An (R)-4-Phenyl-1,3-oxazolidine-2-Thione Mediated Approach to 2, 3-Disubstituted Oxetanes and the Key Hydroxyethyl Isostere of the Hiv Protease Inhibitor Darunavir. Preparation of Non-evans Syn Glycolate Aldol Addition Products. A New Direction for the Curtius Rearrangement in the Dehomologation of Alpha-alkoxycarboxylic Acids

Jordan Michael Witte
Illinois State University, jordanwitte@gmail.com

Follow this and additional works at: https://ir.library.illinoisstate.edu/etd

Recommended Citation
https://ir.library.illinoisstate.edu/etd/1714

This Thesis is brought to you for free and open access by ISU ReD: Research and eData. It has been accepted for inclusion in Theses and Dissertations by an authorized administrator of ISU ReD: Research and eData. For more information, please contact ISUReD@ilstu.edu.
AN (R)-4-PHENYL-1,3-OXAZOLIDINE-2-THIONE MEDIATED APPROACH TO 2,3-DISUBSTITUTED OXETANES AND THE KEY HYDROXYETHYL ISOSTERE OF THE HIV PROTEASE INHIBITOR DARUNAVIR. PREPARATION OF NON-EVANS SYN GLYCOLATE ALDOL ADDITION PRODUCTS. A NEW DIRECTION FOR THE CURTIUS REARRANGEMENT IN THE DEHOMOLOGATION OF ALPHA-ALKOXYCARBOXYLIC ACIDS

JORDAN M. WITTE

160 Pages

Since the emergence of AIDS in the early 1980s, strategies to mitigate the disease have remained a high priority for medical professionals worldwide. While there is no broadly available cure or vaccine for HIV/AIDS at this time, early diagnosis and treatment can drastically reduce the severity of the infection. To this end, antiretroviral drugs are regularly employed to combat the virus and achieve HIV latency in infected patients. One such drug, Darunavir, has been used as a highly effective HIV protease inhibitor. Recently, a growing interest in derivatization of Darunavir to test for improved drug efficacy has prompted great efforts in the synthetic/medicinal chemistry community. However, synthetic constrictions of currently existing routes to Darunavir have made access to its analogues a difficult enterprise. The synthesis described herein is proposed to be an efficient, modular pathway to Darunavir that will allow for the easy production of derivative drug candidates. The discussion begins with the development of a non-Evans syn- asymmetric glycolate aldol addition reaction that serves as the foundation of the proposed synthesis.

KEYWORDS: Asymmetric synthesis; oxazolidine-2-thione; HIV; protease inhibitor; Darunavir.
AN (R)-4-PHENYL-1,3-OXAZOLIDINE-2-THIONE MEDIATED APPROACH TO 2,3-
DISUBSTITUTED OXETANES AND THE KEY HYDROXYETHYL ISOSTERE OF THE
HIV PROTEASE INHIBITOR DARUNAVIR. PREPARATION OF NON-EVANS SYN
GLYCOLATE ALDOL ADDITION PRODUCTS. A NEW DIRECTION FOR
THE CURTIUS REARRANGEMENT IN THE DEHOMOLOGATION
OF ALPHA-ALKOXYCARBOXYLIC ACIDS

JORDAN M. WITTE

A Thesis Submitted in Partial
Fulfillment of the Requirements
for the Degree of

MASTER OF SCIENCE

Department of Chemistry

ILLINOIS STATE UNIVERSITY

2023
AN (R)-4-PHENYL-1,3-OXAZOLIDINE-2-THIONE MEDIATED APPROACH TO 2,3-
DISUBSTITUTED OXETANES AND THE KEY HYDROXYETHYL ISOSTERE OF THE
HIV PROTEASE INHIBITOR DARUNAVIR. PREPARATION OF NON-EVANS SYN
GLYCOLATE ALDOL ADDITION PRODUCTS. A NEW DIRECTION FOR
THE CURTIUS REARRANGEMENT IN THE DEHOMOLOGATION
OF ALPHA-ALKOXYCARBOXYLIC ACIDS

JORDAN M. WITTE

COMMITTEE MEMBERS:
Shawn R. Hitchcock, Chair
Richard Nagorski
Gregory Ferrence
ACKNOWLEDGMENTS

Firstly, I must express my sincerest thanks to my research advisor, Dr. Shawn R. Hitchcock, for taking me under his wing over four years ago as I began my chemistry journey here at ISU. Words cannot adequately describe my gratitude towards him for mentoring me these past four years and providing such invaluable guidance throughout my research efforts. His energy, enthusiasm, and passion for his work has changed me for the better, and I would not be the same person I am today if not for his influence. I would like to thank him for his friendship, patience, and the nurturing environment he always cultivates around himself and others. He made my days (and nights!) working in the lab something to look forward to. It has truly been an awesome privilege to study under his leadership.

I am very thankful to Illinois State University and the Department of Chemistry for providing me with the education I need to head out into the world and be a successful chemist. I also would like to express my thanks to Mr. Emma Ayim, Daniel Wright, Austin Carter, Jasmine Service, and all the other students who worked with me on my projects and to all members of the Hitchcock group. I would like to also thank the faculty and staff at the Department of Chemistry - ISU, especially my thesis committee members, Dr. Richard Nagorski and Dr. Gregory Ferrence. To my ISU classmates: Cyrus Gudeman and Lizzi Lopez, I must express my gratitude as well. Their friendship, shared laughter, and frequent late nights together have given me many cherished memories. Last but most certainly not the least, I would like to thank my family. I am forever grateful to them for their love, prayers, and sacrifices they made in educating me and preparing me for my future.

J. M. W.
# CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACKNOWLEDGMENTS</td>
<td>i</td>
</tr>
<tr>
<td>CONTENTS</td>
<td>ii</td>
</tr>
<tr>
<td>TABLES</td>
<td>iv</td>
</tr>
<tr>
<td>FIGURES</td>
<td>v</td>
</tr>
<tr>
<td>SCHEMES</td>
<td>vi</td>
</tr>
<tr>
<td>CHAPTER I: A SURVEY OF THE ASYMMETRIC ALDOL REACTION MEDIATED BY EVANS-TYPE CHIRAL AUXILIARIES</td>
<td>1</td>
</tr>
<tr>
<td>Introduction</td>
<td>1</td>
</tr>
<tr>
<td>Asymmetric Glycolate Aldol Additions</td>
<td>6</td>
</tr>
<tr>
<td>Conclusions</td>
<td>11</td>
</tr>
<tr>
<td>CHAPTER II: DISCOVERY AND DEVELOPMENT OF A PROTOCOL FOR THE SYNTHESIS OF NON-EVANS SYN ALDOL ADDITION PRODUCTS USING A GLYCOLATE ALDOL REACTION</td>
<td>12</td>
</tr>
<tr>
<td>Introduction</td>
<td>12</td>
</tr>
<tr>
<td>Results and discussion</td>
<td>13</td>
</tr>
<tr>
<td>Experimental</td>
<td>23</td>
</tr>
<tr>
<td>General Remarks</td>
<td>23</td>
</tr>
<tr>
<td>General Procedure for the Asymmetric Glycolate Aldol Addition Reaction</td>
<td>26</td>
</tr>
<tr>
<td>CHAPTER III: SYNTHESIS OF CHIRAL 2,3-DISUBSTITUTED OXETANES</td>
<td>32</td>
</tr>
<tr>
<td>Introduction</td>
<td>32</td>
</tr>
<tr>
<td>Goal of research</td>
<td>36</td>
</tr>
<tr>
<td>Results and discussion</td>
<td>39</td>
</tr>
</tbody>
</table>
TABLES

Table 2.1: Diastereoselective glycolate addition reactions.  
Table 4.1: Optimization of conditions for the bis-sulfonylation reaction.
<table>
<thead>
<tr>
<th>Figure</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Figure 1.1: General reaction for the aldol addition.</td>
<td>1</td>
</tr>
<tr>
<td>Figure 1.2: Some common, commercially available Evans-type chiral auxiliaries.</td>
<td>3</td>
</tr>
<tr>
<td>Figure 1.3: Possible outcomes of the aldol reaction and their respective designations.</td>
<td>6</td>
</tr>
<tr>
<td>Figure 1.4: Model substrate for asymmetric glycolate aldol reactions.</td>
<td>7</td>
</tr>
<tr>
<td>Figure 1.5: Structure of Aflastatin A.</td>
<td>8</td>
</tr>
<tr>
<td>Figure 1.6: The Putative structure of Chagosensine.</td>
<td>9</td>
</tr>
<tr>
<td>Figure 2.1: Structure of the auxiliary acylated carbonyl with p-methoxyphenoxy glycolate protecting group attached.</td>
<td>12</td>
</tr>
<tr>
<td>Figure 2.2: Four possible products of the aldol addition reaction using the oxazolidine-2-thione chiral auxiliary.</td>
<td>16</td>
</tr>
<tr>
<td>Figure 2.3: Hydrolyzed aldol adducts with their respective optical rotations.</td>
<td>17</td>
</tr>
<tr>
<td>Figure 2.4: X-Ray crystal structure of the isolated aldol adduct (2.10b).</td>
<td>17</td>
</tr>
<tr>
<td>Figure 2.5: Favored conformations of the potential aldol addition products and the orientation of the vicinal protons.</td>
<td>21</td>
</tr>
<tr>
<td>Figure 3.1: Structure of paclitaxel (Taxol) with the essential oxetane group highlighted.</td>
<td>32</td>
</tr>
<tr>
<td>Figure 3.2: Structure of some naturally occurring oxetane compounds.</td>
<td>33</td>
</tr>
<tr>
<td>Figure 3.3: Conversion of thalidomide’s critical carbonyl to an oxetane.</td>
<td>34</td>
</tr>
<tr>
<td>Figure 3.4: 500 MHz $^1$H NMR spectrum of 3.25 with heterocyclic protons assigned.</td>
<td>44</td>
</tr>
<tr>
<td>Figure 3.5: Series of additional oxetanes to be prepared.</td>
<td>45</td>
</tr>
<tr>
<td>Figure 4.1: HIV-1 protease enzyme illustrating the mechanism of the catalytic dyad active site.</td>
<td>52</td>
</tr>
<tr>
<td>Figure 4.2: Structure of HIV protease inhibitor, Darunavir (left), and HIV-1 protease active site complexed with Darunavir (right).</td>
<td>53</td>
</tr>
</tbody>
</table>
Figure 4.3. Key domains of Darunavir, with the P1/P1’ & P2/P2’ regions highlighted. 54

Figure 4.4: Examples of Darunavir derivatives. 55

Figure 4.5: X-ray crystal structure of aldol adduct (enantiomer of 4.15). 59

Figure 4.6: Diastereotopic methyl groups of the isobutylamine P1’ ligand as observed in the 500 MHz proton NMR spectrum of 4.16. 61

Figure 4.7: Isolated Staudinger intermediate, a phosphine imide (4.31). 68

Figure 4.8: High resolution mass spectrum of the crude extract of 4.20. 71

Figure 4.9: Some Darunavir analogues the Hitchcock group intends to prepare. 74

Figure 5.1: 500 MHz ¹H NMR spectrum of the crude extract from the test Curtius dehomologation. 95

Figure 5.2: 500 MHz ¹H NMR spectrum of the crude reaction mixture using alpha-methoxyphenylacetic acid (5.30). 96

Figure 5.3: High resolution mass spectrum of the Schiff base product (5.35). 100

Figure 5.4: High resolution mass spectrum of alpha-methoxy isocyanate (5.40). 103

Figure 5.5: X-ray crystal structure of 5.42. 106

Figure 5.6: X-ray crystal structure of 5.49. 108
<table>
<thead>
<tr>
<th>Scheme</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scheme 1.1:</td>
<td>Decarboxylative asymmetric aldol reaction mediated by a chiral catalyst.</td>
<td>2</td>
</tr>
<tr>
<td>Scheme 1.2:</td>
<td>Example reaction of an auxiliary acylation and subsequent asymmetric aldol using an Evans-type chiral oxazolidinone.</td>
<td>4</td>
</tr>
<tr>
<td>Scheme 1.3:</td>
<td>Proposed chair-like transition state of an Evans aldol reaction.</td>
<td>5</td>
</tr>
<tr>
<td>Scheme 1.4:</td>
<td>One of the asymmetric glycolate aldol reactions employed by Evans and coworkers towards the synthesis of Aflastatin A.</td>
<td>8</td>
</tr>
<tr>
<td>Scheme 1.5:</td>
<td>Asymmetric glycolate aldol reaction used by Heinrich and coworkers.</td>
<td>9</td>
</tr>
<tr>
<td>Scheme 1.6:</td>
<td>Asymmetric aldol reaction reported by Mellado-Hidalgo.</td>
<td>10</td>
</tr>
<tr>
<td>Scheme 2.1:</td>
<td>Acylation of the oxazolidine-2-thione with p-methoxyphenoxyacetic acid.</td>
<td>13</td>
</tr>
<tr>
<td>Scheme 2.2:</td>
<td>Asymmetric glycolate aldol addition as reported by Crimmins and McDougall, 2003, showing the non-Evans anti-diastereomer as the favored product after proceeding through the proposed open transition state.</td>
<td>15</td>
</tr>
<tr>
<td>Scheme 2.3:</td>
<td>Asymmetric glycolate aldol attempted using the p-methoxyphenoxy system, depicting the anticipated non-Evans anti-stereochemistry.</td>
<td>16</td>
</tr>
<tr>
<td>Scheme 2.4:</td>
<td>Proposed alternate mechanism for the formation of the non-Evans syn-product.</td>
<td>22</td>
</tr>
<tr>
<td>Scheme 3.1:</td>
<td>Intramolecular oxetane ring-opening in ascospiroketal total synthesis.</td>
<td>35</td>
</tr>
<tr>
<td>Scheme 3.2:</td>
<td>Proposed route to chiral oxetanes using an asymmetric aldol reaction.</td>
<td>37</td>
</tr>
<tr>
<td>Scheme 3.3:</td>
<td>Potential byproducts of the sulfonylation reaction.</td>
<td>38</td>
</tr>
<tr>
<td>Scheme 3.4:</td>
<td>Formation of the model aldol system for the oxetane proof of concept.</td>
<td>40</td>
</tr>
<tr>
<td>Scheme 3.5:</td>
<td>Reductive cleavage of the chiral auxiliary with the release of diol (3.19).</td>
<td>40</td>
</tr>
<tr>
<td>Scheme 3.6:</td>
<td>Attempted chemoselective sulfonylation of 3.19, resulting in formation of several byproducts (3.22) (3.23).</td>
<td>41</td>
</tr>
</tbody>
</table>
Scheme 3.7: Putative effect of DMAP displacement catalyst on the NsCl (3.20) substrate.

Scheme 3.8: Cyclization reaction to form oxetane (3.25).

Scheme 3.9: Example cyclization of a 1,3-diol under Mitsunobu conditions.

Scheme 4.1: The industrial synthetic pathway to Darunavir.

Scheme 4.2: The Hitchcock group’s proposed synthetic pathway to Darunavir.

Scheme 4.3: Cyclization of D-phenylglycinol (4.12) to the chiral auxiliary (4.13).

Scheme 4.4: Acylation of 4.13 with 4-methoxyphenoxyacetic acid (4.23).

Scheme 4.5: Asymmetric titanium mediated glycolate aldol with phenylacetaldehyde.

Scheme 4.6: Trans-amidation of the aldol adduct (4.15) using isobutylamine (4.24).

Scheme 4.7: Reduction of the amide (4.16) to an amine (4.17).

Scheme 4.8: Bis-nosylation of amino alcohol (4.17).

Scheme 4.9: Nucleophilic substitution reaction using sodium azide.

Scheme 4.10: Originally proposed route to Darunavir.

Scheme 4.11: Results of the attempted hydrogenation reaction.

Scheme 4.12: Attempted Staudinger reaction on 4.19.

Scheme 4.13: Deprotection of the azide substrate.

Scheme 4.14: Mechanism of deprotection for the p-methoxyphenoxy group.

Scheme 4.15: Reduction of the deprotected azido alcohol substrate.

Scheme 4.16: Acylation of the hydroxy ethyl isostere of Darunavir with the P2 ligand.


Scheme 5.1: The Curtius rearrangement.

Scheme 5.2: The proposed alternative route for the Curtius rearrangement.
Scheme 5.3: Potential outcomes from the use of a leaving group that is too labile. 90

Scheme 5.4: Curtius dehomologation by the application of alkoxy leaving groups. 92

Scheme 5.5: Trapping intermediates in the proposed Curtius dehomologation reaction. 93

Scheme 5.6: Isocyanate trapping to yield carbamate esters and urea derivatives. 94

Scheme 5.7: Alternate Curtius dehomologation using (COCl)$_2$ and NaN$_3$. 97

Scheme 5.8: Attempted capture of the isocyanate using an amine nucleophile. 98

Scheme 5.9: Reattempted formation of urea 5.32 using DPPA conditions. 99

Scheme 5.10: Attempted isocyanate capture using methanol via the DPPA method. 100

Scheme 5.11: Low temperature acyl azide synthesis resulting in formation of isocyanate. 102

Scheme 5.12: Milder Curtius rearrangement to capture isocyanate. 105

Scheme 5.13: Potential pathway taken by 5.43 to give diazo compound (5.49). 107
CHAPTER I: A SURVEY OF THE ASYMMETRIC ALDOL REACTION MEDIATED BY EVANS-TYPE CHIRAL AUXILIARIES

Introduction

The aldol addition reaction is a well-known and extensively employed means of forming new carbon-carbon bonds in organic chemistry.\textsuperscript{1a-c} Fundamentally, the aldol addition involves the reaction between enolizable carbonyl compounds with aldehydes or ketones, the products of which are \(\beta\)-hydroxy carbonyl compounds. Depending on the conditions used, the reaction may also lead to the formation of condensation products – \(\alpha,\beta\)-unsaturated carbonyl compounds. For the addition reaction, a key component of interest lies in the selective synthesis of certain stereoisomers, since the adducts that are formed can introduce up to two new stereogenic centers depending on the initial level of substitution of the enolizable carbonyl compound (Figure 1.1).

\[ \begin{array}{c}
\text{R}^1\text{\begin{tikzpicture}
  \node at (0,0) [shape=circle,draw,fill=white,minimum size=10pt] (center) {\text{H}};
  \node at (-0.5,0.5) [shape=circle,draw,fill=white,minimum size=10pt] (top) {\text{R}^2};
  \node at (-0.5,-0.5) [shape=circle,draw,fill=white,minimum size=10pt] (bottom) {\text{R}^1};
  \node at (0.5,0.5) [shape=circle,draw,fill=white,minimum size=10pt] (right) {\text{H}};
  \node at (0.5,-0.5) [shape=circle,draw,fill=white,minimum size=10pt] (left) {\text{R}^2};
  \draw (center) -- (top);
  \draw (center) -- (bottom);
  \draw (center) -- (right);
  \draw (center) -- (left);
\end{tikzpicture}} \\
\text{+} \\
\text{\begin{tikzpicture}
  \node at (0,0) [shape=circle,draw,fill=white,minimum size=10pt] (center) {\text{H}};
  \node at (-0.5,0.5) [shape=circle,draw,fill=white,minimum size=10pt] (top) {\text{R}^3};
  \node at (-0.5,-0.5) [shape=circle,draw,fill=white,minimum size=10pt] (bottom) {\text{R}^3};
  \node at (0.5,0.5) [shape=circle,draw,fill=white,minimum size=10pt] (right) {\text{R}^3};
  \node at (0.5,-0.5) [shape=circle,draw,fill=white,minimum size=10pt] (left) {\text{R}^2};
  \draw (center) -- (top);
  \draw (center) -- (bottom);
  \draw (center) -- (right);
  \draw (center) -- (left);
\end{tikzpicture}} \\
\text{aldol addition} \\
\rightarrow \\
\text{\begin{tikzpicture}
  \node at (0,0) [shape=circle,draw,fill=white,minimum size=10pt] (center) {\text{H}};
  \node at (-0.5,0.5) [shape=circle,draw,fill=white,minimum size=10pt] (top) {\text{R}^2};
  \node at (-0.5,-0.5) [shape=circle,draw,fill=white,minimum size=10pt] (bottom) {\text{R}^2};
  \node at (0.5,0.5) [shape=circle,draw,fill=white,minimum size=10pt] (right) {\text{R}^1};
  \node at (0.5,-0.5) [shape=circle,draw,fill=white,minimum size=10pt] (left) {\text{R}^3};
  \draw (center) -- (top);
  \draw (center) -- (bottom);
  \draw (center) -- (right);
  \draw (center) -- (left);
  \node at (0.25,0.25) {\text{\textsuperscript{*}}};
  \node at (0.25,-0.25) {\text{\textsuperscript{*}}};
\end{tikzpicture}} \\
\text{R}^3
\] 

\textbf{Figure 1.1:} General reaction for the aldol addition. New stereocenters are denoted with an asterisk.

