Scheme 4.4 Future Plans

4.5 Conclusions

In this chapter, the previous Wood group synthetic efforts towards the total synthesis of the phomoidrides have been summarized. Based on these previous results, a new approach was developed wherein a deleterious ester group was removed and a Whartong fragmentation enabled. Further refinement revealed that subtle electronic effects of a tandem phenolic oxidation/Diels-Alder sequence could be addressed by the incorporation of electron deficient sulfonates (e.g., a triflate or nosylate).
4.6 Experimental Section

4.6.1 Materials and Methods

**General.** Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran (THF) was dried either by distillation from sodium/benzophenone or by passing through activated alumina columns. Methylene chloride (DCM), diethyl ether (Et₂O), benzene (PhH), toluene (Tol) and acetonitrile (MeCN) were dried by passing through activated alumina columns. Dimethylformamide (DMF) was dried over activated molecular sieves or by passing through activated alumina columns. MeOH was distilled over magnesium oxide. All other commercially obtained reagents were used as received. All reactions were monitored by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm). Flash chromatography was performed with indicated solvents using silica gel (particle size 0.032-0.063) purchased from Silicycle. Microwave experiments were performed using a Biotage Initiator® or CEM Discover microwave reactor. ¹H NMR spectra were recorded at 500 MHz, 400 MHz or 300 MHz using a Bruker AM-500, Bruker Avance DPX-500, Bruker AM-400, Varian Inova 400, Varian Inova 300 or Varian Mercury Inova 300 instrument. ¹³C NMR spectra were recorded at 125 MHz, 100 or 75 MHz using a Bruker AM-500, Bruker Avance DPX-500, Bruker AM-400, Varian Inova 400, Varian Inova 300 or Varian Mercury Inova 300 instrument. Chemical shifts are reported relative to internal chloroform (¹H, δ = 7.26, ¹³C, δ = 77.1) as indicated. Splitting patterns are reported as such, app = apparent, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet. Infrared spectra were recorded on a
Nicolet Avatar 320 FT-IR. High-resolution mass spectra were acquired at the Colorado State University CIF using an Agilent 6210 TOF LCMS.

4.6.2 Preparative Procedures

Preparation of Compound 466

![Reaction Scheme]

To a solution of 442 (403.0 mg, 1 mmol, 1 equiv.) in EtOH (10 mL) was added NaBH$_4$ (20 mg, 0.5 mmol, 0.5 equiv.) and Pd(PPh$_3$)$_4$ (29 mg, 0.03 mmol, 0.03 equiv.). The mixture was stirred overnight then filtered through Celite and concentrated under reducing pressure to give crude phenol (368.2 mg, 100%).

To a solution of crude phenol in THF (10 mL) was added NaH (26.4 mg, 1.1 mmol, 1.1 equiv.). The mixture was stirred for 5 min at room temperature then cooled to -78 °C. The solution was added to n-BuLi (0.75mL, 1.2 mmol, 1.2 equiv., 1.6 M) dropwise and stirred for 30 minutes. The mixture was added to DMF (0.23 mL, 3 mmol, 3 equiv.), stirred for 3 h at -78 °C then warmed to room temperature. The solution was stirred overnight and quenched by H$_2$O (1 mL). The layers were separated and the aqueous layer was washed with EtOAc (2 × 2 mL). The combined organic layers were washed with brine (4 mL), dried over Na$_2$SO$_4$, filtered and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography.
(gradient elution, 10%- 20% EtOAc/ Hexanes) to yield 466 (308.4 mg, 98.6%) as brown solid.

**Compound 466**: FTIR(NaCl/ thin film) 3308, 2935, 2874, 1662, 1585, 1506, 1456, 1290, 1216, 1138, 1025, 1290, 1216, 1138, 1025, 1024, 968, 736, 696 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 10.37 (s, 1H), 7.53- 7.31 (m, 6H), 6.64 (s, 1H), 6.52- 6.40 (m, 1H), 5.66- 5.38 (m, 2H), 5.11 (s, 2H), 4.05 (t, $J$=6.6 Hz, 2H), 2.56- 2.38 (m, 2H), 1.68 (t, $J$=6.2 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 188.2, 158.2, 153.5, 140.7, 136.2, 128.8, 128.6, 128.4, 127.5, 126.4, 117.9, 110.4, 100.4, 71.1, 69.4, 32.5, 18.1; HRMS (TOF LCMS) calc’d for C$_{19}$H$_{21}$O$_4$ [M-H] 311.1283, found 311.1291.

**Preparation of Compound 465**

To a solution of 466 (43.5 mg, 0.14 mmol, 1 equiv.) in DCE (4.5 mL) was added Pb(OAc)$_4$ ( 225.7 mg, 0.17 mmol, 1.4 equiv.). The solution was heated to reflux and stirred overnight. The mixture was cooled to room temperature, filtered through Celite and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%- 50% EtOAc/ Hexanes) to yield 465 (67.4 mg, 41%) as brown oil.

**Compound 465**: FTIR(NaCl/ thin film) 3402, 2959, 2927, 1741, 1662, 1616, 1456, 1374, 1221, 1178 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 10.00 (d, $J$= 4.2 Hz, 1H),
7.44- 7.29 (m, 5H), 5.28- 5.06 (m, 2H), 4.11- 3.98 (m, 1H), 3.75- 3.56 (m, 2H), 2.15-
1.90 (m, 6H), 1.83- 1.72 (m, 1H), 1.66- 1.50 (m, 1H), 1.00 (dd, J=4.2, 6.8 Hz, 3H); 13C
NMR (100 MHz, CDCl3) δ 199.8, 184.4, 170.1, 169.1, 135.3, 129.0, 127.9, 127.6, 115.7,
94.0, 72.9, 62.0, 57.2, 38.7, 37.7, 36.9, 28.6, 20.9, 20.9; HRMS (TOF LCMS) calc’d for

**Preparation of Compound 470**

![Chemical Structure](chart)

To a solution of 3,4-dihydroxy benzaldehyde (437) (6.9 g, 50 mmol, 5 equiv.) in
acetone (120 mL) was added K2CO3 (6.9 g, 50 mmol, 5 equiv.) and iodide 436 (1.96 g,
10 mmol, 1 equiv.). The solution was heated to reflux and stirred overnight. The mixture
was cooled to room temperature, filtered through Celite and concentrated under reducing
pressure. The residue was loaded onto silica and purified by column chromatography
(gradient elution, 10%- 20% EtOAc/ Hexanes) to yield 470 (867 mg, 52%) as yellow oil.

**Compound 470:** FTIR(NaCl/ thin film) 3409, 2937, 1686, 1609, 1586, 1569,
1461, 1276, 1203, 1126, 1015, 969 cm⁻¹; 1H NMR (400 MHz, CDCl3) δ 9.82 (s, 1H),
7.43 (d, J=1.8 Hz, 1H), 7.40 (dd, J=1.9, 8.1 Hz, 1H), 6.94 (d, J=8.2 Hz, 1H), 5.89 (s, 1H),
5.72- 5.34 (m, 2H), 4.12 (t, J=6.7 Hz, 2H), 2.57- 2.48 (m, 2H), 1.68 (dd, J=1.1, 6.3 Hz,
3H); 13C NMR (100 MHz, CDCl3) δ 191.2, 151.3, 146.4, 130.7, 128.8, 125.9, 124.6,
114.2, 111.3, 68.9, 32.4, 18.1; HRMS (TOF LCMS) calc’d for C$_{12}$H$_{13}$O$_3$ [M-H] 205.0865, found 205.0867.

**Preparation of Compound 482**

![Reaction Scheme](image)

To a solution of 470 (180 mg, 0.87 mmol, 1 equiv.) in DCE (8.7 mL) was added Pb(OAc)$_4$ (394 mg, 0.89 mmol, 1.02 equiv.). The solution was heated to reflux and stirred overnight. The mixture was cooled to room temperature, filtered through Celite and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%-50% EtOAc/Hexanes) to yield 480 (119 mg, 54%) as yellow oil.

To the residue in DCM (8 mL) was added silica (720 mg) and stirred for two days. The mixture was filtered through Celite and concentrated under reducing pressure to yield crude 482 (110 mg, 100%) as yellow oil.

**Compound 480**: FTIR(NaCl/ thin film) 2961, 2925, 1748, 1684, 1623, 1370, 1211, 1086, 1002 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.60 (s, 1H), 7.20 (dd, $J$=1.5, 6.8 Hz, 1H), 4.05 (ddd, $J$=1.6, 5.9, 12.9 Hz, 1H), 3.93 (dd, $J$=3.3, 6.8 Hz, 1H), 3.76 (s, 1H), 3.70 (dd, $J$=3.4, 12.4 Hz, 1H), 2.12-1.95 (m, 2H), 1.98 (s, 3H), 1.85-1.79 (m, 1H), 1.68-1.61 (m, 1H), 0.88 (d, $J$=6.9 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 201.7, 188.6,
168.8, 147.9, 141.5, 92.9, 62.7, 50.7, 43.1, 37.3, 34.8, 28.2, 21.7, 20.1;  HRMS (TOF LCMS) calc’d for C$_{14}$H$_{17}$O$_{5}$ [M+H] 265.1076, found 265.1071.

**Compound 482:** FTIR(NaCl/ thin film) 3419, 2961, 2927, 2871, 1742, 1680, 1622, 1374, 1092, 1064, 1008 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.62 (s, 1H), 7.36 (dd, $J$=1.7, 6.8 Hz, 1H), 3.95 (ddt, $J$=1.2, 5.8, 12.6 Hz, 1H), 3.75 (t, $J$=2.1 Hz, 1H), 3.67 (td, $J$=3.0, 12.7 Hz, 1H), 3.59 (s, 1H), 3.06 (dd, $J$=2.3, 6.7 Hz, 1H), 2.23- 2.11 (m, 1H), 2.05- 1.90 (m, 1H), 1.89- 1.81 (m, 1H), 1.73- 1.62 (m, 1H), 0.92 (d, $J$=6.9 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 208.5, 188.6, 151.1, 139.7, 89.9, 61.7, 50.5, 45.0, 37.0, 33.8, 28.5, 19.9; HRMS (TOF LCMS) calc’d for C$_{12}$H$_{13}$O$_{4}$ [M-H] 221.0814, found 221.0818.

**Preparation of Compound 481**

![Diagram](image)

To a solution of 470 (4.12 mg, 0.02 mmol, 1 equiv.) in xylene (1.0 mL) was added Pb(OAc)$_4$ (8.9 mg, 0.02 mmol, 1.02 equiv.). The solution was heated to reflux and stirred overnight. The mixture was cooled to room temperature, filtered through Celite and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 10%- 20%EtOAc/ Hexanes) to yield 481 (2.5 mg, 47%) as yellow solid.

**Compound 481:** FTIR(NaCl/ thin film) 2922, 2854, 1776, 1656, 1504, 1445, 1299, 1257, 1202, 1102, 969 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 11.27 (d, $J$=2.4 Hz,
1H), 9.74 (d, J=2.3 Hz, 1H), 7.40 (dd, J=2.4, 8.8 Hz, 1H), 6.61 (dd, J=2.3, 8.8 Hz, 1H), 5.66- 5.34 (m, 2H), 4.06 (td, J=2.2, 6.7 Hz, 2H), 2.47 (q, J=6.7 Hz, 2H), 2.34 (d, J=2.4 Hz, 3H), 1.68 (d, J=6.2 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 194.9, 168.4, 157.9, 155.1, 132.6, 128.6, 127.3, 125.9, 116.3, 104.7, 69.0, 32.4, 20.4, 18.2; HRMS (TOF LCMS) calc’d for C14H15O5 [M-H] 263.0920, found 263.0923.

Preparation of Compound 483

![Chemical Structure of 483](image)

To a solution of 482 (74 mg, 0.33 mmol, 1 equiv.) in THF (3.3 mL) was added TMSCl (84 µL, 0.66 mmol, 2 equiv.) and Et3N (0.19 mL, 0.33 mmol, 2 equiv.) at room temperature. The solution was stirred for 3 days. The mixture was filtered through Celite and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 10%- 20%EtOAc/ Hexanes) to yield 483 (20 mg, 21%) as yellow oil.

**Compound 483**: FTIR(NaCl/ thin film) 2960, 2927, 2872, 1750, 1684, 1507, 1249, 1151, 995, 847 cm⁻¹; ¹H NMR (400 MHz, CDCl3) δ 9.62 (s, 1H), 7.28 (dd, J=1.7 Hz, 6.8, 1H), 3.87 (dd, J=5.7, 12.7 Hz, 1H), 3.63 (s, 1H), 3.58 (dd, J=2.8, 12.7 Hz, 1H), 2.85 (dd, J=3.2, 6.8 Hz, 1H), 2.11- 2.02 (m, 1H), 1.93- 1.82 (m, 1H), 1.74- 1.70 (m, 1H), 1.59- 1.52 (m, 1H), 0.86 (d, J=7.0 Hz, 3H), 0.08 (s, 9H); 13C NMR (100 MHz, CDCl3) δ
206.6, 189.0, 151.8, 139.6, 91.7, 61.5, 51.2, 48.4, 37.1, 34.4, 28.6, 20.0, 1.7; HRMS (TOF LCMS) calc’d for C_{15}H_{23}O_{4}Si [M+H] 295.1366, found 295.1396.

