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SYNTHESES OF α,α-DISUBSTITUTED-α-AMINO ACIDS
AND IMIDAZOLINES DERIVED FROM OXAZOL-5(4H)-ONES

presented by

Jason Scott Fisk

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of the requirements for the

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Major Professor's Signature

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SYNTHESES OF α,α-DISUBSTITUTED-α-AMINO ACIDS AND IMIDAZOLINES DERIVED FROM OXAZOL-5(4H)-ONES

By

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ABSTRACT

SYNTHESES OF α,α-DISUBSTITUTED-α-AMINO ACIDS AND IMIDAZOLINES DERIVED FROM OXAZOL-5(4H)-ONES

By

Jason Scott Fisk

The research presented in this dissertation focuses primarily on the development of new synthetic organic methodology utilizing oxazol-5(4H)-ones for the purpose of producing biologically useful heterocyclic compounds. The initial chapter describes and illustrates the general reactivity patterns of oxazol-5(4H)-ones using examples from the current literature. The remainder of the chapters describes studies pertaining to the use of oxazol-5(4H)-ones for synthesizing two different classes of molecules: α,α-disubstituted-α-amino acids and 2-imidazolines.

The first study presented in this dissertation involves a brief structure activity relationship (SAR) investigation of a class of 2-imidazolines found to inhibit NF-κB mediated gene transcription. Previous studies within our research group indicated that oxazol-5(4H)-ones undergo Lewis acid promoted [3+2] cycloadditions with imines to diastereoselectively afford highly substituted 2-imidazolines. Select members of this class of 2-imidazolines were previously found to be relatively potent inhibitors of NF-κB mediated gene transcription. In a collaborative effort to optimize this class of compounds for their ability to inhibit NF-κB mediated gene transcription, our research group conducted a SAR study. Small libraries of 2-imidazolines were synthesized from oxazol-5(4H)-ones and subsequently evaluated for their ability to inhibit NF-κB mediated gene

transcription in both human cervical epithelial (HeLa) cells and human whole blood. Included in this dissertation are the results of this structure activity relationship study, along with a description of the synthetic procedures used to prepare the compounds.

The second study presented in this dissertation describes the development of a novel alkylation reaction of oxazol-5(4H)-ones and its use towards the syntheses of α,α-disubstituted-α-amino acids. The reaction is best described as an intermolecular ene-type reaction of oxazol-5(4H)-ones with enol ethers. This dissertation describes the initial discovery of the reaction along with the exploration of the reaction's substrate scope and mechanism. Using this chemistry, oxazol-5(4H)-ones were alkylated using enol ethers and subsequently derivatized to afford a variety of α,α-disubstituted-α-amino esters. In addition, investigations using Brønsted acid catalysis for improving the overall diastereoselectivity of these reactions are discussed.

This dissertation is dedicated to my late grandmothers: Rose Fisk and Jane Byers. The completion of these studies would not have been possible without the love, guidance and inspiration they provided me throughout my life.

ACKNOWLEDGEMENTS

The successful completion of the requirements for a research doctorate degree in the field of science can be an overwhelming experience involving both harsh disappointments as well as breathtaking triumphs. Often for one to effectively accomplish this task, one must call upon others for help in overcoming the physical and mental challenges at hand. During the course of these studies, I was fortunate enough to have such a support group. Without their help, I truly believe that I would have been successfully at completing this dissertation. Therefore, I would like to take the time to formally thank these people.

To begin with, I would like to thank my graduate advisor, Professor Jetze J. Tepe, for the opportunity to study in his research group. The research experience Professor Tepe provided me not only allowed me improve my expertise as a synthetic chemist, but also helped me to grow overall as a scientist. His style of graduate student advisement was very complimentary to the manner in which I prefer to learn and advance. He allowed me to study relatively independently, thus providing me the opportunity to direct my research in a manner which I found fulfilling. He listened to my thoughts regarding my studies, and only provided criticism when absolutely needed. He also allowed me to learn from my mistakes, never getting too upset as I made them.

Secondly, I would like thank my advisory committee members: Professor William Wulff, Professor Babak Borhan, and Professor Aaron Odom. From an outsider's perspective, it would appear that I did not take full advantage of my

advisory committee as I did not all too often seek their advice or guidance. However, I learned a great deal from them by just merely observing the manner in which they conducted themselves as advisors and scientists. They are truly professionals and do a brilliant job of relaying the knowledge they have learned from their own experiences to their students and other colleagues. As I continue to establish my career, these gentlemen will continue to be role models that I will aspire to become.

Last but certainly not least, I would like to thank my family and friends for their love and support during my dissertation studies. It is not the chemistry or long nights in the lab that I will remember most, but rather the interaction I had with my friends and family. Their love and support during this time meant more to me than they will ever know. I can only hope that the relationships that I established during these studies will continue for the rest of my life. Of these people, I would like to especially thank my wife, Professor Jaime Curtis-Fisk, for her love and support during these studies. She stood by me during both the good and the bad days of graduate school. I love her very dearly, and I look forward to life with her for many years to come.

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KEY TO SYMBOLS AND ABBREVIATIONS

Ac - Acetyl

ALLN – N-acetyl-leucinyl-leucinyl-norleucinal

Ar - Aryl

Bn – Benzyl

CSA – Camphor sulphonic acid

DCE – Dichloroethane

DCC - Dicyclohexylcarbodiimide

DIBALH – Diisobutylaluminum hydride

DKR – Dynamic kinetic resolution

DMAP – 4-dimethylamino pyridine

DMEM – Dulbecco's modified eagle's medium

DMF – Dimethyl formamide

DMSO – Dimethyl sulfoxide

DNA – Deoxyribonucleic acid

DOS – Diversity oriented synthesis

EA – Elemental analysis

EC_{50} – Half maximal effective concentration

EDCI – Ethyldimethylaminopropyl carbodiimide

ELISA – Enzyme linked immunosorbent assay

ESI – Electrospray mass spectrometry

Et - Ethyl

EWG – Electron withdrawing group

FAB – Fast atom bombardment

FDA – Food and drug administration

FMO – Frontier molecular orbital

HeLa – Human cervical epithelial

HOMO – Highest occupied molecular orbital

HPLC – High pressure liquid chromatography

HRMS – High resolution mass spectrometry

IC_{50} – Half maximal inhibitory concentration

I-κB – Inhibitory kappa B

IL– Interleukin

IR - Infrared

LA – Lewis acid

LRMS – Low resolution mass spectrometry

Luc – Luciferase

LUMO – Lowest unoccupied molecular orbital

Me - Methyl

MS – Mass spectrometry

NF-κB – Nuclear transcription factor kappa B

NMR – Nuclear magnetic resonance

Ph – Phenyl

RA – Rheumatoid arthritis

R&D – Research and development

SAR – Structure activity relationship

^{t}Bu – *tert*-butyl

TFA – Trifluoroacetic acid

TFAA – Trifluoroacetic anhydride

TfOH – Triflic acid

THF - Tetrahydrofuran

TIPS – Triisopropylsilyl

TLC – Thin layer chromatography

TMS – Trimethylsilyl

TNF-α – Tumor necrosis factor alpha

TOS – Target oriented synthesis

Ts - Tosyl

UV – Ultraviolet

CHAPTER I

OXAZOL-5(4H)-ONES AS TEMPLATES FOR GENERATING DIVERSE LIBRARIES OF BIOLOGICALLY INTERESTING COMPOUNDS

A. The need for chemical diversity in the drug discovery process

Modern drug discovery involves screening libraries of small molecules for their ability to affect preselected biological targets including proteins and/or biological pathways.[1] The completion of the human genome project has presented researchers with many more potential drug targets that were previously unknown. However, during recent years there has been a steady decline in the number of prescription drugs approved by the Food and Drug Administration (FDA).[2,3] Furthermore, relatively few of the new prescription pharmaceuticals approved by the FDA could be classified as significant improvements over existing drugs.[2,3] Several factors have contributed to the decline in the approval of new pharmaceuticals including the increased expense of researching and developing novel drug candidates.

A second and perhaps more controllable reason for the decline in new drug approvals lies in the structural diversity of the small molecule libraries being screened for drug leads.[3,4] Although pharmaceutical companies are constantly combing nature for new drug leads, most small molecule collections come from commercial suppliers or previous medicinal chemistry projects. These libraries tend to be somewhat focused and lack structural diversity. However, the proteins that carry out biological processes essential

for life are generally complex macromolecules containing high levels of structural diversity. This suggests that the molecular libraries we screen for drug leads should contain a complimentary amount of structural diversity.

Synthetic organic chemists rely on three main approaches for synthesizing small molecules. The first approach is target oriented synthesis (TOS), which relies primarily on nature to discover potential synthetic targets. Synthetic targets may be identified by screening natural product extracts or proposed by means of spectroscopic analysis of target proteins. The second approach that synthetic organic chemists rely on is medicinal or combinatorial chemistry. This involves the structural optimization of an identified drug candidate through the synthesis of analogues. Both TOS and medicinal/combinatorial approaches involve the synthesis of small molecules to perturb a predetermined biological target. Synthetic routes using both approaches are generally linear and/or convergent (Figure I-1). They are planned in a reverse-synthetic order where complex molecules are transformed into simple and smaller precursors by mentally performing chemical reactions in reverse order.

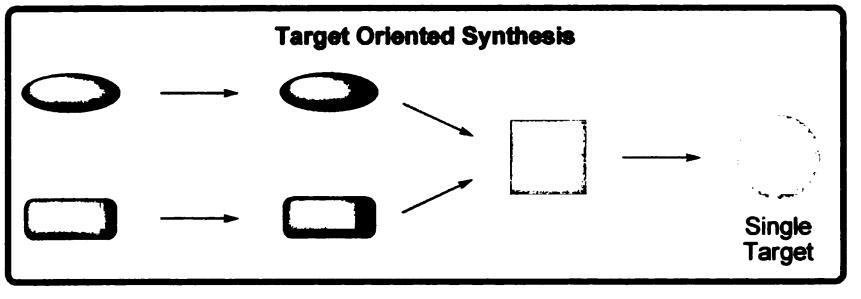


Figure I-1. Convergent synthetic pathway of target oriented synthesis.

Both TOS and medicinal/combinatorial chemistry approaches tend not to efficiently generate libraries of structurally diverse compounds. The goal of both approaches is to access very focused portions of chemical space (Figure I-2, **A**).[3,4] Although synthetic intermediates are generated along the synthetic pathway, many of the structures resemble that of the previous. Molecules with very similar structures quite often possess similar biological profiles. More recently, synthetic chemists have begun to utilize a third approach for generating small molecule libraries referred to as diversity oriented synthesis (DOS). In constrast to TOS and medicinal/combinatorial chemistry approaches, the goal of DOS is to create small molecule libraries comprised of compounds encompassing broad areas of chemical space (Figure I-2, **B**). The combination of DOS along with TOS and medicinal chemistry approaches will hopefully lead to the identification of new drug leads and ultimately to the treatment of disease.

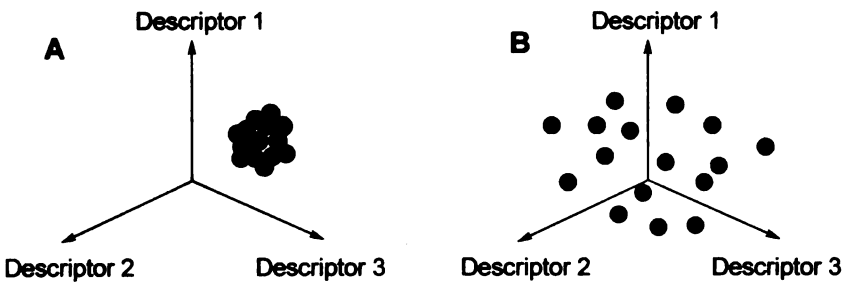


Figure I-2. Comparison of TOS and DOS in terms of structural diversity.

B. Diversity oriented synthesis

During recent years, diversity oriented synthesis has become increasingly important to the development of new pharmaceuticals.[3,4] New synthetic methods are allowing for efficient and rapid production of libraries of small yet complex molecules of biological importance. Screening of these libraries leads not only to identification of new drug candidates, but also to simultaneous identification of therapeutic protein targets with their small molecule regulators.

In contrast to the convergent synthetic pathways used in TOS and medicinal/combinatorial chemistry, DOS rapidly produces libraries of compounds in a divergent manner (Figure I-3). DOS approaches aim to access areas of poorly populated or even vacant chemical space. There typically is no specified target in diversity oriented synthesis, thus retro-synthetic analysis is not applicable to planning. Instead, researchers must utilize more of a "forward-synthetic analysis" when proposing to use DOS. Chemists are to imagine generating complex and diverse molecules from simple precursors. DOS approaches rely on diversity-generating reactions, which are defined as the transformation of similar compounds into diverse libraries of molecules. Synthetic pathways should be no longer than three to five steps and therefore should avoid protection group manipulation when possible. To generate the highest levels of structural diversity, one must utilize reactions that generate molecules containing diversity in terms of core structure, stereochemistry, and functional group appendages.

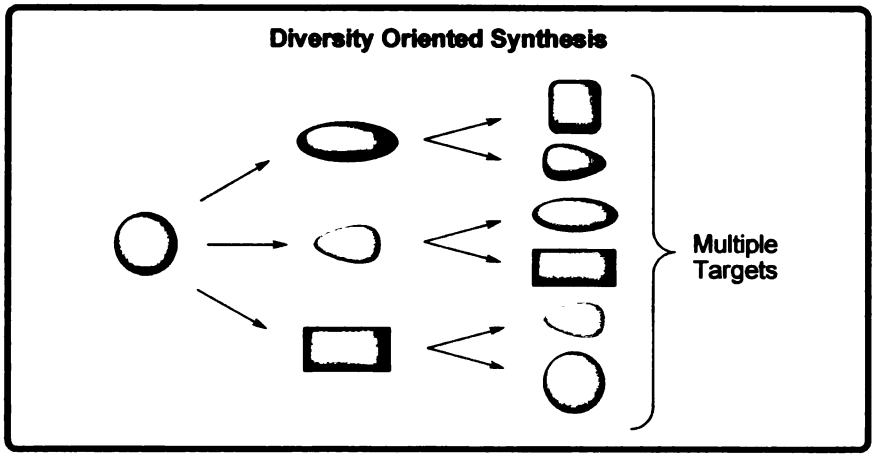


Figure I-3. Divergent pathway of diversity oriented synthesis.

C. Introduction to oxazol-5(4H)-ones

Oxazolones have proven to be very useful substrates in the field of synthetic organic chemistry.[5] They exist in five different isomeric forms as illustrated in Figure I-4. Each isomeric form of oxazolone has unique attributes quite different from the others, making the class of molecules appealing for various applications. As a part of our research program focused on creating highly diverse libraries of small heterocyclic compounds for the purpose of discovering novel biologically active compounds, we have focused on the use of oxazol-5(4H)-ones (also called azlactones) due to their availability and chemical versatility.[6,7]

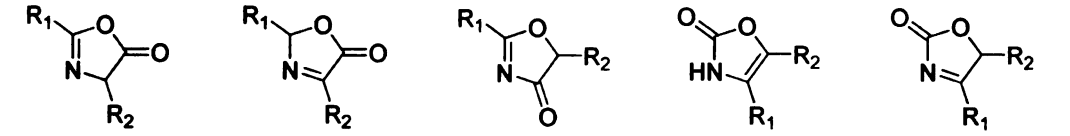
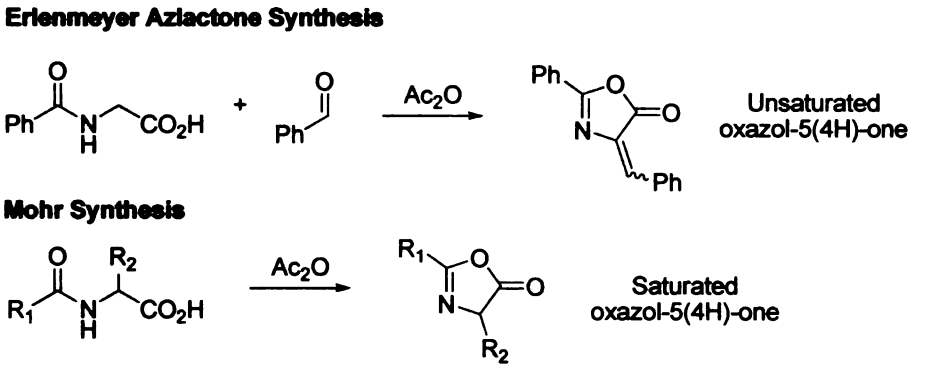


Figure I-4. Various isomeric forms of oxazolones.

Oxazol-5(4H)-ones or azlactones are generally divided into two different classes: saturated and unsaturated (Scheme I-1). The first unsaturated oxazol-5(4H)-one was synthesized by Plöchl more than a century ago in 1883 via a condensation of benzaldehyde with hippuric acid in the presence of acetic anhydride.[8] However, it was Erlenmeyer who established the first correct structure of oxazol-5(4H)-ones naming them "azlactones" in 1900.[9,10] Erlenmeyer was also one of the first scientists to explore the use of other aldehydes in the reaction and to establish the use of unsaturated oxazol-5(4H)-ones as precursors to new amino acid derivatives. The first saturated oxazol-5(4H)-one was not synthesized until 1908 by Mohr and co-workers, as it is believed that researchers before him failed to appreciate the ease at which saturated oxazol-5(4H)-ones can hydrolyze in the presence of moisture.[11] Since that time, new and more efficient methods for producing oxazol-5(4H)-ones have been developed, some of which will be described in the following section.



Scheme I-1. Erlenmeyer and Mohr syntheses of oxazol-5(4H)-ones.

After the early work of Plöchl, Erlenmeyer, and Mohr, the chemistry of oxazol-5(4H)-ones remained fairly unexplored and was mainly limited to using oxazol-5(4H)-ones to make amino acid derivatives. It was not until the 1940's, at which time the structure of penicillin was incorrectly thought to be an oxazol-5(4H)-one,[12] that the chemical potential of oxazol-5(4H)-ones as synthetic intermediates was realized. Although it was eventually determined that the structure of penicillin actually contained a beta lactam ring system instead of an oxazol-5(4H)-one ring, the information obtained from these studies led way to the future development of new chemistry using the oxazol-5(4H)-one scaffold.

A variety of methods appear in the literature for naming oxazol-5(4H)-ones.[10,13] The ring is generally numbered according to the Hantzsch-Wildman rules giving priority to the oxygen atom and numbering the ring in the direction of the nitrogen atom as shown in Figure I-5.[13] One method refers to the oxazol-5(4H)-one substrate as an amino acid derivative.[10] For example, the oxazol-5(4H)-one derived from N-benzoyl alanine would be refered to as

benzoyl alanine azlactone. A second method for naming oxazol-5(4H)-ones describes the substrate as a dihydrooxazole.[13] The oxazol-5(4H)-one derived from N-benzoyl alanine would then be referred to as 5-keto-4-methyl-2-phenyl -4,5-dihydrooxazole. This dissertation will primarily use a third system which consists of naming the scaffold as an oxazolone derivative. The compound is given the parent name of oxazol-5(4H)-one and the substituents are described in correspondence to their position on the ring. Using this system the oxazolone prepared from N-benzoyl alanine would be described as 4-methyl-2-phenyl-5(4H)-oxazolone.

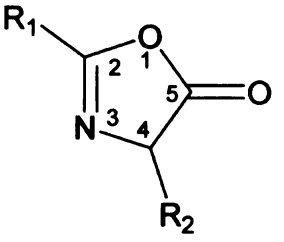
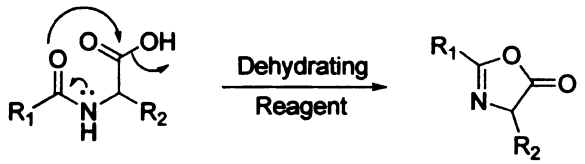


Figure I-5. Numbering of the oxazol-5(4H)-one ring system according to the Hantzsch-Wildman rules.

D. Oxazol-5(4H)-ones as templates in diversity oriented synthesis

Oxazol-5(4H)-ones have multiple features that make them attractive for use as building blocks in diversity oriented synthesis.[7] To begin with, oxazol-5(4H)-ones are easily synthesized from the cyclodehydration of N-acyl-α-amino acids (Scheme I-2). A variety of N-acyl-α-amino acids are available for purchase from commercial suppliers. Furthermore, they are also easily synthesized either under Schotten-Baumann conditions or from the acylation of α-amino esters followed by hydrolysis.[14] As seen in the pioneering studies of Erlenmeyer and Mohr, N-acyl-α-amino acids are traditionally converted into

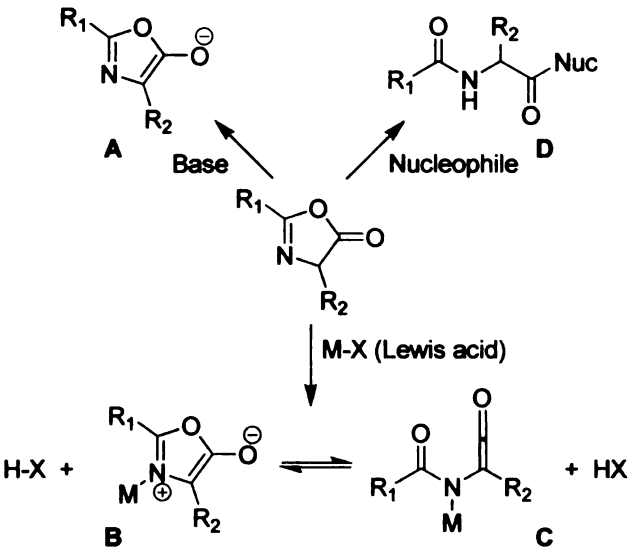
oxazol-5(4H)-ones by refluxing them in acetic anhydride.[9,10] These methods are often met with product isolation struggles directly associated with the problematic removal of the acid byproducts. Presently, oxazol-5(4H)-ones are routinely synthesized in high purity under much milder conditions allowing for them to be subsequently used without the need for further purification. These methods generally consist of using relatively more reactive dehydrating reagents such as activated anhydrides (e.g. trifluoroacetic anhydride) or carbodiimides (e.g. DCC or EDCI).[15]



Scheme I-2. Synthesis of oxazol-5(4H)-ones.

In addition to their ready accessibility, oxazol-5(4H)-ones contain numerous reactive sites allowing for a diverse set of possible transformations. The pluripotent reactivity of oxazol-5(4H)-ones allows for the rapid generation of a wide range of compounds making oxazol-5(4H)-ones ideal starting materials for DOS.[16] The acidic nature of the proton(s) found at the C-4 position (pKa ~ 9)[17] of the oxazol-5(4H)-one scaffold allows for the easy formation of an oxazole enolate, which can react with a range of electrophiles to form both O-alkylated and C-alkylated products (Scheme I-3, **A**). Alternatively, the use of Lewis acids with the oxazol-5(4H)-ones results in the formation of either the 1,3-dipole **B** (also known as a münchnone) or the reactive ketene intermediate **C** (Scheme I-3), each yielding the possibility of synthesizing novel heterocyclic compounds via

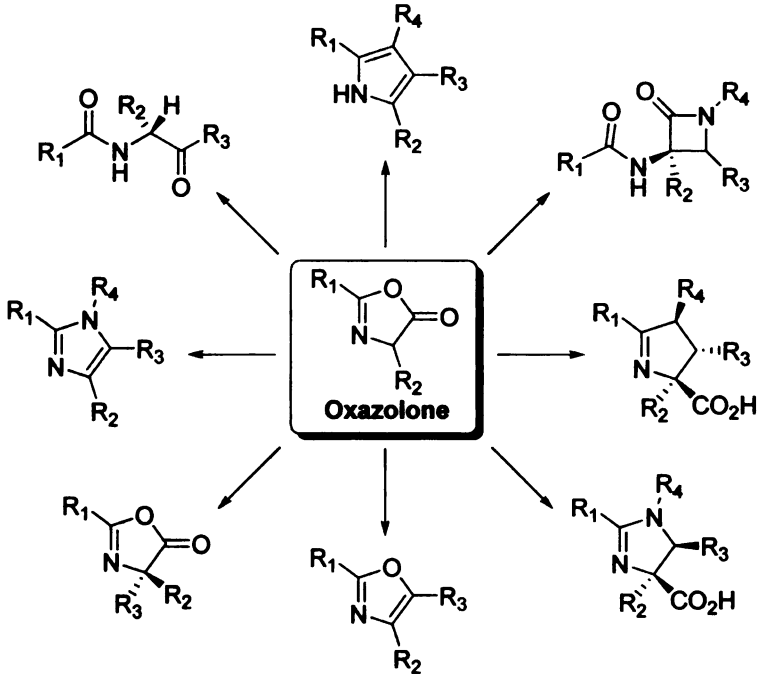
cycloaddition reactions.[18] Additionally, the oxazol-5(4H)-one ring contains a relatively electrophilic carbonyl susceptible to reaction with a wide range of nucleophiles including alcohols, amines, and hydrides to form various types of protected amino acids (Scheme I-3, **D**).



Scheme I-3. Pluripotent reactivity of oxazol-5(4H)-ones.

This diverse reactivity of oxazol-5(4H)-ones makes them excellent substrates for synthesizing a wide variety of useful and biologically interesting molecules (Scheme I-4). Highly substituted heterocyclic scaffolds can be directly accessed from oxazol-5(4H)-ones relatively easily and in a stereoselective manner. Furthermore, natural and unnatural amino acids can also be easily isolated in enantiopure form using oxazol-5(4H)-one intermediates. The remainder of this chapter will aim to illustrate how the pluripotent reactivity of oxazol-5(4H)-ones allows for a wide range of

transformations, which in turn leads to the preparation of diverse libraries of biologically interesting compounds.



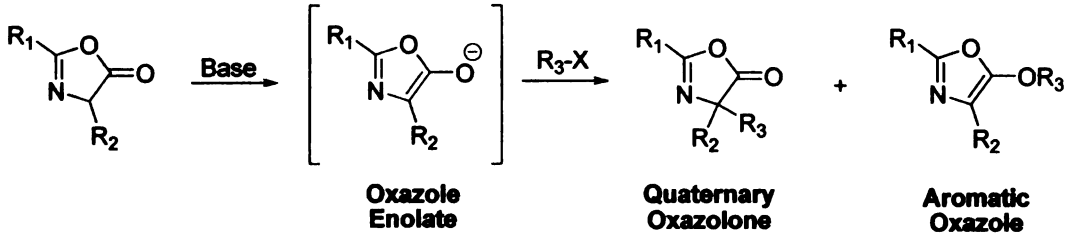
Scheme I-4. Oxazol-5(4H)-ones as building blocks to create diverse libraries of compounds.

E. Oxazol-5(4H)-one transformations associated with their acidity

As compared to their acyclic N-acyl-α-amino acid precursors, oxazol-5(4H)-ones are considerably more acidic.[17,19] Their relatively high acidity in combination with their cyclic/less sterically encumbering structures allows for a variety of transformations generally difficult to perform with acyclic α-amino acids. These transformations include the alkylation, acylation, allylation, and arylation of oxazol-5(4H)-ones, each of which potentially results in the formation of quaternary substituted oxazolones. Subsequent nucleophilic ring opening of

quaternary substituted oxazolones produces a variety of interesting molecules, including novel α,α-disubstituted α-amino acids.

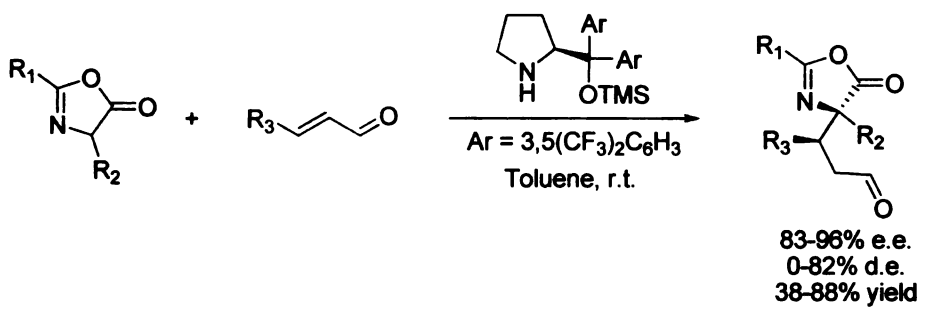
1. Alkylation of oxazol-5(4H)-ones. One of the more traditional methods for synthesizing α,α-disubstituted α-amino acids involves the alkylation of oxazol-5(4H)-ones. Treatment of oxazol-5(4H)-ones with mild bases such as triethylamine or Hünig's base results in the deprotonation of the oxazol-5(4H)-one and formation of an aromatic oxazole enolate.[20] Formation of these oxazole enolates while in the presence of highly reactive electrophiles leads to the formation of the desired quaternary substituted oxazolones (Scheme I-5).[21] These reactions often suffer from the formation of undesired side products primarily due to competitive O-alkylation of the enolate intermediates. Recent developments optimizing the reaction conditions have allowed for the use of a wider range of electrophiles,[21] although O-alkylation still remains a problem with many substrates.



Scheme I-5. Alkylation of oxazol-5(4H)-ones with alkyl halides.

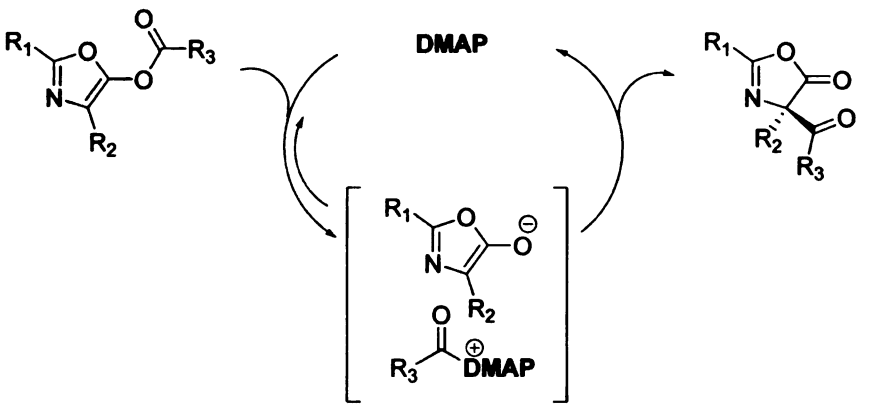
A variety of more regioselective methods have appeared in the literature as of late for the alkylation of oxazol-5(4H)-ones. One of the more recent methods for alkylating oxazol-5(4H)-ones was reported by Jørgensen and co-

workers in 2008.[22] The authors reported an organocatalytic enantioselective Michael addition of oxazol-5(4H)-ones to α,β-unsaturated aldehydes (Scheme I-6). Although these reactions generally proceed with low to moderate diastereoselectivity, they do produce two new stereogenic centers in relatively high yields and moderate to excellent enantioselectivity.



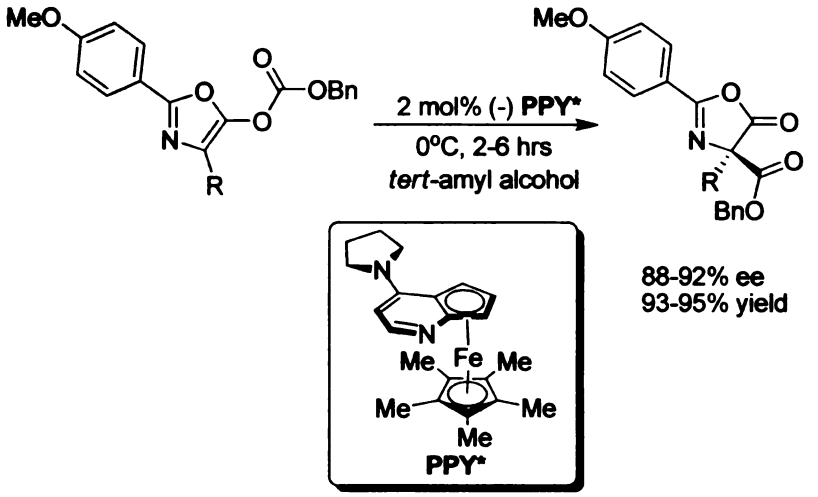
Scheme I-6. Michael addition of oxazol-5(4H)-ones to α,β-unsaturated aldehydes.

2. Acylation of oxazol-5(4H)-ones. The traditional method for synthesizing 4-acyl substituted oxazol-5(4H)-ones is the Steglich rearrangement. The reaction was first discovered by Steglich and co-workers in 1970.[23] The authors reported a nucleophilic base (e.g. DMAP) catalyzed rearrangement of O-acylated oxazoles to form C-4 acylated oxazolones (Scheme I-7). The initial reaction of DMAP with the O-acylated oxazole is believed to be reversible, while formation of the product appears to be an irreversible process (Scheme I-7).[24] Since the initial discovery of the reaction, a variety of chiral nucleophiles have been developed for catalyzing the reaction to make new enantiomerically enriched oxazolone scaffolds.[25]



Scheme I-7. Steglich rearrangement of O-acyl oxazoles.

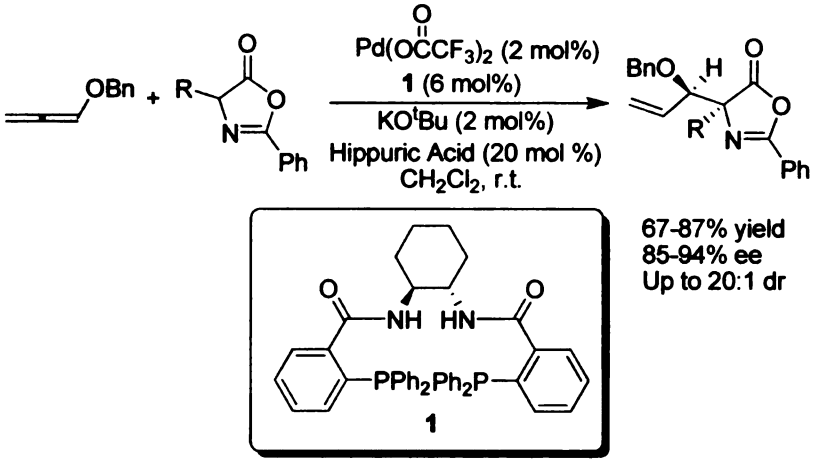
The first asymmetric Steglich rearrangment of oxazol-5(4H)-ones was reported in 1998 by Fu and co-workers.[24,26] The authors reported the use of a chiral ferrocene-fused DMAP derivative, **PPY***, for promoting the asymmetric acyl migration (Scheme I-8). Alkyl substituents at the 2 position of the oxazol-5(4H)-one scaffold generally provide lower enantioselectivity than aryl and heteroaryl substituents at that same position. The reaction tolerates a variety of substituents at the C-4 position of the oxazol-5(4H)-one resulting in high enantioselectivity (Scheme I-8). Choosing the appropriate migrating acyl group can enhance the stereoselectivity of the reaction. The use of benzyl substituted acyl groups tend to result in higher stereoselectivity than most aliphatic groups.[24]



Scheme I-8. Fu's enantioselective Steglich rearrangement.

3. Allylation of oxazol-5(4H)-ones. A third transformation resulting in the formation of quaternary oxazolones is the allylation of oxazol-5(4H)-ones.[27] A variety of transition-metal catalyzed methods have been reported for the allylation of oxazol-5(4H)-ones.[27-29] One of the more recent methods for the allylation of oxazol-5(4H)-ones was reported by Trost and co-workers in 2003. The authors reported a palladium-catalyzed addition of oxazol-5(4H)-ones to electron rich allenes (Scheme I-9).[29] Their methodology avoids any regioselectivity problems by electronically biasing one end of the allene with an electron rich alkoxy group. Overall the reaction works very well, generating two new stereogenic centers including a quaternary center at the C-4 position of the oxazolone ring. Oxazol-5(4H)-ones with aliphatic substitutions at the C-4 position provide the best results affording the products in moderate yields (67-87%) with excellent enantiomeric excesses (90-94%) (Scheme I-9). Furthermore, the diastereoselectivity observed in these reactions was also

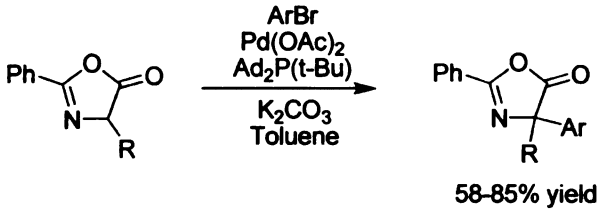
reported to be relatively high, usually occurring in approximately a 20:1 ratio (Scheme I-9).



Scheme I-9. Palladium catalyzed allylation of oxazol-5(4H)-ones using allenes.

4. Arylation of oxazol-5(4H)-ones. The arylation of oxazol-5(4H)-ones at the C-4 position results in the formation of novel quaternary aryl-glycine derivatives.[30,31] In 2003, Hartwig and co-workers reported the first palladium catalyzed arylation of oxazol-5(4H)-ones for the synthesis of quaternary amino acids (Scheme I-10).[30] The reaction involves the coupling of the sp^2 carbon of arenes with the enolate of oxazol-5(4H)-ones. Their catalyst system consisted of using $Pd(OAc)_2$ along with the sterically hindered electron rich ligand $Ad_2P(t\text{-}Bu)$ (Scheme I-10). The reaction provides reasonable yields with a wide range of aryl bromide substrates. The use of electron rich or electron neutral aryl groups provides the best results (75-85%), whereas electron poor aryl groups tend to afford slightly lower yields (~60%). Aryl groups with the potential to undergo Heck reactions, such as 4-bromostyrene, underwent the desired

coupling reaction in good yields (75%). A wide range of oxazol-5(4H)-one substrates consisting of both aliphatic and aromatic substituents undergo the desired coupling reaction in good yields.



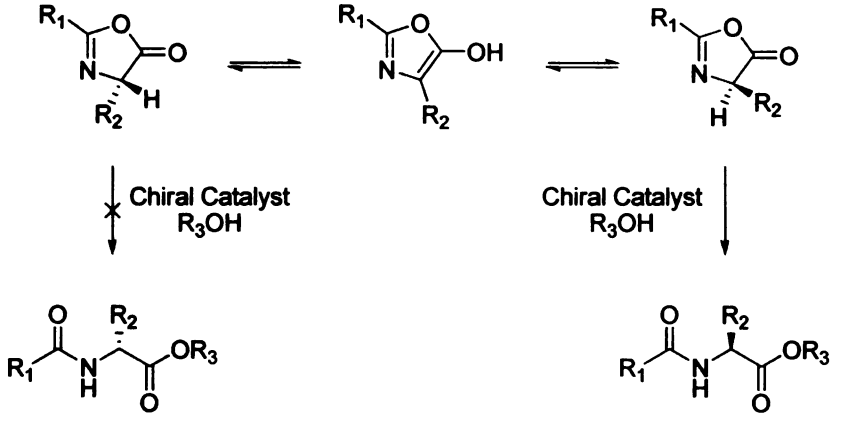
Scheme I-10. Arylation of oxazol-5(4H)-ones.

F. Oxazol-5(4H)-one transformations associated with their electrophilicity

The oxazol-5(4H)-one scaffold contains a highly electrophilic carbonyl that readily undergoes a variety of transformations including hydrolysis, alcoholysis, aminolysis, hydride reduction, and Friedel-Crafts reactions to generate both α-amino acids as well as novel heterocyclic compounds.[16] Early studies involving oxazol-5(4H)-ones include their participation as intermediates during peptide coupling reactions. These studies indicated that oxazol-5(4H)-one intermediates are primarily responsible for the racemization of amino acid residues when peptides are coupled with nucleophiles using reagents such as DCC.[12]

More recent work has taken advantage of not only the ability of oxazol-5(4H)-ones to rapidly epimerize, but also their highly electrophilic character to generate α-amino acid derivatives. The dynamic kinetic resolution of oxazol-5(4H)-ones has proven to be very useful for the preparation of enantiomerically pure α-amino acids (Scheme I-11).[32] During the process, a chiral catalyst (small molecule or enzyme) preferentially activates one of the

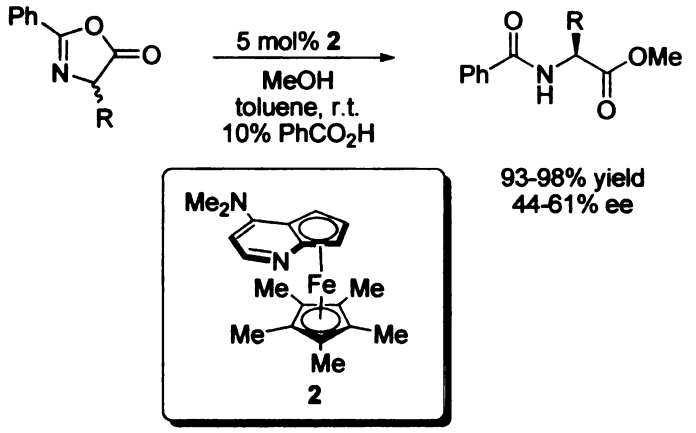
two enantiomers of the oxazol-5(4H)-one racemate towards irreversible alcoholysis, thus forming an amino ester product. Simultaneously, the unreactive enantiomer undergoes epimerization to the more reactive enantiomer, which subsequently undergoes alcoholysis in the presence of the catalyst theoretically allowing for complete conversion of the racemate to the desired stereoisomer (Scheme I-11).[32]



Scheme I-11. Dynamic kinetic resolution of oxazol-5(4H)-ones.

The dynamic kinetic resolution of oxazol-5(4H)-ones has been reported using both enzymatic[33] and small molecule catalyst systems.[34,35] One of the first succesful examples using a small molecule to catalyze the dynamic kinetic resolution of oxazol-5(4H)-ones was demonstrated by Fu and co-workers in 1998 (Scheme I-12).[35] The authors described the use of the chiral ferrocene-fused DMAP derivative **2** to catalyze the methanolysis of oxazol-5(4H)-one substrates resulting in enantiomerically enriched amino acids.[26] Examples using both 4-aryl-oxazol-5(4H)-ones and 4-alkyl-oxazol-5(4H)-ones provided α-amino esters in excellent yields (>90%) with moderate

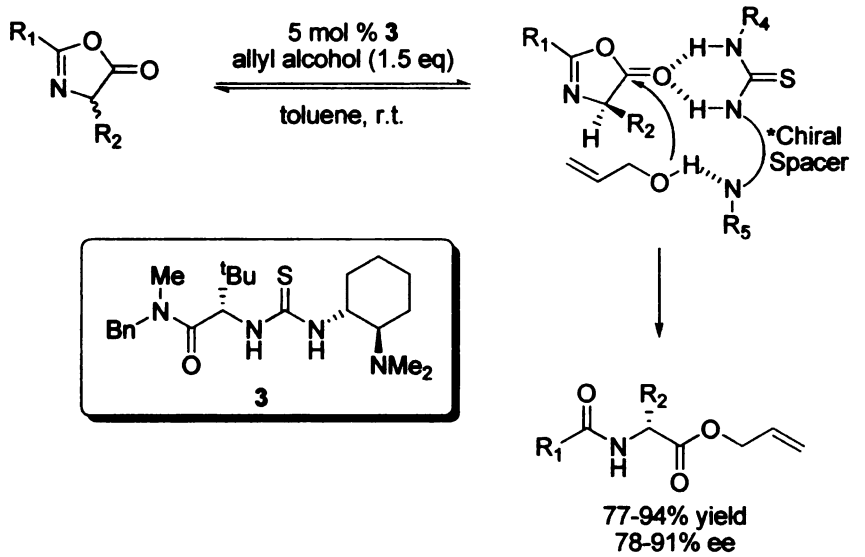
enantioselectivity (44-61% e.e.) (Scheme I-12). The authors also reported the stereochemical outcome of the reaction to be solvent dependent with toluene furnishing the highest level of enantioselectivity. Adding steric bulk to the alcohol nucleophile increases the enantioselectivity of the reaction, albeit with highly increased reaction times.



Scheme I-12. Fu's DKR of oxazol-5(4H)-ones.

More recent work in this area was published by Berkessel and co-workers in 2005 utilizing urea and thiourea bifunctional organocatalysts to promote the dynamic kinetic resolution of oxazol-5(4H)-ones.[34] The Lewis acidic urea moiety of the catalyst activates the oxazol-5(4H)-one carbonyl via hydrogen bonding, while a tethered Lewis basic portion of the catalyst presumably directs the approach of the nucleophile by means of a second hydrogen bonding interaction (Scheme I-13). These catalysts work well with a wide range of oxazol-5(4H)-ones providing enantiomeric excesses up to 91%. Analogous to Fu's studies, the use of smaller primary alcohols results in higher conversion rates than bulkier alcohols with allyl alcohols affording the

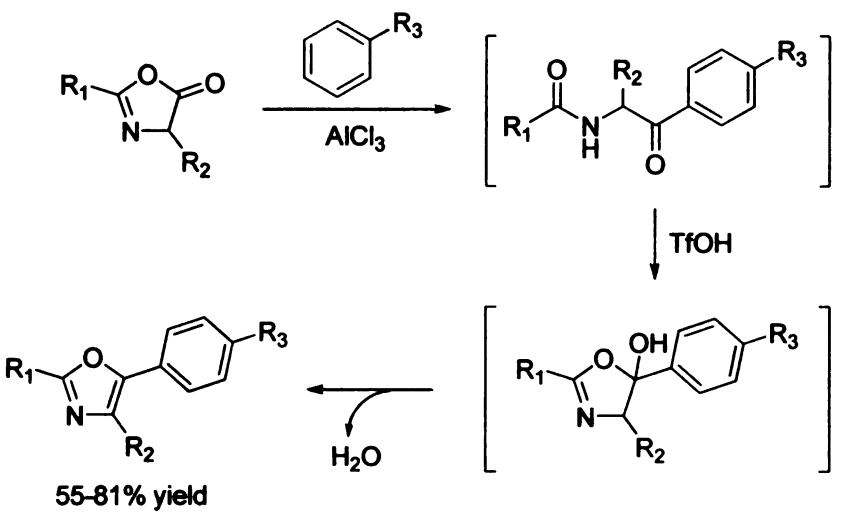
highest yields. To complement the theory that complexation of the catalyst to the substrate occurs via hydrogen bonding, solvents capable of accepting hydrogen bonds (e.g. THF) provide little or no stereoselectivity.



Scheme I-13. Thiourea catalyzed DKR of oxazol-5(4H)-ones.

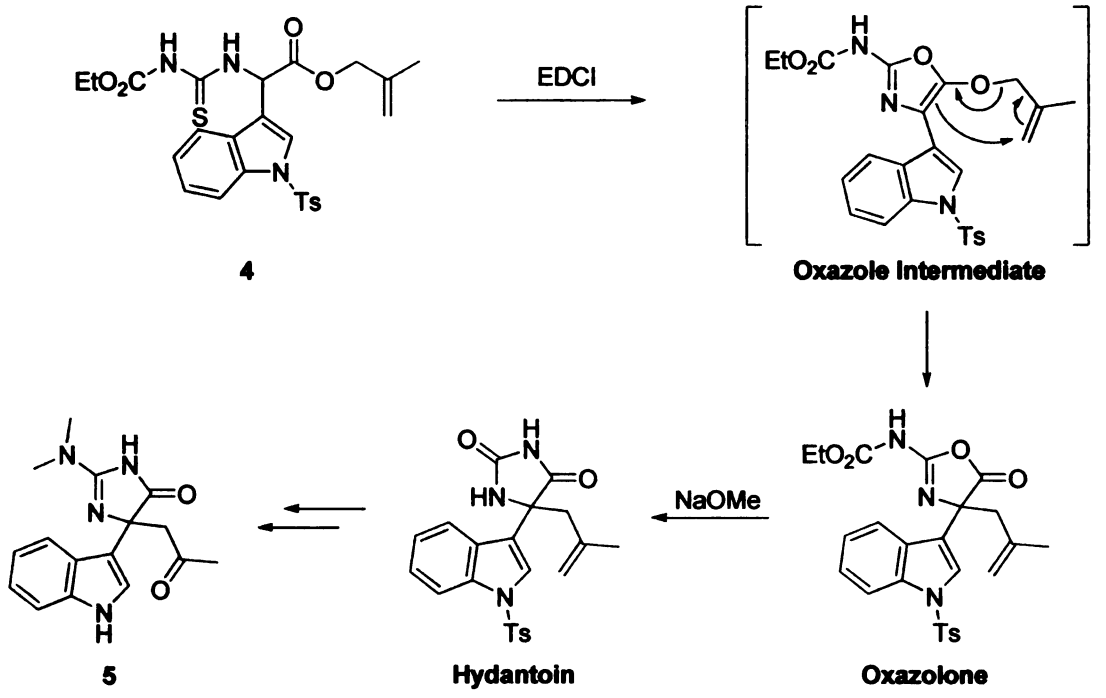
The electrophilic nature of oxazol-5(4H)-ones not only allows for their use in the synthesis of α-amino acids, but also permits access to a variety of heterocycles including oxazoles, hydantoins, thiohydantoins, pyridones, pyrimidinones and many more.[7] In an effort to develop a new route to highly substituted oxazoles, our group recently published a protocol consisting of a one pot Friedel-Crafts / Robinson-Gabriel synthesis for producing 2,4,5-trisubstituted oxazoles from oxazol-5(4H)-ones (Scheme I-14).[36] Previous reports have established the Robinson-Gabriel cyclodehydration of 2-acylamino ketones as one of the most versatile routes for producing oxazoles. Furthermore, 2-acylamino ketones can be readily prepared from oxazol-5(4H)-

ones via Friedel-Crafts reactions.[36] The two reactions can be carried out in tandem utilizing a combination of aluminum chloride and trifluoromethanesulfonic acid, resulting in the formation of oxazoles directly from oxazol-5(4H)-ones. The reaction works well for a wide variety of oxazol-5(4H)-one substrates including both aromatic and alkyl substituted oxazol-5(4H)-ones. As anticipated, the reaction affords the highest yields with either electron neutral or electron rich arenes. Electron deficient arenes provide very little or no product formation. Presumably the oxazol-5(4H)-one is initially activated by aluminum chloride promoting the Friedel-Crafts reaction providing an 2-acylamino ketone intermediate (Scheme I-14). The ketone carbonyl of the intermediate is then protonated by the trifluoromethanesulfonic acid, activating the substrate towards cyclization and subsequent dehydration to the corresponding oxazole.



Scheme I-14. Synthesis of oxazoles from oxazol-5(4H)-ones.

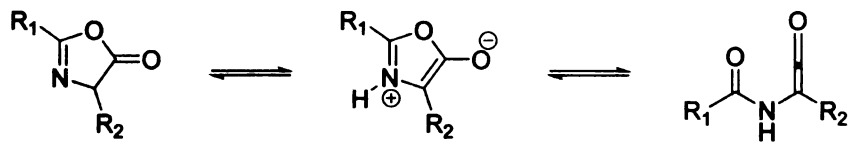
More recently, our research group utilized the electrophilic nature of the oxazol-5(4H)-one scaffold to synthesize a marine alkaloid from the tunicate *Dendrodoa grossularia* (Scheme I-15).[37] The synthesis utilizes two key rearrangements to afford the final compound in rapid and efficient fashion (12 steps). The first rearrangement consists of the cyclodehydration of thiourea **4** to afford an oxazole intermediate, which subsequently undergoes a Claissen rearrangement to produce a quaternary substituted oxazolone.[38,39] The oxazolone intermediate is then treated with sodium methoxide facilitating the second rearrangement to yield a quaternary hydantoin.[39] The synthesis is completed in five additional steps affording the natural product **5** in 13% overall yield.



Scheme I-15. Synthesis of a marine alkaloid from the tunicate *Dendrodoa grossularia.*

G. Cycloaddition reactions of oxazol-5(4H)-ones

Cycloaddition reactions of oxazol-5(4H)-ones have been utilized to generate a wide variety of heterocyclic scaffolds.[7,40,41] Oxazol-5(4H)-ones exist in equilibrium with both their mesoionic (also referred to as a münchnone) and amidoketene isomers (Scheme I-16).[42] The relative concentration of each isomeric form of the molecule is highly dependent on reaction conditions and the substitution pattern of the oxazol-5(4H)-one scaffold. Münchnones are best described as cyclic / aromatic azomethine ylides. Analogous to their acyclic azomethine ylide counterparts, münchnones undergo [3+2] cycloadditions while in the presence of a range of dipolarphiles to afford a variety of highly substituted heterocyclic scaffolds.[43,44] Hypothetically, münchnones exist in equilibrium with a low concentration of their respective amidoketene isomer.[42,45] Although the amidoketene isomers of oxazol-5(4H)-ones have not been observed spectroscopically to date, certain chemical transformations provide plausible evidence for their existence. For example, treatment of oxazol-5(4H)-ones with imines at elevated temperatures results in the formation of highly substituted β-lactams.[41] The β-lactam products are presumed to arise via a [2+2] cycloaddition of the amidoketene isomer of the oxazol-5(4H)-one with the imine.

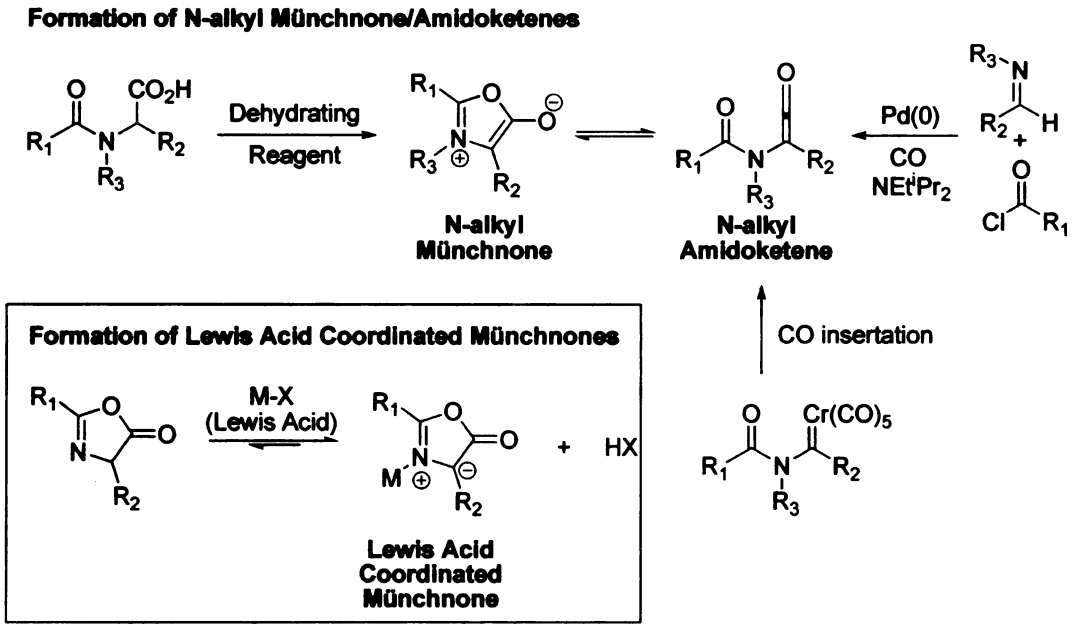


Oxazol-5(4H)-one **Münchnone** **Amidoketene**

Scheme I-16. Equilibrium of oxazol-5(4H)-ones with their münchnone and amidoketene isomers.

Previous studies by Huisgen and co-workers demonstrated that a moderate equilibrium concentration of the münchnone tautomer is necessary to promote 1,3-dipolar cycloadditions of oxazol-5(4H)-ones.[46] The concentration of münchnone tautomer can be increased in a variety of ways including the N-alkylation of the oxazol-5(4H)-ones (Scheme I-17). Huisgen and co-workers first described the synthesis and cycloaddition chemistry of N-alkylated münchnones.[41,46,47] N-alkyl münchnones were generated via the cyclodehydration of N-alkyl, N-acyl amino acids. More recently, Arndtsen and co-workers reported a transition metal catalyzed synthesis of N-alkylated münchnones (Scheme I-17).[48,49] The desired münchnone species was generated utilizing a palladium catalyzed coupling of an imine, acid chloride and carbon monoxide. In addition, Merlic and co-workers reported acylamino carbene complexes to readily undergo carbon monoxide insertion, thus generating N-alkylated münchnones (Scheme I-17).[50] Alternatively, the concentration of the münchnone tautomer may be increased while in the presence of Lewis acids (Scheme I-17).[51-53] Recently, our research group described mild conversions of oxazol-5(4H)-ones to dihydroheterocyclic scaffolds

via Lewis acid promoted [3+2] cycloadditions. This work will be described in more detail in the following chapters of this dissertation.

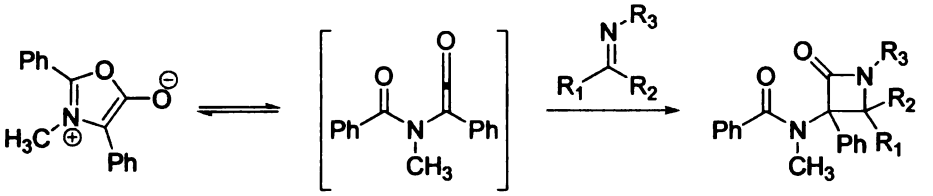


Scheme I-17. Methods for increasing the concentration of the münchnone/amidoketene tautomers.

1. [2+2] cycloadditions utilizing oxazol-5(4H)-ones

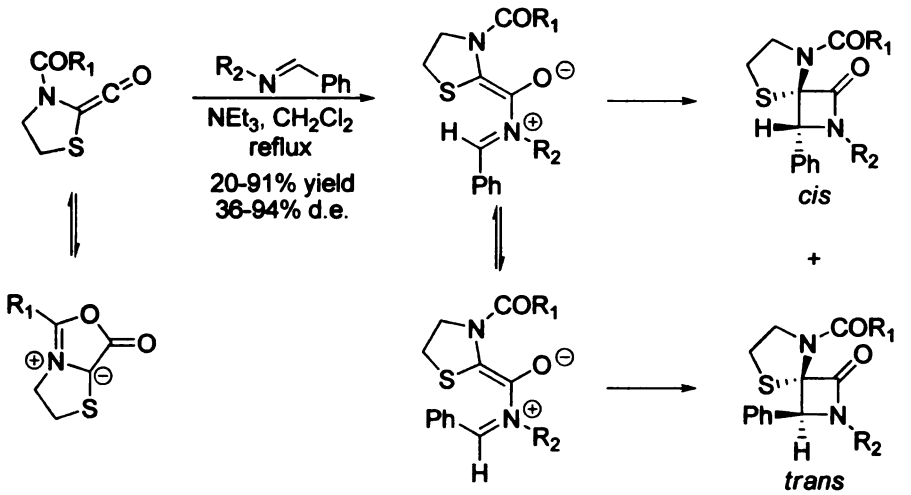
The development of novel and efficient routes to synthesize β-lactams is an area of significant interest primarily due to their antibiotic properties. Previous studies by Staudinger and co-workers established that ketenes undergo thermal [2+2] cycloadditions with imines to form highly substituted β-lactams.[45,47] Oxazol-5(4H)-ones participate in Staudinger-type cycloaddition reactions with imines via their amidoketene isomer (Scheme I-18).[42,54] The first Staudinger reaction of oxazol-5(4H)-ones was demonstrated by Huisgen and co-workers in 1971.[55] The authors proposed münchnones to exist in

equilibrium with a low concentration of amidoketene, which in turn undergoes a [2+2] cycloaddition while in the presence of an imine to afford the observed β-lactam product (Scheme I-18).



Scheme I-18. Staudinger reactions of oxazol-5(4H)-ones.

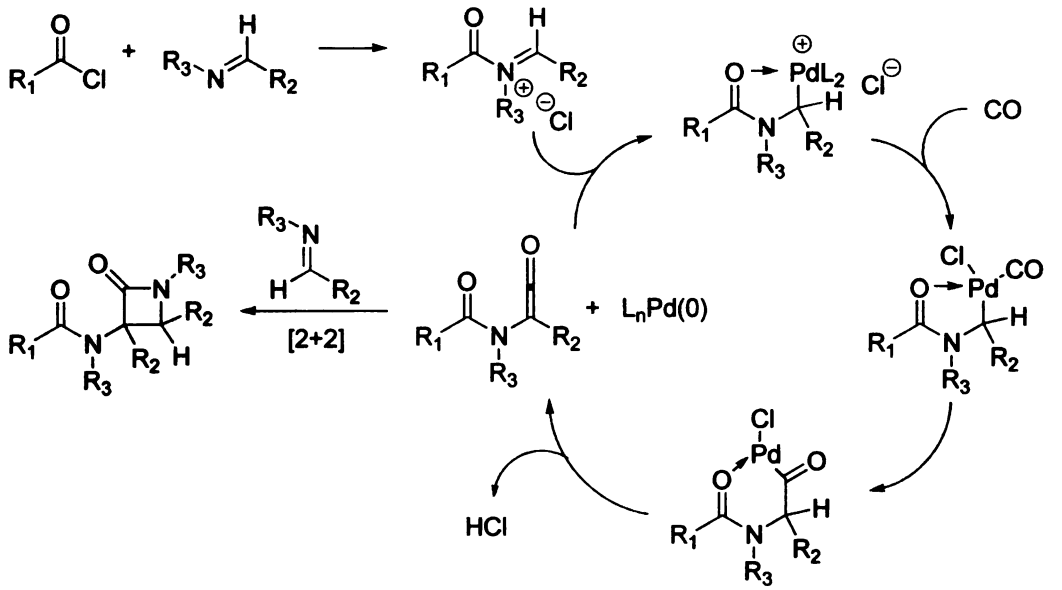
Recenty, Cremonesi and co-workers reported the use of bicyclic münchnones for the diastereoselective synthesis of β-lactams (Scheme I-19).[56] The authors illustrated the ability to control the stereochemical outcome of the reaction through alteration of the imine N-substituent (Scheme I-19, R_2). The reaction afforded primarily the *cis*-β-lactam product (with respect to the sulfur and phenyl groups) when performed with imines substituted with electron withdrawing moieties. Conversely, high yields of *trans*-β-lactams were selectively obtained utilizing imines substituted with electron donating groups.[56] The authors speculate that both products arise from the initial attack of the imine to the least-hindered side of the amidoketene intermediate (Scheme I-19). Electron withdrawing groups destabilize the initial iminium intermediate, thus leading to the *cis*-product. On the other hand, electron donating substituents stabilize the iminium intermediate allotting for double bond isomerization, which consequentially gives rise to the thermodynamically favored *trans*-product.[56]



Scheme I-19. Diastereoselective Staudinger reaction of münchnones.

More recently, Arndsten and co-workers reported a multicomponent palladium-catalyzed synthesis of amidoketenes, which were subsequently treated with imines to afford β-lactams in moderate to high yields (Scheme I-20).[57] Their overall reaction sequence couples four reagents to efficiently provide β-lactams in a single step. The amidoketene species is generated *in situ* starting from an imine, acid chloride and carbon monoxide as shown below in Scheme I-20. The formation of the amidoketene species is initiated by an oxidative addition of an N-acyliminium salt to Pd(0). The resulting palladacyle then undergoes carbon monoxide insertion followed by β-hydride elimination to form the needed amidoketene intermediate. The amidoketene intermediate then undergoes a Staudinger-like [2+2] cycloaddition with an imine to afford the final β-lactam product. For selective β-lactam formation, the authors reported the requirement of base to eliminate HCl from the reaction. Insufficient removal of HCl leads to lower yields of product presumably due to

competing [3+2] cycloaddition pathways. These reactions can be performed either using two equivalents of the same imine or with sequential addition of two different imines.

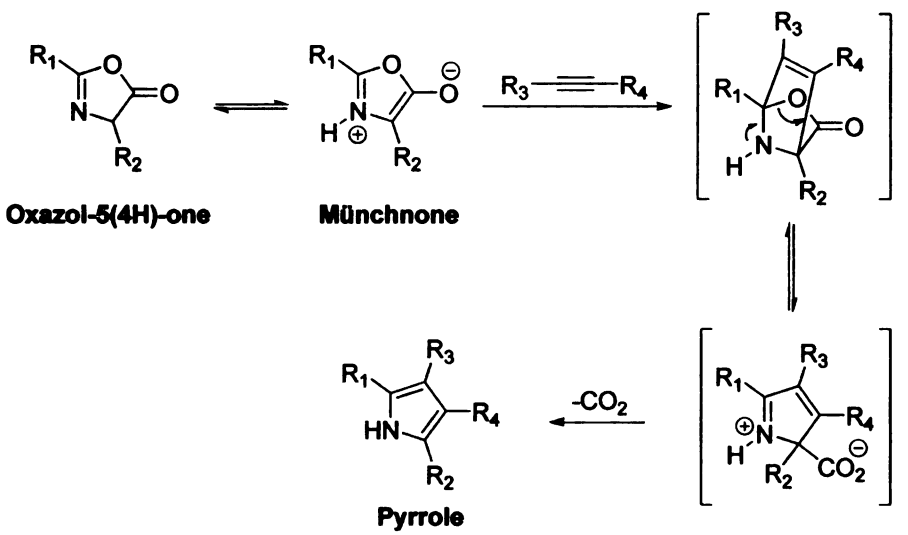


Scheme I-20. Synthesis of β-lactams via palladium catalyzed amidoketene formation.

2. [3+2] cycloadditions utilizing oxazol-5(4H)-ones

A wide variety of heteroaromatic and dihydro-heterocyclic scaffolds are accessible utilizing oxazol-5(4H)-ones by means of their 1,3-dipolar münchnone tautomer. Analagous to acyclic azomethine ylides, münchnones undergo cycloadditions with a variety of dipolarphiles.[43,44] For example, the thermal 1,3-dipolar cycloaddition of münchnones with electron deficient alkynes directly results in the formation of highly substituted pyrroles (Scheme I-21).[18] Mechanistically, these reactions proceed through the initial formation of a bicyclic primary cycloadduct, which subsequentaly undergoes aromatization via the loss of carbon dioxide. This area of research was

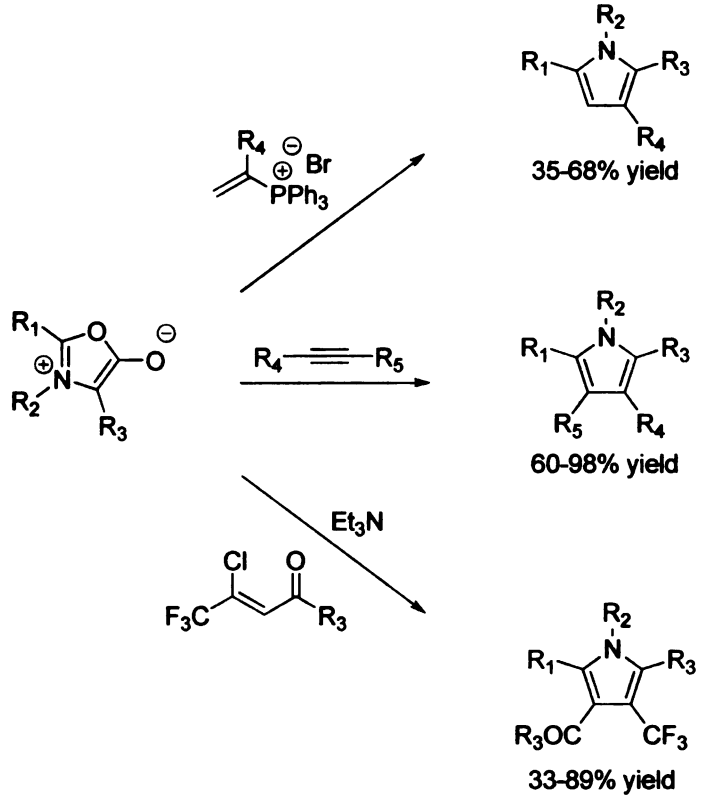
pioneered by Huisgen and co-workers starting in 1970.[46] The authors proposed that a moderate concentration of the mesoionic münchnone tautomer is essential for promoting the 1,3-dipolar cycloaddition reactions of oxazol-5(4H)-ones. The authors reported the preparation of a wide range of pyrroles with diversity at every substituent of a pyrrole scaffold utilizing N-alkylated münchnones (Scheme I-21).[46] N-alkylation of oxazol-5(4H)-ones locks them into their münchnone form, allowing for the formation of a variety of heteroaromatic molecules including pyrroles.[48,50,58]



Scheme I-21. Synthesis of pyrroles from münchnones.

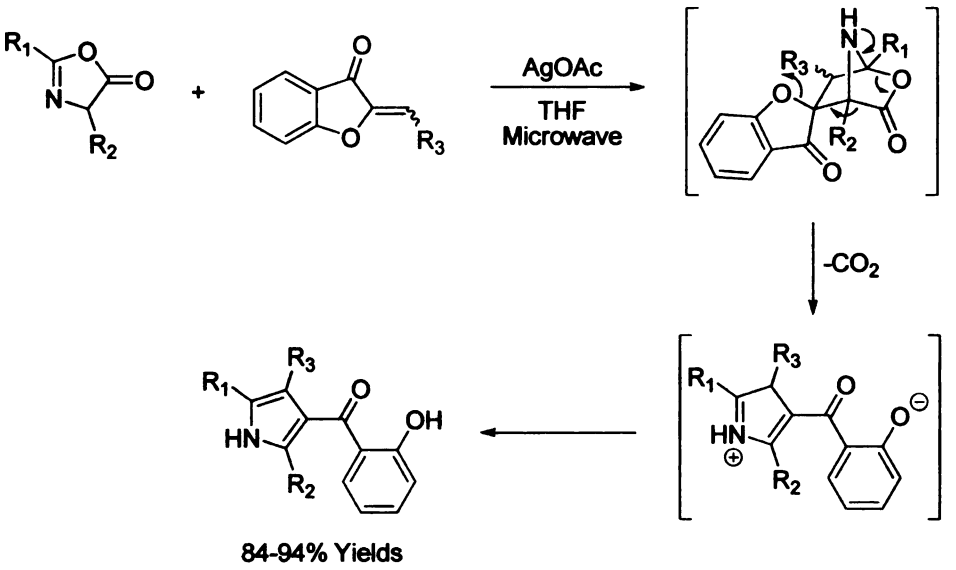
Similarly, pyrroles may also be synthesized from münchnones through their reaction with alkyne equivalents. The regioselective cycloaddition using vinyl phosphonium salts with N-alkyl münchnones has been reported by Clerici and co-workers (Scheme I-22).[40] Münchnones were refluxed (THF/DMF solvent mixture) in the presence of vinyl phosphonium salts resulting in high

yields of the desired pyrroles by way of the decarboxylation of the primary cycloadducts followed by elimination of PPh_3. The regioselectivity observed in the reaction is driven by the strong electrostatic interaction between the phosphonium species and the enolate of the münchnone. Additionally, the regioselective synthesis of pyrroles has been demonstrated in the reaction of münchnones with electron deficient vinyl-chlorinated alkenes (Scheme I-22).[59] Aromatization of the primary cycloadducts to the final pyrrole products is accomplished via decarboxylation of the primary cycloadduct followed by subsequent elimination of the chlorine atom.



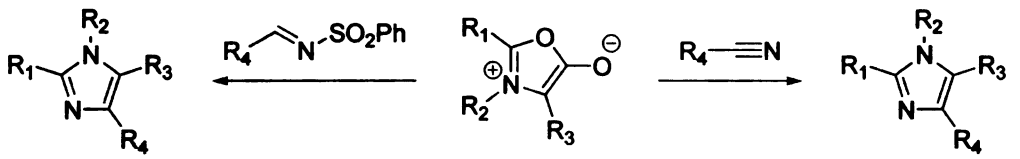
Scheme I-22. Synthesis of pyrroles via [3+2] cycloadditions of münchnones.

More recently, Park and co-workers reported a regioselective synthesis of pyrroles utilizing 1,3-dipolar cycloadditions of α,β-unsaturated benzofuran-3(2H)-ones and münchnones (Scheme I-23). Their method involves the use of AgOAc to generate the needed münchnone species *in situ*, which readily undergoes a [3+2] cycloaddition with an α,β-unsaturated benzofuran-3(2H)-one. Subsequent spontaneous decarboxylation of the primary cycloadduct results in the formation of the desired tetrasubstituted pyrroles in high yields with regioselectivities greater than 99:1. Benzofuranone derivatives more electron withdrawing in nature produced the highest yields and regioselectivities, while benzofuranone derivatives containing more electron donating substituents resulted in decreased reaction rates and regioselectivity.



Scheme I-23. Regioselective synthesis of pyrroles via [3+2] cycloadditions of α,β-unsaturated benzofuran-3(2H)-ones and münchnones.

The construction of the imidazole scaffold has also been accomplished starting from oxazol-5(4H)-ones through the reaction of their münchnone tautomer with nitriles and imines. Early work by Huisgen and co-workers demonstrated the ability of münchnones to undergo thermal cycloadditions with electron deficient nitriles (Scheme I-24).[60] Similar to the reactions of münchnones with alkynes, these reactions proceed by initially forming a bicyclic-cycloadduct, which undergoes decarboxylation resulting in the formation of the imidazole products. The reaction of N-alkyl münchnones with various imines also results in the formation of highly substituted imidazoles. Consonni and co-workers demonstrated that the reaction of münchnones with N-(phenylmethylene)benzenesulphonamides afford imidazoles in moderate yields (Scheme I-24).[61] Aromatization occurs by way of the decarboxylation of the intermediate bicyclic cycloadduct followed by expulsion of benzenesulphinic acid.



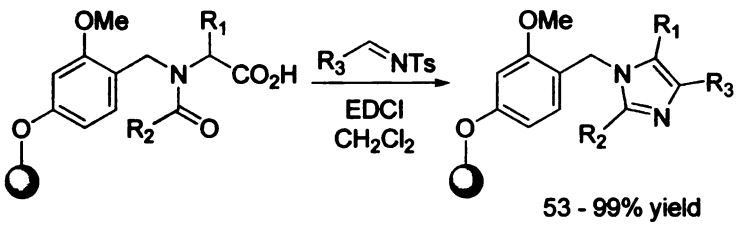
20-65 yield%

41-71% yield

Scheme I-24. Synthesis of imidazoles via [3+2] cycloadditions of münchnones.

The 1,3-dipolar cycloaddition reaction of müchnones with imines often results in low yields of imidazole product due to the formation of a variety of side products including β-lactams and dimerized münchnone. Recent approaches to increase the yield of such cycloadditions include the use of

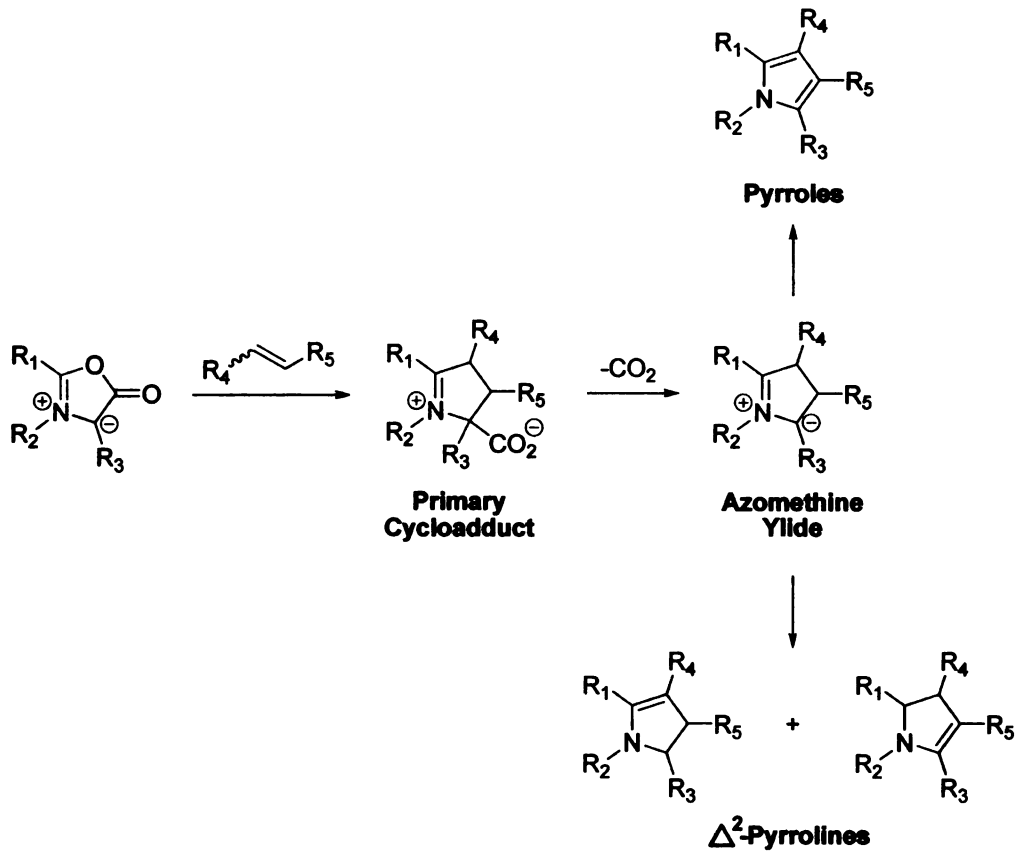
solid supports to prevent the dimerization of the münchnone starting material. Bilodeau and co-workers demonstrated the benefit of this approach by using N-acyl α-amino acids bound to solid support.[62] The N-acyl α-amino acids were cyclodehydrated using EDCI affording resin bound münchnones, which subsequentially underwent the desired 1,3-dipolar cycloaddition reaction with N-tosyl imines to yield polymer-linked imidazoles (Scheme I-25). Liberation from the imidazole product from the solid support resin by heating in acetic acid afforded the desired imidazoles in high yields.



Scheme I-25. Synthesis of imidazoles using solid supports.

Although relatively few examples have been reported, dihydro-heterocyclic scaffolds are accessible utilizing 1,3-dipolar cycloaddition reactions of münchnones.[18,51-53,63-65] Traditional methods for conducting oxazol-5(4H)-one cycloadditions (e.g reflux in acetic anhydride) often lead to heteroaromatic products or complex mixtures of products containing various isomeric mixtures of dihydro-heterocyclic molecules (Scheme I-26). Studies by Gotthardt, Huisgen, and Schaefer illustrated that Δ^2-pyrrolines could be isolated in cycloadditions of münchnones with electron deficient alkenes by decreasing the temperature of the reactions (Scheme I-26).[66] Münchnones were heated at relatively low temperatures (50-100 °C) in xylenes while in the

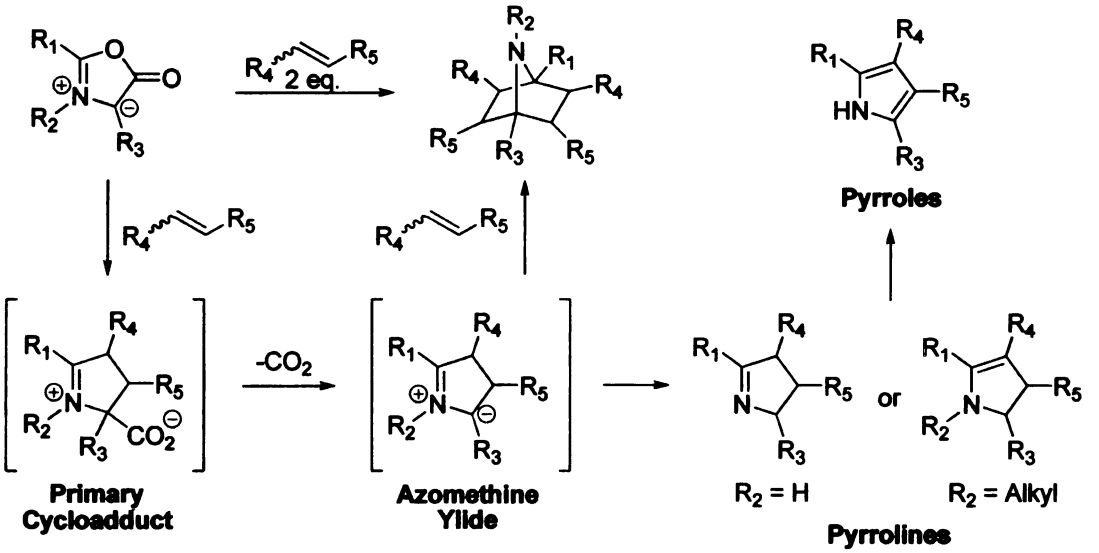
presence of alkenes resulting in primarily the isolation of Δ^2-pyrrolines with small amounts of pyrrole. Unfortunately, the decarboxylation of the primary cycloadducts of these reactions could not be controlled and ultimately led to mixtures of Δ^2-pyrroline regioisomers.



Scheme I-26. Synthesis of Δ^2-pyrrolines from münchnones.