This added synthetic complexity gave rise to major efforts to develop effective, controllable methods to access these adducts with high stereoselectivity. The ability to selectively synthesize systems of a particular stereochemistry is extremely valuable since certain stereoisomers can exhibit differential biological activities.
One such method of exerting stereochemical control lies in the application of chiral catalysts, wherein a chiral molecule (such as chiral transition metal complex or chiral organocatalyst, for example) can coordinate or interact with a substrate to promote a chemical reaction and dictate the stereochemistry of the reaction product.¹ For example, in 2023, Rahman and co-workers developed a mild, highly selective catalytic decarboxylative aldol reaction using chiral salen ligands (1.2a-b) (Scheme 1.1).²

![Scheme 1.1](image)

**Scheme 1.1**: Decarboxylative asymmetric aldol reaction mediated by a chiral catalyst.

In contrast, compounds called chiral auxiliaries – which are of interest to the Hitchcock research group and the focus of this introduction – are temporary chiral functional groups that are
attached to a substrate molecule and used to control the stereochemical outcome of a subsequent reaction (i.e., the aldol addition). The chiral auxiliary is then removed after the reaction, leaving the substrate with the desired stereochemistry.

Chiral oxazolidine-2-thiones and thiazolidine-2-thiones, which are derivatives of the well-known Evans oxazolidinones \(^{3a}\) (Figure 1.2), have been applied to many stereoselective transformations, including aldol reactions (Scheme 1.2). The seminal work by Evans et al. in 1981 paved the way for extensive studies into the nature of these systems.\(^{3b}\)

\begin{figure}[h]
\centering
\begin{tikzpicture}
\node[below=of current bounding box] {1.4};
\node[below=of current bounding box] {1.5};
\node[below=of current bounding box] {1.6};
\node[below=of current bounding box] {1.7};
\end{tikzpicture}
\caption{Some common, commercially available Evans-type chiral auxiliaries.} \end{figure}
Scheme 1.2: Example reaction of an auxiliary acylation and subsequent asymmetric aldol using an Evans-type chiral oxazolidinone.

One model for the observed stereoselectivity of the aldol addition reaction, first proposed by Howard Zimmerman and Marjorie Traxler in 1957, suggests that the aldol proceeds through a chair-like transition state which occurs between the preferred (Z)-enolate of 1.10 and the aldehyde substrate. The arrangement of the aldehyde within the chair-like transition state minimizes the pseudo 1,3-diaxial interactions with the enolate species, resulting in the preferential formation of the favored stereoisomer (Scheme 1.3).
Scheme 1.3: Proposed chair-like transition state of an Evans aldol reaction.

Depending on the nature of the chiral auxiliary, acylated carbonyl species, the electrophile, and the enolization method used, the ultimate stereochemistry favored for a given system can be manipulated to provide the desired product. Concerning the proper nomenclature of the various possible stereoisomers produced, the aldol adducts may be designated as either Evans- or Non-Evans- depending on how the stereochemistry of a given system aligns with Evans’ original work.³⁵ Generally, for asymmetric aldol addition reactions that produce two new stereocenters, four possible designations are used (Figure 1.3).
Asymmetric Glycolate Aldol Additions

A significant variation on the chiral auxiliary guided asymmetric aldol addition involves the introduction of a protected hydroxy group to the alpha-position of the enolizable carbonyl species (Figure 1.4). These systems – prepared through the coupling of a selected chiral auxiliary with an alpha-alkoxy or alpha-phenoxy carboxylic acid – offer a versatile approach for the synthesis of a diverse array of natural products.⁶⁻⁸
Figure 1.4: Model substrate for asymmetric glycolate aldol reactions.

A key component of interest in these glycolate aldol reactions lies in their ability to prepare variably protected diols as their end products. Depending on the planned synthesis, these glycolate protecting groups (R-group from Figure 1.4) may be selected for on the basis of robustness, functional group tolerance, and ease of removal. Some common glycolate protecting groups include methyl groups, benzyl groups, the related p-methoxybenzyl groups, and allylic groups. Less commonly used but of great interest to the Hitchcock research group is the p-methoxyphenoxy protecting group, which presents excellent robustness and is easily removed in the presence of a variety of functional groups.

Recent examples of asymmetric glycolate aldol reactions demonstrate the ongoing utility these reactions offer synthetic organic chemists. In 2022, Evans et al. employed multiple iterative asymmetric glycolate aldol reactions in their synthetic route towards Aflastatin A (Figure 1.5) (Scheme 1.4), a natural product first isolated from the mycelial extract of Streptomyces sp. MRI142.
Figure 1.5: Structure of Aflastatin A.

Scheme 1.4: One of the asymmetric glycolate aldol reactions employed by Evans and coworkers towards the synthesis of Aflastatin A. [Adapted with permission from Evans et al. J. Am. Chem. Soc. 2022, 144, 43, 19953–19972. Copyright 2023 American Chemical Society.]

Likewise, in 2020 Heinrich et al. reported on their efforts towards the synthesis of unusual natural product Chagosensine (Figure 1.6), also utilizing an auxiliary-controlled syn-selective glycolate aldol addition (Scheme 1.5). It was through these studies that the originally proposed structure of Chagosensine came under question. Later, during the same synthesis, an anti-glycolate aldol reaction was used to install the “southern” building block of the molecule.
**Figure 1.6:** The putative structure of Chagosensine. The key region Heinrich and coworkers accessed through an auxiliary-mediated asymmetric glycolate aldol is highlighted.

**Scheme 1.5:** Asymmetric glycolate aldol reaction conditions used by Heinrich and coworkers.
Finally, in 2023, a report on the direct and asymmetric syn-aldol reactions of N-acyl-1,3-oxazinane-2-thiones with dialkyl acetals was reported by Mellado-Hidalgo and colleagues.¹⁵ These reactions were carried out in the presence of 2-5 mol % [DTBM-SEGPHOS]NiCl₂ ((R)-(-)-5,5′-Bis[di(3,5-di-tert-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole, [(4R)-(4,4′-bi-1,3-benzodioxole)-5,5′-diyl]bis[bis(3,5-di-tert-butyl-4-methoxyphenyl)phosphine] 1.22), a chiral catalyst (Scheme 1.6). Interestingly, the oxazinane-2-thione heterocycle was not used as a chiral auxiliary in this case, but rather as a scaffold for the chiral catalyst to coordinate upon, demonstrating the versatility of these heterocycles even without intrinsic chirality.

Scheme 1.6: Asymmetric aldol reaction reported by Mellado-Hidalgo.
Conclusions

To date, asymmetric aldol reactions mediated by chiral auxiliaries are one of the most valuable and strategically important methods for C-C bond formation. The significance of the aldol reaction in constructing chiral building blocks for sophisticated small molecules has spurred ongoing efforts towards the development of improved methods of diastereo- and enantiocontrol. At the time of this writing, the asymmetric glycolate aldol addition reaction remains of high importance for the Hitchcock research group. Described in this thesis are some of the recent projects the group has undertaken. In Chapter 2, a discussion regarding the discovery and subsequent investigation regarding an unexpected stereochemical outcome of an aldol system is presented. In Chapter 3, the preliminary findings of a proposed asymmetric aldol route to chiral oxetanes are examined. Finally, in Chapter 4, the use of an asymmetric glycolate aldol towards the development of a more versatile, modular synthesis of HIV-1 protease inhibitor Darunavir and analogues is described.
CHAPTER II: DISCOVERY AND DEVELOPMENT OF A PROTOCOL FOR THE SYNTHESIS OF NON-EVANS SYN ALDOL ADDITION PRODUCTS USING A GLYCOLATE ALDOL REACTION

Introduction

In connection with an ongoing project focused on the application of the asymmetric glycolate aldol reaction towards the synthesis of anti-malarial agents, the Hitchcock research group became interested in pursuing the development of an anti-selective glycolate addition reaction. In 2003, Crimmins and McDougall had demonstrated that a titanium mediated anti-selective glycolate aldol addition reaction was viable.\textsuperscript{16} The Hitchcock group wanted to explore the possibility of using the Crimmins methodology with a previously developed \textit{p}-methoxyphenoxy glycolate system (2.1) (Figure 2.1), wherein the choice in using \textit{p}-methoxyphenoxy for the glycolate group is due to its robust character as a protecting group.\textsuperscript{17}

![Figure 2.1](image)

**Figure 2.1**: Structure of the auxiliary acylated carbonyl with \textit{p}-methoxyphenoxy glycolate protecting group attached.
To this end, an investigation was launched to determine if this proposed utilization of the Crimmins methodology would be viable. Based on the literature precedent, it was anticipated that these efforts would proceed with relative ease. However, later experiments would begin to introduce uncertainty in the putative mechanistic pathway of the glycolate aldol and raise questions about the reactivity differential of the $p$-methoxyphenoxy glycolate system. In this chapter, details of this investigation are discussed.

**Results and Discussion**

To prepare the auxiliary-bound $p$-methoxyphenoxy glycolate substrate (2.1) for investigation, an acylation between (S)-oxazolidine-2-thione and $p$-methoxyphenoxyacetic acid was carried out using a carbodiimide approach similar to that which was previously described by Andrade and coworkers.$^{18}$ Unlike Andrade’s protocol, which employs $N,N'$-dicyclohexyl carbodiimide (DCC) as the coupling agent, it was decided to use the related compound 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) in its place (Scheme 2.1).

![Scheme 2.1: Acylation of the oxazolidine-2-thione with $p$-methoxyphenoxyacetic acid.](image-url)
The popularity of using EDC as opposed to alternative coupling reagents such as DCC or DIC arises from its urea byproduct, which is easily removed through acidic workup owing to its water solubility. By contrast, the urea byproducts from di-alkyl carbodiimides are insoluble in water and often require chromatographic separation.

After the acylated heterocycle had been obtained, it was carried through an asymmetric aldol reaction using the Crimmins methodology (Scheme 2.2). Upon treatment of 2.1 with titanium tetrachloride at -78 °C, it was subsequently enolized by the addition of one equivalent of triethylamine. This deviation from the Crimmins protocol – in which alkaloid (-)-sparteine was the selected base – was not pursued due to the lack of commercial availability. Although, the exact nature of the non-nucleophilic base (TMEDA (tetramethylethlenediamine), triethylamine, Hünig’s base, etc.) does not affect the stereochemical outcome of the asymmetric aldol reaction, so this deviation was deemed inconsequential. Following the enolization, the system was treated with an additional 3 equivalents of titanium tetrachloride, and freshly distilled phenylacetaldehyde (PhCH₂CHO) was added to complete the addition (Scheme 2.3). Of the four possible stereoisomers possible, the outcome of this reaction was anticipated to yield the non-Evans anti-isomer (2.10d) as the major product (Figure 2.2). The product of this reaction was readily isolated as a crystalline solid in good yield (79%), but unexpectedly did not possess the desired non-Evans anti-stereochemistry. Hydrolysis and subsequent polarimetric evaluation of the isolated product versus an archived Evans syn-adduct previously synthesized revealed optical rotations of nearly identical magnitude (Figure 2.3), strongly suggesting syn-stereochemistry of the adduct. To conclusively determine the absolute and relative
stereochemistries of the product, X-ray diffractometry was conducted and confirmed the adduct as the non-Evans syn-diastereomer (2.10b) (Figure 2.4).

Scheme 2.2: Asymmetric glycolate aldol addition as reported by Crimmins and McDougall, 2003, showing the non-Evans anti-diastereomer as the favored product after proceeding through the proposed open transition state.
 Scheme 2.3: Asymmetric glycolate aldol attempted using the $p$-methoxyphenoxy system, depicting the anticipated non-Evans *anti*- stereochemistry.

**Figure 2.2:** Four possible products of the aldol addition reaction using the oxazolidine-2-thione chiral auxiliary.
Figure 2.3: Hydrolyzed aldol adducts with their respective optical rotations.  

\[ \alpha \]_D^{24} = -45.8 
(CHCl₃, c = 0.100). 

\[ \alpha \]_D^{24} = -46.1 
(CHCl₃, c = 0.95).

Figure 2.4: X-Ray crystal structure of the isolated aldol adduct (2.10b). (Courtesy of Dr. Gregory Ferrence, Department of Chemistry, Illinois State University)
Based on the observed stereochemistry of the aldol adduct, investigations as to the origins of the deviant selectivity were initiated. Concerns grew that the 4 total equivalents of titanium tetrachloride used over the course of the reaction may have triggered an alternate favored transition state. However, upon repeating the previous reaction (Scheme 2.3) with reduced equivalents of TiCl₄ (1-3 additional eq.), it was determined through ¹H NMR analysis of the crude extracts that the non-Evans syn-diastereomer (2.10b) was consistently formed as the major product. Furthermore, it was also determined that 2 total equivalents of TiCl₄ (1 in the first stage, 1 in the second stage) afforded the best yields of product with the greatest diastereoselectivity (>95%).

With the cause of the deviant diastereoselectivity still elusive, attention turned to the aldehyde substrate. To determine if the non-Evans syn-selectivity was a consequence of the chosen aldehyde, a series of aldol addition reactions using various aliphatic, unsaturated, and aromatic aldehydes were performed. The results are summarized in Table 2.1. The observed diastereoselectivities for each successful reaction were determined to also be in excess of 95%.
Table 2.1: Diastereoselective glycolate addition reactions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Product</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhCH&lt;sub&gt;2&lt;/sub&gt;CHO</td>
<td>2.10b</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>PhCH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;CHO</td>
<td>2.13a</td>
<td>46</td>
</tr>
<tr>
<td>3</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;CHO</td>
<td>2.13b</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;CHCHO</td>
<td>2.13c</td>
<td>53</td>
</tr>
<tr>
<td>5</td>
<td>(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;CHCH&lt;sub&gt;2&lt;/sub&gt;CHO</td>
<td>2.13d</td>
<td>53</td>
</tr>
<tr>
<td>6</td>
<td>(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;CCHO</td>
<td>2.13e</td>
<td>n/a</td>
</tr>
<tr>
<td>7</td>
<td>trans-PhCH=CHCHO</td>
<td>2.13f</td>
<td>68</td>
</tr>
<tr>
<td>8</td>
<td>p-NCC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;CHO</td>
<td>2.13g</td>
<td>79</td>
</tr>
<tr>
<td>9</td>
<td>p-BrC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;CHO</td>
<td>2.13h</td>
<td>43</td>
</tr>
<tr>
<td>10</td>
<td>p-NO&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;CHO</td>
<td>2.13i</td>
<td>63</td>
</tr>
<tr>
<td>11</td>
<td>(CH&lt;sub&gt;2&lt;/sub&gt;O)&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;3&lt;/sub&gt;CHO</td>
<td>2.13j</td>
<td>64</td>
</tr>
<tr>
<td>12</td>
<td>2,4-MeOC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;3&lt;/sub&gt;CHO</td>
<td>2.13k</td>
<td>n/a</td>
</tr>
<tr>
<td>13</td>
<td>2-C&lt;sub&gt;10&lt;/sub&gt;H&lt;sub&gt;7&lt;/sub&gt;CHO</td>
<td>2.13l</td>
<td>n/a</td>
</tr>
</tbody>
</table>

<sup>a</sup>All yields are derived from purified compounds (recrystallization or flash chromatography.)
The relative stereochemistries of the isolated glycolate aldol adducts were determined through analysis of the 500 MHz $^1$H NMR spectra. The basis for these assignments stems from an understanding of the Karplus relationship.\textsuperscript{21} The Karplus relationship (or Karplus equation) describes the correlation between the NMR coupling constants ($^3J$) and the dihedral torsion angles between vicinal protons (Figure 2.5). The coupling constants of $\textit{syn}$- and $\textit{anti}$- aldol products are well-documented across many systems,\textsuperscript{22} with $\textit{syn}$- aldol addition products typically having coupling constants ($J$) of 2-6 Hz, and $\textit{anti}$- aldol addition products having coupling constants that typically range between 7-10 Hz. For the synthesized aldol adducts, the coupling constants of the alpha-position protons were measured to span between 1.8 – 3.8 Hz, strongly suggesting $\textit{syn}$- selectivity for all examples (excluding 3 failed reactions – entries 6, 12, & 13 – purportedly due to steric bulk of the selected aldehyde, although these analyses are still ongoing). Furthermore, through comparison of the $^1$H NMR spectra of the putative non-Evans $\textit{syn}$- adducts summarized in Table 2.1 versus those of archival Evans $\textit{syn}$- adducts the Hitchcock group had previously prepared,\textsuperscript{23} the absolute stereochemistries were deduced to possess a non-Evans $\textit{syn}$-configuration.
Figure 2.5: Favored conformations of the potential aldol addition products and the orientation of the vicinal protons.