**Preparation of Compound 484**

To a solution of 483 (14 mg, 0.048 mmol, 1 equiv.) in THF (0.5 mL) was added MeLi (0.1 mL, 0.17 mmol, 3.5 equiv., 1.6M) at -78 °C and the mixture was stirred for 1 hour. The reaction was quenched by H₂O (1 mL). The layers were separated and the aqueous layer was washed with EtOAc (2 × 2 mL). The combined organic layers were washed with brine (4 mL), dried over Na₂SO₄, filtered through Celite and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%- 33% EtOAc/ Hexanes) to yield 484 (15 mg, 100%) as yellow oil.

**Compound 484**: FTIR(NaCl/ thin film) 3452, 2925, 2854, 1738, 1453, 1374, 1248, 1192, 1154, 1092, 1070, 990, 844 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.14 (dd, J=2.4 Hz, 6.8, 1H), 4.36- 4.28 (m, 1H), 3.83 (dd, J=4.6, 11.4 Hz, 1H), 3.60 (td, J=2.9, 12.4 Hz, 1H), 3.09 (s, 1H), 2.51 (dd, J=3.3, 6.7 Hz, 1H), 2.05- 1.97 (m, 1H), 1.90- 1.79 (m, 1H), 1.69- 1.68 (m, 1H), 1.56- 1.44 (m, 2H), 1.24 (d, J=6.9 Hz, 3H), 0.97 (d, J=6.9 Hz, 3H), 0.1 (d, J=1.1 Hz, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 209.1, 141.7, 126.8, 92.4,
HRMS (TOF LCMS) calc’d for C_{16}H_{26}O_{4}SiNa [M+Na] 33.1498, found 33.1492.

**Preparation of Compound 485**

To a solution of 482 (98.9 mg, 0.45 mmol, 1 equiv.) in THF (4.5 mL) was added NaH (11.2 mg, 0.47 mmol, 1.1 equiv.) at room temperature. To this solution was added MeLi (0.83 mL, 1.35 mmol, 3 equiv., 1.6M) at -78 °C and the mixture was stirred for 1 hour. The reaction was quenched by H_{2}O (2 mL). The layers were separated and the aqueous layer was washed with EtOAc (2 x 4 mL). The combined organic layers were washed with brine (8 mL), dried over Na_{2}SO_{4}, filtered and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%-50% EtOAc/Hexanes) to yield 485 (51.3 mg, 48%) as yellow oil.

**Compound 485**: FTIR(NaCl/ thin film) 3402, 2967, 2928, 2870, 1733, 1456, 1374, 1170, 1088, 1023, 973 cm^{-1}; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 6.25 (dt, \(J=1.2\) Hz, 6.8, 1H), 4.32 (ddd, \(J=1.1, 6.4, 12.8\) Hz, 1H), 3.67 (td, \(J=3.3, 12.2\) Hz, 1H), 3.11 (s, 1H), 2.70 (dd, \(J=3.3, 6.6\) Hz, 1H), 2.14-2.05 (m, 1H), 1.99-1.88 (m, 1H), 1.78-1.72 (m, 1H), 1.67-1.59 (m, 1H), 1.27 (d, \(J=6.4\) Hz, 3H), 1.00 (d, \(J=6.9\) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 210.3, 142.6, 126.2, 90.6, 69.0, 61.6, 55.2, 42.5, 37.4, 33.4, 29.4, 21.6, 20.5; HRMS (TOF LCMS) calc’d for C_{13}H_{17}O_{4} [M-H] 237.1127, found 237.1127.
Preparation of Compound 490

To a solution of 470 (33 mg, 0.16 mmol, 1 equiv.) in DCE (1.6 mL) was added Pb(O₂CCH₂CH₃)₄ (492) (112 mg, 0.22 mmol, 1.4 equiv.). The solution was heated to reflux and stirred overnight. The mixture was cooled to room temperature, filtered through Celite and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%–50% EtOAc/Hexanes) to yield 490 (8.5 mg, 27%) as yellow oil.

**Compound 490**: FTIR(NaCl/ thin film) 2927, 1748, 1683, 1456, 1362, 1166, 1131, 1080 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.64 (s, 1H), 7.21 (dd, J=2.5 Hz, 6.8, 1H), 4.10 (ddd, J=2.0, 5.1, 11.2 Hz, 1H), 4.00 (dd, J=3.3, 12.2 Hz, 1H), 3.81 (s, 1H), 3.76 (td, J=3.6, 12.4 Hz, 1H), 2.30 (q, J=7.7, 2H), 2.19–2.00 (m, 2H), 1.88–1.82 (m, 1H), 1.73–1.63 (m, 1H), 1.07 (d, J=7.6 Hz, 3H), 0.92 (d, J=7.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 201.7, 188.5, 169.0, 147.8, 141.6, 92.9, 62.7, 50.7, 43.2, 37.4, 34.8, 28.3, 28.2, 20.1, 8.9; HRMS (TOF LCMS) calc’d for C₁₅H₁₉O₅ [M+H] 279.1233, found 279.1222.

Preparation of Compound 492
To a solution of 482 (45 mg, 0.49 mmol, 1 equiv.) in Tol (5 mL) was added phosphorus ketene 497 (164 mg, 0.54 mmol, 1.1 equiv.) at -78 °C. The solution was warmed to room temperature and stirred overnight. The mixture was filtered through Celite and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%- 50% EtOAc/ Hexanes) to yield 492 (16 mg, 36%) as yellow oil.

**Compound 492**: FTIR(NaCl/ thin film) 2958, 2926, 1783, 1680, 1649, 1453, 1358, 1166, 1150, 1117, 974, 876 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.45 (s, 1H), 7.12 (dd, J=1.2, 6.4 Hz, 1H), 5.39 (s, 1H), 4.20 (s, 1H), 4.06- 3.97 (m, 2H), 3.35 (dd, J=2.4, 6.5 Hz, 1H), 2.27- 2.19 (m, 1H), 2.07- 1.97 (m, 1H), 1.91- 1.82 (m, 1H), 1.58- 1.52 (m, 1H), 0.80 (d, J=7.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 187.5, 172.9, 172.7, 149.7, 147.9, 109.8, 104.8, 62.0, 40.1, 40.0, 39.1, 35.4, 27.9, 20.4; HRMS (TOF LCMS) calc’d for C₁₄H₁₅O₄ [M+H] 247.0970, found 247.0961.

**Preparation of Compound 502**

![Diagram]

To a solution of 480 (mg, mmol, equiv.) in THF (mL) was added Pd/C (mg, mmol, mL), H₂ (1 atm) and the mixture was stirred overnight at room temperature. The mixture was filtered through Celite and concentrated under reducing pressure. The
residue was loaded onto silica and purified by column chromatography (gradient elution, 20%-50% EtOAc/Hexanes) to yield 502 (160 mg, 89%) as orange solid.

**Compound 502:** FTIR(NaCl/thin film) 3406, 2957, 2876, 1738, 1376, 1158, 1120, 1085, 1057 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 9.80 (s, 1H), 3.91 (dd, $J$=5.9, 12.5 Hz, 1H), 3.54 (td, $J$=3.1, 12.5 Hz, 1H), 3.00 (s, 1H), 2.65 (t, $J$=8.8 Hz, 1H), 2.28-2.19 (m, 1H), 2.12-2.07 (m, 1H), 2.01 (ddd, $J$=1.9, 8.0, 14.0 Hz, 1H), 1.97-1.89 (m, 2H), 1.81-1.75 (m, 1H), 1.42-1.35 (m, 1H), 1.00 (d, $J$=7.3 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 213.6, 201.5, 94.0, 62.1, 49.9, 44.6, 38.5, 38.3, 31.9, 31.2, 21.9, 20.8; HRMS (TOF LCMS) calc’d for C$_{12}$H$_{15}$O$_4$ [M-H] 223.0970, found 223.0974.

**Preparation of Compound 516**

![Chemical structure of 470 and 516](image)

To a solution of 470 (1.15 g, 5.55 mmol, 1 equiv.) in acetone (11 mL) was added allyl bromide (0.60 mL, 7.21 mmol, 1.3 equiv.) and K$_2$CO$_3$ (1.54 g, 1.11 mmol, 2 equiv.) at reflux. The solution was stirred overnight and cooled to room temperature, filtered through Celite and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 10%-20% EtOAc/Hexanes) to yield 516 (1.41 g, 100%) as brown solid.

**Compound 516:** FTIR(NaCl/thin film) 3406, 2957, 2876, 1738, 1596, 1584, 1436, 1270, 1168, 1133, 1014, 969, 929, 808 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 9.83 (s, 1H), 7.45 (d, $J$=1.9 Hz, 1H), 7.41 (dd, $J$=1.7, 8.0 Hz, 1H), 6.96 (d, $J$=8.2 Hz, 1H), 6.00 (ddt,
\[ J=5.2, 10.4, 20.0 \text{ Hz}, 1H \), 5.66- 5.48 (m, 2H), 5.45 (dq, \( J=1.6, 17.4 \text{ Hz}, 1H \), 5.30 (dq, \( J=1.6, 17.4 \text{ Hz}, 1H \), 4.64 (dt, \( J=1.4, 5.1 \text{ Hz}, 2H \), 4.09 (t, \( J=7.1 \text{ Hz}, 2H \), 2.60- 2.50 (m, 2H), 1.68 (dd, \( J=1.2, 7.4 \text{ Hz}, 3H \);} \)

\( \text{C NMR (100 MHz, CDCl}_3) \delta 191.0, 154.6, 148.9, 132.9, 130.0, 128.5, 126.9, 126.2, 117.9, 112.0, 111.9, 69.9, 68.9, 32.4, 18.2; \) HRMS (TOF LCMS) calc’d for \( \text{C}_{15}\text{H}_{19}\text{O}_3 [\text{M+H}] 247.1334 \), found 247.1327.

**Preparation of Compound 517, 518**

![Diagram](image)

Method 1: to a solution of 516 (131 mg, 0.53 mmol, 1 equiv.) in DCM (8 mL) was added PhSeSePh (6.8 mg, 0.02 mmol, 0.04 equiv.), \( \text{H}_2\text{O}_2 \) (0.70 ml, 0.86 mmol, 1.25 equiv., 30%) and the mixture was stirred at room temperature overnight. To the solution was added 10% aqueous \( \text{Na}_2\text{S}_2\text{O}_3 \) (2mL). The layers were separated and the aqueous layer was washed with DCM (2 × 8 mL). The combined organic layers were washed with brine (16 mL), dried over \( \text{Na}_2\text{SO}_4 \), filtered and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%- 50% EtOAc/ Hexanes) to yield 517 (20 mg, 19%) as orange solid and 518 (47.4 mg, 50%) as pale yellow oil.
Method 2: to a solution of 527 (4.3 g, 12.13 mmol, 1 equiv.) in MeOH (350 mL) was added HCl (35 mL, conc.) and stirred at room temperature for 3h. The solution was neutralized by NaOH (90 mL, 2N). MeOH was removed under reducing pressure. The aqueous layer was washed with EtOAc (2 × 200 mL). The combined organic layers were washed with brine (400 mL) and dried over Na₂SO₄, filtered and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%- 50% EtOAc/ Hexanes) to yield 518 (3.0 g, 100%) as pale yellow oil.

**Compound 517:** FTIR(NaCl/ thin film) 3380, 2965, 2928, 1603, 1511, 1288, 1603, 1511, 1455, 1288, 1219, 1172, 1124, 1022, 931, 834 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.70 (d, J=8.6 Hz, 1H), 6.56- 6.51 (m, 1H), 6.43 (d, J=2.6 Hz, 1H), 6.31 (dq, J=2.5, 8.4 Hz, 1H), 6.00 (ddt, J=5.2, 10.4, 20.2 Hz, 1H), 5.38- 5.30 (m, 1H), 5.24- 5.18 (m, 1H), 4.48 (d, J=5.0 Hz, 2H), 4.08- 3.99 (m, 2H), 2.97- 2.87 (m, 2H), 2.14- 2.02 (m, 1H), 1.93- 1.82 (m, 1H), 1.30 (d, J=5.1 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 151.3, 149.7, 142.1, 133.2, 117.7, 116.4, 106.8, 102.7, 69.7, 67.2, 57.7, 55.4, 32.2, 17.6; HRMS (TOF LCMS) calc’d for C₁₄H₁₇O₄ [M-H] 249.1127, found 247.1130.