Studies by Huisgen and co-workers explored the mechanism by which the primary cycloadducts obtained from münchnone cycloadditions with alkenes decarboxylate and form pyrroline and pyrrole products.[46,66] Their studies indicated that the initial loss of carbon dioxide leads to the formation of a relatively reactive cyclic azomethine ylide (Scheme I-27). Evidence of the

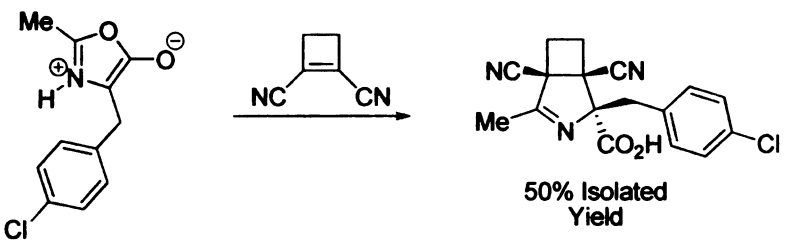
cyclic azomethine intermediate was illustrated through the addition of a second equivalent of the dipolarphile, which readily prompted a second [3+2] cycloaddition affording a new azabicyclo-[2,2,1]-heptane product.[46,66] Both the pyrroline and pyrrole products are believed to derive from the newly formed azomethine ylide intermediate. Protonation of the cyclic azomethine ylide either from a 1,2 prototropic shift (R_2 = H) or an external proton source (R_2 = alkyl) leads to the formation of Δ^1-pyrrolines and Δ^2-pyrrolines respectively (Scheme I-27). Subsequent oxidation of the resulting pyrroline species ultimately leads to the formation of aromatic pyrrole products.



Scheme I-27. Reaction of oxazol-5(4H)-ones with two equivalents of alkene to afford bicyclic heterocyclic scaffolds.

Relatively few examples regarding the isolation of primary cycloaddition adducts from intermolecular cycloaddition reactions of münchnones have been reported. Padwa and co-workers previously disclosed the isolation of primary cycloaddition adducts from intramolecular cycloadditions of münchnones with

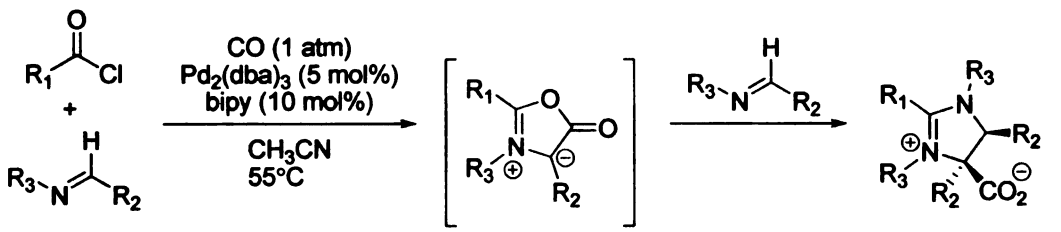
terminal alkenes.[18] Likewise, Maryanoff and co-workers described the isolation of a Δ^1-pyrroline-5-carboxylic acid in the intermolecular cycloaddition of a münchnone with 1,2-dicyanobutene (Scheme I-28).[63] In each of the above cases, decarboxylation is presumably prevented due to the steric constraints of the cycloadduct products. These studies not only provided support for previously proposed reaction mechanisms, but provided the first indications that the cycloadditions of münchnones with alkenes proceed with *exo*-stereochemistry.



Scheme I-28. Maryanoff's isolated primary cycloadduct.

As stated earlier, it is thought that the relatively harsh reaction conditions traditionally employed in münchnone cycloaddition reactions (refluxing in acetic anhydride) helps to facilitate the decarboxylation of the primary cycloadduct thus generating decarboxylated heterocyclic products. In 2001, Arndtsen and co-workers reported a method in which an imine, acid chloride and carbon monoxide could be coupled using palladium catalysis to generate münchnones under much milder reaction conditions.[67] Exposure of the generated münchnone species to a second equivalent of imine resulted in the isolation of carboxylate subsituted imidazolines (Scheme I-29). The authors attributed their ability to isolate the primary cycloadducts to their mildly acidic reaction conditions. Elimination of the HCl generated during

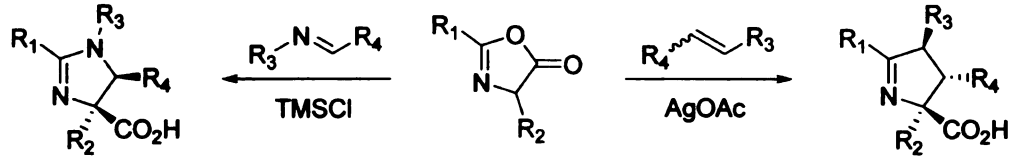
these reaction results predominately in the formation of undesired β-lactam byproducts, illustrating perhaps the active dipolarphile may indeed be the HCl salt of the imine substrate. These reactions were diastereoselective generating imidazoline products as single diastereomers with the stereochemistry illustrated in Scheme I-29 as determined by X-ray crystallography.



Scheme I-29. Arndtsen's synthesis of 2-imidazoline carboxylates.

Recently, Lewis acids have been demostrated to increase the concentration münchnone tautomers under much milder conditions allowing for the isolation of various dihydro-heterocyclic scaffolds. In 2004, we reported a silver acetate mediated cycloaddition of oxazol-5(4H)-ones with electron deficient alkenes.[53] These reactions stereoselectively proceeded in moderate to high yields affording Δ^1-pyrrolines (Scheme I-30). The reactions also proceeded with exo-selectivity as seen in Maryanoff's studies.[53] An enantioselective version of this chemistry was later reported by Toste and co-workers in which the authors utilized cationic gold to catalyze the reaction.[65] In addition, we previously reported a silicon mediated 1,3-dipolar cycloaddition of oxazol-5(4H)-ones with imines to afford highly substituted imidazolines.[52] The stereochemical outcome of the reaction is highly dependent on the

substitution pattern of the oxazol-5(4H)-one scaffold. The above methodology involving Lewis acid mediated cycloadditions of oxazol-5(4H)-ones with both imines and alkenes will be described in more detail in the following chapters of this dissertation.



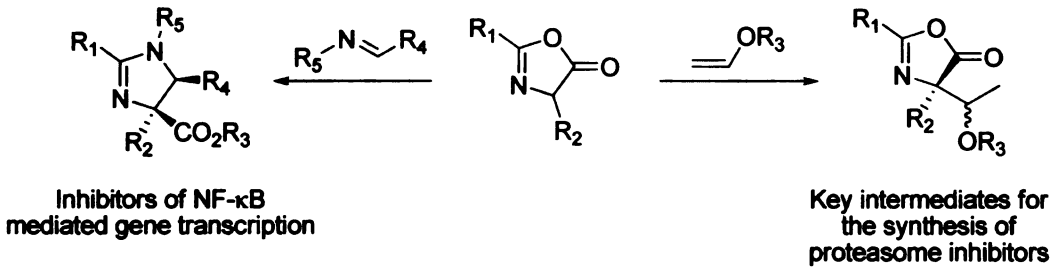
Scheme I-30. Lewis acid mediated cycloadditions of oxazol-5(4H)-ones.

H. Current work

Since their initial discovery, oxazol-5(4H)-ones have emerged as an important class of compounds for synthesizing biologically interesting targets. As demonstrated throughout this chapter, the oxazol-5(4H)-one scaffold contains numerous reactive sites allowing for a large diversity of transformations. The reseach presented during the remainder of this dissertation illustrates the potential of using oxazol-5(4H)-ones in diversity oriented synthesis drug discovery programs. The following chapters include both the development of new chemistry using oxazol-5(4H)-ones to rapidly create small libraries of novel molecules, as well as the evaluation of the molecular libraries for biological function.

The first project presented in this dissertation involves the synthesis and evaluation of small libraries of 2-imidazolines for their ability to inhibit NF-κB mediated gene transcription (Scheme I-31). Previously we reported that oxazol-5(4H)-ones undergo diastereoselective [3+2] cycloadditions with

imines while in the presence of Lewis acids to afford highly substituted 2-imidazolines.[51,52] Furthermore, this class of imidazolines were found to be potent inhibitors of NF-κB mediated gene transcription.[68] Due to the potential therapeutic value of inhibiting NF-κB mediated gene transcription,[44,69] we undertook a structure activity relationship study of this class of compounds with the hopes of optimizing the compounds as potential drug candidates. This project was done in collaboration with Dr. Daljinder Kahlon and Theresa Lansdell. The data obtained from the structure activity relationship study as well as the synthesis of the compounds is presented in detail in the following chapter.



Scheme I-31. Research presented in this dissertation.

The second research project presented in this disseration involves the development of a new method for the alkylation of oxazol-5(4H)-ones.[16] We discovered oxazol-5(4H)-ones to undergo ene-type alkylation reactions with enol ethers to generate quaternary substituted oxazolones (Scheme I-31).[16] These quaternary substituted oxazol-5(4H)-ones represent pivotal intermediates for synthesizing a variety of biologically interesting molecules including *tert*-alkyl amino hydroxy carboxylic acids. The last two chapters of

this dissertation describe our current findings on this new methodology including the scope and mechanism of the reaction. Furthermore, this dissertation also includes the use of Brønsted acid catalysis for improving the stereoselectivity of the reaction.[70] Also included is the use of this chemistry in synthesizing a class of molecules known to be potent inhibitors of the 20S proteasome.

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CHAPTER II

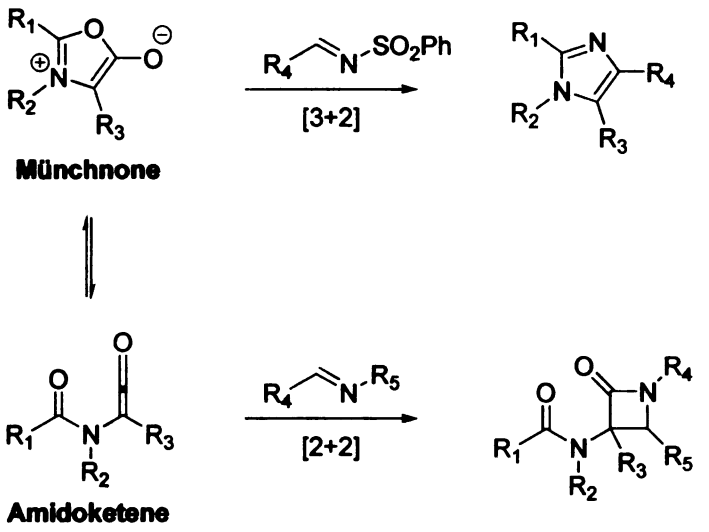
INHIBITION OF NF-κB MEDIATED GENE TRANSCRIPTION BY 2-IMIDAZOLINES DERIVED FROM OXAZOL-5(4H)-ONES

A. Synthesis of 2-imidazolines via münchnone/imine cycloadditions.

The imidazoline scaffold is found in a variety of molecules exhibiting biologically interesting properties.[1] Imidazoline derivatives have been illustrated to exhibit a wide range of biological activity including anti-inflammatory, anti-nociceptive, immuno-modulating, antioxidant activities and many more.[2,3] Furthermore, molecules containing imidazoline cores have been shown to possess anti-cancer relevant properties.[3,4,5] In addition to exhibiting a wide range of biological activity, imidazolines have also proven to be useful substrates in synthetic organic chemistry. Imidazolines are convenient building blocks for the synthesis of a variety of biologically interesting molecules including azapenams, dioxocyclams, and diazapinones.[6] They also have been illustrated to be valuable substrates in asymmetric catalysis both as chiral catalysts and as chiral auxiliaries. Enantiopure imidazolines serve as useful intermediates for the synthesis of various chiral ligands including 1,2-diamines.[7] Additionally, imidazolines have served as precursors to chiral catalysts such as N-heterocyclic carbenes.[8,9]

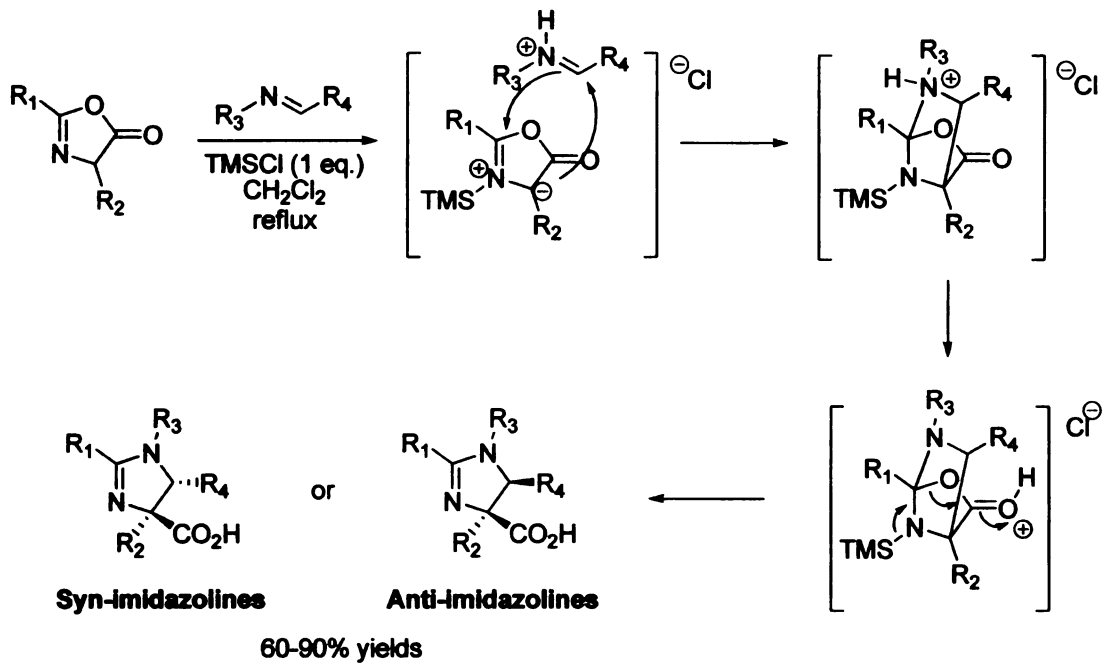
As a result of their biological and chemical significance, new methods for synthesizing highly substituted 2-imidazolines are still of high interest. Traditional

methods for their preparation include the condensation of 1,2-diamines to construct aminals, which are subsequently reduced to afford the desired imidazolines.[10] Interestingly, relatively few examples have been reported using oxazol-5(4H)-ones to synthesize 2-imidazolines.[11-13] Cycloadditions of imines with the 1,3-mesoionic tautomer of oxazol-5(4H)-ones, münchnones, present researchers with an ideal opportunity to synthesize 2-imidazolines with high levels of structural diversity.[9,14] Unfortunately, cycloaddition reactions of münchnones with imines are generally plagued by the formation of undesired side products.[9,14-16] Highly substituted β-lactams are often produced in high yields upon heating oxazol-5(4H)-ones in the presence of imines.[17] Previous studies have indicated that β-lactams are produced from oxazol-5(4H)-ones via Staudinger-like [2+2] cycloadditions of their amidoketene isomer (Scheme II-1).[18] Investigations by Huisgen and co-workers established that N-alkylation of münchnones increases the concentration of the mesoionic tautomer required to facilitate the desired [3+2] cycloaddition. To this end, Consonni and coworkers successfully illustrated that N-alkyl münchnones undergo [3+2] cycloadditions with N-(phenylmethylene)benzenesulphonamides to afford fully substituted imidazoles (Scheme II-1).[19] The authors propose that aromatization occurs through the decarboxylation of the intermediate cycloadduct followed by expulsion of benzenesulphinic acid.



Scheme II-1. Traditional cycloadditions of münchnones/amidoketenes with imines.

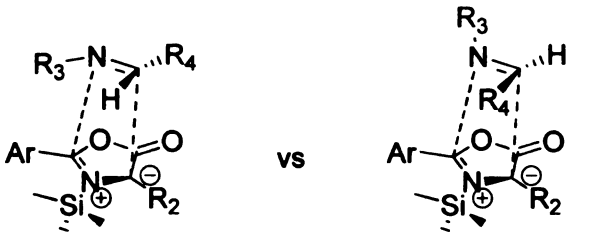
Recently, we pioneered the use of Lewis acids as mild and effective reagents for promoting [3+2] cycloaddition reactions of oxazol-5(4H)-ones.[12,13,20] Lewis acids coordinate to oxazol-5(4H)-ones increasing the equilibrium concentration of their mesoionic münchnone tautomers. The relatively mild conditions at which the münchnones are generated prevent the decarboxylation of primary cycloadducts, thus allowing for the isolation of dihydro-heterocycles such as 2-imidazolines. We demonstrated that imidazolines with four point diversity can be diastereoselectively produced via a silicon mediated 1,3-dipolarcycloadditions of oxazol-5(4H)-ones with imines (Scheme II-2).[13] Oxazol-5(4H)-ones were treated with TMSCl while in the presence of imines affording highly substituted 2-imidazoline products.



Scheme II-2. Lewis acid mediated synthesis of imidazolines.

Interestingly, varying the substitution pattern of the oxazol-5(4H)-one precursors allows for the selective generation of either anti-imidazolines or syn-imidazolines (with respect to the R_2 and R_4 substituents, Scheme II-2). The diastereoselectivity of these reactions appears to be the result of a combination of steric and electronic factors. The reaction of 2-aryloxazol-5(4H)-ones with imines results predominantly in the formation of anti-imidazolines (Figure II-1). The high diastereoselectivity is attributed to a steric interaction between the bulky silyl moiety and the R_4 substituent of the imine causing a preferential *endo* approach of the imine.[13] Complete reversal of diastereoselectivity was observed utilizing 2-alkyl-4-aryloxazol-5(4H)-ones and imines substituted with aryl R_4 substituents.[21] The *syn* diastereoselectivity appears to result from either π-stacking or edge to face interactions between

the aryl R_4 and R_2 substituents. An increase in *syn* selectivity was noted when using π-donating R_2 groups and π-accepting R_4 groups, supporting the rationale for reversal of diastereoselectivity. Little or no diastereoselectivity is observed in reactions involving 2,4-dialkyloxazol-5(4H)-ones with imines.



Endo-Favored **Exo-Disfavored**

Figure II-1. Origin of diastereoselectivity using 2-aryloxazol-5(4H)-ones.

B. 2-imidazolines as inhibitors of NF-κB mediated gene transcription.

NF-κB is a mammalian transcription factor responsible for the regulation of more than 150 genes.[22,23] The inhibition of the NF-κB signaling pathway has been a focus of intense academic and industrial research as a target for development novel pharmaceuticals.[24] Since NF-κB is a pivotal regulator of a number of genes associated with immune, inflammatory and anti-apoptotic responses, it is recognized as an attractive target for controlling various disease states such as cancer and arthritis.[25,26] A variety of small molecule inhibitors of NF-κB mediated gene transcription have been developed, some of which have gone through or are currently undergoing clinical trials (Figure II-3). Perhaps the most common method for impeding NF-κB mediated gene transcription is via the inhibition of the proteolytic activity of the 26S proteasome.[27] The most successful example of a 26S proteasome inhibitor is Bortezomib (also known as Velkade or PS-

341).[28,29] Currently, Bortezomib is clinically used as a treatment of multiple myeloma.[29,30] Other known 26S proteasome inhibitors include MG-132,[31] N-acetyl-leucinyl-leucinyl-norleucinal (ALLN)[32] and the natural products Lactacystin[33] and Salinosporamide A.[34] Other small molecule inhibitors of NF-κB mediated gene transcription include general kinase inhibitors (e.g. hymenialdisines),[35-37] specific IKK inhibitors (e.g. PS-1145 and BMS-345541), inhibitors of I-κB ubiquitination (e.g. Ro106-9920)[38] and many more.

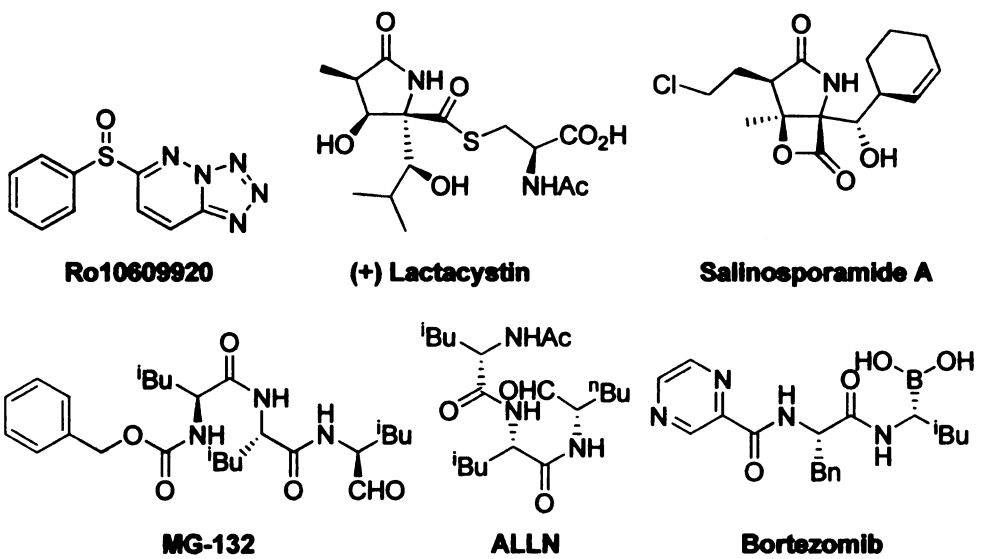
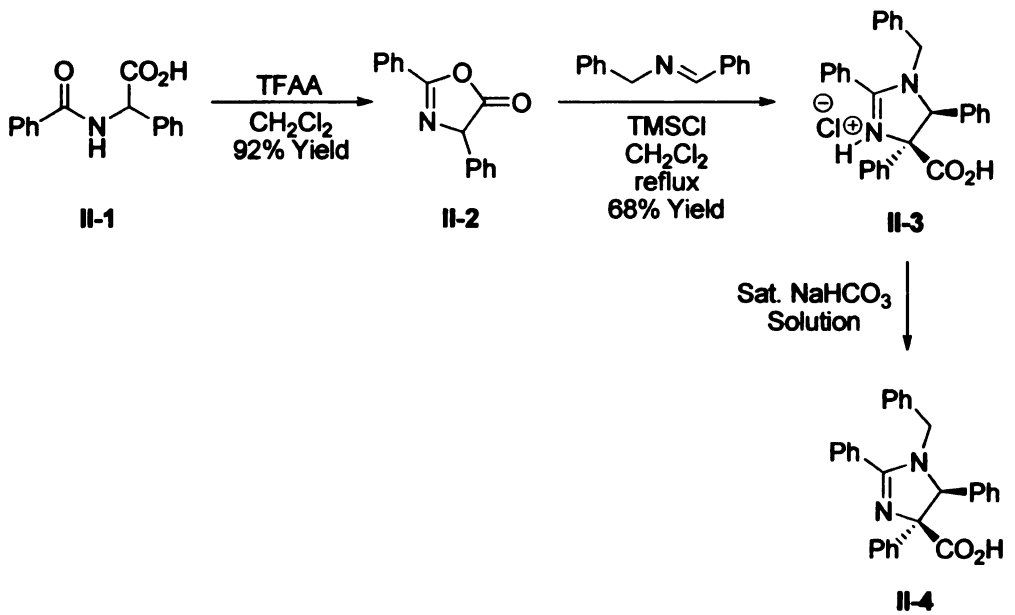


Figure II-2. Small molecule inhibitors of NF-κB mediated gene transcription.

In 2002, we reported the oxazol-5(4H)-one derived imidazoline **II-4** to be a potent inhibitor of NF-κB mediated gene transcription via the inhibition of I-κB degradation (Scheme II-3).[36,39] Imidazoline **II-4** inhibited NF-κB mediated gene transcription in human cervical epithelial (HeLa) cells activated by TNF-α with an EC_{50} = 0.95 μM. In addition, imidazoline **II-4** was found not to induce apoptosis as a single agent, but did increase the efficacy of several chemotherapeutic reagents (e.g. camptothecin and cis-platin) illustrating its potential value in the

treatment of cancer. The synthesis of imidazoline **II-4** is outlined in Scheme II-3 below.[12,13] Cyclodehydration of N-benzoyl phenyl glycine with TFAA afforded oxazol-5(4H)-one **II-2** in 92% yield. Oxazol-5(4H)-one **II-2** was subsequently treated with TMSCl while in the presence of N-benzylidene-1-phenylmethanamine to afford imidazoline **II-3** as the hydrochloride salt. Treatment of imidazoline **II-3** with saturated sodium bicarbonate afforded imidazoline **II-4** as a white crystalline solid.



II-1 **II-2** **II-3** **II-4**

Scheme II-3. Synthesis of the NF-κB inhibitor imidazoline **II-4.**

C. NF-κB mediated gene transcription

As stated earlier, NF-κB is a transcription factor responsible for the regulation of a wide variety of genes.[22,23] Genes regulated by NF-κB include those related to stress,[40] inflammatory stimuli,[41] activation of immune cell function,[42] cellular proliferation, apoptosis,[43] and oncogenesis.[44] Specific proteins regulated by NF-κB include various cytokines (IL-1, IL-2, TNF-α, and IL-6), chemokines (IL-8 and

RANTES), cell adhesion molecules (ICAM 1, VCAM-1, and E-selectin), growth factors, cyclin D1, cyclooxygenase (COX-2), matrix metalloproteinase (MMP-9) as well as many others.[45-48] The misregulation of NF-κB mediated gene transcription is associated with a variety of diseases including rheumatoid arthritis,[26,49] inflammatory bowel disease,[50] and cancer.[51] For example, the deregulation of TNF-α expression has been related to many diseases including Crohn's disease, rheumatoid arthritis (RA), multiple sclerosis and Alzheimer's disease.[52] Increased levels of TNF-α, IL-6 and IL-1β have been found in primary fibroblast-like synoviocytes from patients with rheumatoid arthritis and osteoarthritis.[26,41,53] Furthermore, the levels of NF-κB-DNA binding are much greater in patients with rheumatoid arthritis, which is consistent with the observed increased levels of pro-inflammatory cytokine production.[54]

Structurally, NF-κB is a multi-subunit complex consisting of various members of the Rel family of transcription factors including NF-κB1 (p105/p50), NF-κB2 (p100/p52), RelA (p65), RelB, and c-Rel.[23,55] These subunits can exist as a variety of heterodimers and homodimers and are used to control the selectivity of certain DNA control elements.[45,56] In most unstimulated mammalian cells, NF-κB exists primarily as a p50/p50 homodimer or as a p50/p65 heterodimer. While in its inactive form, NF-κB exists in the cytoplasm as a complex with its inhibitory protein, I-κB (Figure II-3). The NF-κB signaling pathway is initiated by a variety of extracellular stimuli including antineoplastic agents, viruses, phorbol esters, oxidative stress, and cytokines (e.g. TNF-α and IL-1β).[57] Upon activation of the NF-κB pathway, IKK kinases phosphorylate I-κB

on serines 32 and 36.[58] This is followed by subsequent ubiquitinylation and degradation of I-κB by the 26S proteosome.[42,47] Upon proteolytic degradation of I-κB, NF-κB is released allowing for its translocation into the nucleus.[59] Once inside the nucleus, it binds to various DNA control elements thus initiating gene transcription.[48,60]

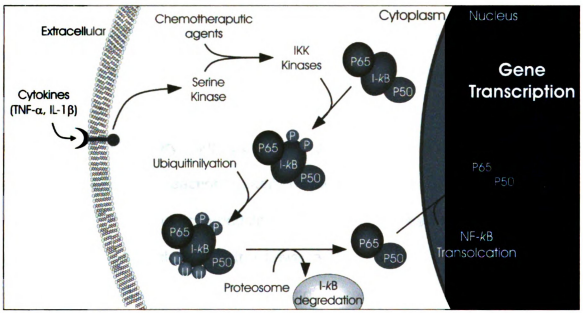


Figure II-3. Mechanistic activation of the transcription factor NF-κB.

D. Development of a new class of 2-imidazoline based NF-κB inhibitors

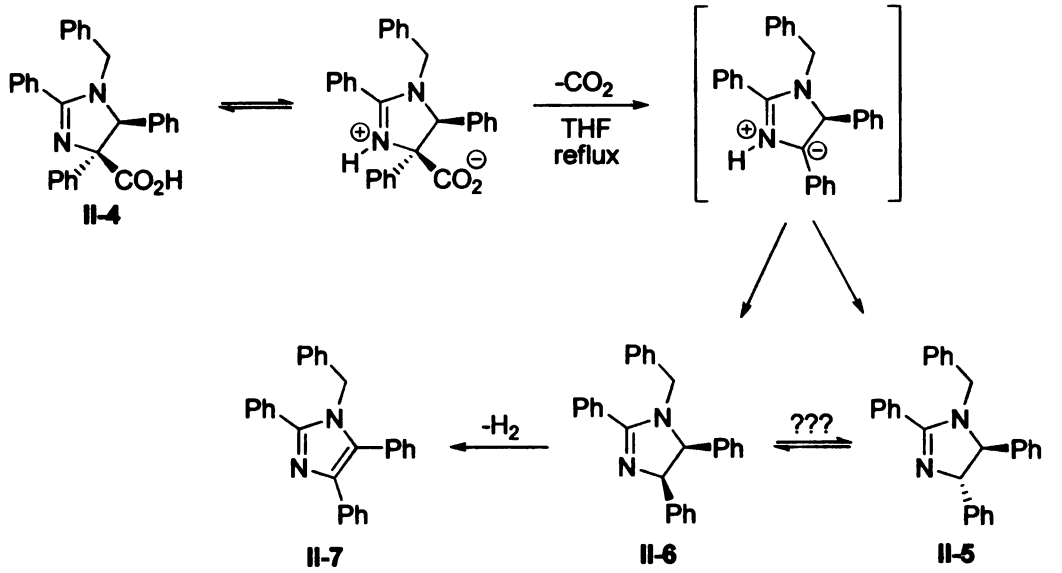
The inhibition of NF-κB mediated gene transcription is recognized as an attractive method for potentially treating a wide variety of disease states.[61] To this end, the development of novel small molecule regulators of NF-κB mediated gene transcription is of great value. As previously mentioned, prior studies in our research group found imidazoline **II-4** to be a relatively potent inhibitor of NF-κB mediated gene transcription.[36,39] In addition, imidazoline **II-4** represents a new

class of molecule for the inhibition of NF-κB signaling pathways. As a part of our diversity oriented synthesis research program aimed at the development of new biologically interesting compounds, we set out to optimize imidazoline **II-4** for its ability to inhibit the NF-κB mediated gene transcription.

While imidazoline **II-4** was demonstrated to be a potent inhibitor of NF-κB mediated gene transcription, questions regarding the structural integrity of the compound made imidazoline **II-4** an unlikely candidate for pharmaceutical use. Imidazoline **II-4** is a primary cycloadduct obtained from a [3+2] cycloaddition reaction of a münchnone with an imine. Early studies regarding münchnone cycloaddition chemistry illustrated that the primary cycloaddition adducts generated from these reactions readily decarboxylate and aromatize to afford a variety of hetero-aromatic products.[15,37,62] In comparison to earlier methods (refluxing in acetic anhydride), the Lewis acid mediated cycloaddition used to synthesize imidazoline **II-4** was conducted under relatively milder conditions.[12,13,15,20,37,62] The mild reaction conditions (reflux in dichloromethane) utilized in the synthesis is more than likely responsible for preventing the decarboxylation/aromatization of the product imidazoline **II-4**.

Although new reaction methodology allowed for the synthesis and isolation of imidazoline **II-4**, the tendency of this class of primary cycloadducts to decarboxylate led us to investigate the structural stability of the compound. Exposure of imidazoline **II-4** to slightly elevated temperatures did in fact lead to decarboxylation and generation of imidazolines **II-5** and **II-6** and imidazole **II-7** (Scheme II-4). The decarboxylation of imidazoline **II-4** is believed to take place

as outlined in Scheme II-4.[63] Upon being exposed to slightly elevated temperatures, imidazoline **II-4** decarboxylates generating an azomethine ylide intermediate. The azomethine ylide intermediate then undergoes a 1,2-prototopic shift affording imidazolines **II-5** and **II-6**. While imidazole **II-7** is likely produced from the oxidation of both imidazolines **II-5** and **II-6**,[64] only imidazoline **II-6** has been demonstrated to undergo aromatization in our laboratories. However, it should be noted that 4,5-diaryl 2-imidazolines, such as imidazolines **II-5** and **II-6**, have previously been demonstrated to exist in equilibrium under a variety of conditions.[65,66] This leads to the possibility that imidazoline **II-5** may potentially aromatize to imidazole **II-7** by equilibrating to imidazoline **II-6** followed by subsequent aromatization.



Scheme II-4. Decarboxylation of imidazoline **II-4**.

The propensity of imidazoline **II-4** to decarboxylate under relatively mild reaction conditions prompted us to question if imidazoline **II-4** was the molecule

responsible for inhibiting NF-κB signaling or if it was merely a precursor to the actual reactive species.[9] To help answer this question, degradation products **II-5**, **II-6**, and **II-7** were isolated and evaluated for their ability to inhibit NF-κB mediated gene transcription (Table II-1). Compounds **II-5**, **II-6**, and **II-7** were evaluated for their ability to inhibit NF-κB mediated gene transcription in HeLa cells activated by TNF-α using a luciferase-based reporter assay (See experimental section). In addition, the three compounds were further evaluated for their ability to inhibit IL-6 production in human whole blood stimulated by IL-1β. Both assays illustrated that all three degradation products were less active than their precursor, imidazoline **II-4,** for inhibiting NF-κB mediated gene transcription. Of the degradation products, the trans-aryl 2-imidazoline **II-5** illustrated the best inhibitory properties inhibiting NF-κB mediated luciferin production with an EC_{50} value of 4.6 μM and IL-6 production with an IC_{50} value equal to 2.5 μM (Table II-1). The cis-aryl 2-imidazoline **II-6** was found to be slightly less effective in the luciferase reporter assay affording an EC_{50} value of 11.0 μM, while interestingly provided very similar results for inhibiting IL-6 production with an IC_{50} equal to 2.4 μM (Table II-1). The fully aromatized imidazole **II-7** exhibited no ability to inhibit NF-κB mediated gene transcription in the luciferase based reporter assay, and thus was not analyzed using the human whole blood assay (Table II-1). These results seem to indicate that parent molecule imidazoline **II-4** is most likely the molecular species responsible for the nanomolar activity observed in our previous studies, although current studies are still ongoing to further validate this conclusion.

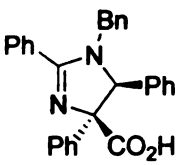
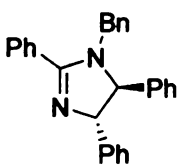
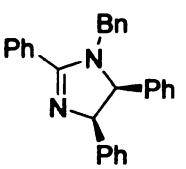
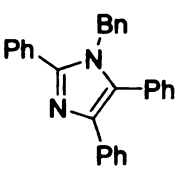
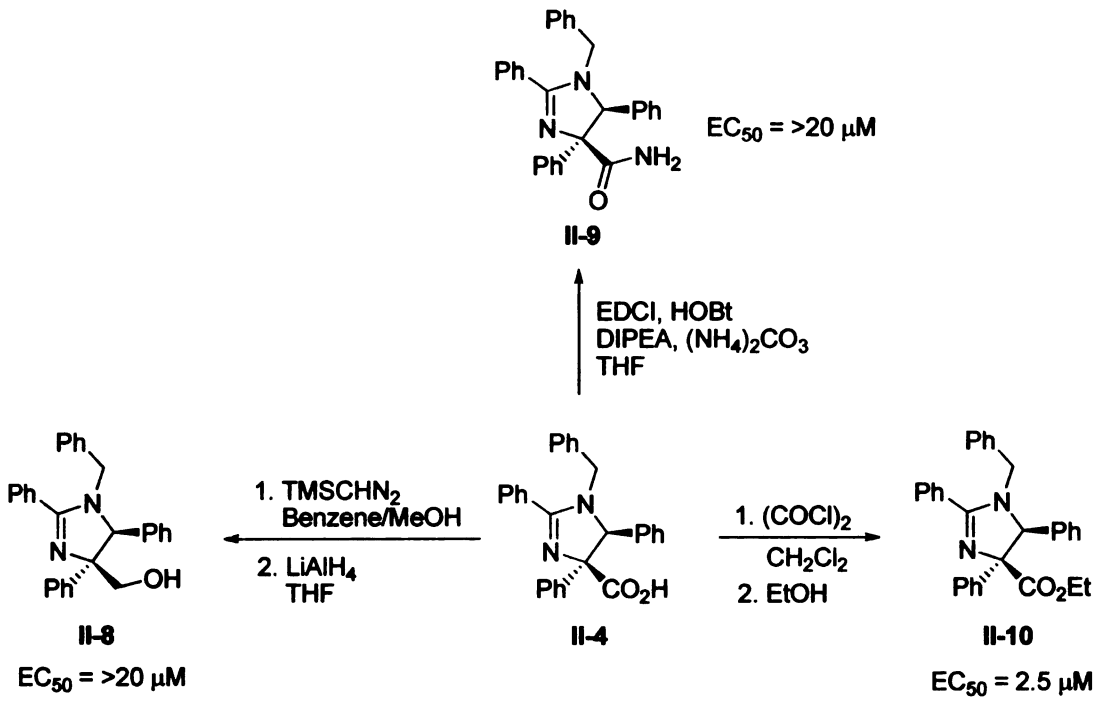
Compound Number	Compound Structure	Inhibition of HeLa NF-kB Luc EC_{50} (μM)	Inhibition of IL-6 in human blood IC_{50} (μM)
II-4		0.95	>20
II-5		4.6	2.5
II-6		11.0	2.4
II-7		>20	—

Table II-1. Evaluation of the degradation products produced from imidazoline **II-4** for their ability to inhibit NF-κB signaling pathways.

Simultaneous to the structural integrity studies regarding imidazoline **II-4**, other members of our research group focused on its derivatization with aspirations of discovering a compound illustrating increased stability while maintaining a similar biological profile. To this end, Dr. Daljinder Kahlon synthesized imidazoline derivatives **II-8**, **II-9**, and **II-10** starting from imidazoline **II-4**.[9] Esterification of imidazoline **II-4** using $TMSCHN_2$ followed by subsequent reduction with $LiAlH_4$ afforded alcohol substituted imidazoline **II-8**. Primary amide substituted imidazoline **II-9** was synthesized via an EDCI mediated coupling of

imidazoline **II-4** with $(NH_4)_2CO_3$. Finally, imidazoline **II-4** was treated with $(COCl)_2$ producing an acid chloride intermediate, which was subsequently treated with ethanol affording the ethyl ester substituted imidazoline **II-10**. Compounds **II-8**, **II-9**, and **II-10** were next evaluated for their ability to inhibit NF-κB mediated gene transcription in HeLa cells using the luciferase based reporter assay. Both imidazolines **II-8** and **II-9** were devoid of any ability to inhibit NF-κB mediated luciferase production in HeLa cells, while imidazoline **II-10** illustrated relatively good activity with an EC_{50} value of 2.5 μM.



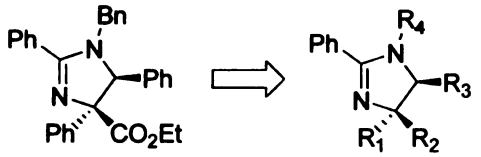
Scheme II-5. Derivatization of imidazoline **II-4**.

Upon discovering the ethyl ester substituted imidazoline **II-10** to be a potent inhibitor of NF-κB mediated gene transcription, Dr. Kahlon and Dr. Daniel Jones further evaluated imidazoline **II-10** for its structural stability.[9] Small molecules containing ester moieties are often susceptible to hydrolysis by blood

and cellular esterases. To this end, imidazoline **II-10** was evaluated for its ability to resist hydrolysis in human whole blood to ensure that imidazoline **II-10** was in fact the active compound and not just a pro-drug of imidazoline **II-4**. Incubation of imidazoline **II-10** in human whole blood for 24 hours at 37°C afforded no degradation of the compound as determined by LC/MS analysis providing plausible evidence that imidazoline **II-10** was not a pro-drug for imidazoline **II-4**.

E. Structure activity relationship study of trans-2-imidazolines

Upon discovering imidazoline **II-10** to be a relatively potent inhibitor of NF-κB mediated gene transcription, we next sought to structurally optimize the molecule for its ability to inhibit NF-κB mediated gene transcription.[67] Structural optimization of this novel class of molecules would not only possibly lead to more effective inhibitors of NF-κB signaling, but may also provide further insight into their inhibitory mechanism. In a collaborative effort to structurally optimize these compounds for their ability to inhibit NF-κB mediated gene transcription, Dr. Daljinder Kahlon and I synthesized a variety of analogues of imidazoline **II-10**. We systematically synthesized a series of analogues of **II-10,** varying four different positions of the imidazoline scaffold (Figure II-4, R_1 – R_4). The compounds were synthesized via Lewis acid mediated 1,3-dipolar cycloaddition reactions of oxazol-5(4H)-ones with imines as described previously.[12,13,21]



II-10

Figure II-4. Structure activity relationship study of imidazoline **II-10**.

The imidazoline analogues were then evaluated for their ability to inhibit NF-κB mediated gene transcription using a luciferase based reporter assay in human cervical epithelial (HeLa) cells with a stably transfected NF-κB-luc gene. The cells were treated in the presence or absence various concentrations of the imidazolines. The proteasome inhibitor MG-132 and DMSO (vehicle) were used as positive and negative controls, respectively. Cells were pretreated for 30 minutes with the imidazolines/controls followed by TNF-α stimulation. Treatment with the cytokine TNF-α, initiated the NF-κB signaling pathway, thus leading to the degradation of the inhibitory protein I-κB (Figure II-5). Upon being released into the cytoplasm, NF-κB was then translocated into the nucleus where it bound to DNA and initiated the transcription of various genes including those responsible for the production of the enzyme luciferase. Luciferase production was evaluated after 8 hours. All samples were normalized to the TNF-α activation control. Treatment of the HeLa/NF-κB-luc cells with imidazolines without any TNF-α activation did not induce a significant amounts of luciferase activity, indicating that the imidazolines did not stimulate the NF-κB pathway.

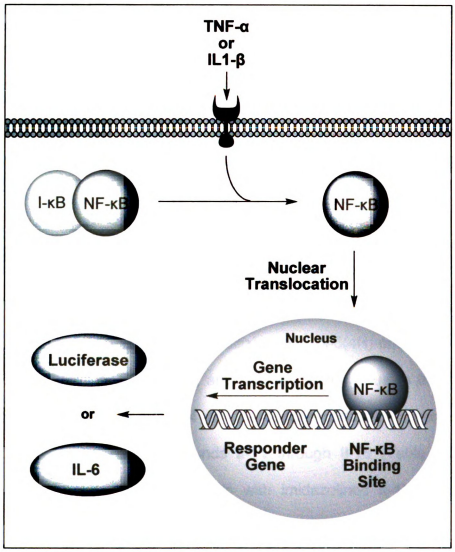


Figure II-5. Methods for analyzing NF-κB inhibition.

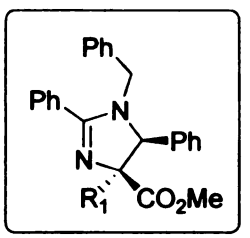
The compounds were further evaluated for their ability to inhibit production of the cytokine IL-6 in human whole blood by Theresa Lansdell. Human whole blood was activated with IL-1β inducing the production of cyctokine, IL-6, via NF-κB mediated gene transcription (Figure II-5). Plasma was harvested and IL-1β induced IL-6 production was measured 22 hours after stimulation using a human IL-6 ELISA (R&D Systems). The circulating IL-6 levels in IL-1β stimulated

samples were significantly higher than in unstimulated or the vehicle treated blood. Pretreatment of the blood for 2 hours with the imidazolines, followed by IL-1β stimulation resulted in a strong dose dependent inhibition of IL-6 production, as compared to the no-drug treated control. The inhibitory properties of all the imidazolines evaluated in this study are summarized in the following sections.

F. Structure activity relationship investigation of R_1.

The structural optimization studies of the oxazol-5(4H)-one derived imidazoline **II-10** was initiated by first examining the R_1 substituent of the scaffold. These derivatives were readily synthesized utilizing oxazol-5(4H)-ones derived from phenyl glycine, alanine, tryptophan, and phenyl-alanine. Due to the increased stability of imidazoline **II-10** over **II-4**, all intermediate imidazolines were esterified with $TMSCHN_2$ to provide compounds **II-11** through **II-15** (Table II-2). Pre-treatment of the HeLa NF-κB-luc cells with imidazolines **II-11** through **II-15** followed by TNF-α stimulation resulted in a dose dependent decrease in luciferase production (Table II-2). Imidazolines **II-11** and **II-15** were the most effective at inhibiting NF-κB mediated luciferin production with EC_{50} values of 7.2 μM and 5.9 μM respectively (Table II-2). Compounds **II-11** to **II-15** were also evaluated for their ability to inhibit NF-κB mediated IL-6 production in IL-1β stimulated human blood. Human whole blood was incubated with the imidazolines **II-11** to **II-15**, for 2 hours and then activated with IL-1β inducing an NF-κB mediated cytokine response. Similar to the HeLa NF-κB-luc assays, compounds **II-11** and **II-15** were found to be the most potent with IC_{50} values of

3.0 μM and 4.0 μM, respectively for the inhibition of IL-6 production. Since compound **II-11** was found to be slightly more potent than compound **II-15**, the remainder of the compounds found in this study were derived from 2,4-diphenyl-5(4H)-oxazolone **II-2**.



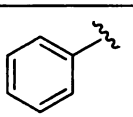
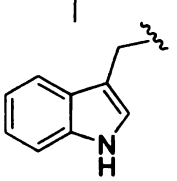
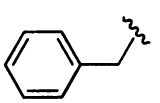
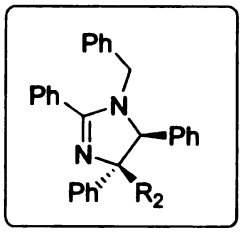
Compound	R_1	Inhibition of HeLa NF-kB Luc EC_{50} (μM)	Inhibition of IL-6 in human blood IC_{50} (μM)
II-11		7.5	3.0
II-12		~20	6.3
II-13		18.0	6.6
II-14		11.2	16.2
II-15		5.9	4.0

Table II-2. Structure activity relationship study of R_1.

G. Structure activity relationship investigation of R_2.

The next series of derivatives synthesized were designed to evaluate the ester functional group of imidazoline **II-10**. Previously, we found that the ester or carboxylic acid moieties found in imidazolines **II-10** and **II-4** respectively to be

critical for their activity.[9,68] Imidazolines containing other functional groups (e.g. amides and alcohols) were found to be less active than their respective ester or carboxylic acid derivatives.[9] Therefore, ester substituted imidazolines **II-16** through **II-18** were synthesized via the esterification of imidazoline **II-4**. All esters (**II-10**, **II-11**, **II-16** to **II-18**) were found to be excellent NF-κB inhibitors. Consistent with our previous studies, the primary amide substituted imidazoline **II-9** was devoid of any significant activity in both assays (Table II-3). Interestingly, complete removal of the R_2 substituent did not result in complete loss of inhibitory function (Table II-3, compound **II-5**) although a reduction in potency was noted (EC_{50} = 5.5 μM and IC_{50} = 2.5 μM). The ethyl ester substituted imidazoline **II-10** provided the best results inhibiting NF-κB mediated luciferin and IL-6 production with an EC_{50} value of 2.5 μM and IC_{50} value of 0.8 μM respectively. Due to its potency and stability against hydrolysis by esterases,[9] the ethyl ester substituted imidazoline **II-10** was further evaluated through functionalization of its R_3 and R_4 moieties (Tables II-4 and II-5).



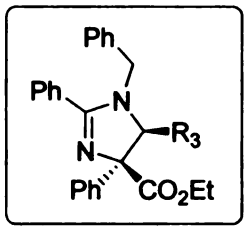
Compound	R_2	Inhibition of HeLa NF-kB Luc EC_{50} (μM)	Inhibition of IL-6 in human blood IC_{50} (μM)
II-11	CO_2Me	7.5	3.0
II-10	CO_2Et	2.5	0.8
II-16	$CO_2{}^nPr$	2.3	1.9
II-17	$CO_2{}^iPr$	3.5	2.0
II-18	CO_2Bn	3.5	6.0
II-9	$CONH_2$	>20	18.1
II-5	H	5.5	2.5

Table II-3. Structure activity relationship study of R_2.

H. Structure activity relationship study of R_3.

We next examined the R_3 position of the ethyl ester substituted imidazoline **II-10**. A series of imidazolines (II-19 to II-26) containing various aromatic R_3 substituents were synthesized and subsequently evaluated for their ability to inhibit NF-κB mediated gene transcription (Table II-4). Minor structural changes had significant affects on overall potency of the imidazolines analyzed. Substitution of this moiety with hetero-aromatic substituents seemed to cause a

decrease in activity. The 4-pyridino-substituted imidazoline **II-19** was devoid of activity in our HeLa NF-κB-luc assay and showed relatively weak activity (Table II-4, IC_{50} = 12.4 μM) in our whole blood assay. Furthermore, the 2-furyl substituted imidazoline **II-27** only exhibited moderate activity towards inhibiting luciferase production (EC_{50} = 7.8 μM), while illustrating a relatively good capability to inhibit IL-6 production (IC_{50} = 1.9 μM). On the other hand, the para-chloro substituted imidazoline **II-24** proved to be the most potent analogue in this series inhibiting NF-κB mediated luciferin and IL-6 production with an EC_{50} value of 1.9 μM and IC_{50} value of 0.3 μM respectively. As seen previously, the two assays corresponded well in terms of their relative potencies. The only possible exception was the aniline substituted imidazoline **II-21**, which illustrated relatively weak activity in the HeLa NF-κB-luc assay (Table II-4, EC_{50} = 10 μM) but showed excellent activity (Table II-4, IC_{50} = 0.5 μM) in our whole blood assay. Overall, this data indicated that increasing the lipophilic nature of the R_3 substituent increased the overall inhibitory activity of the compounds.



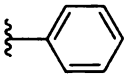
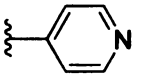
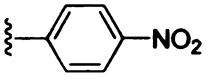
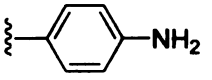
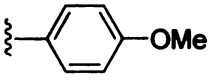
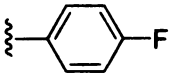
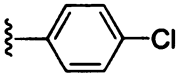
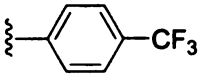
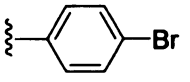
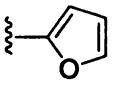
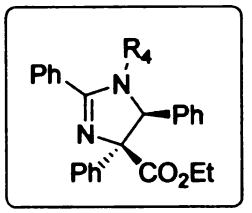
Compound	R_3	Inhibition of HeLa NF-kB Luc EC_{50} (μM)	Inhibition of IL-6 in human blood IC_{50} (μM)
II-10		2.5	0.8
II-19		>20	12.4
II-20		3.4	0.5
II-21		10.4	0.5
II-22		3.6	1.3
II-23		5.0	1.2
II-24		1.5	0.3
II-25		1.4	0.8
II-26		1.5	—
II-27		7.6	1.9

Table II-4. Structure activity relationship study of R_3.

I. Structure activity relationship study of R_4.

We next synthesized and analyzed imidazolines **II-28** to **II-37** to analyze the structural activity relationship of the fourth domain (Table II-4, R_4 substituent). This substituent proved to be the most sensitive to derivatization. Substitution of

the R_4 group of imidazoline **II-10** by benzyl groups containing lipophilic substituents increased its activity as indicated by the compounds **II-28** to **II-33**. The para-bromobenzyl imidazoline **II-32** provided the best results in this set of compounds inhibiting NF-κB mediated luciferin and IL-6 production with an EC_{50} value equal to 1.6 μM and IC_{50} value of 0.5 μM respectively. Debenzylation of imidazoline **II-10** afforded imidazoline **II-37**, which was found to be inactive in both assays. Interestingly, replacement of the benzyl moiety found in imidazoline **II-10** with electron deficient substituents almost completely abrogated any inhibitory activity. For example, replacement of the benzyl substituent with an acyl group (Table II-5, compound **II-36**) resulting in complete loss of activity. In addition, tosyl and benzoyl substituted imidazolines **II-34** and **II-35** provided no inhibition of NF-κB luciferin production and only moderate efficacy in our whole blood assay (Table II-5, IC_{50} values of 6.6 μM and 5.9 μM respectively).



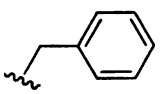
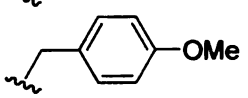
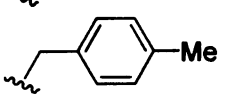
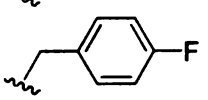
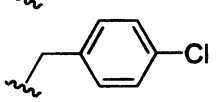
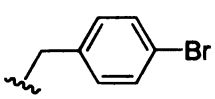
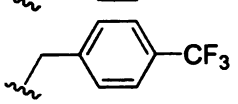
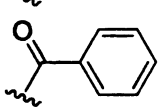
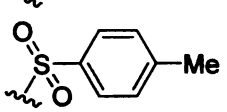
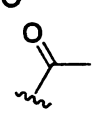
Compound	R_4	Inhibition of HeLa NF-kB Luc EC_{50} (μM)	Inhibition of IL-6 in human blood IC_{50} (μM)
II-10		2.5	0.8
II-28		5.5	1.4
II-29		2.5	4.6
II-30		4.7	1.2
II-31		4.2	1.6
II-32		1.6	0.5
II-33		6.7	1.5
II-34		20	6.6
II-35		>20	5.9
II-36		>20	>20
II-37		>20	>20

Table II-5. Structure activity relationship study of R_4.

J. Experimental

1. General.

Reactions were carried out in flame-dried glassware under nitrogen atmosphere. All reactions were magnetically stirred and monitored by TLC with 0.25 μm pre-coated silica gel plates using UV light to visualize the compounds. Column chromatography was carried out on Silica Gel 60 (230-400 mesh) supplied by EM Science. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise noted. Infrared spectra were recorded on a Nicolet IR/42 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity Plus-500 spectrometer. Chemical shifts are reported in ppm relative to tetramethylsilane (0.00 ppm) and $CHCl_3$ (7.26 ppm for ^{1}H NMR) and $CDCl_3$ (77.0 ppm ^{13}C NMR) as the internal standards. The following abbreviations are used to denote the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Gas chromatography / low resolution mass spectra were recorded on a Hewlet-Packard 5890 Series II gas chromatograph connected to a TRIO-1 EI mass spectrometer. HRMS were obtained at the Mass Spectrometry Facility of Michigan State University with a JEOL JMS HX-110 mass spectrometer. Melting points were obtained using an Electrothermal® capillary melting point apparatus and are uncorrected.

2. Materials.

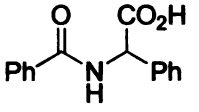
Reagents and solvents were purchased from commercial suppliers and used without further purification. Anhydrous methylene chloride and benzene were

dispensed from a delivery system which passes the solvents through a column packed with dry neutral alumina. Anhydrous TMSCl required for these reactions was distilled from calcium hydride.

3. Compound synthesis and characterization.

Imidazolines **II-11** to **II-15**, **II-16** to **II-18**, and **II-28** to **II-33** were all prepared using procedures previously reported.[9,12,13,67] Imidazolines **II-8 and II-9** were also prepared using reported procedures.[9] These compounds were prepared and fully characterized by Dr. Daljinder Kahlon. Imidazole **II-7** was an observed byproduct from the decarboxylation of imidazoline **II-4**. Imidazole **II-7** had been previously prepared in our laboratories by Christopher Hupp. His spectroscopic data was used to confirm the structure of imidazole **II-7**. For further details regarding either the synthesis or characterization of these compounds, please see the supporting information of the following publication:

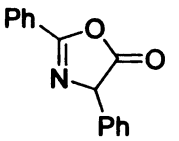
Kahlon, D. K.; Lansdell, T. A.; Fisk, J. S.; Tepe, J. J.; Structural-activity relationship study of highly-functionalized imidazolines as potent inhibitors of nuclear transcription factor-kappaB mediated IL-6 production. *Bioorg. Med. Chem.* **2009**, *17*, 3093-3103.[67]



II-1

2-benzamido-2-phenylacetic acid (II-1): A solution of 2-phenylglycine (12.0 g, 79.4 mmol) in 150 mL of 1M NaOH solution was treated dropwise with benzoyl chloride (12.3 g, 87.3 mmol) at 0 °C. The solution was stirred overnight while being allowed to warm to room temperature. The solution was then washed with

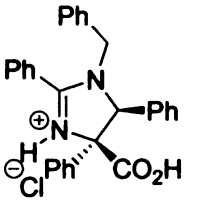
EtOAc (1x100mL), cooled to 0 °C, and acidified with 2M HCl. The aqueous solution was then washed again with EtOAc (3x100mL). The combined EtOAc washes were dried over magnesium sulfate and concentrated *in vacuo*. The resulting crude solid was recrystallized using EtOAc/Hexanes to afford 14.5 g (71% yield) of the title compound as a white crystalline solid. (m.p. = 178 °C – 179 °C) ^{1}H NMR (500 MHz, DMSO-d_6): δ 5.61 (d, J = 7.5 Hz, 1H), 7.34 – 7.39 (m, 3H), 7.44 – 7.53 (m, 5H), 7.92 (d, J = 8.0 Hz, 2H), 9.02 (d, J = 7.5 Hz, 1H), 12.92 (bs, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 56.82, 127.69, 127.88, 128.15, 128.18, 128.39, 131.45, 133.75, 137.11, 166.30, 171.92; IR (neat): 3306 cm^{-1}, 3054 cm^{-1}, 2923 cm^{-1}, 1734 cm^{-1}, 1653 cm^{-1}; LRMS (EI): *m/z* calcd for $C_{15}H_{13}NO_3$, 255.3; found, 255.4.



II-2

2,4-diphenyl-5(4H)-oxazolone (II-35): A solution of N-benzoyl-2-phenylglycine **II-34** (10.0 g, 39.2 mmol) in 250 mL of anhydrous dichloromethane was treated with trifluoroacetic anhydride (8.6 g, 41.1 mmol) at room temperature for 12 hours. The solution was then washed with saturated $NaHCO_3$ (3x100 mL) and brine (1x100mL), dried over sodium sulfate, and concentrated *in vacuo* resulting in 8.5 g (92% yield) of the title compound as a yellow solid (m.p. = 80 °C – 81 °C). The title compound was used as is without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) (TMS): δ 5.53 (s, 1H), 7.33 – 7.44 (m, 5H), 7.50 – 7.53 (m, 2H), 7.59 – 7.63 (m, 1H), 8.07 – 8.09 (m, 2H); ^{13}C NMR + **DEPT** (125 MHz,

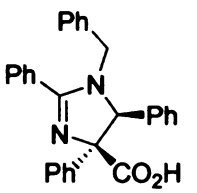
$CDCl_3$) (TMS): δ 68.02, 125.50, 126.82, 128.13, 128.75, 128.90, 129.01, 133.15, 133.29, 162.74, 176.06; IR (KBr): 3063 cm^{-1}, 3032 cm^{-1}, 1827 cm^{-1}, 1649 cm^{-1}; LRMS(EI): *m/z* calcd for $C_{15}H_{11}NO_2$, 237.3; found, 236.9.



II-3

dl-(4S,5S)-1-benzyl-2,4,5-triphenyl-4,5-dihydro-1H-imidazole-4-carboxylic acid hydrochloride (II-3): A solution of benzyl amine (3.2 g, 29.5 mmol) and benzaldehyde (3.1 g, 29.5 mmol) in 200 mL of anhydrous benzene was refluxed under nitrogen for 2 hours and then concentrated *in vacuo.* The resulting residue was redissolved into 300 mL of anhydrous dichloromethane. Then 2,4-diphenyl-5(4H)-oxazolone **II-2** (7.0 g, 29.5 mmol) and chlorotrimethylsilane (4.2 g, 38.4 mmol) were added and the mixture was refluxed under nitrogen for 12 hours. The solution was concentrated *in vacuo* and the resulting residue was resuspended in EtOAc producing 9.4g (68% yield) of the title compound as a white solid precipitate. The spectra matches that of previously published literature.[9,12] (m.p. = 154 °C – 155 °C) ^{1}H NMR (500 MHz, DMSO-d_6): δ 4.18 (d, J = 16 Hz, 1H), 4.86 (d, J = 16 Hz, 1H), 5.59 (s, 1H), 6.71 (d, J = 7.5 Hz, 2H), 7.08-7.11 (m, 2H), 7.17-7.20 (m, 1H), 7.45-7.59 (m, 8H), 7.72-7.77 (m, 4H), 7.82-7.85 (m, 1H), 7.97 (d, J = 7.5 Hz, 2H), 12.86 (bs, 1H), 13.99 (bs, 1H); ^{13}C NMR + **DEPT** (125 MHz, DMSO-d_6): δ 48.67 (-CH2), 73.86 (-CH), 75.91 (quaternary –C), 121.39 (aromatic –CH), 125.74 (aromatic –CH), 127.21 (aromatic –CH), 128.31

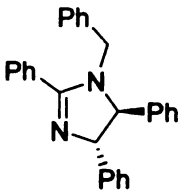
(aromatic –CH), 128.67 (aromatic –CH), 128.89 (aromatic –CH), 129.05 (aromatic –CH), 129.11 (aromatic –CH), 129.45 (aromatic –CH), 129.55 (aromatic –CH), 129.95 (aromatic –CH), 132.80 (quaternary aromatic –C), 133.17 (quaternary aromatic –C), 134.26 (quaternary aromatic –C), 139.18 (quaternary aromatic –C), 165.66, 167.64; LRMS (EI): *m/z* calcd for $C_{29}H_{25}N_2O_2Cl$, 469.0; found, 387.8 ($-CO_2$).



II-4

dl-(4S,5S)-1-benzyl-2,4,5-triphenyl-4,5-dihydro-1H-imidazole-4-carboxylic acid (II-4): A solution of imidazoline **II-3** (5.0 g, 10.7 mmol) in 100 mL of dichloromethane was washed with saturated sodium bicarbonate solution (2 X 100 mL) and brine solution (1 X 100 mL). The solution was then dried over sodium sulfate and concentrated *in vacuo*. The resulting crude solid was purified via crystallization (dichloromethane / hexanes) to afford 3.8 g (83% yield) of the title compound as a white crystalline solid. The spectra matches that as previously published literature.[9] (m.p. = 118 °C - 120 °C) ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.77 (d, J = 16 Hz, 1H), 4.59 (d, J = 16 Hz, 1H), 4.92 (s, 1H), 6.59 (d, J = 7.5 Hz, 2H), 7.05-7.08 (m, 1H), 7.26-7.32 (m, 5H), 7.36-7.39 (m, 5H), 7.46-7.49 (m, 1H), 7.49-7.52 (m, 2H), 7.86 (d, J = 7.5 Hz, 1H), 9.18 (bs, 1H); ^{13}C NMR + DEPT (125 MHz, $CDCl_3$): δ 48.35 (-CH2), 75.58 (-CH), 79.04 (quaternary –C), 122.86 (quaternary aromatic –C), 125.73 (aromatic –CH),, 126.70 (aromatic –

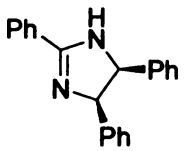
CH), 127.36 (aromatic –CH), 127.91 (aromatic –CH), 128.18 (aromatic –CH), 128.85 (aromatic –CH), 128.91 (aromatic –CH), 128.97 (aromatic –CH),129.27 (aromatic –CH), 132.93 (aromatic –CH), 133.74 (quaternary aromatic –C), 136.01 (quaternary aromatic –C), 143.15 (quaternary aromatic –C), 164.70, 167.96; IR (neat): 3061 cm^{-1}, 2700 cm^{-1}, 1633 cm^{-1}, 1550 cm^{-1}, 1340 cm^{-1}



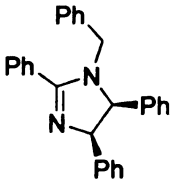
II-5

dl-(4S,5S)-1-benzyl-2,4,5-triphenyl-4,5-dihydro-1H-imidazole (II-5): The title compound was isolated in small amounts via a decarboxylation of imidazoline **II-4**. A solution of imidazoline **II-4** (0.7 g, 1.62 mmol) in 100 mL of THF was refluxed for 5 hours. The solution was then concentrated *in vacuo* resulting in a crude mixture of imidazolines **II-5** and **II-6** and imidazole **II-7** in a 2:1:1 ratio respectively. The crude residue was then purified via column chromatography (10% MeOH / 90% CH_2Cl_2) affording 112 mg (18% yield) of the title compound as a white solid. (m.p. = 78 °C – 80 °C) ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.99 (d, J = 16 Hz, 1H), 4.41 (d, J = 8.5 Hz, 1H), 4.77 (d, J = 15.5 Hz, 1H), 5.07 (d, J = 8.5 Hz, 1H), 7.00-7.01 (m, 2H), 7.18-7.23 (m, 2H), 7.24-7.30 (m, 4H), 7.31-7.33 (m, 2H), 7.34-7.39 (m, 3H), 7.42-7.45 (m, 2H), 7.53-7.55 (m, 3H), 7.88-7.90 (m, 2H); ^{13}C NMR + DEPT (125 MHz, $CDCl_3$): δ 49.63, (-CH2), 72.57 (-CH), 77.95 (-CH), 126.72 (aromatic –CH), 126.96 (aromatic –CH), 127.13 (aromatic –CH), 127.42 (aromatic –CH), 127.72 (aromatic –CH), 127.94 (aromatic –CH), 128.34

(aromatic –CH), 128.42 (aromatic –CH), 128.58 (aromatic –CH), 128.65 (aromatic –CH), 128.81 (aromatic –CH), 130.07 (aromatic –CH), 131.34 (aromatic quaternary –C), 136.42 (aromatic quaternary –C),141.82 (aromatic quaternary –C), 143.90 (aromatic quaternary –C), 165.91; IR (neat): 3063 cm^{-1}, 3030 cm^{-1}, 1595 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{24}N_2$ [M+H], 389.2018; found, 389.2020.



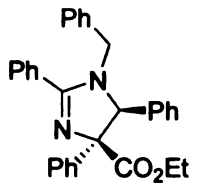
dl-(4R,5S)-2,4,5-triphenyl-4,5-dihydro-1H-imidazole: This compound was made according to a reported literature procedure.[65] A solution of benzaldehyde (10.0 g, 94.2 mmol) and hexamethyldisalizane (18.2 g, 113.0 mmol) was treated with benzoic acid (57.5 mg, 0.5 mmol) and heated to 120 °C for 22 hours. The solution was then dissolved into 50 mL of toluene and washed with sat. $NaHCO_3$ (2 x 50 mL), water (1 x 50 mL), and brine (1 x 50 mL). The solution was then dried over magnesium sulfate and concentrated *in vacuo*. The resulting residue was purified via column chromatography (10% MeOH, 90% CH_2Cl_2) affording 5.8 g (62% yield) of the title compound as a white solid. (m.p. = 123 ° - 124 °C) ^1H NMR (500 MHz, $CDCl_3$): δ 4.90 (bs, 1H), 5.43 (s, 2H), 6.95-7.15 (m, 10H), 7.47-7.50 (m, 2H), 7.51-7.60 (m, 1H), 7.97-8.10 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) (TMS): δ 70.70, 126.68, 127.21, 127.45, 127.53, 128.54, 130.05, 130.93, 138.98; IR (neat): 3385 cm^{-1}, 3165 cm^{-1}, 3028 cm^{-1}, 1599 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{21}H_{18}N_2$ [M+H], 299.1548; found, 299.1541.



II-6

dl-(4R,5S)-1-benzyl-2,4,5-triphenyl-4,5-dihydro-1H-imidazole (II-6): A solution of dl-(4R,5S)-2,4,5-triphenyl-4,5-dihydro-1H-imidazole (0.3 g, 1.01 mmol) and benzyl bromide (0.2 g, 1.06 mmol) in 20 mL of anhydrous benzene was treated with triethyl amine (0.2 g, 2.02 mmol). The solution was refluxed for 15 hours and then washed with saturated $NaHCO_3$ (2x20mL) and brine (1x20mL). The solution was then dried over sodium sulfate and concentrated *in vacuo*. The resulting crude residue was purified via column chromatography (10% MeOH / 90% CH_2Cl_2) affording 77 mg (20% yield) of the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.85 (d, J = 15.5 Hz, 1H), 4.77 (d, J = 16 Hz, 1H), 4.92 (d, J = 11.5 Hz, 1H), 5.55 (d, J = 11 Hz, 1H), 6.90-6.96 (m, 5H), 6.97-7.00 (m, 4H), 7.02-7.09 (m, 3H), 7.25-7.29 (m, 3H), 7.50-7.53 (m, 3H), 7.81-7.83 (m, 2H); ^{13}C NMR + DEPT (125 MHz, $CDCl_3$): δ 48.97 (-CH2), 68.38 (-CH), 72.94 (-CH), 126.23 (aromatic –CH), 127.07 (aromatic –CH), 127.30 (aromatic –CH), 127.52 (aromatic –CH), 127.80 (aromatic –CH), 127.86 (aromatic –CH), 127.93 (aromatic –CH), 128.07 (aromatic –CH), 128.54 (aromatic –CH), 128.56 (aromatic –CH), 128.72 (aromatic –CH), 130.18 (aromatic –CH), 131.17 (aromatic quaternary –C), 136.64 (aromatic quaternary –C), 136.82 (aromatic quaternary –C), 139.32 (aromatic quaternary –C), 167.15; IR (neat): 3030 cm^{-1},

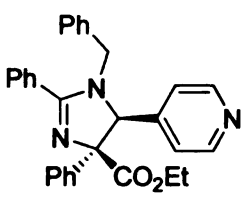
2924 cm^{-1}, 1595 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{24}N_2$ [M+H], 389.2018; found, 389.2017.



II-10

(4S,5S)-ethyl-1-benzyl-2,4,5-triphenyl-4,5-dihydro-1H-imidazole-4-carboxylate (II-10): A solution of dl-(4S,5S)-1-benzyl-2,4,5-triphenyl-4,5-dihydro-1H-imidazole-4-carboxylic acid hydrochloride **II-3** (4.0 g, 8.53 mmol) and oxalyl chloride (3.25 g, 25.6 mmol) in 200 mL of anhydrous dichloromethane was treated with 200 µL of DMF at 0°C. The solution was stirred for 3 hours and then concentrated *in vacuo*. The resulting yellow solid was cooled to 0 °C and treated with 125 mL of ethanol and stirred for 4 hours. The solution was concentrated *in vacuo* and then dissolved into 100 mL of dichloromethane before being washed with saturated $NaHCO_3$ (3 x 100 mL) and brine (1 x 100 mL). The solution was then dried over sodium sulfate and then concentrated *in vacuo*. The resulting crude residue was purified via silica gel column chromatography (40% EtOAc / 60% Hexanes) affording 3.6 g (92% yield) of the title compound as a white solid (m.p. = 87 ° - 89 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.82 (t, J = 7 Hz, 3H), 3.61 (dq, J_1 = 11 Hz, J_2 = 7.5 Hz, 1H), 3.73 (dq, J_1 = 11 Hz, J_2 = 7.5 Hz, 1H), 3.85 (d, J = 16 Hz, 1H), 4.64 (d, J = 16 Hz, 1H), 4.94 (s, 1H), 6.74 (d, J = 7.5 Hz, 2H), 7.04-7.07 (m, 2H), 7.09-7.12 (m, 1H), 7.25-7.30 (m, 1H), 7.32-7.40 (m, 7H), 7.45-7.48 (m, 3H), 7.73-7.77 (m, 4H); ^{13}C NMR + DEPT (125 MHz, $CDCl_3$): δ 13.46 (-

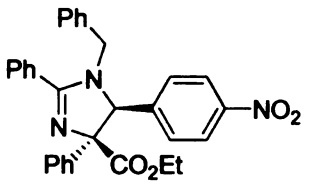
CH3), 48.61 (-CH2), 60.95 (-CH2), 73.78 (-CH), 82.89 (quaternary –C), 126.80 (aromatic –CH), 127.12 (aromatic –CH), 127.30 (aromatic –CH), 127.34 (aromatic –CH), 127.97 (aromatic –CH), 128.15 (aromatic –CH), 128.27 (aromatic –CH), 128.37 (aromatic –CH), 128.44 (aromatic –CH), 128.55 (aromatic –CH), 128.82 (aromatic –CH), 130.26 (aromatic –CH), 130.65 (quaternary aromatic –C), 136.67 (quaternary aromatic –C), 137.95 (quaternary aromatic –C), 144.15 (quaternary aromatic –C), 165.39, 170.78; IR (neat): 3063 cm^{-1}, 2960 cm^{-1}, 1732 cm^{-1}, 1595 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{31}H_{28}N_2O_2$ [M+H], 461.2229; found, 461.2225.



II-19

dl-(4S,5S)-ethyl-1-benzyl-2,4-diphenyl-5-(pyridin-4-yl)-4,5-dihydro-1H-imidazole-4-carboxylate (II-19): A solution of benzyl amine (0.2 g, 2.11 mmol) and 4-pyridylcarboxaldehyde (0.2 g, 2.11 mmol) in 50 mL of anhydrous benzene was reflux under nitrogen for 12 hours and then concentrated *in vacuo*. The resulting residue was redissolved into 50 mL of anhydrous dichloromethane. Then 2,4-diphenyl-5(4H)-oxazolone **II-2** (0.5 g, 2.11 mmol) and chlorotrimethylsilane (0.3 g, 2.74 mmol) were added and the mixture was refluxed under nitrogen for 12 hours. The solution was concentrated *in vacuo* and the resulting residue was resuspended in EtOAc producing a white solid precipitate (0.4 g) which was isolated via filtration. The white solid was then

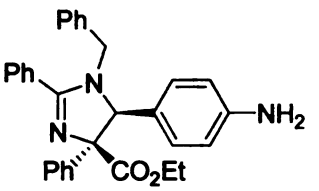
dissolved into 50 mL of dichloromethane, cooled to 0 °C, and treated with oxalyl chloride (0.3 g, 2.68 mmol) and DMF (30 μL). The solution was stirred for 2 hours, concentrated *in vacuo,* and redissolved into 20 mL of EtOH before being left to stir overnight. The solution was concentrated *in vacuo* and then dissolved into dichloromethane before being washed with saturated $NaHCO_3$ (3 x 50 mL) and brine (1 x 50 mL). The solution was then dried over sodium sulfate and then concentrated *in vacuo.* The resulting crude residue was purified via column chromatography (100% EtOAc) to afford 220 mg (23% yield) of the title compound as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.83 (t, J = 7.5 Hz, 3H), 3.66 (dq, J_1 = 11 Hz, J_2 = 7 Hz, 1H), 3.75 (dq, J_1 = 11 Hz, J_2 = 7.5 Hz, 1H), 3.83 (d, J = 15.5 Hz, 1H), 4.62 (d, J = 15.5 Hz, 1H), 4.86 (s, 1H), 6.74 (d, J = 7.5 Hz, 2H), 7.05-7.08 (m, 2H), 7.12-7.14 (m, 1H), 7.28-7.37 (m, 5H), 7.49-7.52 (m, 3H), 7.71-7.72 (m, 2H), 7.79-7.81 (m, 2H), 8.63 (d, J = 6 Hz, 2H); ^{13}C NMR + DEPT (125 MHz, $CDCl_3$): δ 13.39 (-CH3), 49.24 (-CH2), 61.20 (-CH2), 72.62 (-CH), 83.06 (quaternary –C), 122.95 (aromatic –CH), 126.49 (aromatic –CH), 127.14 (aromatic –CH), 127.56 (aromatic –CH), 127.61 (aromatic –CH), 128.11 (aromatic –CH), 128.43 (aromatic –CH), 128.65 (aromatic –CH), 128.77 (aromatic –CH), 129.93 (aromatic quaternary –C), 130.60 (aromatic –CH), 135.86 (quaternary aromatic –C), 143.34 (aromatic quaternary –C), 147.28 (aromatic quaternary –C), 149.93 (aromatic –CH), 165.71, 170.23; IR (neat): 3063 cm^{-1}, 2982 cm^{-1}, 1734 cm^{-1}, 1597 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{30}H_{27}N_3O_2$ [M+H], 462.2182; found, 462.2177.



II-20

dl-(4S,5S)-ethyl-1-benzyl-5-(4-nitrophenyl)-2,4-diphenyl-4,5-dihydro-1H-imidazole-4-carboxylate (II-20): A solution of benzyl amine (0.2 g, 2.11 mmol) and 4-nitrobenzaldehyde (0.3 g, 2.11 mmol) in 50 mL of anhydrous benzene was reflux under nitrogen for 12 hours and then concentrated *in vacuo.* The resulting residue was redissolved into 50 mL of anhydrous dichloromethane. Then 2,4-diphenyl-5(4H)-oxazolone **II-2** (0.5 g, 2.11 mmol) and chlorotrimethylsilane (0.3 g, 2.74 mmol) were added and the mixture was refluxed under nitrogen for 24 hours. The solution was concentrated *in vacuo* and the resulting residue was resuspended in EtOAc producing a white solid precipitate (0.6 g) which was isolated via filtration. The white solid was then dissolved into 25 mL of dichloromethane, cooled to 0 °C, and treated with oxalyl chloride (0.5 g, 3.56 mmol) and DMF (30 µL). The solution was stirred for 2 hours, concentrated *in vacuo,* and redissolved into 25 mL of EtOH before being left to stir overnight. The solution was concentrated *in vacuo* and then dissolved into dichloromethane before being washed with saturated $NaHCO_3$ (3 x 50 mL) and brine (1 x 50 mL). The solution was then dried over sodium sulfate and then concentrated *in vacuo.* The resulting crude solid was purified via column chromatography (50% EtOAc, 50% hexanes) affording 540 mg (51% yield) of the title compound as a white solid. (m.p. = 173 °C – 174 °C) ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.83 (t, J = 7.5 Hz,

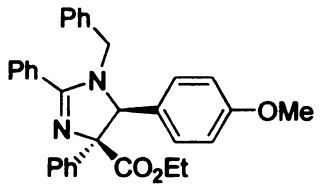
3H), 3.64 (dq, J_1 = 11 Hz, J_2 = 7 Hz, 1H), 3.74 (dq, J_1 = 11 Hz, J_2 = 7 Hz, 1H), 3.81 (d, J = 16 Hz, 1H), 4.60 (d, J = 16 Hz, 1H), 4.93 (s, 1H), 6.71 (d, J = 7.5 Hz, 2H), 7.03-7.10 (m, 2H), 7.10-7.13 (m, 1H), 7.27-7.35 (m, 3H), 7.48-7.51 (m, 3H), 7.54 (d, J = 8.5 Hz, 2H), 7.67-7.69 (m, 2H), 7.77-7.80 (m, 2H), 8.21 (d, J = 9.5 Hz, 2H); ^{13}C NMR + DEPT (125 MHz, $CDCl_3$): δ 15.59 (-CH3), 49.46 (-CH2), 61.30 (-CH2), 73.16 (-CH), 83.32 (quaternary –C), 123.61 (aromatic –CH), 126.49 (aromatic –CH), 127.25 (aromatic –CH), 127.69 (aromatic –CH), 127.75 (aromatic –CH), 128.24 (aromatic –CH), 128.53 (aromatic –CH), 128.76 (aromatic –CH), 128.87 (aromatic –CH), 128.96 (aromatic –CH), 129.98 (aromatic –CH), 130.74 (aromatic –CH), 135.83 (quaternary aromatic –C), 143.45 (quaternary aromatic –C), 146.09 (quaternary aromatic –C), 147.76 (quaternary aromatic –C), 165.78, 170.42; IR (neat): 3063 cm^{-1}, 2982 cm^{-1}, 1732 cm^{-1}, 1597 cm^{-1}, 1350 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{31}H_{27}N_3O_4$ [M+H], 506.2080; found, 506.2076.