With these results in hand, it can now be proposed that the N-p-methoxyphenoxacycloxazolidine-2-thione (2.1) does not follow the same mechanistic pathway as proposed by Crimmins and McDougall.\textsuperscript{16} A new argument may be made that the p-methoxyphenoxoglycolate protecting group that causes the alternate route to be followed. One putative mechanistic pathway is illustrated in Scheme 2.4, wherein the -OPMP group, due either to its steric volume or lower capacity for coordination with the TiCl\textsubscript{4} (or some combination thereof), causes a closed transition state (2.14) to be favored. This pathway would give rise to the non-Evans syn- result.
Scheme 2.4: Proposed alternate mechanism for the formation of the non-Evans syn-product. This mechanism suggests a closed transition state, as opposed to the open TS for which Crimmins and McDougall argued.
Experimental

General Remarks:

Unless otherwise noted, all chemical agents and solvents were purchased and used without further purification. All reactions were conducted under a dried nitrogen atmosphere in either flame or oven dried glassware. Unless otherwise noted, all $^1$H and proton decoupled $^{13}$C NMR spectra were collected in deuterated chloroform (CDCl₃) using a Bruker Ultra-shield Avance III NMR spectrometer operating at either 500 MHz of 400 MHz ($^1$H NMR) and 125 MHz or 100 MHz ($^{13}$C NMR), respectively. Chemical shifts were reported in parts per million ($\delta$ scale) and coupling constant ($J$ values) are reported in Hertz (Hz). Tetramethylsilane (TMS) was used as an internal standard ($\delta = 0$ ppm). Optical rotation data were collected on a JASCO P-1010 digital polarimeter operating at 589 nm in an 8 × 100 nm cell. Infrared spectra were recorded using NaCl plates. IR values are reported in reciprocal centimeters (cm⁻¹) and were measured either as a nujol mull or as a neat liquid film from an evaporated chloroform solution. For ESI-HRMS, samples were prepared in concentrations of 5-25 ppm in high-performance liquid chromatography grade methanol/water/formic acid (1:1:0.01). Melting points were recorded on a Mel-Temp apparatus. High resolution mass spectra were obtained using a ThermoScientific Q-Exactive ESI mass spectrometer equipped with an Orbitrap mass analyzer. The parts per million (ppm) mass error is reported as the absolute value.
(4S)-4-Phenyl-1,3-oxazolidine-2-thione (2.2). To a flame-dried, nitrogen-purged 1000 mL round bottom flask fitted with a Claisen adapter with a pressure equalizing addition funnel and a condenser and equipped with a large stir bar were added L-phenylglycinol (13.72 g, 100.0 mmol), ethanol (100 mL), potassium carbonate (6.95 g, 50.0 mmol), and carbon disulfide (12.1 mL, 200 mmol). The reaction was heated (50 °C) using a heating mantle and a variable transformer, and hydrogen peroxide (17 mL, 150 mmol) was added dropwise. The reaction becomes very exothermic during the addition of hydrogen peroxide. The reaction mixture was stirred for a period of 15 min. The reaction mixture was cooled to ambient temperature and gravity filtered into a 500 mL round bottom flask. The residue from the reaction flask was washed with ethyl acetate (3 × 80 mL), combined with the filtered reaction mixture, and the solvent was removed by rotary evaporation. The residue was re-dissolved in ethyl acetate (200 mL) and extracted with HCl (2 × 50 mL). The organic layer was washed with brine (20 mL), dried over MgSO₄, and filtered. The solvent was removed by rotary evaporation, and the crude product was recrystallized using hexanes and ethyl acetate to yield the product as a yellow, crystalline solid (13.7 g, 76.5 mmol, 77% yield). Melting point: 121 – 123 °C. [α]D²³ = +71.6 (c = 0.100, CHCl₃). ¹H NMR (500 MHz, CDCl₃): δ 7.71 (s, 1H), 7.46-7.32 (m, 5H), 5.12 (dd, J = 8.9, 7.0 Hz, 1H), 5.00 (app. triplet, J = 8.9 Hz, 1H), 4.49 (dd, J = 8.9, 7.0 Hz, 1H) ppm. ¹³C {¹H} NMR (125 MHz, CDCl₃): δ 189.7, 138.0, 129.2, 129.2, 126.3, 77.7, 60.2 ppm. IR (mineral oil): 1519, 1215, 1167, 761, 699 cm⁻¹. ESI-HRMS m/z: [M + H]⁺ calcd for C₉H₉NNaOS⁺, 202.0297; found, 202.0294. Mass error = 1.5 ppm.
(4S)-3-[(p-Methoxyphenoxy)acetyl]-4-phenyl-1,3-oxazolidine-2-thione (2.1). To a flame-dried, nitrogen-purged 1000 mL round bottom flask equipped with a stir bar were added oxazolidine-2-thione (2.2) (11.07 g, 61.4 mmol), methylene chloride (200 mL), p-methoxy phenoxy acetic acid (11.24 g, 61.4 mmol), EDC (12.9 g, 67.5 mmol), and DMAP (1.90 g, 15.4 mmol). The reaction mixture was stirred overnight and then extracted. The reaction mixture was sequentially treated with HCl (1 M, 50 mL), NaOH (1 M, 2 × 50 mL), and brine (50 mL). The organic layer was collected, dried over MgSO₄, and gravity filtered. The solvent was removed by rotary evaporation. The crude product was recrystallized using ethyl acetate and hexanes to afford the product as a crystalline solid (17.53 g, 83%). Mp: 108 – 109 °C. [α]D²³ = +83.2 (CHCl₃, c = 1.00). ¹H NMR (400 MHz, CDCl₃): δ 7.40-7.30 (m, 5H), 6.82-6.76 (m, 4H), 5.73 (dd, J = 9.0, 3.3 Hz, 1H), 5.57 (d, J = 17.7 Hz, 1H), 5.45 (d, J = 17.7 Hz, 1H), 4.90 (triplet, J = 9.0 Hz, 1H), 4.58 (dd, J = 9.0, 3.3 Hz, 1H), 3.74 (s, 3H) ppm. ¹³C {¹H} NMR (100 MHz, CDCl₃): δ 185.0, 168.9, 154.5, 151.8, 138.2, 129.3, 129.0, 126.3, 115.9, 114.7, 75.4, 70.2, 62.0, 55.7 ppm. IR (CHCl₃): 1724, 1211, 821, 780 cm⁻¹. ESI-HRMS m/z: [M + Na]⁺ calcd for C₁₈H₁₇NNaO₄S⁺, 366.0770; found, 366.0777. Mass error = 1.9 ppm.
General Procedure for the Asymmetric Glycolate Aldol Addition Reaction:

To a flame-dried, nitrogen-purged 1000 mL round bottom flask equipped with a large stir bar were added acylated thione (2.1) (3.00 g, 8.73 mmol), and anhydrous methylene chloride (300 mL). The reaction vessel was chilled to -78 °C with a dry ice/ethanol bath, and titanium tetrachloride (1 M in CH₂Cl₂, 9.6 mL, 9.6 mmol) was added dropwise by syringe. This solution was stirred for 30 min, at which point triethylamine (2.7 mL, 19.2 mmol) was added by syringe. The color of the solution transitioned from an amber color to that of deep purple upon addition of triethylamine. This solution was stirred for 30 minutes, at which point another addition of titanium tetrachloride (9.6 mL, 9.6 mmol) was added via syringe. Care was taken to ensure that the -78 °C temperature was maintained throughout these additions. The reaction was stirred for a final 30-minute interval, at which point the aldehyde (19.2 mmol) was added to the reaction vessel. The reaction mixture was allowed to stir for a final 3.5 hours, after which point brine (30 mL) was added to quench the reaction. The reaction contents were allowed to gradually warm up to room temperature, transferred to a separatory funnel, and then extracted twice with 1 M HCl (30 mL). The organic layer was separated from the aqueous later and subsequently washed with brine (30 mL), dried over MgSO₄, and gravity filtered. The solvent was then removed by rotary evaporation to yield the crude reaction product, which was purified either through recrystallization or flash chromatography.
(4S)-3-[(2R',3S')-3-hydroxy-2-(p-Methoxyphenoxy)-4-phenylbutanoyl]-4-phenyl-1,3-oxazolidine-2-thione (2.10b). The crude product was recrystallized using hexanes and ethyl acetate to yield the product as a white, crystalline solid (7.65 mmol, 87% yield). Mp: 183 – 184 °C. [α]$_D^{24}$ = +102.3 (CHCl$_3$, c = 1.05). $^1$H NMR (400 MHz, CDCl$_3$): δ 7.39-7.16 (m, 11H), 6.86-6.80 (m, 4H), 5.71 (dd, $J$ = 9.2, 5.8 Hz, 1H), 4.86 (app. triplet, $J$ = 9.2 Hz, 1H), 4.56-4.50 (m, 1H), 4.48 (dd, $J$ = 9.2, 5.8 Hz, 1H), 3.77 (s, 3H), 3.06-2.95 (m, 2H) ppm. $^{13}$C $^{1}$H NMR (100 MHz, DMSO-d$_6$): δ 186.5, 170.2, 154.3, 152.0, 138.8, 138.2, 130.0, 129.1, 128.7, 128.5, 127.0, 126.6, 116.6, 115.1, 79.1, 75.1, 72.9, 62.6, 55.8, 40.4 ppm. IR (CHCl$_3$): 3424, 1717, 1216, 757 cm$^{-1}$. ESI-HRMS $m/z$: [M + Na]$^+$ calcd for C$_{26}$H$_{25}$NNaO$_5$S$^+$, 486.1346; found, 486.1346. Mass error = 0 ppm.
(4S)-3-[(2'R,3'S)-3-Hydroxy-2-(p-methoxyphenoxy)-4-methylpentanoyl]-4-phenyl-1,3-oxazolidine-2-thione (2.13c). The crude product was recrystallized using hexanes and ethyl acetate to yield the product as a white, crystalline solid (1.94 g, 4.66 mmol, 53% yield). Mp: 140-141°C. $[\alpha]_D^{24} = +259.9$ (CHCl$_3$, $c = 0.20$). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.39-7.29 (m, 5H), 7.02 (d, $J = 1.8$ Hz, 1H), 6.85-6.79 (m, 4H), 5.73 (dd, $J = 9.3$, 6.5 Hz, 1H), 4.88 (t, $J = 9.3$ Hz, 1H), 4.50 (dd, $J = 9.3$, 6.5 Hz, 1H), 3.93 (ddd, $J = 10.2$, 8.4, 1.8 Hz, 1H), 3.74 (s, 3H), 2.05-1.95 (m, 1H), 1.60 (d, $J = 10.2$ Hz, 1H), 1.06 (d, $J = 6.7$ Hz, 3H), 1.01 (d, $J = 6.7$ Hz, 3H) ppm. $^{13}$C {$^1$H} NMR (125 MHz, CDCl$_3$): $\delta$ 185.5, 171.1, 154.6, 151.2, 136.7, 129.1, 126.6, 116.0, 114.8, 77.5, 76.7, 74.7, 62.8, 55.7, 32.4, 19.2, 19.1 ppm. IR (CDCl$_3$): 3575, 1722, 1507, 1341, 1301, 1228, 826 cm$^{-1}$. ESI-HRMS $m/z$: [M + Na]$^+$ calcd for C$_{22}$H$_{25}$NNaO$_5$S$^+$, 438.1346; found, 438.1355. Mass error = 2.1 ppm.
(4S)-3-[(2'R,3'S)-3-Hydroxy-2-(p-methoxyphenoxy)-5-phenyl-(4E)-pentenoyl]-4-phenyl-1,3-oxazolidine-2-thione (2.13f). The crude product was purified over silica using a gradient solvent system (90:10 → 70:30, hexanes/ethyl acetate) to yield the title material as colorless oil that formed an amorphous foam under high vacuum (2.81 g, 5.90 mmol, 68% yield). \([\alpha]_D^{24} = -184.0 \text{ (CHCl}_3, c = 0.21)\). ¹H NMR (500 MHz, CDCl₃): \(\delta\) 7.34-7.21 (m, 10H), 7.10 (d, \(J = 3.7\) Hz, 1H), 6.89 (d, \(J = 9.1\) Hz, 2H), 6.80 (d, \(J = 9.1\) Hz, 2H), 6.60 (d, \(J = 16.0\) Hz, 1H), 6.38 (dd, \(J = 16.0, 6.6\) Hz, 1H), 5.72 (dd, \(J = 9.2, 4.9\) Hz, 1H), 4.95-4.92 (m, 1H), 4.83 (t, \(J = 9.2\) Hz, 1H), 4.47 (dd, \(J = 9.2, 4.9\) Hz, 1H), 3.74 (s, 3H), 2.47 (d, \(J = 7.4\) Hz, 1H) ppm. ¹³C {¹H} NMR (125 MHz, CDCl₃): \(\delta\) 185.5, 169.8, 154.9, 151.3, 137.4, 136.3, 133.1, 129.2, 129.1, 128.5, 128.0, 126.9, 126.4, 126.3, 116.9, 114.9, 78.8, 74.8, 73.6, 62.5, 55.7 ppm. IR (CHCl₃): 3563, 1718, 1219, 1035, 828, 754 cm⁻¹. ESI-HRMS \(m/z\): [M + Na]⁺ calcd for \(C_{27}H_{25}NNaO_{5}S^+\), 498.1346; found, 498.1363. Mass error = 3.4 ppm.
(4S)-3-[(2′R,3′S)-3-Hydroxy-2-(p-methoxyphenoxy)-3-(p-nitrophenyl)propanoyl]-4-phenyl-1,3-oxazolidine-2-thione (2.13i). The crude product was purified by flash chromatography on silica gel using a solvent gradient (90:10 to 70:30; hexanes: ethyl acetate) and was recovered as an orange oil that formed an amorphous foam under high vacuum (2.72 g, 5.50 mmol, 63% yield). \([\alpha]_D^{24} = +124.1\) (CHCl\(_3\), \(c = 0.95\)). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 8.13 (d, \(J = 8.9\) Hz, 2H), 7.62 (d, \(J = 8.9\) Hz, 2H), 7.44-7.39 (m, 3H), 7.35-7.31 (m, 2H), 7.20 (d, \(J = 2.8\) Hz, 1H), 6.75-6.69 (m, 4H), 5.79 (dd, \(J = 9.2, 5.0\) Hz, 1H), 5.55 (dd, \(J = 7.3, 2.8\) Hz, 1H), 4.91 (t, \(J = 9.2\) Hz, 1H), 4.59 (dd, \(J = 9.2, 5.0\) Hz, 1H), 3.72 (s, 3H), 2.75 (broad singlet, 1H) ppm. \(^{13}\)C \(^1\)H NMR (125 MHz, CDCl\(_3\)): \(\delta\) 185.4, 169.4, 155.1, 150.7, 147.6, 146.3, 137.0, 129.5, 129.4, 127.3, 126.6, 123.4, 116.8, 114.8, 79.1, 74.9, 72.9, 62.6, 55.7 ppm. IR (CHCl\(_3\)): 3559, 1720, 1507, 1216, 830, 761 cm\(^{-1}\). ESI-HRMS \(m/z\): [M + Na]\(^+\) calcd for \(C_{25}H_{22}N_2NaO_7S\)\(^+\), 517.1040; found, 517.1044. Mass error = 0.8 ppm.
(4S)-3-[(2′R,3′S)-3-Hydroxy-2-(p-methoxyphenoxy)-3-(2-piperonyl)propanoyl]-4-phenyl-1,3-oxazolidine-2-thione (2.13j). The crude product was recrystallized using hexanes and ethyl acetate to yield the product as a white, crystalline solid (2.77 g, 5.60 mmol, 64% yield). Mp: 146-148°C. $[\alpha]_{D}^{24} = +213.9$ (CHCl$_3$, $c = 0.26$). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.40-7.33 (m, 3H), 7.30-7.28 (m, 2H), 7.07 (d, $J = 2.8$ Hz, 1H), 7.02 (d, $J = 1.7$ Hz, 1H), 6.91 (dd, $J = 8.1$, 1.7 Hz, 1H), 6.77-6.73 (m, 4H), 6.70 (d, $J = 8.1$ Hz, 1H), 5.92 (s, 2H), 5.75 (dd, $J = 9.2$, 5.4, 1H), 5.34 (dd, $J = 7.6$, 2.8, 1H), 4.86 (t, $J = 9.2$ Hz, 1H), 4.52 (dd, $J = 9.2$, 5.4 Hz, 1H), 3.72 (s, 3H), 2.49 (d, $J = 7.6$ Hz, 1H) ppm. $^{13}$C $\{^1$H$\}$ NMR (125 MHz, CDCl$_3$): $\delta$ 185.4, 170.0, 154.9, 151.2, 147.6, 147.3, 137.1, 133.2, 129.3, 129.2, 126.5, 119.9, 117.0, 114.7, 108.0, 107.3, 101.0, 79.9, 74.7, 73.3, 62.6, 55.7 ppm. IR (CDCl$_3$): 3548, 1719, 1228, 1197, 910, 827, 732 cm$^{-1}$. ESI-HRMS $m/z$: [M + Na]$^+$ calcd for C$_{26}$H$_{23}$NNaO$_7$S$, 526.1087$; found, 516.1106. Mass error = 3.7 ppm.
CHAPTER I: SYNTHESIS OF CHIRAL 2,3-DISUBSTITUTED OXETANES

Introduction

Oxetanes are a class of 4-membered heterocycles consisting of three carbon atoms and one oxygen atom. Recently, a growing interest in the oxetane moiety has been founded upon an ever-increasing range of applications they offer across various scientific disciplines.²⁴ Oxetanes present themselves as both stable motifs in medicinal chemistry and as reactive intermediates for further synthesis.

Oxetanes appear in a variety of natural products and are recognized for the important biological activity they can impart to a molecule when present. Arguably the most famous example of this is Taxol (Figure 3.1), the chemotherapeutic agent first isolated from the Pacific yew tree in 1971.²⁵ Structure/activity relationship (SAR) studies carried out on Taxol have demonstrated that its biological activity is largely contingent on the presence of the oxetane ring – wherein significantly reduced activity is observed when the oxetane ring is substituted with related ring structures or altogether absent.²⁶²⁷

Figure 3.1: Structure of paclitaxel (Taxol) with the essential oxetane group highlighted.
Other notable examples of oxetane-containing natural products include: Oxetanocin A (3.2), a soil bacteria-derived compound that has been shown to inhibit the \textit{in vivo} replication of human immunodeficiency virus (HIV),\textsuperscript{28} Oxetin (3.3), a \textit{Streptomyces}-derived antibacterial/herbicidal compound,\textsuperscript{29} and thromboxane A2 (3.4), an important signaling molecule that helps trigger formation of new platelets and facilitates platelet aggregation.\textsuperscript{30} For these compounds (Figure 3.2), the structural features provided by the oxetane rings are understood to be imperative for the observed characteristics.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{oxetane_compounds.png}
\caption{Structure of some naturally occurring oxetane compounds.}
\end{figure}

In medicinal chemistry, oxetanes have shown promise as favorable substitute groups for commonly occurring functionalities. In particular, the use of oxetanes as replacements for carbonyl groups has been of considerable interest due to similar dipoles and hydrogen bonding properties.\textsuperscript{31} In 2013, Carreira and co-workers published on a structural modification of the infamous drug ‘thalidomide’, in which the carbonyl C=O directly adjacent to the alpha-chiral center was replaced with an oxetane ring (Figure 3.3).\textsuperscript{32} For thalidomide, its \textit{R}-isomer functions as a nausea relief medication, while the \textit{S}-isomer is a teratogen. Under physiological conditions,
these two isomers readily interconvert through what is understood to be an enol-type mechanism, which affords both the $R$ and $S$ enantiomers. Notably, the oxetane-derivatized compound was shown to be stable to racemization in human serum after an incubation period of 5 hrs., demonstrating that carbonyl substitution with oxetane can prevent epimerization of stereocenters in the alpha-position.

![Thalidomide 3.5 → Oxetano-thalidomide 3.6](image)

**Figure 3.3:** Conversion of thalidomide’s critical carbonyl to an oxetane. [Adapted with permission from Burkhard et al. *Org. Lett.* **2013**, *15*, 17, 4312–4315. Copyright 2023 American Chemical Society.]