**Compound 518:** FTIR(NaCl/ thin film) 3401, 2918, 1604, 1510, 1451, 1288, 1219, 1122, 1015, 968 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.70 (d, J=8.6 Hz, 1H), 6.45 (d, J=2.7 Hz, 1H), 6.33 (dd, J=2.8, 8.6 Hz, 1H), 6.04 (ddt, J=5.2, 10.5, 20.1 Hz, 1H), 5.62- 5.45 (m, 2H), 5.40 (dq, J=1.6, 17.3 Hz, 1H), 5.26 (dq, J=1.2, 10.6 Hz, 1H), 4.90 (s, 1H), 4.52 (dd, J=1.4, 5.1 Hz, 2H), 3.94 (t, J=7.0 Hz, 2H), 2.50- 2.42 (m, 2H), 1.67 (d, J=6.7 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 150.6, 150.0, 143.0, 133.4, 127.7, 127.0,
117.7, 116.5, 106.9, 103.1, 70.5, 70.6, 32.9, 18.2; HRMS (TOF LCMS) calc’d for C_{14}H_{19}O_{3} [M+H] 234.1334, found 235.1331.

**Preparation of Compound 519**

![](image)

To a solution of 518 (447.1 mg, 1.90 mmol, 1 equiv.) in DCM (4 mL) was added Tf_{2}O (0.35 mL, 2.10, 1.1 equiv.) and pyridine (0.31 mL, 3.80 mmol, 2 equiv.) at 0 °C. The solution was warmed to room temperature and stirred overnight. The solvent was removed under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 9%-15% EtOAc/Hexanes) to yield 519 (592.3 mg, 85%) as pale yellow oil.

**Compound 519**: FTIR(NaCl/ thin film) 2923, 1608, 1508, 1422, 1217, 1018, 956, 860 cm⁻¹; \(^1H\) NMR (400 MHz, CDCl\(_3\)) δ 6.88-6.71 (m, 3H), 6.02 (ddt, J=5.1, 10.4, 20.8 Hz, 1H), 5.62-5.44 (m, 2H), 5.40 (dq, J=1.5, 17.4 Hz, 1H), 5.29 (dq, J=1.0, 10.6 Hz, 1H), 4.56 (dt, J=1.3, 5.2 Hz, 2H), 3.98 (t, J=6.9 Hz, 2H), 2.53-2.43 (m, 2H), 1.66 (dd, J=1.2, 6.7 Hz, 3H); \(^13C\) NMR (100 MHz, CDCl\(_3\)) δ 149.3, 149.0, 143.0, 132.6, 128.3, 126.5, 118.4, 113.6, 113.5, 108.2, 70.4, 69.4, 32.6, 18.2; HRMS (TOF LCMS) calc’d for C\(_{12}\)H\(_{12}\)O\(_3\) [M-C\(_3\)H\(_5\)] 325.0358, found 325.0361.
Preparation of Compound 520, 522

To a solution of 519 (592 mg, 1.62 mmol, 1 equiv.) in EtOH (1.6 mL) was added NaBH₄ (30.6 mg, 0.81 mmol, 0.5 equiv.) and Pd(PPh₃)₄ (56 mg, 0.04 mmol, 0.03 equiv.). The mixture was stirred overnight then filtered through Celite and concentrated under reducing pressure to give crude phenol 520 (527 mg, 100%).

To a solution of crude phenol in DCE (16 mL) was added Pb(OAc)₄ (1.0 g, 2.27 mmol, 1.4 equiv.) at reflux. After stirring for 5 minuets, additional DCE (80 ml) was added. The mixture was stirred overnight. NaBH₄ (20 mg, 0.5 mmol, 0.5 equiv.) and Pd(PPh₃)₄ (29 mg, 0.03 mmol, 0.03 equiv.). The reaction was cooled to room temperature then filtered through Celite and concentrated under reducing pressure. To this residue in DCM (20 mL) was added silica (2.0 g) and stirred at room temperature overnight. The mixture was filtered through Celite and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%- 50% EtOAc/ Hexanes) to yield 522 (383.4 mg, 81%) as brown oil.

**Compound 520:** FTIR(NaCl/ thin film) 3521, 2937, 1608, 1505, 1422, 1275, 1219, 1142, 1106, 1019, 957, 866 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.88- 6.64 (m, 3H), 5.88- 5.72 (m, 1H), 5.68- 5.34 (m, 2H), 4.03 (t, J=6.5 Hz, 2H), 2.53- 2.35 (m, 2H), 1.67 (dd, J=1.2, 6.3 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 146.9, 145.8, 143.4, 128.8,
126.1, 112.7, 112.0, 108.4, 69.3, 32.5, 18.1; HRMS (TOF LCMS) calc’d for C$_{12}$H$_{12}$O$_{3}$ [M-H] 325.0358, found 325.0364.

**Compound 522:** FTIR(NaCl/ thin film) 3392, 2965, 2932, 2876, 1751, 1653, 1425, 1217, 1140, 901, 840 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 6.23 (dd, J=2.6, 7.6 Hz, 1H), 3.92 (dd, J=6.7, 12.6 Hz, 1H), 3.60 (td, J=3.0, 12.6 Hz, 1H), 3.62- 3.58 (m, 1H), 3.17 (q, J=2.5 Hz, 1H), 2.84 (dd, J=3.2, 7.6 Hz, 1H), 2.22- 2.12 (m, 1H), 2.05- 1.84 (m, 2H), 1.71- 1.66 (m, 1H), 1.15 (d, J=6.8 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 205.4, 145.1, 119.7, 90.1, 61.6, 57.8, 43.0, 37.2, 35.2, 28.7, 20.2; HRMS (TOF LCMS) calc’d for C$_{12}$H$_{12}$F$_{3}$O$_{3}$S [M-H] 341.0307, found 341.0310.

**Preparation of Compound 525**

![Reaction Scheme]

To a solution of 2,4-dihydroxy benzaldehyde (440) (37 g, 267.9 mmol, 1 equiv.) in acetone (1.4 L) was added BOMCl (25 g, 160.7 mmol, 0.6 equiv.) and K$_2$CO$_3$ (37 g, 267.9, 1 equiv.) at reflux. The mixture was stirred overnight. The reaction was cooled to room temperature then filtered through Celite and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 5%- 10% EtOAc/ Hexanes) to yield 525 (15.1 g, 40%) as orange solid.

**Compound 525:** FTIR(NaCl/ thin film) 2923, 2854, 1651, 1629, 1578, 1501, 1453, 1216, 1157, 1087, 996, 957 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 11.37 (s, 1H).
9.75 (s, 1 H), 7.46 (d, J=8.6 Hz, 1H), 7.42- 7.30 (m, 5H), 6.69 (dd, J=2.2, 8.6 Hz, 1H), 6.65 (d, J=2.1 Hz, 1H), 5.34 (s, 2H), 4.72 (s, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 194.8, 164.6, 164.3, 136.9, 135.9, 128.7, 128.3, 128.2, 116.2, 109.3, 103.7, 92.1, 70.7; HRMS (TOF LCMS) calc’d for C$_{15}$H$_{13}$O$_4$ [M-H] 257.0814, found 257.0819.

**Preparation of Compound 526, 527**

![Chemical Structures](image)

To a solution of 525 (2.9 g, 11.2 mmol, 1 equiv.) in acetone (23 mL) was added allyl bromide (1.23 mL, 14.6 mmol, 1.3 equiv.) and K$_2$CO$_3$ (3.1g, 22.4 mmol, 2 equiv.) at reflux. The mixture was stirred overnight. The reaction was cooled to room temperature then filtered through Celite and concentrated under reducing pressure. To this residue in DCM (82 mL) was added $m$-CPBA (4 g, 16.3 mmol, 1.4 equiv.) at reflux and stirred for 3 hours. The reaction was cooled to room temperature. DCM was removed under reducing pressure. To this residue in MeOH (20 mL) was added saturated aqueous Na$_2$CO$_3$ (200 mL) and stirred at room temperature overnight. The aqueous layer was washed with EtOAc (2 x 200 mL). The combined organic layers were washed with brine (400 mL), dried over Na$_2$SO$_4$, filtered and concentrated under reducing pressure to yield crude 426 (2.7 g, 100%).
To a solution of crude 526 in acetone (41 mL) was added Cs$_2$CO$_3$ (9.4 g, 29.0 mmol, 2.5 equiv.), iodide 436 (5.55 g, 29.0 mmol, 2.5 equiv.) at reflux and stirred overnight. The reaction was cooled to room temperature then filtered through Celite and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%-33% EtOAc/Hexanes) to yield 4527 (2.5 g, 61%) as yellow oil.

**Compound 526**: FTIR (NaCl/ thin film) 3532, 3065, 3031, 2895, 1613, 1509, 1455, 1380, 1264, 1227, 1170, 1085, 1024, 933, 837 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.41-7.28 (m, 5H), 6.87 (d, $J$=8.5 Hz, 1H), 6.70 (d, $J$=2.6 Hz, 1H), 6.57 (dd, $J$=2.6, 8.6 Hz, 1H), 6.08 (ddt, $J$=5.2, 10.5, 20.9 Hz, 1H), 5.34 (s, 2H), 5.39 (d, $J$=1.6 Hz, 1H), 5.32 (dd, $J$=1.2, 10.4 Hz, 1H), 5.24 (s, 2H), 4.75 (s, 2H), 4.57 (dd, $J$=1.2, 5.4 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 151.2, 146.0, 141.2, 137.6, 132.9, 128.7, 128.2, 128.1, 118.7, 114.7, 109.1, 102.9, 93.6, 70.0, 70.0; HRMS (TOF LCMS) calc’d for C$_{17}$H$_{17}$O$_4$ [M-H] 285.1127, found 285.1131.

**Compound 527**: FTIR (NaCl/ thin film) 2918, 2866, 1595, 1508, 1436, 1421, 1261, 1221, 1174, 1086, 928 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.45-7.29 (m, 5H), 6.82 (d, $J$=8.6 Hz, 1H), 6.80 (d, $J$=2.8 Hz, 1H), 6.63 (dd, $J$=2.6, 8.5 Hz, 1H), 6.05 (ddt, $J$=5.2, 10.5, 20.9 Hz, 1H), 5.56-5.48 (m, 2H), 5.46-5.37 (m, 1H), 5.31-5.24 (m, 1H), 5.22 (s, 2H), 4.72 (s, 2H), 4.60-4.53 (m, 2H), 3.92 (t, $J$=6.9 Hz, 2H), 2.53-2.43 (m, 2H), 1.68 (d, $J$=5.8 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 165.9, 152.2, 149.7, 144.3, 137.5, 133.5, 128.6, 128.2, 128.0, 127.7, 127.0, 117.6, 115.7, 108.0, 104.8, 93.3, 70.1, 70.0, 32.9, 18.2; HRMS (TOF LCMS) calc’d for C$_{22}$H$_{27}$O$_4$ [M+H] 355.1909, found 355.1896.
Preparation of Compound 528

To a solution of 522 (348 mg, 1.02 mmol, 1 equiv.) in DCM (10 mL) was added TMSOTf (0.2 mL, 1.12 mmol, 1.1 equiv.) and Et₃N (0.17 mL, 1.12, 1.1 equiv.) at -78 °C and stirred for 5 min. The reaction was quenched by aqueous NaHCO₃ (0.5 mL). The aqueous layer was washed with DCM (2 × 20 mL). The combined organic layers were washed with brine (40 mL) and dried over Na₂SO₄, filtered and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%–33% EtOAc/Hexanes) to yield 528 (349.4 mg, 77%) as green oil and recover starting material 522 (73.4 mg).

**Compound 528:** FTIR (NaCl/ thin film) 2962, 2931, 2875, 1575, 1653, 1427, 1218, 1141, 1092, 934, 847 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.15 (dd, J=2.8, 7.7 Hz, 1H), 3.86 (dd, J=5.7, 12.7 Hz, 1H), 3.52 (td, J=2.9, 12.8 Hz, 1H), 3.07 (t, J=2.7 Hz, 1H), 2.66 (dd, J=3.2, 7.7 Hz, 1H), 2.12–2.04 (m, 1H), 1.94–1.73 (m, 2H), 1.60–1.51 (m, 1H), 1.11 (d, J=6.9 Hz, 3H), 0.11 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 203.8, 145.2, 119.3, 91.8, 61.3, 58.3, 45.9, 37.2, 35.6, 28.7, 20.2, 1.57; HRMS (TOF LCMS) calc’d for C₁₅H₂₁F₃O₆SSi [M+Na] 437.0678, found 437.0677.
Preparation of Compound 529

To a solution of diisopropylamine (0.62 mL, 4.42 mmol, 5.25 equiv.) in THF (3.4 mL) at −20 °C was added n-BuLi (2.2 mL, 3.54 mmol, 4.2 equiv., 1.6 M hexanes solution) dropwise over 5 minutes. The resultant mixture was stirred at −20 °C for 5 minutes, and then cooled to −78 °C for 30 minutes. To this mixture was added methyl-3-(dimethylamino)propionate (0.73 mL, 3.0 mmol, 3.5 equiv.) dropwise over five minutes. The reaction mixture was stirred at −78 °C for thirty minutes, 0 °C for 15 min, and room temperature for 15 min, and then cooled to −78 °C.