II-21

dl-(4S,5S)-ethyl-5-(4-aminophenyl)-1-benzyl-2,4-diphenyl-4,5-dihydro-1H-imidazole-4-carboxylate (II-21): A solution of dl-(4S,5S)-ethyl-1-benzyl-5-(4-nitrophenyl)-2,4-diphenyl-4,5-dihydro-1H-imidazole-4-carboxylate **II-20** (0.1 g, 0.2 mmol) H_2O (36 mg, 2.0 mmol) in 10 mL of ethanol was treated with $SnCl_2{\cdot}2H_2O$ (0.3 g, 1.2 mmol). The solution was heated to reflux for 2 hours and cooled to

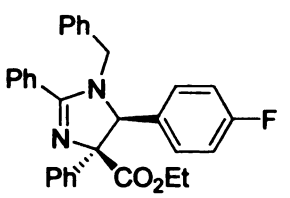
room temperature before being poured over ice (~50 g). The pH of the resulting aqueous solution was adjusted (pH = 8) using $NaHCO_3$ powder. The solution was then washed with EtOAc (3x50 mL). The combined EtOAc washes were dried over sodium sulfate and concentrated *in vacuo*. The resulting residue was purified via column chromatography (EtOAc) to afford 57 mg (60% yield) of the title compound as a white solid. (m.p. = 60 °C – 62 °C) ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.91 (t, J = 7.5 Hz, 3H), 3.68-3.82 (m, 4H) 3.86 (d, J = 16 Hz, 1H), 4.60 (d, J = 15.5 Hz, 1H), 4.86 (s, 1H), 6.68 (d, J = 8.5 Hz, 2H), 6.78 (d, J = 7.5 Hz, 2H), 7.08-7.16 (m, 3H), 7.18 (d, J = 8 Hz, 2H), 7.27-7.30 (m, 1H), 7.35-7.36 (m, 2H), 7.47-7.50 (m, 3H), 7.75-7.78 (m, 4H); ^{13}C NMR + DEPT (125 MHz, $CDCl_3$): δ13.57 (-CH3), 48.24 (-CH2), 60.86 (-CH2), 73.48 (-CH), 82.51 (quaternary –C), 114.84 (aromatic –CH), 126.78 (aromatic –CH), 127.07 (aromatic –CH), 127.16 (aromatic –CH), 127.19 (aromatic –CH), 127.86 (aromatic –CH), 128.29 (aromatic –CH), 128.46 (aromatic –CH), 128.70 (aromatic –CH), 129.18 (aromatic –CH), 130.09 (aromatic –CH), 130.84 (quaternary aromatic –C), 136.88 (quaternary aromatic –C), 144.24 (quaternary aromatic –C), 146.51 (quaternary aromatic –C), 165.19, 170.96; IR (KBr): 3460 cm^{-1}, 3373 cm^{-1}, 3063 cm^{-1}, 1732 cm^{-1}, 1614 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{31}H_{29}N_3O_2$ [M+H], 476.2338; found, 476.2332.



II-22

dl-(4S,5S)-ethyl-1-benzyl-5-(4-methoxyphenyl)-2,4-diphenyl-4,5-dihydro-1H-imidazole-4-carboxylate (II-22): A solution of benzyl amine (0.2 g, 1.91 mmol) and p-anisaldehyde (0.3 g, 1.91 mmol) in 50 mL of anhydrous benzene was reflux under nitrogen for 3 hours and then concentrated *in vacuo.* The resulting residue was redissolved into 50 mL of anhydrous dichloromethane. Then 2,4-diphenyl-5(4H)-oxazolone **II-2** (0.5 g, 1.91 mmol) and chlorotrimethylsilane (0.3 g, 2.48 mmol) were added and the mixture was refluxed under nitrogen for 12 hours. The solution was concentrated *in vacuo* and the resulting residue was resuspended in EtOAc producing a white solid precipitate (450 mg) which was isolated via filtration. The crude solid was then dissolved into 20 mL of EtOH, treated with 1 mL of concentrated H_2SO_4, and refluxed for 42 hours. The solution was concentrated *in vacuo* and then dissolved into dichloromethane before being washed with saturated $NaHCO_3$ (3 x 50 mL) and brine (1 x 50 mL). The solution was then dried over sodium sulfate and then concentrated *in vacuo.* The resulting crude solid was purified via column chromatography (50% EtOAc / 50% Hexanes) to afford 336 mg (36% yield) of the title compound as an off-white solid. (m.p. = 143 °C – 144 °C) ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.85 (t, J = 7 Hz, 3H), 3.64 (dq, J_1 = 10.5 Hz, J_2 = 7.5 Hz, 1H), 3.74 (dq, J_1 = 10.5 Hz, J_2 = 7 Hz, 1H), 3.80 (d, J = 16 Hz, 1H), 3.81 (s, 3H), 4.57 (d, J = 15.5 Hz, 1H), 4.86 (s, 1H),

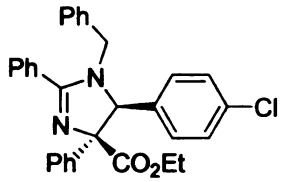
6.74 (d, J = 7.5 Hz, 2H), 6.89 (d, J = 8.5 Hz, 2H), 7.04-709 (m, 2H), 7.09-7.20 (m, 1H), 7.25-7.33 (m, 5H), 7.44-7.47 (m, 3H), 7.72-7.74 (m, 4H); ^{13}C NMR + DEPT (125 MHz, $CDCl_3$): δ 13.58 (-CH3), 48.45 (-CH2), 55.25 (-CH3), 60.94 (-CH2), 73.33 (-CH), 82.66 (quaternary –C), 113.82 (aromatic –CH), 126.79 (aromatic –CH), 127.12 (aromatic –CH), 127.27 (aromatic –CH), 127.30 (aromatic –CH), 127.94 (aromatic –CH), 128.37 (aromatic –CH), 128.53 (aromatic –CH), 128.77 (aromatic –CH), 129.34 (aromatic –CH), 129.76 (aromatic –CH), 130.20 (aromatic –CH), 130.76 (aromatic quaternary –C), 136.76 (aromatic quaternary –C), 144.17 (aromatic quaternary –C), 159.59 (aromatic quaternary –C), 165.30, 170.90; IR (neat): 3032 cm^{-1}, 2934 cm^{-1}, 1732 cm^{-1}, 1595 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{32}H_{30}N_2O_3$ [M+H], 491.2335; found, 491.2332.



II-23

dl-(4S,5S)-ethyl-1-benzyl-5-(4-fluorophenyl)-2,4-diphenyl-4,5-dihydro-1H-imidazole-4-carboxylate (II-23): A solution of benzyl amine (0.2 g, 2.11 mmol) and 4-fluorobenzaldehyde (0.3 g, 2.11 mmol) in 50 mL of anhydrous benzene was reflux under nitrogen for 12 hours and then concentrated *in vacuo.* The resulting residue was redissolved into 50 mL of anhydrous dichloromethane. Then 2,4-diphenyl-5(4H)-oxazolone **II-2** (0.5 g, 2.11 mmol) and chlorotrimethylsilane (0.3 g, 2.74 mmol) were added and the mixture was refluxed under nitrogen for 12 hours. The solution was concentrated *in vacuo*

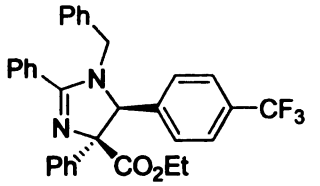
and the resulting residue was resuspended in EtOAc producing a white solid precipitate (216 mg) which was isolated via filtration. The crude solid was then dissolved into 15 mL of EtOH, treated with 1 mL of concentrated H_2SO_4, and refluxed for 48 hours. The solution was concentrated *in vacuo* and then dissolved into dichloromethane before being washed with saturated $NaHCO_3$ (3 x 50 mL) and brine (1 x 50 mL). The solution was then dried over sodium sulfate and then concentrated *in vacuo.* The resulting crude solid was purified via column chromatography (50% EtOAc / 50% Hexanes) to afford 124 mg (12% yield) of the title compound as a white solid. (m.p. = 96 °C – 97 °C) ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.84 (t, J = 7.5 Hz, 3H), 3.67 (dq, J_1 = 10.5 Hz, J_2 = 7.5 Hz, 1H), 3.76 (dq, J_1 = 10.5 Hz, J_2 = 7 Hz, 1H), 3.84 (d, J = 16 Hz, 1H), 4.63 (d, J = 15.5 Hz, 1H), 4.92 (s, 1H), 6.75-6.78 (m, 2H), 7.06-7.12 (m, 4H), 7.12-7.16 (m, 1H), 7.28-7.42 (m, 5H), 7.48-7.54 (m, 3H), 7.72-7.80 (m, 4H); ^{13}C NMR + DEPT (125 MHz, $CDCl_3$): δ 13.53 (-CH3), 48.73 (-CH2), 61.04 (-CH2), 73.01 (-CH), 82.78 (quaternary –C), 115.35 (d, J = 21.6 Hz, aromatic -CH), 126.68 (aromatic –CH), 127.11 (aromatic –CH), 127.39 (aromatic –CH), 127.43 (aromatic –CH), 128.01 (aromatic –CH), 128.40 (aromatic –CH), 128.59 (aromatic –CH), 128.77 (aromatic –CH), 129.73 (d, J = 8 Hz, aromatic –CH), 130.37 (aromatic –CH), 130.43 (aromatic –CH), 133.77 (d, J = 3 Hz, quaternary aromatic –C), 136.40 (quaternary aromatic –C), 143.90 (quaternary aromatic –C), 162.61 (d, J = 245 Hz, quaternary aromatic –C), 165.39, 170.70; IR (neat): 3063 cm^{-1}, 2982 cm^{-1}, 1732 cm^{-1}, 1597 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{31}H_{27}N_2O_2F$ [M+H], 479.2135; found, 479.2130.



II-24

dl-(4S,5S)-ethyl-1-benzyl-5-(4-chlorophenyl)-2,4-diphenyl-4,5-dihydro-1H-imidazole-4-carboxylate (II-24): A solution of benzyl amine (2.7 g, 25.3 mmol) and 4-chlorobenzaldehyde (3.6 g, 25.3 mmol) in 250 mL of anhydrous benzene was reflux under nitrogen for 24 hours and then concentrated *in vacuo.* The resulting residue was redissolved into 250 mL of anhydrous dichloromethane. Then 2,4-diphenyl-5(4H)-oxazolone **II-2** (6.0 g, 25.3 mmol) and chlorotrimethylsilane (3.6 g, 32.9 mmol) were added and the mixture was refluxed under nitrogen for 18 hours. The solution was concentrated *in vacuo* and the resulting residue was resuspended in EtOAc producing a white solid precipitate (7.9 g) which was isolated via filtration. The white solid was then dissolved into 250 mL of dichloromethane, cooled to 0 °C, and treated with oxalyl chloride (6.0 g, 47.1 mmol) and DMF (300 µL). The solution was stirred for 3 hours, concentrated *in vacuo,* and redissolved into 250 mL of EtOH before being left to stir overnight. The solution was concentrated *in vacuo* and then dissolved into dichloromethane before being washed with saturated $NaHCO_3$ (3 x 200 mL) and brine (1 x 200 mL). The solution was then dried over sodium sulfate and then concentrated *in vacuo.* The resulting crude solid was recrystallized using EtOAc/Hexanes to afford 6.23 g (50% yield) of the title compound as a white crystalline solid. (m.p. = 165 °C – 166 °C) ^1H NMR (500 MHz, $CDCl_3$) (TMS): δ

0.86 (t, J = 7 Hz, 3H), 3.63 (dq, J_1 = 11 Hz, J_2 = 7 Hz, 1H), 3.73 (dq, J_1 = 10.5 Hz, J_2 = 7 Hz, 1H), 3.80 (d, J = 15.5 Hz, 1H), 4.61 (d, J = 15.5 Hz, 1H), 4.87 (s, 1H), 6.74 (d, J = 7 Hz, 2H), 7.05-7.08 (m, 2H), 7.11-7.12 (m, 1H), 7.26-7.29 (m, 1H), 7.31-7.36 (m, 6H), 7.47-7.49 (m, 3H), 7.70-7.72 (m, 2H), 7.75-7.77 (m, 2H); ^{13}C **NMR + DEPT** (125 MHz, $CDCl_3$) (TMS): δ 13.55 (-CH3), 48.83 (-CH2), 61.12 (-CH2), 73.10 (-CH), 82.87 (quaternary –C), 126.68 (aromatic –CH), 127.17 (aromatic –CH), 127.46 (aromatic –CH), 127.49 (aromatic –CH), 128.06 (aromatic –CH), 128.45 (aromatic –CH), 128.63 (aromatic –CH), 128.65 (aromatic –CH), 128.81 (aromatic –CH), 129.49 (aromatic –CH), 130.41 (quaternary aromatic –C), 130.43 ((aromatic –CH), 134.08 (quaternary aromatic –C), 136.35 (quaternary aromatic –C), 136.63 (quaternary aromatic –C),143.84 (quaternary aromatic –C), 165.48, 170.65; IR (KBr): 3063 cm^{-1}, 2980 cm^{-1}, 1732 cm^{-1}, 1595 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{31}H_{27}ClN_2O_2$ [M+H], 495.1833; found, 495.1834.

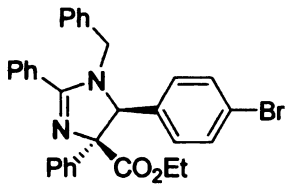


II-25

dl-(4S,5S)-ethyl-1-benzyl-2,4-diphenyl-5-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1H-imidazole-4-carboxylate (II-25): A solution of benzyl amine (0.5 g, 2.11 mmol) and 4-trifluoromethyl-benzaldehyde (0.4 g, 2.11 mmol) in 50 mL of anhydrous benzene was reflux under nitrogen for 2 hours and then concentrated *in vacuo.* The resulting residue was redissolved into 50 mL of anhydrous

dichloromethane. Then 2,4-diphenyl-5(4H)-oxazolone **II-2** (0.5 g, 2.11 mmol) and chlorotrimethylsilane (0.3 g, 2.74 mmol) were added and the mixture was refluxed under nitrogen for 24 hours. The solution was concentrated *in vacuo* and the resulting residue was resuspended in EtOAc producing a white solid precipitate (0.7 g) which was isolated via filtration. The crude solid was then dissolved into 15 mL of EtOH, treated with 1 mL of concentrated H_2SO_4, and refluxed for 64 hours. The solution was concentrated *in vacuo* and then dissolved into dichloromethane before being washed with saturated $NaHCO_3$ (3 x 50 mL) and brine (1 x 50 mL). The solution was then dried over sodium sulfate and then concentrated *in vacuo.* The resulting crude solid was purified via column chromatography (40% EtOAc / 60% Hexanes) to afford 159 mg (14% yield) of the title compound as a white crystalline solid. (m.p. = 155 °C – 156 °C) ^{1}H NMR (500 MHz, $CDCl_3$) (TMS): δ 0.78 (t, J = 7 Hz, 3H), 3.63 (dq, J_1 = 11 Hz, J_2 = 7 Hz, 1H), 3.73 (dq, J_1 = 10.5 Hz, J_2 = 7 Hz, 1H), 3.82 (d, J = 16 Hz, 1H), 4.62 (d, J = 15.5 Hz, 1H), 4.94 (s, 1H), 6.73 (d, J = 7.5 Hz, 2H), 7.04-7.10 (m, 2H), 7.11-7.13 (m, 1H), 7.27-7.32 (m, 1H), 7.32-7.36 (m, 2H), 7.48-7.50 (m, 3H), 7.52 (d, J = 7.5 Hz, 2H), 7.64 (d, J = 8 Hz, 2H), 7.71-7.73 (m, 2H), 7.78-7.80 (m, 2H); ^{13}C NMR + DEPT (125 MHz, $CDCl_3$) (TMS): δ 13.36 (-CH3), 49.05 (-CH2), 61.13 (-CH2), 73.21 (-CH), 83.07 (quaternary –C), 125.35 (q, *J* = 3.6 Hz, aromatic –CH), 123.97 (q, J = 270 Hz, quaternary –C), 126.62 (aromatic –CH), 127.16 (aromatic –CH), 127.51 (aromatic –CH), 127.56 (aromatic –CH), 128.10 (aromatic –CH), 128.44 (aromatic –CH), 128.65 (aromatic –CH), 128.83 (aromatic –CH), 130.46 (q, *J* = 32 Hz, quaternary –C), 130.53 (aromatic –CH),

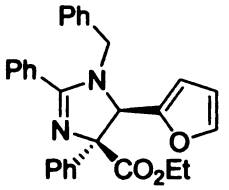
136.13 (aromatic quaternary –C), 142.44 (aromatic quaternary –C), 143.68 (aromatic quaternary –C), 165.59, 170.49; IR (neat): 3065 cm^{-1}, 2982 cm^{-1}, 1734 cm^{-1}, 1597 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{32}H_{27}N_2O_2F$ [M+H], 529.2103; found, 529.2110.



II-26

(4S,5S)-ethyl-1-benzyl-5-(4-bromophenyl)-2,4-diphenyl-4,5-dihydro-1H-imidazole-4-carboxylate (II-26): A solution of benzyl amine (0.2 g, 2.11 mmol) and 4-bromobenzaldehyde (0.4 g, 2.11 mmol) in 50 mL of anhydrous benzene was reflux under nitrogen for 3 hours and then concentrated *in vacuo.* The resulting residue was redissolved into 50 mL of anhydrous dichloromethane. Then 2,4-diphenyl-5(4H)-oxazolone **II-2** (0.5 g, 2.11 mmol) and chlorotrimethylsilane (0.3 g, 2.74 mmol) were added and the mixture was refluxed under nitrogen for 16 hours. The solution was concentrated *in vacuo* and the resulting residue was resuspended in EtOAc producing a white solid precipitate (0.7 g) which was isolated via filtration. The crude solid was then dissolved into 50 mL of EtOH, treated with 1 mL of concentrated H_2SO_4, and refluxed for 24 hours. The solution was concentrated *in vacuo* and then dissolved into dichloromethane before being washed with saturated $NaHCO_3$ (3 x 20 mL) and brine (1 x 20 mL). The solution was then dried over sodium sulfate and then concentrated *in vacuo.* The resulting crude residue was purified via

column chromatography (40% EtOAc / 60% Hexanes) to afford 201 mg (18% yield) of the title compound as a white solid. (m.p. = 186 °C - 188 °C) ^{1}H NMR (500 MHz) ($CDCl_3$): δ 0.87 (t, J = 7 Hz, 3H), 3.69 (dq, J_1 = 10.5 Hz, J_2 = 7 Hz, 1H), 3.77 (dq, J_1 = 10.5 Hz, J_2 = 7 Hz, 1H), 3.82 (d, J = 16 Hz, 1H), 4.62 (d, J = 16 Hz, 1H), 4.87 (s, 1H), 6.75 (d, J = 7.5 Hz, 2H), 7.07-7.10 (m, 2H), 7.13-7.16 (m, 1H), 7.27-7.31 (m, 3H), 7.33-7.36 (m, 2H), 7.49-7.53 (m, 5H), 7.72-7.74 (m, 2H), 7.76-7.79 (m, 2H); ^{13}C NMR + DEPT (125 MHz) ($CDCl_3$): δ 13.55 (-CH3), 48.8 (-CH2), 61.13 (-CH2), 73.14 (-CH), 82.83 (quaternary –C), 122.20 (quaternary aromatic –C), 126.66 (aromatic –CH), 127.15 (aromatic –CH), 127.45 (aromatic –CH), 127.49 (aromatic –CH), 128.05 (aromatic –CH), 128.44 (aromatic –CH), 128.63 (aromatic –CH), 128.80 (aromatic –CH), 129.80 (aromatic –CH), 130.37 (quaternary aromatic –C), 130.43 (aromatic –CH), 131.60 (aromatic –CH), 136.31 (quaternary aromatic –C), 137.15 (quaternary aromatic –C), 143.80 (quaternary aromatic –C), 165.48, 170.63; IR (neat): 3100 cm^{-1}, 2981 cm^{-1}, 1730 cm^{-1}, 1595 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{31}H_{28}N_2O_2Br$ [M+H], 539.1334; found, 539.1338.

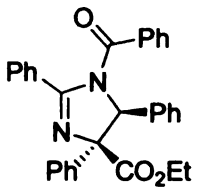


II-27

dl-(4S,5R)-ethyl-1-benzyl-5-(furan-2-yl)-2,4-diphenyl-4,5-dihydro-1H-imidazole-4-carboxylate (II-27): A solution of benzyl amine (0.2 g, 2.11 mmol) and 2-furylaldehyde (0.2 g, 2.11 mmol) in 50 mL of anhydrous benzene was

reflux under nitrogen for 3 hours and then concentrated *in vacuo*. The resulting residue was redissolved into 50 mL of anhydrous dichloromethane. Then 2,4-diphenyl-5(4H)-oxazolone **II-2** (0.5 g, 2.11 mmol) and chlorotrimethylsilane (0.3 g, 2.74 mmol) were added and the mixture was refluxed under nitrogen for 22 hours. The solution was concentrated *in vacuo* and the resulting residue was resuspended in EtOAc producing a white solid precipitate (0.5 g) which was isolated via filtration. The crude solid was then dissolved into 15 mL of EtOH, treated with 1 mL of concentrated H_2SO_4, and refluxed for 21 hours. The solution was concentrated *in vacuo* and then dissolved into dichloromethane before being washed with saturated $NaHCO_3$ (3 x 20 mL) and brine (1 x 20 mL). The solution was then dried over sodium sulfate and then concentrated *in vacuo*. The resulting crude residue was purified via column chromatography (40% EtOAc / 60% Hexanes) to afford 238 mg (25% yield) of the title compound as a yellow oil. ^{1}H NMR (500 MHz) ($CDCl_3$): δ 1.01 (t, J = 7 Hz, 3H), 3.86 (dq, J_1 = 10.5 Hz, J_2 = 7 Hz, 1H), 3.94 (dq, J_1 = 10.5 Hz, J_2 = 7 Hz, 1H), 3.88 (d, J = 15.5 Hz, 1H), 4.54 (d, J = 15.5 Hz, 1H), 5.01 (s, 1H), 6.36-6.39 (m, 2H), 6.81-6.83 (m, 2H), 7.08-7.13 (m, 2H), 7.25-7.28 (m, 1H), 7.31-7.34 (m, 2H), 7.43-7.46 (m, 4H), 7.71-7.75 (m, 4H); ^{13}C NMR + DEPT (125 MHz) ($CDCl_3$): δ 13.72 (-CH3), 49.01 (-CH2), 61.27 (-CH2), 67.97 (-CH), 81.21 (quaternary –C), 109.30, (aromatic –CH), 110.50 (aromatic –CH), 126.55 (aromatic –CH), 127.08 (aromatic –CH), 127.30 (aromatic –CH), 127.43 (aromatic –CH), 128.03 (aromatic –CH), 128.39 (aromatic –CH), 128.46 (aromatic –CH), 128.68 (aromatic –CH), 130.17 (aromatic –CH), 130.65 (quaternary aromatic –C), 136.51 (quaternary aromatic –

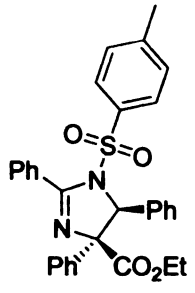
C), 142.51 (aromatic –CH), 143.34 (quaternary aromatic –C), 151.41 (quaternary aromatic –C), 165.47, 170.75; IR (neat): 3063 cm^{-1}, 2980 cm^{-1}, 1734 cm^{-1}, 1597 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{26}N_2O_3$ [M+H], 451.2016; found, 451.2005.



II-34

(4S,5S)-ethyl-1-benzoyl-2,4,5-triphenyl-4,5-dihydro-1H-imidazole-4-carboxylate (II-34): A solution of *dl*-(4*S*,5*S*)-ethyl-2,4,5-triphenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate **II-37** (100 mg, 0.27 mmol) and triethylamine (30.4 mg, 0.3 mmol) in 20 mL of anhydrous dichloromethane was treated with benzoyl chloride (45.0 mg, 0.32 mmol) and DMAP (~20 mg). The solution was stirred at room temperature for 24 hours and then washed with 2M HCl solution (2 x 20mL), saturated $NaHCO_3$ solution (2 x 20mL), and brine solution (1 x 20mL). The solution was then dried over sodium sulfate and concentrated *in vacuo*. The resulting residue was purified via silica gel column chromatography using silica gel (30% ethyl acetate / 70% hexane as eluant) to afford the product as a white solid (94 mg, 73% yield). (mp 61 °- 63 °C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.82 (t, 3H, *J* = 6.5 Hz), 3.71 (dq, J_1 = 11 Hz, J_2 = 7.5 Hz, 1H), 3.79 (dq, J_1 = 10.5 Hz, J_2 = 7 Hz, 1H), 5.91 (s, 1H), 7.02-7.06 (m, 4H), 7.18-7.24 (m, 3H), 7.28-7.31 (m, 1H), 7.36-7.40 (m, 4H), 7.45-7.49 (m, 4H), 7.65-7.67 (m, 2H), 7.85-7.87 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$ + **DEPT**): δ 131.41 (-CH3), 61.44 (-CH2), 74.49 (-CH), 82.86 (quaternary –C), 126.51 (aromatic –CH), 127.54 (aromatic –CH),

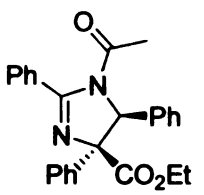
127.77 (aromatic –CH), 128.04 (aromatic –CH), 128.32 (aromatic –CH), 128.35 (aromatic –CH), 128.57 (aromatic –CH), 128.59 (aromatic –CH), 128.61 (aromatic –CH), 128.90 (aromatic –CH), 130.62 (aromatic quaternary –C), 130.80 (aromatic –CH), 131.27 (aromatic –CH), 134.62 (aromatic quaternary –C), 137.95 (aromatic quaternary –C), 140.59 (aromatic quaternary –C), 161.12, 168.76, 169.41; **IR** (neat): 3061 cm^{-1}, 2982 cm^{-1}, 1749 cm^{-1}, 1721 cm^{-1}, 1599 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{31}H_{27}N_2O_3$ [M+H], 475.2022; found, 475.2028



II-35

dl-(4S,5S)-ethyl-2,4,5-triphenyl-1-tosyl-4,5-dihydro-1H-imidazole-4-carboxylate (II-35): A solution of dl-(4S,5S)-ethyl-2,4,5-triphenyl-4,5-dihydro-1H-imidazole-4-carboxylate **II-37** (155 mg, 0.42 mmol) and triethyl amine (42.5 mg, 0.42 mmol) in 20 mL of anhydrous dichloromethane was treated with tosyl chloride (87.4 mg, 0.46 mmol) and DMAP (~10mg). The solution was stirred at room temperature for 22 hours and then washed with 2M HCl solution (2x20mL), saturated $NaHCO_3$ (2x20mL), and brine (1x20mL). The solution was then dried over sodium sulfate and concentrated *in vacuo*. The resulting residue was purified via precipitation (CH_2Cl_2/Hexanes) to afford 160 mg (73% yield) of the title compound as a white solid. (m.p. = 150 °- 151 °C) ^1H NMR (500 MHz)

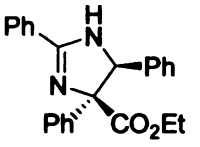
($CDCl_3$): δ 0.71 (t, J = 7 Hz, 3H), 2.24 (s, 3H), 3.49 (dq, J_1 = 10.5 Hz, J_2 = 7 Hz, 1H), 3.57 (dq, J_1 = 10.5 Hz, J_2 = 7 Hz, 1H), 5.78 (s, 1H), 6.79 (d, J = 7.5 Hz, 2H), 6.96 (d, J = 8.5 Hz, 2H), 7.23-7.36 (m, 3H), 7.37-7.44 (m, 3H), 7.49-7.56 (m, 4H), 7.57-7.60 (m, 2H), 7.89-7.91 (m, 2H); ^{13}C NMR (125 MHz) ($CDCl_3$): δ 13.29, 21.43, 61.59, 75.16, 83.26, 126.67, 127.05, 127.34, 127.47, 127.79, 128.11, 128.54, 128.61, 129.20, 129.81, 130.25, 131.58, 134.74, 138.53, 142.20, 144.08, 160.07, 169.04; IR (neat): 3065 cm^{-1}, 3034 cm^{-1}, 1736 cm^{-1}, 1599 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{31}H_{28}N_2O_4S$ [M+H], 525.1848; found, 525.1859.



II-36

dl-(4S,5S)-ethyl-1-acetyl-2,4,5-triphenyl-4,5-dihydro-1H-imidazole-4-carboxylate (II-36): A solution of dl-(4S,5S)-ethyl-2,4,5-triphenyl-4,5-dihydro-1H-imidazole-4-carboxylate **II-37** (100 mg, 0.3 mmol), acetic anhydride (32.7 mg, 0.32 mmol), Et_3N (30.1 mg, 0.3 mmol) and 20 mL of anhydrous dichloromethane was treated with DMAP (~ 10 mg). The solution was stirred for 48 hours and then washed with 2M HCl (2 x 20 mL) and brine (1 x 20 mL). The solution was then dried over sodium sulfate and concentrated *in vacuo.* The resulting crude residue was purified via column chromatography (30% EtOAc / 70% Hexanes) to afford 93 mg (84% yield) of the title compound as a white solid. ^1H NMR (500 MHz, $CDCl_3$): δ 0.75 (t, J = 7 Hz, 3H), 1.72 (s, 3H), 3.62 (dq, J_1 = 10.5 Hz, J_2 = 7.5 Hz, 1H), 3.70 (dq, J_1 = 10.5 Hz, J_2 = 7 Hz, 1H), 5.88 (s, 1H), 7.30-7.38 (m,

4H), 7.40-7.49 (m, 4H), 7.50-7.53 (m, 1H), 7.73 (d, J = 7 Hz, 2H), 7.78-7.80 (m, 2H); ^{13}C NMR + DEPT (125 MHz, $CDCl_3$): δ 13.35 (-CH3), 24.84 (-CH3), 61.41 (-CH2), 72.77 (-CH), 82.42 (quaternary –C), 126.47 (aromatic –CH), 127.36 (aromatic –CH), 127.71 (aromatic –CH), 128.24 (aromatic –CH), 128.51 (aromatic –CH), 128.57 (aromatic –CH), 128.64 (aromatic –CH), 131.13 (aromatic –CH), 131.36 (quaternary aromatic –C), 138.07 (quaternary aromatic –C), 141.04 (quaternary aromatic –C), 160.01, 167.43, 169.31; IR (neat): 3065 cm^{-1}, 2982 cm^{-1}, 1736 cm^{-1}, 1684 cm^{-1}, 1624 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{26}H_{24}N_2O_3$ [M+H], 413.1865; found, 413.1906.



II-37

dl-(4S,5S)-ethyl-2,4,5-triphenyl-4,5-dihydro-1H-imidazole-4-carboxylate (II-37): A solution of dl-(4S,5S)-ethyl-1-benzyl-2,4,5-triphenyl-4,5-dihydro-1H-imidazole-4-carboxylate **II-10** (790 mg, 1.72 mmol), 10 mL of cyclohexene and 50 mL of anhydrous THF was treated with 300 mg of 10% Pd/C. The solution was stirred under reflux for 24 hours and then filtered through celite. The resulting solution was concentrated *in vacuo* resulting in a yellowish crude solid. The solid was recrystallized (EtOAc/Hexanes) to afford 553 mg (87% yield) of the product as a crystalline white solid (m.p. = 140 °C - 142 °C). ^1H NMR (500 MHz, $CDCl_3$): δ 0.75 (t, J = 7 Hz, 3H), 3.46-3.52 (m, 1H), 3.67 (dq, J_1 = 11 Hz, J_2 = 7.5, 1H), 5.53 (bs, 1H), 6.13 (bs, 1H), 7.25-7.34 (m, 6H), 7.37-7.40 (m, 2H), 7.42-7.45 (m,

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2H), 7.48-7.51 (m, 1H), 7.78 (d, J = 8 Hz, 2H), 8.00 (d, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.23, 29.80, 61.61, 83.95, 126.43, 127.69, 127.72, 127.81, 127.93, 128.19, 128.30, 128.47, 129.81, 131.16, 140.04, 143.25, 162.83, 171.33; IR (neat): 3368 cm^{-1}, 3063 cm^{-1}, 2982 cm^{-1}, 1730 cm^{-1}, 1599 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{24}H_{22}N_2O_2$ [M+H], 371.1760; found, 371.1761.

4. Cell culture.

The human cell line HeLa-NF-κB-luc was purchased from Panomics Inc (Fremont, CA). The cells were maintained in Dulbecco's Modified Eagle's medium (DMEM, Gibco Invitrogen, Fredrick, MD) containing 4.5 g/L glucose, 3.7 g/L bicarbonate, and supplemented with 5% fetal bovine serum, 100 U/mL penicillin, 100 μg/mL streptomycin, 1 mM sodium pyruvate, 0.2 mM L-glutamine and 100 μg/mL of hygromycin B (Roche). The human cell line HeLa was purchased from ATCC (Rockville, MD). The cells were maintained in DMEM media containing 4.5 g/L glucose, 3.7 g/L bicarbonate, and supplemented with 10% fetal bovine serum, 100 U/mL penicillin, 100 mg/mL streptomycin, 1 mM sodium pyruvate, and 0.2 μM L-glutamine. Cells were cultured at 37 °C, 5% CO_2 atmosphere, 97% relative humidity and were routinely passaged by trypsin-EDTA (Life technologies, Gran Island NY) treatment to maintain a cell density between 2×10^5 to 1×10^6.

5. NF-κB-Luc reporter assay.

HeLa NF-κB-luc cells (~5.0 x 10^5 cells/mL) were seeded into a 96 well white opaque plate using DMEM medium supplemented with 5% fetal bovine serum, 100 U/mL penicillin, 100 µg/mL streptomycin, 1 mM sodium pyruvate, 0.2 mM L-glutamine and 100 µg/mL of hygromycin B. The cells were incubated for approximately 24 hours (37 °C, 5% CO_2 atmosphere, 97% relative humidity). The media was then replaced with DMEM medium supplemented with 100 U/mL penicillin and 100 µg/mL streptomycin. Cell cultures were pretreated with vehicle (1% DMSO), 50 µM MG-132, or imidazoline (final concentrations of 20, 10, 5, 1, 0.5, 0.1, 0.05 µM) for 30 minutes at 37 °C, 5% CO_2 atmosphere with 97% relative humidity. Then TNF-α was added to a final concentration of 25 ng/mL and the samples were further incubated 8 hours. The plate was then equilibrated back to room temperature and treated with 100 µL of Steady-Glo assay reagent in each well. The contents of the plate were gently stirred for 5 minutes and the luminescence of each well was measured using a Veritas microplate luminometer. All reported data are the average of two independent experiments. The data was normalized to TNF-α activation and the EC_{50} values were calculated using the equation for the sigmodial curve for variable slope.

Imidazolines **II-8** to **II-18**, **II-28** to **II-34** and **II-37** were all evaluated by Dr. Daljinder Kahlon for their ability to inhibit NF-κB mediated gene transcription using the luciferase based reporter assay in human cervical epithelial (HeLa) cells. The data obtained for the remainder of the imidazolines found within this chapter are as follows:

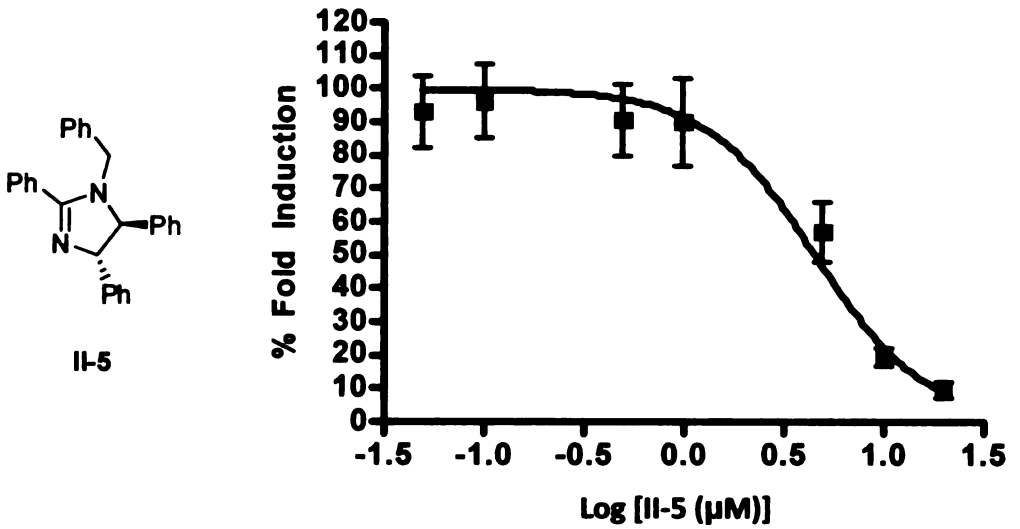


Figure II-6. Dose response curve of imidazoline **II-5.**

Equation

Equation:Sigmoidal dose-response (variable slope)
Y=Bottom + (Top-Bottom)/(1+10^((LogEC50-X)*HillSlope))
;X is the logarithm of concentration. Y is the response
Y starts at Bottom and goes to Top with a sigmoid shape.
;This is identical to the "four parameter logistic equation"

Sigmoidal dose-response (variable slope)

Best-fit values	
BOTTOM	0.0
TOP	100.0
LOGEC50	0.6615
HILLSLOPE	-1.573
EC50	4.587
Std. Error	
LOGEC50	0.06644
HILLSLOPE	0.2199
95% Confidence Intervals	
LOGEC50	0.5167 to 0.8063
HILLSLOPE	-2.052 to -1.094
EC50	3.287 to 6.402
Goodness of Fit	
Degrees of Freedom	12
R^2 (unweighted)	0.9053
Weighted Sum of Squares ($1/Y^2$)	0.4776
Absolute Sum of Squares	1680
Sy.x	11.83

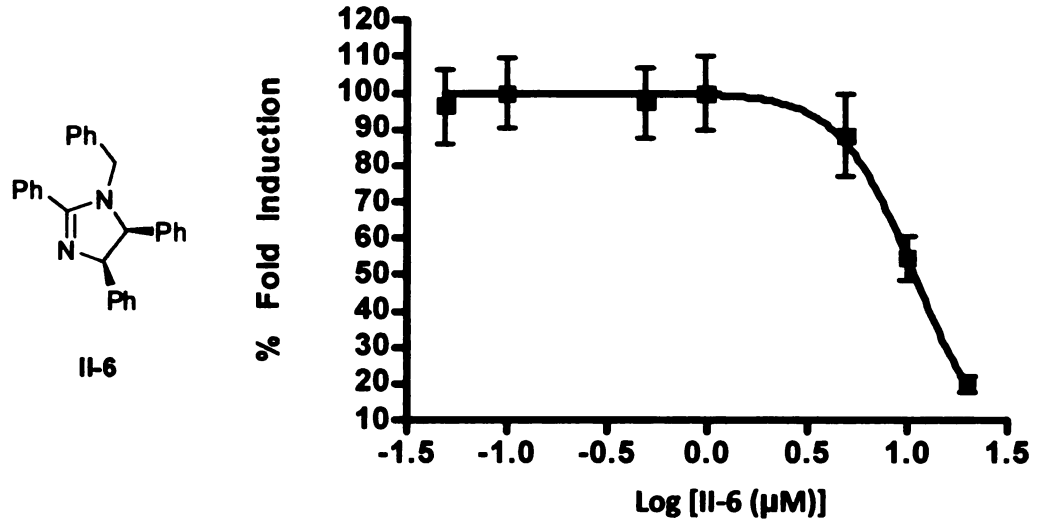


Figure II-7. Dose response curve of imidazoline **II-6.**

Equation

Equation:Sigmoidal dose-response (variable slope)
Y=Bottom + (Top-Bottom)/(1+10^((LogEC50-X)*HillSlope))
;X is the logarithm of concentration. Y is the response
;Y starts at Bottom and goes to Top with a sigmoid shape.
;This is identical to the "four parameter logistic equation"

Sigmoidal dose-response (variable slope)

Best-fit values	
BOTTOM	0.0
TOP	100.0
LOGEC50	1.041
HILLSLOPE	-2.323
EC50	10.98
Std. Error	
LOGEC50	0.02614
HILLSLOPE	0.2636
95% Confidence Intervals	
LOGEC50	0.9836 to 1.098
HILLSLOPE	-2.898 to -1.749
EC50	9.630 to 12.52
Goodness of Fit	
Degrees of Freedom	12
R^2 (unweighted)	0.9063
Weighted Sum of Squares ($1/Y^2$)	0.1684
Absolute Sum of Squares	1170
Sy.x 9.876	

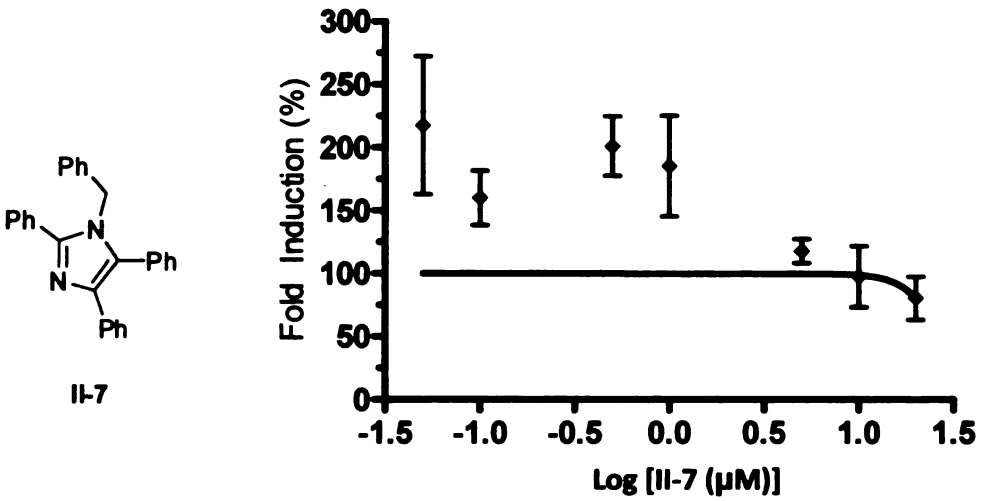


Figure II-8. Dose response curve of imidazole **II-7**.

Equation

Equation:Sigmoidal dose-response (variable slope)
Y=Bottom + (Top-Bottom)/(1+10^((LogEC50-X)*HillSlope))
;X is the logarithm of concentration. Y is the response
;Y starts at Bottom and goes to Top with a sigmoid shape.
;This is identical to the "four parameter logistic equation"

Sigmoidal dose-response (variable slope)

Best-fit values	
BOTTOM	0.0
TOP	100.0
LOGEC50	1.442
HILLSLOPE	-4.380
EC50	27.67
Std. Error	
LOGEC50	1.271
HILLSLOPE	38.93
95% Confidence Intervals	
LOGEC50	-1.328 to 4.212
HILLSLOPE	-89.20 to 80.44
EC50	0.04703 to 16276
Goodness of Fit	
Degrees of Freedom	12
R^2 (unweighted)	-0.7661
Weighted Sum of Squares ($1/Y^2$)	2.353
Absolute Sum of Squares	83736
Sy.x	83.53

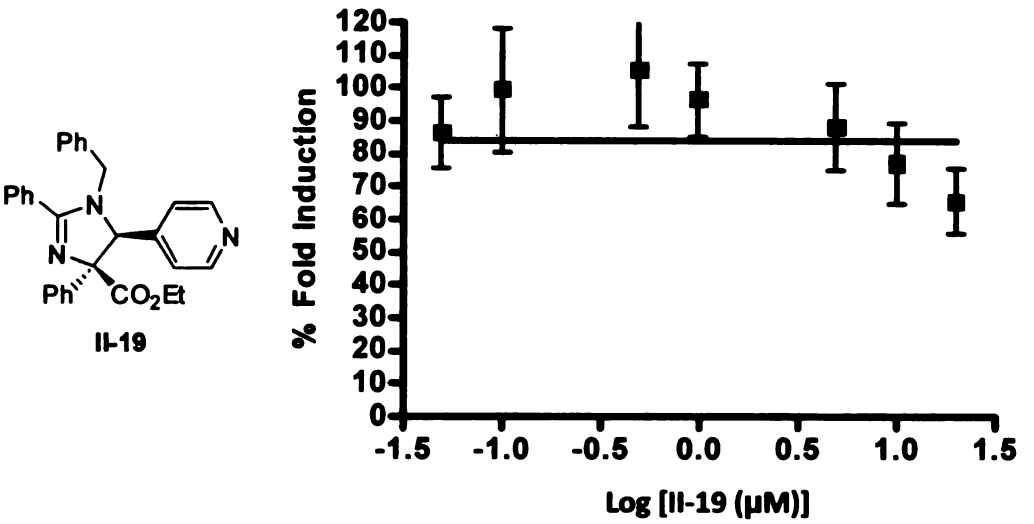


Figure II-9. Dose response curve of imidazoline **II-19.**

Equation

Equation:Sigmoidal dose-response (variable slope)
Y=Bottom + (Top-Bottom)/(1+10^((LogEC50-X)*HillSlope))
;X is the logarithm of concentration. Y is the response
;Y starts at Bottom and goes to Top with a sigmoid shape.
;This is identical to the "four parameter logistic equation"

Sigmoidal dose-response (variable slope)

Best-fit values	
BOTTOM	0.0
TOP	100.0
LOGEC50	-16000000
HILLSLOPE	4.577e-008
EC50	0.0
Std. Error	
LOGEC50	6.437e+013
HILLSLOPE	0.1846
95% Confidence Intervals	
LOGEC50	-140300000000000 to 1.403e+014
HILLSLOPE	-0.4022 to 0.4022
EC50	
Goodness of Fit	
Degrees of Freedom	12
R^2 (unweighted)	-0.04894
Weighted Sum of Squares ($1/Y^2$)	0.6642
Absolute Sum of Squares	5107
Sy.x	20.63

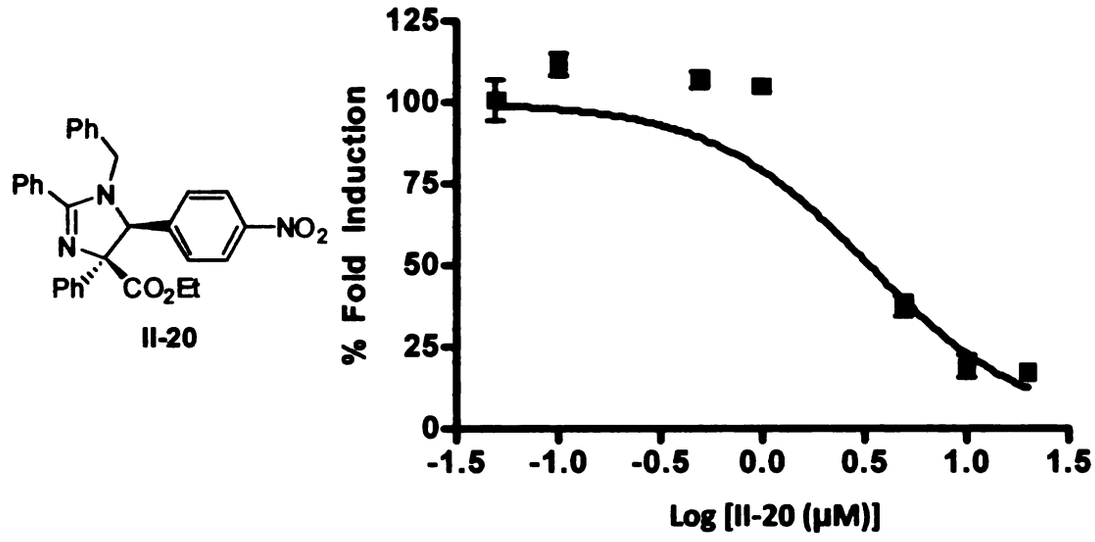


Figure II-10. Dose response curve of imidazoline **II-20.**

Equation

Equation:Sigmoidal dose-response (variable slope)
Y=Bottom + (Top-Bottom)/(1+10^((LogEC50-X)*HillSlope))
;X is the logarithm of concentration. Y is the response
;Y starts at Bottom and goes to Top with a sigmoid shape.
;This is identical to the "four parameter logistic equation"

Sigmoidal dose-response (variable slope)

Best-fit values	
BOTTOM	0.0
TOP	100.0
LOGEC50	0.5274
HILLSLOPE	-1.103
EC50	3.368
Std. Error	
LOGEC50	0.09375
HILLSLOPE	0.2016
95% Confidence Intervals	
LOGEC50	0.3231 to 0.7317
HILLSLOPE	-1.542 to -0.6633
EC50	2.104 to 5.391

Goodness of Fit	
Degrees of Freedom	12
R^2 (unweighted)	0.8888
Weighted Sum of Squares ($1/Y^2$)	0.5685
Absolute Sum of Squares	2622
Sy.x	14.78

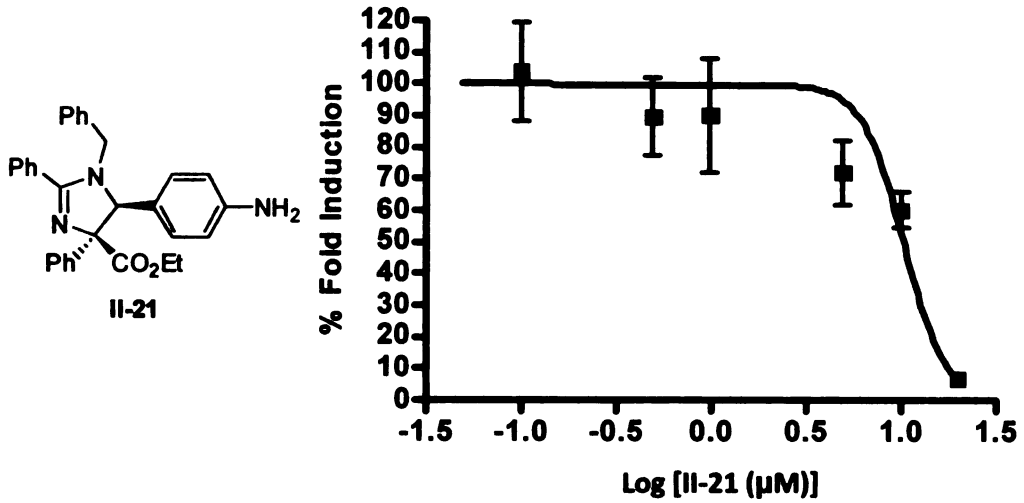


Figure II-11. Dose response curve of imidazoline **II-21.**

Equation

Equation:Sigmoidal dose-response (variable slope)
Y=Bottom + (Top-Bottom)/(1+10^((LogEC50-X)*HillSlope))
;X is the logarithm of concentration. Y is the response
;Y starts at Bottom and goes to Top with a sigmoid shape.
;This is identical to the "four parameter logistic equation"

Sigmoidal dose-response (variable slope)

Best-fit values	
BOTTOM	0.0
TOP	100.0
LOGEC50	1.018
HILLSLOPE	-3.997
EC50	10.42
Std. Error	
LOGEC50	0.04253
HILLSLOPE	0.6514
95% Confidence Intervals	
LOGEC50	0.9251 to 1.110
HILLSLOPE	-5.417 to -2.578
EC50	8.416 to 12.89

Goodness of Fit	
Degrees of Freedom	12
R^2 (unweighted)	0.7016
Weighted Sum of Squares ($1/Y^2$)	0.7730
Absolute Sum of Squares	6579
Sy.x	23.42

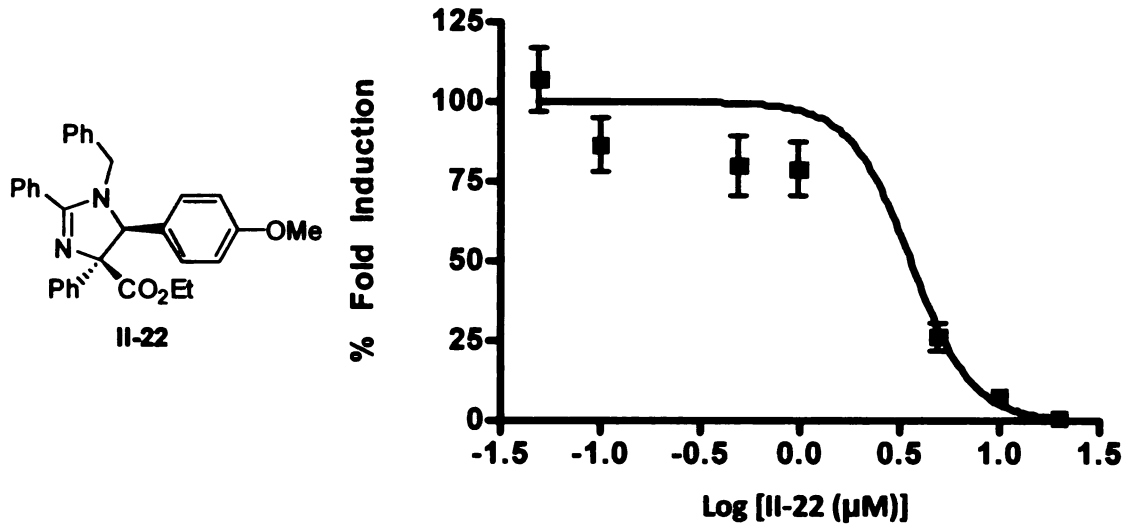


Figure II-12. Dose response curve of imidazoline **II-22.**

Equation

Equation:Sigmoidal dose-response (variable slope)
Y=Bottom + (Top-Bottom)/(1+10^((LogEC50-X)*HillSlope))
;X is the logarithm of concentration. Y is the response
;Y starts at Bottom and goes to Top with a sigmoid shape.
;This is identical to the "four parameter logistic equation"

Sigmoidal dose-response (variable slope)

Best-fit values	
BOTTOM	0.0
TOP	100.0
LOGEC50	0.5606
HILLSLOPE	-2.827
EC50	3.636
Std. Error	
LOGEC50	0.04631
HILLSLOPE	0.2267
95% Confidence Intervals	
LOGEC50	0.4597 to 0.6615
HILLSLOPE	-3.321 to -2.333
EC50	2.882 to 4.587
Goodness of Fit	
Degrees of Freedom	12
R^2 (unweighted)	0.8824
Weighted Sum of Squares ($1/Y^2$)	0.9896
Absolute Sum of Squares	2657
Sy.x	14.88

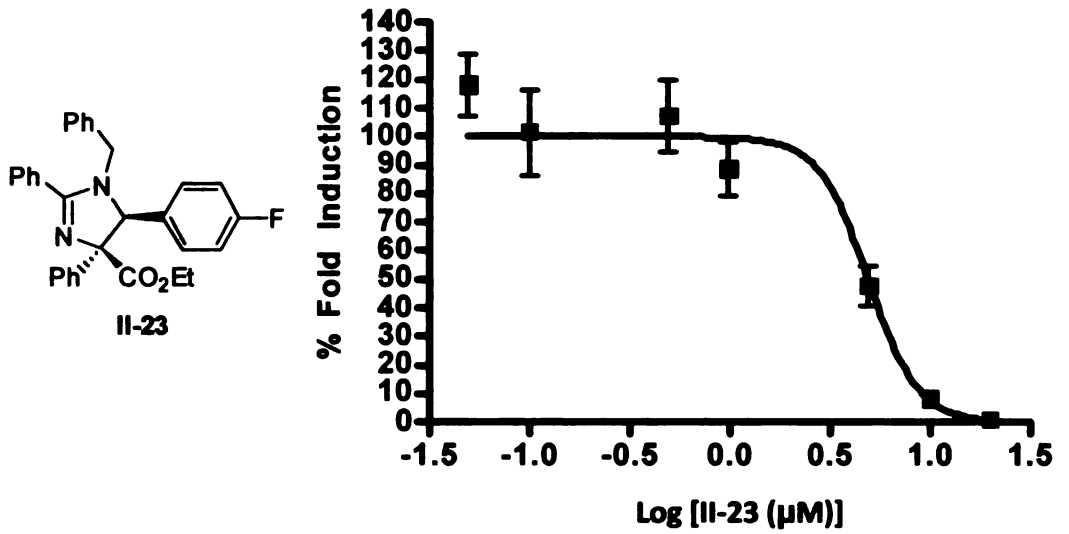


Figure II-13. Dose response curve of imidazoline **II-23.**

Equation

Equation:Sigmoidal dose-response (variable slope)
Y=Bottom + (Top-Bottom)/(1+10^((LogEC50-X)*HillSlope))
;X is the logarithm of concentration. Y is the response
;Y starts at Bottom and goes to Top with a sigmoid shape.
;This is identical to the "four parameter logistic equation"

Sigmoidal dose-response (variable slope)

Best-fit values	
BOTTOM	0.0
TOP	100.0
LOGEC50	0.6955
HILLSLOPE	-3.501
EC50	4.960
Std. Error	
LOGEC50	0.02404
HILLSLOPE	0.1814
95% Confidence Intervals	
LOGEC50	0.6431 to 0.7479
HILLSLOPE	-3.896 to -3.106
EC50	4.396 to 5.596
Goodness of Fit	
Degrees of Freedom	12
R^2 (unweighted)	0.9216
Weighted Sum of Squares ($1/Y^2$)	0.3893
Absolute Sum of Squares	2316
Sy.x	13.89

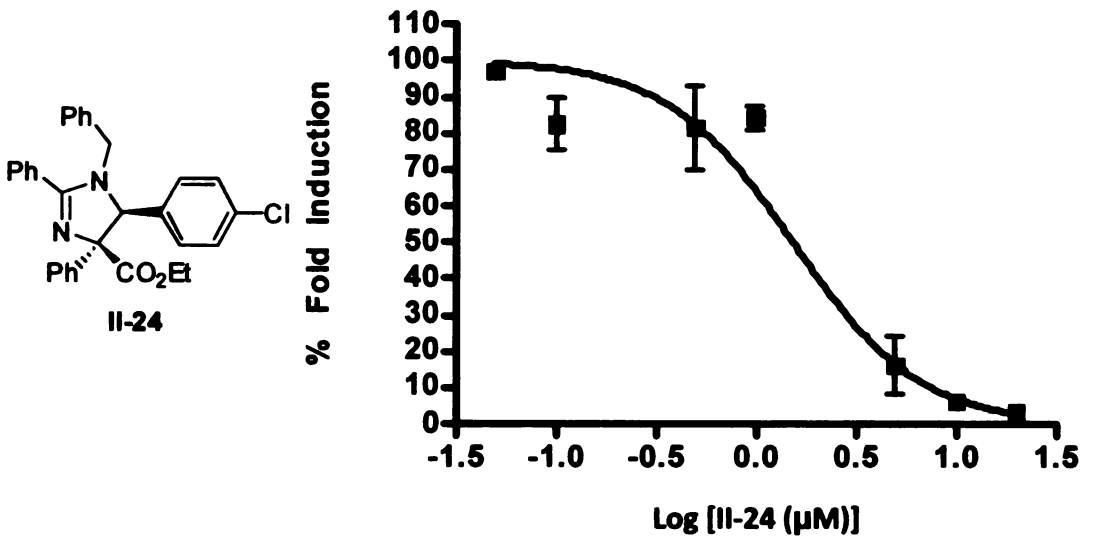


Figure II-14. Dose response curve of imidazoline **II-24.**

Equation

Equation:Sigmoidal dose-response (variable slope)
Y=Bottom + (Top-Bottom)/(1+10^((LogEC50-X)*HillSlope))
;X is the logarithm of concentration. Y is the response
;Y starts at Bottom and goes to Top with a sigmoid shape.
;This is identical to the "four parameter logistic equation"

Sigmoidal dose-response (variable slope)

Best-fit values	
BOTTOM	0.0
TOP	100.0
LOGEC50	0.1865
HILLSLOPE	-1.372
EC50	1.536
Std. Error	
LOGEC50	0.1216
HILLSLOPE	0.2049
95% Confidence Intervals	
LOGEC50	-0.07849 to 0.4515
HILLSLOPE	-1.818 to -0.9252
EC50	0.8347 to 2.828
Goodness of Fit	
Degrees of Freedom	12
R^2 (unweighted)	0.9176
Weighted Sum of Squares ($1/Y^2$)	1.296
Absolute Sum of Squares	1784
Sy.x	12.19

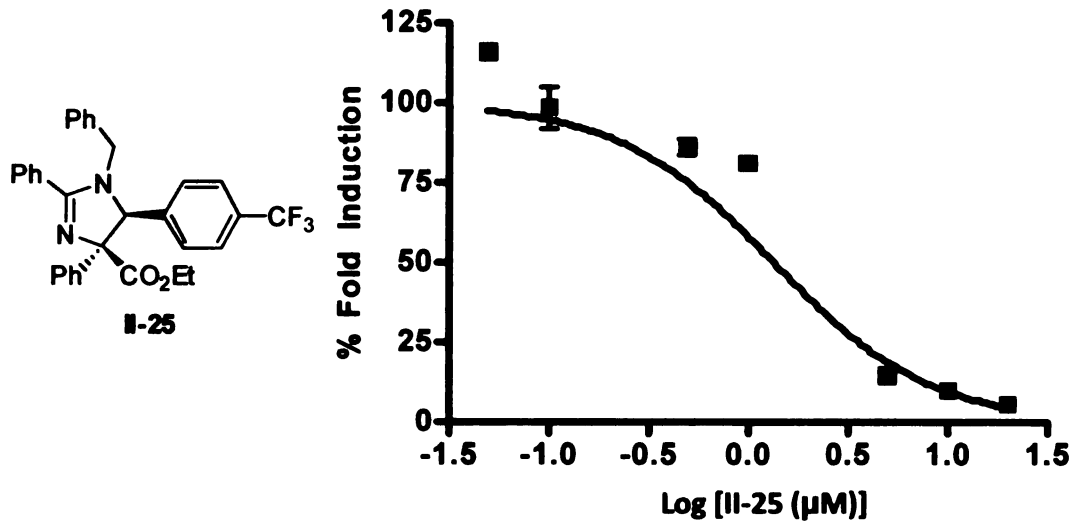


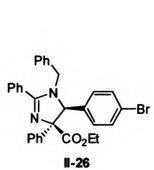
Figure II-15. Dose response curve of imidazoline **II-25.**

Equation

Equation:Sigmoidal dose-response (variable slope)
Y=Bottom + (Top-Bottom)/(1+10^((LogEC50-X)*HillSlope))
;X is the logarithm of concentration. Y is the response
;Y starts at Bottom and goes to Top with a sigmoid shape.
;This is identical to the "four parameter logistic equation"

Sigmoidal dose-response (variable slope)

Best-fit values	
BOTTOM	0.0
TOP	100.0
LOGEC50	0.1328
HILLSLOPE	-1.114
EC50	1.358
Std. Error	
LOGEC50	0.08592
HILLSLOPE	0.1163
95% Confidence Intervals	
LOGEC50	-0.05440 to 0.3200
HILLSLOPE	-1.367 to -0.8605
EC50	0.8823 to 2.090
Goodness of Fit	
Degrees of Freedom	12
R^2 (unweighted)	0.9193
Weighted Sum of Squares ($1/Y^2$)	0.5104
Absolute Sum of Squares	2147
Sy.x	13.37



II-26

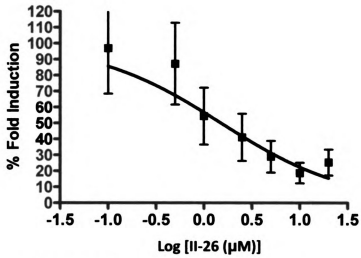


Figure II-16. Dose response curve of imidazoline **II-26.**

Equation

Equation:Sigmoidal dose-response (variable slope)
Y=Bottom + (Top-Bottom)/(1+10^((LogEC50-X)*HillSlope))
;X is the logarithm of concentration. Y is the response
;Y starts at Bottom and goes to Top with a sigmoid shape.
;This is identical to the "four parameter logistic equation"

Sigmoidal dose-response (variable slope)

Best-fit values	
BOTTOM	0.0
TOP	100.0
LOGEC50	0.1806
HILLSLOPE	-0.6560
EC50	1.516
Std. Error	
LOGEC50	0.2083
HILLSLOPE	0.1962
95% Confidence Intervals	
LOGEC50	-0.2733 to 0.6346
HILLSLOPE	-1.084 to -0.2285
EC50	0.5329 to 4.311
Goodness of Fit	
Degrees of Freedom	12
R^2 (unweighted)	0.6390
Weighted Sum of Squares ($1/Y^2$)	2.023
Absolute Sum of Squares	5723
Sy.x	21.84

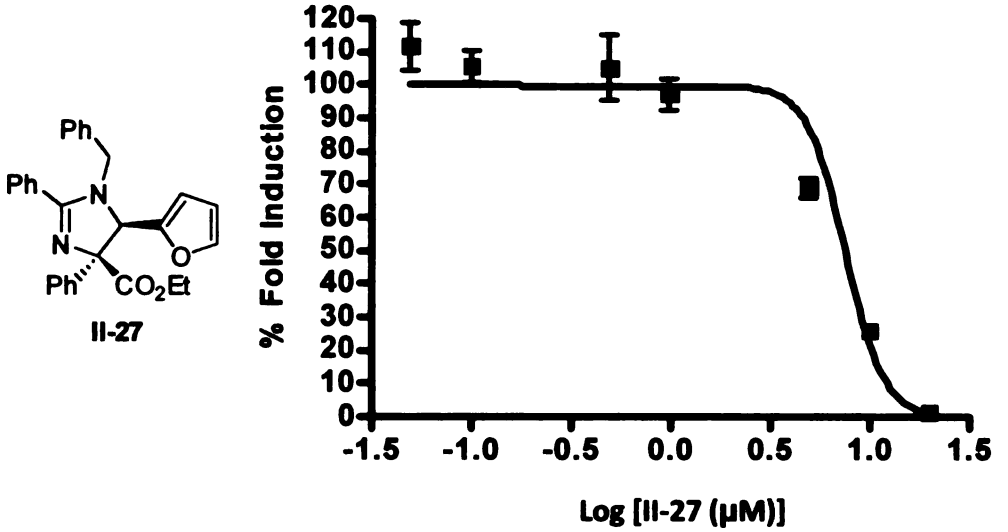


Figure II-17. Dose response curve of imidazoline **II-27.**

Equation

Equation:Sigmoidal dose-response (variable slope)
Y=Bottom + (Top-Bottom)/(1+10^((LogEC50-X)*HillSlope))
;X is the logarithm of concentration. Y is the response
;Y starts at Bottom and goes to Top with a sigmoid shape.
;This is identical to the "four parameter logistic equation"

Sigmoidal dose-response (variable slope)

Best-fit values	
BOTTOM	0.0
TOP	100.0
LOGEC50	0.8822
HILLSLOPE	-4.538
EC50	7.625
Std. Error	
LOGEC50	0.01939
HILLSLOPE	0.2486
95% Confidence Intervals	
LOGEC50	0.8400 to 0.9245
HILLSLOPE	-5.080 to -3.997
EC50	6.918 to 8.404
Goodness of Fit	
Degrees of Freedom	12
R^2 (unweighted)	0.9361
Weighted Sum of Squares ($1/Y^2$)	0.2804
Absolute Sum of Squares	1504
Sy.x	11.20

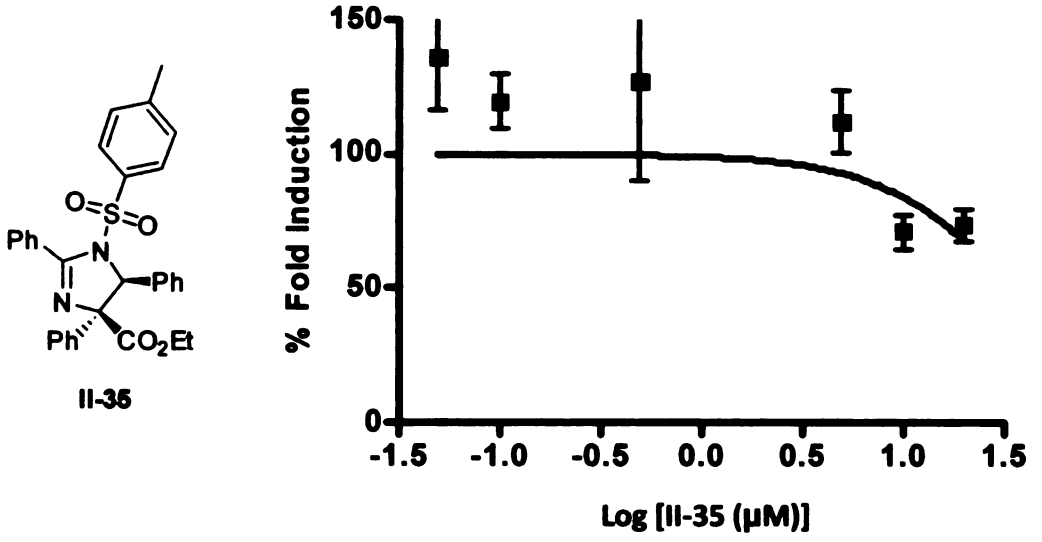


Figure II-18. Dose response curve of imidazoline **II-35.**

Equation

Equation:Sigmoidal dose-response (variable slope)
Y=Bottom + (Top-Bottom)/(1+10^((LogEC50-X)*HillSlope))
;X is the logarithm of concentration. Y is the response
;Y starts at Bottom and goes to Top with a sigmoid shape.
;This is identical to the "four parameter logistic equation"

Sigmoidal dose-response (variable slope)

Best-fit values	
BOTTOM	0.0
TOP	100.0
LOGEC50	1.562
HILLSLOPE	-1.288
EC50	36.47
Std. Error	
LOGEC50	0.4649
HILLSLOPE	1.505
95% Confidence Intervals	
LOGEC50	0.5489 to 2.575
HILLSLOPE	-4.567 to 1.992
EC50	3.539 to 375.9
Goodness of Fit	
Degrees of Freedom	12
R^2 (unweighted)	-0.004981
Weighted Sum of Squares ($1/Y^2$)	0.9391
Absolute Sum of Squares	15189
Sy.x	35.58

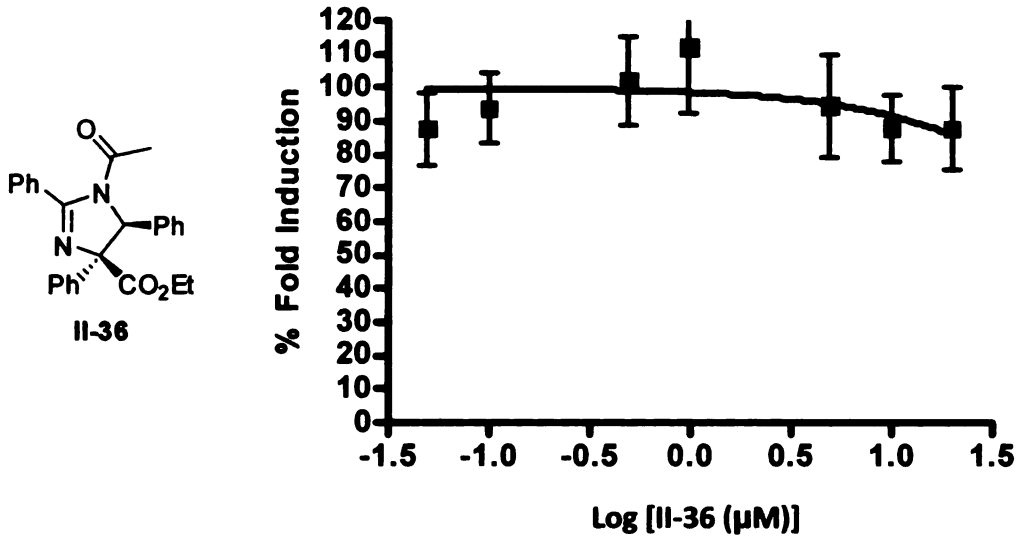


Figure II-19. Dose response curve of imidazoline **II-36.**

Equation

Equation:Sigmoidal dose-response (variable slope)
Y=Bottom + (Top-Bottom)/(1+10^((LogEC50-X)*HillSlope))
;X is the logarithm of concentration. Y is the response
;Y starts at Bottom and goes to Top with a sigmoid shape.
;This is identical to the "four parameter logistic equation"

Sigmoidal dose-response (variable slope)

Best-fit values	
BOTTOM	0.0
TOP	100.0
LOGEC50	2.225
HILLSLOPE	-0.8564
EC50	167.8
Std. Error	
LOGEC50	1.824
HILLSLOPE	1.448
95% Confidence Intervals	
LOGEC50	-1.749 to 6.198
HILLSLOPE	-4.010 to 2.298
EC50	0.01783 to 1.579e+006
Goodness of Fit	
Degrees of Freedom	12
R^2 (unweighted)	0.06122
Weighted Sum of Squares ($1/Y^2$)	0.3488
Absolute Sum of Squares	3321
Sy.x	16.64

6. Human whole blood IL-1β challenge.

All experiments utilizing human whole blood were conducted by Theresa Lansdell. For further information regarding specific experimental details, please see the following publication:

Kahlon, D. K.; Lansdell, T. A.; Fisk, J. S.; Tepe, J. J.; Structural-activity relationship study of highly-functionalized imidazolines as potent inhibitors of nuclear transcription factor-kappaB mediated IL-6 production. *Bioorg. Med. Chem.* **2009**, *17,* 3093-3103.

7. General procedure (whole blood assay).

After obtaining the appropriate approval for de-identified human cell lines, human whole blood was obtained through the Jasper Research Clinic, Kalamazoo, MI, from a single healthy, fasted human volunteer and was collected in glass citrated tubes by venipuncture. Only samples with a white blood count falling within the normal range (4800-10,800 white blood cells per liter) were used. To support the viability of white blood cells, blood was diluted 1:10 in RPMI-1640 media supplemented with 10% fetal bovine serum, 100 U/mL penicillin, and 100 µg/mL streptomycin. Aliquots of diluted blood (1 mL) were preincubated with vehicle (0.1% DMSO, final concentration) or imidazoline (final concentrations were 10, 3, 1, 0.3 and 0.1 µM) for 2 hours at 37° C, 5% CO_2. IL-1β (Roche) was added to a final concentration of 200 U/mL and the samples were further incubated for 18 hours at 37 °C, 5% CO_2. At the end of the incubation period, the blood samples were centrifuged at 3000 RPM for 5 minutes. The plasma was removed, snap frozen and stored at -80 °C. IL-6 levels were determined by ELISA (R & D Systems).

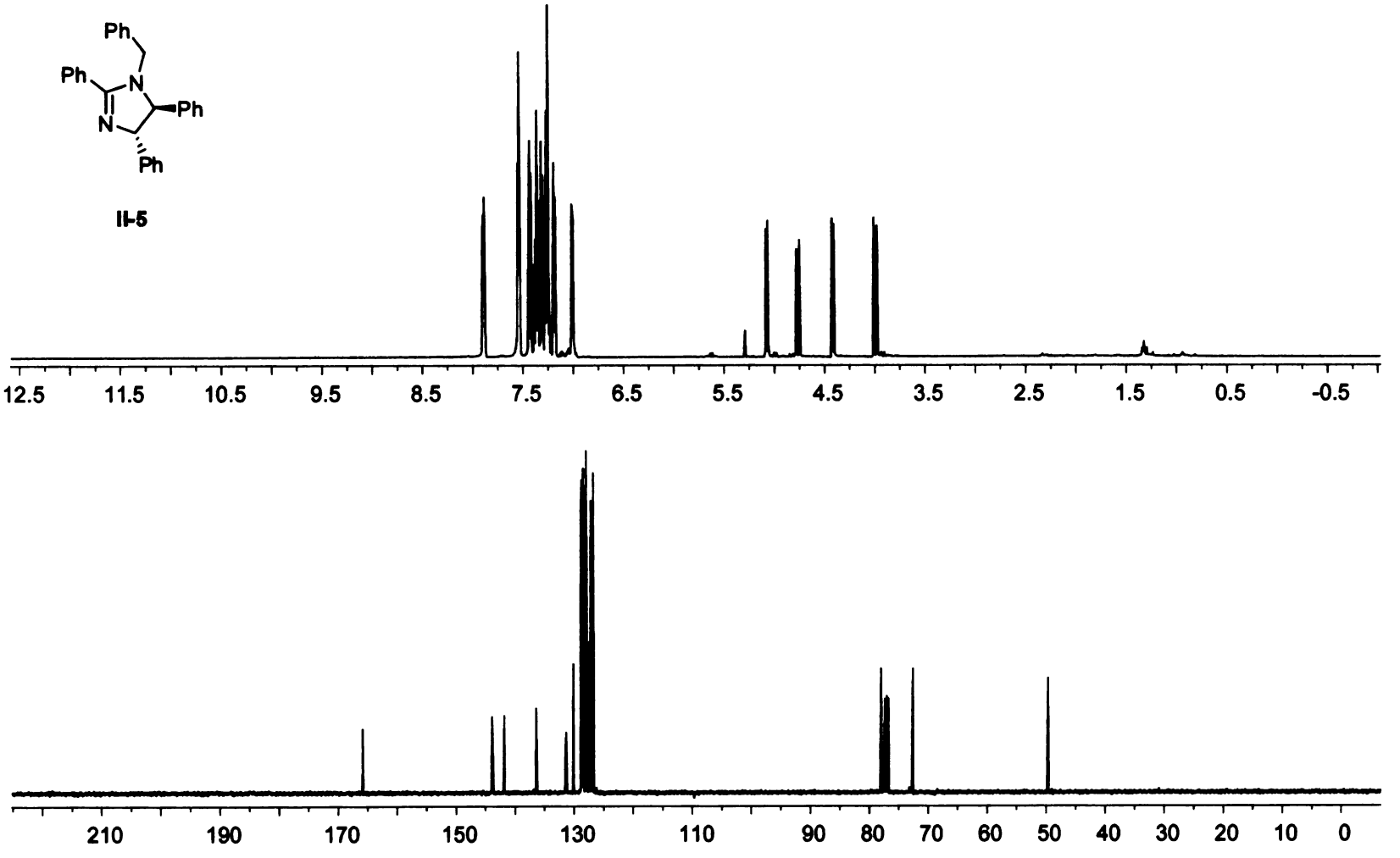


Figure II-20. NMR spectra of imidazoline **II-5**.