In addition to carbonyl replacement, oxetanes have also been shown to serve as effective substitutes for geminal-dimethyl groups, morpholine rings, and metabolically vulnerable methylene units.³³-³⁴ Due to these and the other intriguing properties of oxetanes, medicinal chemists will often insert these groups into existing compounds to tune a drug’s pharmacokinetic profile.³⁵

Synthetically, oxetanes may be used as reactive intermediates, as the strain present in the ring makes them susceptible to ring-opening reactions. Under acidic conditions, oxetanes can be opened using simple hydroxyl nucleophiles to afford 1,3-glycols.³⁶ Other nucleophiles, such as amines, lithium enolates, hydrides, and Grignard reagents have also been shown to open oxetane
In addition to intermolecular ring-opening reactions, intramolecular openings have also been demonstrated. In 2015, Britton and authors reported a total synthesis of the spirocyclic natural product ‘ascospiroketal’ which utilized an intramolecular ring opening to generate a 5-membered ring (3.8 & 3.9) (Scheme 3.1).³⁹

**Scheme 3.1:** Intramolecular oxetane ring-opening in ascospiroketal total synthesis. [Adapted with permission from Britton et al. Angew. Chem., Int. Ed. 2015, 54, 211−214. Copyright 2023 John Wiley and Sons.]

Given the diverse potential of oxetanes and their increasing utility within the chemical sciences, several synthetic routes to afford these heterocycles have been developed. For example, classic reactions such as the Williamson etherification ⁴⁰ and Paternò–Büchi cycloaddition ⁴¹ have been widely employed for many decades. However, these reactions, while popular, are often limited in scope due to low yields, substrate limitations, and poor selectivity.⁴⁰ As such, the demand for new, more versatile syntheses of oxetanes remains very strong.
Goal of Research

For this body of research, the Hitchcock group seeks to develop a new route to produce 2,3-disubstituted chiral oxetanes with high stereoselectivity. Described herein are the preliminary findings from the proposed four-step protocol to afford these oxetanes, of which the first step – an asymmetric glycolate aldol reaction using a Crimmins-type chiral auxiliary \(^{42}\) – is used to establish the stereochemistry of the ultimate oxetane product.

In the proposed synthetic pathway (Scheme 3.2), work begins with the asymmetric glycolate aldol reaction. The Hitchcock research group has previously demonstrated that \(N\)-(p-methoxyphenoxy)acetyl-oxazolidine-2-thione (3.10) can serve as a template for conducting titanium-catalyzed asymmetric aldol addition reactions and afford enantiomerically and diasteromerically enriched (>95:5) aldol addition products (3.11). These acylated thiones were previously used as the basis for a recently published work by the Hitchcock group \(^{23}\) that described the synthesis of chiral \(\beta\)-lactones, another class of 4-membered heterocycles closely related to oxetanes.
Scheme 3.2: Proposed route to chiral oxetanes using an asymmetric aldol reaction.

For these aldol addition reactions, the Hitchcock group plans to eventually employ a diverse catalog of both alkyl and aromatic aldehydes, with the ultimate goal being to probe the effects of alkyl and aromatic substituents on the ease of cyclization to the oxetane in the final step.

Following the synthesis of the aldol addition products, a reduction using sodium borohydride is carried out to cleave the chiral auxiliary and afford a 1,3-diol product. The cleaved chiral auxiliary may then be extracted away under basic conditions due to the relative acidity of the oxazolidine-2-thione N-H. Care must be taken during extraction since the diol products are suspected to have mild water-solubility.
With the 1,3-diol (3.13) in hand, the proposed synthesis continues with the subsequent treatment of 1 stoichiometric equivalent of \( p \)-nitrobenzenesulfonyl chloride (NsCl) and triethylamine. This will be conducted to selectively convert the primary hydroxyl into a suitable leaving group for cyclization. Care must be taken during this process to avoid any undesirable byproducts, particularly sulfonylation at the secondary hydroxyl (3.16) and bis-sulfonylated adducts (3.17) (Scheme 3.3). The effects of concentration and presence of a catalyst on this reaction will be investigated.

\[
\begin{align*}
\text{OH} & \quad \text{OH} \\
\text{OPMP} & \quad \text{R}
\end{align*}
\]

\[
\text{NsCl, Et}_3\text{N} \quad \text{CH}_2\text{Cl}_2
\]

\[
\begin{align*}
\text{ONs} & \quad \text{OH} \\
\text{OPMP} & \quad \text{R}
\end{align*}
\]

\[
\begin{align*}
\text{ONs} & \quad \text{OH} \\
\text{OPMP} & \quad \text{R}
\end{align*}
\]

\[
\begin{align*}
\text{ONs} & \quad \text{ONs} \\
\text{OPMP} & \quad \text{R}
\end{align*}
\]

\[
\begin{align*}
3.13 & \quad 3.14 & \quad 3.16 & \quad 3.17
\end{align*}
\]

**Scheme 3.3:** Potential byproducts of the sulfonylation reaction.

For the final step – the cyclization – treatment of 3.14 with a base of sufficient strength and application of heat is anticipated to afford 3.15 via an intramolecular displacement of the nosyl-bearing group. For this reaction, a study will be conducted to identify the optimal base and solvent combination for this process. It will be necessary to reconcile having a base of sufficient strength for cyclization while also ensuring that solubility is not an issue. With the oxetane products in hand, and provided that these derivatives are reasonably stable under ambient conditions, these compounds will be fully characterized (NMR, FT-IR, ESI-HRMS).

Ultimately, provided this proposed route proves effective in affording the target oxetane products, this pathway should – in principle – garner high utility due to the relative ease of
substituent modification at the 2 and 3 positions. For modification at the 2-position, deprotection of the -OPMP group will need to be carried out first. Assuming that the cyclization reactions are successful, this may be investigated as well.

Results and Discussion

At the time of this writing, this body of work remains only partially complete and is still ongoing. However, the initial proof of concept has been satisfactorily achieved. In this chapter is described the preliminary investigation carried out thus far to evaluate the feasibility of the proposed synthetic route to these chiral oxetanes.

The initial focus of this work was to select a model, acylated auxiliary species that would serve as the precursor substrate for the aldol addition and subsequent reactions towards the oxetane target. These were prepared in accordance with methods similar to those previously described in Chapter 2, again using a 4-phenyl-1,3-oxazolidine-2-thione chiral auxiliary. For this exploratory synthesis, an aldol adduct based off of phenylacetaldehyde was selected as the model substrate (Scheme 3.4). To conserve the amounts of titanium tetrachloride used, only 1 equivalent was employed for the aldol reaction (as opposed to the amount used for the non-Evans \(\text{syn}\) protocol of Chapter 2, which employed 2 equivalents). This single equivalent affords addition adducts with Evans \(\text{syn}\) stereochemistry.\(^{23}\)
Scheme 3.4: Formation of the model aldol system for the oxetane proof of concept.

Once the aldol product (3.18) was isolated in its diasteromerically pure form through recrystallization, it was then subjected to a sodium borohydride reductive cleavage to remove the chiral auxiliary. This was initially attempted by dissolving the aldol product in THF and adding NaBH₄. However, due to observed solubility issues of the aldol adduct in THF, methanol was added to aid in the dissolution of the material, in which it dissolves very well. Methanol, by nature of being a protic solvent, does react with NaBH₄ to product H₂ gas. However, this reaction is fairly slow, so by using a slight excess of NaBH₄, complete cleavage of the auxiliary can still be easily achieved (Scheme 3.5).

Scheme 3.5: Reductive cleavage of the chiral auxiliary with the release of diol (3.19).
The desired 1,3-diol (3.19) was isolated via column chromatography using a hexanes/EtOAc eluent in reasonable yield of 77%. Even so, this yield was believed to be compromised as a result of the poor ultraviolet (UV) activity of 3.19 as visualized on silica-based thin layer chromatography (TLC) plates. Visualization of the product using various stains (potassium permangante – 1.5% KMnO₄ in 5% w/v potassium carbonate in water, and p-anisaldehyde stain in 5% v/v sulfuric acid/ethanol) also proved to be suboptimal.

Proceeding with the proposed route, the 1,3-diol product (3.19) was activated for intramolecular cyclization through the chemoselective introduction of p-nitrobenzenesulfonyl chloride (NsCl) (3.20) in the presence of DMAP (dimethylaminopyridine) and triethylamine (Scheme 3.6). Ideally, this reaction was intended to proceed with the preferential sulfonylation of the primary alcohol. However, upon analysis of the ¹H NMR spectrum following basic work-up, it became apparent that a mixture of products had been formed. Chromatographic separation and analysis of the mixture components later proved that the initial concerns of byproduct formation as described in Scheme 3.3 had been realized, with the reaction proceeding with poor chemoselectivity, along with some diol even undergoing a double sulfonylation (3.23) (Scheme 3.6). For this reaction, the desired product (3.21) was obtained in a low yield of 37%.

Scheme 3.6: Attempted chemoselective sulfonylation of 3.19, resulting in formation of several byproducts (3.22) (3.23).
Dissatisfied with the results of the initial sulfonylation reaction, a second reaction was conducted using the same diol substrate (3.19), this time changing the conditions to more dilute concentration (0.30 molar \( \rightarrow \) 0.15 molar) and forgoing the addition of the DMAP catalyst. The rational behind removing the DMAP catalyst – it is argued – is that the attack of the NsCl species by DMAP over-activates the substrate and enhances its electrophilicity (3.24) (Scheme 3.7), thereby reducing the competitive barrier between the nucleophilicity of the primary and secondary alcohols. In a nutshell, the primary alcohol of 3.19 is much more likely to react with 3.20 than the secondary alcohol. Conversely, since 3.24 possesses such enhanced reactivity, the primary and secondary alcohols will have comparable ability to react.

\[
\begin{align*}
\text{NsCl - 3.20} & \quad \text{Activated substrate; Enhanced electrophilicity} \\
& \quad \text{3.24}
\end{align*}
\]

**Scheme 3.7:** Putative effect of DMAP displacement catalyst on the NsCl (3.20) substrate.

Under these new conditions the reaction was observed to proceed with significantly enhanced chemoselectivity, and – following chromatographic purification – the desired product (3.21) was obtained with a nearly quantitative return.
With the activated diol now in possession, an attempt at cyclization reaction was performed. To do this, 3.21 was dissolved in a 50:50 MeOH:THF solvent system, and potassium carbonate was added. The system was heated to reflux and allowed to stir overnight (Scheme 3.8).

Scheme 3.8: Cyclization reaction to form oxetane (3.25).

Following workup and purification by flash chromatography over silica, the major product was isolated. The 500 MHz $^1$H spectrum (Figure 3.4), 125 MHz $^{13}$C NMR spectrum, and electrospray ionization high resolution mass (ESI-HRMS) spectrometry data obtained during the characterization process revealed that the formation of a chiral 3-(p-methoxyphenoxy) oxetane (3.25) was successful, providing an isolated chemical yield of 85%.
Figure 3.4: 500 MHz $^1$H NMR spectrum of 3.25 with heterocyclic protons assigned.

With the discovery that the intramolecular cyclization is feasible, the Hitchcock group is currently evaluating other synthetic means to achieve the oxetane formation from the same system. For the proposed synthetic pathway as depicted in Scheme 3.2, a total of four steps (starting from the asymmetric aldol) were needed to obtain the oxetane target. Currently under investigation in the Hitchcock group is the cyclization of the 1,3-diol species under Mitsunobu conditions (Scheme 3.9). Operating under the same general principle as the previous method, in which the primary alcohol is selectively activated and subsequently cyclized, so too would the Mitsunobu reaction, in which activating reagents triphenylphosphine (TPP), diethyl azodicarboxylate (DEAD), or diisopropyl azodicarboxylate (DIAD) append to the primary hydroxyl and enable cyclization after the application of heat. Mitsunobu reactions have demonstrated use for intramolecular cyclizations.$^{45,46}$ The primary advantage to a Mitsunobu
cyclization over the previous route is that the transformation would proceed with the 1,3-diol forming the oxetane in a single step. Currently, preliminary evidence suggests that the formation of 2,3-disubstituted oxetanes via this method is possible, however optimization and yields will be needed before committing to the synthesis of the planned substrates (Figure 3.5).

Scheme 3.9: Example cyclization of a 1,3-diol under Mitsunobu conditions.

Figure 3.5: Series of additional oxetanes to be prepared.
Experimental

General Remarks:

Unless otherwise noted, all chemical agents and solvents were purchased and used without further purification. All reactions were conducted under a nitrogen atmosphere in either flame or oven dried glassware. Unless otherwise noted, all $^1$H and proton decoupled $^{13}$C NMR spectra were collected in deuterated chloroform (CDCl$_3$) using a Bruker Ultra-shield Avance III NMR spectrometer operating at either 500 MHz of 400 MHz ($^1$H NMR) and 125 MHz or 100 MHz ($^{13}$C NMR), respectively. Chemical shifts were reported in parts per million (δ scale) and coupling constant (J values) are reported in Hertz (Hz). Tetramethyldisilane (TMS) was used as an internal standard (δ = 0 ppm). Optical rotation data were collected on a JASCO P-1010 digital polarimeter operating at 589 nm in an 8 × 100 nm cell. Infrared spectra were recorded using NaCl plates. IR values are reported in reciprocal centimeters (cm⁻¹) and were measured either as a nujol mull or as a neat liquid film from an evaporated chloroform solution. For ESI-HRMS, samples were prepared in concentrations of 5-25 ppm in high-performance liquid chromatography grade methanol/water/formic acid (1:1:0.01). Melting points were recorded on a Mel-Temp apparatus. High resolution mass spectra were obtained using a ThermoScientific $Q$-Exactive ESI mass spectrometer equipped with an Orbitrap mass analyzer. The parts per million (ppm) mass error is reported as the absolute value.
(2R,3R)-1,3-dihydroxy-2-(p-methoxyphenoxy)-4-phenylbutane (3.19). To a flame-dried, nitrogen purged 250 mL round bottom flask was added aldol substrate 3.18 (2.49 g, 5.37 mmol), 12 mL MeOH, 24 mL THF, and sodium borohydride (0.41 g, 10.75 mmol). The reaction was stirred overnight. The reaction was quenched with ethyl acetate (80 mL) and HCl (20 mL). The organic layer was washed with brine (20 mL) and dried with magnesium sulfate. The solvent was expelled via rotary evaporation. The product was the purified via chromatography over silica using a 7:3 hexanes/EtOAc solvent system as the eluent. The final product was obtained as white solid (1.92 g, 4.13 mmol, 77% yield). ¹H NMR (500 MHz, CDCl₃): δ 7.30-7.27 (m, 2H), 7.23-7.21 (m, 1H), 7.18-7.16 (m, 2H), 6.93 (d, J = 9.1 Hz, 2H), 6.83 (d, J = 9.1 Hz, 2H), 4.18-4.12 (m, 2H), 3.97-3.92 (m, 1H), 3.87-3.83 (m, 1H), 3.78 (s, 3H), 2.98 (dd, J = 13.6, 5.7 Hz, 1H), 2.91 (dd, J = 13.6, 7.8 Hz, 1H), 2.42 (d, J = 5.6 Hz, 1H), 2.11 (t, J = 5.6 Hz, 1H) ppm. ¹³C {¹H} NMR (125 MHz, CDCl₃): δ 154.7, 152.0, 137.8, 129.4, 128.6, 126.6, 118.0, 114.8, 80.1, 73.3, 62.2, 55.7, 39.9 ppm. ESI-HRMS m/z: [M + Na]⁺ calcd for C₁₇H₂₀NaO₄⁺, 311.1254; found, 311.1250. Mass error = 1.3 ppm. [α]D²⁰ = +80.6 (CHCl₃, c = 0.280).
(2R,3R)-3-Hydroxy-2-(p-methoxyphenoxy)-1-(p-nitrobenzenesulfonyl)4-phenylbutane (3.21). To a flame dried, nitrogen purged 100 mL round bottom flask was added diol (3.19) (0.671 g, 2.33 mmol), dichloromethane (16.0 mL), and p-nitrobenzene sulfonyl chloride (0.541 g, 2.44 mmol). The reaction vessel was cooled to 0°C in an ice bath. Once cooled, triethylamine (0.36 mL, 2.56 mmol) was added in dropwise fashion and the reaction was stirred overnight. The reaction was quenched with dichloromethane (80 mL) and 1 M HCl (20 mL). The organic layer was washed with brine (20 mL), dried with magnesium sulfate, and gravity filtered. The system was concentrated under reduced pressure to yield a solid that was washed with ether to afford the pure target in near quantitative yield. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta 8.27 (d, J = 9.0 \text{ Hz}, 2H)\), \(7.96 (d, J = 9.0 \text{ Hz}, 2H)\), \(7.29-7.26 (m, 2H)\), \(7.25-7.22 (m, 1H)\), \(7.10-7.08 (m, 2H)\), \(6.78-6.74 (m, 4H)\), \(4.43 (dd, J = 10.7, 5.1 \text{ Hz}, 1H)\), \(4.38 (dd, J = 10.7, 6.1 \text{ Hz}, 1H)\), \(4.28-4.26 (m, 1H)\), \(4.02-3.97 (m, 1H)\), \(3.77 (s, 3H)\), \(2.88 (m, 2H)\), \(1.96 (d, J = 7.2 \text{ Hz}, 1H)\) ppm. \(^{13}\)C \({^1}\)H NMR (125 MHz, CDCl\(_3\)): \(\delta 155.0, 151.4, 150.7, 141.3, 136.9, 129.3, 129.2, 128.8, 126.9, 124.3, 117.4, 114.8, 77.3, 71.8, 69.6, 55.7, 39.7 \text{ ppm}\). ESI-HRMS m/z: [M + Na]\(^+\) calcd for C\(_{23}\)H\(_{23}\)NNaO\(_8\)S\(^+\), 496.1037; found, 495.1034. Mass error = 0.6 ppm. \([\alpha]\)\(_D^{24}\) = \(-823.3\) (CHCl\(_3\), \(c = 0.06\)).
(2R,3R)-2-benzyl-3-(p-methoxyphenoxy)oxetane (3.25). To a flame dried, nitrogen purged 100 mL round bottom flask equipped with a condenser and heating mantle was added activated diol (3.21) (0.351 g, 0.74 mmol), 6.0 mL of a 1:1 THF/MeOH solvent system, and potassium carbonate (0.205 g, 1.48 mmol). The material was heated to reflux and allowed to stir overnight. The reaction was cooled and subsequently diluted with ethyl acetate (80 mL) and then extracted with 1 M HCl (15 mL). The organic layer was separated and then washed with 15 mL of a saturated brine solution, dried over magnesium sulfate, and gravity filtered. The solvent was removed under reduced pressure, and the crude extract was purified over silica using a 9:1 hexanes/EtOAc solvent system as the eluent. The purified oxetane product was obtained as a viscous oil (0.170 g, 0.63 mmol, 85% yield). $^1$H NMR (500 MHz, CDCl$_3$): δ 7.19-7.15 (m, 4H), 7.11-7.08 (m, 1H), 6.73 (d, $J$ = 9.1 Hz, 2H), 6.60 (d, $J$ = 9.1 Hz, 2H), 5.11-5.03 (m, 2H), 4.80 (dd, $J$ = 7.3, 5.9 Hz, 1H), 4.56 (dd, $J$ = 7.3, 4.9 Hz, 1H), 3.67 (s, 3H), 3.17 (dd, $J$ = 14.3, 7.7 Hz, 1H), 3.11 (dd, $J$ = 14.3, 5.7 Hz, 1H) ppm. $^{13}$C {$^1$H} NMR (125 MHz, CDCl$_3$): δ 154.4, 151.2, 137.4, 129.4, 128.4, 126.3, 115.6, 114.9, 87.0, 75.5, 71.8, 55.7, 36.7 ppm. ESI-HRMS m/z: [M + Na]$^+$ calcd for C$_{17}$H$_{18}$NaO$_3$, 293.1148; found, 293.1152. Mass error = 1.4 ppm.
CHAPTER IV: EFFORTS TOWARDS THE SYNTHESIS OF THE HIV PROTEASE INHIBITOR DARUNAVIR VIA AN ASYMMETRIC ALDOL REACTION

Introduction

Since the emergence of AIDS (acquired immunodeficiency syndrome) in the early 1980s, strategies to mitigate the disease remain a high priority for medical professionals worldwide.⁴⁷ According to the World Health Organization (WHO), as of 2022, an estimated 38 million people are currently infected with human immunodeficiency virus (HIV), the causative agent of AIDS, and another 1.5 million contract the virus annually.⁴⁷ While the incidence of this disease occurs on a global scale, its spread is most prevalent on the African continent, where approximately 65% of all documented cases occur.⁴⁸

Clinically, HIV can manifest a wide spectrum of symptoms over the course of infection.⁴⁸ Following initial exposure an individual may not experience any symptoms for 2-4 weeks, and about two-third of people will develop flu-like illness. Proceeding the acute stage of sickness, the virus enters what is referred to as clinical latency – a stage in which the virus still multiplies, but at low levels. People in the clinical latency stage may not experience any symptoms at all. Without treatment, this stage can last from roughly three years to over 2 decades.⁴⁸ The final and most fatal stage of HIV is progression to AIDS, and is defined as when an infected individual has a CD4⁺ T immune cell count below 200 cells/µL. At this stage, the immune system cannot adequately defend against opportunistic infections. The life expectancy after progression to AIDS is less than three years.⁴⁸
While there is no broadly available cure or vaccine for HIV/AIDS at this time, early diagnosis and treatment can drastically reduce the severity of the infection, rendering the potentially fatal disease into a manageable chronic condition. To this end, antiretroviral drugs are regularly employed to combat the virus and achieve HIV latency in infected patients. Currently, over 30 such drugs have been approved for use in the United States by the FDA. However, growing concerns due to the emergence of drug-resistant strains of HIV have led some to speculate as to the long-term viability of the currently available drug catalog. As such, the development of new and improved drugs remains an important enterprise for medicinal and synthetic chemists.