A solution of 528 (349 mg, 0.84 mmol) in THF (8.4 mL) was added enolate dropwise over 1 minute at −78 °C. The solution was slowly warmed to room temperature and stirred for 1 hour. The reaction was quenched with 1M AcOH in THF (5mL) and allowed to warm to room temperature. At which point the reaction mixture was treated with H₂O (5mL) and EtOAc (5mL). The aqueous layer was extracted with EtOAc (2 x 10mL), and the combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, and concentrated under reducing pressure.

To the solution of this residue solution in DCM (8.5 mL) was added m-CPBA (312 mg, 1.27 mmol, 1.5 equiv.) at -78 °C and the mixture was stirred for 20 minutes. To the solution was added basic Al₂O₃ (400 mg) and stirred overnight at room temperature. The mixture was filtered through Celite and concentrated under reducing pressure. The
residue was loaded onto silica and purified by column chromatography (gradient elution, 5%-10% EtOAc/Hexanes) to yield 529 (132.6 mg, 31%) as colorless oil.

**Compound 529:** FTIR (NaCl/ thin film) 3440, 2959, 2926, 1710, 1663, 1424, 1323, 1214, 1143, 1055 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 5.88 (dd, \(J\)=2.7, 7.7 Hz, 1H), 5.85 (s, 1H), 5.62 (s, 1H), 5.50-5.47 (m, 1H), 4.66 (td, \(J\)=4.7, 12.3 Hz, 1H), 3.92 (ddd, \(J\)=0.7, 7.1, 11.8 Hz, 1H), 3.77 (s, 1H), 2.76 (t, \(J\)=2.5 Hz, 1H), 2.58-2.51 (m, 1H), 2.44 (dd, \(J\)=3.8, 7.6 Hz, 1H), 1.88-1.66 (m, 3H), 1.05 (d, \(J\)=7.0 Hz, 3H), 0.09 (s, 9H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 167.6, 148.5, 143.4, 119.4, 114.7, 99.1, 82.3, 63.2, 52.1, 50.6, 47.1, 39.5, 29.1, 28.7, 20.9, 1.8; HRMS (TOF LCMS) calc’d for C\(_{19}\)H\(_{26}\)F\(_3\)O\(_8\)SSi [M-H] 499.1070, found 499.1081.

**Preparation of Compound 530**

To a solution of 529 (132.6 mg, 0.27 mmol, 1 equiv.) in THF (2.6 mL) was added TBAF (1.32 mL, 1.35 mmol, 5 equiv.) and AcOH (76 µL, 1.35 mmol, 5 equiv.) at room temperature. The mixture was stirred overnight. The reaction was quenched by H\(_2\)O (2 mL). The aqueous layer was extracted with EtOAc (2 x 5mL), and the combined organic layers were washed with brine (10 mL), dried over Na\(_2\)SO\(_4\), and concentrated under reducing pressure. The residue was loaded onto silica and purified by column
chromatography (gradient elution, 20%-50% EtOAc/Hexanes) to yield 530 (85.1 mg, 31%) as yellow solid.

**Compound 530:** FTIR(NaCl/ thin film) 3421, 2963, 2928, 1773, 1653, 1423, 1283, 1214, 1141, 1078, 1005, 907 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 6.46 (s, 1H), 6.01 (s, 1H), 5.86 (dd, \(J=2.7, 7.7\) Hz, 1H), 4.47 (td, \(J=4.2, 11.3\) Hz, 1H), 4.15-4.05 (m, 1H), 3.28-3.22 (m, 1H), 2.86 (dd, \(J=2.6, 7.4\) Hz, 1H), 2.44-2.33 (m, 1H), 2.06-1.92 (m, 1H), 1.83-1.71 (m, 2H), 1.07 (d, \(J=7.0\) Hz, 3H); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 167.4, 166.2, 149.7, 140.6, 127.3, 113.3, 104.1, 64.2, 52.6, 42.6, 38.8, 31.4, 28.3, 20.7; HRMS (TOF LCMS) calc’d for C\(_{15}\)H\(_{16}\)F\(_3\)O\(_7\)S [M+H] 397.0569, found 397.0559.

**Preparation of Compound 538**

![Diagram](image)

To a solution of 528 (53.6 mg, 0.13, 1 equiv.) in MeCN (1.30 mL) was added CuI (22 mg, 0.13, 1 equiv.), (-)-proline (30 mg, 0.26, 2 equiv.), NH\(_4\)OAc (22.5 mg, 0.26, 2 equiv.), K\(_3\)PO\(_4\) (55 mg, 0.26, 2 equiv.) and morpholine (0.12 mL, 0.17 mmol, 1.1 equiv.). The mixture was heated to reflux and stirred overnight. The reaction was cooled to room temperature, filtered through Celite and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%-50% EtOAc/Hexanes) to yield 538 (20 mg, 39%) as yellow solid.
Compound 538: FTIR (NaCl/thin film) 2927, 2874, 1737, 1656, 1420, 1211, 1142, 1079, 834, 612 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 9.25 (dd, $J$=2.7, 7.6 Hz, 1H), 5.06 (t, $J$=3.3 Hz, 1H), 4.03 (dd, $J$=3.2, 12.9 Hz, 1H), 3.31 (d, $J$=3.3 Hz, 1H), 3.19-3.06 (m, 1H), 2.89-2.77 (m, 1H), 2.69 (q, $J$=2.7 Hz, 1H), 1.96-1.72 (m, 5H), 1.69-1.54 (m, 2H), 1.53-1.43 (m, 1H), 1.01 (d, $J$=6.9 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 151.0, 114.6, 110.4, 102.1, 72.7, 63.1, 57.7, 48.7, 44.5, 39.0, 35.0, 33.0, 28.3, 23.6, 21.0; HRMS (TOF LCMS) calc’d for C$_{16}$H$_{21}$F$_3$NO$_5$S [M+H] 395.1093, found 395.1096.

Preparation of Compound 546

\[
\begin{array}{c}
\text{HO} \quad \text{O} \quad \text{O} \quad \text{OH} \\
\text{518} \quad \text{Pd(PPh$_3$)$_4$, NaBH$_4$, EtOH, r.t.} \quad \text{(quant. yield)} \quad \text{HO} \quad \text{O} \quad \text{OH} \\
\text{546}
\end{array}
\]

To a solution of 518 (156 mg, 0.67 mmol, 1 equiv.) in EtOH (4.7 mL) was added Pd(PPh$_3$)$_4$ (15.6 mg, 0.02 mmol, 0.03 equiv.) and NaBH$_4$ (8.8 mg, 0.34 mmol, 0.5 equiv.) at room temperature. The mixture was stirred overnight, filtered through Celite and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%-33% EtOAc/Hexanes) to yield 546 (150 mg, 100%) as brown oil.

Compound 546: FTIR (NaCl/thin film) 3404, 2936, 1607, 1510, 1469, 1386, 1296, 1219, 1148, 1117, 1022, 965, 846, 791 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 6.72 (d, $J$=8.6 Hz, 1H), 6.47 (d, $J$=1.9 Hz, 1H), 6.28 (dd, $J$=1.9, 8.7 Hz, 1H), 5.69-5.41 (m, 2H), 4.80-4.30 (m, 2H), 3.98 (t, $J$=6.5 Hz, 2H), 2.45 (q, $J$=6.2 Hz, 2H), 1.69 (d, $J$=6.2 Hz, 2H).
Hz, 3H); $^1^3$C NMR (100 MHz, CDCl$_3$) $\delta$ 150.6, 147.1, 140.2, 128.5, 126.8, 113.9, 106.1, 102.9, 69.9, 32.8, 18.2; HRMS (TOF LCMS) calc’d for C$_{11}$H$_{13}$O$_3$ [M-H] 193.0865, found 193.0864.

**Preparation of Compound 540**

![Chemical structure](image)

To a solution of 518 (94 mg, 0.40 mmol, 1 equiv.) in DCM (1 mL) was added AcCl (31 µL, 0.44 mmol, 1.1 equiv.) and pyridine (65 µL, 0.80 mmol) at room temperature. The mixture was stirred overnight, filtered through Celite and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 10%- 20% EtOAc/ Hexanes) to yield 540 (90 mg, 81.2%) as orange oil.

**Compound 540:** FTIR(NaCl/ thin film) 2919, 2869, 1763, 1602, 1508, 1423, 1369, 1263, 1203, 1154, 1017 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.83 (d, $J=8.5$ Hz, 1H), 6.62 (dd, $J=2.6$, 5.4 Hz, 1H), 6.59 (d, $J=2.6$ Hz, 1H), 6.03 (ddt, $J=5.1$, 10.5, 20.9 Hz, 1H), 5.61- 5.43 (m, 2H), 5.39 (dq, $J=1.5$, 17.4 Hz, 1H), 5.24 (dq, $J=1.3$, 10.5 Hz, 1H), 4.53 (dt, $J=1.5$, 5.2 Hz, 2H), 3.96 (t, $J=7.0$ Hz, 2H), 2.50- 2.42 (m, 2H), 2.23 (s, 3H), 1.65 (dd, $J=1.1$, 5.9 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 169.8, 149.0, 146.8, 144.4, 133.1, 12.8, 126.7, 117.6, 114.1, 113.5, 108.5, 70.1, 69.4, 32.7, 21.1, 18.1; HRMS (TOF LCMS) calc’d for C$_{16}$H$_{21}$O$_4$ [M+H] 277.1440, found 277.1440.
Preparation of Compound 547

To a solution of 540 (59 mg, 0.21 mmol, 1 equiv.) in EtOH (2 mL) was added Pd(PPh₃)₄ (7.5 mg, 0.006 mmol, 0.03 equiv.) and NaBH₄ (4 mg, 0.11 mmol, 0.5 equiv.) at room temperature. The mixture was stirred overnight, filtered through Celite and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%-33% EtOAc/Hexanes) to yield 547 (49.3 mg, 98%) as brown solid.

**Compound 547:** FTIR (NaCl/ thin film) 3451, 2935, 1762, 1605, 1505, 1370, 1280, 1207, 1140, 1015, 968 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.81 (d, J=8.7 Hz, 1H), 6.68 (d, J=2.8 Hz, 1H), 6.55 (d,d J=2.6, 8.7 Hz, 1H), 5.76-5.74 (m, 1H), 5.67-5.42 (m, 2H), 4.02 (t, J=6.7 Hz, 2H), 2.50-2.42 (m, 2H), 2.26 (s, 3H), 1.65 (dq, J=1.2, 6.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 169.9, 146.6, 144.9, 143.9, 128.5, 126.5, 112.6, 112.3, 108.7, 69.3, 32.7, 21.2, 18.1; HRMS (TOF LCMS) calc’d for C₁₆H₁₅O₄ [M-H] 235.090, found 235.0974.

Preparation of Compound 541

225
To a solution of 2-methyl-3-nitrobenzoic acid in DCM (1 mL) was added DCC (247.6 mg, 1.2 mmol, 1.2 equiv.) and DMAP (12.2 mg, 0.1 mmol, 0.1 equiv.) at room temperature. The mixture was stirred for 10 minutes. Then 518 (230 mg, 1 mmol, 1 equiv.) was added and stirred overnight. The reaction was filtered through Celite and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 10%- 20% EtOAc/ Hexanes) to yield 541 (128 mg, 33%) as brown oil.

**Compound 541:** FTIR (NaCl/ thin film) 3083, 2920, 2869, 1742, 1603, 1530, 1506, 1251,1215, 1152, 1102, 1082, 1022 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.23 (dd, $J$=1.2, 8.0 Hz, 1H), 7.90 (dd, $J$=1.1, 8.1 Hz, 1H), 7.46 (t, $J$=8.1 Hz, 1H), 6.92 (dd, $J$=1.7, 7.4 Hz, 1H), 6.77 (s, 1H), 6.76 (dd, $J$=2.7, 8.5 Hz, 1H), 6.07 (ddt, $J$=5.2, 10.2, 20.9 Hz, 1H), 5.66- 5.47 (m, 2H), 5.43 (dq, $J$=1.5, 17.2 Hz, 1H), 5.29 (dq, $J$=1.4, 10.5 Hz, 1H), 4.60 (dt, $J$=1.5, 5.2 Hz, 2H), 4.03 (t, $J$=7.0 Hz, 2H), 2.71 (s, 3H), 2.55- 2.49 (m, 2H), 1.69 (dd, $J$=1.1, 5.9 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 167.4, 165.0, 152.3, 149.3, 147.3, 144.2, 134.2, 134.0, 133.1, 132.5, 128.0, 127.4, 126.7, 117.9, 114.3, 113.6, 108.4, 70.3, 69.6, 32.7, 18.2, 16.4; HRMS (TOF LCMS) calc’d for C$_{22}$H$_{24}$NO$_6$ [M+H] 398.1604, found 398.1595.