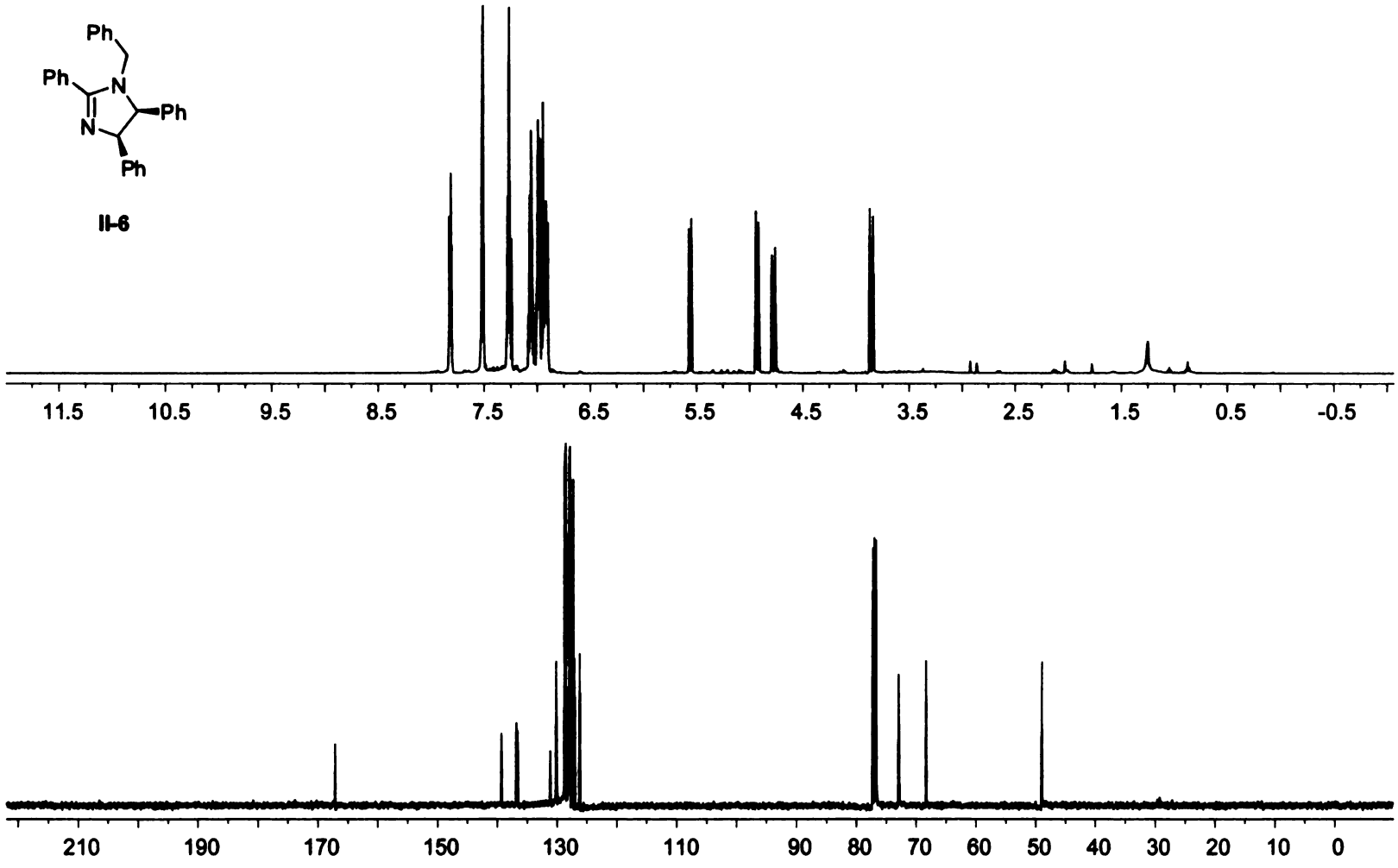


Figure II-21. NMR spectra of imidazoline **II-6.**

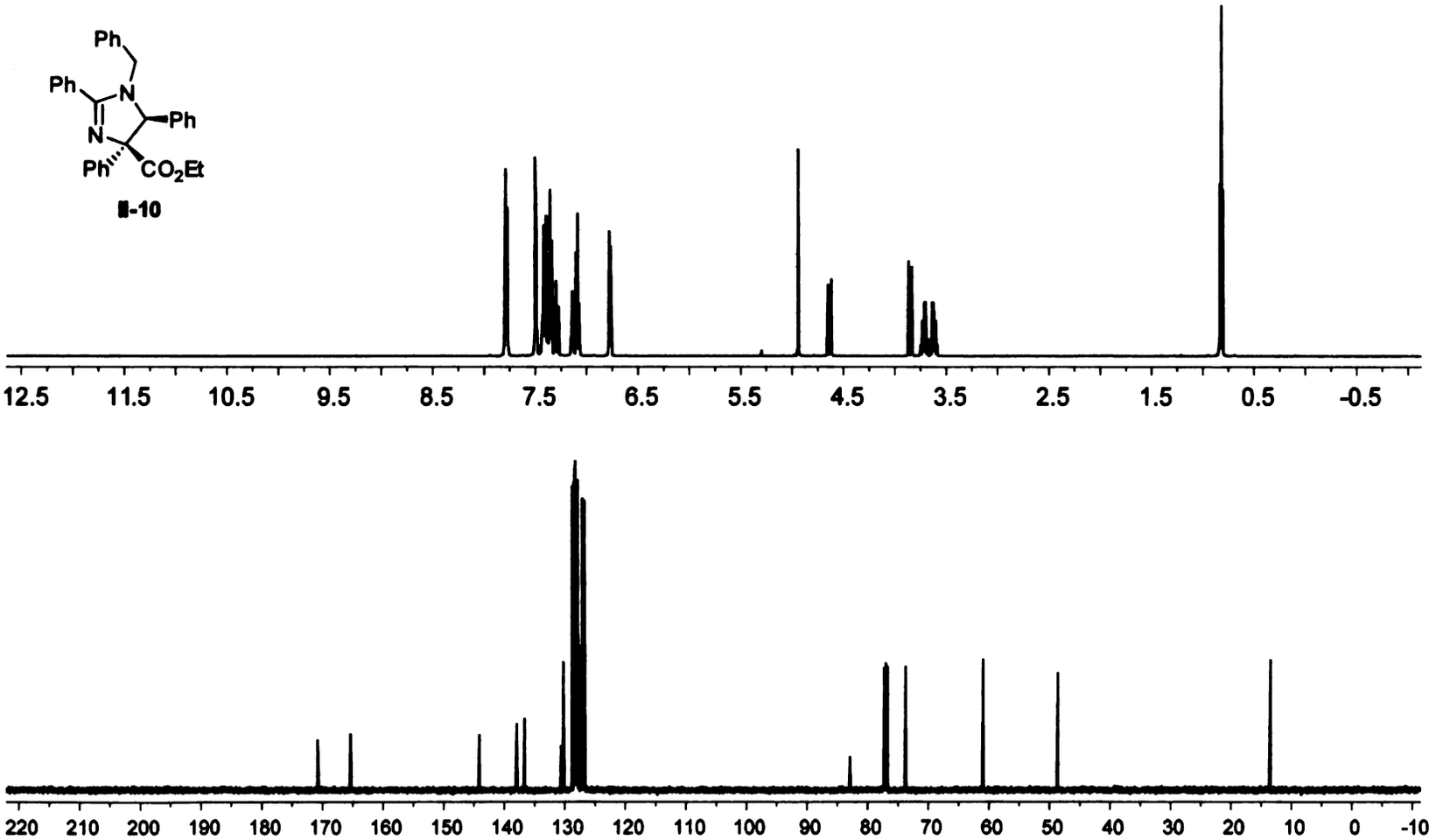


Figure II-22. NMR spectra of imidazoline **II-10.**

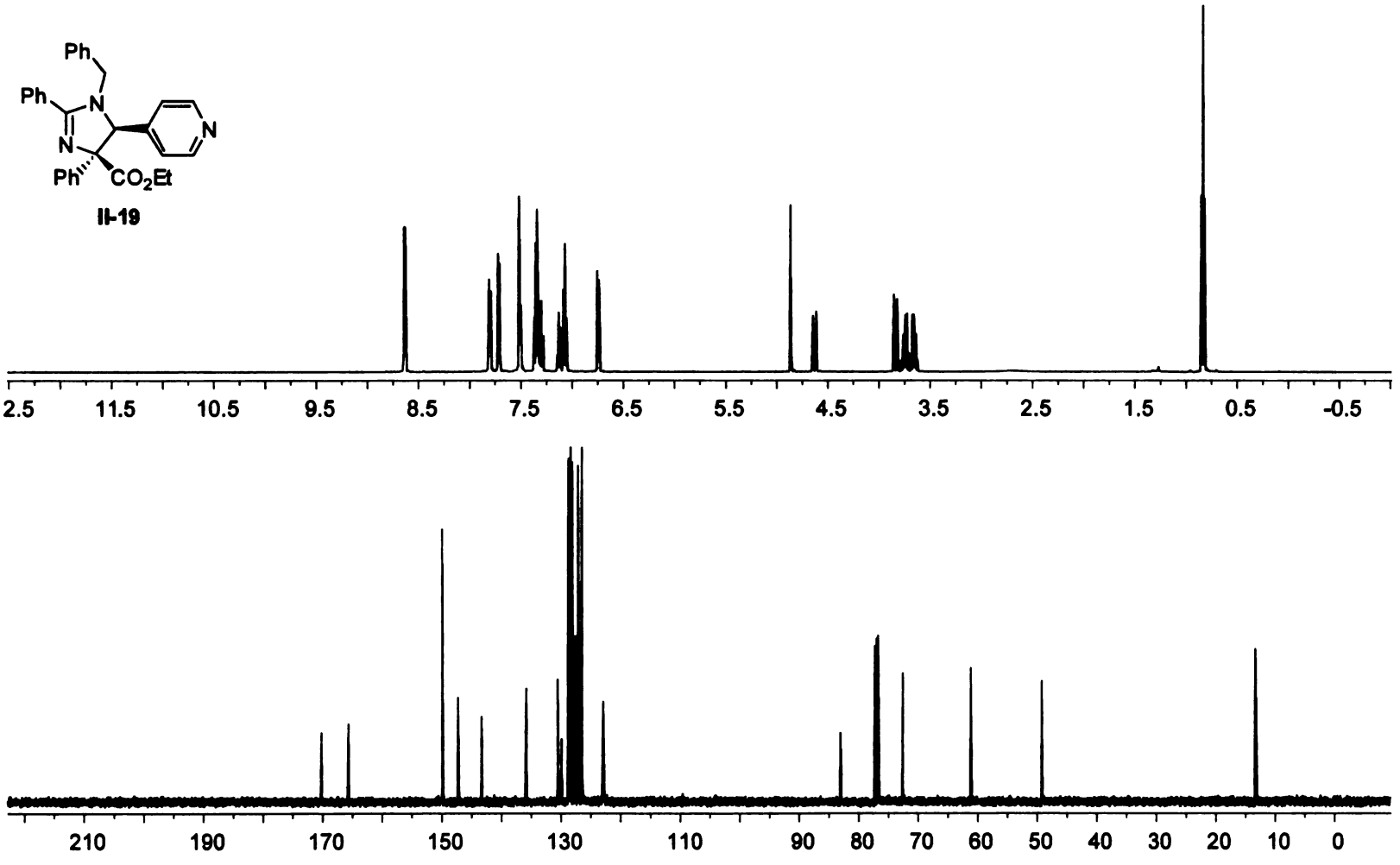


Figure II-23. NMR spectra of imidazoline **II-19.**

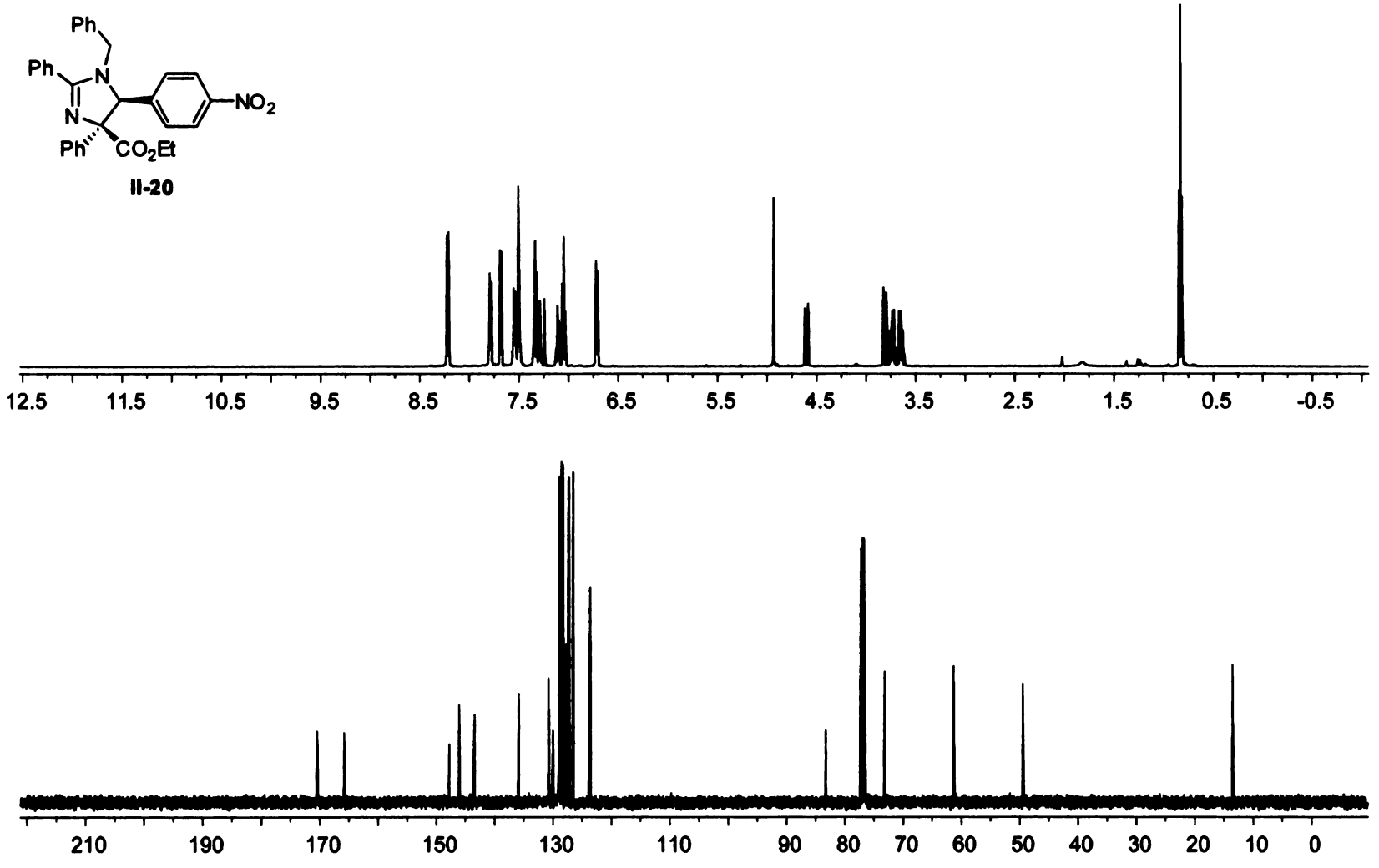


Figure II-24. NMR spectra of imidazoline **II-20.**

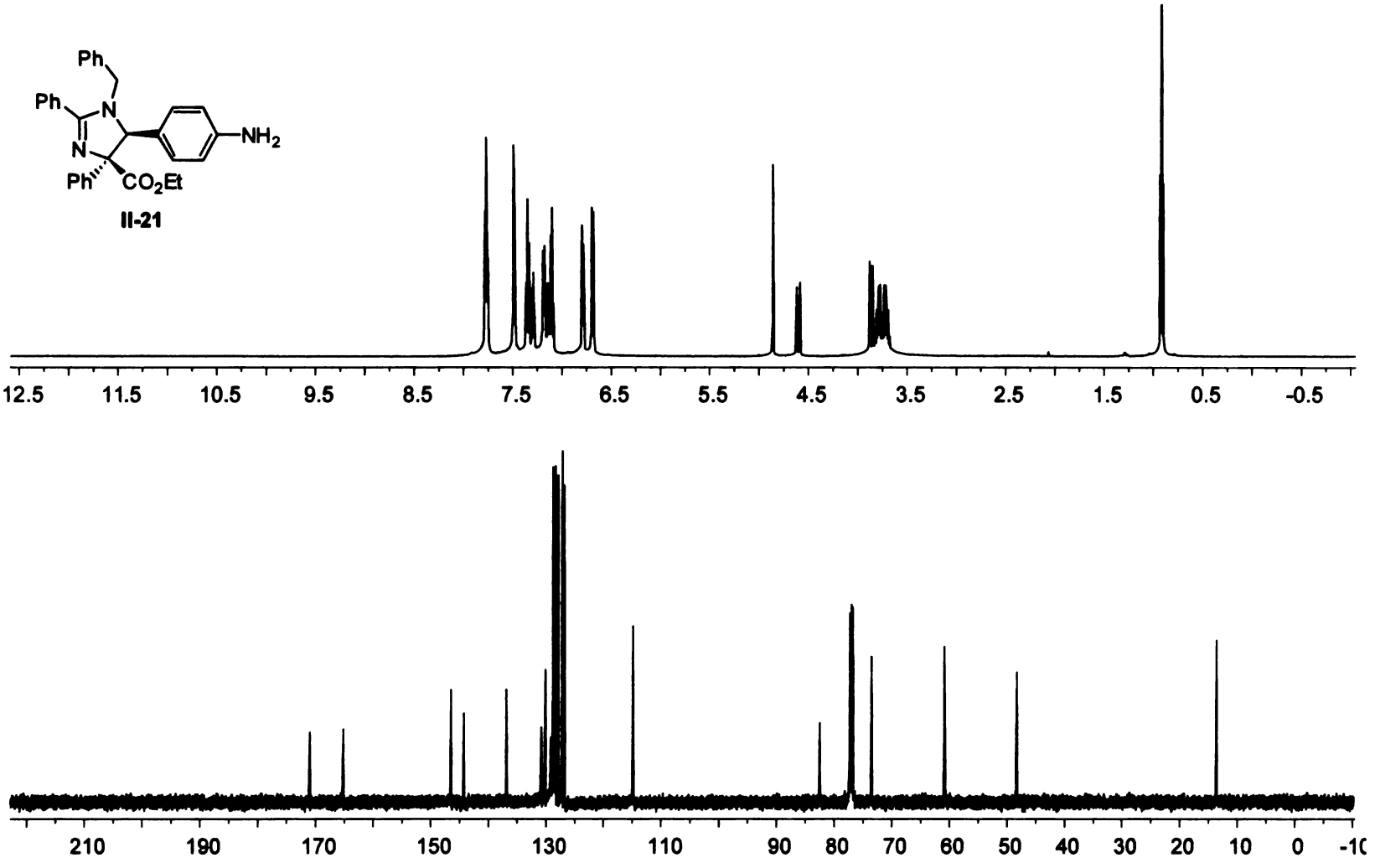


Figure II-25. NMR spectra of imidazoline **II-21.**

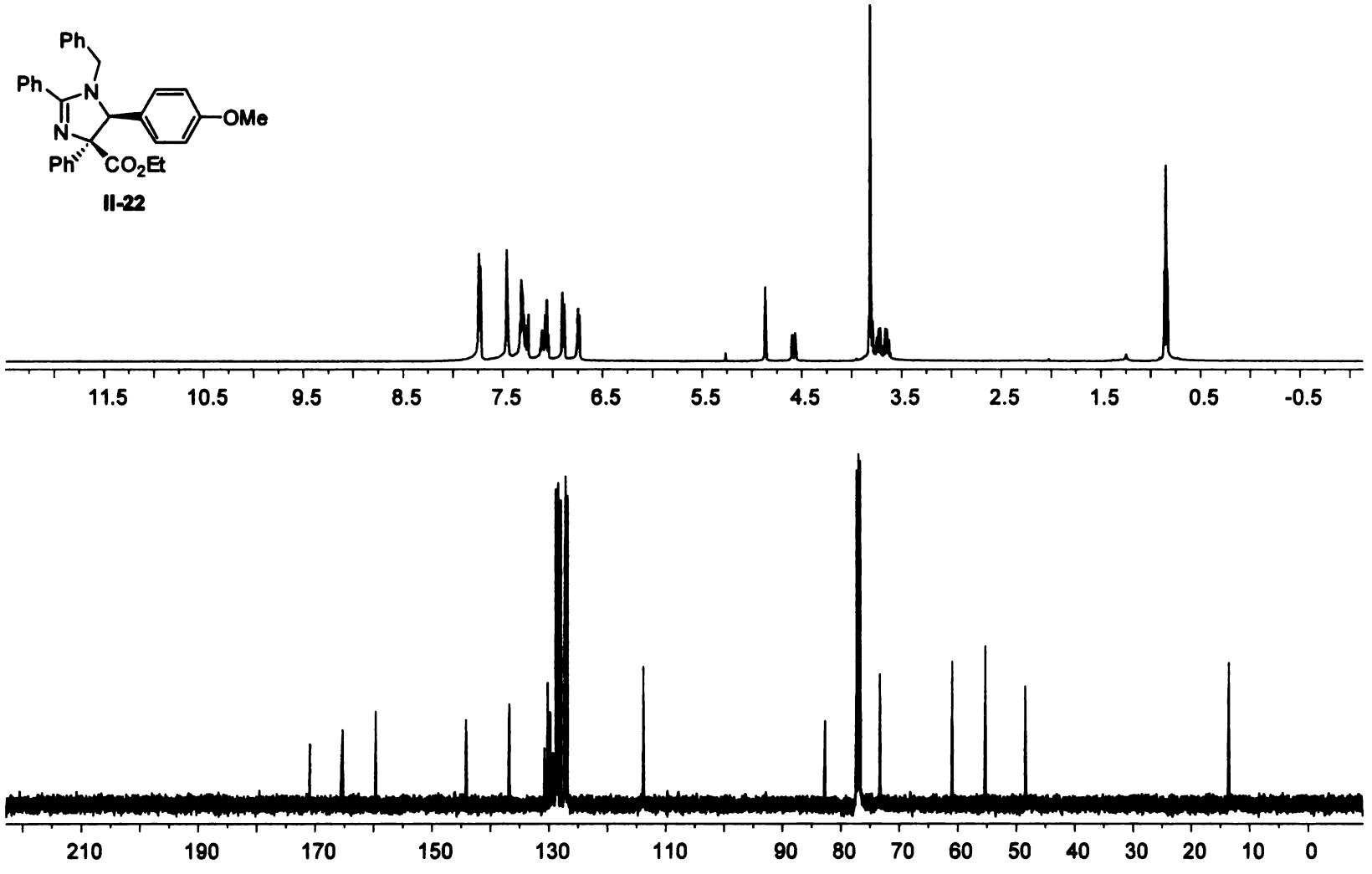


Figure II-26. NMR spectra of imidazoline **II-22.**

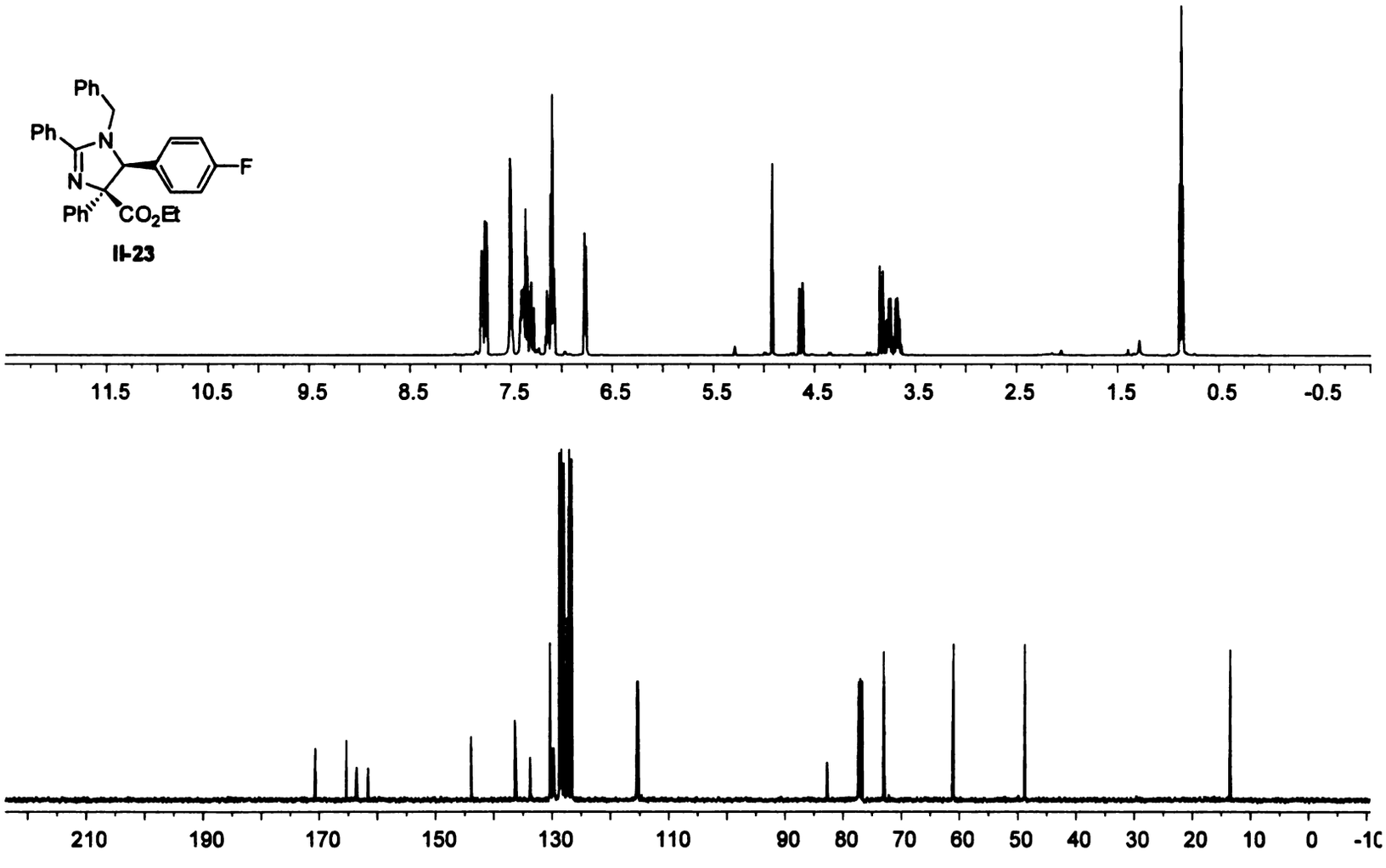


Figure II-27. NMR spectra of imidazoline **II-23.**

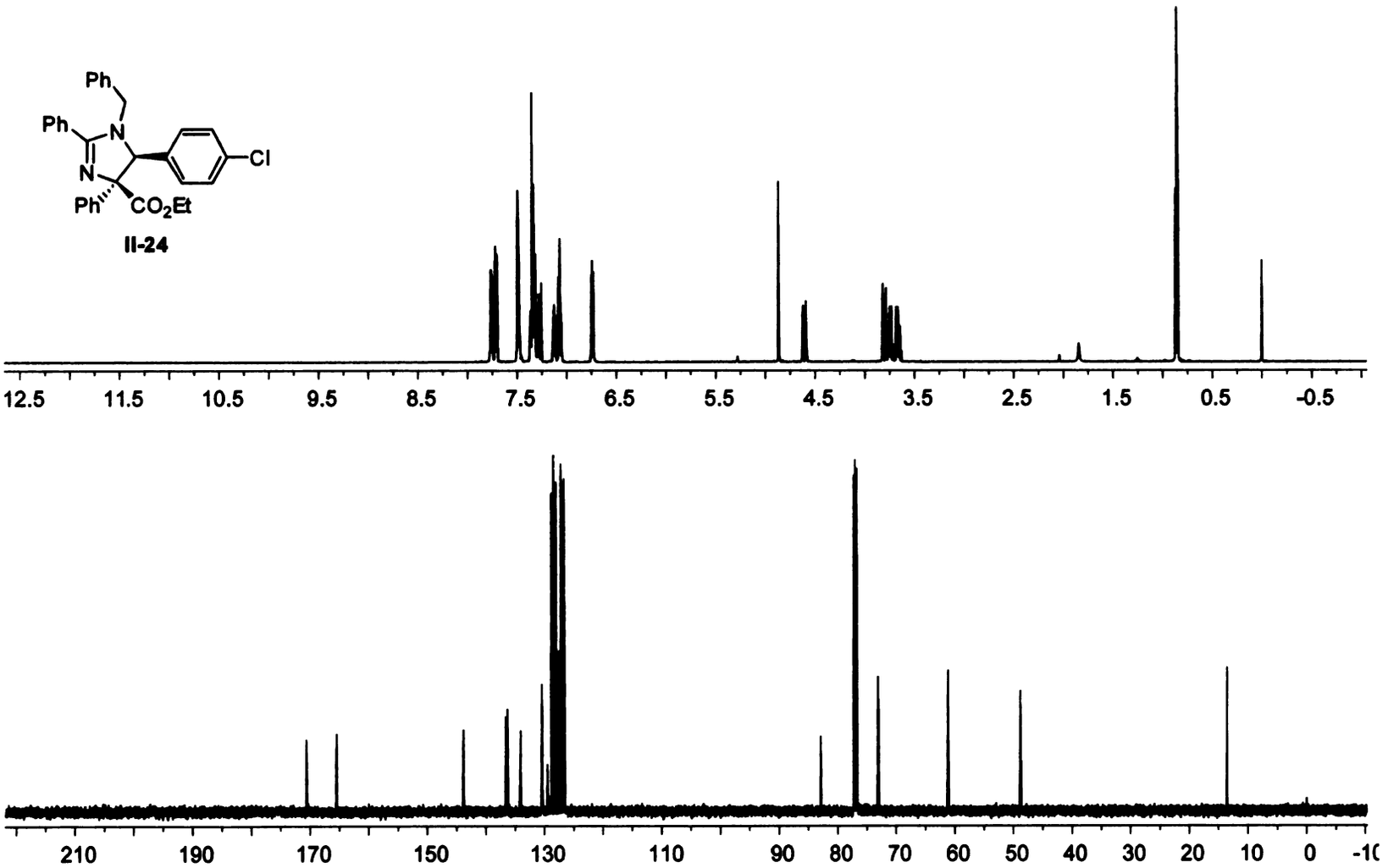


Figure II-28. NMR spectra of imidazoline **II-24.**

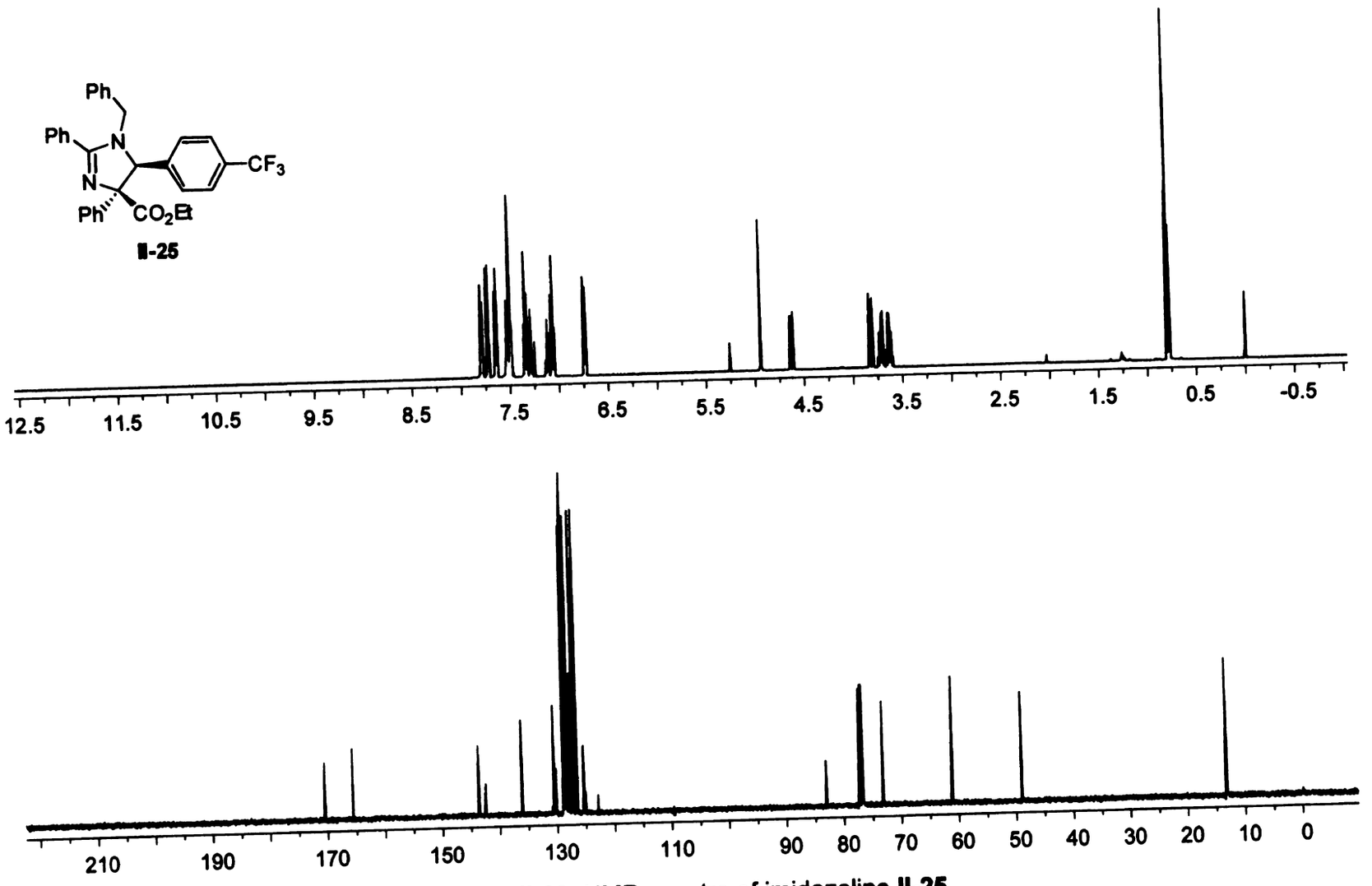


Figure II-29. NMR spectra of imidazoline **II-25.**

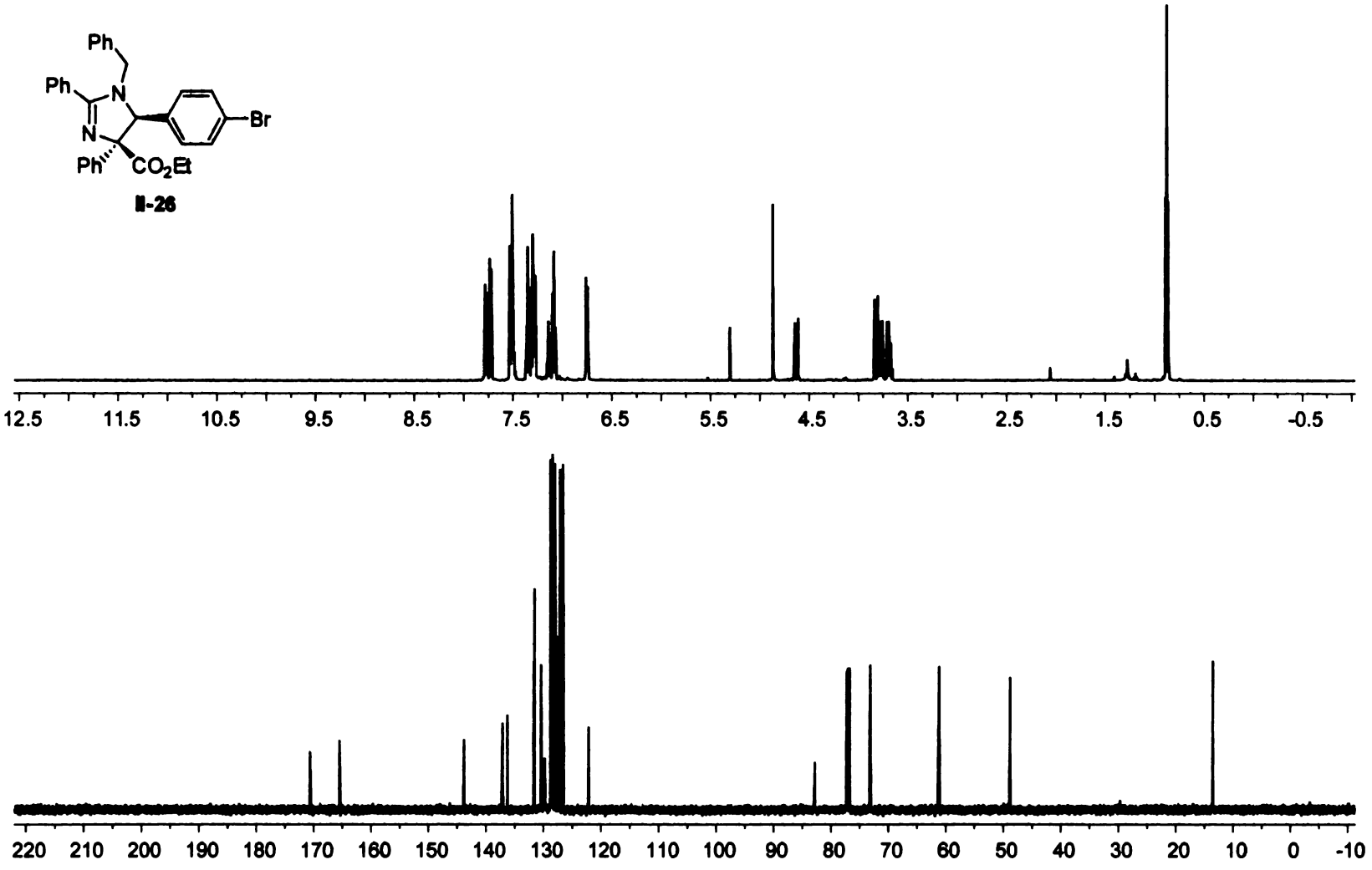


Figure II-30. NMR spectra of imidazoline **II-26.**

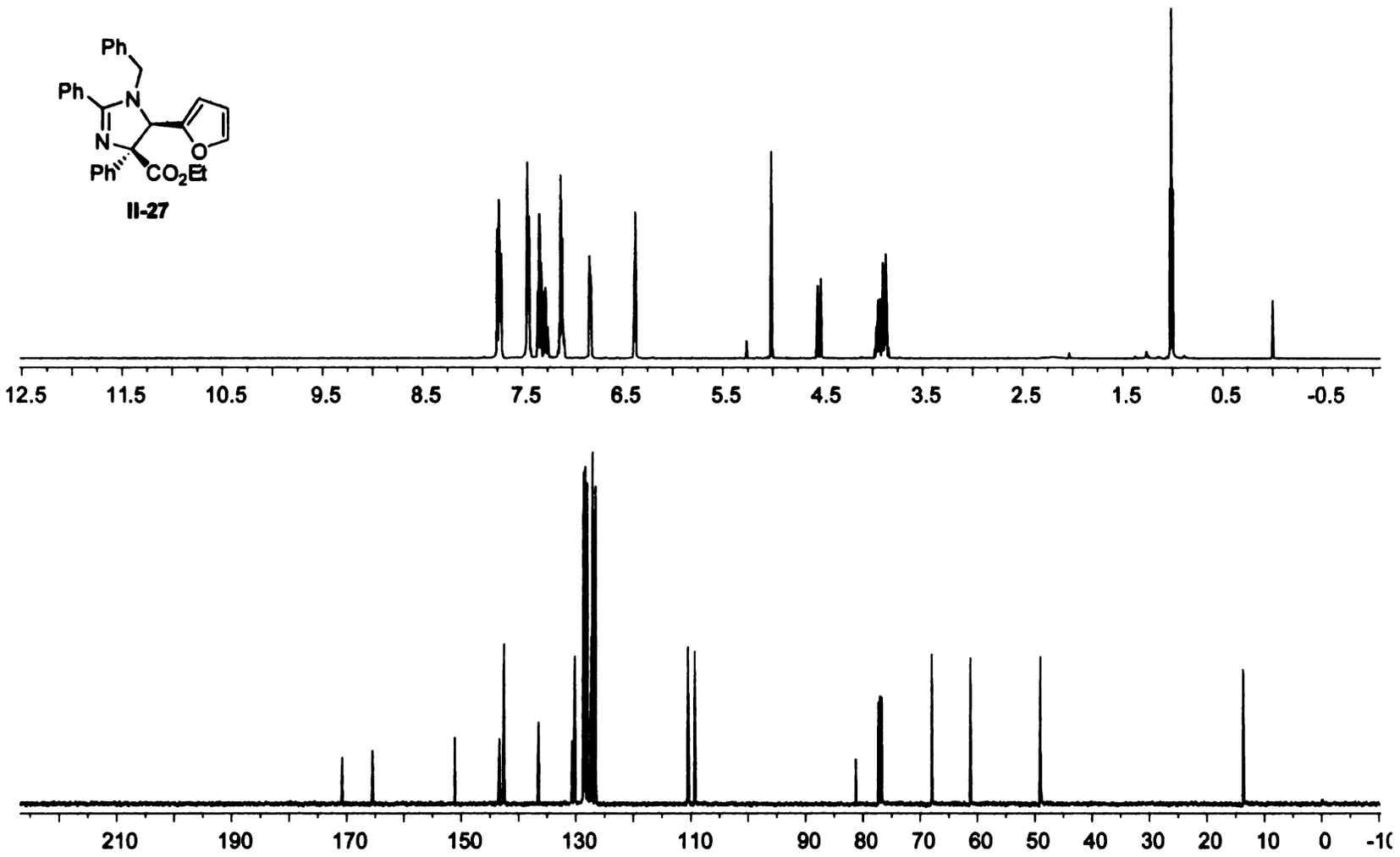


Figure II-31. NMR spectra of imidazoline **II-27.**

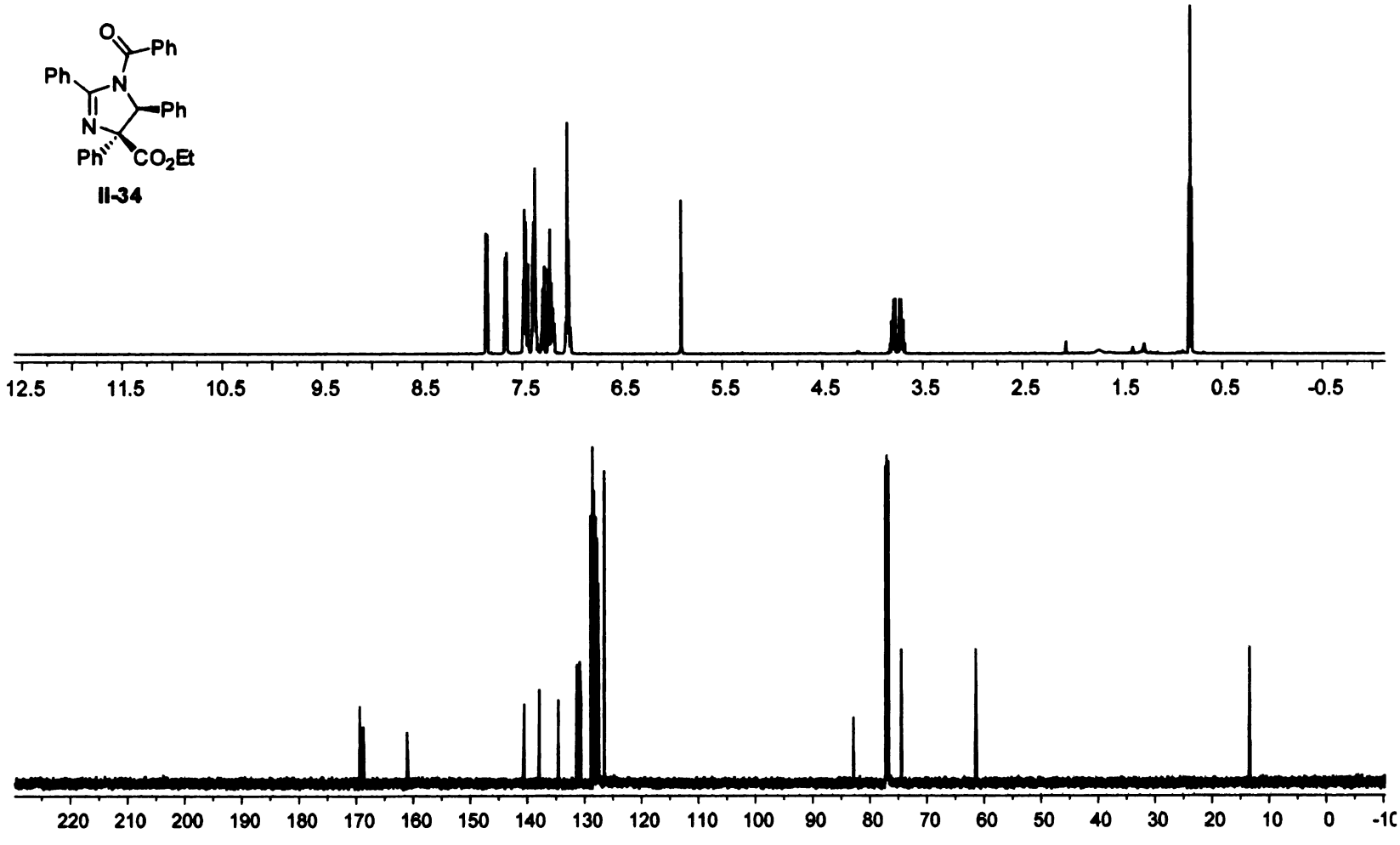


Figure II-32. NMR spectra of imidazoline **II-34.**

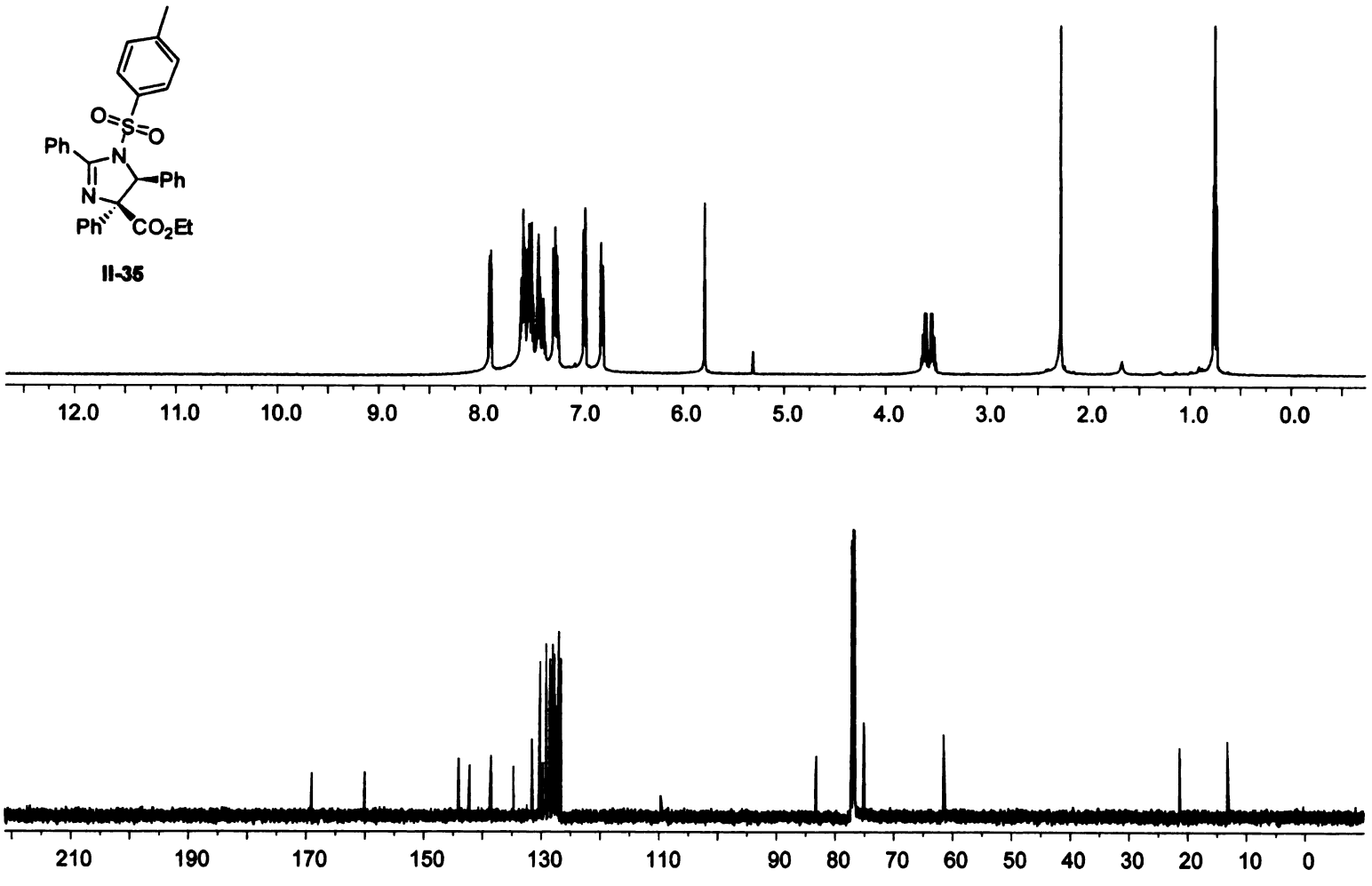


Figure II-33. NMR spectra of imidazoline **II-35.**

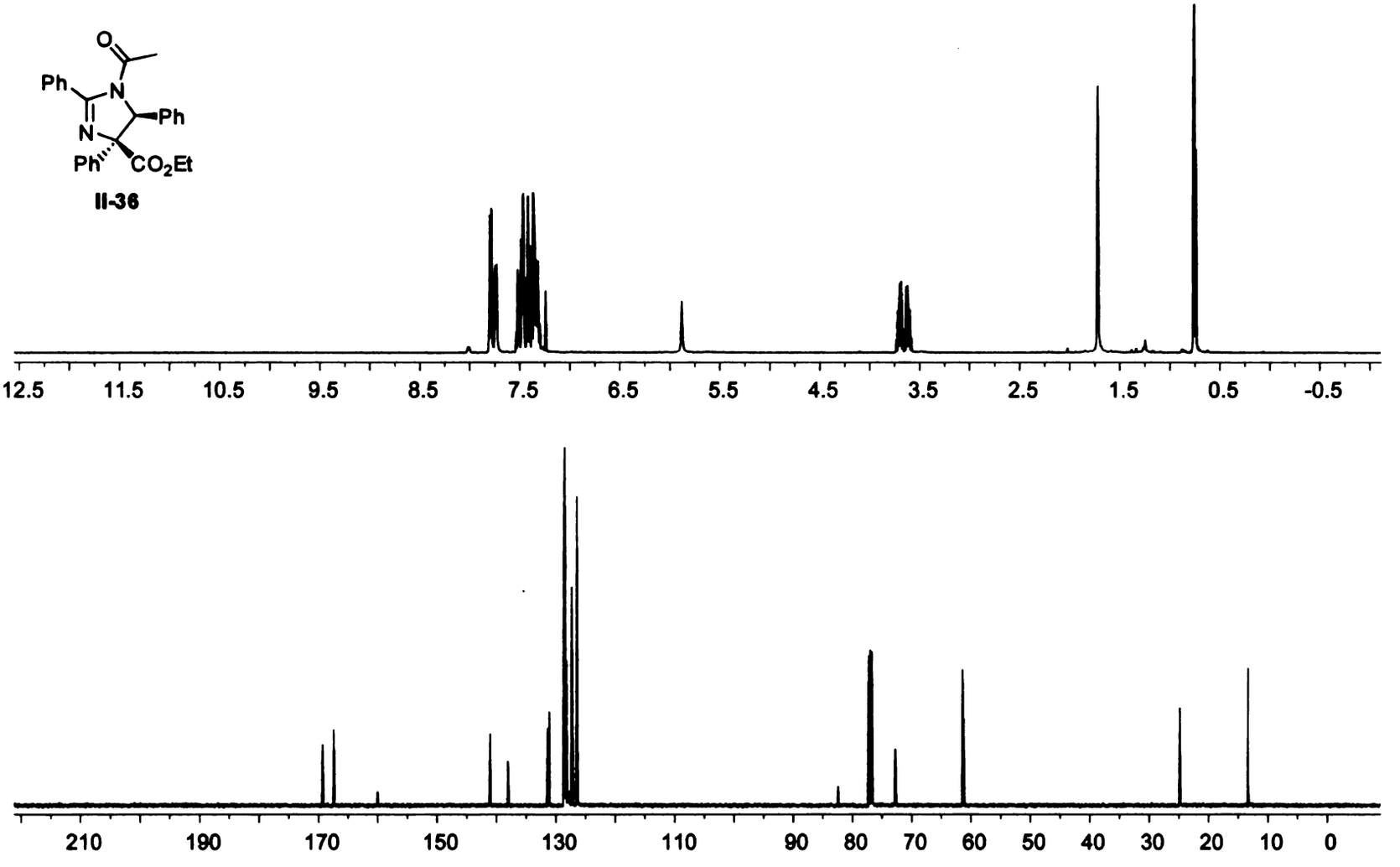


Figure II-34. NMR spectra of imidazoline **II-36.**

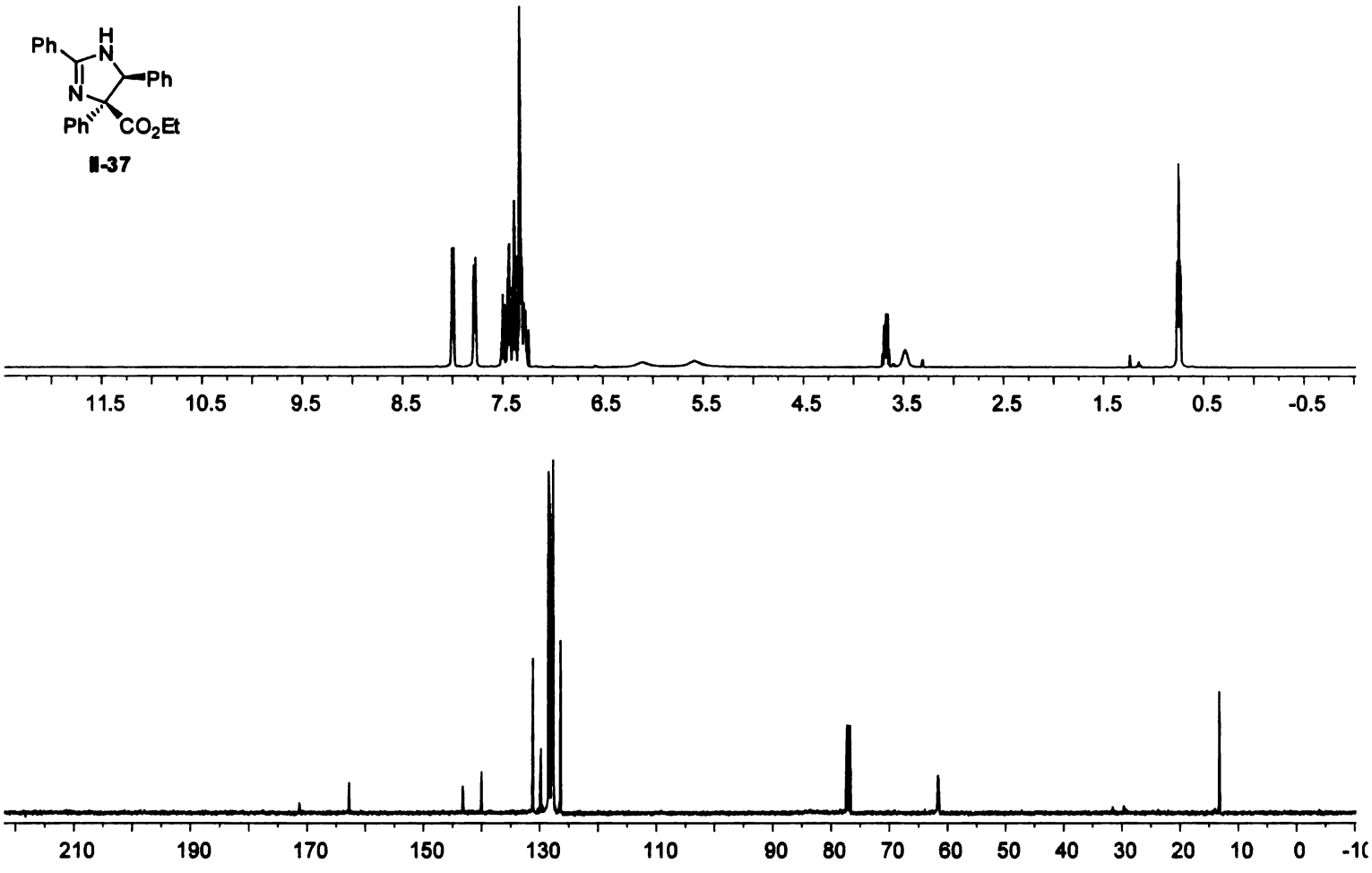


Figure II-35. NMR spectra of imidazoline **II-37.**

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CHAPTER III

INTERMOLECULAR REACTIONS OF OXAZOL-5(4H)-ONES WITH ALKENES: FROM CYCLOADDITION TO ALKYLATION REACTIONS

A. Synthesis of Δ^1-pyrrolines via münchnone/alkene cycloadditions

Highly substituted Δ^1-pyrroline scaffolds can be found in the structure of numerous biologically interesting natural products including myosmine, amathaspiramide E, broussonetine U1, veracintine, and many more (Figure III-1).[1] Molecules containing Δ^1-pyrroline scaffolds have been shown to exhibit a wide range of biological activity including anti-viral, anti-tumor and immunoactivity.[2] In addition to exhibiting a wide range of biological activity, Δ^1-pyrrolines have also exhibited value in terms of being both biosynthetic[3] and synthetic intermediates.[4] Their structures contain up to three contiguous stereogenic centers and one prochiral center masked as a cyclic imine. Due to their wide range of biological activity and their synthetic usefulness, novel methods for constructing highly substituted Δ^1-pyrrolines are still of great interest to the scientific community.

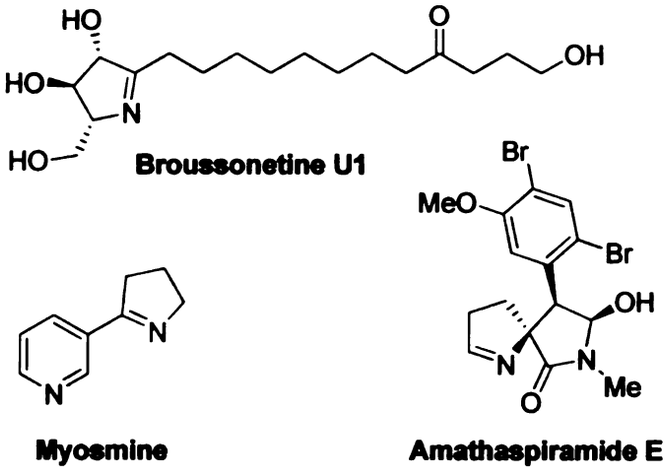
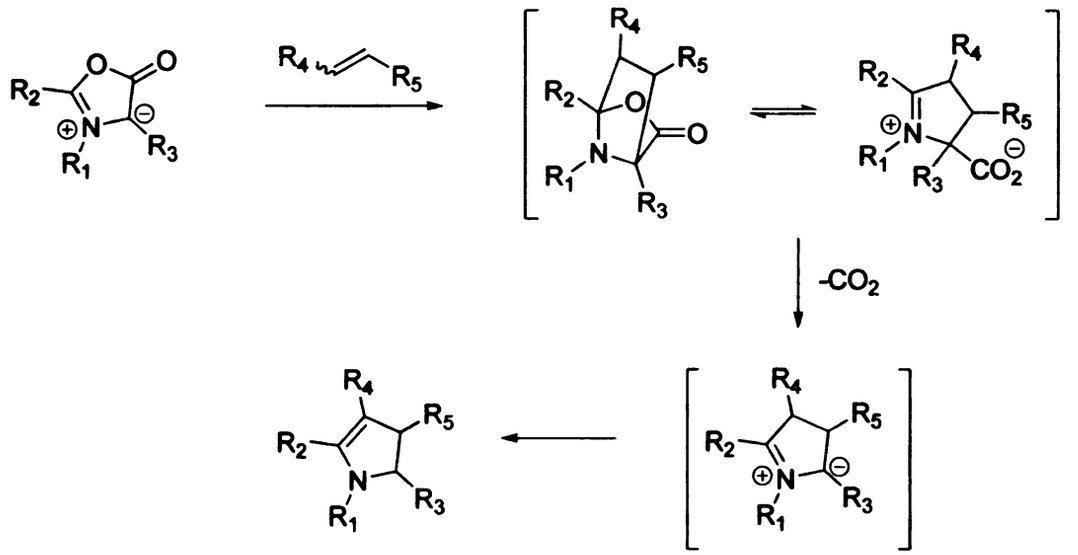


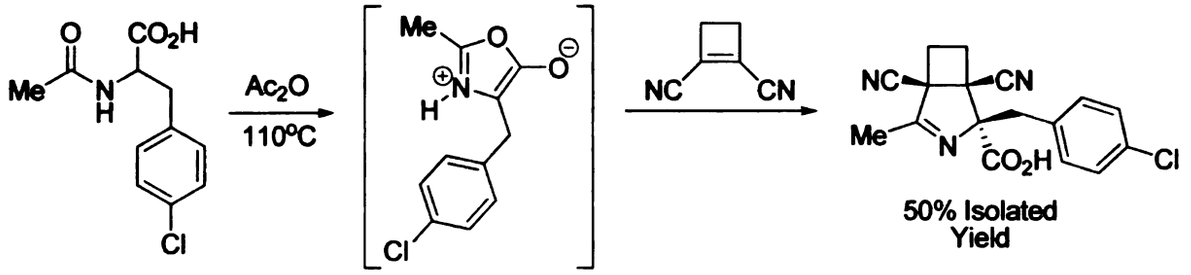
Figure III-1. Naturally occurring Δ^1-pyrrolines.

Oxazol-5(4H)-ones have been shown to be useful materials for generating a variety of nitrogen containing heterocycles by way of 1,3-dipolar cycloadditions of their münchnone tautomers.[5-7] Until recently though, cycloaddition reactions of münchnones had not been thought of as a general method for synthesizing Δ^1-pyrrolines. Early investigations by Gotthardt, Huisgen, and Schaefer illustrated that thermal cycloadditions of N-alkylated münchnones with alkenes result in the formation of a variety of products including pyrrolines and pyrroles (Scheme III-1).[8,9] Although current mechanistic evidence suggests that these reactions proceed through the initial formation of Δ^1-pyrroline cycloadducts, generally only Δ^2-pyrrolines along with pyrroles were isolated in early studies. The formation of the Δ^2-pyrroline products are thought to come about from the decarboxylation of the primary cycloadduct followed by double bond isomerization (Scheme III-1).[9,10]



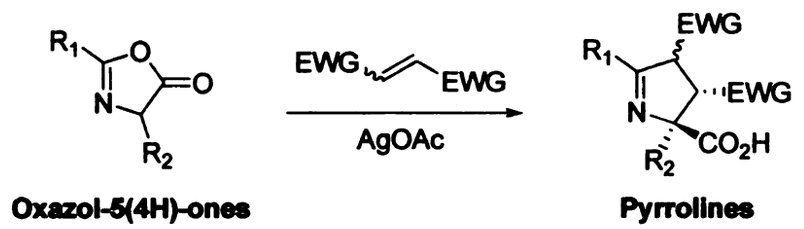
Scheme III-1. Formation of Δ^2-pyrrolines from N-alkylated münchnones.

Relatively few examples exist in the literature where primary cycloadducts from the cycloadditions of münchnones with alkenes were isolated.[10-14] In 1989, Maryanoff and co-workers reported the isolation and characterization of a stable Δ^1-pyrroline-5-carboxylic acid resulting from the cycloaddition of a münchnone with 1,2-dicyanocyclobutene (Scheme III-2).[11] In contrast to previous studies of acyclic azomethine ylides cycloadditions, only the exo-cycloadduct was observed in the reaction.[15] The decarboxylation of the primary cycloadduct is presumably hindered by the structural constraints of the fuse-bicyclic product. In follow up studies, the authors reported the decarboxylation of the primary cycloadduct under elevated temperatures (reflux in decalin).



Scheme III-2. Isolation of a primary cycloadduct from an intermolecular cycloaddition of a münchnone.

Recently, milder methods for generating münchnones using Lewis acids have been reported allowing for the isolation of the Δ^1-pyrroline primary cycloaddition adducts from a wider range of substrates.[12,14] In 2004, we reported the use of AgOAc to promote the diastereoselective synthesis of Δ^1-pyrrolines starting from oxazol-5(4H)-ones and electron deficient alkenes (Scheme III-3).[14] The reactions proceeded with moderate to good yields of product formation with high diastereoselectivity. As seen in Maryanoff's studies (Scheme III-2), these reactions produced primarily *exo*-cycloadducts.[10,11]

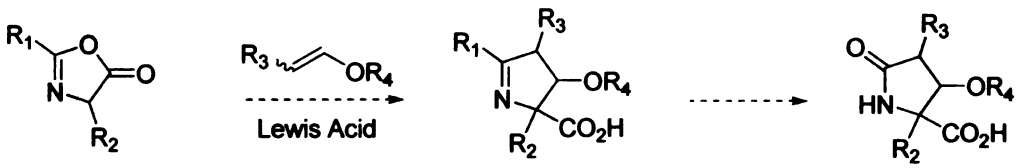


Scheme III-3. Lewis acid mediated cycloaddition of oxazol-5(4H)-ones with electron deficient alkenes.

B. Proposed cycloaddition of münchnones with enol ethers

To further extend the classes of heterocyclic scaffolds accessible by way of cycloadditions of münchnones with alkenes, we proposed to develop a mild

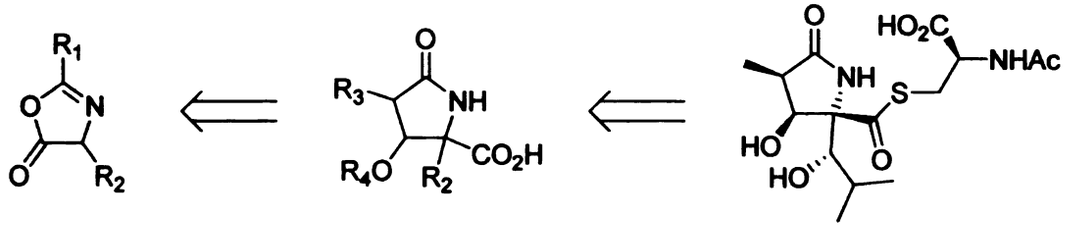
method to promote a cycloaddition reaction between oxazol-5(4H)-ones and enol ethers (Scheme III-4). As seen in our previous studies, we envisioned utilizing Lewis acids to generate münchnones while in the presence of the electron rich enol ethers.[7,12,14] The development of such methodology would greatly benefit our diversity oriented synthesis program aimed at discovering new heterocyclic molecules for the treatment of disease by allowing access to novel Δ^1-pyrroline scaffolds.[5,16] Furthermore, we envisioned using the pyrroline products as templates to access other highly substituted heterocyclic molecules. For example, proper substitution of the substituent at the 2-position (R_1) of the Δ^1-pyrroline scaffold would allow for hydrolysis of the molecule to generate novel pyrrolidines (Scheme III-4).[17]



Scheme III-4. Proposed cycloaddition of oxazol-5(4H)-ones with enol ethers.

The development of such methodology would allow ready accessibility to a range of biologically interesting molecules, including the natural product Lactacystin (Scheme III-5). Lactacystin is a pyrrolidinone-based secondary metabolite first isolated by Omura and co-workers in 1991 from the culture broth of *Streptomyces sp.* OM-6519.[18,19] Lactacystin exhibits remarkably selective and potent irreversible inhibition of the mammalian 20S proteasome.[20] It inhibits the 20S proteasome by covalently acylating the enzyme's N-terminal threonine residue via its corresponding β-lactone analogue, Omuralide.[20] Multiple

syntheses along with several structure-activity relationship studies of Lactacystin have been reported.[21] Even though many elegant syntheses of Lactacystin have been reported, new routes to the molecule may provide additional insight into its biological mechanism and access to more active analogues.



(+)-Lactacystin

Scheme III-5. Retrosynthetic analysis of a proposed synthesis of Lactacystin using oxazol-5(4H)-ones.

To the best of our knowledge, to date there are no reports of cycloadditions occurring between münchnones derived from oxazol-5(4H)-ones and electron rich alkenes (e.g. enol ethers). This may be in part due to the energy gap between the frontier molecular orbitals (FMOs) of the dipole and alkene involved.[22] The transition states of concerted 1,3-dipolar cycloaddition reactions are governed by FMO interactions. The highest occupied molecular orbital (HOMO) of the dipole may interact with the lowest unoccupied molecular orbital (LUMO) of the alkene.[22] Conversely, the HOMO of the alkene may also interact with the LUMO of the dipole.[22] Sustmann and co-workers classified 1,3-dipolar cycloaddition reactions into three different categories (Types I to III, Figure III-2).[23] In Type I 1,3-dipolar cycloadditions, the dominant FMO interaction occurs between the HOMO of the dipole and the LUMO of the alkene, whereas

Type III 1,3-dipolar cycloadditions proceed via a dominant interaction of the alkene HOMO and the LUMO of the dipole. In Type II 1,3-dipolar cycloaddition reactions, the relative energies of the FMOs of the dipole and alkene are energetically similar allowing for either HOMO/LUMO interactions to occur.

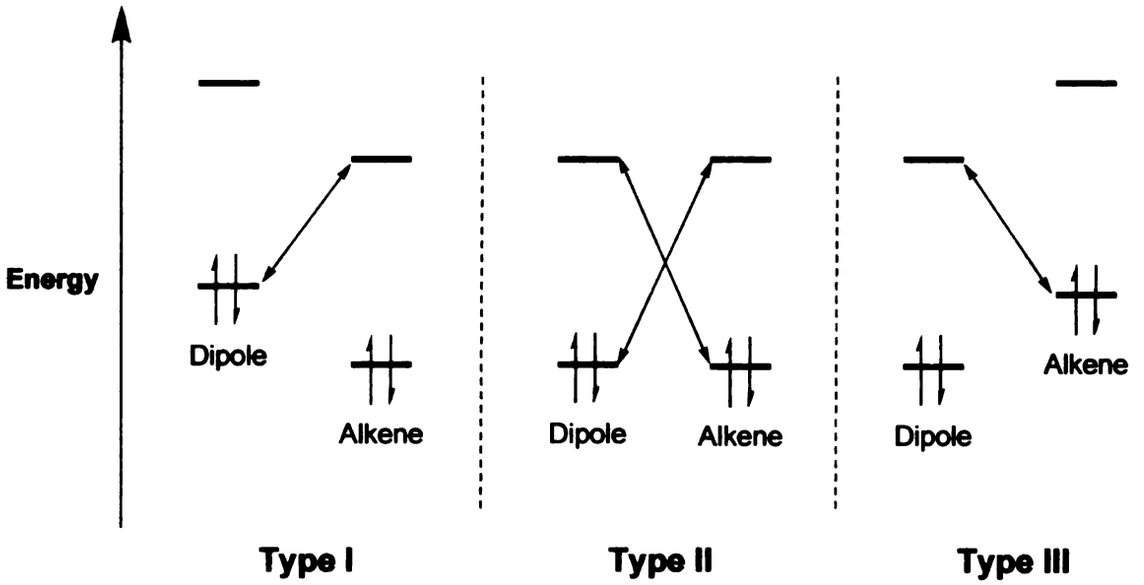
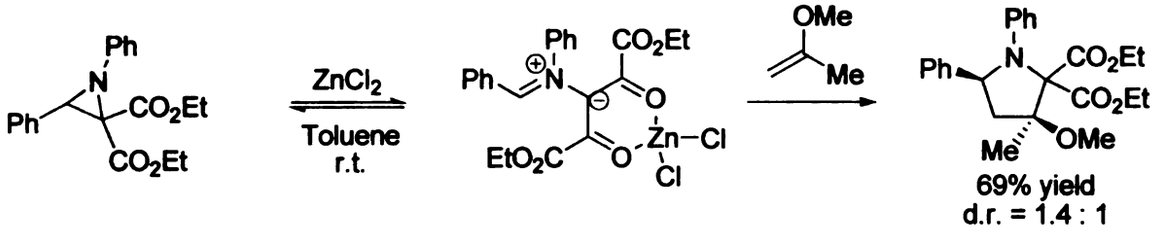


Figure III-2. Sustmann's classification of 1,3-dipolar cycloaddition reactions.

Traditionally azomethine ylides, such as münchnones, are considered to be electron rich 1,3-dipoles.[15] They are classified as having relatively high energy FMOs causing them to typically participate in Type I cycloadditions where the dominant FMO interaction occurs between the HOMO of the azomethine ylide and the LUMO of the dipolarphile (Figure III-2).[15] Azomethine ylides are known to readily undergo cycloadditions with electron deficient alkenes, presumably due to a narrow HOMO/LUMO energy gap.[15] Since the FMOs associated with electron rich alkenes (e.g. enol ethers) tend to be higher in energy than their electron deficient counterparts, their ability to participate in

Type I 1,3-dipolar cycloaddition reactions with azomethine ylides may be dismal due to a large energy difference between the FMOs involved.

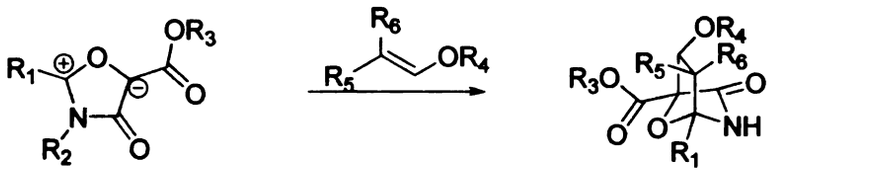
Recent reports in the literature illustrate precedence that 1,3-dipolar cycloaddition reactions between münchnones and enol ethers may be feasible though. In 2004, Johnson and co-workers reported a Lewis acid promoted carbon to carbon bond cleavage of aziridines to form azomethine ylides, which subsequently underwent [3 + 2] cycloaddition reactions with enol ethers to form highly substituted pyrrolidines (Scheme III-6).[24] These 1,3-dipolar cycloaddition reactions occurred with moderate to good yields but relatively poor diastereoselectivity. They proposed their Lewis acid coordinated azomethine ylide intermediates to be extremely electron poor thus allowing it, according to the Sustmann classification of 1,3-dipolar cycloadditions, to undergo a Type III cycloaddition.[23]



Scheme III-6. Johnson's 1,3-dipolar cycloaddition between azomethine ylides and enol ethers.

In addition, Austin and co-workers published a diastereoselective cycloaddition between vinyl ethers and isomünchnones (Scheme III-7). The reactions occur in very high yields (82% to >98%) and with near complete diastereoselectivity.[25,26] For every dipole evaluated in the study, the endo orientation of the alkoxy group of the enol ether was maintained. Furthermore,

the authors have also reported the use of chiral auxiliaries for conducting these reactions enantioselective with d.e.'s up to 95%.[26] Isomünchnones also readily undergo 1,3-dipolar cycloadditions with electron deficient alkenes illustrating that these dipoles probably proceed through a Type II cycloaddition according to the Sustmann classification of 1,3-dipolar cycloadditions.[23]



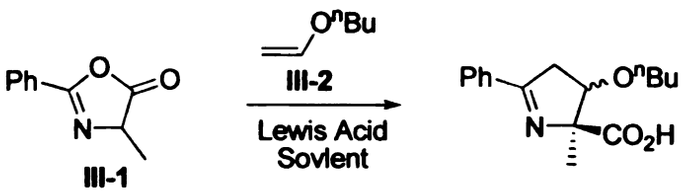
Yields = 82-98%
Only endo adducts observed

Scheme III-7. Austin's endo-selectlive 1,3-dipolar cycloaddition of isomünchnones and enol ethers.

C. Attempted cycloadditions using 2-phenyl-4-methyl-5(4H)-oxazolone and enol ethers

We initiated our studies on the 1,3-dipolar cycloaddition between oxazol-5(4H)-ones and enol ethers by evaluating a variety of Lewis acids for their ability to promote the 1,3-dipolar cycloaddition between 2-phenyl-4-methyl-5(4H)-oxazolone **III-1** and *n*-butyl vinyl ether **III-2**. Based on our previous studies involving Lewis acid promoted cycloaddition reactions of oxazol-5(4H)-ones, we chose TMSCl and AgOAc to begin our investigation (Table III-1). A solution of 2-phenyl-4-methyl-5(4H)-oxazolone **III-1** (1 equivalent) and *n*-butyl vinyl ether **III-2** (3 equivalents) was treated with either TMSCl or AgOAc (3 equivalents). The solutions were stirred for 48 hours at either room temperature or refluxing in THF and then analyzed for pyrroline formation. Unfortunately, no desired cycloaddition products were observed in any of the reactions. Most of these

reactions resulted in the recovery of the starting oxazol-5(4H)-one, although some decomposition of the starting enol ether could also be observed.



Entry	Lewis Acid	Solvent	Temp.(°C)	Yield
1	TMSCl	CH_2Cl_2	25	No Reaction
2	TMSCl	THF	67	No Reaction
3	AgOAc	THF	25	No Reaction
4	AgOAc	THF	67	No Reaction

Table III-1. Reaction of 4-methyl-2-phenyl-5(4H)-oxazolone **III-1** with butyl vinyl ether **III-2** in the presence of Lewis acids.

D. Reversing the electronics of the reaction

One possible explanation as to the failure of our initial cycloaddition attempts using oxazol-5(4H)-ones and enol ethers may lie in the energy gap between the frontier molecular orbitals involved.[22] As stated earlier, münchnones are considered to be electron rich 1,3-dipoles.[15] They are classified as having relatively high energy FMOs causing them to typically participate in Type I cycloadditions with electron deficient alkenes where the dominant FMO interaction occurs between the HOMO of the azomethine ylide and the LUMO of the alkene (Figure III-3, **A**).[15] Since the frontier molecular orbitals associated

with electron rich alkenes (e.g. enol ethers) tend to be relatively higher in energy, their ability to participate in 1,3-dipolar cycloadditions with azomethine ylides may be dismal due to a large energy difference between the FMOs involved (Figure III-3, **B**).

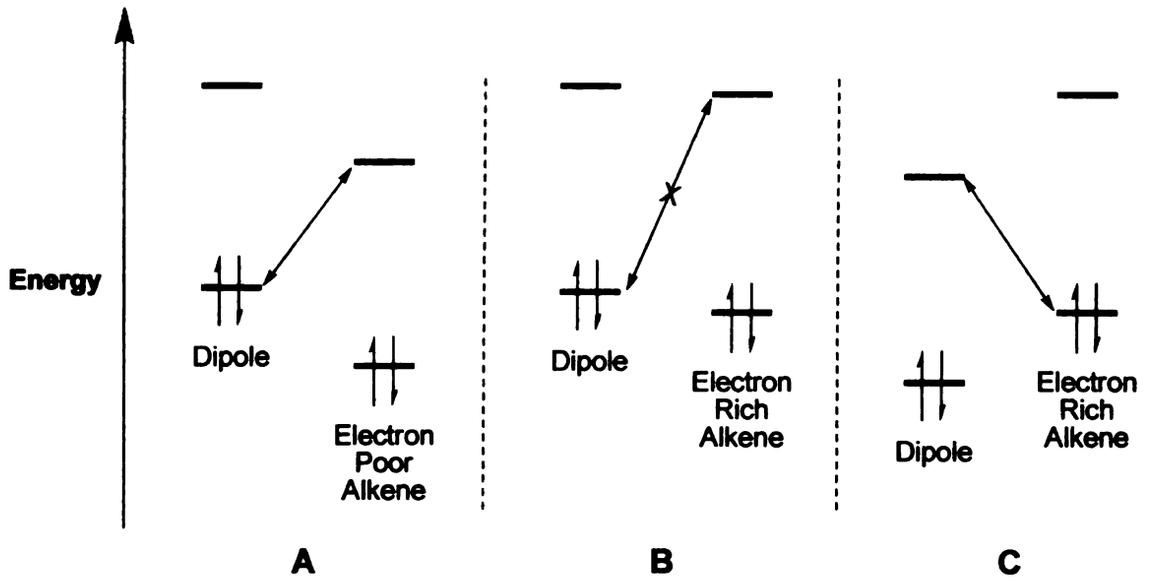


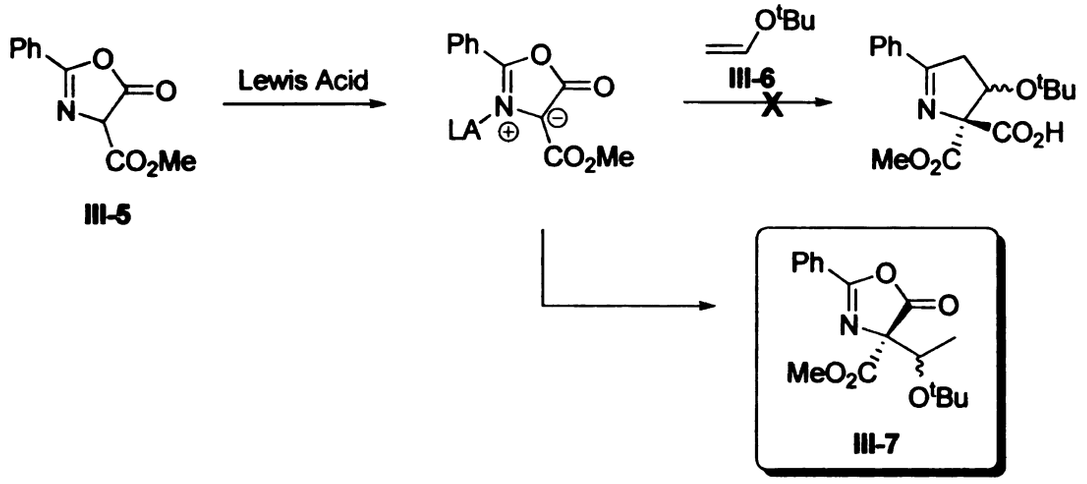
Figure III-3. Frontier molecular orbital explanation of the cycloaddition between münchnones and alkenes.

We hypothesized that stabilization of the münchnone species involved would lower the energy levels of its corresponding FMOs, potentially allowing it to undergo either a Type II or Type III cycloaddition with enol ethers (Figure III-3, **C**). We envisioned two alterations to our reaction conditions that could help facilitate the reaction. One modification would be to change the substitution pattern of the oxazol-5(4H)-one in an attempt to stabilize the dipole. For example, placing an electron withdrawing substituent at the 4-position of the oxazol-5(4H)-one scaffold would help to stabilize the anionic portion of the dipole. A second possible alteration to our initial reaction conditions for promoting the

cycloaddition reaction would be to screen a wider variety of Lewis acids. The strength of the Lewis acid involved in the formation of the münchnone species could play a major role in its stability.[22] Furthermore, coordination of the Lewis acid to the enol ether reactant may also help to promote these cycloadditions.

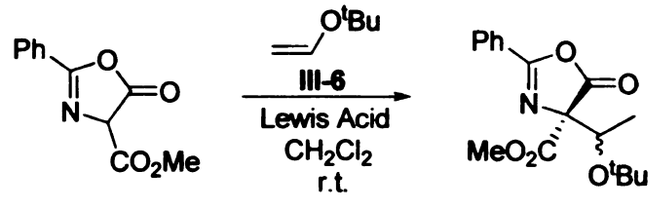
E. Discovery of a novel alkylation reaction of oxazol-5(4H)-ones

The first modification we made to our reaction conditions was to position an electron withdrawing substituent at the 4-position of the oxazol-5(4H)-one scaffold. The ester substituted oxazol-5(4H)-one, 2-phenyl-4-carbmethoxy-5(4H)-oxazolone **III-5,** was synthesized according to a known literature procedure.[27] Treatment of 2-phenyl-4-carbmethoxy-5(4H)-oxazolone **III-5** with a variety of Lewis acids while in the presence of 3 equivalents of *tert*-butyl vinyl ether **III-6** once again resulted in no cycloaddition product. In contrast to our earlier studies though, these reactions did not result in the recovery of the starting oxazol-5(4H)-one. Instead, we observed the formation of a diastereomeric mixture of quaternary substituted oxazolone products **III-7** as illustrated in Scheme III-8.[28]



Scheme III-8. Reaction of 2-phenyl-4-carbmethoxy-5(4H)-oxazolone **III-5** with *tert*-butyl vinyl ether **III-6** to form the quaternary substituted oxazolone **III-7**.