HIV is classified as a retrovirus, meaning that its lifecycle must first follow the reverse direction of the ‘normal’ gene-copying process (DNA → RNA → Protein) before viral replication can take place. During infection, HIV uses a reverse transcriptase enzyme to produce DNA from its RNA genome. This DNA is then incorporated into the genome of an infected cell, where it can then be transcribed back into RNA by the cellular machinery of the central dogma. From there, the RNA is translated into a ‘polyprotein’ which contains the linked transcripts of multiple viral proteins bound in a continuous peptide chain. Cleavage of this polyprotein must occur to allow for the smaller, individual proteins to fold into their active form and assemble new viral units. This cleavage is achieved by an enzyme called HIV protease, which operates through what is known as a ‘catalytic dyad’ mechanism (Figure 4.1). In this mechanism, two aspartate residues in the protease active site facilitate the attack and subsequent cleavage of the polyprotein complex at specific peptide bonds.
A 1988 discovery that inhibition of this protease results in the production of nonfunctional virions triggered an extensive campaign to develop effective agents that could inhibit viral replication *in vivo*. Given the essential role HIV protease serves in the virus life cycle, the enzyme has become a common target for drug design. To date, a total of ten HIV protease inhibitors (PIs) have been approved for use in the United States by the FDA. The most recently approved of these PIs – Darunavir 4.1 (Figure 4.2) – has exhibited broad-spectrum activity against multidrug-resistant variants of HIV. Darunavir and its analogues function as peptidomimetics, effectively imitating the hydrolytic transition state of an amide bond. This allows these compounds to lodge themselves into the protease active site through a significant hydrogen bonding and block its action.
**Goal of Research**

The Hitchcock group is currently interested in the synthesis of Darunavir and its derivatives. Specifically, the group seeks to develop a new, versatile synthetic pathway to Darunavir that also enables easy access into different derivatives that may have improved antiretroviral capabilities. Structure/activity relationship studies carried out on the protease/inhibitor complex have led to the designation of four key motifs surrounding the key hydroxyethyl isostere of Darunavir (Figure 4.3), the so-called P1/P2 moieties. These moieties govern the specific interaction of the inhibitor within the protease active site. Currently, a strong interest exists within the medicinal chemistry community to modify and fine-tune these regions for improved drug efficacy. However, the synthesis of such derivatives remains a difficult enterprise.
Currently, the commercial production of Darunavir employs an eight-step process that utilizes chiral amino acid phenylalanine to establish the stereochemistry of the final product (Scheme 4.1). While this methodology is indeed the most practical for the industrial-scale production of Darunavir specifically, it lacks the synthetic flexibility necessary to easily produce certain Darunavir analogues. This rigidity is the consequence of the pathway’s dependence on having widely available amino acid starting material. Furthermore, while alternative routes to Darunavir that allow for derivatization have been recently demonstrated, such as that by Chiummiento et al., Ghosh et al., and Raines et al. (Figure 4.4), these each possess their own limitations, including: 1) high number of steps, 2) sensitive reactive intermediates (e.g. epoxides) and 3) need for high complexity starting materials. This proposal outlines a new synthetic pathway to Darunavir and derivatives that is both 1) shorter in required number of steps, and 2) uses simple, commonly available starting materials (Scheme 4.2).
Scheme 4.1: The industrial synthetic pathway to Darunavir.\textsuperscript{56}

Figure 4.4: Examples of Darunavir derivatives.
The proposed synthesis begins with an asymmetric glycolate aldol addition reaction using a Crimmins’ chiral auxiliary. This step establishes the chiral template that determines the stereochemistry of the final product, as previously described in Chapters 1 & 2. This step also serves as the key point of introduction for variable P1 ligands, accessible through reaction with various aldehydes. The value in this route to derivatization is that it is only limited – in principle – by the aldehydes able to participate in the aldol addition (versus the relatively less accessible amino acids available when compared to the industrial synthesis of Darunavir).

Scheme 4.2: The Hitchcock group’s proposed synthetic pathway to Darunavir.
Results and Discussion

The initial focus of this work was to develop a large-scale synthesis of the non-Evans’ syn-glycolate aldol adducts (Chapters 1 & 2). Work began with the preparation of (4R)-4-phenyl-1,3-oxazolidine-2-thione (4.13) from commercially available D-phenylglycinol (4.12). For this reaction, 4.12 was dissolved in ethanol and reacted with carbon disulfide in the presence of potassium carbonate with the application of heat to form reactive intermediate 4.21 (Scheme 4.3). Upon dropwise addition of hydrogen peroxide, cyclization proceeds through what is understood to be a disulfide dimer species (4.22) to afford 4.13 in a yield of 78%.

Scheme 4.3: Cyclization of D-phenylglycinol (4.12) to the chiral auxiliary (4.13).
With the oxazolidine-2-thione heterocycle in hand, an acylation reaction was carried out in which the heterocyclic nitrogen was acylated with \( p \)-methoxyphenoxyacetic acid (4.23) using the EDC method previously described in Chapter 2 (Scheme 4.4). The \( p \)-methoxyphenoxy (-OPMP) glycolate protecting group was selected due to difficulties previously encountered with the deprotection of the more commonly used benzyl protecting group (-OBn). This acylation proceeded smoothly to afford 4.14 as a white solid in good yield (81%).

![Scheme 4.4: Acylation of 4.13 with 4-methoxyphenoxyacetic acid (4.23).](image)

With the acylation satisfactorily completed, the asymmetric glycolate aldol reaction could then proceed. Using the methodology described in Chapter 2 of this thesis, a titanium mediated aldol was conducted to selectively afford non-Evans \textit{syn}-adducts (Scheme 4.5). Serendipitously, the target adduct was a white solid that was readily recrystallized in hexanes/EtOAc while the minor diastereomers were able to be washed away. The absolute stereochemistry of the aldol adduct was determined through comparison with a known X-ray crystal structure obtained during
the efforts described in Chapter 2. (Figure 4.5). The optimized reaction gave satisfactory results, with the highest obtained yield being 89% on a 14-gram scale. As previously mentioned, this reaction serves as the entry point for alternate P1 ligands in the inhibitor structure.

Scheme 4.5: Asymmetric titanium mediated glycolate aldol with phenylacetaldehyde (4.23).

Figure 4.5: X-ray crystal structure of aldol adduct (enantiomer of 4.15). (Courtesy of Dr. Gregory Ferrence, Department of Chemistry, Illinois State University)
With the stereochemistry established and the successful scaling of the aldol reaction to a multi-gram level, displacement of the chiral auxiliary was pursued next. One advantage of using a Crimmins’ oxazolidine-2-thione as opposed to a more conventional oxazolidinone chiral auxiliary lies in the ease of removal, wherein the oxazolidine-2-thione is a much better leaving group and more readily displaced by incoming nucleophiles (i.e., amines). To facilitate this removal, aldol adduct 4.15 was dissolved in methylene chloride and incubated with an imidazole displacement catalyst for one hour, at which time isobutylamine (4.24) was added by syringe and stirred overnight to afford the crude amide target (4.16) (Scheme 4.6). This reaction introduces two diastereotopic methyl groups to the molecular system, which (for this system) served as a key diagnostic region for NMR analysis for the remainder of the synthesis (Figure 4.6). The cleaved auxiliary (4.13) was extracted from the crude product using 2 M NaOH. The resultant amide product was obtained in 82% yield following recrystallization in hexanes and ethyl acetate. Concerning the synthesis of Darunavir analogues, this step serves as the introductory point for variable P1’ groups, which are determined by the chosen amine nucleophile.

**Scheme 4.6:** Trans-amidation of the aldol adduct (4.15) using isobutylamine (4.24).
Figure 4.6: Diastereotopic methyl groups of the isobutylamine P1’ ligand as observed in the 500 MHz proton NMR spectrum of 4.16.

For the next step, reduction of the amide bond to an amine was pursued. The use of harsh reagents such as lithium aluminum hydride (LAH) to achieve the amide reduction was undesirable. So, a search for an effective, milder methodology was initiated. In 1993, McKennon et al. reported a series of reductions of the amides bonds of various amino acid systems using the milder reducing agent sodium borohydride (NaBH₄) and stoichiometric iodine (I₂).⁶⁰ Traditionally, sodium borohydride is not powerful enough of a reducing agent to achieve the conversion of amides to amines. However, upon addition of iodine, NaBH₄ is converted into active borane (BH₃), which is strong enough to reduce amides to amines. Accordingly, a reduction of the system using the McKennon methodology was investigated. To do this, amide (4.16) and sodium borohydride were dissolved in tetrahydrofuran (THF) and a solution of molecular iodine (I₂) in THF was added dropwise by addition funnel to the reaction. This system was heated to reflux and allowed to react for a minimum of 15 hours to ensure maximal reduction of the substrate (Scheme 4.7). To quench any remaining borane reagent, methanol
(MeOH), was added to the system and allowed to stir for 30 minutes before work-up. Following aqueous work-up, it was confirmed by proton NMR and HRMS that the reduction was highly efficient in affording the target amino alcohol (4.17) in good yield (89%). The crude extract from this reaction was isolated as a colorless oil of sufficient purity that it was advanced to the next step without further purification.

Scheme 4.7: Reduction of the amide (4.16) to an amine (4.17).60

With the amino-alcohol in-hand, a “double sulfonylation” reaction (or bis-nosylation) with nosyl chloride – a commonly used protecting group in organic chemistry – was carried out (Scheme 4.8). The basis for this reaction was twofold: 1) introduce the sulfonamide functionality, which is a part of the final inhibitor structure, and 2) convert the alcohol into a good leaving group that can be eventually displaced via an S_N2 reaction with inversion of stereochemistry. This inversion of stereochemistry is crucial for preparing inhibitors with the correct three-dimensional structure.
To test the feasibility of this reaction, amino alcohol (4.17) was reacted overnight with 2.5 equivalents of nosyl chloride (4.24) and 2.1 equivalents of TEA in dichloromethane. This reaction was first carried out at cooled temperature due to concerns of a possible intermolecular or intramolecular attack between amine and nosylate. Upon analysis of the crude product following aqueous work-up, suboptimal results were obtained. Owing to the poor nucleophilicity of the alcohol functional group, a mixture of two primary products was observed: the target bis-sulfonylated species (4.18), as well as a mono-sulfonylated byproduct in which the alcohol remains unreacted (4.25). To improve the efficiency of the reaction, adjustments were made by changing several variables: 1) introduction of a chloride displacement catalyst (DMAP), 2) increasing temperature, 3) increasing concentration, and 4) increasing equivalents of triethylamine. The results of this optimization study are described in Table 4.1. Using the optimized conditions (entry 7, Table 4.1), the conversion of 4.17 to 4.18 was able to proceed with an efficiency of 95%.
Table 4.1: Optimization of conditions for the bis-sulfonylation reaction. Product ratios were determined by proton NMR analysis of the crude extracts.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conc. (M)</th>
<th>Temp (°C)</th>
<th>Eq. DMAP</th>
<th>Eq. TEA</th>
<th>Product ratio (4.18:4.25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.15</td>
<td>-5.5</td>
<td>0</td>
<td>2.1</td>
<td>28:72</td>
</tr>
<tr>
<td>2</td>
<td>0.15</td>
<td>-5.5</td>
<td>0.15</td>
<td>2.1</td>
<td>50:50</td>
</tr>
<tr>
<td>3</td>
<td>0.15</td>
<td>-5.5 → RT</td>
<td>0.15</td>
<td>2.1</td>
<td>57:43</td>
</tr>
<tr>
<td>4</td>
<td>0.15</td>
<td>RT</td>
<td>0.15</td>
<td>2.1</td>
<td>57:43</td>
</tr>
<tr>
<td>5</td>
<td>0.30</td>
<td>RT</td>
<td>0.15</td>
<td>2.1</td>
<td>74:26</td>
</tr>
<tr>
<td>6</td>
<td>0.30</td>
<td>RT</td>
<td>0.25</td>
<td>3.0</td>
<td>80:20</td>
</tr>
<tr>
<td>7</td>
<td>0.30</td>
<td>RT</td>
<td>0.75</td>
<td>3.0</td>
<td>95:5</td>
</tr>
</tbody>
</table>

Following the optimized conditions for the bis-sulfonylation reaction, purification was still necessary before moving the material to the next stage of the synthesis. Initial attempts at purification over a silica column with a hexanes/ethyl acetate mobile phase were characterized by disappointingly low yields ranging from 15-30%. This poor return of material was not in agreement with the $^1$H NMR spectra of the crude extracts, which suggested nearly complete
conversion under the optimized conditions. An investigation into the purification stage of the process revealed that use of a hexanes/EtOAc mobile phase was encouraging crystallization of the target product on-column as separation took place, resulting in the loss of significant amounts of material. Thus, through use of a different mobile phase of 1% MeOH/dichloromethane – which has significantly greater dissolving power – an excellent separation, without any notable loss of product on-column, was achieved. The bis-sulfonlated product (4.18) was isolated without further difficulty as a yellow, crystalline solid in good yield (85%).

Having optimized the preparation of the bis-sulfonyl system, the project was moved onto the next step of the synthetic outline: nucleophilic substitution. As mentioned earlier, the intention of this reaction was to introduce a nitrogen functionality with stereospecific inversion at the hydroxy position. To do this, bis-sulfonylated substrate (4.18) was dissolved in dimethyl sulfoxide (DMSO), a good S_N2 solvent, and reacted with sodium azide overnight (Scheme 4.9).

Scheme 4.9: Nucleophilic substitution reaction using sodium azide.
Remarkably, following aqueous work-up of the reaction and $^1$H NMR analysis, it was discovered that this displacement reaction proceeds exceptionally well, with no apparent elimination byproducts or starting material present in the reaction extract. The target azide (4.19) was obtained in nearly quantitative yield and was moved onto the next reaction without requiring further purification.

To proceed with the synthesis, there was initially an interest in hydrogenating the azide product (4.19) to afford the $p$-methoxyphenoxy protected diamine (4.26) which would then be acylated with the Darunavir P2 ligand (4.27) before carrying out the final deprotection on the $p$-methoxyphenoxy group to afford Darunavir (Scheme 4.10).

Scheme 4.10: Originally proposed route to Darunavir.
However, upon treatment of **4.19** with Pd/C and a H₂ balloon, ¹H NMR analysis of the crude extract following work-up suggested that incomplete hydrogenation was taking place and that the intended product (**4.26**) was not forming in appreciable quantity. Mass spectral analysis of the crude residue following work-up suggested that the dominant product formed was a hydroxyl-amine azido compound (**4.29**) (Scheme 4.11), and that the hydrogenation was not occurring efficiently.

**Scheme 4.11**: Results of the attempted hydrogenation reaction.

Reattempted hydrogenations of the azide were carried out using alternative hydrogenation catalysts such as: palladium hydroxide, palladium on carbon wet, platinum on carbon, and Adam’s catalyst, all of which formed similar mixtures of incompletely reduced substrate, even with 48 hours reaction time in some cases. Additionally, hydrogenation reactions in alternative solvent systems – such as 3:1 AcOH/H₂O – were attempted in an effort to encourage faster hydrogenation. The efforts yielded dissatisfactory results in all cases. Through mass spectral analysis of these experiments, it was noted that the p-nitro of the nosyl group was most susceptible to complete reduction, while the azido functionality was highly resistant and often remained intact. Thus, it was proposed that a Staudinger reaction using triphenylphosphine (TPP) in THF could be carried out to selectively target and reduce the azide, leaving the nitro group
intact for an eventual reduction. So, azide substrate (4.19) was reacted with TPP in THF and stirred for 3 hours before workup (Scheme 4.12).

\[ \text{Scheme 4.12: Attempted Staudinger reaction on 4.19.} \]

The attempted Staudinger reaction did not afford the desired amine product, but rather formed an isolable phosphine imide (4.31) (Figure 4.7), which is usually regarded as a highly reactive intermediate in the Staudinger reaction mechanism. The identity of this compound was confirmed through high resolution mass spectrometry.

\[ \text{Figure 4.7: Isolated Staudinger intermediate, a phosphine imide (4.31).} \]
Attempts to cleave the TPP from 4.31 proved cumbersome and inconsistent, requiring harsh conditions (4 M NaOH/reflux) to remove the group. Furthermore, in addition to these difficulties, pursuit of this route would effectively require the implementation of an additional step to the overall synthesis, which was not desired.

Under the realization that these setbacks were hindering the forward progress of the project, it was decided that the synthesis proceed in an alternative direction by performing the deprotection on the azido substrate (4.19) first, as opposed to at the end of the synthesis as originally planned. To do this, 4.19 was dissolved in a 4:1 MeCN/H₂O solvent and reacted with four equivalents of ceric ammonium nitrate (CAN) for 3 hours (Scheme 4.13).

Ceric ammonium nitrate (CAN) is an inorganic compound with the formula (NH₄)₂[Ce(NO₃)₆]. It is a specialized oxidizing agent (single electron oxidant) that is commonly employed as a deprotecting reagent in organic synthesis. In this case, two equivalents of CAN react with the p-methoxyphenoxy ring, releasing the free alcohol (4.20) and producing benzoquinone (4.32) as a byproduct (Scheme 4.14).⁶²

Scheme 4.13: Deprotection of the azide substrate.
Scheme 4.14: Mechanism of deprotection for the \( p \)-methoxyphenoxy group.