**Preparation of Compound 548**

\[
\begin{array}{c}
\text{541} \xrightarrow{\text{Pd(PPh$_3$)$_4$, NaBH$_4$, EtOH, r.t.}} \text{548}
\end{array}
\]
To a solution of 541 (128 mg, 0.33 mmol, 1 equiv.) in EtOH (3 mL) was added Pd(PPh₃)₄ (11.4 mg, 0.01 mmol, 0.03 equiv.) and NaBH₄ (6.2 mg, 0.16 mmol, 0.5 equiv.) at room temperature. The mixture was stirred overnight, filtered through Celite and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%-33% EtOAc/Hexanes) to yield 548 (11.6 mg, 97%) as brown solid.

**Compound 548**: FTIR(NaCl/thin film) 3465, 2924, 2855, 1742, 1605, 1536, 1504, 1354, 1276, 1217, 1141, 1022, 966 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.22 (dd, J=2.4, 7.8 Hz, 1H), 7.91 (dd, J=2.5, 8.1 Hz, 1H), 7.47 (td, J=3.6, 7.9 Hz, 1H), 6.89(dd, J=3.7, 8.6 Hz, 1H), 6.83-6.79 (m, 1H), 6.72-6.67 (m, 1H), 5.84-5.80 (m, 1H), 5.69-5.42 (m 2H), 4.12-4.00 (m, 2H), 2.71 (d, J=1.5 Hz, 3H), 2.57-2.44 (m, 2H), 1.74-1.67 (m, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 165.1, 152.4, 146.9, 144.7, 144.3, 134.2, 134.0, 132.7, 128.7, 127.4, 126.8, 126.5, 112.6, 112.4, 108.7, 69.4, 32.7, 18.2, 16.5; HRMS (TOF LCMS) calc’d for C₁₉H₁₈NO₆ [M-H] 356.1134, found 356.1141.

**Preparation of Compound 543**

![Image of chemical structure](image)

To a solution of 518 (295 mg, 1.26 mmol, 1 equiv.) in DCM (2 mL) was added CIP(O)(OEt)₂ (0.36 mL, 2.52 mmol, 2 equiv.) and pyridine (0.2 mL, 2.52 mmol, 2 equiv.) at room temperature. The reaction was stirred overnight, filtered through Celite and concentrated under reducing pressure. The residue was loaded onto silica and purified by
column chromatography (gradient elution, 33%-50% EtOAc/Hexanes) to yield 543 (140.3 mg, 77%) as brown oil.

**Compound 543:** FTIR(NaCl/ thin film) 2984, 2933, 1601, 1508, 1263, 1221, 1164, 1029, 981 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 6.88-6.68 (m, 3H), 6.05 (ddt, $J$=5.3, 10.5, 21.3 Hz, 1H), 5.63-5.47 (m, 2H), 5.42 (dq, $J$=1.5, 17.4 Hz, 1H), 5.28 (dq, $J$=1.3, 10.4 Hz, 1H), 4.56 (dd, $J$=1.3, 5.2 Hz, 2H), 4.26-4.14 (m, 4H), 3.97 (t, $J$=6.9 Hz, 2H), 2.53-2.45 (m, 2H), 1.67 (dd, $J$=0.9, 6.0 Hz, 3H), 1.34 (t, $J$=7.0 Hz, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 149.3, 146.3, 144.8, 133.2, 127.9, 126.8, 117.8, 114.6, 112.0, 107.3, 70.1, 69.7, 64.7, 64.7, 32.8, 18.2, 16.3, 16.2; HRMS (TOF LCMS) calc’d for C$_{18}$H$_{28}$PO$_6$ [M+H] 371.1624, found 371.1615.

**Preparation of Compound 550**

To a solution of 543 (80 mg, 0.22 mmol, 1 equiv.) in EtOH (2 mL) was added Pd(PPh$_3$)$_4$ (7.5 mg, 0.007 mmol, 0.03 equiv.) and NaBH$_4$ (4.1 mg, 0.11 mmol, 0.5 equiv.) at room temperature. The mixture was stirred overnight, filtered through Celite and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 50%-67% EtOAc/Hexanes) to yield 550 (70 mg, 78.4%) as brown solid.
**Compound 550:** FTIR(NaCl/ thin film) 3399, 2985, 1602, 1507, 1257, 1238, 1031, 987 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.85- 6.66 (m, 3H), 5.86- 5.71 (m, 1H), 5.71- 5.39 (m, 2H), 4.29- 4.14 (m, 4H), 4.01 (t, $J=$7.5 Hz, 2H), 2.53- 2.39 (m, 2H), 1.69 (d, $J=$6.2 Hz, 3H), 1.35 (t, $J=$7.0 Hz, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 146.8, 145.0, 143.4, 128.6, 126.6, 112.7, 111.0, 107.4, 69.4, 64.7, 64.7, 32.7, 18.2, 16.3, 16.2; HRMS (TOF LCMS) calc’d for C$_{15}$H$_{22}$PO$_6$ [M-H] 329.1154, found 329.1165.

**Preparation of Compound 544**

![Reaction scheme](image)

To a solution of 518 (69 mg, 0.29 mmol, 1 equiv.) in DCM (0.6 mL) was added MsCl (0.45 mL, 0.58 mmol, 2 equiv.) and pyridine (0.2 mL, 0.58 mmol, 2 equiv.) at room temperature. The reaction was stirred overnight, filtered through Celite and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%- 33% EtOAc/ Hexanes) to yield 544 (48.6 mg, 55%) as brown oil.

**Compound 544:** FTIR(NaCl/ thin film) 2938, 1601, 1508, 1422, 1366, 1262, 223, 1183, 1140, 1013, 968 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.93- 6.77 (m, 3H), 6.04 (ddt, $J=$5.0, 10.6, 22.0 Hz, 1H), 5.64- 5.46 (m, 2H), 5.42 (dq, $J=$1.8, 17.2 Hz, 1H), 5.29 (dq, $J=$1.0, 10.6 Hz, 1H), 4.58 (d, $J=$5.2 Hz, 2H), 4.00 (t, $J=$7.0 Hz, 2H), 3.10 (s, 3H), 2.54- 2.46 (m, 2H), 1.67 (d, $J=$6.0 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 149.3, 148.3,
142.9, 132.9, 128.2, 126.6, 118.2, 114.1, 113.9, 109.0, 70.3, 69.5, 37.2, 32.7, 18.2; HRMS (TOF LCMS) calc’d for C_{15}H_{21}O_{5}S [M+H] 313.1110, found 313.1105.

**Preparation of Compound 551**

![Reaction Scheme](image)

To a solution of 544 (37 mg, 0.12 mmol, 1 equiv.) in MeOH (1.2 mL) was added Pd(PPh$_3$)$_4$ (4 mg, 0.003 mmol, 0.03 equiv.) and K$_2$CO$_3$ (49 mg, 0.36 mmol, 3 equiv.) at room temperature. The mixture was stirred for 3 hours, filtered through Celite and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 33%-50% EtOAc/Hexanes) to yield 551 (35 mg, 100%) as brown solid.

**Compound 551:** FTIR (NaCl/ thin film) 3466, 2938, 1604, 1505, 1366, 1277, 1230, 1180, 1129, 1020, 959, 832 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 6.94-6.72 (m, 3H), 5.88-5.75 (m, 1H), 5.70-5.36 (m, 2H), 4.04 (t, $J$=7.6 Hz, 2H), 3.11 (s, 3H), 2.62-2.36 (m, 2H), 1.69 (dd, $J$=1.3, 6.3 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 146.9, 145.2, 128.8, 126.3, 113.5, 112.3, 109.1, 69.3, 37.2, 32.6, 182.2; HRMS (TOF LCMS) calc’d for C$_{12}$H$_{17}$O$_5$S [M+H] 273.0797, found 273.0795.
Preparation of Compound 545

To a solution of 518 (5.5 g, 23.5 mmol, 1 equiv.) in DCM (46 mL) was added NsCl (10.4 g, 47 mmol, 2 equiv.) and pyridine (9.5 mL, 117.5 mmol, 5 equiv.) at room temperature. The reaction was stirred overnight, filtered through Celite and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%-50% EtOAc/Hexanes) to yield 545 (7.6 g, 79%) as yellow oil.

**Compound 545:** FTIR(NaCl/thin film) 3097, 2919, 1594, 1547, 1506, 1383, 1262, 1191, 1125, 852 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.97-7.75 (m, 3H), 7.68-7.54 (m, 1H), 6.81-6.63 (m, 3H), 5.94 (ddt, \(J=5.2, 10.4, 21.0\) Hz, 1H), 5.60-5.40 (m, 2H), 5.33 (dq, \(J=1.3, 17.2\) Hz, 1H), 5.21 (dq, \(J=1.3, 10.6\) Hz, 1H), 4.46 (dt, \(J=1.3, 5.2\) Hz, 2H), 3.93 (t, \(J=7.0\) Hz, 2H), 2.49-2.41 (m, 2H), 1.64 (dd, \(J=1.2, 6.1\) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 149.1, 148.9, 148.4, 142.6, 135.5, 132.8, 132.5, 132.9, 128.4, 128.2, 126.5, 124.9, 118.1, 114.5, 113.5, 108.9, 70.1, 69.3, 32.7, 10.2; HRMS (TOF LCMS) calc’d for C\(_{20}\)H\(_{22}\)NO\(_7\)S [M+H] 420.1117, found 420.1105.

Preparation of Compound 552

...
To a solution of 545 (1.16 g, 2.77 mmol, 1 equiv.) in MeOH (28 mL) was added Pd(PPh\(_3\))\(_4\) (161 mg, 0.14 mmol, 0.05 equiv.) and K\(_2\)CO\(_3\) (1.15 g, 8.31 mmol, 3 equiv.) at room temperature. The mixture was stirred for 3 hours, filtered through Celite and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 50%-67% EtOAc/Hexanes) to yield 552 (972.8 mg, 92.2%) as brown solid.

**Compound 552:** FTIR(NaCl/ thin film) 3501, 2939, 1604, 1546, 1503, 1443, 1276, 1230, 1192, 1124, 1109, 960, 832 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.90 (d, \(J\)= 8.5, 3H), 7.84-7.78 (m, 2H), 7.70-7.62 (m, 1H), 6.74 (d, \(J\)=2.5 Hz, 1H), 6.72 (s, 1H), 6.65 (dd, \(J\)=2.5, 8.9 Hz, 1H), 5.63-5.39 (m, 2H), 3.99 (t, \(J\)=6.5 Hz, 2H), 2.57-2.40 (m, 2H), 1.66 (dd, \(J\)=1.0, 6.3 Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 148.9, 146.7, 145.4, 143.0, 135.7, 132.4, 132.2, 128.7, 128.4, 126.3, 125.0, 113.6, 112.1, 109.2, 69.2, 32.6, 18.2; HRMS (TOF LCMS) calc’d for C\(_{17}\)H\(_{16}\)NO\(_7\)S \([\text{M-H}]\) 378.0648, found 378.0656.

**Preparation of Compound 556**

![Chemical structure of 556](image)

To a solution of 550 (89.3 mg, 0.22 mmol, 1 equiv.) in DCE (2.2 mL) was added Pb(OAc)\(_4\) (135 mg, 0.31 mmol, 1.4 equiv.). The solution was heated to reflux and stirred overnight. The mixture was cooled to room temperature, filtered through Celite and
concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 50%-67% EtOAc/Hexanes) to yield 556 (20 mg, 24%) as yellow oil and 476 (35.5 mg, 44%) as yellow oiled.

**Compound 556:** FTIR(NaCl/ thin film) 3418, 2963, 2928, 1745, 1651, 1372, 1268, 1170, 1087, 1025, 972 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.90 (ddd, J= 1.6, 2.5, 7.4 Hz, 1H), 4.27-4.09 (m, 4H), 3.90 (dd, J=5.3, 13.4 Hz, 1H), 3.61 (dt, J=3.2, 12.4 Hz, 1H), 3.08 (t, J=2.6 Hz, 1H), 2.70 (dd, J=3.3, 7.4 Hz, 1H), 2.14-1.80 (m, 4H), 1.72-1.58 (m, 1H), 1.41-1.29 (m, 6H), 1.14 (d, J=6.9 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 207.8, 132.3, 111.3, 90.6, 65.1, 64.9, 61.5, 58.2, 42.2, 37.8, 34.8, 29.3, 20.2, 16.3, 16.2; HRMS (TOF LCMS) calc’d for C₁₅H₂₃PO₇ [M-H] 345.1103, found 345.1113.