The quaternary substituted oxazolone **III-7** was formed in every reaction of 2-phenyl-4-carbmethoxy-5(4H)-oxazolone **III-5** with *tert*-butyl vinyl ether **III-6** independent of the Lewis acid used. Each reaction afforded a relatively high yield of product formation with $ZnCl_2$ producing the highest yield at 98% (Table III-2, entry 2). Interestingly, the diastereomeric ratio of the product mixture was approximately the same irrespective of the Lewis acid screened bringing into question the role of the Lewis acid catalyst. This prompted us to conduct the experiment of reacting 2-phenyl-4-carbmethoxy-5(4H)-oxazolone **III-5** with *tert*-butyl vinyl ether **III-6** without the use of any catalyst. To our delight, the same quaternary oxazolone product **III-7** was formed in quantitative yield and in the same diastereomeric ratio indicating that the use of Lewis acids was not required in the reaction (Scheme III-2, entry 4).



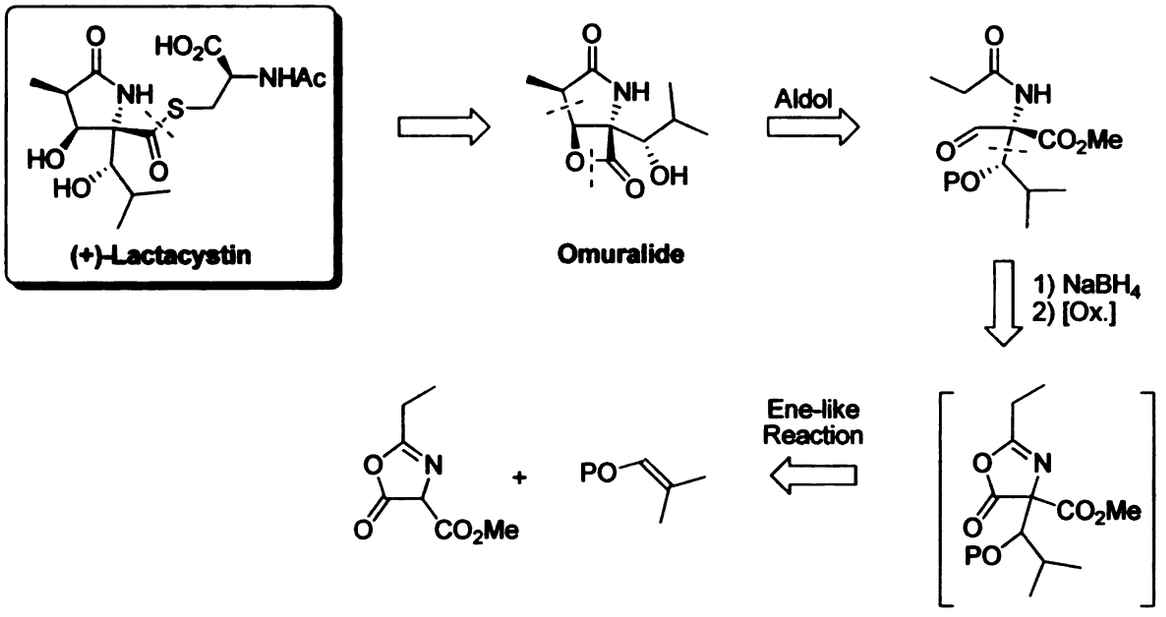
III-5 III-7

Entry	Lewis Acid	Time	D.R.	Yield
1	AgOAc	24 hrs	1.3:1	73%
2	$ZnCl_2$	36 hrs	1.2:1	98%
3	$Ti(OBu)_4$	10 min	1.2:1	70%
4	none	1 hr	1.2:1	99%

Table III-2. Reaction of 2-phenyl-4-carbmethoxy-5(4H)-oxazolone **III-5** with *tert*-butyl vinyl ether **III-6** in the presence of various Lewis acids.

The alkylation of 2-phenyl-4-carbmethoxy-5(4H)-oxazolone **III-5** using *tert*-butyl vinyl ether **III-6** presented us with an interesting synthetic opportunity. First of all, it presented perhaps a novel method for the alkylation of oxazol-5(4H)-ones to form quaternary oxazolone substrates. Quaternary oxazolones are useful intermediates for the synthesis of a variety of substrates including biologically interesting α,α-disubstituted α-amino acids.[18,29] Secondly, dependent on the scope of the reaction, we envisioned utilizing this new alkylation reaction as a key step towards the total synthesis of the Lactacystin family of molecules (Scheme III-9). Alkylation of 2-phenyl-4-carbmethoxy-5(4H)-oxazolone **III-5** with a higher substituted enol ether would directly result in almost the entire carbon skeleton of Lactacystin. Subsequent hydride reduction of the quaternary

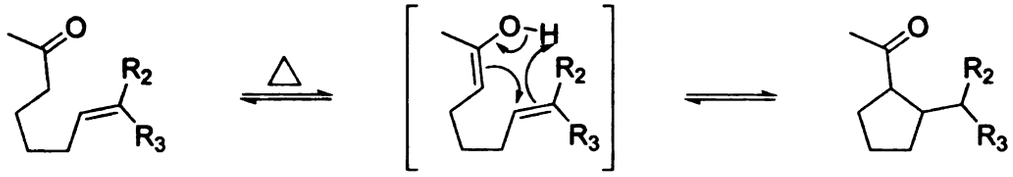
oxazolone intermediate[30] followed by oxidation would produce an amino ester intermediate ideally substituted to complete the synthesis (Scheme III-9).



Scheme III-9. Retrosynthetic route to the synthesis of Lactacystin using an alkylation reaction of an oxazol-5(4H)-one by an enol ether as the key step.

F. Comparison to similar reactions found in literature

1. Conia-ene cyclization. Although this particular reaction appears to be novel, similar types of reactions are often referred to as ene-reactions. Ene reactions represent an atom efficient and powerful reaction for the formation of carbon-carbon bonds.[31] One example of such a reaction is the Conia-ene reaction, a reaction that potentially serves as an alternative to enolate alkylations.[32] Traditionally, the Conia-ene reaction is thought of as an intramolecular ene reaction of unsaturated ketones and aldehydes, in which the carbonyl serves as the ene component via its enol tautomer (Scheme III-10).[32]

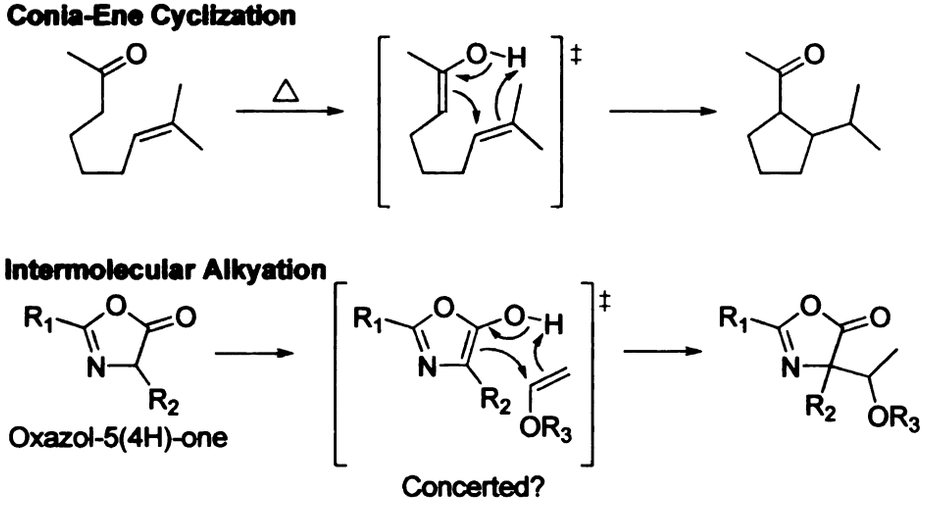


Scheme III-10. General thermal Conia-ene cyclization.

Overall the Conia-ene reaction has not received as much attention in the literature as other types of ene reactions. This may be in part due to the fact that the reaction generally needs to be conducted at very high temperatures to overcome the large activation energy barrier of the reaction.[33] Metal catalyzed versions of the reaction allow for lower temperatures, although enolate generation,[34] strong acid,[35] or photochemical activation[36] are usually required. Recent reports have demonstrated that using catalysts such as gold,[37] nickel, and indium[38] can effectively promote Conia-type ene cyclizations under much milder conditions. More recently the first enantioselective Conia-ene cyclization reaction was reported using a Pd(II) / Yb(III) dual catalyst system.[39]

Intermolecular versions of this type of ene reaction would greatly enhance the utility of ene reactions as an enolate alkylation alternative.[40] The intermolecular alkylation of oxazol-5(4H)-ones using enol ethers represents a possible advancement towards the development of intermolecular Conia-ene reactions.[28] The reaction occurs under very mild conditions without the use of any catalyst. We hypothesized that oxazol-5(4H)-ones would be ideal substrates for the development of an intermolecular ene reaction of this nature based on the ease of formation of the aromatic enol tautomer (Scheme III-11). The overall transformation closely resembles that of the Conia-ene reaction, although differs

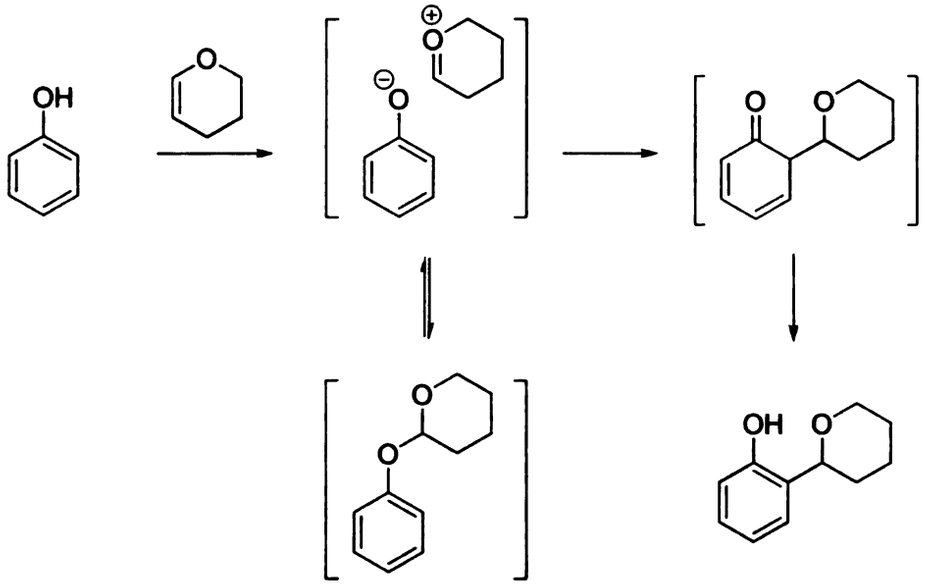
being an intermolecular reaction and also utilizes enol ethers as the enophile rather than alkenes and alkynes.



Scheme III-11. Comparison of the Conia-ene cyclization to the intermolecular alkylation of oxazol-5(4H)-ones using enol ethers.

2. The ortho-alkylation of phenols using alkenes. A second reaction illustrating similarity to the intermolecular alkylation of oxazol-5(4H)-ones using enol ethers is the ortho-alkylation of phenols using alkenes.[41,42] Both reactions involve the C-alkylation of substrates exhibiting high enolic character by alkenes. The ortho-alkylation of phenols using alkenes has drawn much attention from researchers due to the industrial applications of alkylated phenols.[43] These reactions generally provide reaction mixtures consisting of not only ortho and para alkylated products, but also tend to produce O-alkylated products. Mechanistically, it is believed that these reactions initially produce high levels of O-alkylated intermediate followed by a series of ionic rearrangements eventually providing the final C-alkylated products.[42] These reactions may occur without the need for any catalyst, although high temperatures (260 °C to 425 °C) are

generally required. A variety of both homogeneous and heterogeneous catalyst systems have been developed to help both decrease the required temperature of the reactions along with improve the overall regioselectivity.[41]



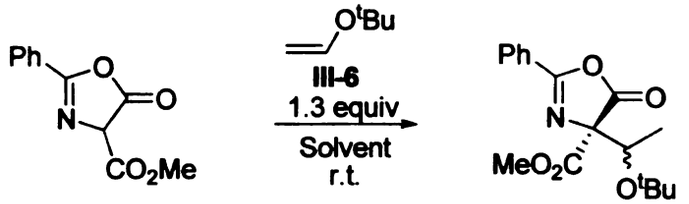
Scheme III-12. The thermal ortho-alkylation of phenols using enol ethers.

Pinhey and co-workers have reported the thermal ortho-alkylation of phenols using enol ethers (Scheme III-12).[44] As compared to earlier reports using unactivated alkenes, the ortho alkylation reaction of phenol by enol ethers occurs under less extreme conditions (~150 °C). The product mixtures obtained in these studies only consisted of O-alkylated and ortho-alkylated products. The authors proposed these reactions to proceed via the initial formation of the O-alkylated ether product, which subsequently dissociates allowing for the formation of the more thermodynamically stable ortho-alkylated phenol product. The absence of para-alkylated product combined with the observation that the electronic nature of the phenol ring had negligible effects on its outcome led the

authors to propose that the ortho-alkylated product was produced via an ene-type mechanism.

G. Solvent screening and product isolation

We initiated our studies of optimizing the intermolecular alkylation of oxazol-5(4H)-ones with enol ethers by screening various solvents. We treated 2-phenyl-4-carbmethoxy-5(4H)-oxazolone **III-5** with *tert*-butyl vinyl ether **III-6** in a variety of solvents. Reaction of 2-phenyl-4-carbmethoxy-5(4H)-oxazolone **III-5** with *tert*-butyl vinyl ether **III-6** provided the desired alkylated oxazolone product in near quantitative yields using most solvents at room temperature (Table III-3). Less polar solvents, such as benzene, provided the highest levels of diastereoselectivity with a diastereomeric ratio of approximately 1.7 to 1 (Table III-3, entry 1), although little or no diastereoselectivity was observed for most solvents. More polar solvents tended to help facilitate the reaction at a faster rate with CH_2Cl_2 producing the most rapid result at 1 hour (Table III-3, entry 2). In addition, solvents containing lone pairs of electrons tended to have longer reaction times as compared to solvents of similar polarity lacking lone electrons. For most solvents, no degradation of the enol ether was observed except in the case of DMSO where very little product was formed largely due to enol ether decomposition (Table III-3, entry 6).

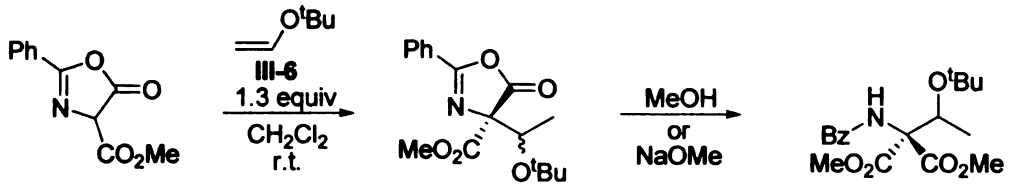


III-5 III-7

Entry	Solvent	Time	d.r.	Yield(%)
1	Benzene	36 hours	1.7 to 1	99
2	CH_2Cl_2	1 hour	1.2 to 1	99
3	THF	19 hours	1.1 to 1	99
4	1,4-dioxane	19 hours	1.1 to 1	99
5	CH_3CN	3 hours	1 to 1	99
6	DMSO-d^6	1 day	1 to1	Low

Table III-3. Screening of various solvents for the reaction of 2-phenyl-4-carbmethoxy-5(4H)-oxazolone **III-5** and *tert*-butyl vinyl ether **III-6**.

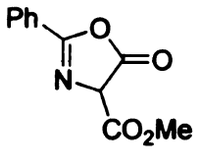
The quaternary oxazolone product **III-7** proved to be moisture sensitive making characterization and separation of the two diastereomeric products relatively difficult. Therefore following the alkylation, the reaction mixture was treated with methanol to provide the more stable quaternary substituted amino malonate derivative **III-8** (Scheme III-13). Treatment of **III-7** with methanol overnight at room temperature produced amino malonate **III-8** in near quantitative yield. It should be noted that we also found that treating quaternary oxazolone intermediate **III-7** with sodium methoxide also provided **III-8** in similar yields but at a much faster rate (~1 hour).



Scheme III-13. Intermolecular alkylation of 2-phenyl-4-carbmethoxy-5(4H)-oxazolone **III-5** with *tert*-butyl vinyl ether **III-6** followed by methanolysis.

H. Scope of enol ether

The methyl ester substituted oxazolone **III-5** was subsequently evaluated for its reactivity with a range of substituted enol ethers. Enol ethers containing different substitution patterns were reacted with 2-phenyl-4-carbmethoxy-5(4H)-oxazolone **III-5** to form quaternary oxazolone adducts, which were then analyzed after methanolysis to form the more stable amino malonate. Unsubstituted enol ethers (*tert*-butyl enol ether **III-6** and *n*-butyl vinyl ether **III-2**) provided the alkylated oxazolones in approximately one hour and in near quantitative yields (Table III-4, entries 1 and 2). Both 2,3-dihydropyran **III-9** and 3,4-dihydro-(2H)-pyran **III-10** also provided the desired products in good yields, albeit with longer reaction times (Table III-4, entries 3 and 4, 2 and 22 hours respectively). A decrease in reactivity was noted for the higher substituted enol ethers **III-11** and **III-12** (Table III-4, entries 5 and 6), which needed to be refluxed in CH_2Cl_2 for 48 hours to facilitate product formation.

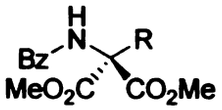


III-5

1) Enol Ether (1.3 eq)

CH_2Cl_2, r.t.

2) MeOH, rt



III-8 and III-13 to III-17

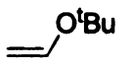
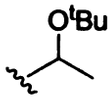
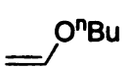
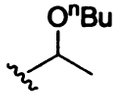
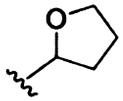
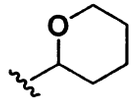
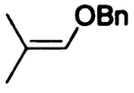
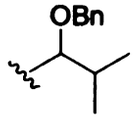
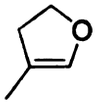
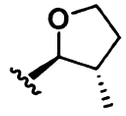
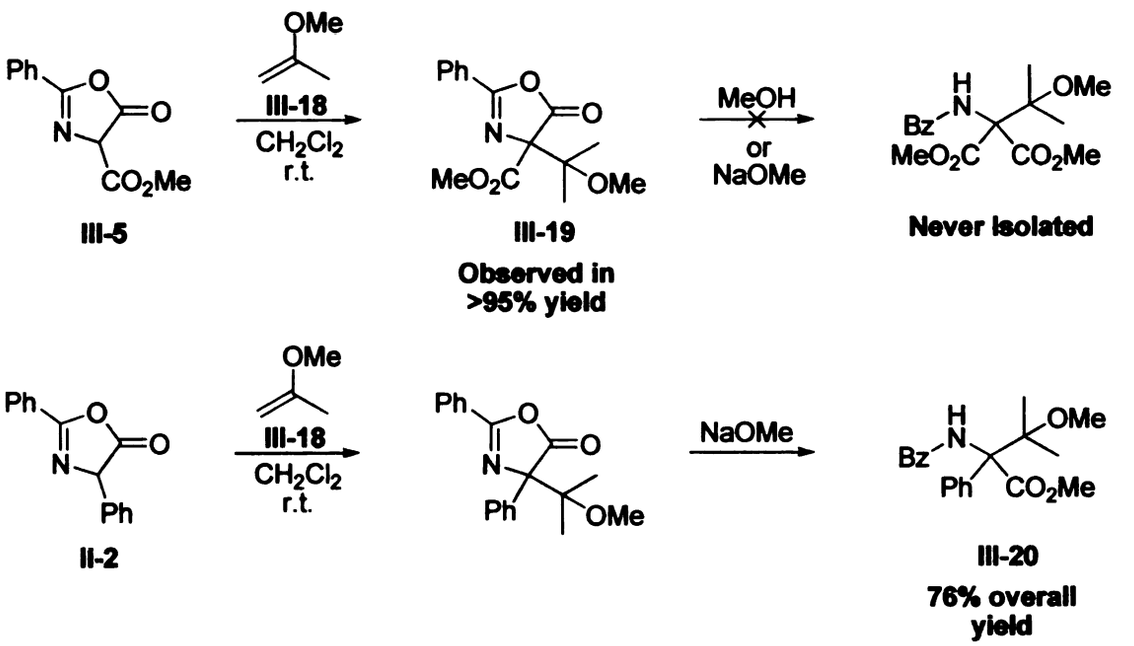
Entry	Enol Ether	R	Time (hrs)	Temp(°C)	%Yield
1	 III-6	 III-8	1	R.T.	99
2	 III-2	 III-13	1	R.T.	98
3	 III-9	 III-14	2	R.T.	99
4	 III-10	 III-15	24	R.T.	99
5	 III-11	 III-16	48	40	68
6	 III-12	 III-17	48	40	81

Table III-4. Reaction of 2-phenyl-4-carbmethoxy-5(4H)-oxazolone **III-5** with enol ethers of varying substitution pattern.

Enol ethers containing alkyl substituents geminal to the alkoxy group (such as 2-methoxypropene **III-18**) produced products less stable as compared to other enol ethers. For instance, treatment of 2-phenyl-4-carbmethoxy-5(4H)-oxazolone **III-5** with 2-methoxypropene **III-18** provided the desired alkylated

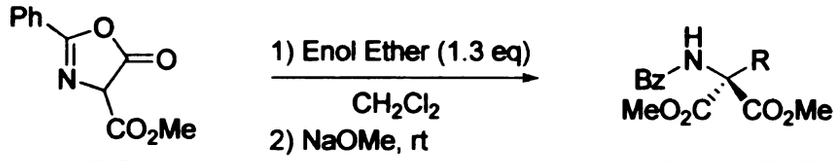
oxazolone product **III-19** within minutes at room temperature (Scheme III-14). Interestingly, **III-19** proved to be considerably unstable and reverted back to the starting materials under either methanolysis conditions or vacuum. Even though the products produced are fairly unstable, it is possible to obtain α-amino esters using 2-methoxypropene **III-18** utilizing less acidic oxazol-5(4H)-ones. For example, the alkylated oxazolone obtained from the reaction of the less acidic 2,4-diphenyl-5(4H)-oxazolone **II-2** with 2-methoxypropene **III-18** smoothly converted to the desired quaternary α-amino ester derivative **III-20** when treated with sodium methoxide.



Scheme III-14. Reactions of oxazol-5(4H)-ones with 2-methoxypropene **III-18**.

We also investigated the replacement of the alkyl protection group of the enol ether some other traditional protection groups. Less substituted silyl enol ethers **III-21** and **III-22** were less reactive than their alkyl enol ether counterparts, but did provide the desired products in reasonable amounts with

yields of 83% and 48% respectively. Disappointingly, the higher substituted silyl enol ether **III-23** provided no product formation when reacted with 2-phenyl-4-carbmethoxy-5(4H)-oxazolone **III-5**. The donating nature of the protection group of the enol ether appears to be critical to the success of these reactions. Replacement of the alkyl or silyl moiety with an electron withdrawing group, such as an acetate, completely abrogates the reaction resulting in isolation of only starting materials (Table III-5, entries 4 and 5). This may be in part due to the need to stabilize positive charge accumulation on the carbon adjacent to the oxygen atom during the reaction.



III-5 **III-26 and III-27**

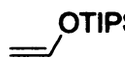
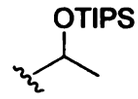
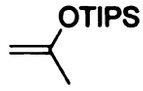
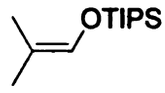
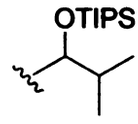
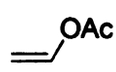
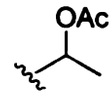
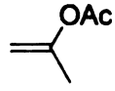
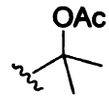
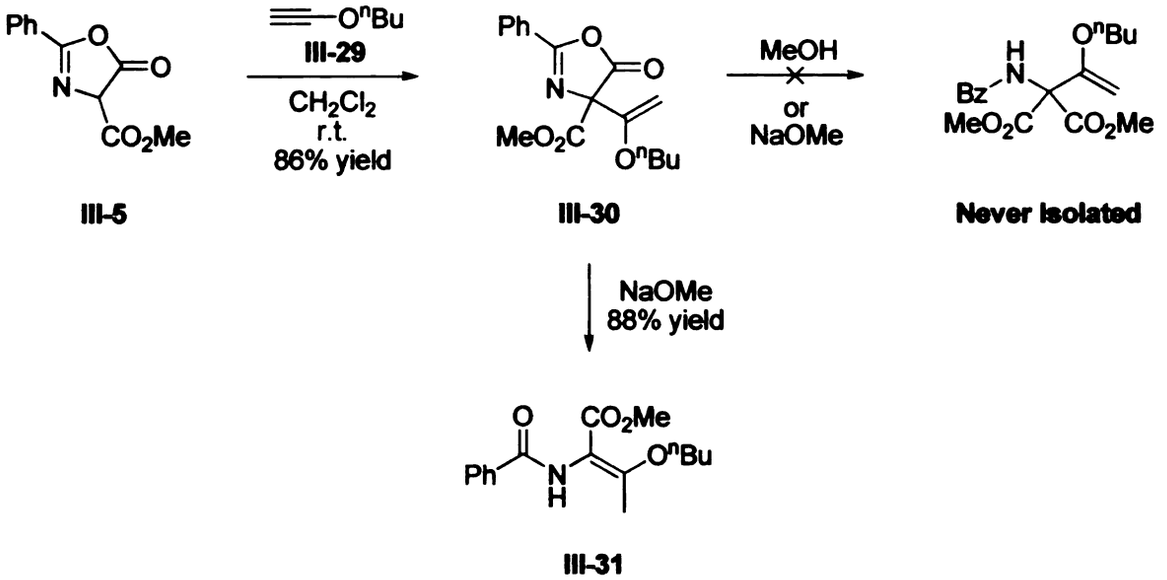
Entry	Enol Ether	R	Time (Hrs)	Temp(°C)	%Yield
1			24	40	83
	III-21	**III-26**			
2			24	R.T.	48
	III-22	**III-27**			
3			24	40	0
	III-23				
4			24	40	0
	III-24				
5			24	40	0
	III-25				

Table III-5. Reaction of 2-phenyl-4-carbmethoxy-5(4H)-oxazolone **III-5** with enol ethers having varying protecting groups.

We also briefly investigated the use of alkoxy alkynes in these intermolecular ene-type alkylation reactions of oxazol-5(4H)-ones (Scheme III-15). Treatment of 2-phenyl-4-carbmethoxy-5(4H)-oxazolone **III-5** with 1-butoxyethyne **III-29** in dichloromethane at room temperature for 24 hours resulted in a 86% yield of alkylated oxazolone product **III-30.** Treatment of

quaternary oxazolone **III-30** with sodium methoxide unexpectedly resulted in the formation unsaturated amino ester **III-31**. Presumably **III-31** is formed by way of a decarboxylation reaction followed by double bond isomerization. Future work in this area would entail the investigation of internally substituted alkoxy alkynes.

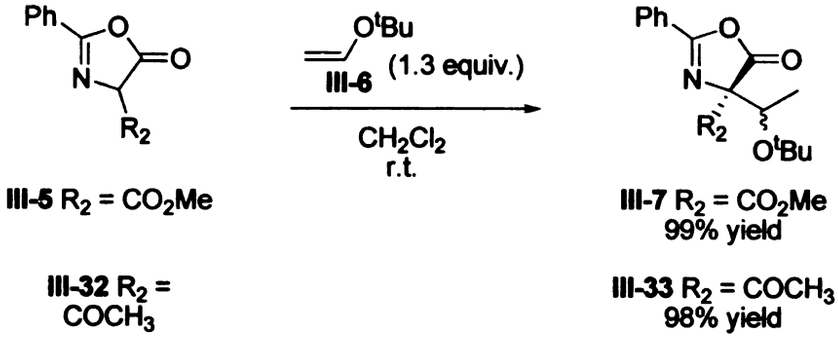


Scheme III-15. Reaction of 2-phenyl-4-carbmethoxy-5(4H)-oxazolone **III-5** with 1-butoxyethyne **III-29** followed by methanolysis.

I. Scope of oxazol-5(4H)-one

In order to further expand the scope of this reaction, the nature of the substituent at the R_2 position of the oxazol-5(4H)-one was explored (Scheme III-16). Various oxazol-5(4H)-ones were reacted with tert-butyl vinyl ether **III-6** and evaluated for quaternary oxazolone product formation. The data supports the hypothesis that increased acidity and enol character of the oxazol-5(4H)-one is helpful for the induction of this ene-type alkylation reaction. Substituents that stabilize the aromatic enol tautomer of the oxazol-5(4H)-one appear to promote the reaction

much more readily than those that do not. For example, acylated oxazol-5(4H)-ones **III-5** and **III-32** reacted readily to provide the ene-products in excellent yields at room temperature (Scheme III-16).



III-5 $R_2 = CO_2Me$

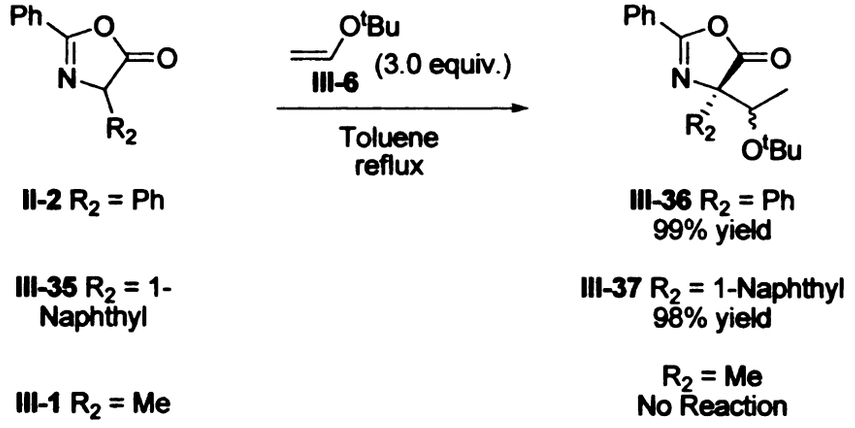
III-32 $R_2 = COCH_3$

III-7 $R_2 = CO_2Me$
99% yield

III-33 $R_2 = COCH_3$
98% yield

Scheme III-16. Intermolecular ene-type alkylation reaction of oxazol-5(4H)-ones **III-5** and **III-32** using *tert*-butyl vinyl ether **III-6**.

Aryl substituted oxazol-5(4H)-ones also provided alkylated products in excellent yields, albeit at higher temperatures (Scheme III-17). Treatment of 2,4-diphenyl-5(4H)-oxazolone **II-2** with *tert*-butyl vinyl ether **III-6** at room temperature in dichloromethane resulted in only trace amounts of product formation at room temperature, while refluxing 4-aryloxazol-5(4H)-ones **II-2** and **III-35** with *tert*-butyl vinyl ether **III-6** in toluene resulted in high yields of quaternary oxazolone products **III-36** and **III-37** respectively. Unfortunately, oxazol-5(4H)-ones containing alkyl substituents have not produced any desired products to date and generally result in the isolation of the starting materials (Scheme III-17).



II-2 R_2 = Ph

III-35 R_2 = 1-Naphthyl

III-1 R_2 = Me

III-36 R_2 = Ph
99% yield

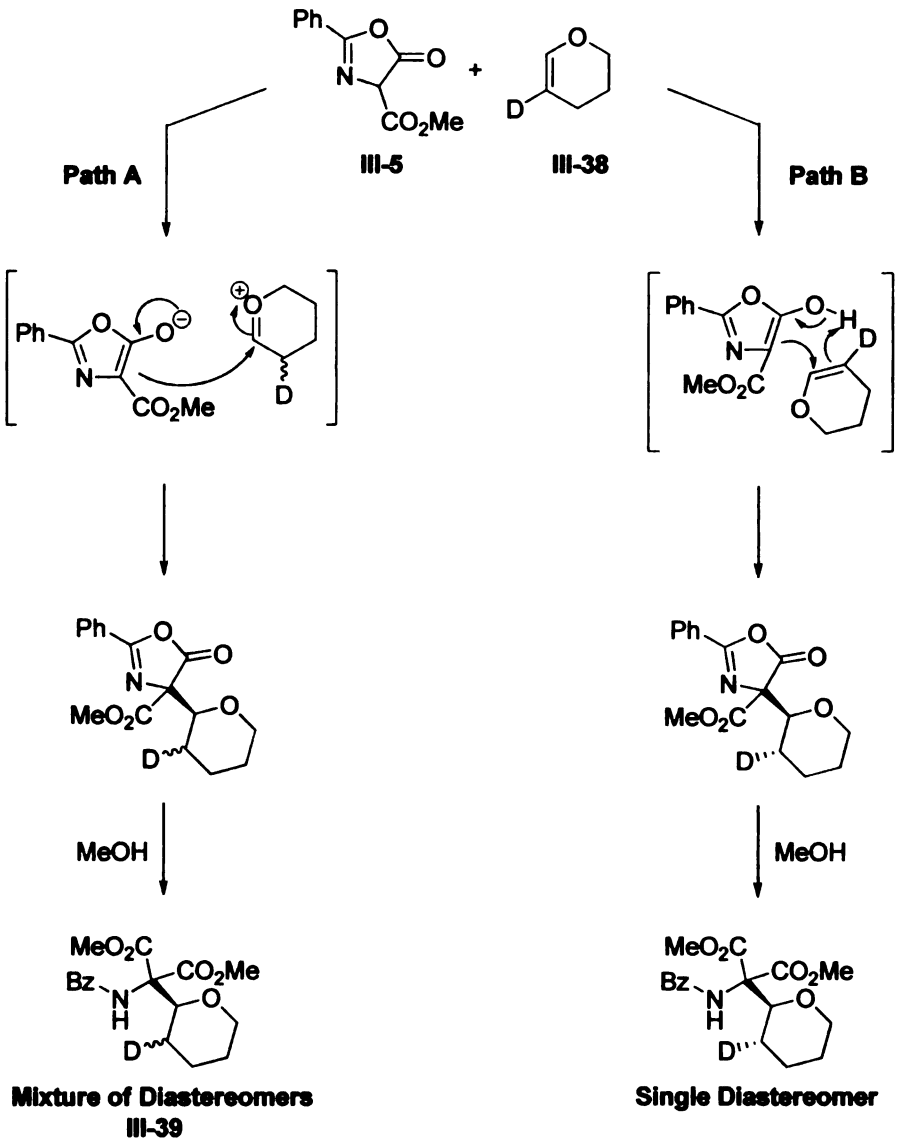
III-37 R_2 = 1-Naphthyl
98% yield

R_2 = Me
No Reaction

Scheme III-17. Reaction of 4-aryloxazol-5(4H)-ones and 4-alkyloxazol-5(4H)-ones with *tert*-butyl vinyl ether **III-6**.

J. Mechanistic investigation

Several experiments were conducted in attempts to gain further insight about the mechanistic nature of these intermolecular ene-type alkylation reactions of oxazol-5(4H)-ones and enol ethers. We hypothesized that these reactions are likely to proceed either through a concerted mechanism or through a stepwise mechanism involving the formation of an oxonium ion intermediate. In an attempt to determine which mechanism these reactions proceed through, we proposed to conduct a deuterium labeling study utilizing a deuterium labeled enol ether. Our first deuterium labeling study involved the treatment of 2-phenyl-4-carbmethoxy-5(4H)-oxazolone **III-5** with 5-deutero-3,4-dihydro-2H-pyran **III-38** (Scheme III-18). Protonation of the enol ether by the acidic oxazol-5(4H)-one followed by condensation on to the resulting oxonium ion (path A) would result in a mixture of diastereomers, where as a concerted reaction (path B) would be stereospecific and result in the formation of one single diastereomer.



Scheme III-18. Mechanistic investigation using the reaction of 2-phenyl-4-carbmethoxy-5(4H)-oxazolone **III-5** and 5-deutero-3,4-dihydro-2H-pyran **III-38**.

We utilizing a variety of NMR techniques to identify the diastereomeric ratio of the product mixture obtained from the treatment of 2-phenyl-4-carbmethoxy-5(4H)-oxazolone **III-5** with 5-deutero-3,4-dihydro-2H-pyran **III-38**. Since the chemical shifts of the two possible product diastereomers were found

to be very similar, we relied on the ^1H NMR integration values of H_a and H_b (Figure III-4) to determine the diastereomeric ratio of the product mixture. A product mixture consisting of a diastereomeric mixture would result in equal deuterium incorporation at both H_a and H_b. On the other hand, if the reaction proceeded through a concerted mechanism, deuterium incorporation would only be observed at H_b. Prior to conducting the experiment, we conducted an HMQC experiment utilizing unlabeled quaternary amino malonate **III-15** to identify the chemical shifts of both H_a and H_b (Figure III-4). Upon analyzing the data obtained from the HMQC experiment, the chemical shifts of H_a and H_b were observed to be at 1.32 ppm and 2.14 ppm respectively.

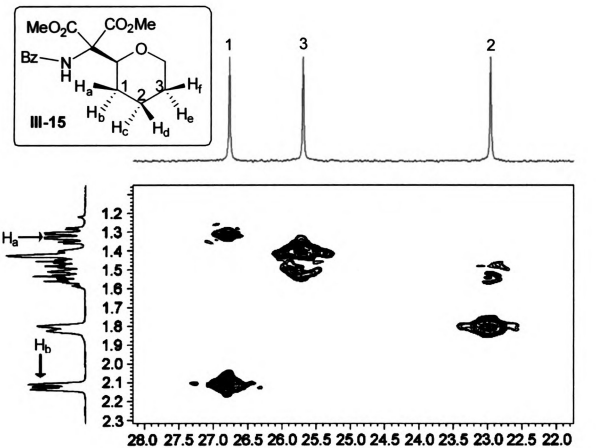


Figure III-4. HMQC spectra of amino malonate **III-15**.

Upon determining the chemical shifts of both H_a and H_b, we next sought to analyze the product mixtures obtained from treatment of 2-phenyl-4-carbmethoxy-5(4H)-oxazolone **III-5** with the deuterium labeled enol ether **III-38.** In our first attempt, we conducted the experiment utilizing a batch of 5-deutero-3,4-dihydro-2H-pyran **III-38** containing only 50% deuterium (Figure III-5). Treatment of 2-phenyl-4-carbmethoxy-5(4H)-oxazolone **III-5** with the deuterium labeled enol ether **III-38** provided the product **III-39** in near quantitative yields after methanol work-up. Upon analyzing the product mixture by ^{1}H NMR, we found that of the signal related to H_a contained 35% deuterium incorporation and the signal from H_b contained approximately 15% deuterium incorporation. This

initial result was inconclusive indicating the actual mechanism of the reaction between 2-phenyl-4-carbmethoxy-5(4H)-oxazolone **III-5** and 5-deutero-3,4-dihydro-2H-pyran **III-38** to lie somewhere in between being totally concerted and stepwise.

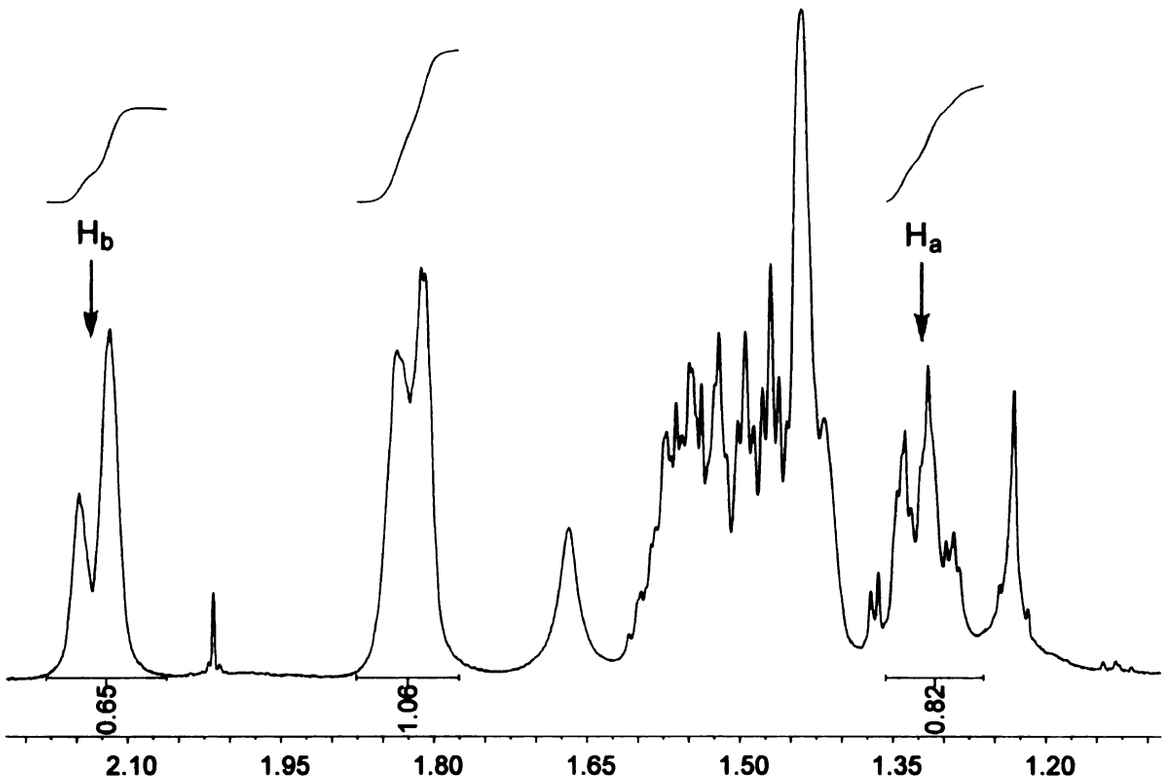


Figure III-5. 1H NMR spectra of the product mixture obtained from treatment of oxazol-5(4H)-one **III-5** with enol ether **III-38** containing 50% deuterium.

Since the initial experiment between oxazol-5(4H)-one **III-5** and enol ether **III-38** was inconclusive, the experiment was repeated in an attempt to gain more concrete evidence as to the mechanism of these ene-type reactions of oxazol-5(4H)-ones with enol ethers. The second experiment was conducting utilizing a fresh batch of 5-deutero-3,4-dihydro-2H-pyran **III-38** which contained approximately 80% deuterium (Figure III-6). Once again, treatment of 2-phenyl-

4-carbmethoxy-5(4H)-oxazolone **III-5** with the deuterium labeled enol ether **III-38** provided the product **III-39** in near quantitative yields after methanol work-up. Analysis of the ^1H NMR spectra provided plausible evidence of a stepwise/unconcerted mechanism with the signals from both H_a and H_b illustrating equal amounts of deuterium incorporation. This suggests that the oxazol-5(4H)-one initially protonates the enol ether producing an oxonium ion intermediate, which is then trapped by the corresponding oxazole enolate.

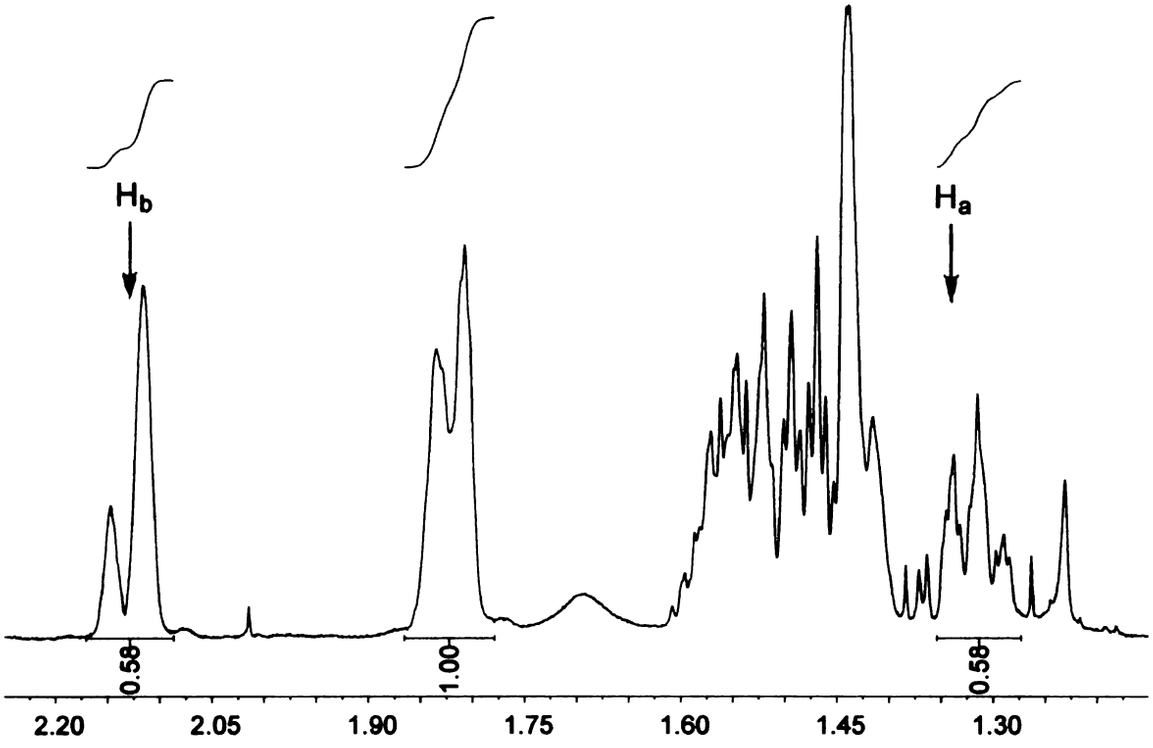
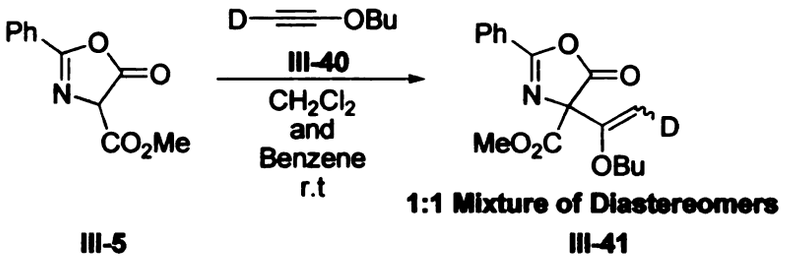


Figure III-6. 1H NMR spectra of the product mixture obtained from treatment of oxazol-5(4H)-one **III-5** with enol ether **III-38** containing 80% deuterium.

A third deuterium labeling study was conducted to confirm the final results from the first study which indicated that these reactions proceed through a stepwise protonation type mechanism.[5] For the third experiment, we synthesized

the deuterium labeled alkoxy alkyne **III-40** and treated it with the 2-phenyl-4-carbmethoxy-5(4H)-oxazolone **III-5** (Scheme III-19). The reaction was conducted in both dichloromethane and benzene to determine if the nature of solvent could affect the reaction mechanism. In each case the reaction resulted in the formation of the of the alkylated oxazolone **III-41** as a 1:1 mixture of diastereomers with yields of 96% and 76% respectively, confirming our prior results that these ene-type intermolecular alkylation reactions of oxazol-5(4H)-ones proceed through a stepwise process.

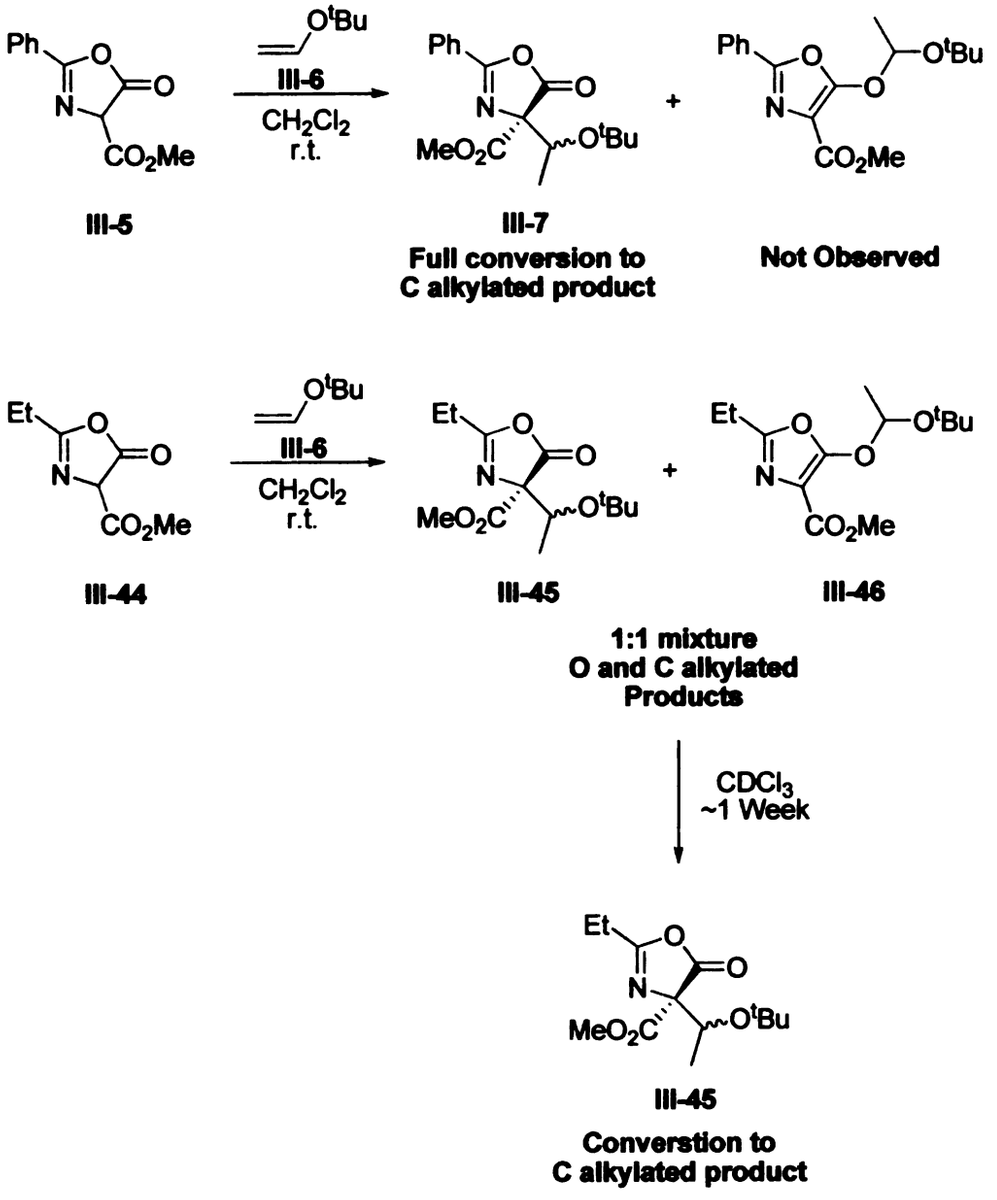


III-5 **III-41**

Scheme III-19. Reaction of 2-phenyl-4-carbmethoxy-5(4H)-oxazolone **III-5** with 2-deuterobutoxy ethyne **III-40**.

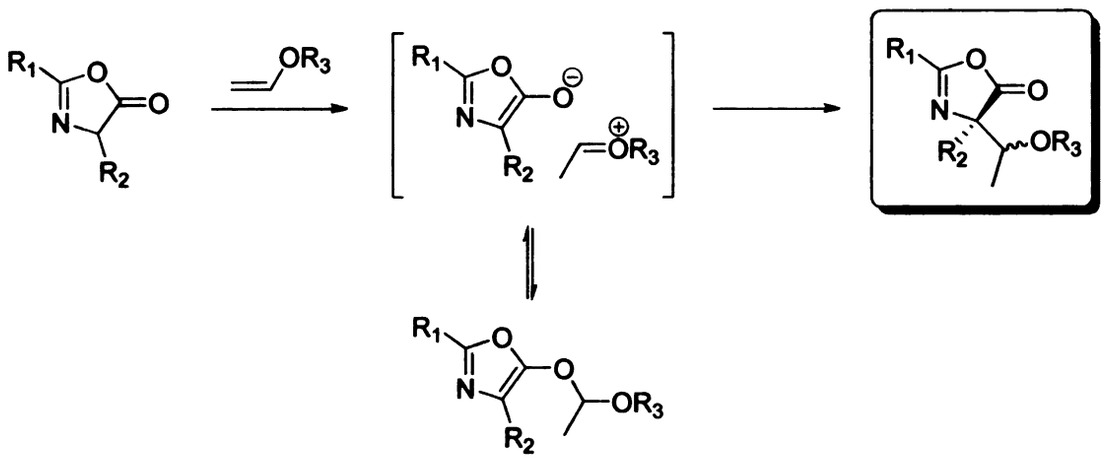
Another piece of mechanistic insight was gained while evaluating the reactivity of 2-alkyloxazol-5(4H)-ones as compared to that of 2-aryloxazol-5(4H)-ones (Scheme III-20).[5] To compare the reactivity of 2-aryloxazol-5(4H)-ones to that of 2-alkyloxazol-5(4H)-ones, we treated 2-ethyl-4-carbmethoxy-5(4H)-oxazolone **III-44** with *tert*-butyl vinyl ether **III-6**. Interestingly, analysis of the crude reaction mixture revealed not only the formation of the desired C-alkylated product **III-45**, but also the presence of its O-alkylated regioisomer **III-46**. Furthermore, upon standing we observed the conversion of the O-alkylated oxazole intermediate **III-46** to the desired C-alkylated products **III-45** along with

some degradation of the enol ether component of the reaction. This observation infers that these ene-type alkylation reactions of oxazol-5(4H)-ones may proceed through an O to C migration, although this was never observed for any of the 2-aryloxazol-5(4H)-ones.



Scheme III-20. Comparison of the reactivity of 2-phenyl-4-carbmethoxy-5(4H)-oxazolone **III-5** and 2-ethyl-4-carbmethoxy-5(4H)-oxazolone **III-44**.

Our current understanding of the mechanism of these reactions is as summarized in Scheme III-21. We propose that initially the oxazol-5(4H)-one protonates the enol ether producing an oxonium ion. The resulting oxazole enolate then traps the oxonium ion forming either an O-alkylated oxazole or a C-alkylated quaternary oxazolone depending upon the steric and/or electronic nature of the starting enol ether and oxazol-5(4H)-one. Oxazole formation via O-acylation appears to be a reversible process and may lead to C-alkylated product over time. The stability of the final C-alkylated products appears to be highly dependent on both the oxazol-5(4H)-one and enol ether used. Further studies are being conducted to further advance our knowledge of these reactions.



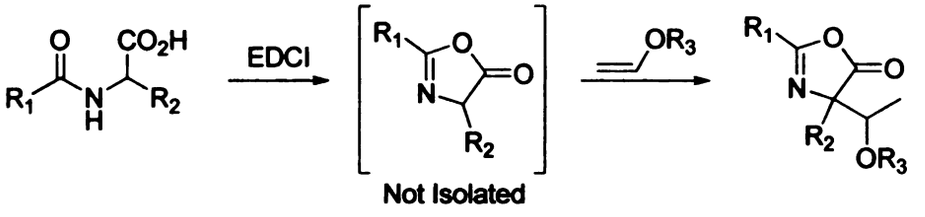
Scheme III-21. Current mechanistic understanding of the alkylation of oxazol-5(4H)-ones with enol ethers.

K. *In situ* oxazol-5(4H)-one formation

Oxazol-5(4H)-ones are moisture sensitive compounds and have the potential to undergo rapid hydrolysis to their corresponding acyclic N-acyl α-amino acids.[45] The rate at which each particular oxazol-5(4H)-one undergoes hydrolytic ring opening is heavily dependent on its substitution pattern from both an electronic

and steric standpoint. Present day dehydrating reagents have allowed for the mild and efficient syntheses of oxazol-5(4H)-ones without the formation of undesired side products.[46] This allows researchers to think about generating and utilizing oxazol-5(4H)-ones without the need to isolate or purify them.

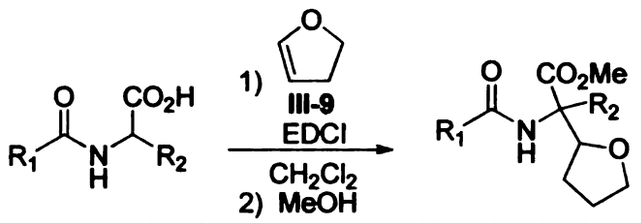
To this extent, we were hopeful to simplify our reactions utilizing oxazol-5(4H)-ones and enol ethers by generating our starting oxazol-5(4H)-ones *in situ*. If successful this would allow us to generate products from highly hydroscopic oxazol-5(4H)-ones without the need for isolating the starting oxazol-5(4H)-one. Additionally, choosing the proper dehydrating reagent would allow the oxazol-5(4H)-one synthesis to be conducted in the same reaction vessel as the ene-type alkylation reaction, thus saving time towards making the desired quaternary α-amino acid derivatives (Scheme III-22).



Scheme III-22. Conducting the intermolecular alkylation reaction of oxazol-5(4H)-ones with enol ethers while generating the starting oxazol-5(4H)-one *in situ*.

To begin our study, we chose EDCI as the cyclodehydrating reagent fearing that the use of other reagents, such as TFAA, would result in the formation of highly acidic side products detrimental to the alkylation chemistry (Table III-6). A solution of 2-(methoxycarbonyl)-2-(benzamido)acetic acid **III-4** was treated with 1.1 equivalents of EDCI while in the presence of 2,3-dihydrofuran **III-9**. To our delight, this reaction resulted in the clean formation of

the desired alkylated oxazolone product as a mixture of diastereomers. The oxazolone product was then treated with methanol and stirred overnight to afford the product malonate **III-14** resulting in an overall (3 steps) 91% yield of product after purification (Table III-6, Entry 1). We next turned our attention to other N-acyl α-amino acids whose corresponding oxazol-5(4H)-ones had previously in our hands been difficult to isolate. Both 2-(methoxycarbonyl)-2-(isobutyramido)acetic acid **III-48** and 2-(methoxycarbonyl)-2-(propionamido)acetic acid **III-43** produced relatively high yields of product when reacted in the presence of both EDCI and 2,3-dihydrofuran **III-9** (Table III-6, entries **III-50** and **III-49** respectively).



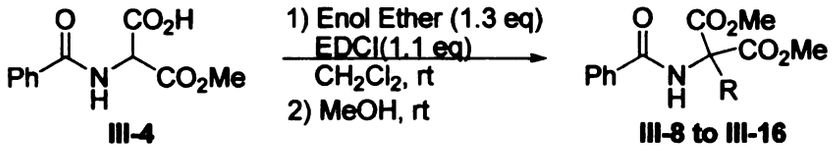
III-4, III-48, III-43 **III-14,III-49, III-50**

Entry	R_1	R_2	Temp.	Yield(%)
III-14	Ph	CO_2Me	R.T.	91
III-49	^iPr	CO_2Me	R.T.	92
III-50	Et	CO_2Me	R.T.	77

Table III-6. Alkylation of various amino acids with 2,3-dihydrofuran **III-9** utilizing oxazol-5(4H)-one intermediates.

Unfortunately our method for alkylating N-acyl α-amino acids with enol ethers utilizing oxazol-5(4H)-one intermediates was not amendable for the use with a wide range of enol ethers (Table III-7). Reaction of 2-(methoxycarbonyl)-

2-(benzamido)acetic acid **III-4** with 3,4-dihydro-2H-pyran **III-10** in the presence of EDCI provided the desired alkylated product **III-15** in 88% yield after methanolysis. All attempts using acyclic enol ethers with this procedure have been unsuccessful thus far. Both *tert*-butyl vinyl ether **III-6** and *n*-butyl vinyl ether **III-2** provided relatively low yields of product formation with yields of 15% and 17% respectively. The higher substituted enol ether **III-11** did not provide any product formation (Table III-7, entry 2).



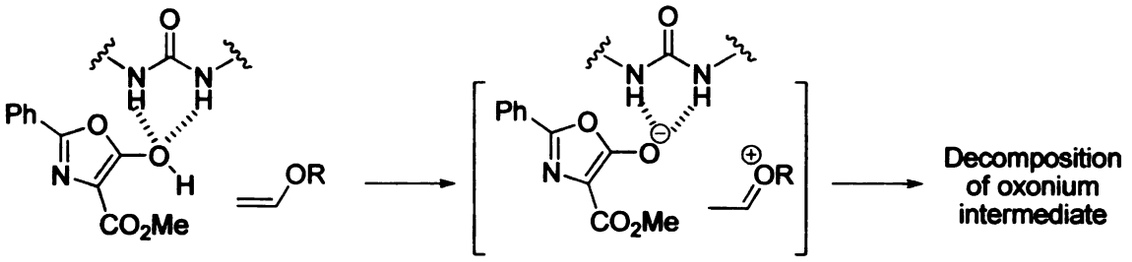
III-4 **III-8 to III-16**

Entry	Enol Ether	R	%Yield
1	**III-10**	**III-15**	88
2	**III-11**	**III-16**	0
3	**III-6**	**III-8**	15
4	**III-2**	**III-13**	17

Table III-7. The alkylation of 2-(methoxycarbonyl)-2-(benzamido)acetic acid **III-4** using various enol ethers via oxazol-5(4H)-one intermediates.

Hydrogen bonding of the urea side product may be to blame for the lack of product formation using acyclic enol ethers (Scheme III-23). Both ureas and

thioureas have been previously reported to increase the acidity of oxazol-5(4H)-ones by hydrogen bonding with the oxazol-5(4H)-one scaffold.[47] Upon formation of the oxonium ion intermediate, it is likely that the urea by product from EDCI stabilizes the resulting oxazole enolate. Stabilization of the oxazole enolate by the urea byproduct could likely lead to the decomposition of the oxonium ion intermediate, thus leading to low product formation.



Scheme III-23. Potential hydrogen bonding interaction between the oxazol-5(4H)-one scaffold and the urea byproduct.

L. Experimental

1. General methods.

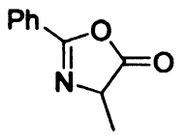
Reactions were carried out in flame-dried glassware under nitrogen atmosphere. Commercial solvents and reagents were used as received. Anhydrous methylene chloride was dispensed from a delivery system which passes the solvents through a column packed with dry neutral alumina. All reactions were magnetically stirred and monitored by TLC with 0.25 μm pre-coated silica gel plates. Column chromatography was carried out on Silica Gel 60 (230-400 mesh) supplied by EM Science. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise noted. Infrared spectra were recorded on a Nicolet IR/42 spectrometer. 1H and 13C NMR spectra were recorded on a Varian Inova-300 spectrometer, a Varian Gemini-300 spectrometer and a Varian Unity Plus-500 spectrometer. Chemical shifts are reported relative to the residue peaks of the solvent $CDCl_3$ (7.24 ppm for 1H and 77.0 ppm for 13C). HRMS were obtained at the Mass Spectrometry Facility of Michigan State University with a JEOL JMS HX-110 mass spectrometer. Gas chromatography / low resolution mass spectra were recorded on a Hewlet-Packard 5890 Series II gas chromatograph connected to a TRIO-1 EI mass spectrometer.

2. Materials.

Reagents and solvents were purchased from commercial suppliers and used without further purification. Anhydrous methylene chloride, benzene, acetonitrile,

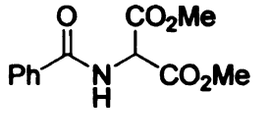
tetrahydrofuran, and 1,4-dioxane were dispensed from a delivery system which passes the solvents through a column packed with dry neutral alumina. Anhydrous toluene and triethyl amine were distilled from calcium hydride. Trifluoroacetic anhydride and EDCI were purchased from Sigma Aldrich, checked for purity and used without further purification.

3. Procedures for synthesis of oxazol-5(4H)-ones.



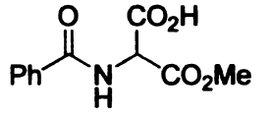
III-1

2-phenyl-4-methyl-5(4H)-oxazolone (III-1): A solution of N-benzoyl alanine (0.15 g, 0.78 mmol) in 20 mL of anhydrous dichloromethane was treated with trifluoroacetic anhydride (0.20 g, 0.93 mmol). The solution was stirred overnight and then washed with saturated sodium bicarbonate (3x50mL) and brine (1x50mL). The solution was then dried over sodium sulfate and concentrated *in vacuo* resulting in 135 mg (99% yield) of the title compound as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) (TMS): δ 1.56 (d, J = 7.5 Hz, 3H), 4.43 (q, J = 7.5 Hz, 1H), 7.47-7.50 (m, 2H), 7.53-7.58 (m, 1H), 7.96-7.98 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) (TMS): δ 16.82, 60.99, 125.87, 127.83, 128.74, 132.70, 161.54, 178.87; IR (KBr): 2986 cm^{-1}, 2937 cm^{-1}, 1829 cm^{-1}, 1653 cm^{-1}; LRMS (EI): *m/z* calcd for $C_{10}H_9NO_2$, 175.2; found, 175.0.



III-3

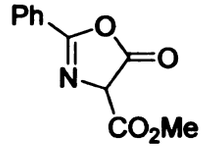
Dimethyl-2-(benzamido)malonate (III-3): A solution of dimethylaminomalonate hydrochloride (6.0 g, 32.7 mmol), triethylamine (9.9 g, 98.1 mmol) and anhydrous CH_2Cl_2 (75 ml) was treated dropwise with benzoyl chloride (4.6 g, 32.7 mmol) in a flame dried round bottom flask. The solution was stirred at room temperature under nitrogen atmosphere for 5 hours. The solution was then washed exhaustively with 2M HCl solution and dried over magnesium sulfate. The solvent was removed under vacuum and the resulting crude solid was recrystallized using EtOAc / Hexanes to yield 6.4 g (77% yield) of the title compound as a white crystalline solid. ^{1}H NMR (300 MHz) ($CDCl_3$): δ 3.84 (s, 6H), 5.38 (d, J = 6.9 Hz, 1H), 7.12 (d, J = 6.9 Hz, 1H), 7.41-7.46 (m, 2H), 7.50-7.55 (m, 1H), 7.81-7.84 (m, 2H); ^{13}C NMR (75 MHz) ($CDCl_3$): 53.55, 100.52, 127.27, 128.66, 132.20, 132.81, 166.79; IR (neat): 3333 cm^{-1}, 3009 cm^{-1}, 2957 cm^{-1}, 1746 cm^{-1}; LRMS(EI): *m/z* calcd for $C_{12}H_{13}NO_5$ 251.2; found, 251.1.



III-4

2-(methoxycarbonyl)-2-(benzamido)acetic acid (III-4): A solution of dimethyl-2-(benzamido)malonate **III-3** (2.0 g, 7.96 mmol) and 50 ml of methanol was cooled to 0 °C and treated dropwise with $LiOH{\cdot}H_2O$ (0.33 g, 7.96 mmol) in 50 ml

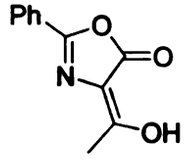
of H_2O over approximately 30 minutes. The solution was stirred over night while being allowed to warm to room temperature. The following morning the methanol was removed under vacuum and the resulting aqueous solution was first washed once with diethyl ether and then acidified using 2M HCl. The solution was washed three more times with diethyl ether and the combined ether layers were dried over magnesium sulfate. The solvent was removed under vacuum and the resulting crude solid was recrystallized in diethyl ether to yield the product as a white crystalline solid (1.75 g, 93% yield). ^{1}H NMR (300 MHz) (DMSO): δ 7.75 (s, 3H), 5.28 (d, J = 7.5 Hz, 1H), 7.48-7.54 (m, 2H), 7.56-7.62 (m, 1H), 7.93-7.96 (m, 2H), 9.20 (d, J = 7.5 Hz, 1H), 13.53 (bs, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$): 52.62, 56.56, 127.65, 128.37, 131.83, 133.01, 166.37, 167.59, 167.70. LRMS(EI): *m/z* calcd for $C_{11}H_{11}NO_5$ 237.2; found, 193.2 (-CO_2).



III-5

2-phenyl-4-carbomethoxy-5(4H)-oxazolone (III-5): A solution of 2-(methoxycarbonyl)-2-(benzamido)acetic acid **III-4** (2.00 g, 8.44 mmol) and 40 mL of anhydrous diethyl ether was treated with TFAA (2.13 g, 10.13 mmol). The solution was stirred for 3 hours during which time a yellow solid precipitated out of the solution. The yellow solid was filtered off and washed with cold diethyl ether. The yellow solid was then further dried under high vacuum yielding 1.77 g (96 % yield) of the title compound (m.p. = 169 °C – 170 °C). ^{1}H NMR (500 MHz)

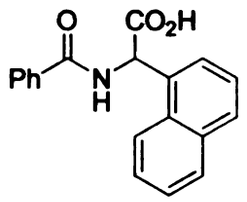
($CDCl_3/C_5D_5N$): δ 3.16 (s, 3H), 6.57-6.60 (m, 1H), 6.66-6.69 (m, 2H), 7.36-7.37 (m, 2H), 14.06 (bs, 1H); ^{13}C NMR + **DEPT** (125 MHz) ($CDCl_3/C_5D_5N$): δ 48.95 (-CO2CH3), 97.68 (quaternary C), 123.74 (aromatic –CH), 127.05 (aromatic –CH), 127.10 (aromatic –CH), 127.50 (quaternary C), 144.85 (quaternary C), 164.10 (quaternary C), 167.24 (quaternary C); IR (KBr): 2970 cm^{-1}, 1777 cm^{-1}, 1630 cm^{-1}, 1495 cm^{-1}, 1458 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{11}H_{10}NO_4$ [M+H], 220.0609; found, 220.0609.



III-32

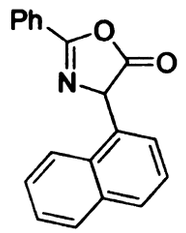
(E)-4-(1-hydroxyethylidene)-2-phenyloxazol-5(4H)-one (III-32): A solution of sodium hippurate (12.5 g, 62.13 mmol) and acetic anhydride (25.4 g, 248.5 mmol) was heated to reflux for 20 minutes. The solution was then cooled and dissolved into 150 mL of diethyl ether. The solution was washed with water (2x50 mL) and concentrated *in vacuo*. The solution was then suspended in a minimal amount of diethyl ether producing a red solid which was isolated via filtration. The solid was then dried under vacuum affording 1.2 g (9.5% yield) of the title compound as a red solid. (m.p. = 190 °C – 191°C) ^1H NMR (500 MHz, $CDCl_3$/Pyridine-d^5): δ 2.21 (s, 2H), 6.99-7.05 (m, 3H), 7.47 (d, J = 7.5 Hz, 2H), 7.65 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$/Pyridine-d^5): δ 18.47, 112.88, 125.75, 126.52, 127.83, 130.03, 152.87, 167.19, 171.69; IR (KBr): 3010 cm^{-1}, 1734 cm^{-1},

1701 cm^{-1}, 1662 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{11}H_9NO_3$ [M+H], 204.0661; found, 204.0653.



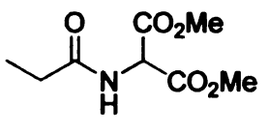
III-34

2-benzamido-2-(naphthalen-1-yl)acetic acid (III-34): A solution of 1-naphthylglycine (2.0 g, 9.93 mmol) in 30 mL of 1M NaOH was treated dropwise with benzoyl chloride (1.5 g, 10.9 mmol) at 0 °C. The solution was stirred overnight while being allowed to warm to room temperature. The solution was then washed once with EtOAc and the acidified with 2M HCl. The aqueous solution was washed again with EtOAc (3x50 mL) and the combined EtOAc washes were dried over sodium sulfate and concentrated *in vacuo.* The resulting crude solid was recrystallized affording 2.9 g (97% yield) of the title compound as a white solid. (m.p. = 210 °C – 212 °C) ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.30 (d, J = 7.5 Hz, 1H), 7.18-7.41 (m, 6H), 7.44-7.47 (d, J = 7 Hz, 1H), 7.65-7.68 (m, 5H), 8.12 (d, J = 8.5 Hz, 1H), 13.10 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 53.32, 123.04, 124.76, 125.27, 125.40, 126.19, 126.80, 127.82, 128.21, 128.45, 130.75, 131.08, 132.79, 133.22, 133.37, 166.17, 172.38; IR (neat): 3431 cm^{-1}, 3059 cm^{-1}, 1724 cm^{-1}, 1651 cm^{-1}; LRMS (EI): *m/z* calcd for $C_{19}H_{15}NO_3$, 305.3; found, 305.3.



III-35

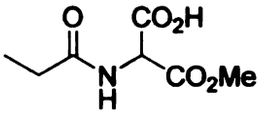
2-phenyl-4-(1-naphthyl)oxazol-5(4H)-one (III-35): Using the general procedure, cyclodehydration of N-benzoyl-naphthylglycine **III-34** (0.2 g, 0.66 mmol) with trifluoroacetic anhydride (0.15 g, 0.73 mmol) resulted in 0.19 g of product as a yellow solid in a 98% yield. ^{1}H NMR (500 MHz) ($CDCl_3$): δ 6.29 (1H, s), 7.41 (2H, m), 7.54 (3H, m), 7.63 (2H, m), 7.90 (2H, m), 8.12 (2H, dd, J_1 = 5 Hz, J_2 = 7 Hz), 8.18 (1H, d, J = 8.5 Hz); ^{13}C NMR (125 MHz) ($CDCl_3$): 65.7, 123.6, 124.8, 125.2, 125.5, 126.2, 126.9, 128.1, 128.8, 128.9, 129.3, 129.7, 130.9, 133.2, 134.1, 163.0, 175.6; IR (neat): 3061 cm^{-1}, 1826 cm^{-1}, 1653 cm^{-1}; EI(LRMS) (m/z): 287.



III-42

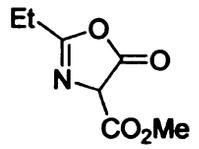
Dimethyl-2-(propionamido)malonate (III-42): A solution of dimethyl amino malonate hydrochloride (3.0 g, 16.3 mmol) and triethyl amine (5.0 g, 49.0 mmol) in 40 mL of anhydrous dichloromethane was treated dropwise with propionyl chloride (1.5 g, 16.3 mmol) at room temperature for 12 hours. The solution was then washed with 2M HCl (3x50mL) and dried over sodium sulfate. The solution was next concentrated *in* vacuo and the resulting crude solid was recrystallized

(EtOAc / Hexanes) to afford 2.6 g (77% yield) of the title compound as a white crystalline solid. (m.p. = 121°C – 122 °C) ^{1}H NMR (300 MHz) (DMSO): δ 0.97 (t, J = 7.5 Hz, 3H), 2.20 (q, J = 7.5 Hz, 2H), 3.69 (s, 6H), 5.12 (d, J = 7.5 Hz, 1H), 8.73 (d, J = 7.5 Hz, 1H); ^{13}C NMR (75 MHz) (DMSO): 9.50, 27.66, 52.81, 55.75, 167.02, 173.26. IR (neat): 3296 cm^{-1}, 2936 cm^{-1}, 1740 cm^{-1}, 1649 cm^{-1}, 1539 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_8H_{13}NO_5$ [M+H], 204.0872; found, 204.0869.



III-43

3-methoxy-3-oxo-2-propionamidopropanoic acid (III-43): A solution of dimethyl-2-(propionamido)malonate **III-42** (2.0 g, 9.84 mmol) in 50 mL of methanol was treated dropwise with a solution of LiOH·H_2O (0.4 g, 9.84 mmol) in 50 mL of water at 0 °C. The solution was stirred overnight while being allowed to warm to room temperature. The methanol was then removed under vacuum and the resulting aqueous solution was cooled to 0 °C. The solution was then acidified with 2M HCl (pH = 2) and washed with diethyl ether (3x50mL). The combined diethyl ether washes were dried over magnesium sulfate and concentrated *in vacuo*. The resulting crude solid was purified via recrystallization to afford 1.6 g (84% yield) of the title compound as a white crystalline solid. 1H NMR (300 MHz, DMSO-d^{6}): δ 0.96 (t, J = 7.5 Hz, 3H), 2.19 (q, J = 7.5 Hz, 2H), 3.68 (s, 3H), 5.00 (d, J = 7.5 Hz, 1H), 8.58 (d, J = 7.5 Hz, 1H), 13.47 (bs, 1H); ^{13}C NMR (75 MHz, DMSO-d^{6}): δ 9.62, 27.73, 52.62, 56.10, 167.73, 173.29;

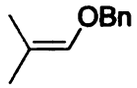


III-44

2-ethyl-4-carbomethoxy-5(4H)-oxazolone (III-44): Using the general procedure, TFAA (0.38 g, 1.80 mmol) was added to a suspension of 2-(methoxycarbonyl)-2-(propionamido)acetic acid (0.15 g, 0.80 mmol) in diethyl ether (3 mL), and water (16.5 mg, 0.92 mmol) was added once the reaction had been cooled. Collection of the precipitate afforded 0.11 g of the title compound (80% yield). The title compound is moisture sensitive and relatively unstable only allowing for partial characterization. ^{1}H NMR (500 MHz) ($CDCl_3/C_5D_5N$): δ 1.24 (t, J = 7.6 Hz, 3 H), 2.67 (q, J = 7.6 Hz, 2 H), 3.82 (s, 3 H), 15.83 (s, 1 H); ^{13}C NMR + DEPT (125 MHz) ($CDCl_3/C_5D_5N$): δ 8.5 (-CH_3), 19.8 (-CH_2), 48.0 (-CH_3), 161.8 (quaternary -C); IR (KBr): 3040 cm^{-1}, 1789 cm^{-1}, 1629 cm^{-1}, 1495 cm^{-1}, 1269 cm^{-1}.

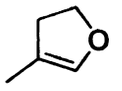
4. Procedures for synthesis of enol ethers:

The following enol ethers used in these studies were purchased and used as received: **III-2** (n-butyl vinyl ether), **III-6** (*tert*-butyl vinyl ether), **III-9** (2,3-dihydrofuran), **III-10** (3,4-dihydro-(2H)-pyran), **III-18** (2-methoxypropene), **III-24** (vinyl acetate) and **III-25** (prop-1-en-2-yl acetate). All other enol ethers used in these studies were prepared as follows:



III-11

((2-methylprop-1-enyloxy)methyl)benzene (III-11): A solution of $AlCl_3$ (8.7 g, 65.1 mmol) and triethylamine (13.2 g, 130.3 mmol) in 100 mL of anhydrous diethyl ether was stirred at room temperature for 2 hours. The solution was then treated with (2-methylpropane-1,1-diyl)bis(oxy)bis(methylene)dibenzene (8.8 g, 32.6 mmol) and then refluxed for 24 hours. The solution was then washed with 10% NaOH solution (2x100 mL) and dried over sodium sulfate. The solution was concentrated *in vacuo* and the resulting residue was purified via column chromatography (10% diethyl ether/ 90% hexanes) to afford 4.95 g (94% yield) of the title compound as a clear oil. ^1H NMR (500 MHz, $CDCl_3$): δ 1.53 (s, 3H), 1.64 (s, 3H), 4.72 (s, 2H), 5.87 (s, 1H), 7.27-7.36 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.09, 19.53, 73.27, 111.22, 127.30, 127.65, 128.37, 138.09, 139.70; LRMS (EI): *m/z* calcd for $C_{11}H_{14}O$, 162.2; found, 162.1.