The reaction was worked up in bicarbonate and subsequently purified by flash chromatography to afford the target as a red oil with poor initial yield (25%). This loss of material was attributed towards suboptimal extraction conditions, as well as prolonged reaction time. The presence of ceric ammonium nitrate is known to adversely affect extractions by introducing emulsions between the organic and aqueous phases in the separatory funnel, confounding their separation. Furthermore, CAN is a highly reactive species, so the possibility of an overreaction even with a 3-hour runtime must be considered. Thus, the reaction was conducted again – this time with only a 90-minute incubation period – and was then subjected to a brine-only extraction to help reduce the severity of emulsion formation. The product was again purified over silica using the previous conditions to afford the target (4.20) with an improved yield of 45%. Whilst this yield represents nearly double that of the initial, optimization of this step is still ongoing.
Of note for this reaction, with the loss of the -OPMP protecting group, the diagnostic methyl singlet resonance from the $^1$H NMR analysis was no longer present, rendering the analysis by NMR alone more difficult. High resolution mass spectrometry was utilized to help determine the identity of the major species for the final steps (Figure 4.8).

**Figure 4.8:** High resolution mass spectrum of the crude extract of 4.20.

With the azido alcohol in hand, the hydrogenation was reattempted using conditions identical to that of the attempted hydrogenation of the protected azide substrate (Scheme 4.15). Remarkably, the hydrogenation was now observed to proceed with excellent efficiency, resulting in near quantitative conversion of the nitro and azido groups to their corresponding amines (4.33).
Scheme 4.15: Reduction of the deprotected azido alcohol substrate.

While it remains unclear as to the exact reason the previous hydrogenations on the -OPMP protected substrate (4.19) were unsuccessful, one speculative explanation may place blame on either a sterically or electronically suppressive influence exerted from the -OPMP group onto the activated catalyst, which could have slowed and/or stopped the reduction part-way. Another possibility may lie in the suboptimal quality of the various catalysts used at the time, although this was not tested for. Regardless, the synthesis was able to proceed through this alternative pathway with the same efficiency (same number of total steps) as the original route.

With the hydrogenation step conquered and the key hydroxyethyl diamine isostere of Darunavir now readily accessible, all that remained was to acylate the aliphatic amine with the Darunavir P2 ligand. To carry out the acylation, diamine (4.33) was reacted with 2,5-dioxopyrrolidin-1-yl ((3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl) carbonate (4.27), colloquially referred to as the “Bis-THF” carbonate. This carbonate is commercially available and is used for Darunavir’s industrial production. This reaction was carried out in THF in the presence of TEA and allowed to stir for 17 hours to complete the acylation (Scheme 4.16). An
abundance of literature examples are available for this acylation reaction, thus, troubleshooting/optimization was not of major concern for this step.\textsuperscript{54-58,59}

**Scheme 4.16:** Acylation of the hydroxy ethyl isostere of Darunavir with the key P2 ligand.

The reaction mixture was concentrated under reduced pressure and purified by flash chromatography using 50% EtOAc/CH\textsubscript{2}Cl\textsubscript{2} as the eluent to yield compound **4.1**, Darunavir, as an amorphous solid in 52% yield, comparable to literature values.\textsuperscript{54}

With the main synthesis of Darunavir complete, refinement of the overall process is underway at the time of this writing. Apart from the optimization of the deprotection step, interest currently lies in the feasibility of combining the final hydrogenation/acylation into a single-pot reaction. There is currently strong preliminary evidence to suggest that this reaction is a viable approach (Scheme 4.17), although further evaluation will be necessary.

Conclusions

With the viability of the synthetic route now supported, the Hitchcock research group seeks to prepare a series of P1-modified Darunavir analogues, with the ultimate goal being to test the biological efficacy of each. Each of these planned derivatives will be accessed by use of different aldehydes for the aldol addition reaction (Figure 4.9).

Figure 4.9: Some Darunavir analogues the Hitchcock group intends to prepare.
Experimental

General Remarks:

All chemical agents and solvents were purchased and used without further purification. All reactions were conducted under a nitrogen atmosphere in either flame or oven dried glassware. Unless otherwise noted, all $^1$H and proton decoupled $^{13}$C NMR spectra were collected in deuterated chloroform (CDCl$_3$) using a Bruker Ultra-shield Avance III NMR spectrometer operating at either 500 MHz of 400 MHz ($^1$H NMR) and 125 MHz or 100 MHz ($^{13}$C NMR), respectively. Chemical shifts were reported in parts per million ($\delta$ scale) and coupling constant ($J$ values) are reported in Hertz (Hz). Tetramethylsilane (TMS) was used as an internal standard ($\delta = 0$ ppm). Optical rotation data were collected on a JASCO P-1010 digital polarimeter operating at 589 nm in an 8 $\times$ 100 nm cell. Infrared spectra were recorded using NaCl plates. IR values are reported in reciprocal centimeters ($\text{cm}^{-1}$) and were measured either as a nujol mull or as a neat liquid film from an evaporated chloroform solution. For ESI-HRMS, samples were prepared in concentrations of 5-25 ppm in high-performance liquid chromatography grade methanol/water/formic acid (1:1:0.01). Melting points were recorded on a Mel-Temp apparatus. High resolution mass spectra were obtained using a ThermoScientific Q-Exactive ESI mass spectrometer equipped with an Orbitrap mass analyzer. The parts per million (ppm) mass error is reported as the absolute value.
(4R)-4-Phenyl-1,3-oxazolidine-2-thione (4.13). To a flame-dried, nitrogen-purged 2000 mL round bottom flask fitted with a Claisen adapter with a pressure equalizing addition funnel and a condenser and equipped with a large stir bar were added D-phenylglycinol (41.16 g, 300.0 mmol), ethanol (300 mL), potassium carbonate (20.85 g, 150.0 mmol), and carbon disulfide (36.3 mL, 600 mmol). The reaction was heated (50 °C) using a heating mantle and a variable transformer, and hydrogen peroxide (51 mL, 450 mmol) was added dropwise. The reaction becomes very exothermic during the addition of the hydrogen peroxide. The reaction mixture was stirred for a period of 15 min. The reaction mixture was cooled to ambient temperature and gravity filtered into a 1000 mL round bottom flask. The residue from the reaction flask was washed with ethyl acetate (3 × 80 mL), combined with the filtered reaction mixture, and the solvent was removed by rotary evaporation. The residue was re-dissolved in ethyl acetate (200 mL) and extracted with HCl (2 × 50 mL). The organic layer was washed with brine (20 mL), dried over MgSO₄, and filtered. The solvent was removed by rotary evaporation, and the crude product was recrystallized using hexanes and ethyl acetate to yield the product as a yellow, crystalline solid (41.9 g, 234 mmol, 78% yield). Melting point: 121 – 122 °C. \([\alpha]_D^{24} = -70.4 (c = 0.2670, \text{CHCl}_3)\). \(^1\)H NMR (400 MHz, CDCl₃): \(\delta\) 7.51 (broad singlet, 1H), 7.45-7.30 (m, 5H), 5.11 (dd, \(J = 9.2, 6.9\) Hz, 1H), 5.00 (app. triplet, \(J = 9.2\) Hz, 1H), 4.49 (dd, \(J = 9.2, 6.9\) Hz, 1H) ppm. \(^{13}\)C \(^1\)H NMR (100 MHz, CDCl₃): \(\delta\) 189.7, 138.0, 129.3, 129.1, 126.3, 77.7, 60.2 ppm. IR (CHCl₃): 1519, 1215, 1170, 700 cm⁻¹. ESI-HRMS \(m/z\): [M + H]⁺ calcd for \(C_9H_{16}NOS^+\), 180.0478; found, 180.0481. Mass error = 1.6 ppm.
(4R)-3-[(p-Methoxyphenoxy)acetyl]-4-phenyl-1,3-oxazolidine-2-thione (4.14). To a flame-dried, nitrogen-purged 1000 mL round bottom flask equipped with a stir bar were added oxazolidine-2-thione (4.13) (17.9 g, 100 mmol), methylene chloride (200 mL), p-methoxy phenoxy acetic acid (20.0 g, 110 mmol), EDC (21.1 g, 110 mmol), and DMAP (0.610 g, 5 mmol). The reaction mixture was stirred overnight and then extracted. The reaction mixture was sequentially treated with HCl (1 M, 50 mL), NaOH (1 M, 2 × 50 mL), and brine (50 mL). The organic layer was collected, dried (MgSO₄), and gravity filtered. The solvent was removed by rotary evaporation. The crude product was recrystallized using ethyl acetate and hexanes to afford the product as a crystalline solid (27.80 g, 81 mmol, 81%). Mp: 109 – 110 °C. 

$[\alpha]_D^{25} = -73.9 \ (\text{CHCl}_3, \ c = 1.04)$. $^1$H NMR (400 MHz, CDCl₃): δ 7.41-7.30 (m, 5H), 6.82-6.76 (m, 4H), 5.73 (dd, $J = 9.0, 3.2$ Hz, 1H), 5.57 (d, $J = 17.7$ Hz, 1H), 5.45 (d, $J = 17.7$ Hz, 1H), 4.90 (app. triplet, $J = 9.0$ Hz, 1H), 4.58 (dd, $J = 9.0, 3.2$ Hz, 1H), 3.74 (s, 3H) ppm. $^{13}$C {¹H} NMR (100 MHz, CDCl₃): δ 185.0, 169.0, 154.5, 151.8, 138.2, 129.3, 129.1, 126.3, 115.9, 114.7, 75.4, 70.2, 62.1, 55.7 ppm. IR (CHCl₃): 1721, 1206, 786 cm⁻¹. ESI-HRMS $m/z$: [M + Na]$^+$ calcd for C₁₈H₁₇NNaO₄S $^+$, 366.0770; found, 366.0776. Mass error = 1.6 ppm.
**Phenylbutanoyl]-4-phenyl-1,3-oxazolidine-2-thione (4.15).** To a flame-dried, nitrogen-purged 4000 mL round bottom flask equipped with a large stir bar were added acylated thione (4.14) (12.0 g, 34.9 mmol), and anhydrous methylene chloride (1,200 mL). The reaction vessel was chilled to -78 °C with a dry ice/ethanol bath, and titanium tetrachloride (1 M in CH₂Cl₂, 37.5 mL, 37.5 mmol) was added dropwise by syringe. This solution was stirred for 30 min, at which point triethylamine (11 mL, 77 mmol) was added by syringe. The color of the solution transitioned from an amber color to that of deep purple upon addition of the triethylamine. This solution was stirred for 30 minutes, at which point another addition of titanium tetrachloride (37.5 mL, 37.5 mmol) was added via syringe. Care was taken to ensure that the -78 °C temperature was maintained throughout these additions. The reaction was stirred for a final 30-minute interval, at which point freshly distilled phenylacetaldehyde (8.5 mL, 77 mmol) was added to the reaction vessel by syringe. The reaction mixture was allowed to stir for a final 3.5 hours, after which brine (200 mL) was added to quench the reaction. The reaction contents were allowed to gradually warm up to room temperature, transferred to a separatory funnel, and then extracted twice with 1 M HCl (100 mL). The organic layer was separated from the aqueous later and subsequently washed with brine (100 mL), dried over MgSO₄, and gravity filtered. The solvent was then removed by rotary evaporation to yield the crude reaction product, which was then recrystallized using hexanes and ethyl acetate to afford the pure product as a white, crystalline...
solid (14.34 g, 30.86 mmol, 89% yield). Mp: 184 – 185 °C. $[\alpha]^2_D = -105.8$ (CHCl₃, c = 1.10). ¹H NMR (400 MHz, CDCl₃): $\delta$ 7.38-7.17 (m, 11H), 6.86-6.80 (m, 4H), 5.70 (dd, $J = 9.2, 5.9$ Hz, 1H), 4.85 (app. triplet, $J = 9.2$ Hz, 1H), 4.55-4.51 (m, 1H), 4.48 (dd, $J = 9.2, 5.9$ Hz, 1H), 3.76 (s, 3H), 3.06-2.94 (m, 2H) ppm. ¹³C {¹H} NMR (100 MHz, CDCl₃): $\delta$ 185.4, 170.4, 154.7, 151.1, 137.3, 137.0, 129.7, 129.2, 129.1, 128.5, 126.7, 126.5, 116.3, 114.9, 77.5, 74.7, 73.2, 62.6, 55.7, 40.4 ppm. IR (CHCl₃): 3424, 1717, 1216, 757 cm⁻¹. ESI-HRMS m/z: [M + Na]^+ calcd for C₂₆H₂₅NNaO₅S·Na^+, 486.1346; found, 486.1349. Mass error = 0.6 ppm.

(2S, 3R)-3-hydroxy-N-isobutyl-2-(p-methoxyphenoxy)-4-phenylbutanamide (4.16). To a flame-dried, nitrogen-purged 500 mL round bottom flask equipped with a stir bar were added aldol product (4.15) (10.0 g, 21.57 mmol), methylene chloride (70 mL), and imidazole (4.40 g, 64.70 mmol). The reaction vessel was allowed to stir for 60 minutes, at which point isobutylamine (4.3 mL, 43.10 mmol) was added by syringe. The reaction was stirred overnight and stopped the next day. The reaction contents were diluted with methylene chloride (80 mL), transferred to a separatory funnel, and extracted with 2.0 M NaOH (2 × 40 mL). The organic layer was separated from the aqueous layer and extracted again with 1.0 M HCl (2 × 40 mL). The organic layer was washed with brine (40 mL), dried over magnesium sulfate, and gravity filtered. The solvent was then removed by rotary evaporation to yield the crude reaction product, which was then recrystallized using hexanes and ethyl acetate to
afford the pure product as a white solid (6.33 g, 17.7 mmol, 82% yield). Mp: 102 – 103 °C. 
\[\alpha\]_D^{24} = -6.51 (CHCl₃, c = 1.04). ¹H NMR (500 MHz, CDCl₃): δ 7.27-7.16 (m, 5H), 6.88 (d, \( J = 9.3 \) Hz, 2H), 6.84 (d, \( J = 9.3 \) Hz, 2H), 6.60 (broadened triplet, 1H), 4.49 (d, \( J = 3.0 \) Hz, 1H), 4.30 (broad singlet, 1H), 3.78 (s, 3H), 3.17-3.09 (m, 2H), 2.97 (dd, \( J = 13.8, 5.2 \) Hz, 1H), 2.90 (dd, \( J = 13.8, 8.4 \) Hz, 1H), 2.77 (d, \( J = 7.5 \) Hz, 1H), 1.80-1.70 (m, 1H), 0.86 (d, \( J = 6.7 \) Hz, 3H), 0.85 (d, \( J = 6.7 \) Hz, 3H) ppm. ¹³C {¹H} NMR (125 MHz, CDCl₃): δ 170.3, 155.1, 151.3, 137.7, 129.4, 128.5, 126.6, 116.6, 115.0, 80.7, 73.0, 55.7, 46.4, 39.6, 28.5, 20.0, 19.9 ppm. IR (nujol): 3310, 1653, 1215 cm⁻¹. ESI-HRMS m/z: [M + Na]⁺ calcd for C₂₁H₂₇NNaO₄S⁺, 380.1832; found, 380.1840. Mass error = 2.1 ppm.

(2R,3S)-2-hydroxy-4-(isobutylamino)-3-(p-methoxy phenoxy)-1-phenylbutane (4.17). To a flame-dried, nitrogen purged 1000 mL round bottom flask mounted over a heating mantle with variable transformer and fitted with a Claisen adapter equipped with a condenser and pressure equalizing addition funnel were added β-hydroxyamide (4.16) (13.26 g, 37.09 mmol) and THF (180 mL). Sodium borohydride (3.37 g, 89.01 mmol) was added incrementally to the flask and stirring was initiated. A solution of iodine (10.36 g, 40.80 mmol) in THF (70 mL) was prepared and added to the additional funnel, whereafter dropwise addition of this solution into the reaction flask was completed over the course of 15 minutes. The reaction was heated to reflux and was allowed to stir overnight. The reaction was gradually

80
cooled to 0 °C and methanol (50 mL) was added and the system was stirred for 30 minutes to quench the active borane reagent. The mixture was concentrated under reduced pressure, and then extracted with EtOAc (150 mL) and 1 M NaOH (3 × 50 mL). The organic layer was washed with brine (50 mL), dried over magnesium sulfate, and gravity filtered. The solvent was then removed by rotary evaporation to afford the corresponding amino alcohol as a colorless oil that was used in the next step without further purification (11.36 g, 33.06 mmol, 89% yield). \([\alpha]^{24}_D = -52.5\) (CHCl₃, c = 1.17). ¹H NMR (500 MHz, CDCl₃): \(\delta\) 7.26-7.14 (m, 5H), 6.88-6.82 (m, 4H), 4.19 (td, \(J = 7.0, 1.9\) Hz, 1H), 4.08-4.06 (m, 1H), 3.78 (s, 3H), 3.27 (dd, \(J = 12.7, 4.3\) Hz, 1H), 3.03-2.93 (m, 2H), 2.73 (dd, \(J = 12.7\) Hz, 2.4 Hz, 1H), 2.42 (dd, \(J = 11.5, 6.5\) Hz, 1H), 2.32 (dd, \(J = 11.5, 7.0\) Hz, 1H), 1.73-1.65 (m, 1H), 0.89 (d, \(J = 6.7\) Hz, 3H), 0.88 (d, \(J = 6.7\) Hz, 3H) ppm. ¹³C {¹H} NMR (100 MHz, CDCl₃): \(\delta\) 154.4, 151.7, 138.7, 129.5, 128.4, 126.2, 117.3, 114.9, 76.6, 75.9, 58.0, 55.7, 50.6, 39.8, 28.2, 20.6, 20.5 ppm. IR (CHCl₃): 3168, 1218, 827, 754 cm⁻¹. ESI-HRMS m/z: [M + H]⁺ calcd for C₂₁H₃₀NNaO₃⁺, 344.2220; found, 344.2220. Mass error = 0.0 ppm.
(2R,3R)-3-(p-Methoxyphenoxy)-4-((p-nitrobenzene-N-isobutyl)-sulfonamido)-1-phenyl-2-(p-nitrobenzenesulfonato) butane (4.18). To a nitrogen-purged 250 mL round bottom flask equipped with a stir bar were added amino alcohol (4.17) (5.54 g, 16.1 mmol), dichloromethane (50 mL), and vigorous stirring was initiated. Once the amino alcohol substrate had fully dissolved, p-nitrobenzenesulfonyl chloride (8.95 g, 40.3 mmol), DMAP (1.48 g, 12.1 mmol), and triethylamine (6.80 mL, 48.3 mmol) were added. Vigorous stirring was maintained, and the system was allowed to stir overnight. The reaction contents were diluted with dichloromethane (80 mL), transferred to a separatory funnel, and extracted with 1 M HCl (2 × 40 mL). The organic layer was then washed with brine (40 mL), dried over magnesium sulfate, gravity filtered, and concentrated under reduced pressure. Purification by flash chromatography on SiO₂ with 1% MeOH/CH₂Cl₂ provided the desired bis-sulfonylated product, which was then recrystallized using hexanes and ethyl acetate to afford the target as a yellow, crystalline solid (9.14 g, 12.8 mmol, 80% yield). Mp: 161-162 °C. [α]D²⁴ = +113.1 (CHCl₃, c = 1.02). ¹H NMR (500 MHz, CDCl₃): δ 8.19 (d, J = 8.9 Hz, 2H), 7.98 (d, J = 8.9 Hz, 2H), 7.96 (d, J = 8.9 Hz, 2H), 7.50 (d, J = 8.9 Hz, 2H), 7.06 (t, J = 7.4 Hz, 1H), 6.96 (t, J = 7.4 Hz, 2H), 6.77 (d, J = 9.2 Hz, 2H), 6.73 (d, J = 7.4 Hz, 2H), 6.69 (d, J = 9.2 Hz, 2H), 4.80-4.77 (m, 1H), 4.68-4.65 (m, 1H), 3.87 (d, J = 15.5 Hz, 1H), 3.78 (s, 3H), 3.62 (dd, J = 15.5, 9.4 Hz, 1H), 3.28 (dd, J = 13.6, 8.6 Hz, 1H), 3.11 (dd, J = 13.6, 6.6 Hz, 1H), 3.05 (dd, J = 14.6, 2.2 Hz, 1H), 2.64 (dd, J = 14.6, 10.8 Hz, 1H).
Hz, 1H), 2.15-2.06 (m, 1H), 0.96 (d, J = 6.7 Hz, 3H), 0.95 (d, J = 6.7 Hz, 3H) ppm. $^{13}$C {${}^1$H} NMR (100 MHz, CDCl$_3$): δ 155.0, 150.4, 149.8, 149.7, 146.0, 140.5, 135.6, 129.0, 128.7, 128.6, 128.3, 126.9, 124.3, 124.0, 116.3, 114.9, 82.5, 75.6, 56.2, 55.7, 46.7, 34.1, 26.3, 19.9, 19.8 ppm.