**Preparation of Compound 557**

To a solution of 551 (158 mg, 0.58 mmol, 1 equiv.) in DCE (5.8 mL) was added Pb(OAc)₄ (362 mg, 0.81 mmol, 1.4 equiv.). The solution was heated to reflux and stirred overnight. The mixture was cooled to room temperature, filtered through Celite and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 50%-67% EtOAc/Hexanes) to yield 557 (20 mg, 42.1%) as brown oil.
**Compound 557:** FTIR (NaCl/ thin film) 2961, 2936, 1743, 1650, 1368, 1183, 1120, 972, 817 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 5.99 (dd, \(J= 2.5, 7.6\) Hz, 1H), 4.02 (dd, \(J=2.1, 12.5\) Hz, 1H), 3.66 (td, \(J=3.6, 12.3\) Hz, 1H), 3.54 (dd, \(J=3.4, 7.6\) Hz, 1H), 3.16 (q, \(J=2.4\) Hz, 1H), 3.12 (s, 3H), 2.13- 1.94 (m, 2H), 2.02 (s, 3H), 1.90- 1.84 (m, 1H), 1.67- 1.58 (m, 1H), 1.13 (d, \(J=6.9\) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 200.4, 168.8, 146.7, 112.5, 93.5, 62.3, 57.9, 41.3, 38.2, 37.5, 35.9, 28.4, 21.6, 20.3; HRMS (TOF LCMS) calc’d for C\(_{14}\)H\(_{19}\)O\(_7\)S [M+H] 331.0852, found 331.0848.

**Preparation of Compound 558, 559**

![Diagram of compound preparation](image)

To a solution of 551 (972.8 mg, 2.56 mmol, 1 equiv.) in DCE (25 mL) was added Pb(OAc)\(_4\) (1.59, 3.58 mmol, 1.4 equiv.). The solution was heated to reflux and stirred overnight. The mixture was cooled to room temperature, filtered through Celite and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 50%- 67% EtOAc/ Hexanes) to yield 558 (814.5 mg, 72.7%) as brown oil and 559 (45.2 mg, 4.2%) as yellow solid.

**Compound 558:** FTIR (NaCl/ thin film) 3418, 2959, 2926, 1743, 1545, 1385, 1251, 1193, 1110, 1022, 820 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.16- 8.02 (m, 1H), 7.91- 7.72 (m, 3H), 6.04 (dd, \(J=2.5, 7.6\) Hz), 4.03 (ddd, \(J= 2.3, 6.6, 13.5\) Hz, 1H), 3.76 (dd, \(J=2.2, 7.6\) Hz, 1H), 3.62 (td, \(J=2.6, 12.2\) Hz, 1H), 3.16 (t, \(J= 2.5\) Hz, 1H), 2.07- 2.02
(m, 2H), 2.00 (s, 3H), 1.90- 1.5 (m, 1H), 1.67- 1.59 (m, 1H), 1.13 (d, J=6.9 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 200.0, 168.6, 146.0, 135.8, 132.4, 132.2, 128.5, 125.3, 117.0, 116.0, 93.4, 62.5, 57.4, 40.5, 37.3, 35.9, 28.4, 21.8, 20.2; HRMS (TOF LCMS) calc’d for C$_{19}$H$_{19}$NO$_9$SNa [M+Na] 460.0678, found 460.0677.

**Compound 559**: FTIR(NaCl/ thin film) 3383, 2959, 2930, 1741, 1718, 1220, 1169, 1154, 1088, 1057 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.01 (dd, J= 5.1, 13.8 Hz, 1H), 3.68 (td, J=3.2, 12.0 Hz, 1H), 3.63- 3.63 (m, 1H), 3.51 (td, J=2.9, 12.5 Hz, 1H), 3.18 (t, J=3.5 Hz, 1H), 2.68 (dd, J=3.2, 7.4 Hz, 1H), 2.13- 2.04 (m, 1H), 1.95- 1.78 (m, 2H), 1.64- 1.56 (m, 1H), 1.12 (d, J=6.9 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 206.6, 148.5, 144.6, 135.9, 133.3, 132.4, 127.7, 125.1, 119.7, 90.2, 61.5, 57.8, 42.8, 37.1, 34.9, 28.8, 20.2; HRMS (TOF LCMS) calc’d for C$_{17}$H$_{21}$N$_2$O$_8$S [M+NH$_4$] 413.1019, found 413.1025.

**Preparation of Compound 537**

![Chemical diagram](image)

To a solution of **558** (470 mg, 1.08 mmol, 1 equiv.) in MeCN (5.4 mL) was added PhSH (0.88 mL, 8.64 mmol, 8 equiv.) and KOH (120 mg, 2.16 mmol, 2 equiv.) at room temperature. The mixture was stirred for 30 minutes and quenched by aqueous HCl (2 mL, 1N). The aqueous layer was washed by EtOAc (2 x 6mL), and the combined organic
layers were washed with brine (12 mL), dried over Na₂SO₄, and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%- 50% EtOAc/ Hexanes) to remove PhSH.

To the product mixture in DCM (20 mL) was added silica (2 g) and stirred at room temperature for 2 days. The solution was filtered through Celite and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 33%- 67% EtOAc/ Hexanes) to yield 537 (370.5 mg, 96%) as brown oil.

**Compound 537:** FTIR(NaCl/ thin film) 3389, 2961, 1744, 1478, 1193, 1112, 1089, 822 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.01 (d, J= 7.7 Hz, 1H), 7.87- 7.80 (m, 2H), 7.76- 7.68 (m, 1H), 6.03 (dd, J=2.5, 7.6 Hz, 1H), 3.85 (dd, J=5.5, 12.5 Hz, 1H), 3.68- 3.55 (m, 1H), 3.22 (d, J=2.8 Hz, 1H), 2.85 (dd, J=3.6, 20.5 Hz, 1H), 2.40- 2.28 (m, 2H), 2.27- 2.17 (m, 1H), 2.14- 1.99 (m, 2H), 1.64- 1.54 (m, 1H), 1.11 (d, J=7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 206.7, 203.6, 93.5, 71.0, 61.9, 39.7, 39.1, 37.3, 33.8, 30.8, 21.1; HRMS (TOF LCMS) calc’d for C₂₂H₂₈NaO₈ [M+M+Na] 443.1682, found 443.1687.

**Preparation of Compound 561**

![Preparation of Compound 561](image-url)
To a solution of 537 (89 mg, 0.42 mmol, 1 equiv.) in DCM (4.2 mL) was added TMSOTf (0.17 mL, 0.92 mmol, 2.2 equiv.) and Et₃N (0.14 mL, 0.92 mmol, 2.2 equiv.) at -78 °C. The mixture was stirred for 5 min and quenched by saturated aqueous NaHCO₃ (0.5 mL). The aqueous layer was washed by DCM (2 x 5mL) and the combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%-33% EtOAc/Hexanes) to yield 561 (98.2 mg, 82.2%) as yellow oil.

**Compound 561:** FTIR(NaCl/ thin film) 2958, 1755, 1728, 1458, 1400, 1354, 1315, 1250, 1092, 939, 847 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.97 (dd, J= 4.8, 14.1 Hz, 1H), 3.63 (td, J=3.0, 12.5 Hz, 1H), 3.16 (d, J=3.0 Hz, 1H), 2.83 (dd, J=2.9, 19.7 Hz, 1H), 2.26 (dd, J=3.2, 19.6 Hz, 1H), 2.18-2.11 (m, 2H), 2.06-1.95 (m, 2H), 1.55-1.49 (m, 1H), 1.08 (d, J=7.2 Hz, 3H), 0.15 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 205.1, 204.8, 95.5, 71.9, 61.9, 42.2, 39.8, 37.4, 34.3, 30.9, 21.3, 1.8; HRMS (TOF LCMS) calc’d for C₁₄H₂₂NaO₄Si [M+Na] 305.1185, found 305.1186.

**Preparation of Compound 563**

To a solution of 561 (60 mg, 0.21 mmol, 1 equiv.) in DCM (2.1 mL) was added TBSOTf (0.24 mL, 1.1 mmol, 5 equiv.) and Et₃N (0.16 mL, 1.1 mmol, 5 equiv.) at -78 °C.
The mixture was warmed to room temperature and stirred overnight. The reaction was quenched by saturated aqueous NaHCO$_3$ (0.5 mL). The aqueous layer was washed by DCM (2 x 2 mL), and the combined organic layers were washed with brine (4 mL), dried over Na$_2$SO$_4$, and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 5% - 10% EtOAc/Hexanes) to yield 563 (77.8 mg, 92.3%) as yellow oil.

**Compound 563**: FTIR(NaCl/ thin film) 2957, 2929, 1749, 1725, 1643, 1250, 1193, 1153, 1091, 844 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.10 (dd, $J$= 2.2, 7.3 Hz, 1H), 3.82 (dd, $J$=6.1, 12.2 Hz, 1H), 3.55 (td, $J$=2.2, 12.7 Hz, 1H), 2.73 (t, $J$=2.3 Hz, 1H), 2.39 (dd, $J$=3.2, 7.3 Hz, 1H), 2.01- 1.92 (m, 1H), 1.91- 1.80 (m, 1H), 1.75- 1.70 (m, 1H), 1.53-1.49 (m, 1H), 1.07 (d, $J$=7.0 Hz, 3H), 0.9 (s, 9H), 0.17 (s, 6H), 0.14 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 208.2, 149.7, 103.9, 93.2, 61.4, 44.8, 38.5, 34.9, 29.8, 25.7, 20.3, 18.1, 1.9, -4.4, -4.6; HRMS (TOF LCMS) calc’d for C$_{20}$H$_{37}$O$_4$Si$_2$ [M+H] 397.2230, found 397.2223.

**Preparation of Compound 564**

![Diagram](image)

To a solution of diisopropylamine (0.14 mL, 1.03 mmol, 5.25 equiv.) in THF (1 mL) at –20 °C was added $n$-BuLi (0.43 mL, 0.84 mmol, 4.2 equiv., 1.9 M hexanes solution) dropwise over 5 minutes. The resultant mixture was stirred at –20 °C for 5
minutes, and then cooled to –78 ºC for 30 minutes. To this mixture was added methyl-3-(dimethylamino)propionate (0.1 mL, 0.70 mmol, 3.5 equiv.) dropwise over five minutes. The reaction mixture was stirred at –78 ºC for thirty minutes, 0 ºC for 15 min, and room temperature for 15 min, and then cooled to –78 ºC.

A solution of 563 (77.8 mg, 0.2 mmol, 1equiv.) in THF (2 mL) was added enolate dropwise over 1 min at –78 ºC. The solution was slowly warmed to room temperature and stirred for 1 hour. The reaction was quenched with 1M AcOH in THF (5mL) and allowed to warm to room temperature. At which point the reaction mixture was treated with H₂O (2 mL) and EtOAc (2 mL). The aqueous layer was extracted with EtOAc (2 x 5mL), and the combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, and concentrated under reducing pressure.

To the solution of this residue solution in DCM (8.5 mL) was added m-CPBA (170 mg, 0.70 mmol, 3.5 equiv.) at -78 ºC and stirred for 20 minutes. To the solution was added basic Al₂O₃ (200 mg) and stirred overnight at room temperature. The mixture was filtered through Celite and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 5%- 10% EtOAc/Hexanes) to yield 564 (80.2, mg, 84.7%) as colorless oil.

**Compound 564**: FTIR(NaCl/ thin film) 3451, 2955, 1705, 1652, 1322, 1258, 1180, 1023, 938, 911, 842 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.01 (s, 1H), 5.77 (s, 1H), 5.44- 5.31 (m, 1H), 4.74 (dd, J= 2.4, 7.1 Hz, 1H), 4.64 (td, J=4.4, 12.1 Hz, 1H), 3.85 (dd, J=6.7, 11.4 Hz, 1H), 3.74 (s, 3H), 2.44 (t, J=2.3 Hz, 1H), 2.35 (ddd, J=2.3, 4.4, 9.2 Hz, 1H), 2.12 (dd, J=2.8, 7.1 Hz, 1H), 1.83- 1.73 (m, 1H), 1.67- 1.59 (m, 1H), 1.43- 1.37 (m, 1H), 0.95 (d, J=7.0 Hz, 3H), 0.93 (s, 9H), 0.18 (s, 3H), 0.14 (s, 3H), 0.06 (s, 9H); ¹³C
NMR (100 MHz, CDCl₃) δ 170.7, 153.0, 144.1, 119.7, 100.6, 100.1, 82.3, 63.1, 52.9, 51.8, 45.9, 40.9, 29.7, 28.5, 25.7, 21.3, 18.0, 1.8, -4.8; HRMS (TOF LCMS) calc’d for C₂₄H₄₁O₆Si₂ [M-H] 481.2442, found 481.2455.

Preparation of Compound 531

To a solution of 564 (80 mg, 0.17 mmol, 1 equiv.) in THF (1.6 mL) was added TBAF (1.67 mL, 1.7 mmol, 10 equiv.) and AcOH (95 µL, 1.7 mmol, 10 equiv.) at room temperature. The mixture was stirred overnight. The reaction was quenched by H₂O (2 mL). The aqueous layer was extracted with EtOAc (2 x 5mL). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%- 50% EtOAc/ Hexanes) to yield 531 (26 mg, 59%) as yellow solid.