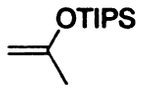
III-12

4-methyl-2,3-dihydrofuran (III-12): A solution of 3-methyldihydrofuran-2(3H)-one (0.5 g, 5.14 mmol) in 20 mL of THF was treated with DIBALH (5.65 mmol) at -78 °C. The solution was stirred for 5 hours and then quenched with 15 mL of MeOH producing a white solid. The white solid was removed via filtration. The filtrate was then concentrated *in vacuo* affording a crude residue. The residue was then diluted with 3 mL of quinoline and treated with 10 mg of TsOH. A

distillation head was placed on the flask and the solution was heated. A crude mixture of the title compound and water distilled over into a flask containing 5 mL of 2M NaOH solution which was cooled to -78 °C during the distillation. The crude mixture was then washed once with diethyl ether. The diethyl ether layer was dried using magnesium sulfate and concentrated under vacuum very carefully affording 63 mg (15% yield) of the title compound as a clear oil. The spectroscopic data was in complete agreement with the literature data.[48]

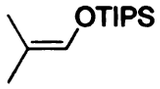
III-21

Triisopropyl(vinyloxy)silane (III-21): Acetaldehyde (1.08 g, 24.5 mmol) was added dropwise to a solution consisting of triisopropylsilyl trifluoromethane sulfonate (3.0 g, 9.79 mmol), triethylamine (1.49 g, 14.7 mmol) and 30 ml of anhydrous CH_2Cl_2 at 0 °C. The solution was stirred for three hours before being washed once with diluted HCl and dried over magnesium sulfate. The solvent was removed under vacuum and the resulting crude oil was purified via column chromatography (pentane) to yield 1.5 g of the desired enol ether as a clear oil (77% yield). ^{1}H NMR (300 MHz), $CDCl_3$: δ 1.06 (d, J = 5.4 Hz, 18H), 1.08-1.20 (m, 3H), 4.06 (d, J = 6.3 Hz, 1H), 4.43 (d, J = 13.2 Hz, 1H), 6.50 (dd, J_1 = 5.4 Hz, J_2 = 13.2 Hz, 1H); ^{13}C NMR (75 MHz) $CDCl_3$: 12.00, 17.69, 93.96, 146.92; IR (neat): 2945 cm^{-1}, 2886 cm^{-1}; LRMS(EI): *m/z* calcd for $C_{11}H_{24}OSi$ 200.4; found, 200.1.



III-22

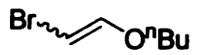
Triisopropyl(prop-1-en-2-yloxy)silane (III-22): Acetone (1.42 g, 24.5 mmol) was added dropwise to a solution consisting of triisopropylsilyl trifluoromethane sulfonate (3.0 g, 9.79 mmol), triethylamine (1.49 g, 14.7 mmol) and 30 ml of anhydrous CH_2Cl_2 at 0 °C. The solution was stirred for four hours before being washed once with brine and dried over magnesium sulfate. The solvent was removed under vacuum and the resulting crude oil was purified via column chromatography (pentane) to yield 1.77 g of the desired enol ether as a clear oil (88% yield). ^1H NMR (500 MHz), $CDCl_3$: δ 1.05 to 1.09 (m, 18H), 1.12 to 1.21 (m, 3H), 1.79 (s, 3H), 4.0 (s, 1H), 4.03 (s, 1H); ^{13}C NMR (125 MHz) $CDCl_3$: 12.59, 17.95, 22.74, 90.46, 156.37; IR (neat): 2945 cm^{-1}, 2869 cm^{-1}, 1278 cm^{-1}, 1053 cm^{-1}; LRMS(EI): *m/z* calcd for $C_{12}H_{26}OSi$ 214.4; found, 214.2.



III-23

triisopropyl(2-methylprop-1-enyloxy)silane (III-23): A solution of isobutyryl aldehyde (0.5 g, 6.9 mmol) and triethylamine (1.1 g, 10.4 mmol) in 25 mL of anhydrous benzene was treated with triisopropylsilyl triflurormethane sulfonate (2.3 g, 7.62 mmol) at room temperature. After 17 hours of stirring the solution was diluted with dichloromethane (25 mL) and washed twice with 2M HCl (2x50mL). The solution was then dried over magnesium sulfate and concentrated *in vacuo*. The crude mixture was purified via column

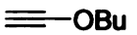
chromatography (hexanes) to afford 1.0 g (63% yield) of the title compound as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05-1.21 (m, 21H), 1.52 (s, 3H), 1.62 (s, 3H), 6.14 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.01, 14.67, 17.78, 19.24, 112.38, 134.02; LRMS (EI): *m/z* calcd for $C_{13}H_{28}OSi$, 228.2; found, 228.1.



III-28

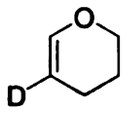
1-(2-bromovinyloxy)butane (III-28): A solution of n-butyl vinyl ether (20.0 g, 200 mmol) in 50 ml of dichloromethane was treated with a solution of bromine (31.9 g, 200 mmol) in 50 ml of dichloromethane dropwise over 1 hour at -78 °C. Then triethylamine (40.4 g, 400 mmol) was added dropwise to the reaction mixture. The solution was stirred for an additional hour at -78 °C before being allowed to warm to room temperature. The solvent was removed under vacuum and replaced with pentane. The solution was filtered to remove the resulting precipitate and the solvent was removed again under vacuum. Distillation of the crude red residue resulted in 18.7 g (52% yield) of product as a 15:1 (cis:trans) mixture of diastereomers according to H^1 NMR. 1-((Z)-2-bromovinyloxy)butane: ^{1}H NMR (500 MHz), CDCl3: δ 0.92 (t, J = 7 Hz, 3H), 1.39 (sextet, J = 7 Hz, 2H), 1.64 (p, J = 7 Hz, 2H), 3.88 (t, J = 7 Hz, 2H), 5.06 (d, J = 4 Hz, 1H), 6.56 (d, J = 4 Hz, 1H); ^{13}C NMR (125 MHz) $CDCl_3$: 13.71, 18.83, 31.71, 73.16, 81.91, 147.62; 1-((E)-2-bromovinyloxy)butane: ^{1}H NMR (500 MHz), CDCl3: δ 0.92 (t, J = 7 Hz, 3H), 1.39 (sextet, J = 7 Hz, 2H), 1.64 (p, J = 7 Hz, 2H), 3.68 (t, J = 7 Hz, 2H), 5.33 (d, J = 12 Hz, 1H), 6.73 (d, J = 12 Hz, 1H); ^{13}C NMR (125 MHz) $CDCl_3$:

13.66, 18.98, 31.06, 69.60, 82.50, 150.63. HRMS (FAB): *m/z* calcd for $C_6H_{12}OBr$ [M+H], 179.0072; found, 179.0162.



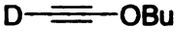
III-29

1-(ethynyloxy)butane (III-29): A solution of diethylamine (5.92 g, 80.9 mmol) in 75 ml of THF was treated with a 2M solution of n-BuLi in pentane at 0 °C. The solution was stirred for 10 mins and then 1-(2-bromovinyloxy)butane **III-28** (5.0 g, 27.9 mmol) was added dropwise over 10 mins. The solution was stirred for 30 mins at 0 °C at which time the volatiles were removed at reduced pressure. The resulting lithium salts were cooled to -78 °C and 75 ml of brine solution was added as quickly as possible making sure to continually swirl the flask contents to reduce freezing rate. The aqueous solution was then extracted with decahydronaphthalene (3 x 30 ml) and the combined decahydronaphthalene fractions were dried over magnesium sulfate. The organic solution was then filtered and the product was purified by vacuum distillation resulting in 1.41 g (51% yield) of product as a clear oil. ^{1}H NMR (500 MHz), CDCl3: δ 0.92 (t, J = 7.5 Hz, 3H), 1.40 (s, J = 7.5 Hz, 2H), 1.49 (s, 1H), 1.71 (p, J = 7 Hz, 2H), 4.05 (t, J = 6.5 Hz, 2H); ^{13}C NMR (125 MHz) $CDCl_3$: 13.53, 18.50, 26.00, 30.59, 78.70, 91.23.



III-38

5-deutero-3,4-dihydro-2H-pyran (III-38): A solution of 3,4-dihydro-(2H)-pyran (15.0 g, 178.3 mmol) and 24 mL of MeOD was treated with 15 mg of TsOH. The solution was refluxed for 12 hours and concentrated *in vacuo*. The resulting residue was redissolved into 24 mL of MeOD and refluxed for an additional 12 hours. Then 10mL of quinoline was added and a distillation head was then placed on the flask. The solution was heated distilling over a crude mixture of MeOH and the title compound. The crude mixture was purified via an additional distillation affording 3.3 g (21% yield, 70% deuterium incorporation) of the title compound as a clear oil. (b.p. = 87 °C) ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.83 (p, J = 6.5 Hz, 2H), 1.92 (t, J = 6.5 Hz, 2H), 3.93 (t, J = 6 Hz, 2H), 4.63-4.65 (m, 0.3H, (70% D)), 6.32 (d, J = 4.5 Hz, 1H); ^{13}C NMR + **DEPT** (125 MHz, $CDCl_3$): δ 19.38, 22.70, 65.74, 100.41 (t, J = 24.6 Hz), 144.02; HRMS (FAB): *m/z* calcd for C_5H_8OD [M+H], 86.0716; found, 86.0715.

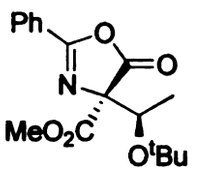


III-40

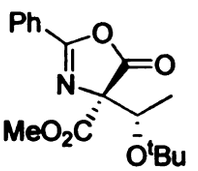
2-deutero-1-butoxyethyne (III-40): A solution of diethylamine (5.92 g, 80.9 mmol) in 75 ml of THF was treated with 32.1 mL of a 2M solution of n-BuLi in pentane at 0 °C. The solution was stirred for 10 minutes and then 1-(2-bromovinyloxy)butane **III-28** (5.0 g, 27.9 mmol) was added dropwise over 10 minutes. The solution was stirred for 30 minutes at 0 °C after which time the

volatiles were removed at reduced pressure. The resulting lithium salts were cooled to -78 °C and 80 ml of D_2O was added as quickly as possible making sure to continually swirl the flask contents to reduce freezing rate. The aqueous solution was then extracted with decahydronaphthalene (3 x 30 ml) and the combined decahydronaphthalene fractions were dried over magnesium sulfate. The organic solution was then filtered and the product was purified by vacuum distillation resulting in 1.17 g (42% yield) of the title compound with 78% deuterium incorporation as a clear oil. ^1H NMR (500 MHz)($CDCl_3$): δ 0.92 (t, J = 7.5 Hz, 3H), 1.40 (sextet, J = 7.5 Hz, 2H), 1.49 (s, 0.22H), 1.71 (p, J = 7 Hz, 2H), 4.05 (t, J = 6.5 Hz, 2H); ^{13}C NMR (125 MHz) ($CDCl_3$): 13.53, 18.50, 26.00, 30.59, 78.70, 90.9 (t, J = 9.1 Hz); HRMS (FAB): *m/z* calcd for $C_6H_{10}OD$ [M + H], 100.0872; found, 100.0872.

5. Alkylation reactions of oxazol-5(4H)-ones and enol ethers.



III-7a



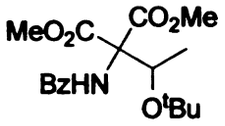
III-7b

Methyl-4-(1-tert-butoxyethyl)-5-oxo-2-phenyl-4,5-dihydrooxazole-4-carboxylate (III-7): A solution of 4-carbmethoxy-2-phenyl-5(4H)-oxazolone (55 mg, 0.25 mmol) **III-5** in 20 mL of dichloromethane was treated with tert-butyl vinyl ether **III-6** at room temperature for 1 hour. The solution was then concentrated *in vacuo* affording 80 mg (99% yield) of the title compound as a clear oil. **III-7a:** ^1H NMR (500 MHz, $CDCl_3$): δ 1.10 (s, 9H), 1.37 (d, J = 6 Hz, 3H), 3.77 (s, 3H), 4.62

(q, J = 6 Hz, 1H), 7.44-7.47 (m, 2H), 7.54-7.57 (m, 1H), 8.03-8.05 (m, 2H); ^{13}C **NMR + DEPT** (125 MHz, $CDCl_3$): δ 18.92 (-**C**H3), 28.50 (-**C**H3), 53.43 (-**C**H3), 70.79 (-**C**H), 75.21 (quaternary –**C**), 81.98 (quaternary –**C**), 125.46 (aromatic quaternary –**C**), 128.33 (aromatic –**C**H), 128.65 (aromatic –**C**H), 132.99 (aromatic –**C**H), 163.22, 165.24, 173.20; **III-7b:** ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.04 (s, 9H), 1.39 (d, J = 6.5 Hz, 3H), 3.78 (s, 3H), 4.42 (q, J = 6.5 Hz, 1H), 7.44-7.47 (m, 2H), 7.54-7.57 (m, 1H), 7.99-8.01 (m, 2H); ^{13}C NMR + **DEPT** (125 MHz, $CDCl_3$): δ 17.23 (-**C**H3), 28.46 (-**C**H3), 53.29 (-**C**H3), 70.31 (-**C**H), 74.99 (quaternary –**C**), 80.49 (quaternary –**C**), 125.34 (aromatic quaternary –**C**), 128.14 (aromatic –**C**H), 128.79 (aromatic –**C**H), 133.05 (aromatic –**C**H), 163.15, 165.64, 171.79; IR (neat): 2976 cm^{-1}, 1830 cm^{-1}, 1751 cm^{-1}, 1653 cm^{-1};

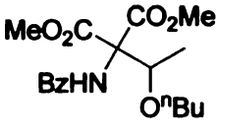
6. General procedure for alkylation reaction:

A solution of oxazolone (0.5 mmol) and enol ether (0.6 mmol to 1.5 mmol) in dry dichloromethane was stirred under nitrogen atmosphere in a flame dried flask for the requisite amount of time as monitored by TLC. The solvent was removed under vacuum and replaced with MeOH. Completion of oxazolone ring opening was monitored by TLC. The solvent was removed under vacuum and the product was isolated if necessary by column chromatography on silica gel with an ethyl acetate / hexanes mixture.



III-8

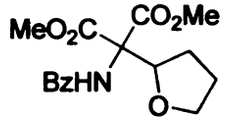
Dimethyl-2-(1-tert-butoxyethyl)-2-(benzamido)malonate (III-8): Using the general procedure, a solution of 2-phenyl-4-carbmethoxy-5(4H)-oxazolone (0.1 g, 0.46 mmol) and tert-butyl vinyl ether (0.06 g, 0.59 mmol) in 20 mL of anhydrous CH_2Cl_2 was stirred at room temperature for 30 min. The resulting ene adduct was stirred in 20 mL MeOH overnight, after which 0.16 g of malonate **III-8** was obtained (99 % yield) as a clear oil. ^{1}H NMR (300 MHz), $CDCl_3$: δ 1.10 (s, 9H), 1.36 (d, J = 6 Hz, 3H), 3.73 (s, 3H), 3.77 (s, 3H), 4.58 (q, J = 6, 1H), 7.23 (bs, 1H), 7.38-7.58 (m, 3H), 7.78-7.82 (m, 2H); ^{13}C NMR + **DEPT** (75 MHz) $CDCl_3$: 19.23 (-**C**H3), 28.84 (-**C**H3), 52.74 (-CO2**C**H3), 53.20 (-CO2**C**H3), 70.59 (quaternary C), 71.52 (-**C**H), 74.43 (quaternary C), 127.20 (aromatic **C**H), 128.56 (aromatic **C**H), 131.79 (aromatic **C**H), 133.75 (aromatic quaternary C), 166.41, 166.62, 168.14; IR (cm^{-1}): 3430, 2979, 1748, 1676; HRMS (FAB): *m/z* calcd for $C_{18}H_{26}NO_6$ [M + H], 352.1757; found, 352.1760.



III-13

Dimethyl-2-(benzamido)-2-(1-butoxyethyl)malonate (III-13): Using the general procedure, a solution of 2-phenyl-4-carbmethoxy-5(4H)-oxazolone (0.1 g, 0.46 mmol) and n-butyl vinyl ether (0.06 g, 0.59 mmol) in 20 mL of anhydrous

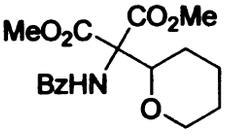
CH_2Cl_2 was stirred at room temperature for 30 min. The resulting ene adduct was stirred in 20 mL MeOH overnight, after which 0.16 g of malonate **III-13** was obtained (98 % yield) as a clear oil. ^1H NMR (300 MHz), $CDCl_3$: δ 0.85 (t, J = 7 Hz, 3H), 1.22-1.34 (m, 2H), 1.32 (d, J = 6 Hz, 3H), 1.37-1.48 (m, 2H), 3.16-3.24 (m, 1H), 3.51-3.59 (m, 1H), 3.73 (s, 3H), 3.81 (s, 3H), 4.33 (q, J = 6 Hz, 1H), 7.32 (bs, 1H), 7.40-7.54 (m, 3H), 7.80-7.83 (m, 2H); ^{13}C NMR + **DEPT** (75 MHz) $CDCl_3$: 13.76 (-CH3), 14.78 (-CH3), 19.21 (-CH2), 31.84 (-CH2), 52.83 (-CO2CH3), 53.40 (-CO2CH3), 68.95 (-CH2), 69.90 (quaternary C), 78.09 (-CH), 127.20 (aromatic CH), 128.55 (aromatic CH), 131.87 (aromatic CH), 133.44 (aromatic quaternary C), 166.33, 166.44, 168.08; IR (cm^{-1}): 3424, 2957, 1747, 1676; HRMS (FAB): *m/z* calcd for $C_{18}H_{26}NO_6$ [M + H], 352.1759; found, 352.1760.



III-14

Dimethyl-2-(benzamido)-2-(tetrahydrofuran-2-yl)malonate (III-14): Using the general procedure, a solution of 2-phenyl-4-carbmethoxy-5(4H)-oxazolone (0.1 g, 0.46 mmol) and 2,3-dihydrofuran (0.04 g, 0.59 mmol) in 20 mL of anhydrous CH_2Cl_2 was stirred at room temperature for 2 hr. The resulting ene adduct was stirred in 20 mL MeOH overnight, after which 0.14 g of malonate **III-14** was obtained (99 % yield) as a clear oil. ^1H NMR (300 MHz), $CDCl_3$: δ 1.70-1.91 (m, 2H), 2.07-2.22 (m, 1H), 2.19-2.32 (m, 1H), 3.67-3.82 (m, 2H), 3.76 (s, 3H), 3.84 (s, 3H), 4.72 (t, J = 7 Hz, 1H), 7.38 (bs, 1H), 7.38-7.54 (m, 3H), 7.80-7.84 (m,

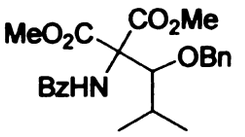
2H); ^{13}C NMR + **DEPT** (75 MHz) $CDCl_3$: 26.01 (-CH2), 27.40 (-CH2), 52.94 (-CO2CH3), 53.77 (-CO2CH3), 68.54 (quaternary C), 68.86 (-CH2), 81.47 (-CH), 127.18 (aromatic CH), 128.63 (aromatic CH), 132.02 (aromatic CH), 133.27 (aromatic quaternary C), 166.43, 166.53, 168.08; IR (cm^{-1}): 3414, 2955, 1743, 1670; HRMS (FAB): *m/z* calcd for $C_{16}H_{20}NO_6$ [M + H], 322.1290; found, 322.1290.



III-15

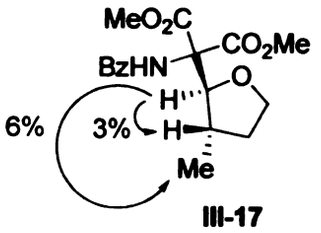
Dimethyl-2-(benzamido)-2-(tetrahydropyran-2-yl)malonate (III-15): Using the general procedure, a solution of 2-phenyl-4-carbmethoxy-5(4H)-oxazolone (0.1 g, 0.46 mmol) and 3,4-dihydro-2H-pyran (0.05 g, 0.59 mmol) in 20 mL of anhydrous CH_2Cl_2 was stirred at room temperature for 22 hr. The resulting ene adduct was stirred in 20 mL MeOH overnight yielding 0.14 g of malonate **III-15** (99 % yield) as a clear colorless oil after silica gel chromatography (20% ethyl acetate / 80% hexanes). ^{1}H NMR (300 MHz), $CDCl_3$: δ 1.26-1.64 (m, 4H), 1.80-1.86 (m, 1H), 2.10-2.18 (m, 1H), 3.38-3.48 (m, 1H), 3.73 (s, 3H), 3.82 (s, 3H), 3.90-3.96 (m, 1H), 4.24 (dd, J = 12 Hz, J = 2 Hz, 1H), 7.39 (bs, 1H), 7.40-7.54 (m, 3H), 7.82-7.86 (m, 2H); ^{13}C NMR + **DEPT** (75 MHz) $CDCl_3$: 22.97 (-CH2), 25.71 (-CH2), 26.78 (-CH2), 52.82 (-CO2CH3), 53.69 (-CO2CH3), 69.14 (quaternary C), 69.42 (-CH2), 80.99 (-CH), 127.22 (aromatic CH), 128.54 (aromatic CH), 131.90 (aromatic CH), 133.33 (aromatic quaternary C), 165.99,

166.41, 168.16; IR (cm^{-1}): 3422, 2953, 1745, 1674; HRMS (FAB): *m/z* calcd for $C_{17}H_{22}NO_6$ [M + H], 336.1445; found, 336.1447.



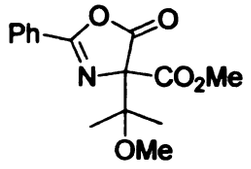
III-16

Dimethyl-2-(benzamido)-2-(1-benzyloxy-2-methylpropyl)malonate (III-16): Using the general procedure, a solution of 2-phenyl-4-carbmethoxy-5(4H)-oxazolone (0.1 g, 0.46 mmol) and 1-benzyloxy-2-methylpropene (0.096 g, 0.59 mmol) in 20 mL of anhydrous CH_2Cl_2 was heated to reflux for 48 hours. The resulting ene adduct was stirred in 20 mL MeOH overnight yielding 0.13 g of malonate **III-16** (68 % yield) as a clear colorless oil after silica gel chromatography (20% ethyl acetate / 80% hexanes). ^1H NMR (300 MHz), $CDCl_3$: δ 0.92 (d, J = 7 Hz, 3H), 1.15 (d, J = 7 Hz, 3H), 2.37-2.45 (m, 1H), 3.70 (s, 3H), 3.77 (s, 3H), 4.44 (d, J = 2 Hz, 1H), 4.59 (d, J = 11 Hz, 1H), 4.68 (d, J = 11 Hz, 1H), 7.24-7.51 (m, 9H), 7.77-7.80 (m, 2H); ^{13}C NMR + **DEPT** (75 MHz) $CDCl_3$: 16.23 (-**C**H3), 23.87 (-**C**H3), 29.78 (-**C**H), 53.08 (-CO2**C**H3), 53.39 (-CO2**C**H3), 70.09 (quaternary C), 75.31 (-**C**H2), 84.97 (-**C**H), 127.14 (aromatic CH), 127.42 (aromatic CH), 127.51 (aromatic CH), 128.25 (aromatic CH), 128.49 (aromatic CH), 128.63 (aromatic CH), 131.90 (aromatic CH), 133.44 (aromatic quaternary C), 138.26 (aromatic quaternary C), 166.41, 167.22, 168.35; IR (cm^{-1}): 3418, 2955, 1743, 1672; HRMS (FAB): *m/z* calcd for $C_{23}H_{28}NO_6$ [M + H], 414.1919; found, 414.1916.



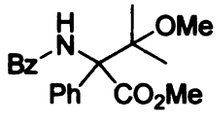
III-17

Dimethyl-2-(benzamido)-2-(tetrahydro-3-methylfuran-2-yl)malonate (III-17): Using the general procedure, a solution of 2-phenyl-4-carbmethoxy-5(4H)-oxazolone (0.05 g, 0.23 mmol) and 2,3-dihydro-4-methylfuran (0.058 g, 0.68 mmol) in 20 mL of anhydrous CH_2Cl_2 was heated to reflux for 24 hours. The resulting ene adduct was stirred in 20 mL MeOH overnight yielding 0.06 g of malonate **III-17** (81 % yield) as a white solid after silica gel chromatography (40% ethyl acetate / 60% hexanes). ^{1}H NMR (300 MHz), $CDCl_3$: δ 1.19 (d, J = 7 Hz, 3H), 1.48-1.56 (m, 1H), 1.80-1.92 (m, 1H), 2.70-2.80 (m, 1H), 3.72-3.84 (m, 1H), 3.77 (s, 3H), 3.82-3.88 (m, 1H), 3.84 (s, 3H), 3.41 (d, J = 5 Hz, 1H), 7.37 (bs, 1H), 7.41-7.52 (m, 3H), 7.80-8.83 (m, 2H); ^{13}C NMR + **DEPT** (75 MHz) $CDCl_3$: 19.77 (-CH3), 34.65 (-CH2), 34.77 (-CH), 52.91 (-CO2CH3), 53.83 (-CO2CH3), 68.02 (-CH2), 68.94 (quaternary C), 88.13 (-CH), 127.18 (aromatic CH), 128.68 (aromatic CH), 132.06 (aromatic CH), 133.28 (aromatic quaternary C), 166.50, 168.10; IR (cm^{-1}): 3414, 2955, 1745, 1672; HRMS (FAB): *m/z* calcd for $C_{17}H_{22}NO_6$ [M + H], 336.1449; found, 336.1447.



III-19

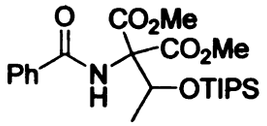
Methyl-4,5-dihydro-4-(2-methoxypropan-2-yl)-5-oxo-2-phenyloxazole-4-carboxylate (III-19): A solution of 2-phenyl-4-carbmethoxy-5(4H)-oxazolone (0.2 g, 0.91 mmol) and 2-methoxy propene (0.09 g, 1.19 mmol) in 20 mL of anhydrous CH_2Cl_2 was stirred at room temperature for 30 min. The resulting ene adduct **III-19** was characterized by NMR. All attempts at ring opening the oxazolone with methanol were unsuccessful due to the reversibility of this reaction. According to the NMR spectra the initial ene reaction resulted in a yield of greater than 95%. ^{1}H NMR (300 MHz), $CDCl_3$: δ 1.52 (s, 3H), 1.55 (s, 3H), 3.12 (s, 3H), 3.76 (s, 3H), 7.40 (m, 3H), 7.99 (m, 2H); ^{13}C NMR (75 MHz) $CDCl_3$: 18.66, 20.39, 49.59, 53.22, 79.81, 82.57, 125.49, 128.30, 128.68, 133.00, 163.13, 165.01, 172.57; IR (cm^{-1}): 2953, 1825, 1755, 1651, 1066.



III-20

methyl 2-benzamido-3-methoxy-3-methyl-2-phenylbutanoate (III-20): A solution of 2,4-diphenyl-5(4H)-oxazolone **II-2** (82 mg, 0.39 mmol) in 20 mL of anhydrous dichloromethane was treated with 2-methoxypropene (36.8 mg, 0.51 mmol) at room temperature for 48 hours. The solution was then treated with NaOMe (1mL of 0.5M) and stirred for three additional hours. The solution was

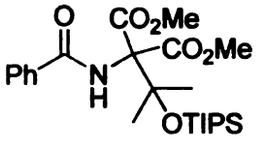
then washed with 2M HCl (1x20 mL), dried over magnesium sulfate and concentrated *in vacuo*. The resulting crude residue was purified via column chromatography (30% ethyl acetate/70% hexanes) to afford 101 mg (76% yield) of the title compound as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.16 (s, 3H), 1.37 (s, 3H), 3.27 (s, 3H), 3.76 (s, 3H), 7.26-7.32 (m, 3H), 7.47-7.50 (m, 2H), 7.53-7.56 (m, 1H), 7.59 (bs, 1H), 7.86-7.90 (m, 4H); ^{13}C NMR + DEPT (125 MHz, $CDCl_3$): δ 20.45 (-CH3), 20.64 (-CH3), 50.10 (-CH3), 52.40 (-CH3), 71.27 (quaternary –C), 80.09 (quaternary –C), 127.13 (aromatic –CH), 127.28, (aromatic –CH), 128.22 (aromatic –CH), 128.32 (aromatic –CH), 128.54 (aromatic –CH), 131.48 (aromatic –CH), 135.07 (quaternary aromatic –C), 136.76 (quaternary aromatic –C), 167.29, 170.61.



III-26

Dimethyl-2-benzamido-2-(1-(triisopropylsilyloxy)ethyl)malonate (III-26): A solution of 2-phenyl-4-carbmethoxy-5(4H)-oxazolone **III-5** (0.1 g, 0.46 mmol), triisopropyl(vinyloxy)silane **III-21** (0.12 g, 0.6 mmol) and 20 mL of anhydrous CH_2Cl_2 was stirred under reflux in a flame dried flask for 36 hours. Then 1 equivalent of NaOMe solution was added to the resulting ene adduct. The solution was stirred for 20 minutes and then washed once with brine. The solution was dried over magnesium sulfate and the solvent was removed under vacuum. The resulting crude oil was purified via column chromatography (25% EtOAc/3% Et_3N/72% hexanes) yielding 172 mg of the title compound **III-26** (83%

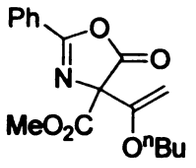
yield) as a clear oil. ^{1}H NMR (500 MHz), $CDCl_3$: δ 0.97-1.06 (m, 21H), 1.43 (d, J = 6.5 Hz), 3.74 (s, 3H), 3.79 (s, 3H), 4.93 (q, J = 6.5 Hz, 1H), 7.33 (bs, 1H), 7.41-7.45 (m, 2H), 7.49-7.52 (m, 1H), 7.79-7.81 (m, 2H); ^{13}C NMR + **DEPT** (75 MHz) $CDCl_3$: 12.91 (-CH), 17.97 (-CH3), 18.04 (-CH3), 19.57 (-CH3), 52.69 (-CO2CH3), 53.34 (-CO2CH3), 70.57 (quaternary C), 72.86 (-CH), 127.06 (aromatic CH), 128.62 (aromatic CH), 131.84 (aromatic CH), 133.60 (aromatic quaternary C), 166.35 (-CO2CH3), 166.41 (-CO2CH3), 168.16 (-CONH); IR (neat): 3426 cm^{-1}, 2947 cm^{-1}, 1748 cm^{-1}, 1676 cm^{-1}; LRMS(EI): *m/z* calcd for $C_{23}H_{37}NO_6Si$ 451.6; found, 452.3.



III-27

Dimethyl-2-benzamido-2-(2-(triisopropylsilyloxy)propan-2-yl)malonate (III-27): A solution of 2-phenyl-4-carbmethoxy-5(4H)-oxazolone (0.1 g, 0.46 mmol), Triisopropyl(prop-1-en-2-yloxy)silane (0.13 g, 0.6 mmol) and 20 mL of anhydrous CH_2Cl_2 was stirred at room temperature in a flame dried flask for 24 hours. Then 1 equivalent of NaOMe solution was added to the resulting ene adduct. The solution was stirred for 20 minutes and then washed once with brine. The solution was dried over magnesium sulfate and the solvent was removed under vacuum. The resulting crude oil was purified via column chromatography (20% EtOAc/3% Et_3N/77% hexanes) yielding 102 mg of the title compound **III-27** (48% yield) as a clear oil. ^{1}H NMR (500 MHz), CDCl3: δ 1.03-1.1 (m, 21H), 1.66 (s, 6H), 3.79 (s, 6H), 7.44-7.47 (m, 3H), 7.51-7.52 (m, 1H), 7.84-7.86 (m, 2H); ^{13}C

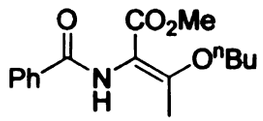
NMR + DEPT (75 MHz) $CDCl_3$: 13.23 (-CH), 18.17 (-CH3), 27.11 (-CH3), 52.78 (-CO2CH3), 72.64 (quaternary C), 79.47 (quaternary C), 127.06 (aromatic CH), 128.53 (aromatic CH), 131.74 (aromatic CH), 133.69 (quaternary aromatic C), 166.26, 167.07; IR (Neat): 3431 cm^{-1}, 2949 cm^{-1}, 1743 cm^{-1}, 1678 cm^{-1}. HRMS (FAB): *m/z* calcd for $C_{24}H_{40}NO_6Si$ [M+H], 466.2625; found, 466.2632.



III-30

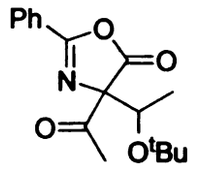
Methyl-4-(1-butoxyvinyl)-5-oxo-2-phenyl-4,5-dihydrooxazole-4-carboxylate (III-30): A solution of 2-phenyl-4-carbmethoxy-5(4H)-oxazolone (0.1 g, 0.46 mmol) in 20 mL of dichloromethane was treated with 1-(ethynyloxy)butane (0.14 g, 1.38 mmol) at room temperature under nitrogen atmosphere for 23 hours. The solution was then washed with saturated $NaHCO_3$ solution (2 x 20 mL) and brine (1 x 20 mL) and dried over magnesium sulfate. The solution was concentrated *in vacuo* resulting in 0.13 g (86% yield) of the title compound as a yellowish oil. ^1H NMR (500 MHz), CDCl3: δ 0.88 (t, J = 7.5 Hz, 3H), 1.37 (s, J = 7.5 Hz, 2H), 1.66 (p, J = 7 Hz, 2H), 3.75-3.81 (m, 2H), 3.82 (s, 3H), 4.26 (d, J = 3 Hz, 1H), 4.45 (d, J = 3 Hz, 1H), 7.46-7.50 (m, 2H), 7.57-7.61 (m, 1H), 8.05-8.07 (m, 2H); ^{13}C NMR + DEPT (125 MHz) $CDCl_3$: 13.61 (-CH3), 19.05 (-CH2), 30.42 (-CH2), 53.77 (-CO2CH3), 68.49 (-CH2), 78.03 (quaternary C), 85.57 (-CH2), 125.01 (aromatic quaternary C), 128.42 (aromatic CH), 128.80 (aromatic CH), 133.49 (aromatic CH), 154.48, 164.16, 164.63, 170.03; IR(neat): 2957 cm^{-1}, 1826 cm^{-1},

1747 cm^{-1}, 1672 cm^{-1}. HRMS (FAB): *m/z* calcd for $C_{17}H_{20}NO_5$ [M+H], 318.1341; found, 318.1350.



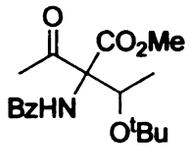
III-31

(E)-methyl-2-benzamido-3-butoxybut-2-enoate (III-31): A solution of methyl-4-(1-butoxyvinyl)-5-oxo-2-phenyl-4,5-dihydrooxazole-4-carboxylate **III-30** (125 mg, 0.39 mmol) in 20 mL of dichloromethane with NaOMe (0.8 mL of 0.5M, 0.39 mmol). The solution was stirred for 10 minutes at room temperature before being washed twice with brine (2 x 20 mL) and dried over magnesium sulfate. The solution was then concentrated *in vacuo* and purified via column chromatography (1:1 ethyl acetate/hexanes) resulting in 100 mg (88% yield) of the title compound as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) (TMS): δ 0.84 (t, J = 7.5 Hz, 3H), 1.32 (sextet, J = 7 Hz, 2H), 1.58 (p, J = 7 Hz, 2H), 3.71 (s, 3H), 3.94 (t, J = 7 Hz, 2H), 7.18 (bs, 1H), 7.39-7.43 (m, 2H), 7.46-7.49 (m, 1H), 7.79-7.81 (m, 2H); ^{13}C NMR + **DEPT** (125 MHz, $CDCl_3$): δ 13.62 (-CH3), 14.31 (-CH3), 18.92 (-CH2), 31.51 (-CH2), 51.64 (-CH3), 67.79 (-CH2), 127.29 (aromatic –CH), 128.55 (aromatic –CH) 131.47 (aromatic –CH), 134.43 (quaternary aromatic –C), 161.35, 166.00.



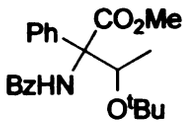
III-33a

4-acetyl-4-(1-tert-butoxyethyl)-2-phenyloxazol-5(4H)-one (III-33a): A solution of 2-phenyl-4-α-hydroxyethylidene-5-oxazolone (0.1 g, 0.49 mmol) and tert-butyl vinyl ether (0.06 g, 0.64 mmol) in 20 mL of anhydrous CH_2Cl_2 was stirred at room temperature for 24 hrs. The solution was washed twice with 20 mL of saturated $NaHCO_3$ solution, once with brine and dried using magnesium sulfate. The solvent was removed under vacuum yielding 0.15 g of oxazolone **III-33a** (1 : 1.2) mixture of diastereomers) in a 98% yield as an orange oil. No further attempt was made to separate the two diastereomers. Diastereomer 1: ^{1}H NMR (300 MHz), $CDCl_3$: δ 1.10 (s, 9H), 1.24 (d, 3H, J = 6 Hz), 2.36 (s, 3H), 4.40 (q, 1H, J = 6 Hz), 7.46-7.52 (m, 2H), 7.55-7.62 (m, 1H), 8.02-8.09 (m, 2H); ^{13}C NMR + **DEPT** (125 MHz) $CDCl_3$: 17.49 (-CH3), 28.46 (-CH3), 28.63 (-CH3), 71.41 (-CH), 75.34 (quaternary C), 85.82 (quaternary C), 125.44 (aromatic quaternary C), 128.08 (aromatic CH), 128.78 (aromatic CH), 132.99 (aromatic CH), 162.31, 171.72, 198.84; Diastereomer 2: ^{1}H NMR (300 MHz), $CDCl_3$: δ 1.11 (s, 9H), 1.29 (d, 3H, J = 6 Hz), 2.25 (s, 3H), 4.57 (q, 1H, J = 6 Hz), 7.46-7.52 (m, 2H), 7.55-7.62 (m, 1H), 8.02-8.09 (m, 2H); ^{13}C NMR + **DEPT** (125 MHz) $CDCl_3$: 18.79 (-CH3), 28.49 (-CH3), 28.53 (-CH3), 71.70 (-CH), 74.94 (quaternary C), 87.47 (quaternary C), 125.57 (aromatic quaternary C), 128.19 (aromatic CH), 128.70 (aromatic CH), 132.94 (aromatic CH), 162.65, 172.59, 199.32; IR (cm^{-1}): 2976, 1836, 1723, 1653.



III-33b

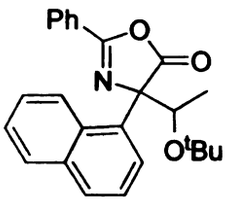
Methyl-3-tert-butoxy-2-acetyl-2-(benzamido)butanoate (III-33b): The resulting ene adduct was stirred in 20 mL MeOH overnight, after which 0.07 g of ester **III-33b** (1 : 1.2 mixture of diastereomers) was obtained (45% yield) as a clear oil upon being concentrated *in vacou* and purification via silica gel column chromatography (20% ethyl acetate / hexanes). No further attempt was made to separate the two diastereomers. ^{1}H NMR (300 MHz), $CDCl_3$: δ 1.11 (s, 9H), 1.17 (s, 9H), 1.26 (d, J = 6 Hz, 3H), 1.30 (d, J = 6 Hz, 3H), 2.12 (s, 3H), 2.26 (s, 3H), 3.75 (s, 3H), 3.87 (s, 3H), 4.65 (q, J = 6 Hz, 1H), 4.72 (q, J = 6 Hz, 1H), 7.37 (bs, 1H), 7.42-7.54 (m, 3H), 7.81-7.87 (m, 2H); ^{13}C NMR + DEPT (75 MHz) $CDCl_3$: 18.99 (-CH3), 19.20 (-CH3), 26.06 (-CH3), 28.85 (-CH3), 29.01 (-CH3), 52.71 (-CO2CH3), 53.27 (-CO2CH3), 70.82 (-CH), 71.37 (-CH), 74.28 (quaternary C), 74.55 (quaternary C), 74.60 (quaternary C), 76.35 (quaternary C), 127.16 (aromatic CH), 127.20 (aromatic CH), 128.59 (aromatic CH), 128.67 (aromatic CH), 131.83 (aromatic CH), 132.02 (aromatic CH), 133.35 (aromatic quaternary C), 133.60 (aromatic quaternary C), 166.42, 166.53, 167.80, 168.51, 197.09, 198.92; IR (cm^{-1}): 3420, 2978, 1749, 1726, 1672; HRMS (FAB): *m/z* calcd for $C_{18}H_{26}NO_5$ [M + H], 336.1810; found, 336.1811.



III-36

Methyl-3-tert-butoxy-2-phenyl-2-(benzamido)butanoate (III-36): Using the general procedure, a solution of 2-phenyl-4-phenyl-5(4H)-oxazolone (0.1 g, 0.42 mmol) and tert-butyl vinyl ether (0.13 g, 1.26 mmol) in 20 mL of anhydrous toluene was stirred at reflux for 8 hrs. The resulting ene adduct was reacted with NaOMe (0.42 mmol) in 20 mL MeOH for one hour. The solvent was then removed under vacuum and the material was partitioned between 30 mL of CH_2Cl_2 and 30 mL of water. The organic layer was dried using magnesium sulfate and the solvent was removed under vacuum yielding 0.14 g of ester **III-36** (3 : 1 mixture of diastereomers) in a 95% yield as a yellow solid. No further attempt was made to separate the two diastereomers. Diastereomer 1: ^{1}H NMR (500 MHz), $CDCl_3$: δ 0.96 (s, 9H), 1.29 (d, 3H, J = 6 Hz), 3.75 (s, 3H), 4.36 (q, 1H, J = 6 Hz), 7.22-7.32 (m, 4H), 7.44-7.48 (m, 2H), 7.50-7.54 (m, 1H), 7.58-7.62 (m, 2H), 7.84-7.86 (m, 2H); ^{13}C NMR + **DEPT** (125 MHz) $CDCl_3$: 19.80 (-CH3), 28.43 (-CH3), 52.48 (-CO2CH3), 69.59 (quaternary C), 73.34 (-CH), 74.80 (quaternary C), 127.08 (aromatic CH), 127.30 (aromatic CH), 127.60 (aromatic CH), 127.65 (aromatic CH), 128.60 (aromatic CH), 131.58 (aromatic CH), 134.76 (aromatic quaternary C), 138.12 (aromatic quaternary C), 166.77, 171.12; Diastereomer 2: ^{1}H NMR (500 MHz), $CDCl_3$: 1.03 (d, 3H, J = 6 Hz), 1.19 (s, 9H), 3.72 (s, 3H), 4.51 (q, 1H, J = 6), 7.28 (m, 4H), 7.44-7.48 (m, 2H), 7.50-7.54 (m, 1H), 7.58-7.62 (m, 2H), 7.84-7.86 (m, 2H); ^{13}C NMR + **DEPT** (125 MHz)

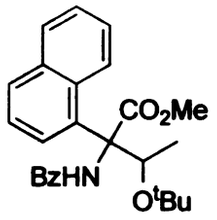
$CDCl_3$: 19.06 (-CH3), 28.87 (-CH3), 52.66 (-CO2CH3), 70.59 (quaternary C), 72.66 (-CH), 74.83 (quaternary C), 127.09 (aromatic CH), 127.27 (aromatic CH), 127.41 (aromatic CH), 127.83 (aromatic CH), 128.60 (aromatic CH), 131.50 (aromatic CH), 135.14 (quaternary aromatic C), 136.21 (quaternary aromatic C), 167.55, 172.17; IR (cm^{-1}): 3416, 2976, 1736, 1670; LRMS (EI) (m/z): 369.



III-37a

4-(1-tert-butoxyethyl)-4-(naphthalen-1-yl)-2-phenyloxazol-5(4H)-one (III-37a): A solution of 2-phenyl-4-naphthyl-5(4H)-oxazolone (0.18 g, 0.6 mmol) and tert-butyl vinyl ether (0.19 g, 1.88 mmol) in 30 mL of anhydrous toluene was stirred at reflux for 15 hrs. The solvent was removed under vacuum yielding 0.24 g of oxazolone **III-37a** (2 : 1) mixture of diastereomers) in a 99% yield as a yellow solid. No further attempt was made to separate the two diastereomers. ^1H NMR (500 MHz), $CDCl_3$: δ 1.03 (d, 3H, J = 7 Hz), 1.12, (d, 3H, J = 7 Hz), 1.14 (s, 9H), 1.16 (s, 9H), 4.93 (q, 1H, J = 7 Hz), 4.99 (q, 1H, J = 7 Hz), 7.15-7.25 (m, 1H), 7.16-7.26 (m, 1H), 7.41-7.54 (m, 4H), 7.42-7.55 (m, 4H), 7.56-7.63 (m, 1H), 7.57-7.63 (m, 1H), 7.81 (d, 1H, J = 8 Hz), 7.82 (d, 1H, J = 8 Hz), 8.10 (d, 2H, J = 7 Hz), 7.92 (d, 2H, J = 7 Hz), 8.05-8.07 (m, 1H), 8.05-8.08 (m, 1H), 8.10 (d, 1H, J = 7 Hz), 8.15 (d, 1H, J = 7 Hz), 9.24 (d, 1H, J = 9 Hz), 9.29 (d, 1H, J = 9 Hz); ^{13}C NMR (125 MHz) $CDCl_3$: 17.18, 18.47, 28.71, 71.63, 72.91, 74.70, 74.99, 81.38, 81.96, 124.57, 124.95, 125.00, 125.26, 125.43, 125.64, 125.76, 125.79, 126.27,

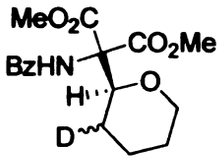
126.34, 126.71, 127.07, 127.21, 127.92, 128.14, 128.18, 128.65, 128.98, 129.07, 129.47, 129.76, 130.79, 131.41, 132.27, 132.38, 132.44, 134.84, 134.97, 159.58, 160.11, 176.18, 178.16; IR (cm^{-1}): 3150, 2976, 1810, 1692; LRMS (EI) (m/z): 388.



III-37b

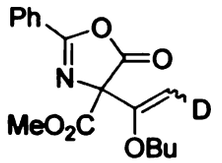
Methyl-3-tert-butoxy-2-(naphthalene-1-yl)-2-(benzamido)butanoate (III-37b): To flame dried round bottom flask was added oxazolone **III-37b** (0.19 g, 0.5 mmol) in 20 mL of MeOH. The solution was treated with NaOMe solution (1M in MeOH, 2 mmol) for 36 hrs at room temperature. The solvent was then removed under vacuum and the material was partitioned between 30 mL of CH_2Cl_2 and 30 mL of water. The organic layer was dried using magnesium sulfate and the solvent was removed under vacuum yielding 0.11 g of ester **III-37b** (2 : 1 mixture of diastereomers) in a 52% yield as a yellow solid. No further attempt was made to separate the two diastereomers. ^1H NMR (500 MHz), $CDCl_3$: δ 1.05 (s, 9H), 1.23 (s, 9H), 1.55 (d, 2H, J = 6 Hz), 1.62 (d, 2H, J = 6 Hz), 3.57 (s, 3H), 3.67 (s, 3H), 5.06 (q, 1H, J = 6 Hz), 5.31 (q, 1H, J = 6 Hz), 7.29-7.51(m, 12H), 7.57 (d, 1H, J = 7 Hz), 7.65 (d, 1H, J = 6 Hz), 7.74-7.82 (m, 8H), 7.85-7.93 (m, 2H), 8.01 (2, 1H, J = 9 Hz), 8.26 (d, 1H, J = 9 Hz); ^{13}C NMR + **DEPT** (125 MHz) $CDCl_3$: 20.38 (-CH3), 21.51 (-CH3), 28.77 (-CH3), 29.15 (-CH3) 52.73 (-CO2CH3), 52.99 (-CO2CH3), 69.05, 69.35, 71.06, 72.87, 74.40, 74.66, 123.18, 123.36, 124.16,

124.72, 124.85, 125.20, 125.41, 126.03, 126.22, 126.99, 127.03, 127.85, 128.44, 128.97, 129.29, 129.52, 131.16, 131.30, 131.46, 131.63, 132.59, 132.75, 133.90, 134.30, 135.11, 135.30, IR (cm^{-1}): 3414, 2976, 1736, 1672; LRMS (EI) (m/z): 420.



III-39

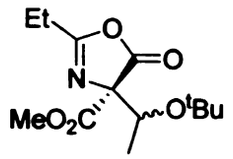
Dimethyl-2-(benzamido)-2-(3-deuterotetrahydropyran-2-yl)malonate (III-39): Using the general procedure, a solution of 2-phenyl-4-carbmethoxy-5(4H)-oxazolone (0.02 g, 0.09 mmol) and a large excess of 5-deutero-3,4-dihydropyran (50% deuterium incorporated) in 20 mL of anhydrous CH_2Cl_2 was stirred at room temperature for 18 hr. The resulting ene adduct was stirred in 20 mL MeOH overnight yielding 0.03 g of malonate **III-39** (99% yield) as a clear colorless oil. ^1H NMR (300 MHz), $CDCl_3$: δ 1.29-1.59 (m, 4H), 1.81-1.84 (m, 0.65H), 2.13 (d, J = 15, 0.65H), 3.43 (td, J = 7 Hz, J = 2 Hz, 1H), 3.73 (s, 3H), 3.82 (s, 3H), 3.91-3.94 (m, 1H), 4.22-4.25 (m, 1H), 7.39 (bs, 1H), 7.42-7.45 (m, 2H), 7.50-7.52 (m, 1H), 7.83-7.85 (m, 2H); ^{13}C NMR + **DEPT** (75 MHz) $CDCl_3$: 22.92 (-CH2), 25.72 (-CH2), 26.82 (-CH2), 52.84 (-CO2CH3), 53.69 (-CO2CH3), 69.20 (quaternary C), 69.45 (-CH2), 80.99 (-CH), 127.26 (aromatic CH), 128.57 (aromatic CH), 131.91 (aromatic CH), 133.41 (aromatic quaternary C), 166.03, 166.44, 168.19; IR (cm^{-1}): 3422, 2953, 1745, 1674; HRMS (FAB): *m/z* calcd for $C_{17}H_{21}NO_6D$ [M+H], 337.1510; found, 337.1510.



1:1 Mixture of Diastereomers

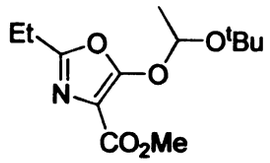
III-41

Methyl-4-(1-butoxy-2-deuterovinyl)-4,5-dihydro-5-oxo-2-phenyloxazole-4-carboxylate (III-41): A solution of 2-phenyl-4-carbmethoxy-5(4H)-oxazolone (0.1 g, 0.46 mmol) in 20 mL of dichloromethane was treated with 2-deutero-1-butoxyethyne **III-40** (67.9 mg, 0.69 mmol) at room temperature under nitrogen atmosphere for 24 hours. The solution was then washed with saturated $NaHCO_3$ solution (2 x 20 mL) and brine (1 x 20 mL) and dried over sodium sulfate. The solution was concentrated *in vacuo* resulting in 0.14 g (96% yield) of the title compound as a yellowish solid as a 1:1 mixture of diastereomers. ^1H NMR (500 MHz), CDCl3: δ 0.88 (t, J = 7.5 Hz, 3H), 1.37 (sextet, J = 7.5 Hz, 2H), 1.66 (p, J = 7 Hz, 2H), 3.75-3.81 (m, 2H), 3.82 (s, 3H), 4.25-4.27 (m, 0.61H), 4.44-4.46 (m, 0.61H), 7.46-7.50 (m, 2H), 7.57-7.61 (m, 1H), 8.05-8.07 (m, 2H); ^{13}C NMR + **DEPT** (125 MHz) $CDCl_3$: δ 13.61 (-CH3), 19.05 (-CH2), 30.42 (-CH2), 53.77 (-CO2CH3), 68.49 (-CH2), 85.57 (t, J = 25.3 Hz, -CHD), 125.01 (aromatic quaternary C), 128.42 (aromatic CH), 128.80 (aromatic CH), 133.49 (aromatic CH), 154.48 (quaternary –C), 164.16 (quaternary –C), 164.63 (quaternary –C), 170.03 (quaternary –C); IR(neat): 2957 cm^{-1}, 1826 cm^{-1}, 1747 cm^{-1}, 1672 cm^{-1}. HRMS (FAB): *m/z* calcd for $C_{17}H_{19}NO_5D$ [M + H], 319.1406; found, 319.1404.



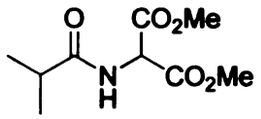
III-45

Methyl-4-(1-tert-butoxyethyl)-2-ethyl-5-oxo-4,5-dihydrooxazole-4-carboxylate (III-45): A solution of 2-ethyl-4-carbmethoxy-5(4H)-oxazolone (50 mg, 0.29 mmol) in 20 mL of dichloromethane was treated with *tert*-butyl vinyl ether **III-6** (37.8 mg, 0.38 mmol) at room temperature. The solution was stirred overnight and then concentrated *in vacuo*. The crude reaction mixture revealed a 1:1 mixture of **III-45** and **III-46**. The crude reaction mixture was allowed to sit at room temperature in $CDCl_3$. Over the course of 5 days the slow conversion of **III-46** to the title compound **III-45** was observed along with some degradation of the enol ether component of the reaction (loss of 2-butene and acetaldehyde). Due to the instability of **III-45** towards moisture, only partial characterization of the compound could be made. Furthermore, the hydroscopic nature of the title compound did not allow for an accurate yield to be calculated. Compound **III-45** was observed as a 1:1 mixture of diastereomers and no attempt was made separate the two diastereomers. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.03 (s, 9H), 1.04 (s, 9H), 1.08-1.26 (m, 12H), 2.41-2.52 (m, 4H), 3.69 (s, 3H), 3.71 (s, 3H), 4.42 (q, J = 6.5 Hz, 1H), 4.83 (q, J = 6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 8.85, 9.41, 16.92, 18.64, 22.32, 22.53, 28.43, 28.54, 53.07, 53.20, 69.66, 70.06, 74.68, 74.76, 79.54, 81.04, 164.99, 165.46, 168.40, 168.42, 171.87, 173.35.



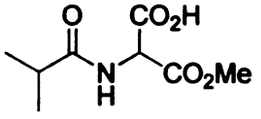
III-46

Methyl-5-(1-*tert*-butoxyethoxy)-2-ethyloxazole-4-carboxylate (III-46): The title compound is an observed intermediate when 2-ethyl-4-carbmethoxy-5(4H)-oxazolone is treated with *tert*-butyl vinyl ether in anhydrous CH_2Cl_2. Since the compound is not produced in pure form during the reaction of 2-ethyl-4-carbmethoxy-5(4H)-oxazolone with *tert*-butyl vinyl ether, the following method was utilized in order to produce the compound in a more pure form for the purpose of characterization: A solution of 2-(methoxycarbonyl)-2-(propionamido)acetic acid (50 mg, 0.26 mmol), *tert*-butyl vinyl ether (39.1 mg, 0.39) and 10 mL of anhydrous CH_2Cl_2 was treated with 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (55.6 mg, 0.29 mmol). The solution was stirred for 20 minutes and then washed once with 10 mL of water. The solution was then dried over sodium sulfate and concentrated *in vacuo* to yield 36 mg (51% yield) of the title compound as a white solid. The compound is fairly unstable so only partial characterization was able to be obtained. ^{1}H NMR (500 MHz) ($CDCl_3$): δ 1.19 (s, 9H), 1.30 (t, J = 7.5 Hz, 3H), 1.54 (d, J = 6 Hz, 3H), 2.96-3.11 (m, 2H), 3.79 (s, 3H), 7.06 (q, J = 6 Hz, 1H); ^{13}C NMR + DEPT (125 MHz) ($CDCl_3$) δ: 9.92 (-CH3), 21.65 (-CH2), 23.45 (-CH3), 27.60 (-CH3), 50.99 (-CO2CH3), 77.70 (quaternary C), 80.82 (-CH), 154.31 (quaternary C), 160.62 (quaternary C), 162.43 (quaternary C).



III-47

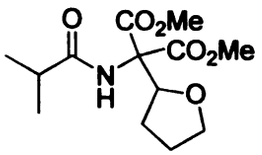
Dimethyl-2-(isobutyramido)malonate (III-47): A solution of dimethylaminomalonate hydrochloride (3.0 g, 16.3 mmol), triethylamine (4.96 g, 49.0 mmol) and anhydrous CH_2Cl_2 (40 ml) was treated dropwise with isobutyrl chloride (1.74 g, 16.3 mmol) in a flame dried round bottom flask. The solution was stirred at room temperature under nitrogen atmosphere for 5 hours. The solution was then washed exhaustively with 2M HCl solution and dried over magnesium sulfate. The solvent was removed under vacuum and the resulting crude solid was recrystallized using EtOAc/Hexanes to yield 2.85 g (81% yield) of the title compound as a white crystalline solid. ^{1}H NMR (300 MHz) ($CDCl_3$): δ 1.14 (d, J = 6.9 Hz, 6H), 2.46 (septet, J = 6.9 Hz, 1H), 3.78 (s, 3H), 5.16, (d, J = 7.2 Hz, 1H), 6.45 (d, J = 7.2 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$): 19.20, 35.02, 53.35, 55.93, 166.85, 176.63; IR (neat): 3296 cm^{-1}, 2972 cm^{-1}, 1755 cm^{-1}, 1647 cm^{-1}; LRMS(EI): *m/z* calcd for $C_9H_{15}NO_5$ 217.2; found, 217.1.



III-48

2-(methoxycarbonyl)-2-(isobutyramido)acetic acid (III-48): A solution of dimethyl-2-(isobutyramido)malonate (2.0 g, 9.2 mmol) and 50 ml of methanol was added to a round bottom flask and cooled to 0 °C. A solution consisting of

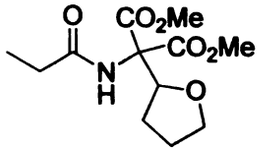
$LiOH \cdot H_2O$ (0.39 g, 9.2 mmol) in 50 ml of H_2O was then added to the flask dropwise over the course of approximately 30 minutes. The solution was stirred over night while being allowed to warm to room temperature. The following morning the methanol was removed under vacuum and the resulting aqueous solution was washed once with diethyl ether. The solution was then acidified using 2M HCl and washed three more times with diethyl ether. The combined ether layers were dried over magnesium sulfate and the solvent was removed under vacuum. The resulting crude solid was recrystallized in diethyl ether to yield the title compound as a white crystalline solid (0.92 g, 49% yield). ^1H NMR (300 MHz) ($CDCl_3$): δ 0.97 (d, J = 6.9 Hz, 6H), 2.58 (septet, J = 6.9 Hz, 1H), 3.68 (s, 3H), 4.99 (d, J = 7.5 Hz, 1H), 8.51 (d, J = 7.5 Hz, 1H), 13.44 (bs, 1H); ^{13}C NMR (75 MHz) (DMSO): 19.32, 33.11, 52.57, 56.00, 167.70, 167.73, 176.51. HRMS (FAB): *m/z* calcd for $C_8H_{12}NO_5$ [M+H], 226.0691; found, 226.0675.



III-49

Dimethyl-2-(isobutyramido)-2-(tetrahydrofuran-2-yl)malonate (III-49): A solution of 2-(methoxycarbonyl)-2-(isobutyramido)acetic acid (0.1 g, 0.49 mmol), EDCI (0.1 g, 0.54 mmol), 2,3-dihydrofuran (0.05 g, 0.64 mmol) and anhydrous CH_2Cl_2 was stirred at room temperature under nitrogen atmosphere for 18 hours. The solution was then washed with brine twice and dried over magnesium sulfate. The solvent was removed under vacuum and replaced with 20 ml of

MeOH. After 48 hours of stirring at room temperature the solvent was removed to yield 0.13 g of the title compound (92% yield) as a clear oil. ^{1}H NMR (500 MHz), $CDCl_3$: δ 1.12 (d, J = 7 Hz, 3H), 1.13 (d, J = 7 Hz, 3H), 1.70-1.80 (m, 1H), 1.78-1.86 (m, 1H), 1.94-2.21 (m, 1H), 2.11-2.20 (m, 1H), 2.44 (septet, J = 7 Hz, 1H), 3.66-3.80 (m, 2H), 3.70 (s, 3H), 3.78 (s, 3H), 4.59 (t, J = 7.5 Hz, 1H), 6.64 (bs, 1H); ^{13}C NMR + DEPT (125 MHz) $CDCl_3$: 19.47 (-CH3), 19.70 (-CH3), 26.28 (-CH2), 27.44 (-CH2), 35.55 (-CH), 53.06 (-CO2CH3), 53.90 (-CO2CH3), 68.31 (quaternary C), 69.06 (-CH2), 81.58 (-CH), 166.73 (-CO2CH3), 168.37 (-CO2CH3), 176.64 (-CONH); IR (neat): 3378 cm^{-1}, 2916 cm^{-1}, 1741 cm^{-1}, 1674 cm^{-1}; LRMS(EI): *m/z* calcd for $C_{13}H_{21}NO_6$ 287.3; found, 288.1.



III-50

Dimethyl-2-(propionamido)-2-(tetrahydrofuran-2-yl)malonate (III-50): A solution of 2-(methoxycarbonyl)-2-(propionamido)acetic acid (0.1 g, 0.53 mmol), EDCI (0.1 g, 0.58 mmol), 2,3-dihydrofuran (0.05 g, 0.69 mmol) and anhydrous CH_2Cl_2 was stirred at room temperature under nitrogen atmosphere for 24 hours. The solution was then washed with brine and dried over magnesium sulfate. The solvent was removed under vacuum and replaced with 20 ml of MeOH. After 48 hours of stirring at room temperature the solvent was removed to yield 0.11 g of the title compound (77% yield) as a clear oil. ^{1}H NMR (500 MHz), $CDCl_3$: δ 1.13 (t, J = 7.5 Hz, 3H), 1.71-1.80 (m, 1H), 1.79-1.87 (m, 1H), 1.97-2.04 (m, 1H), 2.13-

2.20 (m, 1H) 2.26 (qd, J_1 = 7.5 Hz, J_2 = 2.5 Hz, 2H), 3.65-3.73 (m, 1H), 3.71 (s, 3H), 3.73-3.79 (m, 1H), 3.78 (s, 3H), 4.59 (t, J = 7.5 Hz, 1H), 6.62 (bs, 1H); ^{13}C **NMR + DEPT** (125 MHz) $CDCl_3$: 9.57 (-**C**H3), 25.98 (-**C**H2), 27.23 (-**C**H2), 29.34 (-**C**H2), 52.85 (-CO2**C**H3), 53.63 (-CO2**C**H3), 68.13 (quaternary **C**), 68.76 (-**C**H2), 81.26 (-**C**H), 166.47 (-**C**O2CH3), 168.00 (-**C**O2CH3), 173.20 (-**C**ONH); IR (Neat): 3376 cm^{-1}, 2955 cm^{-1}, 1745 cm^{-1}, 1682 cm^{-1}; LRMS(EI): *m/z* calcd for $C_{12}H_{19}NO_6$ 273.3; found, 273.7.

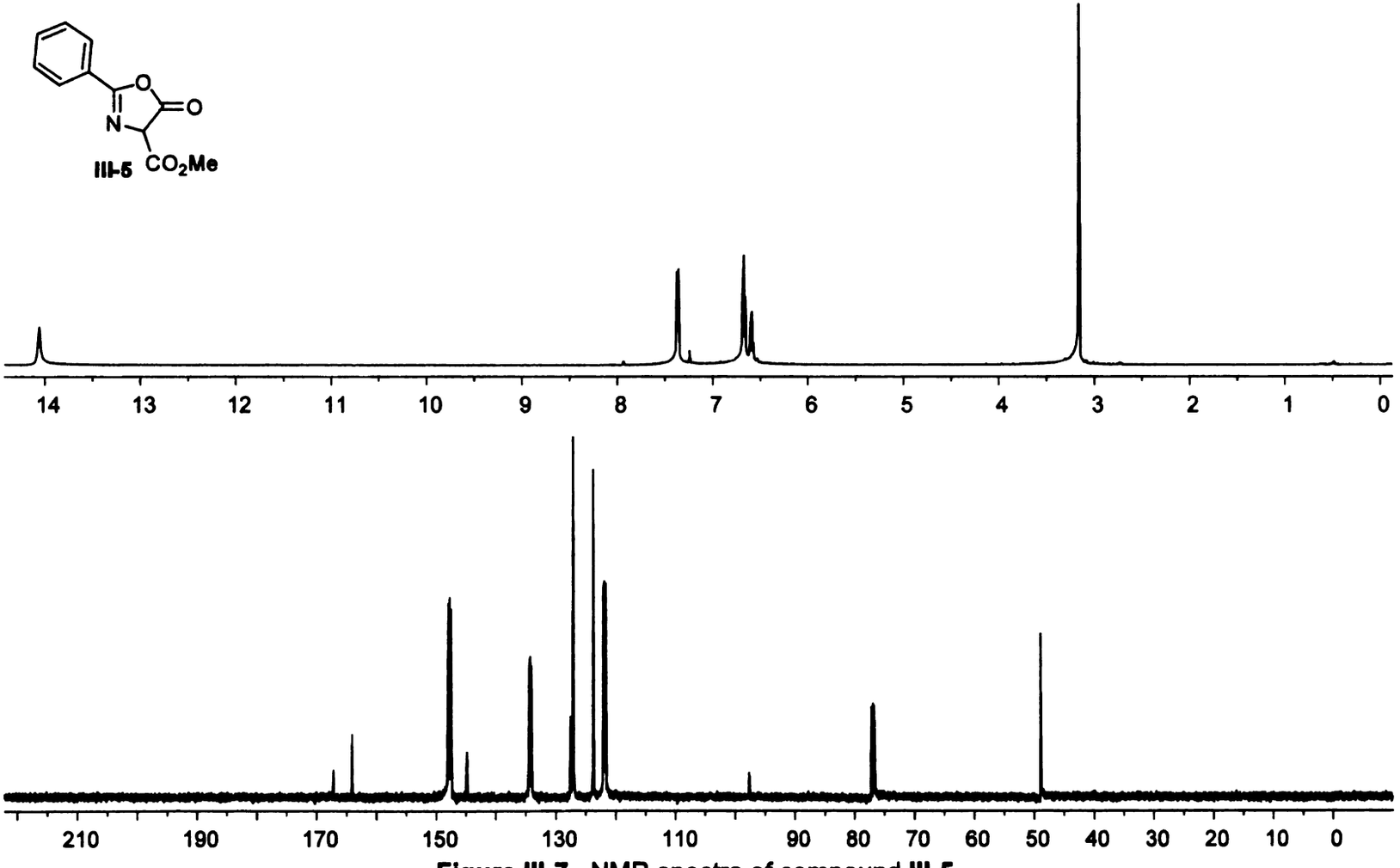


Figure III-7. NMR spectra of compound **III-5**.

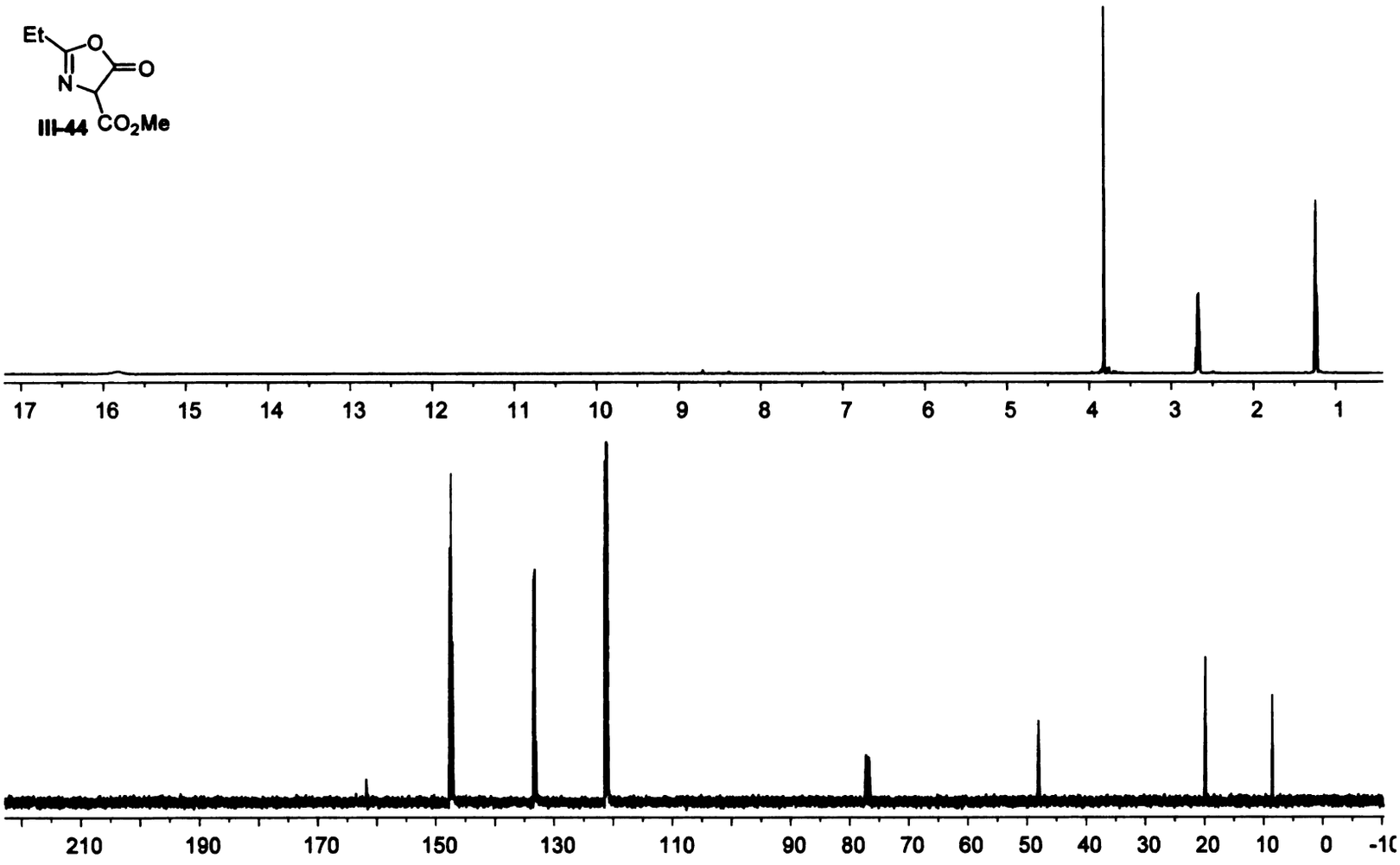


Figure III-8. NMR spectra of compound **III-44**.

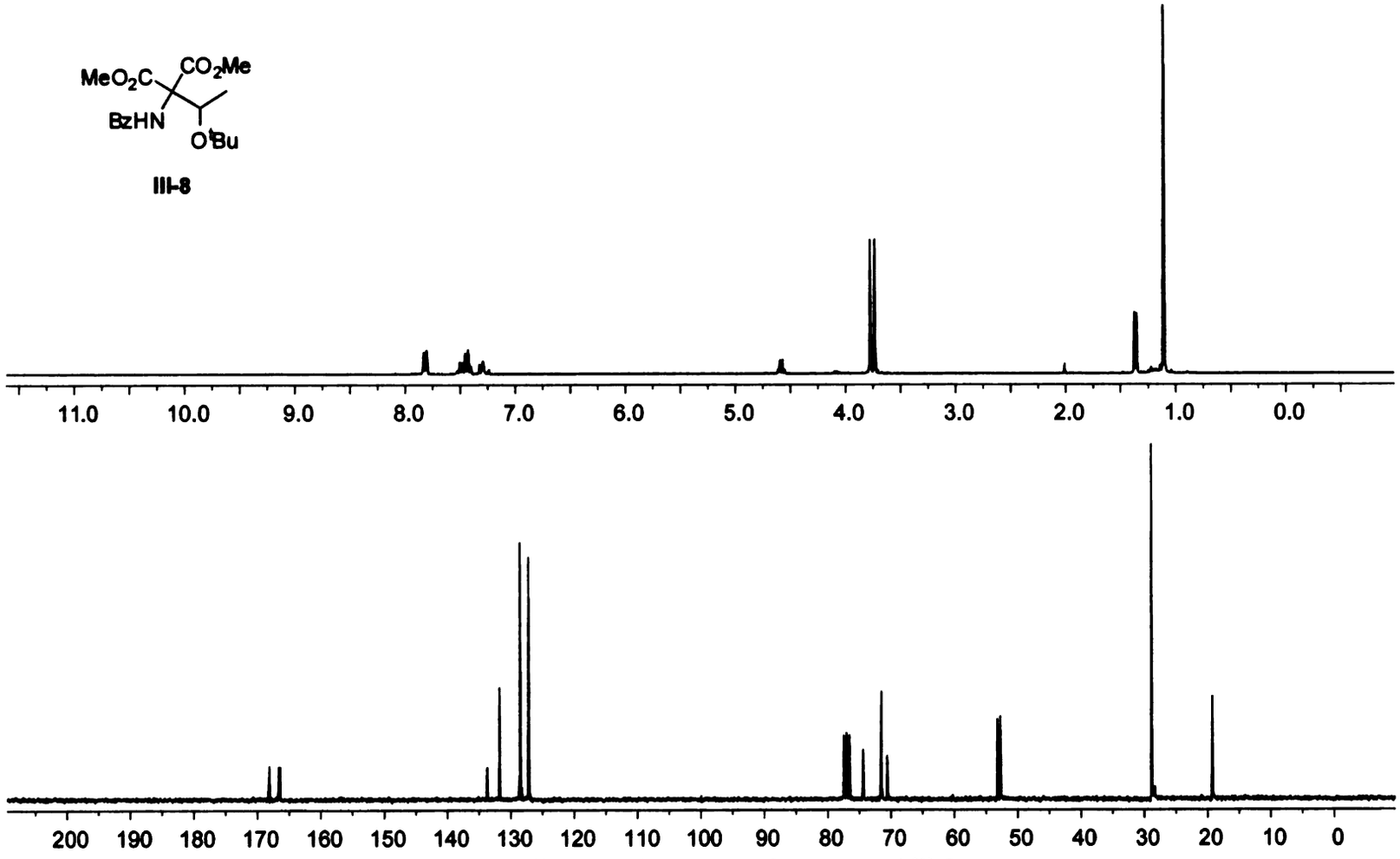


Figure III-9. NMR spectra of compound **III-8**.

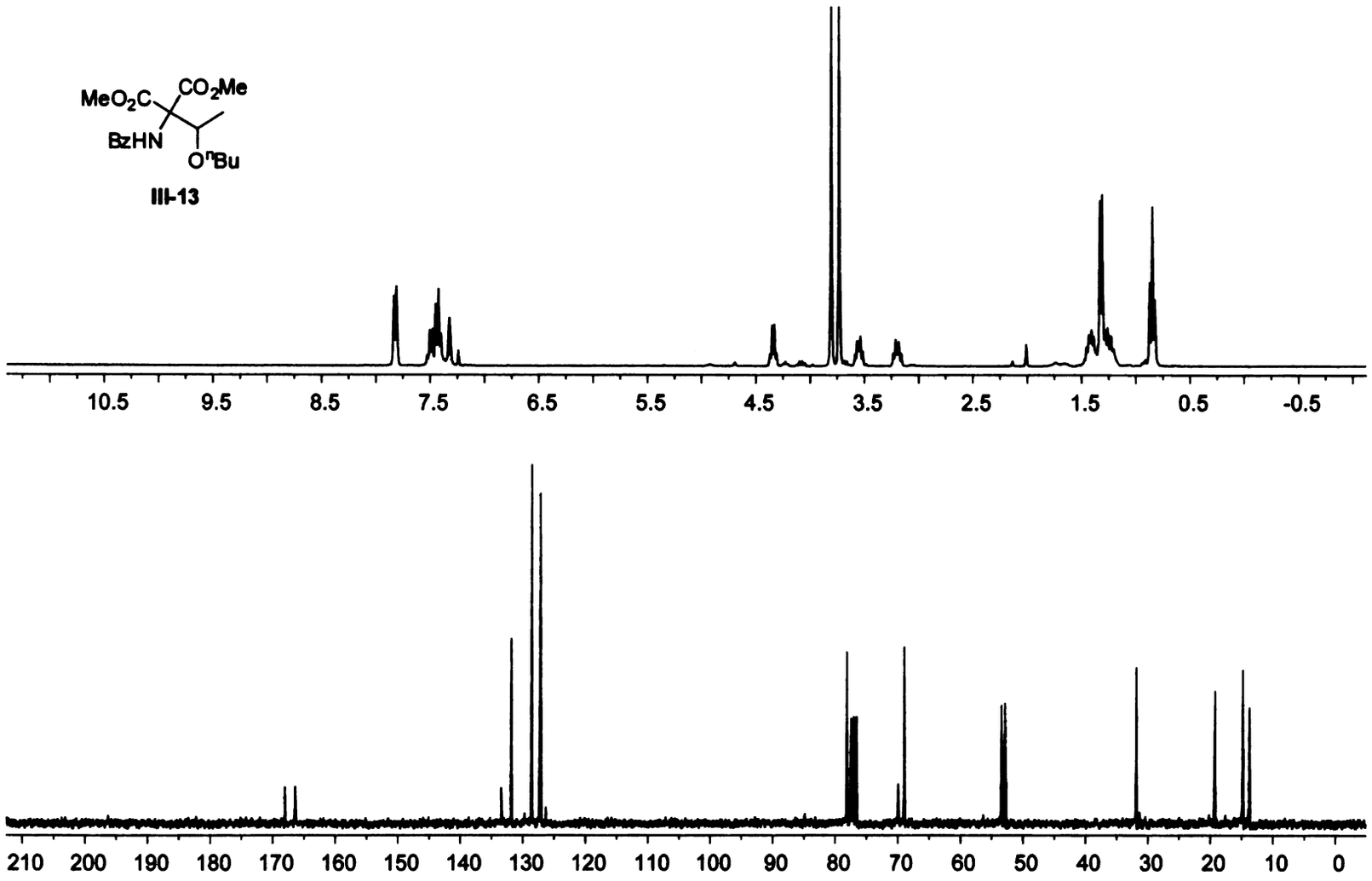


Figure III-10. NMR spectra of compound **III-13**.

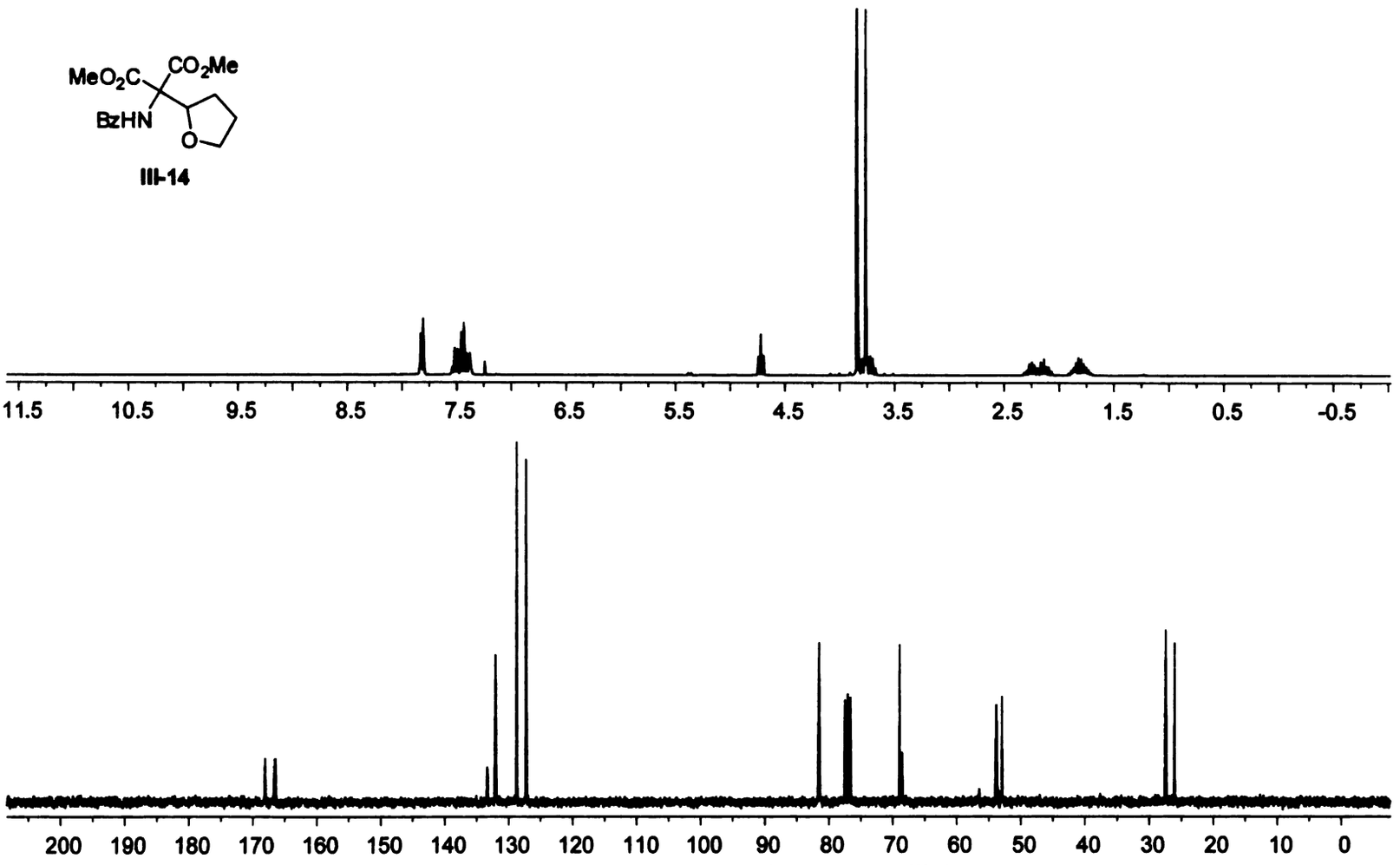


Figure III-11. NMR spectra of compound **III-14**.