IR (CHCl$_3$): 1531, 1350 cm$^{-1}$. ESI-HRMS m/z: [M + Na]$^+$ calcd for C$_{33}$H$_{35}$N$_3$NaO$_{11}$S$_2^+$, 736.1605; found, 736.1606. Mass error = 0.1 ppm.

(2R,3S)-3-azido-2-(p-Methoxyphenoxy)-1-((p-nitro benzene-N-isobutyl)-sulfonamido)-4-phenyl butane (4.19). To a flame-dried, nitrogen-purged 100 mL round bottom flask equipped with a stir bar were added bis-sulfonylated substrate (4.18) (2.00 g, 2.80 mmol) and DMSO (12 mL). After the substrate had fully dissolved, sodium azide (0.551 g, 8.41 mmol) was added, and the system was allowed to stir overnight. The system was transferred to a separatory funnel, diethyl ether (150 mL) was added, and the material was extracted with 1 M HCl (2 × 40 mL). The organic layer was washed with brine (30 mL), dried over magnesium sulfate, and gravity filtered. The solvent was then removed by under reduced pressure to afford the target azide product as a yellow oil that was used in the next step without further purification (1.55 g, 2.79 mmol, near quantitative yield). $[^{[\alpha]}]_D^{24} = +3.51$ (CHCl$_3$, c = 1.05). $^1$H NMR (500 MHz, CDCl$_3$): δ 8.11 (d, J = 8.8 Hz, 2H), 7.84 (d, J = 8.8 Hz, 2H), 7.40-7.25 (m, 5H), 6.64 (d, J = 9.1 Hz, 2H), 6.37 (d, J = 9.1 Hz, 2H), 4.34 (dt, J = 9.3, 2.5 Hz, 1H), 3.94 (td, J = 7.6 Hz, 2.5 Hz, 1H), 3.75 (dd, J = 15.5, 2.3 Hz, 1H), 3.72 (s, 3H), 3.49 (dd, J = 15.5, 9.3 Hz, 1H), 3.23 (dd, J
= 13.6, 8.1 Hz, 1H), 3.02 (dd, J = 13.6, 7.0 Hz, 1H), 2.86 (dd, J = 14.0, 7.9 Hz, 1H), 2.79 (dd, J = 14.0, 7.4 Hz, 1H), 2.08-2.00 (m, 1H), 0.91 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.7 Hz, 3H) ppm. ¹³C {¹H} NMR (100 MHz, CDCl₃): δ 154.6, 149.8, 149.6, 146.0, 136.6, 129.3, 128.9, 128.1, 127.3, 124.2, 116.5, 114.7, 77.9, 63.7, 57.4, 55.6, 47.6, 37.2, 26.7, 20.0, 19.9 ppm. IR (CHCl₃): 2119, 1532, 1350 cm⁻¹. ESI-HRMS m/z: [M + H]⁺ calcd for C₂₇H₃₂N₅O₆S⁺, 554.2068; found, 554.2064. Mass error = 0.7 ppm.

(2R, 3S)-3-azido-2-hydroxy-1-((p-nitrobenzene-N-isobutyl)-sulfonamido)-4-phenyl butane (4.20). To a nitrogen-purged 250 mL round bottom flask equipped with a stir bar was added azide substrate (4.19) (1.89 g, 3.41 mmol). Acetonitrile (56 mL), and deionized water (14 mL) were added in a 4:1 ratio to achieve an overall concentration of 0.05 M. Ceric ammonium nitrate (7.48 g, 13.7 mmol) was added, at which point an immediate dark color change was observed, which resolved to a deep orange color over time. The system was allowed to stir for 90 minutes. The reaction was quenched with brine (20 mL), and the system was placed under rotary evaporation to remove excess acetonitrile. The concentrate was then diluted with diethyl ether (150 mL), transferred to a separatory funnel, and extracted with brine (2 × 20 mL). The organic layer was dried over Mg₂SO₄, gravity filtered, and concentrated under reduced pressure. The resulting crude residue was purified over silica using a mobile phase gradient (95:5 → 80:20 hexanes/EtOAc) to afford the target azido alcohol as a dark, viscous oil.
(0.683 g, 1.53 mmol, 45% yield). \([\alpha]^{23}_D = -3.2\) (CHCl₃, \(c = 1.19\)). ¹H NMR (500 MHz, CDCl₃): δ 8.38 (d, \(J = 8.8\) Hz, 2H), 7.99 (d, \(J = 8.8\) Hz, 2H), 7.35-7.32 (m, 2H), 7.29-7.25 (m, 3H), 3.79-3.75 (m, 1H), 3.66-3.62 (m, 1H), 3.31 (dd, \(J = 15.2, 9.3\) Hz, 1H), 3.20 (dd, \(J = 15.2, 2.4\) Hz, 1H), 3.09-3.04 (m, 3H), 2.93 (dd, \(J = 13.5, 6.9\) Hz, 1H), 2.83 (dd, \(J = 14.1, 8.9\) Hz, 1H), 1.89-1.80 (m, 1H), 0.92 (d, \(J = 6.7\) Hz, 3H), 0.87 (d, \(J = 6.6\) Hz, 3H) ppm. ¹³C {¹H} NMR (100 MHz, CDCl₃): δ 150.1, 144.7, 137.1, 129.3, 128.8, 128.6, 127.0, 124.5, 71.6, 66.6, 58.0, 52.0, 36.8, 26.9, 20.0, 19.8 ppm. IR (CHCl₃): 3515, 2111, 1531, 1350 cm⁻¹. ESI-HRMS \(m/z\): [M + Na]⁺ calcd for \(C_{20}H_{25}N_5NaO_5S^+\), 470.1469; found, 470.1480. Mass error = 2.3 ppm.

(3R, 3aS, 6aR)-Hexahydrofuro[2,3-b]furan-3-yl-((2S, 3R)-4-((4-amino-N-isobutylphenyl)-sulfonamido)-3-hydroxy-1-phenyl-butan-2-yl) carbamate (4.1).

To a nitrogen-purged 250 mL round bottom flask equipped with a stir bar were added azido alcohol (4.20) (0.680 g, 1.52 mmol), MeOH (15 mL), and activated palladium on carbon (70 mg, 10% wt/wt). The flask was equipped with a hydrogen balloon, and the system was stirred for 17 hours. The mixture was then filtered through Celite with ethyl acetate, concentrated under reduced pressure, and reconstituted in THF (15 mL). Carbonate (4.27) (0.412 g, 1.53 mmol) and triethylamine (0.32 mL, 2.28 mmol) was added, and the system was stirred overnight. The
material was concentrated under reduced pressure and subsequently purified over silica using 50% EtOAc/CH₂Cl₂ as the eluent to yield inhibitor (Darunavir) as an amorphous solid (0.429 g, 0.78 mmol, 52% yield). Mp: 74-75 °C. $[\alpha]_{D}^{25} = -2.40$ (CHCl₃, c = 1.04). $^1$H NMR (500 MHz, CDCl₃): δ 7.55 (d, $J = 8.0$ Hz, 2H), 7.29-7.19 (m, 5H), 6.68 (d, $J = 8.0$ Hz, 2H), 5.64 (d, $J = 5.1$ Hz, 1H), 5.03-4.95 (m, 2H), 4.34-4.08 (broad singlet, 2H), 3.96-3.92 (m, 1H), 3.90-3.82 (m, 3H), 3.73-3.65 (m, 3H), 3.19-2.75 (m, 7H), 1.87-1.77 (m, 1H), 1.67-1.58 (m, 1H), 1.54-1.44 (m, 1H), 0.93 (d, $J = 6.6$ Hz, 3H), 0.88 (d, $J = 6.6$ Hz, 3H) ppm. $^{13}$C {$^1$H} NMR (125 MHz, CDCl₃): δ 155.5, 151.0, 137.8, 129.5, 129.4, 128.5, 126.5, 125.9, 114.1, 109.3, 73.4, 72.9, 70.9, 69.6, 58.8, 55.2, 53.7, 45.4, 35.7, 27.3, 25.8, 20.2, 20.0 ppm. IR (CHCl₃): 3492, 3415, 1717, 1151 cm⁻¹.

ESI-HRMS m/z: [M + H]$^+$ calcd for C₂₇H₃₈N₃O₇S⁺, 548.2425; found, 548.2418. Mass error = 1.3 ppm.
CHAPTER V: A NEW DIRECTION FOR THE CURTIUS REARRANGEMENT IN THE DEHOMOLOGATION OF ALPHA-ALKOXYCARBOXYLIC ACIDS

Introduction

The Curtius rearrangement is a well-known organic transformation that involves the synthetic preparation and subsequent thermal decomposition of acyl azides into their corresponding isocyanates. These isocyanates, in turn, may be converted to the corresponding amines (5.8), carbamates (urethanes, 5.6) or substituted urea derivatives (5.7). The Curtius rearrangement, along with the related reactions of the Hoffmann rearrangement, the Lossen rearrangement, and the Schmidt rearrangement are well-established reactions that have been employed in fundamental synthetic organic chemistry for well over a century.

Scheme 5.1: The Curtius rearrangement.
In reviewing the Curtius rearrangement, it became of interest to exploit the synthetic intermediates that form in the molecular rearrangement of the acyl azide. This analysis gave rise to the hypothesis that is the foundation of this project’s proposal: *The Curtius rearrangement can be expanded in its scope by using carboxylic acids with suitable leaving groups in the α-position such that the end products of the rearrangement are dehomologated aldehydes or ketones.* From this hypothesis, the proposed research seeks to exploit the Curtius rearrangement in a new way that allows for the dehomologation of a carbon chain of a carboxylic acid to form an aldehyde or ketone depending on the level of substitution at the alpha-position of the carboxylic acid. This process would involve the introduction of an alpha-leaving group on the carboxylic acid. This leaving group would cause an alteration of the mechanistic pathway of the reaction once the acyl azide had been formed (Scheme 5.2).

![Scheme 5.2: The proposed alternative route for the Curtius rearrangement.](image)

The carboxylic acid (5.9) bearing the leaving group in the alpha-position would be converted to its corresponding acyl azide (5.10). The initial reaction would be expected to occur as it would under the conventional reaction conditions provided that the α-leaving group is not
too labile. From this stage, the formation of the isocyanate (5.11) via the thermal rearrangement of the acyl azide (5.10) would then be expected to occur. It would then be possible to treat the isocyanate in situ with water to form the carbamic acid (5.12) which in turn would decompose to afford the hemiaminal (5.13). Hemiaminals are known to be unstable and consequently 5.13 would be expected to undergo loss of the alpha-leaving group (-X) to form an imine (5.14) which, in turn, would hydrolyze in the aqueous environment to the corresponding carbonyl compound.

The synthetic/mechanistic pathway of Scheme 5.2 is proposed to be a viable route to testing and achieving the hypothesis and goals of this research, i.e., the Curtius rearrangement of suitably substituted carboxylic acids leading to the preparation of dehomologated aldehydes and ketones. While every step in the proposed synthetic pathway is important, the dehomologation via the loss of the leaving group (-X) is the most critical step. The leaving group that is alpha to the carboxylic acid must be suitable for the hydrolytic degradation of the hemiaminal (i.e., Scheme 5.2, 5.13 → 5.14), but it cannot be too labile as to cause side reactions in the formation of acyl azide 5.10. Scheme 5.3 illustrates the potential for side reactions to occur if the leaving group is too labile [e.g., -X = -Br, -Cl, or -OSO₂R (sulfonates)].
If the alpha-leaving group is too labile, then it would be anticipated that the required azide nucleophile would displace the alpha-leaving group via an S_N2 pathway leading to the formation alpha-azido carboxylic acids (5.16). It is also possible that the reaction conditions might induce an E2 elimination yielding the α,β-unsaturated carboxylic acid (5.17). If the acyl azide were to form in the presence of a good leaving group, then it would not be unreasonable for the appendant azido-nitrogen to cause an intramolecular displacement to occur in a manner similar to the action of the appendant azido-nitrogen in the accepted proposed mechanism of the Staudinger reaction. If the azido group participates in an intramolecular nucleophilic attack, i.e., (Scheme 5.3, 5.10b → 5.18), then the formation of a Favorskii-like intermediate could potentially form. This intermediate could then have several pathways leading to the formation of other unwanted byproducts.
To address the potential issues of nucleophilic substitution, elimination and intramolecular displacement, the leaving group employed would need to be resistant to direct displacement by azide or bimolecular elimination. Ideally, the leaving group would need to be susceptible to nucleophilic displacement in the latter transformation that are proposed to take place (Scheme 5.2, 5.13 → 5.14). To this end, the introduction of alkoxy (RO-), acyloxy (RCO2-), and phenoxy (ArO-) substituents at the alpha-position of the carboxylic acid are proposed (Scheme 5.4). These substituents have limited ability to serve as leaving groups based on their relative acidities/basicities [ROH, pK_a (DMSO) ~ 30; ArOH, pK_a (DMSO) ~ 18; RCOOH, pK_a (DMSO) ~11] and thus would be more suitable candidates for the proposed reaction pathway. With these new leaving group candidates in place, the synthetic pathway would proceed as described in Scheme 5.4. The alpha-substituted carboxylic acid 5.19 would be converted to the corresponding acyl azide 5.20 which would then be heated to cause the thermal rearrangement to isocyanate 5.21.
Scheme 5.4: Curtius dehomologation reaction by the application of alkoxy leaving groups.

Treatment of 5.21 with aqueous acid would yield carbamic acid 5.22 that would ultimately yield hemiaminal 5.23 by extrusion of carbon dioxide. Under the mildly acidic hydrolytic conditions the hemiaminal 5.23 would be expected to undergo transformation to imine 5.14 with variable leaving groups of either alpha-alkoxy groups (5.23a), alpha-phenoxy groups (5.23b), or alpha-acyloxy groups (5.23c). Imine 5.14 would then be hydrolyzed under these same conditions to carbonyl compound 5.15. Thus, the overall process of introducing either alpha-alkoxy, alpha-phenoxy, or alpha-acyloxy substituents would potentially lead to a successful application of the proposed Curtius dehomologation reaction pathway. It is proposed that the successful formation of intermediate 5.22 is the key pivot point representing the most important question in the scientific testing of the original hypothesis of this work: “Is it possible to trigger a
chain dehomologation of a carboxylic acid bearing an oxygen-based leaving group via the Curtius rearrangement?"

Capturing mechanistic intermediates: synthesis and Curtius dehomologation of substrates with varying structural components.

In conjunction with the foundational reactions of Phase 1, there will be a mechanistic study that will be carried out in support of defending the hypothesis of this proposal. To this end, O-acetylmandelic acid (5.24) will be employed as an essential starting material (Scheme 5.5). The first proposed intermediate that will be investigated is the isocyanate 5.26 that is proposed to arise from the thermal rearrangement of acyl azide 5.25. The isolation of 5.26 will be achieved by carrying out the reaction as before and directly recovering the isocyanate from the reaction mixture. The presence of an isocyanate can be confirmed by $^1$H and $^{13}$C NMR spectroscopy, infrared spectroscopy (-N=C=O, wavenumber ~2280-2230 cm$^{-1}$) and electrospray ionization high resolution mass spectrometry (ESI-HRMS).

Scheme 5.5: Trapping intermediates in the proposed Curtius dehomologation reaction.
From this stage the next target in probing the reaction will be reacting the isocyanate 5.26 with either alcohols or amines to form and isolate carbamate derivatives 5.27a-c and urea derivatives 5.28a-c, respectively (Scheme 5.6). Provided that these derivatives are reasonably stable under ambient conditions, these compounds will be fully characterized (NMR, FT-IR, ESI-HRMS).

**Scheme 5.6:** Isocyanate trapping to yield carbamate esters and urea derivatives.

**Results and Discussion**

Work began with a simple test of the process illustrated in Scheme 5.5, using a modified protocol similar to that of Xue and coworkers and pioneered by Yamada and coworkers. To a solution of O-acetylmandelic acid (5.24) dissolved in toluene was added diphenylphosphorylazide (DPPA, 1.1 equivalents) and triethylamine (2 equivalents). The reaction was heated to reflux temperature and allowed to stir overnight. After cooling, treatment
of the reaction with aqueous HCl (1 M) and subsequent extraction with ethyl acetate provided a crude oily residue that was analyzed by \( ^1\text{H} \) NMR spectroscopy. Pleasingly, analysis of the 500 MHz \( ^1\text{H} \) NMR spectrum revealed the presence of signals consistent with benzaldehyde (5.29), with the diagnostic aldehydic proton resonance appearing at 10 ppm (Figure 5.1).

![Diagram of the Curtius dehomologation reaction](image)

**Figure 5.1:** 500 MHz \( ^1\text{H} \) NMR spectrum of the crude extract from the test Curtius dehomologation.

While the initial test yielded a very promising result, more data were necessary to support the proof of concept. Thus, the reaction was repeated using the same conditions, but this time using alpha-methoxyphenylacetic acid (5.30) as the carboxylic acid. This substrate was selected to probe the feasibility of the reaction with a worse leaving group (-OCH₃). Following acidic workup, analysis of the crude material by \( ^1\text{H} \) NMR again revealed that target benzaldehyde (5.29) was in the mixture (Figure 5.2).
While the methodology used to prepare the acyl azides for rearrangement was most likely the easiest to perform operationally, it was still considered important that other routes be explored to compare with the DPPA method. The ability to use a broader range of reagents, even if to achieve the same result, is inherently valuable. Thus, using a method described by Chuang and coworkers⁹¹ – which utilizes oxalyl chloride and sodium azide to achieve the conversion of carboxlic acid to acyl azide – a reaction was carried out using O-acetylmandelic acid (5.24) as the model substrate (Scheme 5.7). As with the previous two reactions, benzaldehyde was again observed in the ¹H NMR spectrum of the crude material.

**Figure 5.2:** 500 MHz ¹H NMR spectrum of the crude reaction mixture using alpha-methoxyphenylacetic acid (5.30).
Scheme 5.7: Alternate Curtius dehomologation using (COCl)₂ and NaN₃.