**Compound 531**: FTIR(NaCl/ thin film) 3431, 2924, 1780, 1733, 1289, 1264, 1175, 1076, 1003 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.05 (s, 1H), 5.98 (s, 1H), 4.49 (ddd, J= 5.8, 9.1, 14.5 Hz, 1H), 4.23 (ddt, J=5.2, 11.5, 17.0 Hz, 1H), 3.42- 3.36 (m, 1H), 2.71 (d, J=2.2 Hz, 1H), 2.43- 2.37 (m, 2H), 2.20 (dd, J=3.4, 11.3 Hz, 1H), 2.14- 2.02 (m, 1H), 1.85- 1.73 (m, 2H), 1.31- 1.20 (m, 1H), 1.02 (d, J=7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 170.7, 153.0, 144.1, 119.7, 100.6, 100.1, 82.3, 63.1, 52.9, 51.8, 45.9, 40.9, 29.7, 28.5, 25.7, 21.3, 18.0, 1.8, -4.8; HRMS (TOF LCMS) calc’d for C₂₄H₄₁O₆Si₂ [M-H] 481.2442, found 481.2455.
MHz, CDCl$_3$) $\delta$ 208.6, 166.0, 135.3, 130.1, 104.7, 74.6, 64.1, 61.8, 38.6, 38.3, 37.4, 31.0, 29.9, 20.8; HRMS (TOF LCMS) calc’d for C$_{14}$H$_{15}$O$_5$ [M-H] 263.0920, found 263.0922.

**Preparation of Compound 513**

![Reaction Scheme]

To a solution of 531 (76 mg, 0.29 mmol, 1 equiv.) in DCM (3 mL) was added 519 (0.37 mL, 2.9 mmol, 10 equiv.) and N,N’-Dimethyl aniline (0.39 mL, 2.9 mmol, 20 equiv.) at room temperature. The mixture was stirred for 2 days and concentrated by reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%–50% EtOAc/Hexanes) to yield 513 (58.4 mg, 49%) as brown oil and starting material 531 (10 mg).

**Compound 513 (diastereomer):** FTIR(NaCl/ thin film) 2972, 2929, 1777, 1732, 1286, 1189, 1106, 1071, 1039, 1066, 977 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.69 (s, 1H), 6.62 (s, 1H), 6.00 (s, 1H), 5.85 (s, 1H), 4.85 (t, $J$=4.3, 1H), 4.71 (dd, $J$=4.4, 16, 1H), 4.62 (dd, $J$= 6.1, 12.3 Hz, 1H), 4.53 (dd, $J$=6.1, 12.3 Hz, 1H), 4.14 (dd, $J$=6.6, 12.1 Hz, 2H), 3.56-3.31 (m, 8H), 2.87 (d, $J$=2.4, 1H), 2.76 ($J$=2.4, 1H), 2.62-2.48 (m, 2H), 2.26-1.96 (m, 8H), 1.85-1.78 (m, 2H), 1.72-1.61 (m, 2H), 1.19 (t, $J$=7.1 Hz, 3H), 1.12 (t, $J$=7.0 Hz, 3H), 1.02 (d, $J$=1.7 Hz, 3H), 1.01 (d, $J$=1.7Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 208.7, 208.6, 165.8, 135.8, 135.4, 132.5, 130.3, 106.1, 97.3, 80.1, 79.7, 62.0, 61.8, 38.6, 38.3, 37.4, 31.0, 29.9, 20.8; HRMS (TOF LCMS) calc’d for C$_{14}$H$_{15}$O$_5$ [M-H] 263.0920, found 263.0922.
61.8, 61.5, 61.4, 40.8, 40.4, 38.8, 38.3, 38.6, 38.5, 31.9, 31.8, 29.7, 29.6, 28.7, 28.2, 20.9, 25.2, 15.0; HRMS (TOF LCMS) calc’d for C_{18}H_{23}NaBrO_{6} [M+Na] 437.0576, found 437.0568.

**Preparation of Compound 512**

![Chemical Structures](image)

To a solution of I\textsubscript{2} (216.2 mg, 0.85 mmol, 1 equiv.) in THF (12 mL) was added samarium (186 mg, 0.94, 1.1 equiv.) at room temperature. The mixture was heated to reflux for 3 hours then cooled to room temperature. 0.07 M SmI\textsubscript{2} was ready for reaction.

To a solution of 513 (16 mg, 0.039 mmol, 1 equiv.) in THF (0.4 mL) was added SmI\textsubscript{2} solution (2.7 mL, 0.20 mmol, 5 equiv.) at room temperature. The mixture was stirred for 1 hour then quenched by saturated aqueous NH\textsubscript{4}Cl (0.5 mL) and HCl (0.1 mL, 1 N). At which point the reaction mixture was treated with H\textsubscript{2}O (2 mL) and EtOAc (2 mL). The aqueous layer was extracted with EtOAc (3 x 5mL), and the combined organic layers were washed with brine (10 mL), dried over Na\textsubscript{2}SO\textsubscript{4}, and concentrated under reducing pressure to yield crude 512.

To a solution of 512 (half amount of last step rude product) in DCM (0.2 mL) was added BF\textsubscript{3}•OEt\textsubscript{2} (6 µL, 0.048 mmol, 2.5 equiv.) and propane-1,3-dithiol (5 µL, 0.048 mmol, 2.5 equiv.) at 0 ºC. The mixture was warmed to room temperature and stirred
overnight. The reaction was quenched by H$_2$O (10 µL). At which point the reaction mixture was treated with H$_2$O (1 mL) and EtOAc (1 mL). The aqueous layer was extracted with EtOAc (3 x 1mL), and the combined organic layers were washed with brine (3 mL), dried over Na$_2$SO$_4$, and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 25%-50% EtOAc/ Hexanes) to yield 566 (5 mg, 65%) as yellow oil.

**Compound 512:** FTIR(NaCl/ thin film) 3457, 2918, 1778, 1726, 1480, 1462, 1451, 1358, 1327, 1299, 1273, 1174, 1109, 1080, 1027, 980 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 5.47 (dd, $J$=2.2, 5.7 Hz, 1H) 4.20 (td, $J$=3.1, 12.5 Hz, 1H), 3.99 (dd, $J$=6.0, 12.0 Hz, 1H), 3.78 (dd, $J$=7.2, 9.8, 14.3 Hz, 1H), 3.53 (ddd, $J$=7.0, 9.8, 14.1 Hz, 1H), 2.72 (dd, $J$=6.8, 14.2 Hz, 1H), 2.32 (d, $J$=3.3 Hz, 1H), 2.30 (s, 1H), 2.19 (dd, $J$=2.3, 13.8 Hz, 1H), 2.13 (dd, $J$=2.2, 14.2 Hz, 1H), 2.10-2.07 (m, 1H), 2.01- 1.90 (m, 3H), 1.81 (q, $J$=3.4 Hz, 1H), 1.75- 1.65 (m, 2H), 1.48 (dt, $J$=3.2, 16.5 Hz, 1H), 1.28 (d, $J$=7.5 Hz, 3H), 1.22 (t, $J$=7.2 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 177.7, 109.5, 106.9, 95.9, 77.9, 64.0, 63.0, 57.0, 53.9, 52.1, 44.3, 39.4, 38.4, 37.8, 30.7, 27.8, 21.0, 15.4; HRMS (TOF LCMS) calc’d for C$_{16}$H$_{19}$O$_5$ [M-C2H5O] 291.1233, found 291.1236.

**Preparation of Compound 586**

![Chemical structure of Compound 586](attachment:image.png)
To a solution of 531 (16 mg, 0.06 mmol, 1 equiv.) in DCM (0.6 mL) was added 2-chloroacetic anhydride (20.5 mg, 0.12, 2 equiv.) and pyridine (20 µL, 0.02 mmol, 0.3 equiv.) at room temperature. The mixture was stirred overnight and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 25%-67% EtOAc/Hexanes) to yield 586 (2 mg, 10%) as yellow oil.

**Compound 586:** FTIR(\(\text{NaCl/ thin film}\)) 2960, 2361, 2339, 1743, 1546, 1439, 1387, 1194, 1088, 1023 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 4.89 (dd, \(J=14.0, 22.5\) Hz, 1H) 4.20 (s, 2H), 4.14-4.10 (m, 1H), 4.09 (d, \(J=3.2\) Hz, 1H), 3.61 (d, \(J=1.8\) Hz, 1H), 2.75 (q, \(J=2.2\) Hz, 1H), 2.44-2.36 (m, 1H), 2.32 (d, \(J=2.2\) Hz, 1H), 2.25 (d, \(J=3.5\) Hz, 1H), 2.30 (s, 1H), 1.99-1.91 (m, 2H), 1.72-1.65 (m, 1H), 1.01 (d, \(J=8.2\) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 203.1, 171.3, 167.0, 158.9, 123.6, 105.8, 61.7, 57.6, 56.3, 40.5, 39.0, 38.0, 36.9, 32.5, 29.4, 19.4; HRMS (TOF LCMS) calc’d for C\(_{16}\)H\(_{19}\)O\(_5\) [M+Na] 363.0611, found 363.0611.

**Preparation of Compound 580**

![Chemical structure](image)

To a solution of 477 (100 mg, 0.22 mmol, 1 equiv.) in DCM (3 mL) was added 419 (0.32 mL, 4.40 mmol, 20 equiv.) and N,N’-Dimthyl analine (0.30 mL, 4.40 mmol, 20
equiv.) at room temperature. The mixture was stirred for 2 days and concentrated by reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 20%-50% EtOAc/Hexanes) to yield 580 (60 mg, 50%) as brown oil and starting material 477 (50%).

**Compound 580 (diastereomer):** FTIR (NaCl/thin film) 2974, 2928, 1775, 1651, 1547, 1390, 1367, 1284, 1195, 1123, 1075,905, 824 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.04 (dd, J=4.6, 7.7 Hz, 2H), 7.91-7.82 (m, 4H), 7.79 (td, J=1.5, 7.3 Hz, 2H), 6.24 (s, 1H), 6.19 (s, 1H), 5.79 (s, 1H), 5.82 (s, 1H), 5.75 (ddd, J=2.6, 5.8, 7.9 Hz, 2H), 5.73 (ddd, J=4.0, 5.9, 8.0 Hz, 2H), 4.59 (td, J=3.6, 12.9 Hz, 1H), 4.47 (td, J=3.8, 12.1 Hz, 1H), 4.00 (q, J=5.6 Hz, 2H), 3.54-3.32 (m, 8H), 3.00 (t, J=1.9 Hz, 1H), 2.84 (t, J=2.1 Hz, 1H), 2.63 (ddd, J=2.4, 7.7, 9.3 Hz, 2H), 2.46-2.37 (m, 2H), 2.01-1.85 (m, 2H), 1.75-1.58 (m, 4H), 1.22 (t, J=7.0 Hz, 3H), 1.07 (t, J=6.9 Hz, 3H), 0.98 (d, J=7.0 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 166.3, 149.6, 149.5, 148.5, 135.9, 135.2, 132.9, 131.7, 129.2, 129.0, 126.7, 125.3, 110.6, 110.5, 105.4, 104.8, 97.9, 97.0, 82.4, 81.9, 63.9, 63.6, 62.5, 61.2, 52.4, 52.3, 44.1, 43.6, 40.0, 39.7, 32.3, 32.0, 29.9, 29.6, 28.4, 20.8, 13.2, 15.0; HRMS (TOF LCMS) calc’d for C₂₄H₂₆NBrO₁₀NaS [M+Na] 622.0359, found 622.0358.

**Preparation of Compound 582**

![Diagram of the preparation of Compound 582](image)
To a solution of 580 (31 mg, 0.052 mmol, 1 equiv.) in MeCN (0.7 mL) was added PhSH (71 µL, 0.52 mmol, 10 equiv.) and KOH (7.5 mg, 0.10 mmol, 2 equiv.) at room temperature. The mixture was stirred for 20 minutes then added H2O (1 mL). The aqueous layer was extracted with EtOAc (3 x 1 mL), and the combined organic layers were washed with brine (3 mL), dried over Na2SO4, and concentrated under reducing pressure. The residue was loaded onto silica and purified by column chromatography (gradient elution, 25%-50% EtOAc/Hexanes) to yield 582 (22 mg, 100%) as colorless solid.