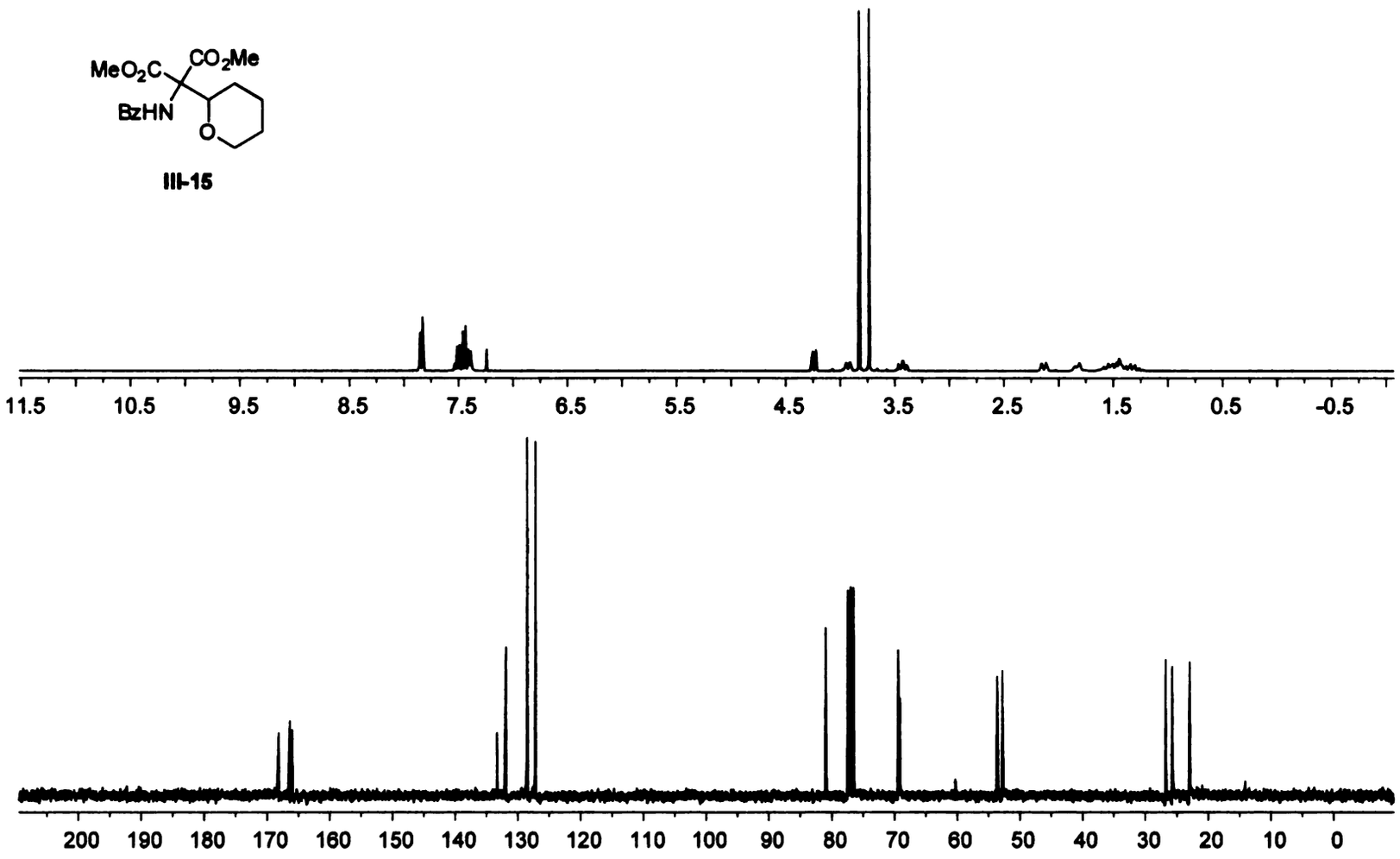


Figure III-12. NMR spectra of compound **III-15**.

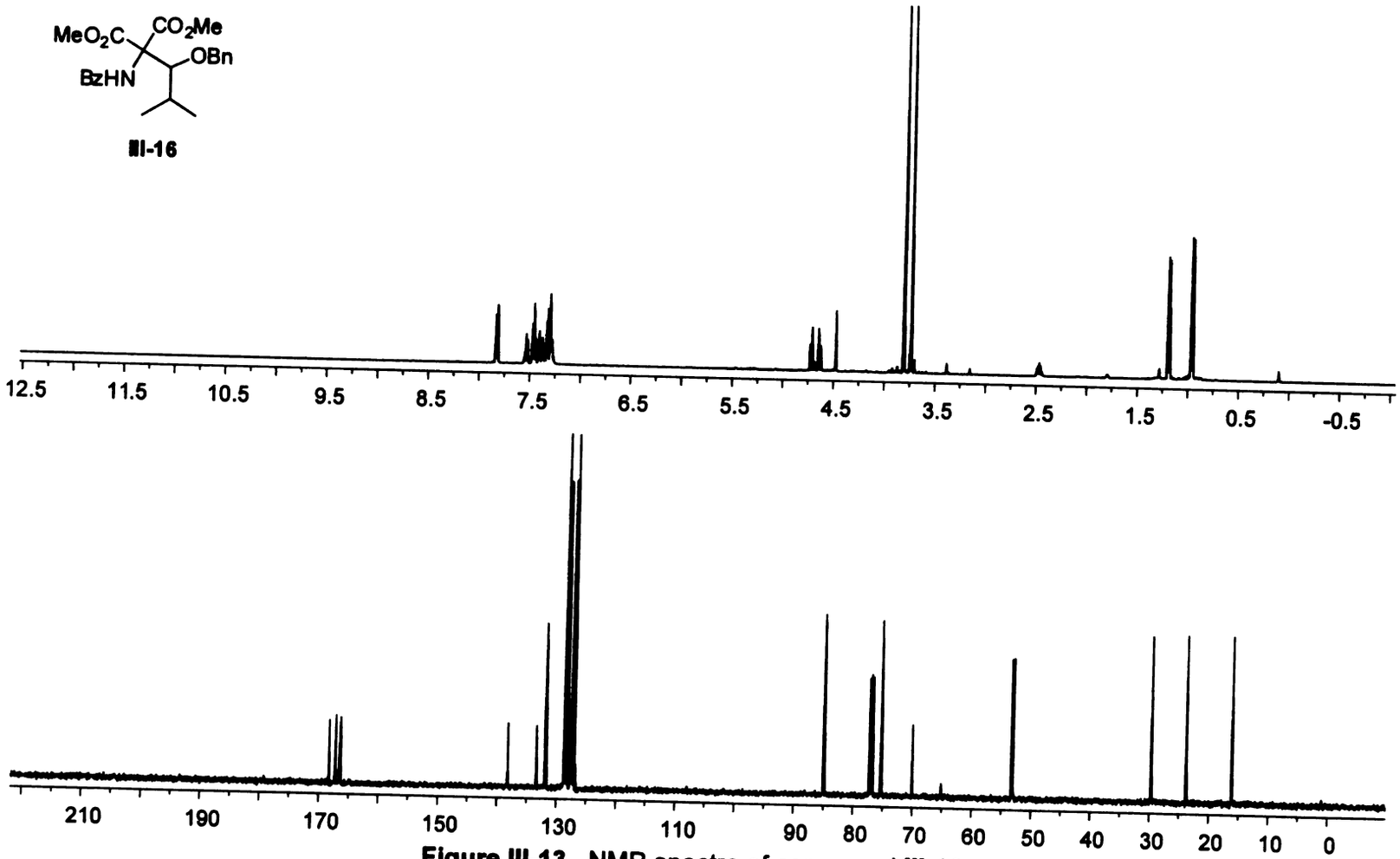


Figure III-13. NMR spectra of compound **III-16**.

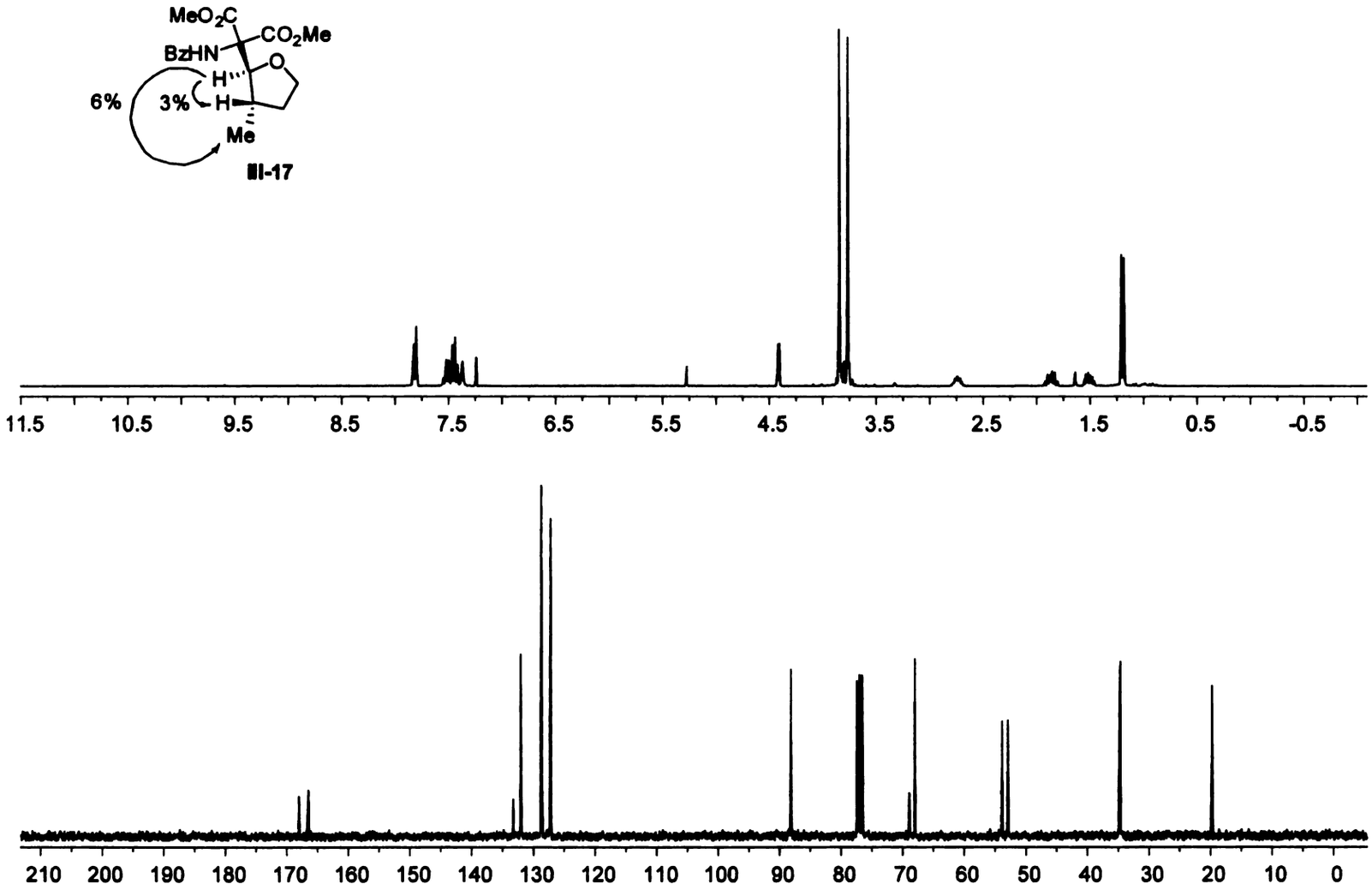


Figure III-14. NMR spectra of compound **III-17**.

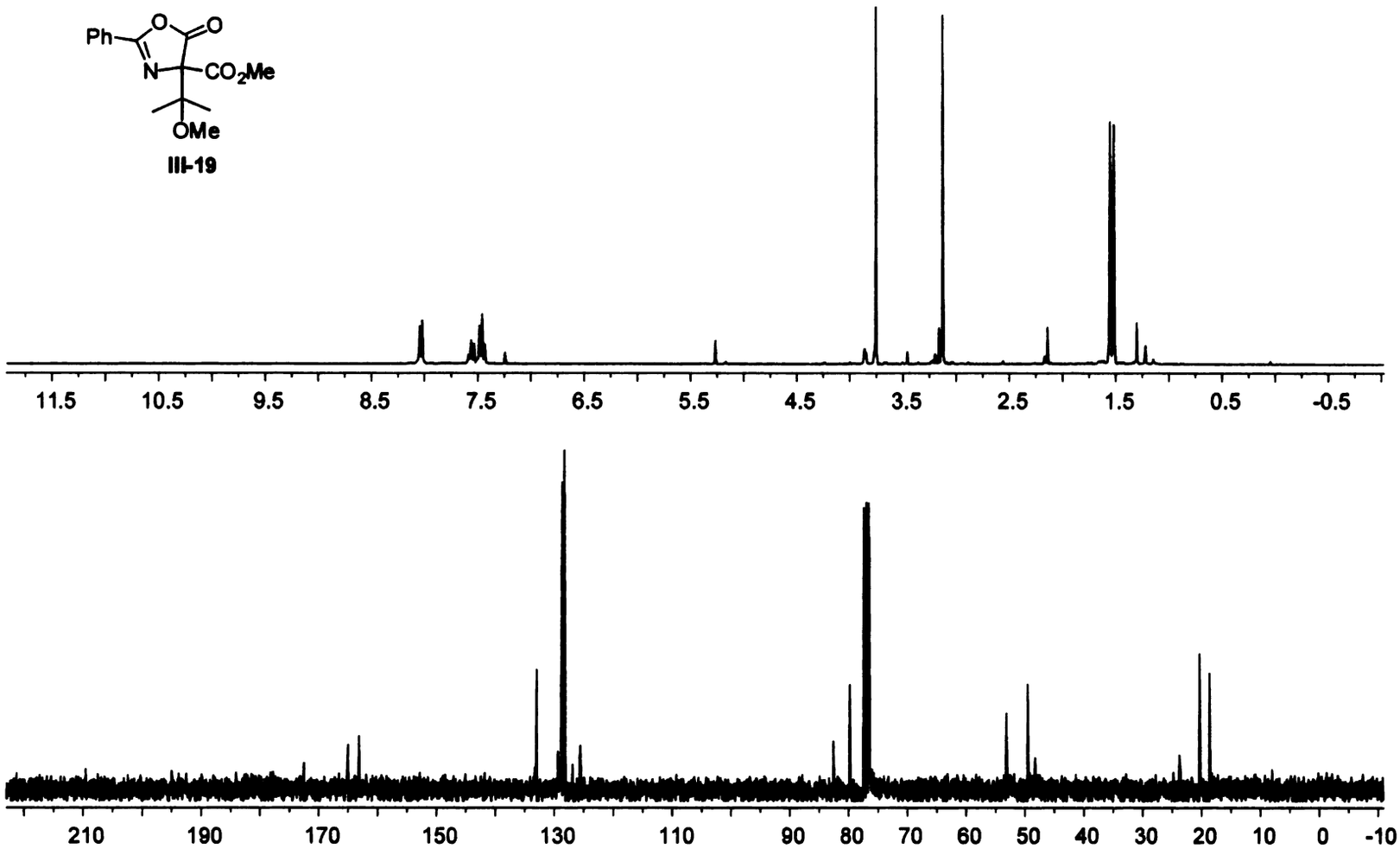


Figure III-15. NMR spectra of compound **III-19**.

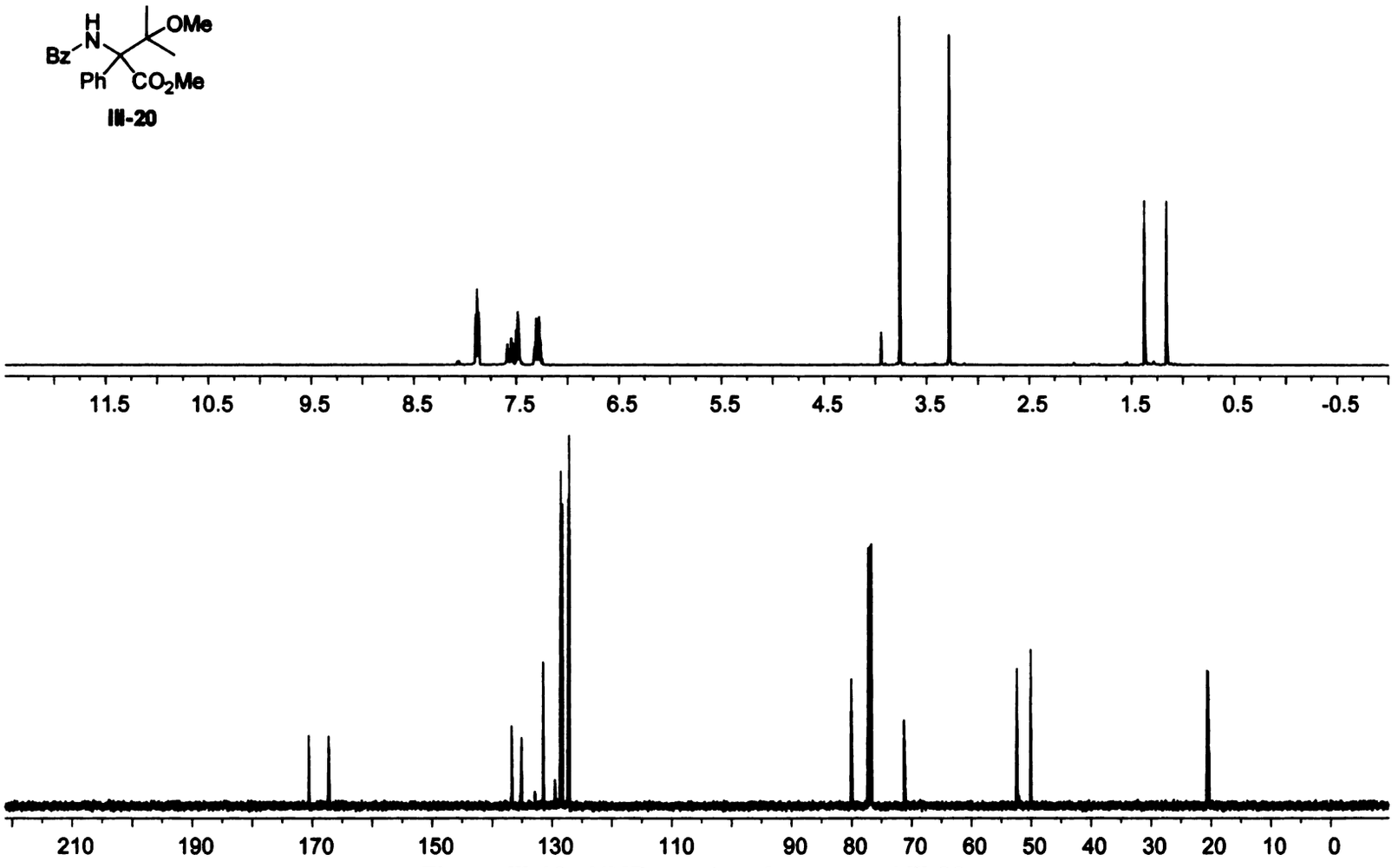


Figure III-16. NMR spectra of compound **III-20**.

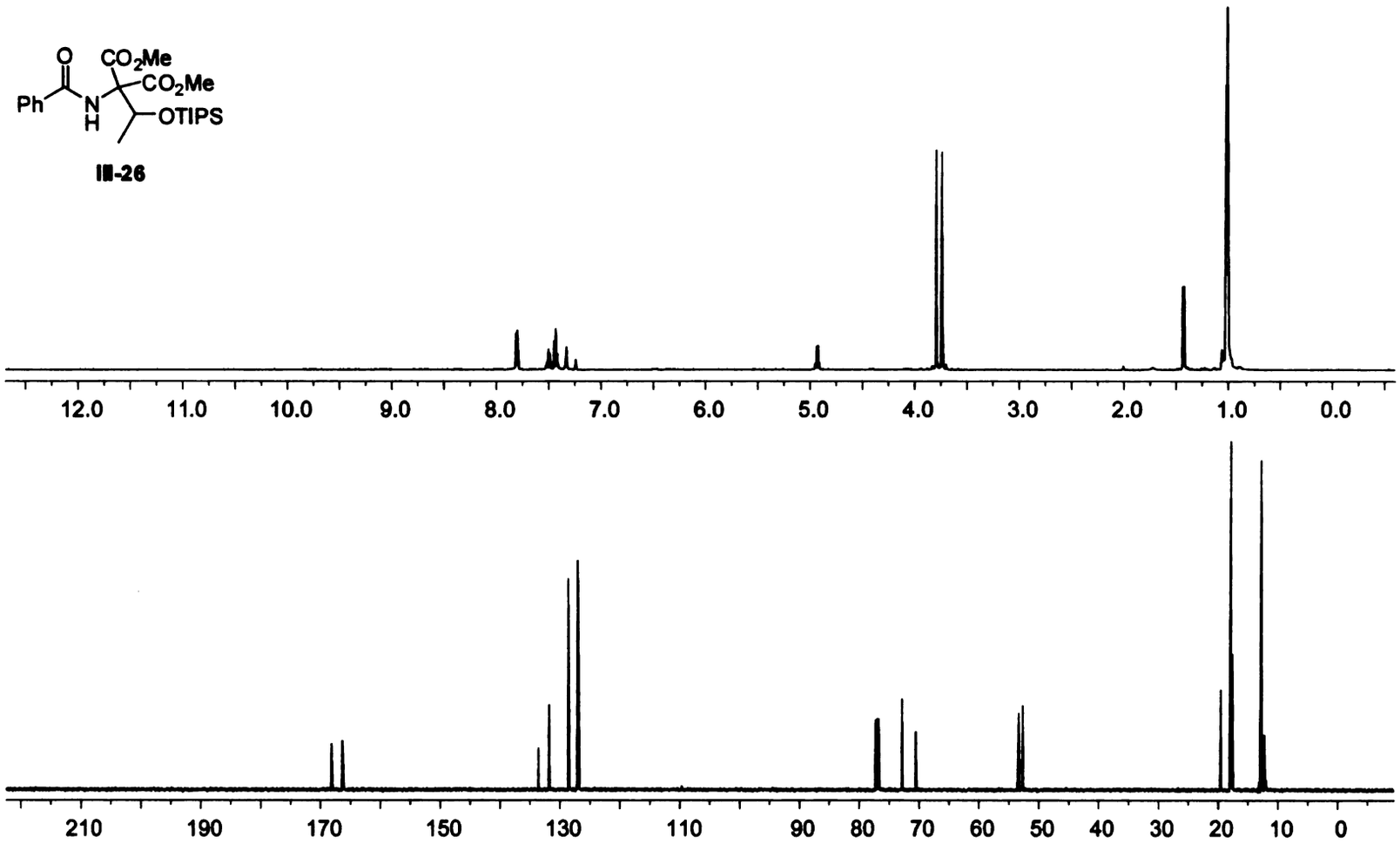


Figure III-17. NMR spectra of compound **III-26**.

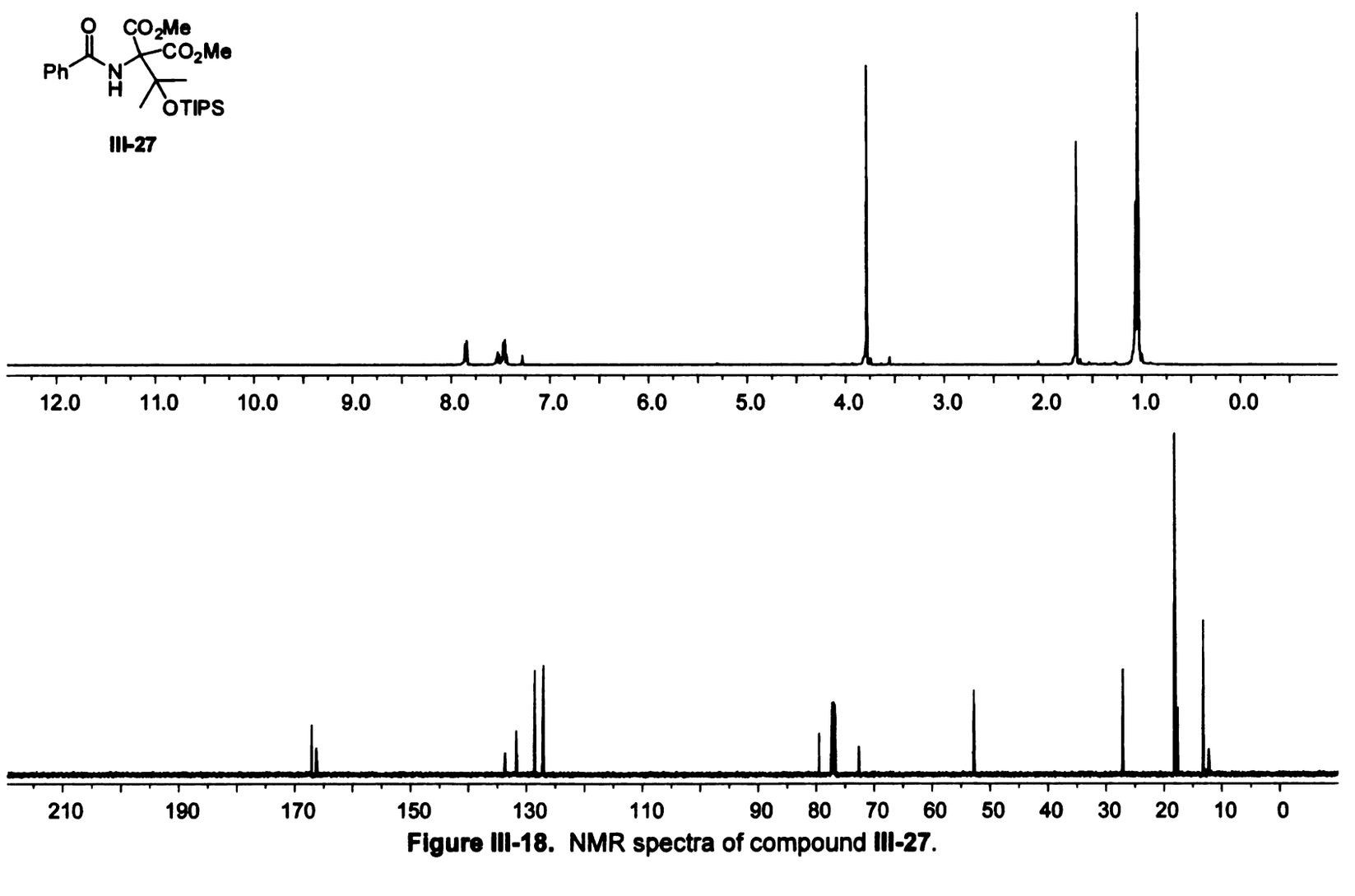


Figure III-18. NMR spectra of compound **III-27**.

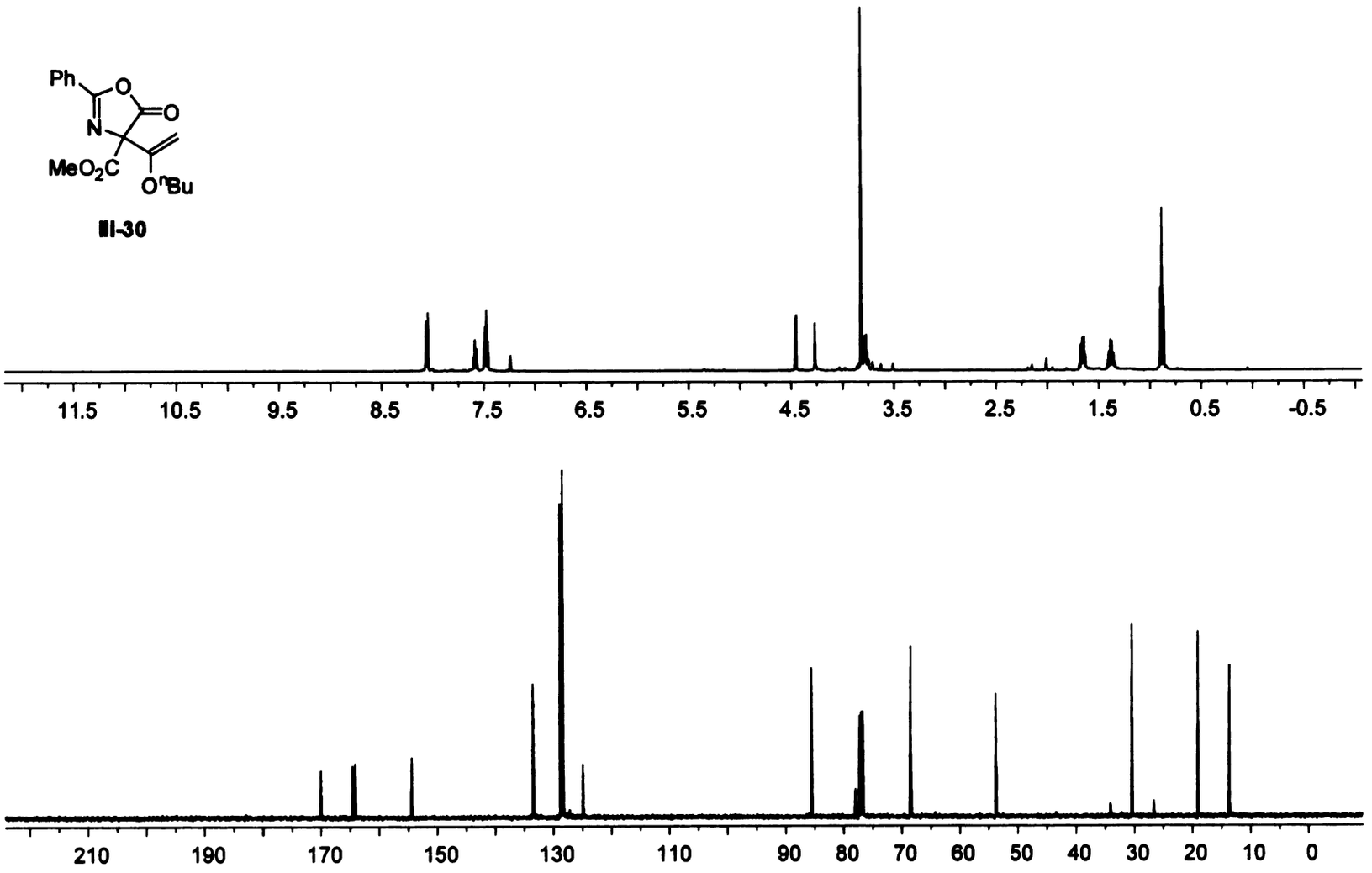


Figure III-19. NMR spectra of compound **III-30**.

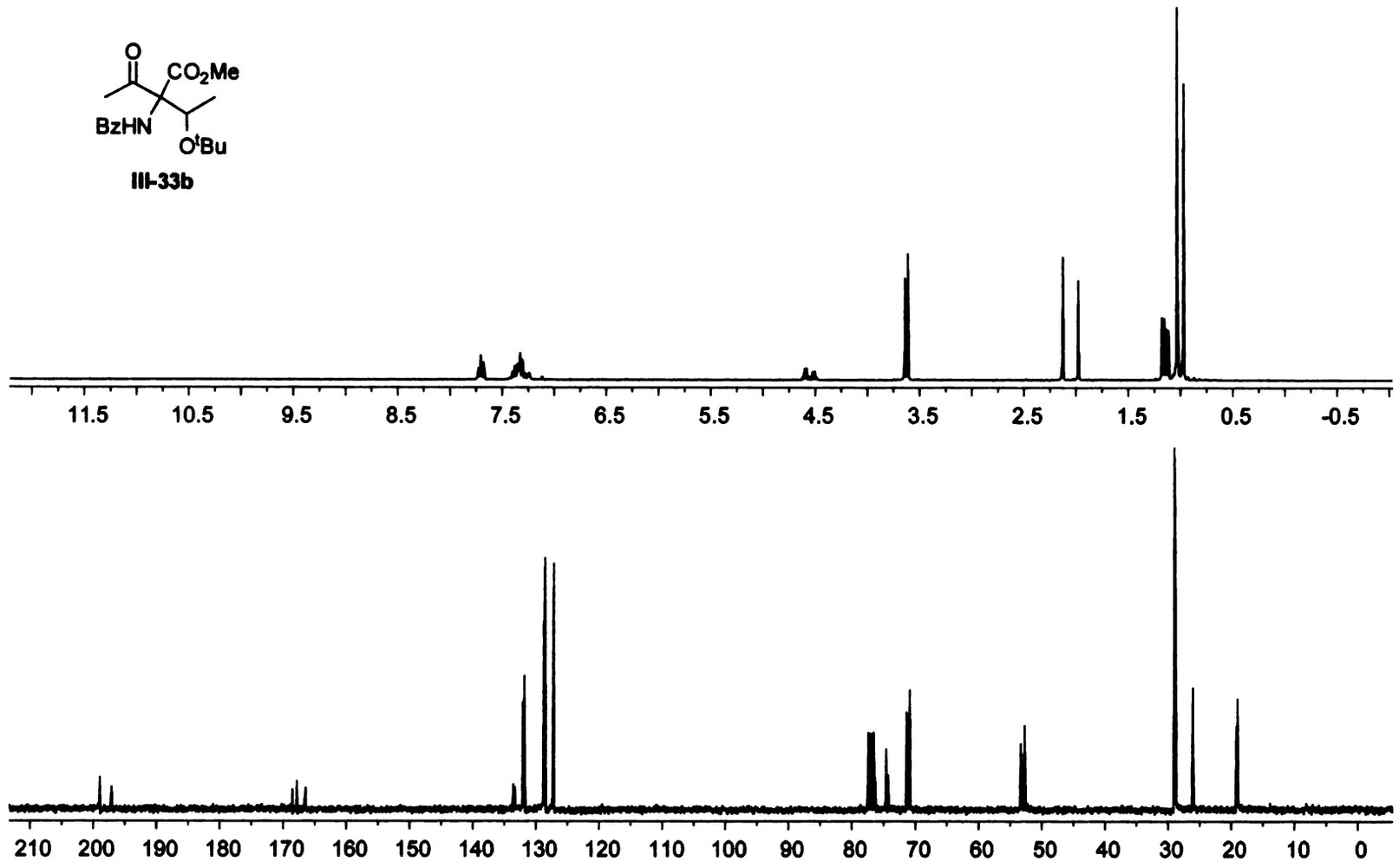


Figure III-20. NMR spectra of compound **III-33b**.

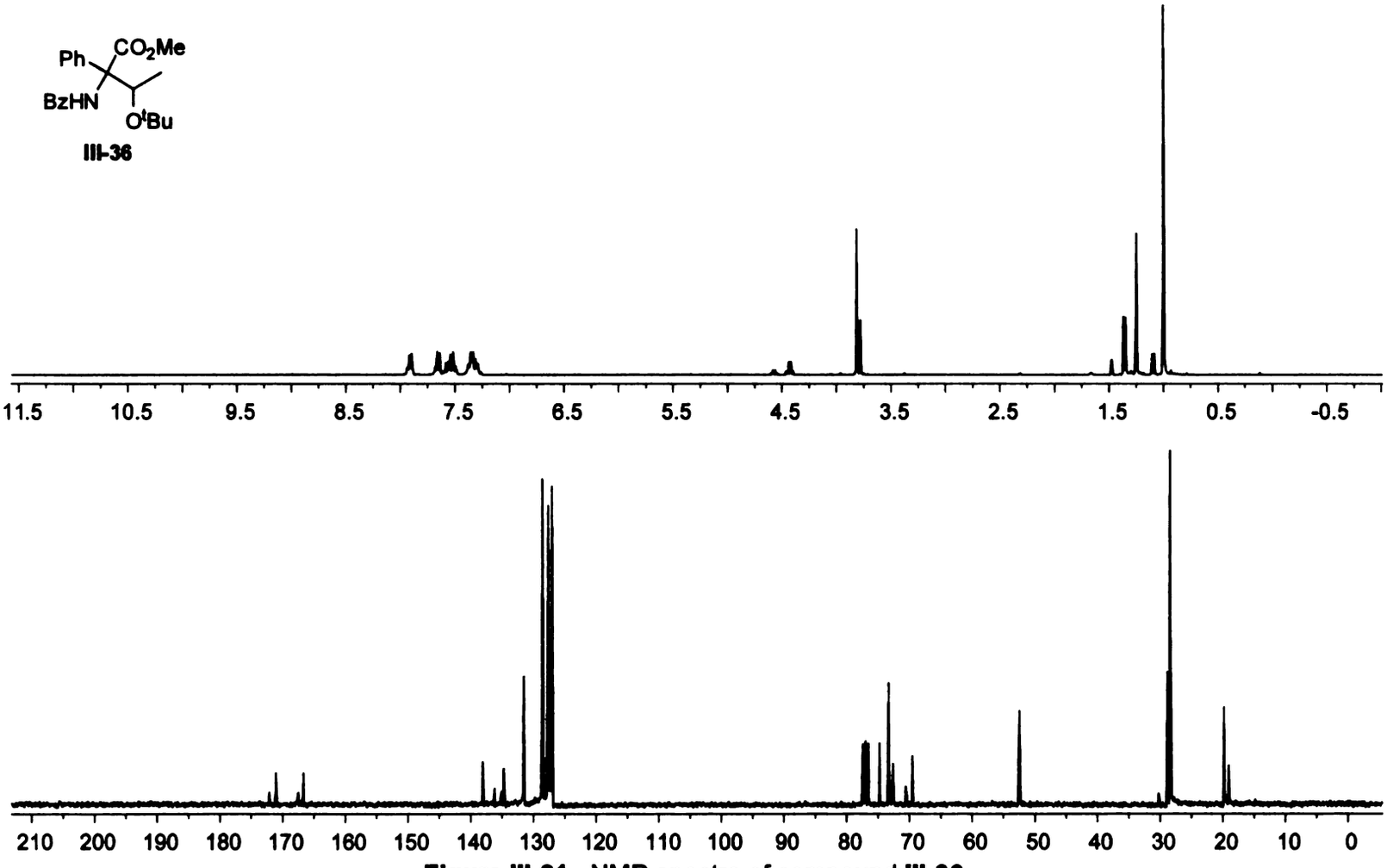


Figure III-21. NMR spectra of compound **III-36**.

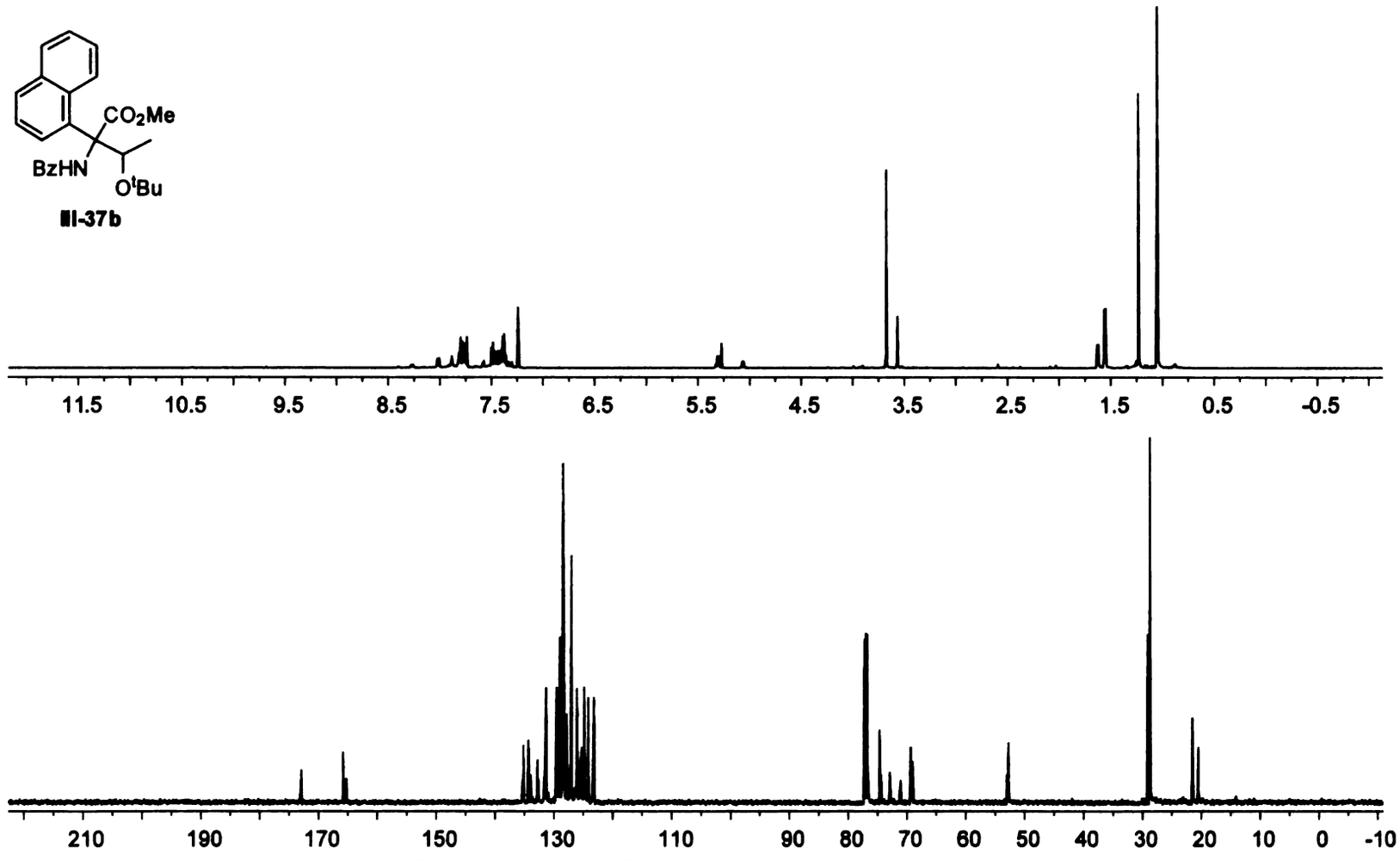


Figure III-22. NMR spectra of compound **III-37b**.

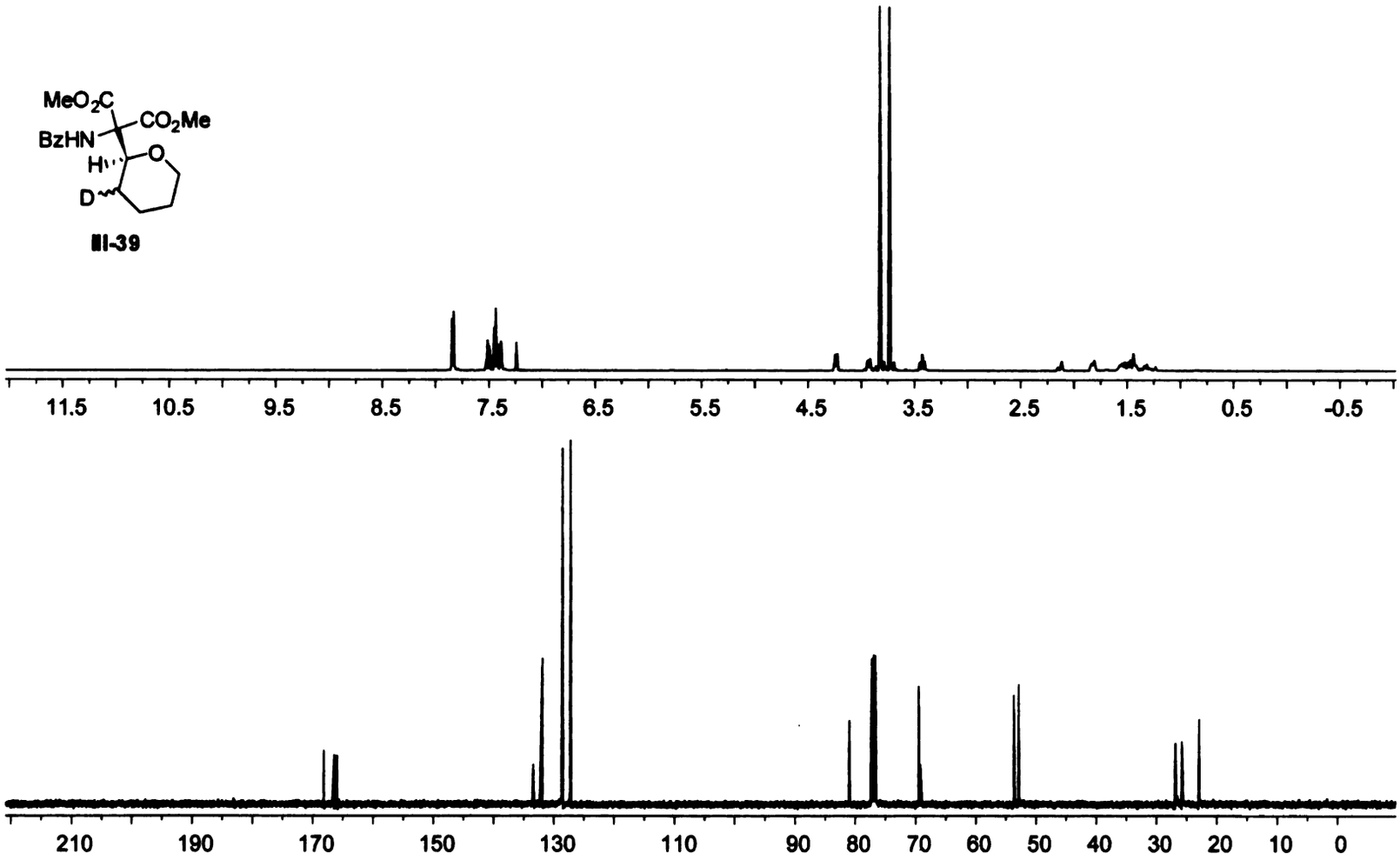


Figure III-23. NMR spectra of compound **III-39**.

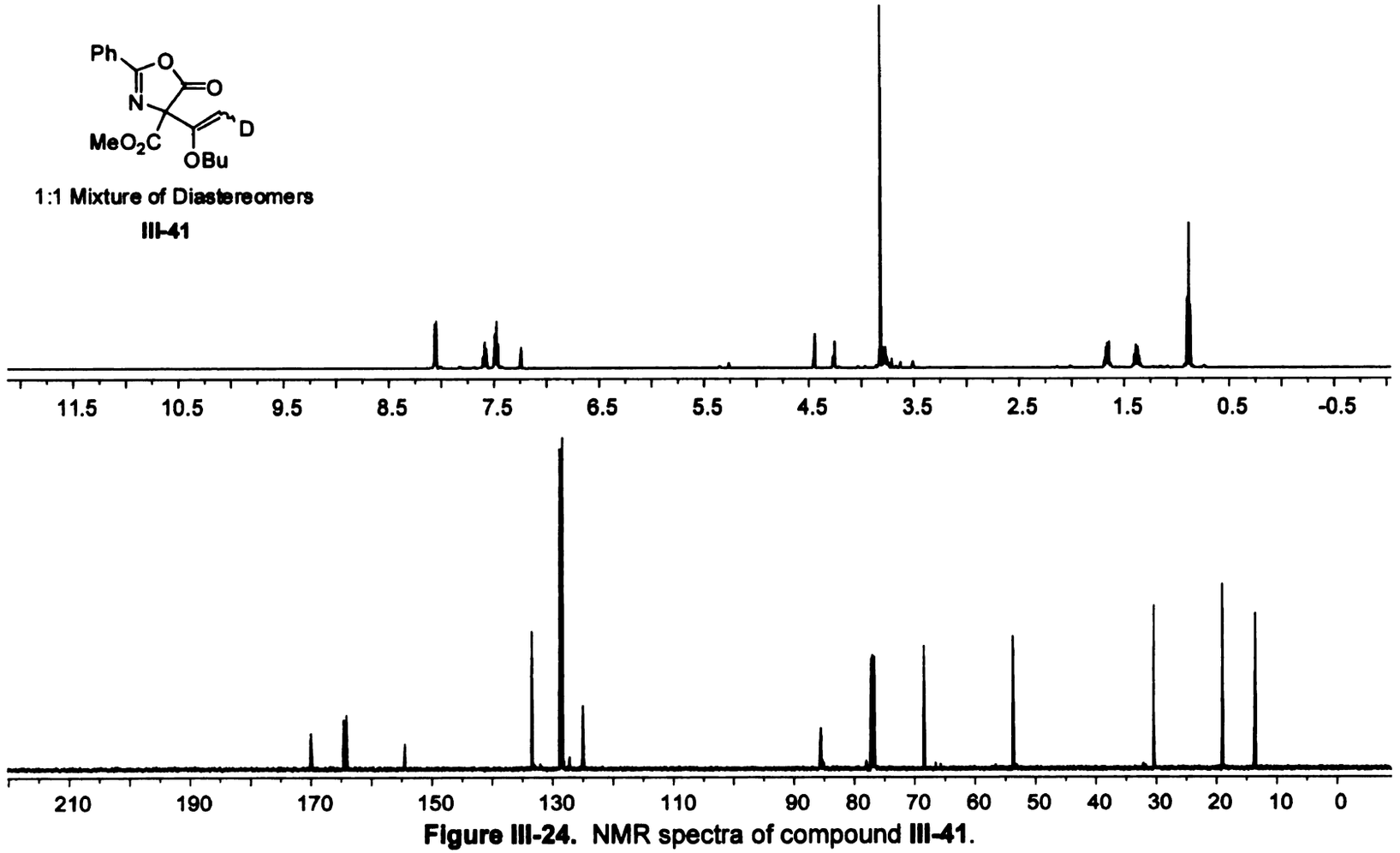


Figure III-24. NMR spectra of compound **III-41**.

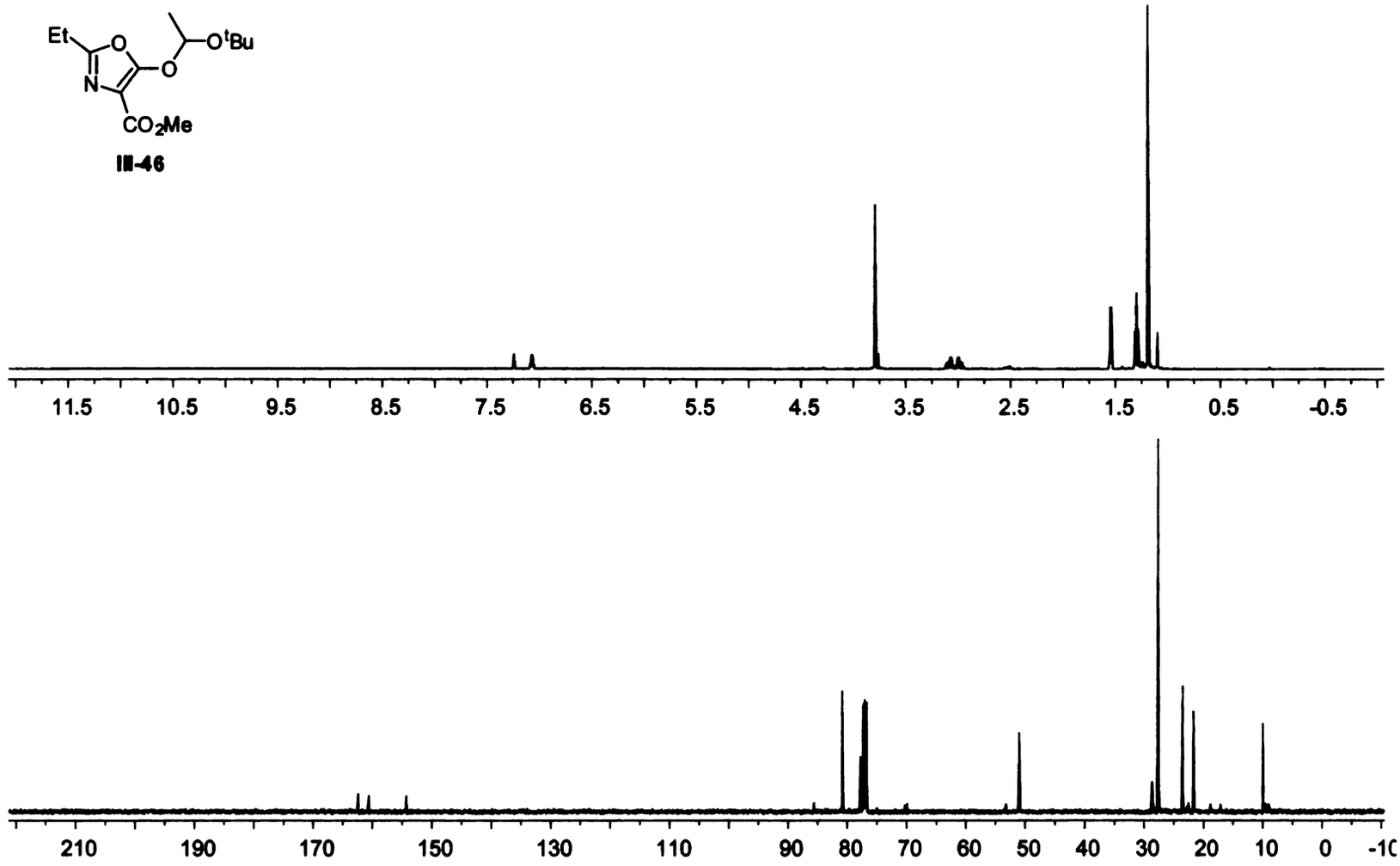


Figure III-25. NMR spectra of compound **III-46**.

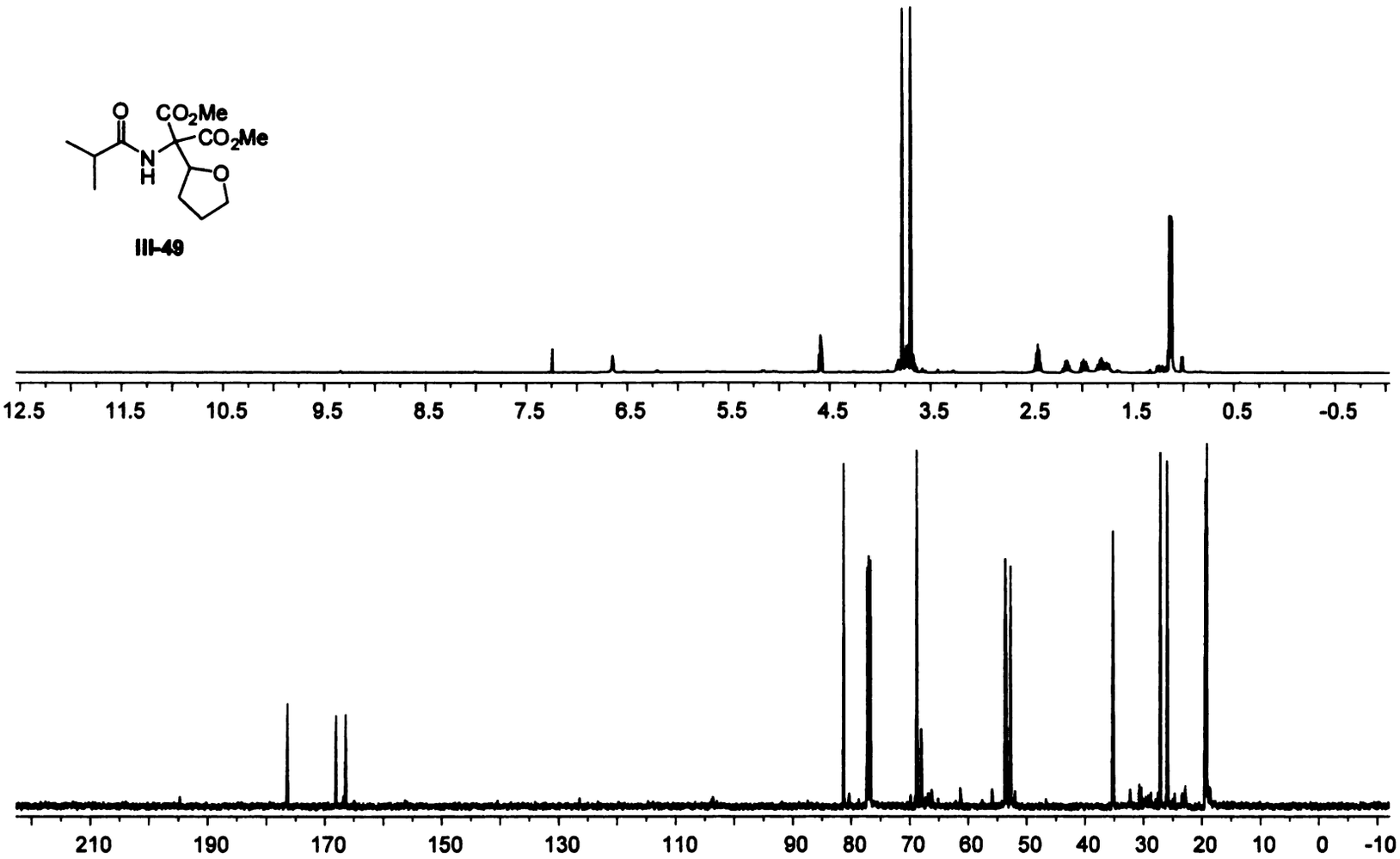
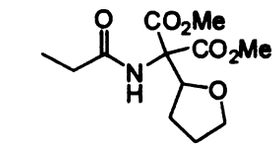


Figure III-26. NMR spectra of compound **III-49**.



III-50

Figure III-27. NMR spectra of compound **III-50**.

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CHAPTER IV

SYNTHESIS OF TERT-ALKYL AMINO HYDROXY CARBOXYLIC ESTERS VIA AN INTERMOLECULAR ALKYLATION REACTION OF OXAZOL-5(4H)-ONES USING ENOL ETHERS

A. Introduction to α,α-disubstituted α-amino acids

Non-proteinogenic amino acids have proven to be valuable substrates for a wide range of applications within the fields of synthetic organic, bioorganic and medicinal chemistry.[1] In particular, α,α-disubstituted α-amino acids (or quaternary α-amino acids) have received considerable attention from the scientific community as of late (Figure IV-1).[2-5] The additional alkyl substituent at the α-carbon of the amino acid changes its physical properties in multiple ways. For example, the additional substituent often helps to sterically constrain the free rotation of the residue's side chain helping to cause unique folding when incorporated into peptides.[1,4] Peptides containing quaternary α-amino acids also tend to have increased hydrophobicity, as well as an increased stability towards both chemical[6] and metabolic[7] decomposition. These unique physical properties make them intriguing tools for the design and study of peptides and proteins. In addition, α,α-disubstituted α-amino acids derivatives can be found in nature either in their free form, or within the structures of many biologically interesting heterocyclic natural molecules.[3,8]

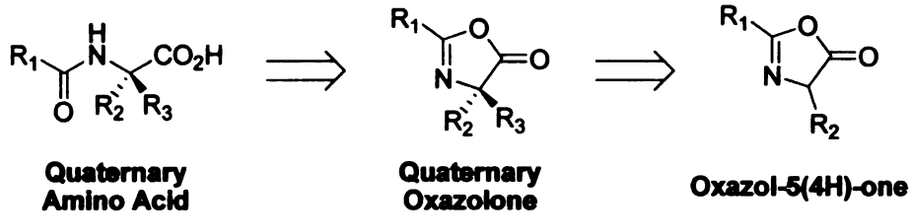
α-amino acid

α,α-disubstituted α-amino acid

Figure IV-1. General structures of both α-amino acids and α,α-disubstituted α-amino acids (quaternary α-amino acids).

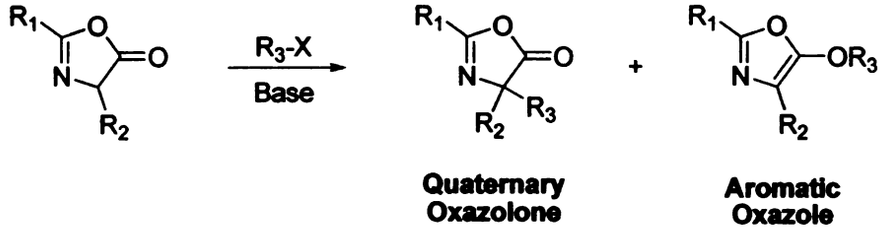
B. Synthesis of α,α-disubstituted α-amino acids using oxazol-5(4H)-ones

The importance of α-amino acids containing quaternary carbons has caused a high interest in the development of new and efficient methods for their synthesis.[2-5,8] Classical methods for their synthesis include the alkylation of α-amino esters protected as imines[9] and the Strecker reaction[10] of ketimines. Oxazol-5(4H)-ones have been proven to be excellent substrates for synthesizing quaternary substituted α-amino acids derivatives.[11,12] Quaternary substituted amino acid derivatives can be directly accessed from the nucleophilic ring opening of quaternary substituted oxazol-5(4H)-ones (Scheme IV-1). Quaternary substituted oxazol-5(4H)-ones can be produced through a variety of methods.[12] The relatively high acidity of the oxazol-5(4H)-one α-protons allows for diverse transformations not traditionally seen when attempting to derivatize α-amino acids themselves.[13,14] In addition, their cyclic structure is less sterically encumbering as compared to their acylic α-amino acid counterparts further helping to assist in derivatization adjacent to the carbonyl.



Scheme IV-1. Synthesis of quaternary amino acids from quaternary oxazolones.

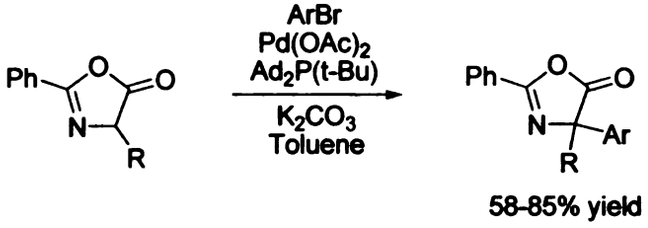
One of the earliest methods for generating alkylated oxazol-5(4H)-ones to construct α,α-disubstituted α-amino acids was reported by Steglich and co-workers in 1979.[13] Oxazol-5(4H)-ones were suspended in polar aprotic solutions and treated with Hünig's base in the presence of highly reactive electrophiles (Scheme IV-2). The resulting quaternary oxazolones were in turn hydrolyzed to afford the desired α,α-disubstituted α-amino acids. When utilizing this chemistry, less reactive electrophiles tend to be problematic and lead to unwanted side products primarily due to competitive O-alkylation of the enolate intermediates. Recent developments optimizing the reaction conditions have allowed for the use of wider range of electrophiles,[15] although O-alkylation still remains a problem with many substrates.



Scheme IV-2. Alkylation of oxazol-5(4H)-ones with alkyl halides.

Recent progress in oxazol-5(4H)-one chemistry has led to the development of novel methods utilizing transition metal catalysts as well as

organocatalysts to overcome the regioselectivity issues associated with the alkylation of oxazol-5(4H)-ones. For example, Trost and co-workers have reported multiple transformations utilizing transition metal catalysis for the allylic alkylation of oxazol-5(4H)-ones (See Chapter 1).[16] Transition metals have also been utilized in the arylation of oxazol-5(4H)-ones to synthesis quaternary aryl glycine derivatives.[17] In 2003, Hartwig and co-workers reported the first palladium catalyzed arylation of oxazol-5(4H)-ones for the synthesis of quaternary amino acids (Scheme IV-3).[18] The reaction involves the coupling of the sp^2 carbon of the aromatic enolate of oxazol-5(4H)-ones with aryl and vinyl bromides. The catalyst system consists of using $Pd(OAc)_2$ along with the sterically hindered electron rich ligand $Ad_2P(t\text{-}Bu)$ (Scheme IV-3).



Scheme IV-3. Hartwig's palladium catalyzed arylation of oxazol-5(4H)-ones.

C. Significance of *tert*-alkyl amino hydroxy carboxylic acids

Included within the class of quaternary substituted non-proteinogenic α-amino acids are amino hydroxy carboxylic acids whose structural features include a carbon core surrounded by alkyl, amino, carboxylic, and hydroxyl functional groups in various combinations.[3,8] Highly substituted amino hydroxy carboxylic acids are structural features present in numerous microorganism metabolites including the sphingofungins, lactacystins, salinosporamides, altemicidines,

oxazolomycins and many others (Figure IV-2).[3,8] The diverse and potent biological activity of these molecules has stimulated many researchers to pursue their total syntheses[19,20,21,22] and in-depth biological evaluations.[23,24] A general method for rapidly and efficiently synthesizing the quaternary amino acid core found within this class of molecules would greatly enhance the rate at which their biological profile could be studied.

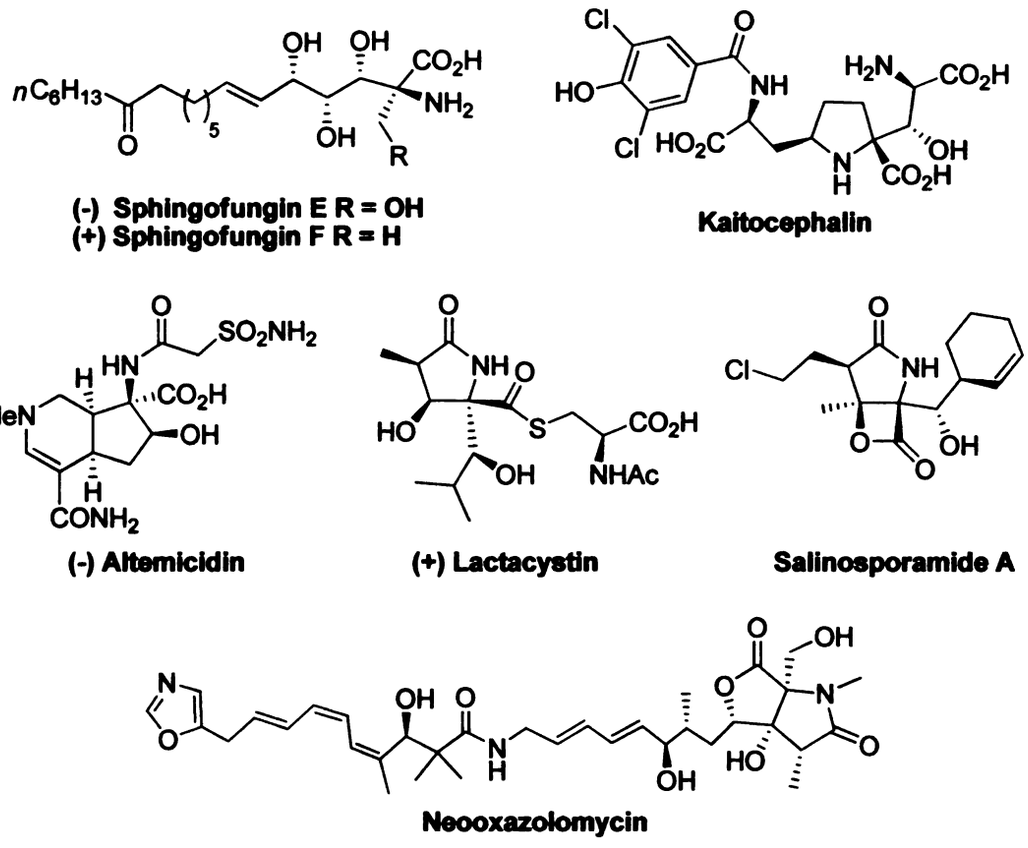


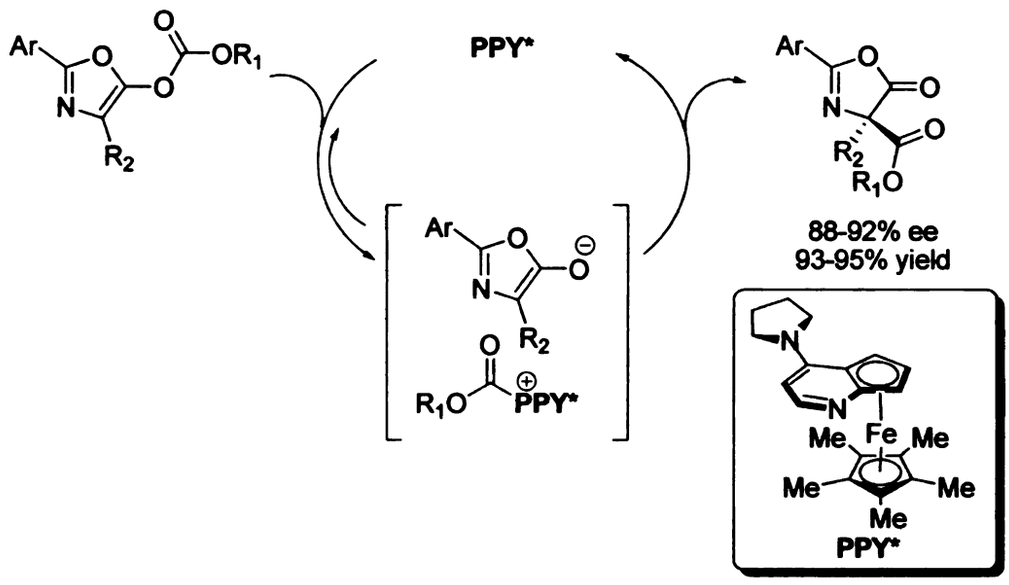
Figure IV-2. Naturally occurring *tert*-alkyl amino hydroxy carboxylic acids.

D. Synthesis of *tert*-alkyl amino hydroxy carboxylic acids using oxazol-5(4H)-ones

Construction of the densely functionalized quaternary carbon center found within molecules containing *tert*-alkyl amino hydroxy carboxylic acid cores has proven

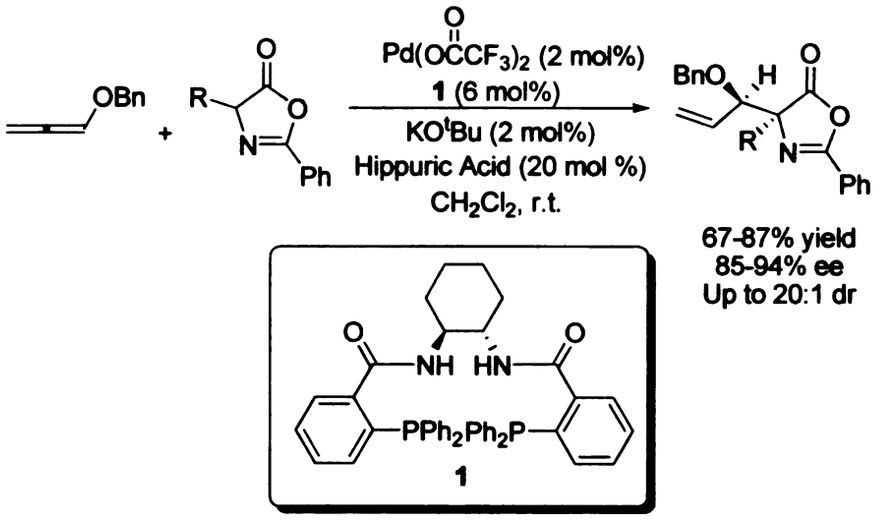
to be a significant synthetic challenge and has been the focus of many research groups.[3,8] A variety of methods have been employed to synthesize molecules containing such quaternary chiral centers, each of which seems to be highly dependent upon the targeted structure. Most of the methods implemented to date have taken advantage of pre-existing chirality within the molecule to establish the desired chiral α-amino acid core. The development of new and general methods for synthesizing *tert*-alkyl amino hydroxy carboxylic acids would greatly compliment previous methods and aid in the development of new methods for synthesizing this biologically interesting class of natural products.

A variety of methods have been developed to synthesize chiral quaternary substituted oxazol-5(4H)-ones ideally substituted for the synthesis *tert*-alkyl amino hydroxy carboxylic acids.[12] One reaction to produce such quaternary oxazolones is the Steglich rearrangement.[25] The Steglich rearrangement is a nucleophilic base catalyzed rearrangement of O-acylated oxazoles to form C-4 acylated oxazolones (Scheme IV-4). This reaction was first discovered by Steglich and co-workers in 1970.[25] The authors found that nucleophilic bases (e.g. DMAP) readily promote the rearrangement forming oxazolones containing a quaternary center (Scheme IV-4). Since the initial discovery of the reaction, chiral nucleophiles have been developed to catalyze the reaction asymmetrically.[26] The first asymmetric Steglich rearrangement was reported in 1998 by Fu and co-workers.[27] The authors reported the use of the DMAP derivative, PPY*, to catalyze the reaction with high levels of enantioselectivity along with relatively high yields (Scheme IV-4).



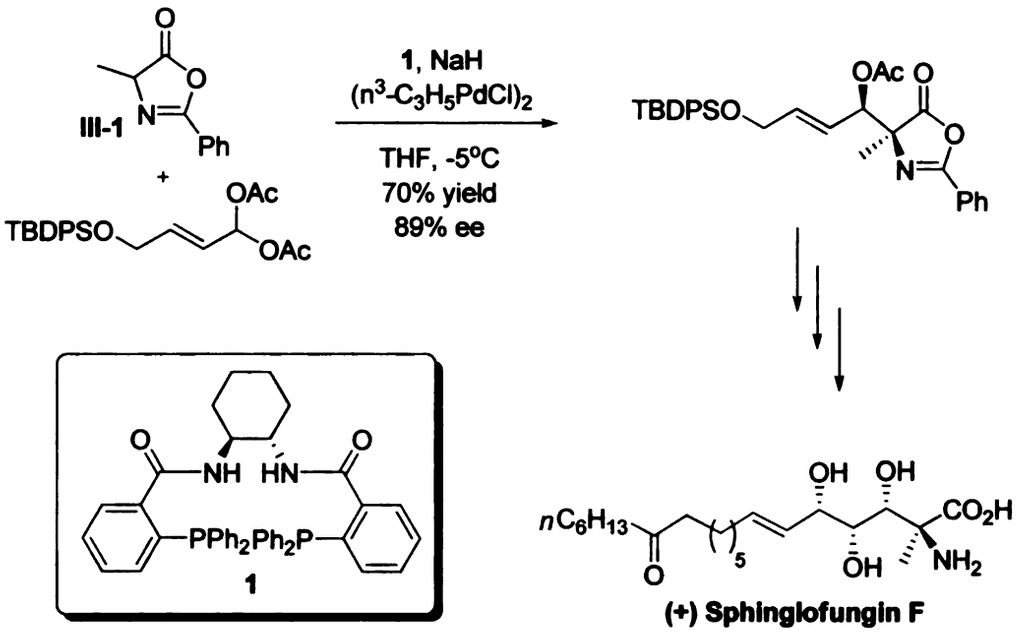
Scheme IV-4. Fu's enantioselecitve Steglich rearrangement.

A more recent method for alkylating of oxazol-5(4H)-ones to form *tert*-alkyl amino hydroxy carboxylic acid precursors was reported by Trost and coworkers involving a palladium-catalyzed addition of oxazol-5(4H)-ones to electron rich allenes (Scheme IV-5).[28] The reaction overcomes regioselectivity problems generally associated with allene chemistry by substituting one end of the allene with an electron rich alkoxy group. The reaction works very well for with oxazol-5(4H)-ones containing aliphatic substitutions at the C-4 position affording the highest yields (67-87%) along with excellent enantiomeric excesses (90-94%) (Scheme IV-5). The diastereoselectivity was also reported to be high in these reactions usually occurring in about a 20:1 ratio. The stereoselectivity of the reaction is induced using their chiral cyclohexyldiamine derived ligand **1**.



Scheme IV-5. Allylic alkylation of oxazol-5(4H)-ones using alkoxy allenes.

Furthermore, oxazol-5(4H)-ones have previously been used to synthesize molecules containing *tert*-alkyl amino hydroxy carboxylic acid cores. In 1998 Trost and Lee reported an asymmetric total synthesis of the naturally occurring *tert*-alkyl amino hydroxy carboxylic acid Sphingofungin F (Scheme IV-6).[29] Sphingofungin F was first isolated by Merck in 1992 as an antifungal agent from the fermentation of *Paecilomyces variotii*.[30] The compound has been found to be a potent inhibitor of the biosynthesis of sphingolipids due to its inhibitory activity against serine palmitoyltransferase.[31] Trost and Lee utilized an asymmetric allylic alkylation of 2-phenyl-4-methyl-5(4H)-oxazolone **III-1** with a *gem*-diacetate as their key step to synthesizing the natural product (Scheme IV-6). The reaction generated the *tert*-alkyl amino hydroxy carboxylic core in 70% yield with 89% ee. The synthesis required only 15 linear steps and proceeded with an impressive 17% overall yield.

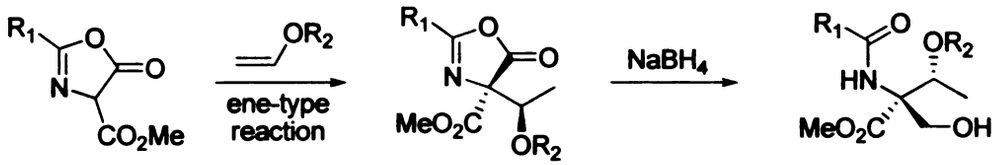


Scheme IV-6. Synthesis of Sphinglofungin F starting from oxazol-5(4H)-one **III-1**.

E. Intermolecular ene-type alkylations of oxazol-5(4H)-ones for the synthesis of *tert*-alkyl amino hydroxy carboxylic acids.

As a part of our research efforts of expanding the chemistry of oxazol-5(4H)-ones for the purpose of creating diverse libraries of heterocyclic compounds, we envisioned utilizing our ene-type alkylation chemistry of oxazol-5(4H)-ones as a general method for synthesizing *tert*-alkyl amino hydroxy carboxylic acid containing molecules (Scheme IV-7).[32,33] The initial alkylation reaction results in the formation of a highly functionalized quaternary center as a pivotal intermediate for the synthesis of α,α-disubstituted α-amino acids.[2] Reduction of the intermediate oxazolone ester products with sodium borohydride[27,34] results in the formation of quaternary nonproteinogenic amino esters ideally functionalized for the synthesis of many of these biologically interesting metabolites. The

remainder of this chapter will focus on our efforts to apply of our ene-type methodology of oxazol-5(4H)-ones towards a general synthesis of *tert*-alkyl amino hydroxy carboxylic esters.[33]



Scheme IV-7. Proposed synthesis of *tert*-alkyl amino hydroxy carboxylic acids.

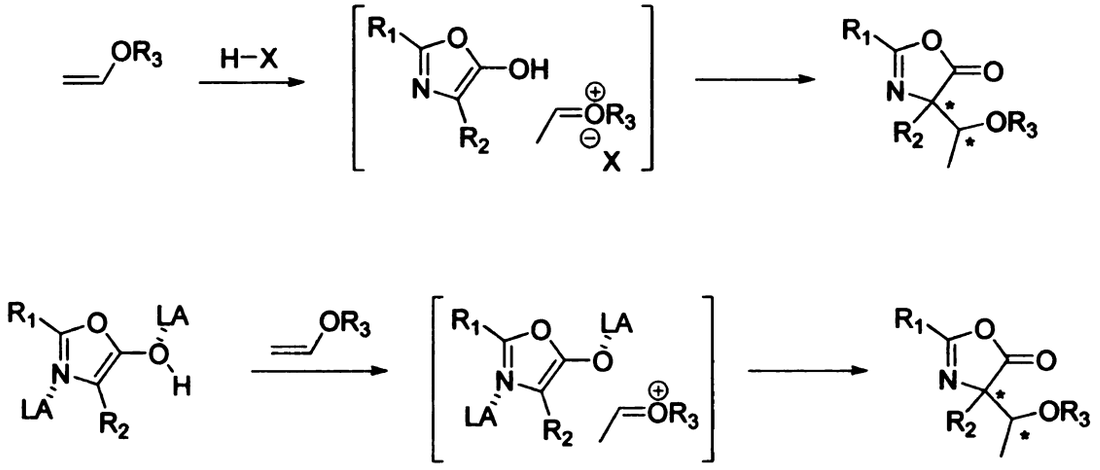
F. Improving the diastereoselectivity using Lewis acids

As reported in the previous chapter, the reaction of oxazol-5(4H)-ones with enol ethers results in the formation of quaternary substituted oxazolone intermediates as mixtures of diastereomers.[32,33] Our initial studies indicated that the ratio of the two product diastereomers is partially dependent upon the nature of the substrates and solvent being used, although it should be noted the diastereomeric ratio is generally approximately 50:50. In order to make this alkylation chemistry of oxazol-5(4H)-ones using enol ethers more appealing for use in synthetic organic chemistry, we sought to develop a method for improving the diastereoselectivity of the reaction.