With the initial benzaldehyde test completed, work proceeded by carrying out a mechanistic study to further support the hypothesis. This would entail observation of the putative intermediates formed over the course of the reaction as depicted in Scheme 5.4. For this study, capture of the isocyanate intermediate (5.21) through derivatization was of greatest initial interest. This capture would be carried out by reaction of 5.26 with some nucleophile (R-NH₂ or R-OH) to form either a urea or carbamate derivative. So, using the conditions as shown in Scheme 5.7, a new reaction was conducted in which 5.24 was treated with oxalyl chloride, sodium azide, and heated to reflux. This was followed by the addition of an amine to form a urea derivative (5.32). Upon purification of the crude reaction mixture and analysis of the 500 MHz ¹H NMR and high-resolution mass spectra, it was revealed that an amide (5.33) had formed as
the major product (Scheme 5.8), with benzaldehyde as the minor product. The expected urea derivative was not observed.

Scheme 5.8: Attempted capture of the isocyanate using an amine nucleophile.

This reaction was repeated using both alpha-acetoxy and alpha-methoxy substituted carboxylic acids, as well as various amine and alcohol nucleophiles. For each reaction, the anticipated urea and carbamate derivatives were not observed, but rather amides and esters were consistently observed as the dominant product with benzaldehyde as a minor product. This strongly implied that reaction of the acyl chloride with the various nucleophiles through a Schotten-Baumann type reaction. The rationale behind these observations is speculative at this time, however poor observed solubility of the sodium azide in various organic solvents (toluene, THF, dichloromethane, & 1,2-dichloroethane) led us to believe that the formation of the acyl azide from the acid chloride was not favored under the given conditions. Contrast this with the benzaldehyde test, which introduced an excess of water to the reaction system and allowed for the solubilization of the azide salt. This solubilized azide nucleophile could – in principle – more
easily attack the acid chloride, which would then undergo rapid rearrangement to the isocyanate and follow the proposed mechanistic pathway. It was also believed that the isocyanate intermediate was too short-lived under reflux conditions (in which ambient moisture makes truly anhydrous conditions difficult to attain) to lend itself to straightforward capture. These considerations, in addition to the fact that this methodology generates more intermediates than the DPPA method, led us to discard the Chuang protocol for the mechanistic study and return to DPPA as the regent of choice for acyl azide formation.

In returning to the original protocol for the Curtius rearrangement, another attempt was made to capture the putative isocyanate intermediate, again with racemic 1-phenylethylamine (5.34). Surprisingly, the anticipated urea derivative – once again – was not observed to form. Instead, a Schiff base that was the condensation product between 5.34 and benzaldehyde was observed as the major product (Scheme 5.9). The identity of this species was determined through literature comparison of the proton NMR and HRMS (Figure 5.3).

Scheme 5.9: Reattempted formation of urea 5.32 using DPPA conditions.
Concerned about the impact of a strong nucleophile on a substrate with a good leaving group, a weaker nucleophile – methanol – was used in an attempt to obtain a methyl carbamate derivative (5.36).

![Figure 5.3: High resolution mass spectrum of the Schiff base product (5.35).](image)

**Figure 5.3:** High resolution mass spectrum of the Schiff base product (5.35).

![Scheme 5.10: Attempted isocyanate capture using methanol via the DPPA method.](image)

**Scheme 5.10:** Attempted isocyanate capture using methanol via the DPPA method.
Yet again, the captured isocyanate remained elusive, with the main product of this reaction being an acetal (5.37) formed between methanol and benzaldehyde (Scheme 5.10).

While the formation of benzaldehyde (and the observed condensation products by extension) was suggestive of the isocyanate, it was not enough to confirm it. With the complications that arose from the derivatization attempts and the complex mixtures of products that formed upon addition of various nucleophiles, it was decided that a direct observation of the isocyanate may prove more straightforward. Thus, to two separate flasks containing either alpha-acetoxy or alpha-methoxy phenylacetic acid was added DPPA and TEA in dichloromethane, and the reactions were stirred under reflux for 1 hour. The flask contents were concentrated under reduced pressure and evaluated through NMR, mass spectrometry, and infrared spectroscopy. Isocyanates show characteristic signals in the infrared (-N=C=O, wavenumber ~2280-2230 cm\(^{-1}\))\(^8\). The results of these experiments were inconclusive, with a complex mixture of products observed and no detectable isocyanate species.

With the inconclusive results following the initial attempts to capture and/or observe the rearrangement products, concerns grew that the acyl azide itself may not be forming as initially suggested. Thus, an attempt was made to isolate and characterize the acyl azide species itself, and thereafter conduct control studies to trigger the rearrangement. If successful, this would further allow for the determination of the threshold of degradation of the isocyanate. So, using conditions as previously described, alpha-acetoxy and alpha-methoxy phenylacetic acid substrates were reacted with DPPA and TEA in acetone (Scheme 5.11). However, in order to prevent the thermal decomposition of the acyl azide into the isocyanate, these reactions were conducted at -5 °C. When the reactions were conducted at cool temperatures, after some time an
observation of aggressive bubbling coming from the reaction flasks were noted. This strongly suggested the release of nitrogen gas, which is characteristic of the Curtius rearrangement mechanism. Following workup and characterization of the major reaction product, it became clear that previously elusive isocyanate species was finally at hand. Using NMR spectroscopy, high resolution mass spectrometry, and infrared spectroscopy, the isocyanate species were finally confirmed to have formed (Scheme 5.11) (Figure 5.4).

Scheme 5.11: Low temperature acyl azide synthesis resulting in formation of isocyanate. The carboxylic acid in this case bears an alpha-methoxy substituent.

Interested in the kinetics of the rearrangement, a series of time-trial studies were carried out. Reactions were re-run in deuterated solvent and progress was monitored in real-time through proton NMR spectroscopy. Using the alpha-substituted carboxylic acids as before, the reactions were prepared using DPPA at high concentration (~0.75 molar) in NMR tubes and spectra were taken in 5-minute time increments. These studies gave rise to observations that suggested the
acyl azide behaves as a transient intermediate (or is so short lived that it cannot be observed on the NMR time scale).

Figure 5.4: High resolution mass spectrum of alpha-methoxy isocyanate (5.40).

Interestingly, the Curtius rearrangement is often referred to as a ‘thermal decomposition’ and conventionally only occurs at elevated temperatures (hence the use of toluene as a common solvent for this reaction, which has a boiling point of 110.6 °C). Thus, the occurrence of a ‘low temperature’, or ‘room-temperature’ Curtius rearrangement is noteworthy. Currently, reports of low-temperature Curtius rearrangements are very limited in the literature, with the few notable exceptions often seeming to be characterized by exotic/unusual substrates and conditions (i.e., Lewis acid or metal additives, strong presence of electron withdrawing substituents, etc.). In the case of the substrates currently under investigation, the presence of an alpha-alkoxy
substituent, the nature of their electron withdrawing capabilities, or by virtue of the substrates being benzylic (or some combination thereof) may be contributing to the observed phenomena. It may be unlikely that the benzylic nature of the carboxylic acid by itself causes the low-temperature rearrangement, as stable acyl azides derived from phenylacetic acid and diphenylacetic acid have been previously isolated. Nevertheless, this discovery of the low-temperature Curtius rearrangement of the substrates helped elucidate the results of the previous experiments carried out at reflux temperatures. It is assumed that the proposed dehomologation is an entropically favored pathway for these alpha-alkoxy substrates to take (irreversible loss of CO₂, and loss of LG). Thus, it is not unreasonable to suggest that the application of heat may have drastically accelerated the degradation of isocyanate to benzaldehyde by reducing the energetic barrier the substrate needed to overcome. This may have led to the observation of condensation products (5.35) (5.37) upon addition of the nucleophiles, as the isocyanate had been missed “by a mile”.

With this newfound knowledge of the room temperature rearrangement, capture of the proposed intermediates was revisited using milder conditions. To a solution of alpha-methoxy phenylacetic acid in acetone was added DPPA and triethylamine. This reaction was not heated to reflux as before and instead allowed to stir at room temperature for 5 hours, at which time 4-nitrobenzyl alcohol (5.41) was added and stirred overnight (Scheme 5.12).
Scheme 5.12: Milder Curtius rearrangement to capture isocyanate.

Following purification and characterization of the major product through $^1$H and $^{13}$C NMR, HRMS, and X-ray crystallography (Figure 5.5), the desired carbamate (5.42) was determined to have been successfully synthesized, supporting the proposed mechanism of the dehomologative Curtius rearrangement!
Figure 5.5: X-ray crystal structure of 5.42. (Courtesy of Dr. Gregory Ferrence, Department of Chemistry, Illinois State University)

Following the successful derivatization of the alpha-alkoxy carboxylic acids, an interest in testing the effects of a more labile leaving group was developed. As suggested earlier, if the alpha-leaving group was too labile, then it would be anticipated that the required azide nucleophile would displace the alpha-leaving group via an $S_N2$ pathway leading the formation alpha-azido carboxylic acids. So, using 4-chlorophenylacetic acid, an alpha-bromination was carried out using $N$-bromosuccinimide (NBS) to afford compound 5.43 (Scheme 5.13). This compound was treated with azide under similar conditions as previously described in an effort to make 4-chlorobenzaldehyde (5.45). The resultant reaction mixture was separated through chromatography and the species were analyzed. As expected, $S_N2$ displacement at the alpha position resulted in the loss of the bromide substituent did occur. A curious minor product of this
reaction was the formation of a crystalline diazide compound (5.49), whose identity was confirmed via X-ray crystallography (Figure 5.6). This product is the likely result of a pathway similar to that depicted in Scheme 5.13, in which an acyl azide formation followed by subsequent Curtius rearrangement to isocyanate is proceeded by an additional attack by a third equivalent of azide, leading to 5.49. A similar minor product was observed during the studies on the alpha-acetoxy system as well, using the Chuang protocol and an excess of sodium azide.

Scheme 5.13: Potential pathway taken by 5.43 to give diazo compound (5.49).
Figure 5.6: X-ray crystal structure of 5.49. (Courtesy of Dr. Gregory Ferrence, Department of Chemistry, Illinois State University)

Conclusions

Ultimately, a successful study in support of the proposed Curtius dehomologation pathway was carried out. Currently, the Curtius project still remains in its very early stages. For future work, the Hitchcock group intends to proceed with the project outline as discussed in the introduction of this chapter. Namely, the group seeks to: 1) create catalog of aldehydes & ketones, 2) test additional substrate to solidify the understanding of the mechanism, 3) further investigate the scope of the reaction and tolerable leaving groups, and 4) probe the stereochemical integrity of the rearrangement.
Experimental

General Remarks:

All chemical agents and solvents were purchased and used without further purification. All reactions were conducted under a nitrogen atmosphere in either flame or oven dried glassware. Unless otherwise noted, all $^1$H and proton decoupled $^{13}$C NMR spectra were collected in deuterated chloroform (CDCl$_3$) using a Bruker Ultra-shield Avance III NMR spectrometer operating at either 500 MHz of 400 MHz ($^1$H NMR) and 125 MHz or 100 MHz ($^{13}$C NMR), respectively. Chemical shifts were reported in parts per million ($\delta$ scale) and coupling constant ($J$ values) are reported in Hertz (Hz). Tetramethysilane (TMS) was used as an internal standard ($\delta = 0$ ppm). Infrared spectra were recorded using NaCl plates. IR values are reported in reciprocal centimeters (cm$^{-1}$) and were measured either as a nujol mull or as a neat liquid film from an evaporated chloroform solution. For ESI-HRMS, samples were prepared in concentrations of 5-25 ppm in high-performance liquid chromatography grade methanol/water/formic acid (1:1:0.01). Melting points were recorded on a Mel-Temp apparatus. High resolution mass spectra were obtained using a ThermoScientific Q-Exactive ESI mass spectrometer equipped with an Orbitrap mass analyzer. The parts per million (ppm) mass error is reported as the absolute value.
**N-(1-methoxy-1-phenylmethyl)-p-nitrobenzyl carbamate (5.42).** To a flame-dried, nitrogen purged, 100 mL round bottom flask was added alpha-methoxyphenylacetic acid (5.38) (0.750 g, 4.51 mmol), triethylamine (0.66 mL, 4.74 mmol), and diphenylphosphoryl azide (1.00 mL, 4.74 mmol). The reaction was stirred for 5 hours at room temperature, at which time 4-nitrobenzyl alcohol (5.41) (0.73 g, 4.74 mmol) was added to the flask. The system was allowed to stir overnight. The system was concentrated under reduced pressure to give a crude extract which was purified over silica using a 85:15 hexanes/EtOAc solvent system as the eluent to afford carbamate (5.42) as a white, crystalline solid (0.285 g, 0.902 mmol, 20% yield). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 8.22 (d, \(J = 8.3 \text{ Hz}, 2\text{H}\)), 7.52 (d, \(J = 8.3 \text{ Hz}, 2\text{H}\)), 7.43-7.33 (m, 5H), 5.87 (d, \(J = 9.5 \text{ Hz}, 1\text{H}\)), 5.36 (d, \(J = 9.5 \text{ Hz}, 1\text{H}\)), 5.25 (s, 2H), 3.47 (s, 3H) ppm. \(^1^3\)C \{\(^1\)H\} NMR (100 MHz, CDCl\(_3\)): \(\delta\) 155.5, 147.7, 143.5, 138.8, 128.8, 128.7, 128.2, 125.9, 123.8, 84.2, 65.5, 55.8 ppm. ESI-HRMS \(m/z\): [M + Na]\(^+\) calcd for \(\text{C}_{16}\text{H}_{16}\text{N}_2\text{NaO}_5^+\), 339.0951; found, 339.0931. Mass error = 5.9 ppm.
REFERENCES


R.; Garrelts, E.; Blumenshine, C. A.; Cooper, T.; Martinez, M.; Hamaker, C. G.; 
Ferrence, G. M.; Hitchcock, S. R. Diastereoselective and Enantioselective Synthesis of α-
p-Methoxyphenoxy-β-Lactones: Dependence on the Stereoelectronic Properties of the β-
Hydroxy-α-p-Methoxyphenoxyacrylic Acid Precursors. J. Org. Chem. 2022, 87 (15), 
9619–9634.

24) Bull, J. A.; Croft, R. A.; Davis, O. A.; Doran, R.; Morgan, K. F. Oxetanes: Recent 
Advances in Synthesis, Reactivity, and Medicinal Chemistry. Chem. Rev. 2016, 116, 
12150-12233.

Agents. VI. The Isolation and Structure of Taxol, a Novel Antileukemic and Antitumor 

26) Marder-Karsenti, R.; Dubois, J.; Bricard, L.; Guenard, D.; Gueritte-Voegelein, F. 
Synthesis and Biological Evaluation of D-Ring-ˈ Modified Taxanes: 5(20)-Azadocetaxel 

27) Wang, M.; Cornett, B.; Nettles, J.; Liotta, D. C.; Snyder, J. P. The Oxetane Ring in 


Oxetin, a New Antimetabolite from an Actinomycete. Fermentation, Isolation, Structure 
and Biological Activity. J. Antibiot. 1984, 37, 1324–1332.
30) Hamberg, M.; Svensson, J.; Samuelsson, B. Thromboxanes: A New Group of

31) Wuitschik, G.; Rogers-Evans, M.; Buckl, A.; Bernasconi, M.; Marki, M.; Godel, T.;
Fischer, H.; Wagner, B.; Parrilla, I.; Schuler, F.; et al. Spirocyclic Oxetanes: Synthesis

32) Burkhard, J. A.; Wuitschik, G.; Plancher, J.-M.; Rogers-Evans, M.; Carreira, E. M.
2013, 15, 4312−4315.

33) Wuitschik, G.; Rogers-Evans, M.; Müller, K.; Fischer, H.; Wagner, B.; Schuler, F.;
Polonchuk, L.; Carreira, E. M. Oxetanes as Promising Modules in Drug Discovery.
Angew. Chem., Int. Ed. 2006, 45, 7736−7739.

34) Burkhard, J.; Carreira, E. M. 2,6-Diazaspiro[3.3]heptanes: Synthesis and Application in

35) Wuitschik, G.; Carreira, E. M.; Wagner, B.; Fischer, H.; Parrilla, I.; Schuler, F.; Rogers-
Evans, M.; Müller, K. Oxetanes in Drug Discovery: Structural and Synthetic Insights. J.

36) Pritchard, J. G.; Long, F. A. The Kinetics of the Hydrolysis of Trimethylene Oxide in
Water, Deuterium Oxide and 40% Aqueous Dioxane 1. J. Am. Chem. Soc. 1958, 80,
4162−4165.


46) Cirrincione, G.; Diana, P. Eight-Membered Rings with Two Heteroatoms 1,3.


50) FDA Approval of HIV Medicines https://hivinfo.nih.gov/understanding-hiv/infographics/fda-approval-hiv-medicines


117
   Interdependence of Inhibitor Recognition in HIV-1 Protease. J. Chem. Theory

   Development and Validation of a Selective, Sensitive and Stability Indicating UPLC–
   MS/MS Method for Rapid, Simultaneous Determination of Six Process Related

   Coupling of Arylboronic Acids with Methyl (E)-4-Bromobut-2-Enoate: Synthesis of
   3931.

   Aoki, M.; Weber, I. T.; Mitsuya, H. Probing Lipophilic Adamantyl Group as the P1-
   Ligand for HIV-1 Protease Inhibitors: Design, Synthesis, Protein X-Ray Structural

59) Graham, B. J.; Windsor, I. W.; Raines, R. T. Inhibition of HIV-1 Protease by a Boronic

60) McKennon, M. J.; Meyers, A. I.; Drauz, K.; Schwarm, M. A Convenient Reduction of

61) Gololobov, Y. G.; Zhmurova, I. N.; Kasukhin, L. F. Sixty Years of Staudinger


APPENDIX A

SELECTED $^1$H AND $^{13}$C NMR SPECTRA
^H NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (100 MHz, DMSO-d$_6$)

Chemical shift values:

- 40.578
- 50.356
- 69.642
- 72.9215
- 75.6350
- 79.9565
- 116.4436
- 116.6510
- 143.8215
- 152.5111
- 152.8811
- 153.8811
- 172.2002
- 172.5002
- 158.2200
$^{1}$H NMR (500 MHz, CDCl$_3$)
$^{13}$C NMR (125 MHz, CDCl$_3$)
$^{1}$H NMR (500 MHz, CDCl$_3$)
$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)
$^{13}$C NMR (125 MHz, CDCl$_3$)

![Chemical Structure](image)
$^{1}$H NMR (500 MHz, CDCl$_3$)
$^{13}$C NMR (125 MHz, CDCl$_3$)
3.19

$^1$H NMR (500 MHz, CDCl$_3$)
$^{13}$C NMR (125 MHz, CDCl$_3$)

3.19
$^1$H NMR (500 MHz, CDCl$_3$)

3.21
$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)
$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (100 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)
$^{13}\text{C} \text{NMR (100 MHz, CDCl}_3\text{)}$
$^1$H NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (100 MHz, CDCl$_3$)
$\text{^1H NMR (500 MHz, CDCl}_3\text{)}$
$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)
$^{13}$C NMR (100 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)
$^{13}$C NMR (100 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)
$^{13}$C NMR (100 MHz, CDCl$_3$)
$^{13}$C NMR (100 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)
$^{13}$C NMR (125 MHz, CDCl$_3$)
\(^1\)H NMR (500 MHz, CDCl\(_3\))
$^{13}$C NMR (100 MHz, CDCl$_3$)