**Compound 582:** FTIR(NaCl/ thin film) 3456, 2958, 2927, 1778, 1728, 1200, 1057, 994, 740 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.48-7.27 (m, 5H), 4.98-4.75 (m, 1H), 4.45-4.35 (m, 1H), 4.30-4.15 (m, 1H), 3.38 (s, 1H), 3.36 (d, J=2.1 Hz, 1H), 2.87 (d, J=2.2 Hz, 1H), 2.57-2.51 (m, 2H), 2.41-2.30 (m, 3H), 2.14-2.01 (m, 1H), 1.92-1.71 (m, 2H), 1.01 (d, J=7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 209.6, 173.1, 134.6, 131.1, 129.4, 127.4, 105.4, 76.2, 63.8, 63.6, 50.0, 38.6, 36.7, 36.5, 33.0, 31.1, 29.8, 20.7; HRMS (TOF LCMS) calc’d for C₂₀H₂₃O₅S [M+H] 375.1266, found 375.1268.
4.7 Notes and References


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Appendix II: Spectra Relevant to Chapter 4
Figure A.4.1 $^1$H NMR (400MHz, CDCl$_3$) of compound 466
Figure A.4.2 Infrared Spectrum (thin film/NaCl) of compound 466.

Figure A.4.3 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 466.
Figure A.4.4 $^1$H NMR (400MHz, CDCl$_3$) of compound 465
Figure A.4.5 Infrared Spectrum (thin film/NaCl) of compound 465.

Figure A.4.6 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 465.
Figure A.4.7 $^1$H NMR (400MHz, CDCl$_3$) of compound 470
Figure A.4.8 Infrared Spectrum (thin film/NaCl) of compound 470.

Figure A.4.9 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 470.
Figure A.4.10 $^1$H NMR (400MHz, CDCl$_3$) of compound 480
Figure A.4.11 Infrared Spectrum (thin film/NaCl) of compound 480.

Figure A.4.12 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 480.
Figure A.4.13 $^1$H NMR (400MHz, CDCl$_3$) of compound 482
Figure A.4.14 Infrared Spectrum (thin film/NaCl) of compound 482.

Figure A.4.15 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 482.
Figure A.4.16 $^1$H NMR (400MHz, CDCl$_3$) of compound 481
Figure A.4.17 Infrared Spectrum (thin film/NaCl) of compound 481.

Figure A.4.18 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 481.
Figure A.4.19 $^1$H NMR (400MHz, CDCl$_3$) of compound 483
Figure A.4.20 Infrared Spectrum (thin film/NaCl) of compound 483.

Figure A.4.21 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 483.
Figure A.4.22 $^1$H NMR (400MHz, CDCl$_3$) of compound 484
Figure A.4.23 Infrared Spectrum (thin film/NaCl) of compound 484.

Figure A.4.24 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 484.
Figure A.4.25 $^1$H NMR (400MHz, CDCl$_3$) of compound 485
Figure A.4.26 Infrared Spectrum (thin film/NaCl) of compound 485.

Figure A.4.27 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 485.
Figure A.4.28 $^1$H NMR (400MHz, CDCl$_3$) of compound 490
Figure A.4.29 Infrared Spectrum (thin film/NaCl) of compound 490.

Figure A.4.30 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 490.
Figure A.4.31 $^1$H NMR (400MHz, CDCl$_3$) of compound 492
Figure A.4.32 Infrared Spectrum (thin film/NaCl) of compound 492.

Figure A.4.33 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 492.
Figure A.4.34 $^1$H NMR (400MHz, CDCl$_3$) of compound 502
Figure A.4.35 Infrared Spectrum (thin film/NaCl) of compound 502.

Figure A.4.36 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 502.
Figure A.4.37 $^1$H NMR (400MHz, CDCl$_3$) of compound 516
Figure A.4.38 Infrared Spectrum (thin film/NaCl) of compound 516.

Figure A.4.39 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 516.
Figure A.4.40 $^1$H NMR (400MHz, CDCl$_3$) of compound 517
Figure A.4.41 Infrared Spectrum (thin film/NaCl) of compound 517.

Figure A.4.42 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 517.
Figure A.4.43 $^1$H NMR (400MHz, CDCl$_3$) of compound 518
Figure A.4.44 Infrared Spectrum (thin film/NaCl) of compound 518.

Figure A.4.45 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 518.
Figure A.4.46 $^1$H NMR (400MHz, CDCl$_3$) of compound 519
Figure A.4.47 Infrared Spectrum (thin film/NaCl) of compound 519.

Figure A.4.48 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 519.
Figure A.4.49 $^1$H NMR (400MHz, CDCl$_3$) of compound 520
Figure A.4.50 Infrared Spectrum (thin film/NaCl) of compound 520.

Figure A.4.51 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 520.
Figure A.4.52 $^1$H NMR (400MHz, CDCl$_3$) of compound 502
Figure A.4.53 Infrared Spectrum (thin film/NaCl) of compound 522.

Figure A.4.54 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 522.
Figure A.4.55 $^1$H NMR (400MHz, CDCl$_3$) of compound 525
Figure A.4.56 Infrared Spectrum (thin film/NaCl) of compound \textbf{525}.

Figure A.4.57 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound \textbf{525}. 
Figure A.4.58 $^1$H NMR (400MHz, CDCl$_3$) of compound 526
Figure A.4.59 Infrared Spectrum (thin film/NaCl) of compound 526.

Figure A.4.60 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 526.
Figure A.4.61 $^1$H NMR (400MHz, CDCl$_3$) of compound 527
Figure A.4.62 Infrared Spectrum (thin film/NaCl) of compound 527.

Figure A.4.63 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 527.
Figure A.4.64 $^1$H NMR (400MHz, CDCl$_3$) of compound 528
Figure A.4.65 Infrared Spectrum (thin film/NaCl) of compound 528.

Figure A.4.66 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 528.
Figure A.4.67 $^1$H NMR (400MHz, CDCl$_3$) of compound 529
Figure A.4.68 Infrared Spectrum (thin film/NaCl) of compound 529.

Figure A.4.69 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 529.
Figure A.4.70 $^1$H NMR (400MHz, CDCl$_3$) of compound 530
Figure A.4.71 Infrared Spectrum (thin film/NaCl) of compound 530.

Figure A.4.72 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 530.
Figure A.4.73 $^1$H NMR (400MHz, CDCl$_3$) of compound 538
Figure A.4.74 Infrared Spectrum (thin film/NaCl) of compound 538.

Figure A.4.75 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 538.
Figure A.4.76 $^1$H NMR (400MHz, CDCl$_3$) of compound 546
Figure A.4.77 Infrared Spectrum (thin film/NaCl) of compound 546.

Figure A.4.78 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 546.
Figure A.4.79 $^1$H NMR (400MHz, CDCl$_3$) of compound 540
Figure A.4.80 Infrared Spectrum (thin film/NaCl) of compound 540.

Figure A.4.81 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 540.
Figure A.4.82 $^1$H NMR (400MHz, CDCl$_3$) of compound 547
Figure A.4.83 Infrared Spectrum (thin film/NaCl) of compound 547.

Figure A.4.84 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 547.
Figure A.4.85 $^1$H NMR (400MHz, CDCl$_3$) of compound 541
Figure A.4.86 Infrared Spectrum (thin film/NaCl) of compound 541.

Figure A.4.87 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 541.
Figure A.4.88 $^1$H NMR (400MHz, CDCl$_3$) of compound 548
Figure A.4.89 Infrared Spectrum (thin film/NaCl) of compound 548.

Figure A.4.90 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 548.
Figure A.4.91 $^1$H NMR (400MHz, CDCl$_3$) of compound 543
Figure A.4.92 Infrared Spectrum (thin film/NaCl) of compound 543.

Figure A.4.93 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 543.
Figure A.4.94 $^1$H NMR (400MHz, CDCl$_3$) of compound 550
Figure A.4.95 Infrared Spectrum (thin film/NaCl) of compound 550.

Figure A.4.96 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 550.
Figure A.4.97 $^1$H NMR (400MHz, CDCl$_3$) of compound 544
Figure A.4.98 Infrared Spectrum (thin film/NaCl) of compound 544.

Figure A.4.99 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 544.
Figure A.4.100 $^1$H NMR (400MHz, CDCl$_3$) of compound 551
Figure A.4.101 Infrared Spectrum (thin film/NaCl) of compound 551.

Figure A.4.102 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 551.
Figure A.4.103 $^1$H NMR (400MHz, CDCl$_3$) of compound 545
Figure A.4.104 Infrared Spectrum (thin film/NaCl) of compound 545.

Figure A.4.105 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 545.
Figure A.4.106 $^1$H NMR (400MHz, CDCl$_3$) of compound 552
Figure A.4.107 Infrared Spectrum (thin film/NaCl) of compound 552.

Figure A.4.108 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 552.
Figure A.4.109 $^1$H NMR (400MHz, CDCl$_3$) of compound 556
Figure A.4.110 Infrared Spectrum (thin film/NaCl) of compound 556.

Figure A.4.111 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 556.
Figure A.4.112 $^1$H NMR (400MHz, CDCl$_3$) of compound 557
Figure A.4.113 Infrared Spectrum (thin film/NaCl) of compound 557.

Figure A.4.114 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 557.
Figure A.4.115 $^1$H NMR (400MHz, CDCl$_3$) of compound 558
Figure A.4.116 Infrared Spectrum (thin film/NaCl) of compound 558.

Figure A.4.117 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 558.
Figure A.4.118 $^1$H NMR (400MHz, CDCl$_3$) of compound 559
Figure A.4.119 Infrared Spectrum (thin film/NaCl) of compound 559.

Figure A.4.120 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 559.
Figure A.4.121 $^1$H NMR (400MHz, CDCl$_3$) of compound 537
Figure A.4.122 Infrared Spectrum (thin film/NaCl) of compound 537.

Figure A.4.123 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 537.
Figure A.4.124 $^1$H NMR (400MHz, CDCl$_3$) of compound 561
Figure A.4.125 Infrared Spectrum (thin film/NaCl) of compound 561.

Figure A.4.126 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 561.
Figure A.4.127 $^1$H NMR (400MHz, CDCl$_3$) of compound 563
Figure A.4.128 Infrared Spectrum (thin film/NaCl) of compound 563.

Figure A.4.129 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 563.
Figure A.4.130 $^1$H NMR (400MHz, CDCl$_3$) of compound 564
Figure A.4.131 Infrared Spectrum (thin film/NaCl) of compound 564.

Figure A.4.132 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 564.
Figure A.4.133 $^1$H NMR (400MHz, CDCl$_3$) of compound 531
Figure A.4.134 Infrared Spectrum (thin film/NaCl) of compound 531.

Figure A.4.135 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 531.
Figure A.4.136 $^1$H NMR (400MHz, CDCl$_3$) of compound 513
Figure A.4.137 Infrared Spectrum (thin film/NaCl) of compound 513.

Figure A.4.138 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 513.
Figure A.4.139 $^1$H NMR (400MHz, CDCl$_3$) of compound 512
Figure A.4.140 Infrared Spectrum (thin film/NaCl) of compound 512.

Figure A.4.141 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 512.
Figure A.4.142 $^1$H NMR (400MHz, CDCl$_3$) of compound 586
Figure A.4.143 Infrared Spectrum (thin film/NaCl) of compound 586.

Figure A.4.144 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 586.
Figure A.4.145 $^1$H NMR (400MHz, CDCl$_3$) of compound 580
Figure A.4.146 Infrared Spectrum (thin film/NaCl) of compound 580.

Figure A.4.147 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 580.
Figure A.4.148 $^1$H NMR (400MHz, CDCl$_3$) of compound 582
Figure A.4.149 Infrared Spectrum (thin film/NaCl) of compound 582.

Figure A.4.150 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 582.
About the Author

Ping Dong was born on July 13, 1978 to Jinghuan Zhang and Wangliang Dong. Ping Dong was raised in Fushun city of Liaoning province at the northeast of China. Ping Dong began his education at Fushun Town 4th elementary school. After 6 years study, he enter Fushun City 25th middle school for 3 years study. After passing the high school entrance examination in 1994, he was admitted to Fushun City 2nd middle school for further education.

After 3 years’ study, Ping passed the national undergraduate entrance examination to begin his undergraduate study at Xiamen University in 1997. In this peaceful and beautiful coast city in the southeast of China, Ping spent 4 years on studying in chemistry. For his interest on the new arising research field of nano-chemistry at that time, he decided to pursue a graduate study on nano materials synthesis by electronic chemistry in Xiamen University. In 2001, Ping joined Professor Zhonhua Lin’s research group for studying the synthesis and growth mechanism of nano polyanaline in alumina template by electronic chemistry method where he began to show some interest on organic chemistry. After 3 years graduate study, he received M.S. degree in chemistry in 2004.

In the fall of 2005, Ping Dong joined Professor Fraser Fleming’s research group for organic graduate study in Duquesne University, Pittsburg of PA. He spent a year for studying the Grignard reagent addition on substrates containing nitrile group and found out that he was really fascinated on the total synthesis of nature products. Therefore, Ping joined Colorado State University at Fort Collins, CO in the fall of 2006 where luckily he
began his graduate study and research on the total synthesis of nature products in Wood Lab. Ping Dong will receive his Doctorate Degree at fall in 2010.