During our previous mechanistic studies, we determined these reactions likely involve the initial formation of an oxonium ion intermediate as a direct result of the protonation of the enol ether by the acidic oxazol-5(4H)-one.[32] The intermediate oxonium ion is then trapped by the oxazol-5(4H)-one substrate to form the new quaternary center (Chapter III). Based off these observations, we envisioned using a catalyst to either increase the acidity of the oxazol-5(4H)-one

or to directly initiate the formation of the oxonium ion species (Scheme IV-8). Either method would hopefully help to improve the overall stereoselectivity of the reaction by means of the complexation of the catalyst to the reacting species.

Lewis acids have previously been used to complex with oxazol-5(4H)-ones to promote stereoselective transformations adjacent to their carbonyl. For example, previous reports have illustrated the use of Lewis acids to catalyze the dynamic kinetic resolutions of oxazol-5(4H)-ones to synthesize enantiomerically pure α-amino acids.[35] Furthermore, Lewis acids have been used to catalyze similar reactions such as the *ortho*-alkylation of phenols (Chapter III).[36,37] In addition, Lewis acids have been used to catalyze other carbon to carbon bond forming reactions utilizing enol ethers. For example, both cationic gold as well as trifluoroacetic acid has been used to catalyze the addition of enol ethers to 1,3-dicarbonyl containing substrates. [38]

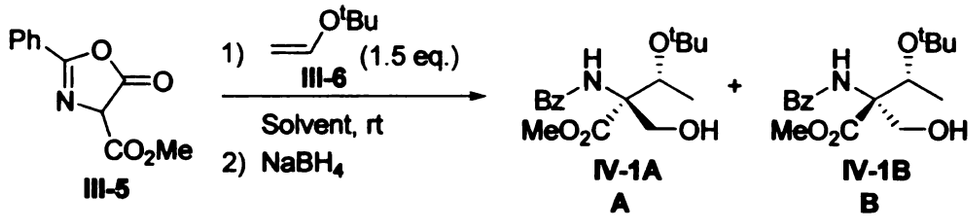


Scheme IV-8. Proposed Lewis acid catalysis for improving the stereoselectivity of the alkylation reactions between oxazol-5(4H)-ones and enol ethers.

G. Optimization of reaction conditions for improving diastereoselectivity

During our previous studies, we observed these ene-type alkylation reactions of oxazol-5(4H)-ones and enol ethers to proceed with little or no diastereoselectivity.[32] In an effort to make this synthetic approach more broadly applicable, we initiated a study screening various reaction conditions with hopes to improve the overall diastereoselectivity of the reaction.

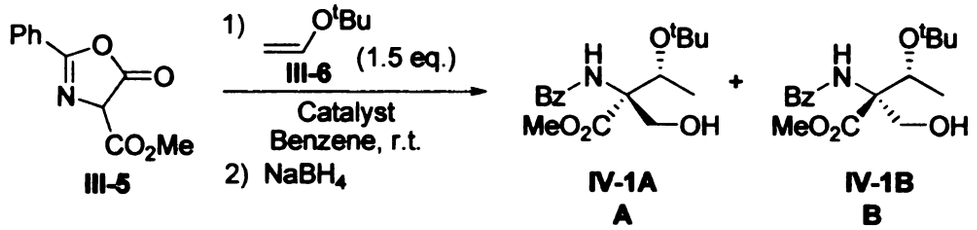
We began our study by first attempting to optimize the solvent being used in these reactions. The reaction of 4-carbmethoxy-2-phenyl-5(4H)-oxazolone **III-5** and *tert*-butyl vinyl ether **III-6** was performed in various solvents. The resulting quaternary oxazolone was reduced to the corresponding amino alcohol using sodium borohydride. The diastereomeric ratio of the product mixture was determined using integration values obtained from the ^{1}H NMR spectra. Most solvents screened resulted little or no diastereoselectivity in the reaction of 4-carbmethoxy-2-phenyl-5(4H)-oxazolone **III-5** and *tert*-butyl vinyl ether **III-6**. The use of more polar solvents tended to result in faster product formation with CH_2Cl_2 producing the most rapid result at 1 hour (Table IV-1, entry 2). In addition, solvents containing lone pairs of electrons tended to have longer reaction times as compared to solvents of similar polarity lacking lone electrons. The use of highly polar solvents such as DMSO yielded very little product presumably due to enol ether decomposition (Table IV-1, entry 5). The use of less polar solvents such as benzene did provide improved stereoselectivity with a diastereomeric ratio of approximately 1.7 : 1, but also decreased the rate of reaction considerably (Table IV-1, condition 4).



Conditions	Solvent	Time (h)	A:B	% Yield
1	CH_3CN	3	50 : 50	90
2	CH_2Cl_2	1	55 : 45	91
3	THF	19	52 : 48	90
4	Benzene	36	67 : 33	90
5	DMSO	24	50 : 50	Low

Table IV-1. Reaction of 4-carbmethoxy-2-phenyl-5(4H)-oxazolone **III-5** with *tert*-butyl vinyl ether **III-6** followed by reduction with sodium borohydride.

Upon examining the reaction solvent, next we turned our attention to exploring Lewis acid catalysis with the hope of increasing the reaction rate and diastereoselectivity. We initiated this study by screening a variety of Brønsted acids in the reaction of 4-carbmethoxy-2-phenyl-5(4H)-oxazolone **III-5** with *tert*-butyl vinyl ether **III-6**. To our delight, we found a substoichiometric amount (10 mol%) of diphenyl phosphate **IV-3** to improve both the reaction rate and diastereoselectivity (Table IV-2, catalyst IV-3). Brønsted acids less acidic than diphenyl phosphate **IV-3** also improved the diastereoselectivity of the reaction, but did little for increasing the reaction rate (Table IV-2, catalyst IV-2). The use of more acidic Brønsted acids resulted in lower yields of desired product, presumably due to either enol ether or product decomposition (Table IV-2, catalysts IV-4 and IV-5).



Catalyst	Catalyst	Time (hr)	A:B	% Yield
IV-2	3,5-Dinitrobenzoic acid	16	70 : 30	90
IV-3	Diphenyl phosphate	3	75 : 25	90
IV-4	CSA	1	74 : 26	83
IV-5	TFA	48	67 : 33	81
IV-6	$Ti(O^iPr)_4$	48	67 : 33	61
IV-7	$Yb(OTf)_3$	48	– : –	0
IV-8	TMSOTf	48	– : –	0
IV-9	$Zn(OTf)_2$	48	52 : 48	24
IV-10	$Cu(OTf)_2$	48	– : –	0

Table IV-2. Screening of various Lewis acids in the reaction of 4-carbmethoxy-2-phenyl-5(4H)-oxazolone **III-5** with *tert*-buyl vinyl ether **III-6**.

Several additional oxaphilic and azaphilic Lewis acids were screened resulting in little or no product formation and low diastereoselectivity (Table IV-2, catalysts IV-6 through IV-10). The significant rate enhancement found when using Brønsted acids and not other Lewis acids suggests that the catalyst protonates the enol ether forming an oxonium ion, although coordination to the oxazol-5(4H)-one substrate cannot be dismissed. All of the conditions used in Table IV-1 and Table IV-2 produced the same major diastereomer whose relative

stereochemistry was determined *via* crystal structure, which is depicted in Figure IV-3 below.

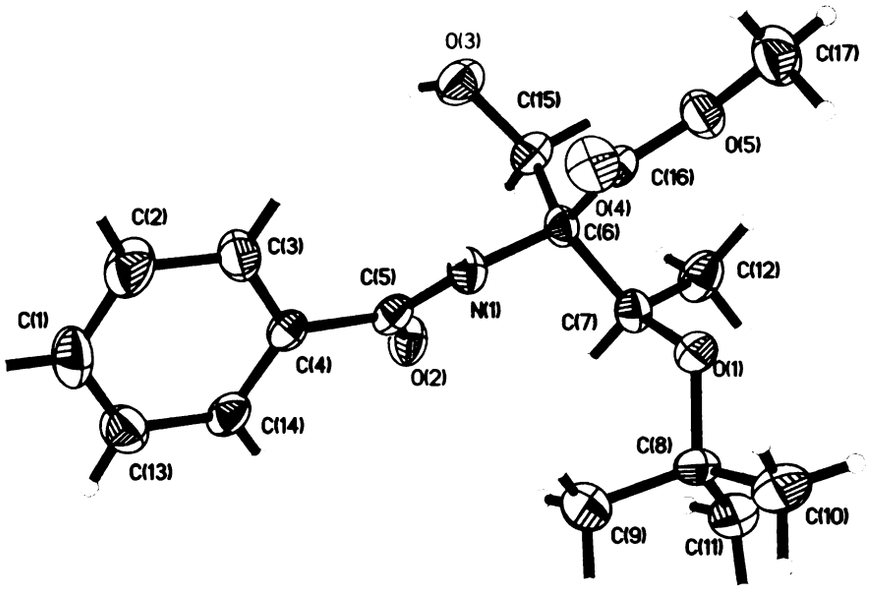
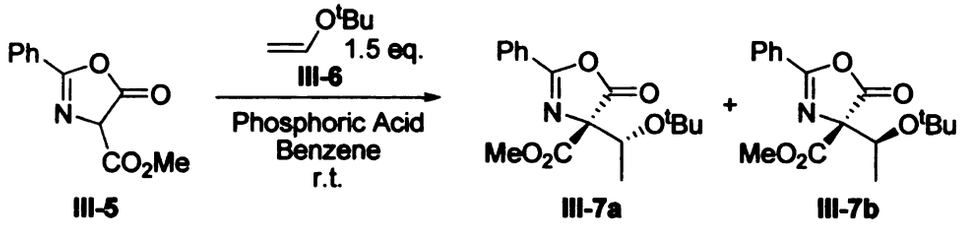


Figure IV-3. Crystal structure of compound **IV-1A**.

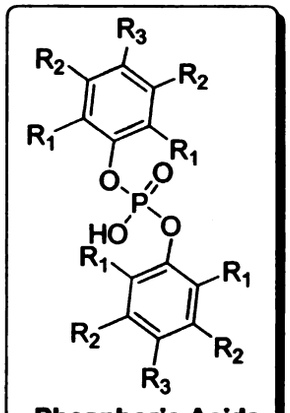
H. Other phosphoric acids

Upon determining diphenyl phosphate **IV-3** to have the optimal acidity for both increasing the reaction rate as well as the reaction diastereoselectivity, we decided to screen a variety of other phosphoric acid derivatives. We synthesized a small library of phosphoric acid derivatives that both sterically and electronically differed from diphenyl phosphate **IV-3**. To compare the phosphoric acid derivatives **IV-11** through **IV-15**, 4-carbmethoxy-2-phenyl-5(4H)-oxazolone **III-5** was treated with *tert*-butyl vinyl ether **III-6** in the presence of 10 mol% of each catalyst. Unfortunately, the majority of the phosphoric acid catalysts screened

did little for improving the reaction diastereoselectivity any more than using diphenyl phosphate **IV-3**. The use of bis(4-methoxyphenyl)phosphate **IV-11** resulted in very similar yields and diastereoselectivity (Table IV-3, phosphoric acid **IV-11**) when compared to diphenyl phosphate **IV-3**. Substituting alkyl groups on the aryl rings either at the R_1 or R_2 resulted in a slight decrease in the diastereoselectivity of the reaction (Table IV-3, phosphoric acids **IV-12** and **IV-13**).



Phosphoric Acid	R_1	R_2	R_3	(A : B)	Yield (%)
IV-3	H	H	H	75 : 25	99
IV-11	H	H	OMe	75 : 25	99
IV-12	Me	H	H	73 : 25	99
IV-13	H	^{t}Bu	H	74 : 26	99

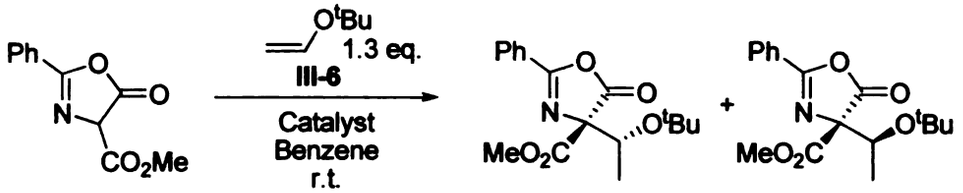


Phosphoric Acids IV-3 to IV-13

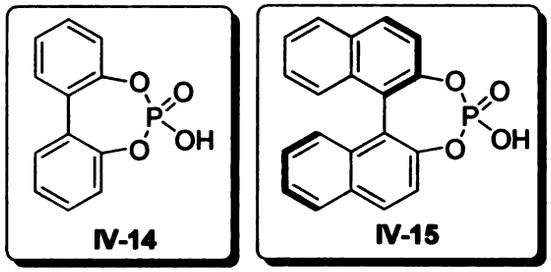
Table IV-3. Screening of other diaryl phosphoric acid derivatives in the reaction of 4-carbmethoxy-2-phenyl-5(4H)-oxazolone **III-5** and *tert*-butyl vinyl ether **III-6**.

We also examined two additional phosphoric acid derivatives whose conformation differed in the fact that the two aryl groups of the acid were covalently linked together (Scheme IV-9, catalysts **IV-14** and **IV-15**). Achiral 2,2'-

biphenylphosphoric acid **IV-14** provided a similar diastereomeric ratio and yield as seen with diphenyl phosphate **IV-3.** Chiral BINOL derived phosphoric acid **IV-15** provided the highest diastereoselectivity of any of the catalysts investigated with a diastereomeric ratio of 79 to 21, but provided no observable enantioselectivity as determined by chiral HPLC (Scheme IV-9). Future work in this area may consist of the synthesis and evaluation of other BINOL derivatives for not only improving the diastereoselectivity of the reaction, but also hopefully inducing enantioselectivity during the transformation.



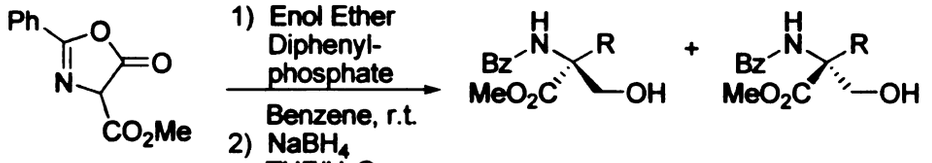
Catalyst	Time (h)	A:B	e.e.	% Yield
IV-14	22	76 : 24	—	98
IV-15	18	79 : 21	2	99



Scheme IV-9. Reaction of 4-carbmethoxy-2-phenyl-5(4H)-oxazolone **III-5** and *tert*-butyl vinyl ether **III-6** in the presence of catalysts **IV-14** and **IV-15.**

I. Various enol ethers

Utilizing the reaction conditions we optimized for improving the diastereoselectivity of these reactions, the scope of the reaction was further explored. Exposing 4-carbmethoxy-2-phenyl-5(4H)-oxazolone **III-5** to various vinyl enol ethers in the presence of 10% of diphenyl phosphate resulted in high yields of the desired products after sodium borohydride reduction (Table IV-4). The *tert*-butyl and benzyl protecting groups yielded better diastereoselectivity than the ethyl protecting group (Table IV-4, entries 1-3), indicating that enol ethers containing more sterically demanding oxygen protecting groups generally produce better diastereoselectivities. The less reactive higher substituted enol ethers resulted in lower yields of products and required the use of heat (Table IV-4, entries 4-6) to produce the desired products in good yields. Both 1-butoxyethyne **III-29** and 2-methoxypropene **III-18** (Table IV-4, entries 7 and 8, respectively) also provided reasonable yields of products.



III-5 **IV-1a to IV-26a** **A** **IV-1b to IV-26b** **B**

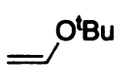
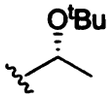
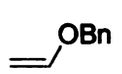
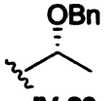
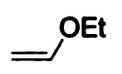
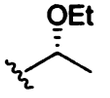
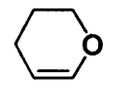
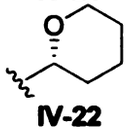
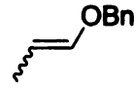
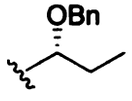
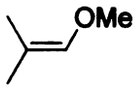
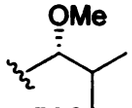
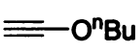
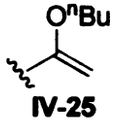
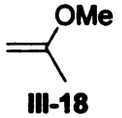
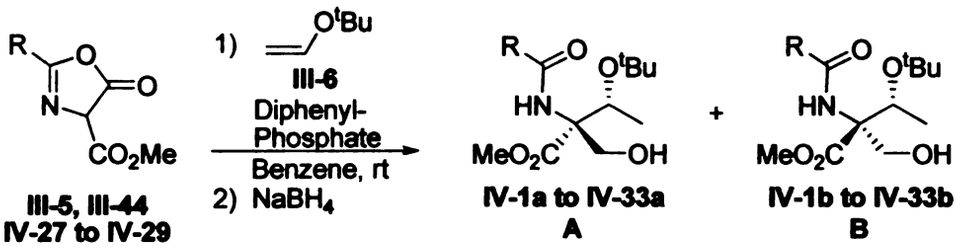
Entry	Substrate	R	Temp (°C)	A:B	% Yield
1	 **III-6**	 **IV-1**	25	75 : 25	90
2	 **IV-16**	 **IV-20**	25	75 : 25	77
3	 **IV-17**	 **IV-21**	25	67 : 33	85
4	 **III-10**	 **IV-22**	50	38 : 62	57
5	 (5:1 trans to cis) **IV-18**	 **IV-23**	50	69 : 31	48
6	 **IV-19**	 **IV-24**	50	60 : 40	33
7	 **III-29**	 **IV-25**	25	– : –	67
8	 **III-18**	 **IV-26**	25	– : –	62

Table IV-4. Reaction of various enol ethers with 4-carbmethoxy-2-phenyl-5(4H)-oxazolone **III-5** under the optimized reaction conditions.

J. Various oxazol-5(4H)-ones

The role of the 2-position of the oxazol-5(4H)-one scaffold was investigated for its effect on reactivity and selectivity (Table IV-5). Several oxazol-5(4H)-ones with varying substitutions at the 2-position were prepared and were reacted with *tert*-butyl vinyl ether **III-6** in the presence of diphenyl phosphate **IV-3**. Oxazol-5(4H)-ones with aryl substituents afforded high yields of product formation and erosion of diastereoselectivity was observed as electron deficiency increased (Table IV-5, entries 1-3). Stereoselectivity was all but lost when oxazol-5(4H)-ones containing alkyl substituents were used (Table IV-5, entries 4 and 5).



III-5, III-44
IV-27 to IV-29

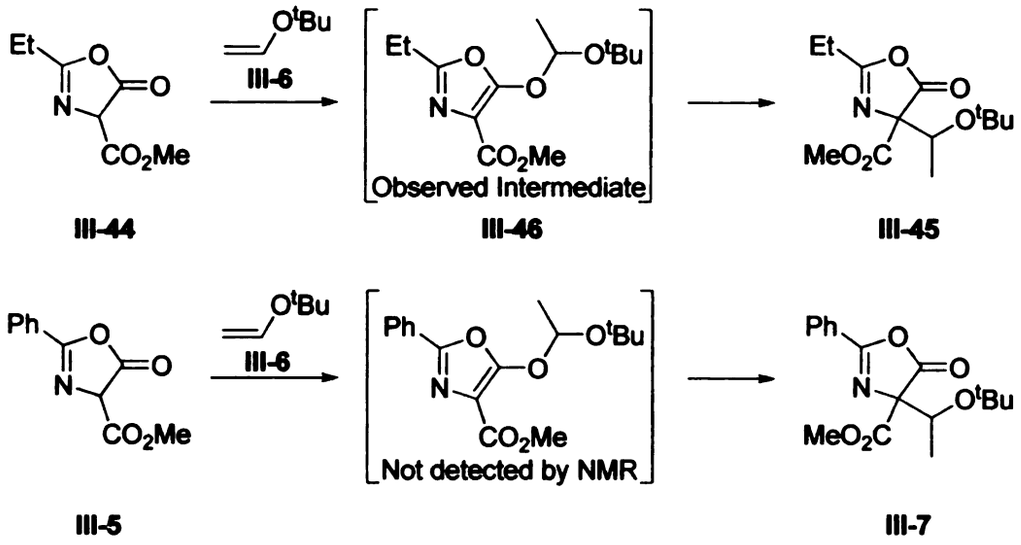
IV-1a to IV-33a
A

IV-1b to IV-33b
B

Entry	R	A:B	% Yield
1	Ph **III-5**	75 : 25	90
2	4-MeO-Ph **IV-27**	74 : 26	88
3	4-CF_3-Ph **IV-28**	67 : 33	81
4	Et **III-44**	43 : 57	50
5	Bn **IV-29**	52 : 48	58

Table IV-5. The reaction of various oxazol-5(4H)-ones with *tert*-butyl vinyl ether **III-6** under the optimized reaction conditions.

The decrease in both stereoselectivity and yield in the reactions involving 2-alkyl-oxazolones as compared to those involving 2-aryl-oxazolones may potentially be explained by a difference in mechanism. To investigate this phenomenon, we treated both 4-carbmethoxy-2-ethyl-5(4H)-oxazolone **III-44** and 4-carbmethoxy-2-phenyl-5(4H)-oxazolone **III-5** with *tert*-butyl vinyl ether **III-6** in the absence of catalyst (Scheme IV-10). Analysis of the crude reaction mixtures revealed an O-alkylated oxazole intermediate in the reaction involving 4-carbmethoxy-2-ethyl-5(4H)-oxazolone **III-44** while the 4-carbmethoxy-2-phenyl-5(4H)-oxazolone **III-5** reaction produced only C-alkylated product. Upon standing, we observed the conversion of the O-alkylated intermediate to the C-alkylated product along with some degradation of the enol ether component. This observation infers that these ene-type reactions might proceed through an O to C migration, although this was never observed for any of the 2-aryl substituted oxazol-5(4H)-ones.

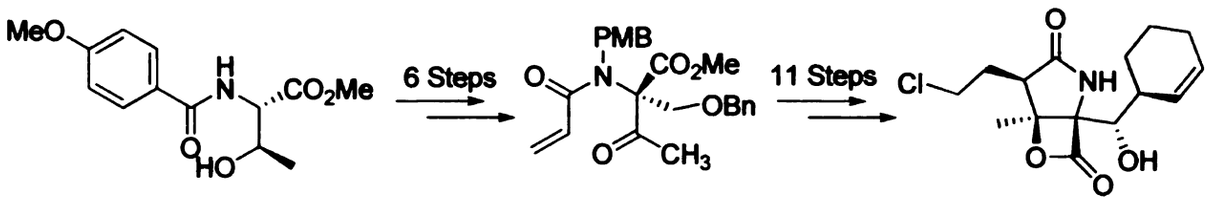


Scheme IV-10. Comparison of the reactivity between 2-aryl-oxazol-5(4H)-ones and 2-alkyloxazol-5(4H)-ones.

K. Application of the alkylation methodology towards the synthesis of Salinosporamide A

Salinosporamide A is a pyrrolidinone-based natural product isolated from the marine bacterium *Salinospora* in 2003 by Fenical and co-workers.[39] Salinosporamide A exhibits remarkably selective and potent irreversible inhibition of the mammalian 26S proteasome, which is emerging as a novel target in anticancer therapy.[40] The compound structure and biological activity is similar to the naturally occurring metabolite Lactacystin (Chapter III). The structure of the natural product comprises of a highly functionalized fused bicyclic pyrrolidinone/β-lactone core, which is critical for its biological activity.[39,41] Many of the structural features necessary for the biological activity of Salinosporamide A have been identified through a combination of structure activity relationship studies and x-ray crystallography.[42,43]

The total synthesis of Salinosporamide A and other naturally related compounds has been completed by many research groups,[43-45] including that of E. J. Corey.[46] Corey's synthesis of Salinosporamide A consists of 17 linear steps starting from an N-acylated threonine methyl ester derivative (Scheme IV-11). During the synthesis, Corey and co-workers generate intermediate **IV-34**, which undergoes a Baylis-Hillman cyclization to yield the core pyrrolidinone scaffold of the natural product Salinosporamide A.

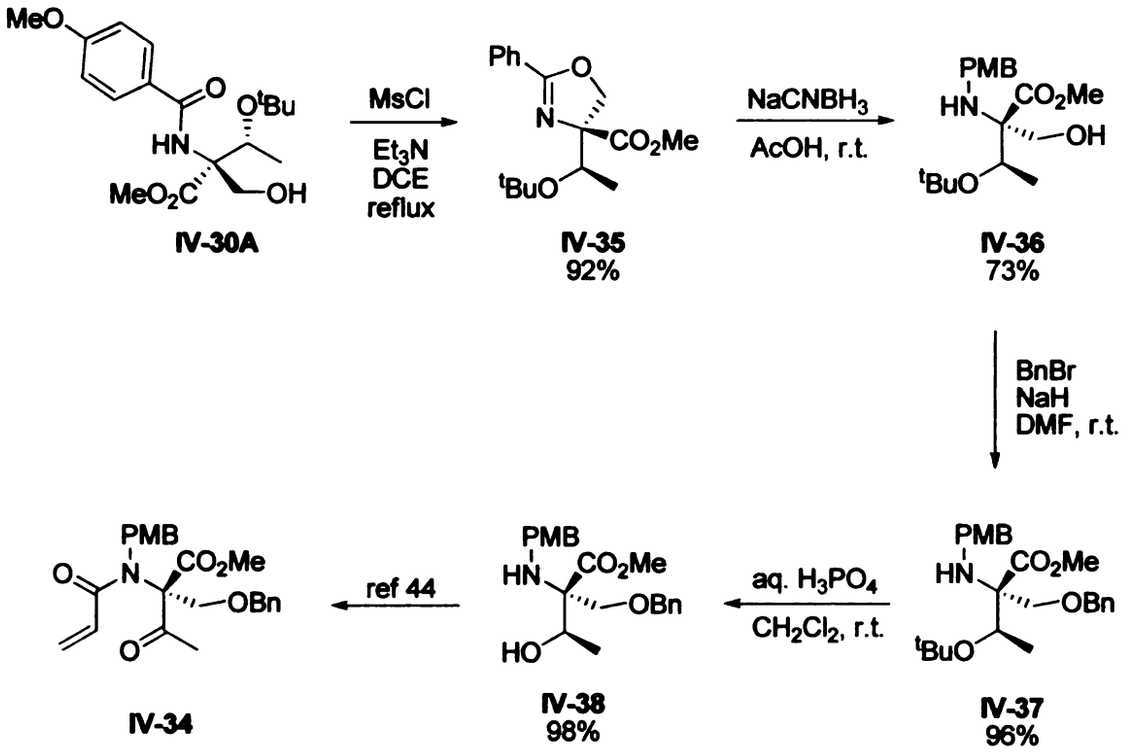


IV-34 **Salinosporamide A**

Scheme IV-11. Corey's synthesis of Salinosporamide A.

To illustrate the potential of using ene-type alkylations of oxazol-5(4H)-ones and enol ethers towards the synthesis of compounds containing *tert*-alkyl amino hydroxy carboxylic acid cores, Robert A. Mosey of the Tepe research lab synthesized Corey's key intermediate **IV-34** starting from compound **IV-30A** (Scheme IV-12).[47] Mosey's synthesis of compound **IV-34** began with the cyclodehydration of **IV-30A** with MsCl to form oxazoline **IV-35**, which was subsequently reduced to amino alcohol **IV-36** using sodium borocyanohydride. Protection of the primary alcohol found in **IV-36** followed by deprotection of the *tert*-butyl group in amino ester **IV-37** using aqueous phosphoric acids afforded amino alcohol **IV-38**.[48] Acylation of **IV-38** with acrylyl chloride utilizing Corey's

conditions followed by Dess Martin oxidation of the secondary alcohol produced Corey's key intermediate **IV-34**.[46]



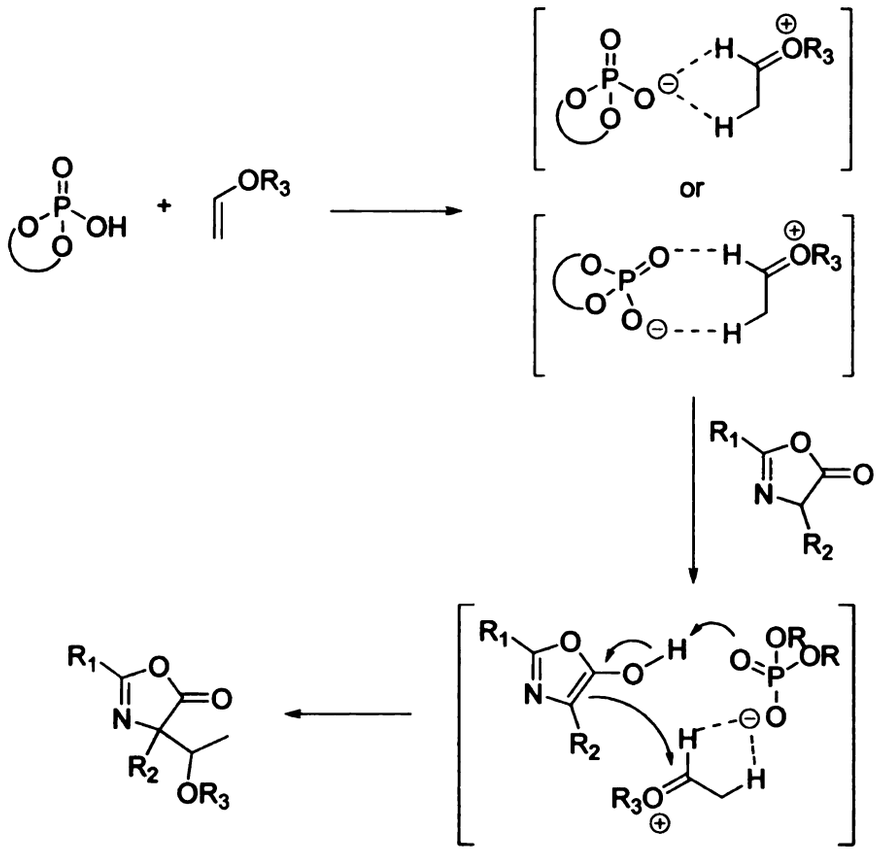
Scheme IV-12. Synthesis of Corey's intermediate **IV-34** starting from **IV-30A**.

L. Chiral Brønsted acid catalyzed ene-type reactions of oxazol-5(4H)-ones and enol ethers as reported by Terada and co-workers.

Chiral Brønsted acids have emerged as very useful catalysts for promoting a wide variety of enantioselective chemical transformations. This class of organocatalysts is typically divided into two different classes: neutral and strong.[37,45,49] Neutral chiral Brønsted acids rely on their ability to hydrogen bond to Lewis basic heteroatom sites of the substrates involved, thus providing a chiral environment for the desired transformation to occur. These catalysts consist of chiral ureas, thioureas, alcohols, amides, and many more.[37,45,49] On the contrary,

stronger chiral Brønsted acids are much more acidic allowing them to initially protonate the reactants producing a highly electrophilic substrate. Coordination of the chiral conjugate base of the catalyst to the newly formed electrophilic substrate establishes a chiral environment helping to afford the enantioselectivity observed in corresponding reactions. Found within this class of chiral Brønsted acids are carboxylic acids, sulfonic acids, Lewis acid coordinated alcohols, ammonium salts and phosphoric acids.[37,45,49]

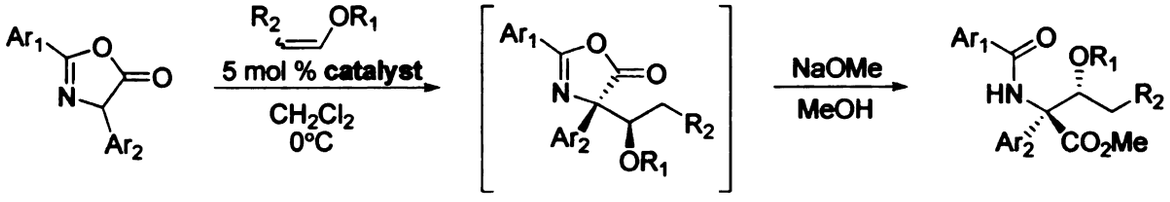
Given our results utilizing achiral phosphoric acids for increasing the diastereoselectivity of our ene-type reactions of oxazol-5(4H)-ones with enol ethers, we rationalized that chiral phosphoric acids may not only help increase the diastereoselectivity but also the enantioselectivity of these reactions. Protonation of the starting enol ether by the chiral phosphoric acid would result in the formation of an ion pair ion consisting of an oxonium ion stabilized by the chiral conjugate base of the phosphoric acid (Scheme IV-13). Studies by Terada and co-workers have demonstrated through a combination of DFT studies and deuterium labeling studies that oxonium ions are likely to be stabilized by phosphonates via hydrogen bonding interactions as illustrated in Scheme IV-13 below.[4] The acidic protons of the oxonium ion are proposed to interact with the anionic sites of the chiral conjugate base. Formation of the chiral oxonium / phosphonate ion pair results in the formation of a highly electrophilic center which would subsequently undergo an ene-type reaction while in the presence of the oxazol-5(4H)-one substrate.



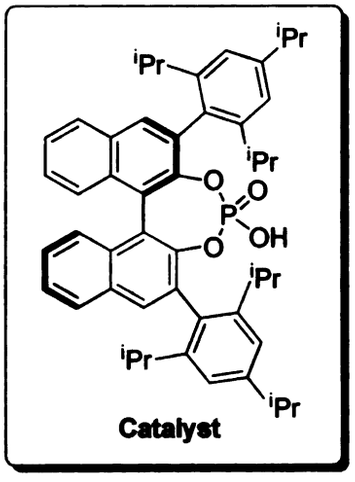
Scheme IV-13. Enantioselective ene-type reaction of oxazol-5(4H)-ones and enol ethers.

Unfortunately, soon after our initial publication regarding the diastereoselective Brønsted acid catalysis of our ene-type methodology, Terada and co-workers reported the first enantioselective version of the chemistry.[4] They demonstrated the use of chiral BINOL phosphoric acids for promoting the enantioselective ene-type reaction of oxazol-5(4H)-ones with enol ethers (Scheme IV-14). Their methodology provided high yields of quaternary oxazolones with excellent diastereoselectivity and enantioselectivity. The products major diastereomer obtained in their reactions illustrated the same stereochemical relationship as we observed in our reactions. The quaternary oxazolones generated in the reactions were subsequently treated with sodium

methoxide to provide novel α,α-disubstituted α-amino acid derivatives with high levels of enantiomeric excess. Their studies indicated that aromatic substituents more electron-donating in nature at the Ar_1 position helped to increase the stereoselectivity of the reaction. Enol ethers containing larger protecting groups (e.g. *tert*-butyl) exhibited higher diastereoselectivity than those with less sterically demanding protecting groups (e.g. *n*-butyl).



Yields up to 99%
d.r. up to 98:2
e.e. up to 98%



Scheme IV-14. Terada's enantioselective ene-type reaction of oxazol-5(4H)-ones and enol ethers.

M. Experimental

1. General information.

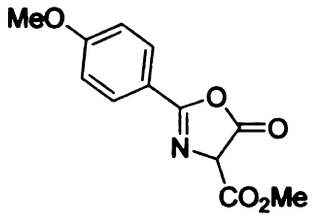
Reactions were carried out in flame-dried glassware under nitrogen atmosphere. All reactions were magnetically stirred and monitored by TLC with 0.25 μm pre-coated silica gel plates using either UV light or iodine to visualize the compounds. Column chromatography was carried out on Silica Gel 60 (230-400 mesh) supplied by EM Science. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise noted. Infrared spectra were recorded on a Nicolet IR/42 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity Plus-500 spectrometer. Chemical shifts are reported relative to the residue peaks of the solvent ($CDCl_3$: 7.24 ppm for ^{1}H and 77.0 ppm for ^{13}C) (DMSO-d_6: 2.49 ppm for ^{1}H and 39.5 ppm for ^{13}C). The following abbreviations are used to denote the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, and m = multiplet. Diastereomeric ratios were determined using the integration values obtained from ^{1}H NMR. Gas chromatography / low resolution mass spectra were recorded on a Hewlet-Packard 5890 Series II gas chromatograph connected to a TRIO-1 EI mass spectrometer. HRMS were obtained at the Mass Spectrometry Facility of Michigan State University with a JEOL JMS HX-110 mass spectrometer. Elemental analysis data were obtained on a Perkin Elmer 2400 Series II CHNS/O analyzer. Melting points were obtained using an Electrothermal® capillary melting point apparatus and are uncorrected.

2. Materials.

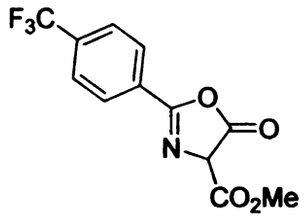
Reagents and solvents were purchased from commercial suppliers and used without further purification. Anhydrous methylene chloride, benzene, acetonitrile, and tetrahydrofuran were dispensed from a delivery system which passes the solvents through a column packed with dry neutral alumina. Ethyl vinyl ether **IV-17**, *tert*-butyl vinyl ether **III-6**, 3,4-dihydro-2H-pyran **III-10**, 2-methoxy propene **III-18**, trifluoroacetic anhydride, diphenyl phosphate **IV-3**, camphor sulfonic acid **IV-4**, trifluoroacetic acid **IV-5**, and 3,5-dinitrobenzoic acid **IV-2** were all purchased from Sigma Aldrich, checked for purity and used without further purification.

3. General procedure for the synthesis of oxazol-5(4H)-ones IV-27 to IV-29:

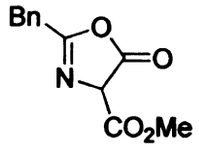
Oxazol-5(4H)-ones **IV-27** through **IV-29** were synthesized using a known literature procedure.[4] A suspension of carboxylic acid in anhydrous diethyl ether was treated with TFAA (2.2 equiv.) dropwise and then stirred for 1.5 hours. The reaction was then cooled to 0 °C and water (1.1 equiv.) was added dropwise, after which the ice bath was removed and the reaction stirred for an additional 1.5 hours. The reaction was cooled in a freezer for 30 minutes causing the oxazole-5(4H)-one product to precipitate out of solution which was collected *via* filtration and washed with cold diethyl ether. The oxazol-5(4H)-ones were then analyzed and used without further purification.



IV-27



IV-28



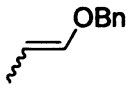
IV-29

2-(4-methoxyphenyl)-4-carbomethoxy-5(4H)-oxazolone (IV-27), 2-(4-(trifluoromethyl)phenyl)-4-carbomethoxy-5(4H)-oxazolone (IV-28), and 2-benzyl-4-carbomethoxy-5(4H)-oxazolone (IV-29): Oxazol-5(4H)-ones **IV-27** to **IV-29** were all prepared according to a modified published procedure. The procedure used is very similar to the general procedure written above. These compounds were prepared and fully characterized by Robert A. Mosey. For further details regarding either the synthesis or characterization of these compounds, please see the PhD thesis of Robert A. Mosey or the supporting information of the following publication:

Mosey, R. A.; Fisk, J. S.; Friebe, T. L.; Tepe, J. J. *Org. Lett.* **2008**, *10*, 825-828.

4. Synthesis of other enol ethers.

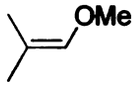
The following enol ethers used in these studies were purchased and used as received: **IV-6** (*tert*-butyl vinyl ether), **IV-10** (3,4-dihydro-(2H)-pyran), **IV-18** (2-methoxypropene), **IV-17** (ethyl vinyl ether). Synthesis and characterization regarding **III-28** (1-butoxyethyne) can be found in chapter III. Benzyl vinyl ether **IV-16** was made Robert A. Mosey according to a literature procedure.[50] All other enol ethers used in these studies were prepared as follows:



(5 : 1 mixture of diastereomers)

IV-18

1-((prop-1-enyloxy)methyl)benzene (IV-18): This compound was made according to a literature procedure.[51] A solution of aluminum chloride (3.12 g, 23.40 mmol) in 60 mL of diethyl ether was treated with triethylamine (4.73g, 46.79 mmol) dropwise over 10 minutes. The solution was stirred for 2 hours and then 1-((1-(benzyloxy)propoxy)methyl) benzene (3.00 g, 11.70 mmol) was added dropwise over 10 minutes. The solution was stirred under reflux for 24 hours after which it was washed with 10% NaOH (2 x 50 mL) and dried over magnesium sulfate. The solution was concentrated *in vacuo* and the resulting crude oil was purified via column chromatography (hexanes) yielding 0.51 g (29% yield) of the title compound as a yellowish oil (5 : 1 mixture of trans to cis isomers). The spectra matches that previously reported in the literature.[52] **Trans Isomer:** ^{1}H NMR (500 MHz) ($CDCl_3$): δ 1.62 (dd, J_1 = 1.5 Hz, J_2 = 7 Hz, 3H), 4.43 (p, J = 7 Hz, 1H), 4.79 (s, 2H), 6.02 (dq, J_1 = 7 Hz, J_2 = 1.5 Hz, 1H), 7.28-7.36 (m, 5H); ^{13}C NMR (125 MHz) ($CDCl_3$): δ 9.32, 73.48, 101.85, 127.26, 127.52, 128.44, 137.36, 145.17; **Cis Isomer:** ^{1}H NMR (500 MHz) ($CDCl_3$): δ 1.55 (dd, J_1 = 1.5 Hz, J_2 = 7 Hz, 3H), 4.70 (s, 2H), 4.86-4.92 (m, 1H), 6.30 (dq, J_1 = 12.5 Hz, J_2 = 1.5 Hz, 1H), 7.28-7.36 (m, 5H); ^{13}C NMR (125 MHz) ($CDCl_3$): δ 12.60, 71.09, 99.45, 127.52, 127.77, 128.43, 137.36, 146.26.

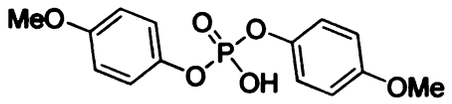


IV-19

1-methoxy-2-methylprop-1-ene (IV-19): This compound was made according to literature procedure.[53] A solution of 1,1-dimethoxy-2-methylpropane (16.2 g, 137 mmol) in 10 mL of quinoline was treated with a substoichiometric amount of toluene sulfonic acid (~75 mg). A simple distillation head was placed on the flask. The solution was heated and the desired product was distilled over (b.p. = 69 °C, lit b.p. = 70 °C) as it formed resulting in 8.5 g (72% yield) of the title compound as a clear oil. The spectra matches that previously reported in the literature. ^{1}H NMR (500 MHz) ($CDCl_3$): δ 1.52 (s, 3H), 1.58 (s, 3H), 3.51 (s, 3H), 5.72 (s, 1H); ^{13}C NMR (125 MHz) ($CDCl_3$): δ 14.78, 19.45, 59.15, 110.28, 141.40. LRMS(EI): *m/z* calcd for $C_5H_{10}O$ 86.1 found, 86.2.

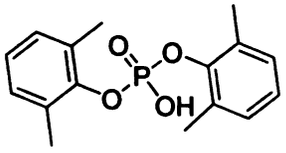
5. Synthesis of phosphoric acid derivatives.

The following phosphoric acids used in these studies were purchased and used as received: **IV-3** (diphenyl phosphate) and **IV-15** ((R)-(-)-1,1'-binaphthyl-2,2'-diylhydrogenphosphate). All other phosphoric acids used in these studies were prepared as follows:



IV-11

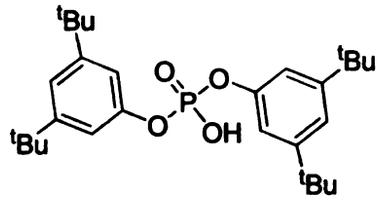
Bis(4-methoxyphenyl)phosphate (IV-11): A solution of 4-methoxy phenol (1.0 g, 8.06 mmol), triethyl amine (0.85 g, 8.46 mmol) and 20 mL of anhydrous CH_2Cl_2 was treated with $POCl_3$ (0.62 g, 4.03 mmol) dropwise at 0°C over twenty minutes. The solution was stirred for 2 hours and then washed with 1M HCl (3 x 20 mL). It was dried over sodium sulfate and the solution was concentrated *in vacuo*. The resulting brown oil was dissolved into 10 mL of acetone and treated with 2 mL of water. After 2 hours of stirring, the solution was partitioned between CH_2Cl_2 and water. Upon separation of the layers the CH_2Cl_2 phase was dried over sodium sulfate and concentrated *in vacuo*. The resulting solid was recrystallized using EtOAc and hexanes to yield 0.5 g (39% yield) of the title compound as a white crystalline solid. ^{1}H NMR (500 MHz), $CDCl_3$: δ 7.34 (s, 6H), 6.77 (d, J = 9 Hz, 4H), 7.04 (d, J = 9.5 Hz, 4H), 11.20 (bs, 1H); ^{13}C NMR (125 MHz) $CDCl_3$: 55.54, 55.62, 114.59, 114.60, 121.03, 121.07, 143.97, 144.03, 156.89, 156.90.



IV-12

Bis(2,6-dimethylphenyl)phosphate (IV-12): A solution of 2,6-dimethylphenol (0.98 g, 8.0 mmol), triethyl amine (0.85 g, 8.4 mmol) and 20 mL of anhydrous CH_2Cl_2 was treated with $POCl_3$ (0.61 g, 4.0 mmol) dropwise at 0°C over twenty

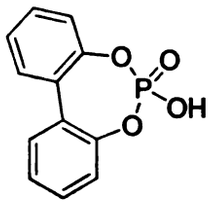
minutes. The solution was stirred for 2 hours and then washed with 1M HCl (3 x 20 mL). It was dried over sodium sulfate and the solution was concentrated *in vacuo.* The resulting brown oil was dissolved into 10 mL of acetone and treated with 2 mL of water. After 2 hours of stirring, the solution was partitioned between CH_2Cl_2 and water. Upon separation of the layers the CH_2Cl_2 phase was dried over sodium sulfate and concentrated *in vacuo.* The resulting solid was recrystallized using EtOAc and hexanes to yield 0.57 g (45% yield) of the title compound as a white crystalline solid. ^1H NMR (500 MHz), $CDCl_3$: 2.21 (s, 12H), 6.92-7.00 (m, 6H), 10.93 (bs, 1H); ^{13}C NMR (125 MHz) $CDCl_3$: 16.75, 16.70, 125.20, 125.21, 128.93, 128.94, 130.34, 130.37, 148.05, 148.12; LRMS(EI): *m/z* calcd for $C_{16}H_{19}O_4P$ 306.3 found, 306.0.



IV-13

Bis(3,5-*tert*-butylphenyl)phosphate (IV-13): A solution of 3,5-di-*tert*-butyl phenol (1.65 g, 8.0 mmol), triethyl amine (0.85 g, 8.4 mmol) and 20 mL of anhydrous CH_2Cl_2 was treated with $POCl_3$ (0.61 g, 4.0 mmol) dropwise at 0°C over twenty minutes. The solution was stirred for 1 hour and then washed with 1M HCl (3 x 20 mL). It was dried over sodium sulfate and the solution was concentrated *in vacuo.* The resulting clear oil was dissolved into 10 mL of acetone and treated with 2 mL of water. After 12 hours of stirring, the solution was partitioned between CH_2Cl_2 and water. Upon separation of the layers the

CH_2Cl_2 phase was dried over sodium sulfate and concentrated *in vacuo* yielding the title compound as a clear oil. The product was used in subsequent steps without further purification. ^1H NMR (500 MHz), $CDCl_3$: δ 1.31 (s, 36H), 7.07 (s, 4H), 7.22 (s, 2H), 11.61 (bs, 1H); ^{13}C NMR (125 MHz) $CDCl_3$: 31.80, 35.22, 114.01, 119.50, 150.03, 152.31.

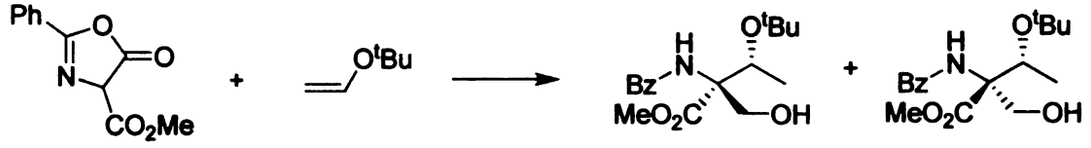


IV-14

2,2'-biphenylphosphoric acid (IV-14): A solution of 2,2'biphenol (1.0 g, 5.37 mmol) and 8.7 mL of pyridine was treated dropwise with $POCl_3$ (1.65 g, 10.8 mmol) at room temperature over 20 minutes. The solution was then stirred at room temperature for 4 hours before being cooled to 0 °C. The solution was then treated dropwise with 9 mL of water and stirred for an additional 30 minutes. The solution was then partitioned between CH_2Cl_2 and water. The CH_2Cl_2 layer was washed with 1M HCl (3 x 50 mL), dried over sodium sulfate, and concentrated *in vacuo* to yield 0.3 g (23% yield) of the title compound as an off-white solid. The compound was used without further purification. ^1H NMR (500 MHz), DMSO-d^6: δ 7.27 (d, J = 8 Hz, 2H), 7.38 (t, J = 7.5 Hz, 2H), 7.49 (t, J = 8 Hz, 2H), 7.61 (d, J = 8 Hz, 2H), 13.19 (bs, 1H); ^{13}C NMR (125 MHz) DMSO-d^6: 121.43, 121.47, 125.89, 128.44, 129.74, 129.98, 148.16, 148.23; LRMS(EI): *m/z* calcd for $C_{12}H_9O_4P$ 248.2 found, 248.0.

6. Synthesis of *tert*-alkyl amino hydroxy carboxylic esters:

General procedure for alkylation reaction. To a stirring suspension of oxazolone (0.5 mmol) in 20 mL of solvent were successively added enol ether (0.75 mmol) and diphenyl phosphate (0.05 mmol) under nitrogen atmosphere for the requisite amount of time as monitored by TLC. The reaction was washed successively with saturated $NaHCO_3$ solution and brine before being dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction was diluted in THF and cooled to 0°C before $NaBH_4$ (1 mmol) and cold H_2O were added. The reaction stirred at 0°C until complete by TLC. Saturated NH_4Cl solution was added and the organic layer was extracted with CH_2Cl_2 (x3). The combined organic extractions were dried ($MgSO_4$) and concentrated. The crude reaction mixtures were purified via column chromatography on silica gel (diethyl ether / CH_2Cl_2).



III-5 **III-6** **IV-1A** Major Diastereomer **IV-1B** Minor Diastereomer

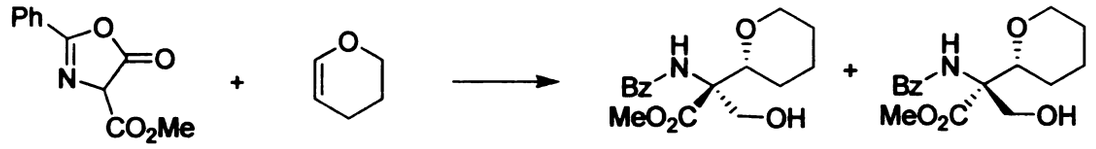
Methyl-2-benzamido-3-*tert*-butoxy-2-(hydroxymethyl)butanoate (IV-1): Using the general procedure, a suspension of 4-carbmethoxy-2-phenyl-5(4H)-oxazolone **III-5** (0.10 g, 0.46 mmol), *tert*-butyl vinyl ether **III-6** (69.11 mg, 0.69 mmol), diphenyl phosphate **IV-3** (11.51 mg, 0.05 mmol) and 20 mL of anhydrous benzene was stirred at room temperature for 1 hour. After washings, the crude reaction intermediate was diluted in 2 mL THF and cooled to 0 °C before $NaBH_4$ (34.8 mg, 0.92 mmol) and water (30 mL) were added. Purification via silica gel

chromatography (7% ether / 93% CH_2Cl_2) afforded 0.14 g of the title compound (90% yield) as a 3:1 ratio of diastereomers.

IV-1A (Major Diastereomer) (solid, m.p. = 83 – 85 °C): ^{1}H NMR (500 MHz) ($CDCl_3$): δ 1.12 (s, 9H), 1.30 (d, J = 6.3 Hz, 3H), 3.79 (s, 3H), 3.95 (dd, J_1 = 7.2 Hz, J_2 = 11.6 Hz, 1H), 4.26 (dd, J_1 = 6.3 Hz, J_2 = 11.7 Hz, 1H), 4.37 (q, J = 6.3 Hz, 1H), 4.57 (t, J = 6.7 Hz, 1H), 7.41–7.46 (m, 3H), 7.50 (t, J = 7.4 Hz, 1H), 7.79 (d, J = 7.7 Hz, 2H). ^{13}C NMR + **DEPT** (125 MHz) ($CDCl_3$) δ: 17.9 (-CH_3), 28.6 (-CH_3), 52.6 (-CH_3), 64.1 (-CH_2), 69.8 (-CH), 72.1 (quaternary C), 75.2 (quaternary C), 127.1 (aromatic CH), 128.7 (aromatic CH), 131.8 (aromatic CH), 134.6 (aromatic quaternary C), 169.4 (quaternary C), 171.3 (quaternary C). IR (neat): 3412 cm^{-1}, 3320 cm^{-}1, 1736 cm^{-1}, 1653 cm^{-1}, 1522 cm^{-1}, 1487 cm^{-1}. MS (GCMS), calcd for $C_{17}H_{25}NO_5$ (M^+) – CH_2OH: 292.15. Found: 290.9. Anal. Calcd. For $C_{17}H_{25}NO_5$: C, 63.14; H, 7.79; N, 4.33. Found: C, 63.04; H, 7.73; N, 4.55.

IV-1B (Minor Diastereomer) (solid, m.p. = 76 °C – 79 °C): ^{1}H NMR (500 MHz) ($CDCl_3$): δ 1.13 (d, J = 6.2 Hz, 3H), 1.16 (s, 9H), 3.74 (s, 3H), 3.83 (t, J = 11.8 Hz, 1H), 3.95 (dd, J_1 = 2.8 Hz, J_2 = 11.8 Hz, 1H), 4.27 (q, J = 6.2 Hz, 1H), 5.71 (dd, J_1 = 2.8 Hz, J_2 = 11.6 Hz, 1H), 7.26 (bs, 1H), 7.42 – 7.54 (m, 3H), 7.79 (dd, J_1 = 3.2 Hz, J_2 = 5.3 Hz, 2H). ^{13}C NMR (125 MHz) + **DEPT** ($CDCl_3$) δ: 19.1 (-CH_3), 28.7 (-CH_3), 52.7 (-CH_3), 64.6 (-CH_2), 68.6 (-CH), 70.0 (quaternary C), 74.8 (quaternary C), 127.0 (aromatic CH), 128.6 (aromatic CH), 131.8 (aromatic CH), 134.2 (aromatic quaternary C), 167.7 (quaternary C), 171.2 (quaternary C). IR (neat): 3405 cm^{-1}, 3584 – 3156 cm^{-1}, 1752 cm^{-1}, 1669 cm^{-1}, 1520 cm^{-1}, 1487cm^{-1}.

MS (GCMS), calcd for $C_{17}H_{25}NO_5$ (M^+): 323.17. Found: 324.6. Anal. Calcd. For $C_{17}H_{25}NO_5$: C, 63.14; H, 7.79; N, 4.33. Found: C, 61.94; H, 7.94; N, 4.38.



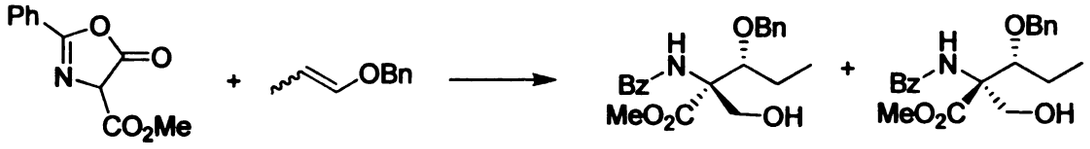
III-5 **III-10** **IV-22A** Major Diastereomer **IV-22B** Minor Diastereomer

Methyl-2-(benzamido)-2-(tetrahydro-2H-pyran-2-yl)-3-hydroxypropanoate (IV-22): Using the general procedure, a suspension of 4-carbmethoxy-2-phenyl-5(4H)-oxazolone **III-5** (0.1 g, 0.46 mmol), 3,4-dihydro-2H-pyran **III-10** (58.0 mg, 0.69 mmol), and diphenyl phosphate **IV-3** (11.5 mg, 0.05 mmol) in 20 mL of anhydrous benzene was stirred at 50 °C for 18 hours. After washings, the crude reaction intermediate was diluted in 2 mL THF and cooled to 0 °C before $NaBH_4$ (34.8 mg, 0.92 mmol) and water (1 mL) were added. Purification via silica gel chromatography (20% ether / 80% CH_2Cl_2) afforded 0.08 g of the title compound (57% yield) as a 1.6 :1 ratio of diastereomers.

IV-22A (Major Diastereomer) (oil): ^{1}H NMR (500 MHz) ($CDCl_3$): δ 1.39-1.50 (m, 1H), 1.49-1.58 (m, 4H), 1.85-1.89 (m, 1H), 3.45 (td, J_1 = 10 Hz, J_2 = 3 Hz, 1H), 3.76 (s, 3H), 3.86 (t, J = 11.5 Hz, 1H), 3.93 (dd, J_1 = 2 Hz, J_2 = 11 Hz, 1H), 3.97-4.00 (m, 1H), 4.02 (dd, J_1 = 3 Hz, J_2 = 12 Hz, 1H), 5.36 (dd, J_1 = 3 Hz, J_2 = 11 Hz, 1H), 7.07 (bs, 1H), 7.42-7.45 (m, 2H), 7.49-7.52 (m, 1H), 7.77-7.79 (m, 2H); ^{13}C NMR + DEPT (125 MHz) ($CDCl_3$): δ 22.56 (-CH2), 25.43 (-CH2), 25.78 (-CH2), 52.80 (-CO2CH3), 63.37 (-CH2), 68.94 (-CH2), 70.38 (quaternary C),

79.70 (-CH), 127.05 (aromatic –CH), 128.61 (aromatic –CH), 128.61 (aromatic –CH), 131.82 (aromatic –CH), 134.46 (quaternary aromatic C), 169.15 (quaternary C), 171.05 (quaternary C); IR (neat): 3410 cm^{-1}, 3360 cm^{-1}, 2947 cm^{-1}, 1743 cm^{-1}, 1657 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{16}H_{22}NO_5$ [M + H], 308.1496; found, 308.1498.

IV-22B (Minor Diastereomer) (solid, m.p. = 132 °C – 134 °C): ^1H NMR (500 MHz) ($CDCl_3$): δ 1.46-1.54 (m, 4H), 1.74-1.78 (m, 1H), 1.86-1.90 (m, 1H), 3.44 (t, J = 10Hz, 1H), 3.76 (s, 3H), 3.91 (d, J = 10.5 Hz, 1H), 4.01-4.07 (m, 2H), 4.19 (d, J = 11.5 Hz, 1H), 4.30 (t, J = 6.5 Hz, 1H), 7.30 (bs, 1H), 7.40-7.43 (m, 2H), 7.48-7.51 (m, 1H), 7.77-7.79 (m, 2H); ^{13}C NMR + DEPT (125 MHz) ($CDCl_3$): δ 23.08 (-CH2), 25.68 (-CH2), 26.67 (-CH2), 52.64 (-CO2CH3), 64.15 (-CH2), 67.92 (quaternary C), 69.47 (-CH2), 78.90 (-CH), 127.12 (aromatic –CH), 128.55 (aromatic –CH), 131.80 (aromatic –CH), 134.16 (quaternary aromatic C), 167.88 (quaternary C), 170.41 (quaternary C); IR (KBr): 3449 cm^{-1}, 3358 cm^{-1}, 2946 cm^{-1}, 1743 cm^{-1}, 1655 cm^{-1}, 1527 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{16}H_{22}NO_5$ [M + H], 308.1495; found, 308.1498.



III-5 **IV-18** **IV-23A** Major Diastereomer **IV-23B** Minor Diastereomer

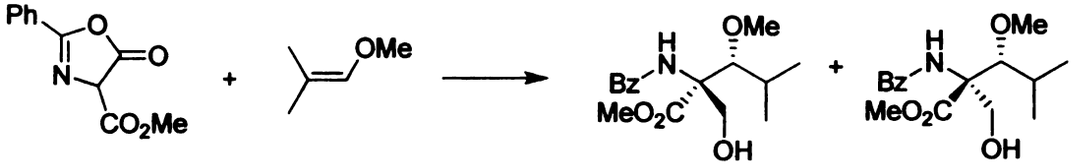
Methyl-2-(benzamido)-3-(benzyloxy)-2-(hydroxymethyl)pentanoate (IV-23): Using the general procedure, a suspension of 4-carbmethoxy-2-phenyl-5(4H)-

oxazolone **III-5** (100.0 mg, 0.46 mmol), 1-((prop-1-enyloxy)methyl)benzene **IV-18** (102.3 mg, 0.69 mmol), and diphenyl phosphate **IV-3** (11.5 mg, 0.05 mmol) in 20 mL of anhydrous benzene was stirred at room temperature for 21 hours. After washings, the crude reaction intermediate was diluted in 2 mL THF and cooled to 0 °C before $NaBH_4$ (34.8 mg, 0.92 mmol) and water (1 mL) were added. Purification via silica gel chromatography (10% ether / 90% CH_2Cl_2) afforded 0.08 g of the title compound (48% yield), separated as a 69 : 31 ratio of diastereomers.

IV-23A (Major Diastereomer) (solid, m.p. = 85 °C – 87 °C): ^{1}H NMR (500 MHz) ($CDCl_3$): δ 1.09 (t, J = 7 Hz, 3H), 1.72-1.82 (m, 1H), 1.81-1.89 (m, 1H), 3.85 (s, 3H), 4.01 (dd, J_1 = 5.5 Hz, J_2 = 10 Hz, 1H), 4.23 (dd, J_1 = 3 Hz, J_2 = 9.5 Hz, 1H), 4.37-4.43 (m, 2H), 4.66 (d, J = 11.5 Hz, 1H), 4.71 (d, J = 11 Hz, 1H), 7.25-7.34 (m, 5H), 7.39 (bs, 1H), 7.40-7.44 (m, 2H), 7.50-7.54 (m, 1H), 7.73-7.75 (m, 2H); ^{13}C NMR + DEPT (125 MHz) ($CDCl_3$): δ 11.10 (-CH3), 24.53 (-CH2), 52.90 (-CO2CH3), 64.48 (-CH2), 69.74 (quaternary C), 75.36 (-CH2), 81.59 (-CH), 127.04 (aromatic –CH), 127.61 (aromatic –CH), 127.77 (aromatic –CH), 128.40 (aromatic –CH), 128.62 (aromatic –CH), 131.90 (aromatic –CH), 133.84 (quaternary aromatic C), 137.85 (quaternary aromatic C), 167.70 (quaternary C), 171.35 (quaternary C); IR (KBr): 3406 cm^{-1}, 3390 cm^{-1}, 2973 cm^{-1}, 1744 cm^{-1}, 1651 cm^{-1}, 1526 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{21}H_{26}NO_5$ [M + H], 372.1813; found, 372.1811.

IV-23B (Minor Diastereomer) (oil): ^{1}H NMR (500 MHz) ($CDCl_3$): δ 1.30 (t, J = 7.5 Hz, 3H), 1.52-1.64 (m, 2H), 3.77 (s, 3H), 3.88 (t, J = 11.5 Hz, 1H), 4.04-4.09

(m, 2H), 4.51 (d, J = 11 Hz, 1H), 4.59 (d, J = 11 Hz, 1H), 5.60 (dd, J_1 = 3 Hz, J_2 = 11.5 Hz, 1H), 7.13 (bs, 1H), 7.27-7.36 (m, 5H), 7.40-7.43 (m, 2H), 7.49-7.52 (m, 1H), 7.74-7.76 (m, 2H); ^{13}C NMR + DEPT (125 MHz) ($CDCl_3$): δ 10.51 (-CH3), 23.26 (-CH2), 52.78 (-CO2CH3), 64.01 (-CH2), 71.15 (quaternary C), 74.01 (-CH2), 82.72 (-CH), 127.08 (aromatic –CH), 127.89 (aromatic –CH), 128.08 (aromatic –CH), 128.49 (aromatic –CH), 128.66 (aromatic –CH), 131.89 (aromatic –CH), 134.34 (quaternary aromatic C), 137.36 (quaternary aromatic C), 169.18 (quaternary C), 171.51 (quaternary C); IR (neat): 3408 cm^{-1}, 3310 cm^{-1}, 3030 cm^{-1}, 2951 cm^{-1}, 1749 cm^{-1}, 1660 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{21}H_{26}NO_5$ [M + H], 372.1813; found, 372.1811.



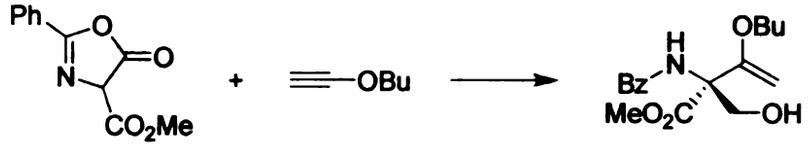
III-5 IV-19 IV-24A Major Diastereomer IV-24B Minor Diastereomer

Methyl-2-(benzamido)-3-(methoxy)-2-(hydroxymethyl)-4-methylpentanoate (IV-24): Using the general procedure, a suspension of 4-carbmethoxy-2-phenyl-5(4H)-oxazolone **III-5** (0.1 g, 0.46 mmol), 1-methoxy-2-methylprop-1-ene **IV-19** (59.4 mg, 0.69 mmol), and diphenyl phosphate **IV-3** (11.5 mg, 0.05 mmol) in 20 mL of anhydrous benzene was stirred at 50 °C for 15 hours. After washings, the crude reaction intermediate was diluted in 2 mL THF and cooled to 0 °C before $NaBH_4$ (34.8 mg, 0.92 mmol) and water (1 mL) were added. Purification via silica

gel chromatography (15% ether / 85% CH_2Cl_2) afforded 0.05 g of the title compound (33% yield), separated as a 1.5:1 ratio of diastereomers.

IV-24 (Major Diastereomer) (oil): ^{1}H NMR (500 MHz) ($CDCl_3$): δ 1.06 (dd, J_1 = 7 Hz, J_2 = 1.5 Hz, 6H), 1.86 (septet of doublets, J_1 = 7 Hz, J_2 = 3 Hz, 1H), 3.56 (s, 3H), 3.77 (s, 3H), 3.77-3.80 (m, 1H), 3.81 (d, J = 2.5 Hz, 1H), 4.21 (d, J = 7 Hz, 1H), 4.40 (d, J = 11.5 Hz, 1H), 6.96 (bs, 1H), 7.41-7.45 (m, 2H), 7.49-7.52 (m, 1H), 7.74-7.76 (m, 2H); ^{13}C NMR + DEPT (125 MHz) ($CDCl_3$): δ 16.48 (-CH3), 22.19 (-CH3), 31.12 (-CH), 52.55 (-CO2CH3), 62.52 (-CH3), 65.02 (-CH2), 68.29 (quaternary –C), 84.41 (-CH), 127.05 (aromatic –CH), 128.67 (aromatic –CH), 131.87 (aromatic –CH), 134.02 (quaternary aromatic C), 167.49, 171.88; IR (neat): 3416 cm^{-1}, 2959 cm^{-1}, 1736 cm^{-1}, 1662 cm^{-1}, 1514 cm^{-1}, 1481 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{16}H_{24}NO_5$ [M + H], 310.1652; found, 310.1654.

IV-24B (Minor Diastereomer) (oil): ^{1}H NMR (500 MHz) ($CDCl_3$): δ 0.96 (d, J = 6.5 Hz, 3H), 1.05 (d, J = 7 Hz, 3H), 1.87 (septet of doublets, J_1 = 6.5 Hz, J_2 = 2 Hz, 1H), 3.41 (s, 3H), 3.80 (s, 3H), 3.87 (t, J = 11.5 Hz, 1H), 4.02 (dd, J_1 = 12 Hz, J_2 = 2.5 Hz, 1H), 5.84 (dd, J_1 = 11.5 Hz, J_2 = 2.5 Hz, 1H), 7.13 (bs, 1H), 7.43-7.47 (m, 2H), 7.51-7.53 (m, 1H), 7.77-7.80 (m, 2H); ^{13}C NMR + DEPT (125 MHz) ($CDCl_3$): δ 16.35 (-CH3), 21.86 (-CH3), 29.33 (-CH3), 52.96 (-CO2CH3), 61.14 (-CH3), 63.78 (-CH2), 70.57 (quaternary C), 86.40 (-CH), 127.02 (aromatic –CH), 128.74 (aromatic –CH), 131.93 (aromatic –CH), 134.37 (quaternary aromatic –C), 168.54, 172.00; IR (neat): 3408 cm^{-1}, 3306 cm^{-1}, 2959 cm^{-1}, 1749 cm^{-1}, 1658 cm^{-1}, 1522 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{16}H_{24}NO_5$ [M + H], 310.1652; found, 310.1654.



III-5 **III-29** **IV-25**

Methyl-2-(benzamido)-3-butoxy-2-(hydroxymethyl)but-3-enoate (IV-25): Using the general procedure, a suspension of 4-carbmethoxy-2-phenyl-5(4H)-oxazolone **III-5** (0.11 g, 0.49 mmol) and butoxyethyne **III-29** (72.7 mg, 0.74 mmol) in 20 mL of anhydrous dichloromethane was stirred at room temperature overnight. After concentration, the crude reaction intermediate was diluted in 3 mL THF and cooled to -41°C before anhydrous EtOH (1.5 mL) and $NaBH_4$ (92.7 mg, 2.45 mmol) was added. Purification via silica gel chromatography (15% ether / 85% CH_2Cl_2) afforded 0.11 g of the title compound (67% yield) as an oil. ^1H NMR (500 MHz) ($CDCl_3$): δ 0.90 (t, J = 7.4 Hz, 3 H), 1.33 – 1.41 (m, 2 H), 1.60 – 1.68 (m, 2 H), 3.40 (dd, J_1 = 5.1 Hz, J_2 = 8.7 Hz, 1 H), 3.70 – 3.76 (m, 2 H), 3.80 (s, 3 H), 4.15 (dd, J_1 = 8.7 Hz, J_2 = 11.3 Hz, 1 H), 4.26 (d, J = 3.7 Hz, 1 H), 4.32 (d, J = 3.7 Hz, 1 H), 4.47 (dd, J_1 = 4.9 Hz, J_2 = 11.4 Hz, 1 H), 7.33 (bs, 1 H), 7.41 – 7.46 (m, 2 H), 7.49 – 7.54 (m, 1 H), 7.77 – 7.81 (m, 2 H). ^{13}C NMR + **DEPT** (125 MHz) ($CDCl_3$): δ 13.7 (-CH_3), 19.2 (-CH_2), 30.6 (-CH_2), 53.3 (-CH_3), 64.1 (-CH_2), 67.9 (-CH_2), 84.6 (-CH_2), 127.1 (aromatic CH), 128.7 (aromatic CH), 131.9 (aromatic CH), 134.0 (aromatic quaternary C), 156.6 (quaternary C), 167.2 (quaternary C), 170.8 (quaternary C); IR (neat): 3575-3125 cm^{-1}, 3416 cm^{-1}, 1742 cm^{-1}, 1651 cm^{-1}, 1287 cm^{-1}, 1225 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{17}H_{24}NO_5$ [M+H], 322.1656; found, 322.1654.

methyl-2-benzamido-3-benzyloxy-2- (hydroxymethyl)butanoate (IV-20), methyl-2-benzamido-3-ethoxy-2-(hydroxymethyl)butanoate (IV-21), Methyl-2-(benzamido)-2-(hydroxymethyl)- 3-methoxy-3-methylbutanoate (IV-26), methyl-2-(4-methoxybenzamido)-3-*tert*-butoxy-2-(hydroxymethyl)butanoate (IV-30), methyl-2-(4-(trifluoromethyl)benzamido) -3-*tert*-butoxy -2-(hydroxymethyl) butanoate (IV-31), methyl-3-*tert*-butoxy-2-(hydroxymethyl)-2-(propionamido)butanoate (IV-32) and methyl-2-(2-phenylacetamido)-3-*tert*-butoxy-2-(hydroxymethyl)butanoate (IV-33): *Tert*-alkyl amino hydroxy carboxylic esters **IV-20**, **IV-21**, **IV-26**, and **IV-30** to **IV-33** were all prepared using the general procedure written above. These compounds were prepared and fully characterized by Robert A. Mosey. For further details regarding either the synthesis or characterization of these compounds, please see the Ph.D. thesis of Robert A. Mosey or the supporting information of the following publication:

Mosey, R. A.; Fisk, J. S.; Friebe, T. L.; Tepe, J. J. *Org. Lett.* **2008**, *10*, 825-828.

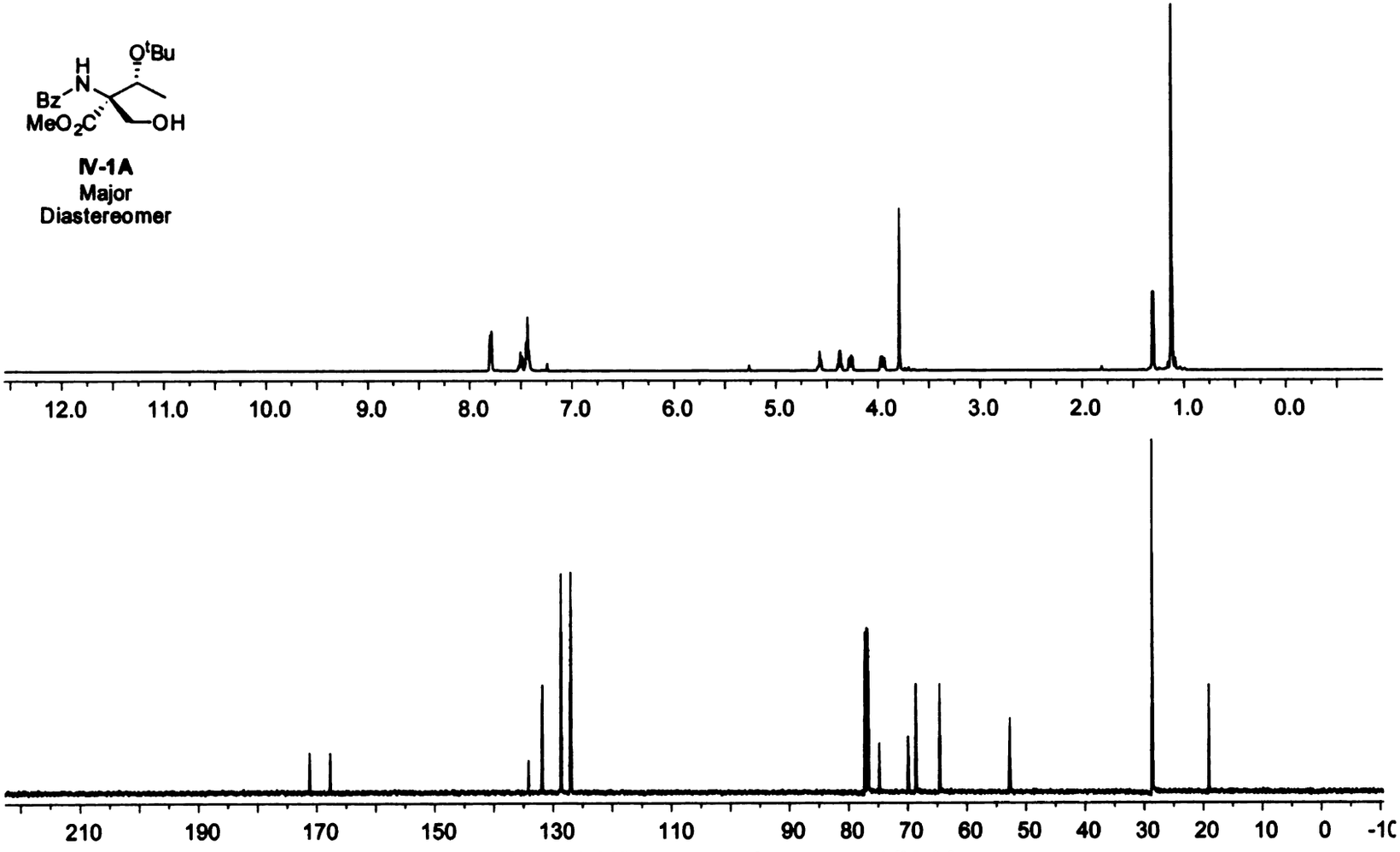


Figure IV-4. NMR spectra of compound **IV-1A.**

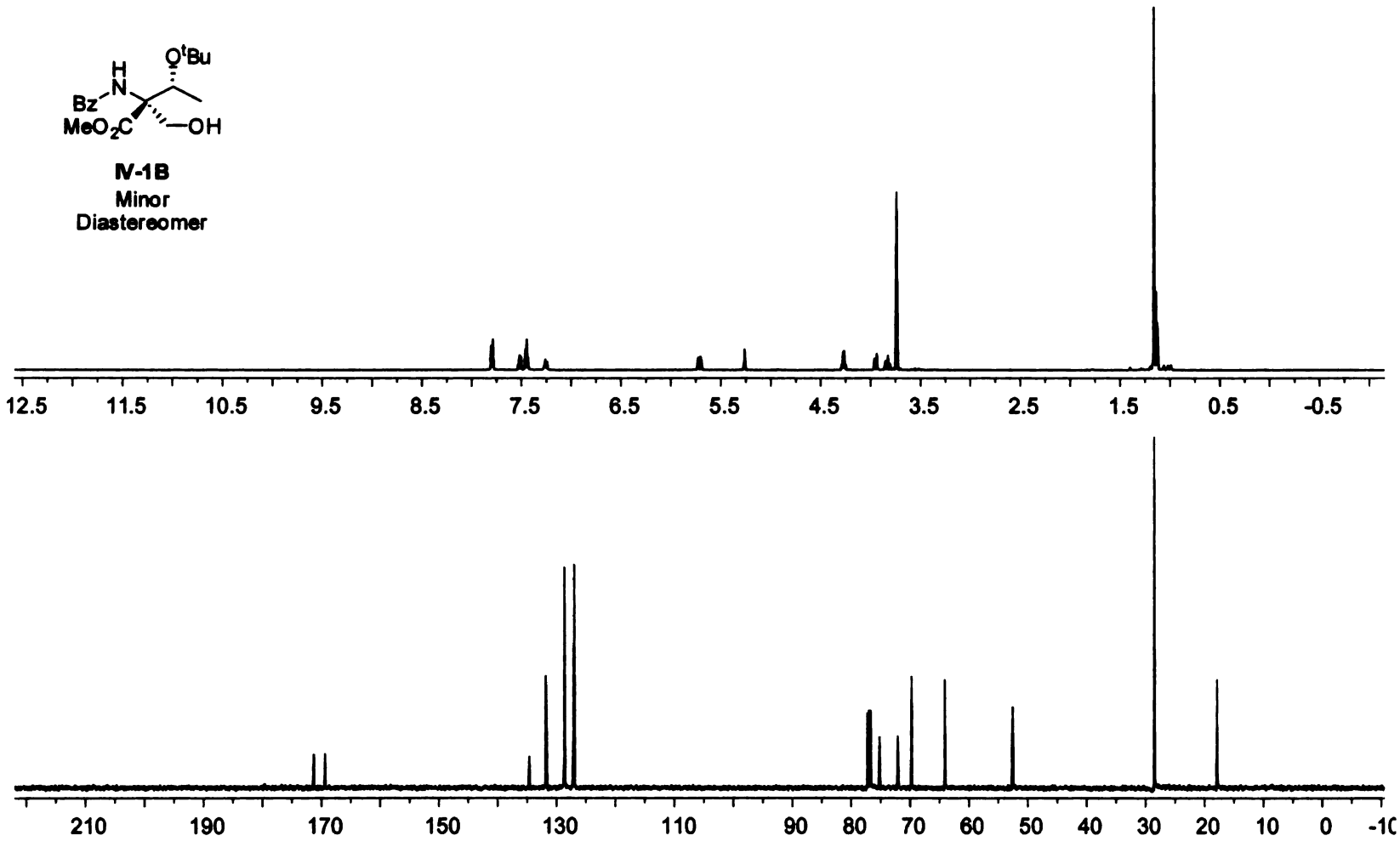


Figure IV-5. NMR spectra of compound **IV-1B.**

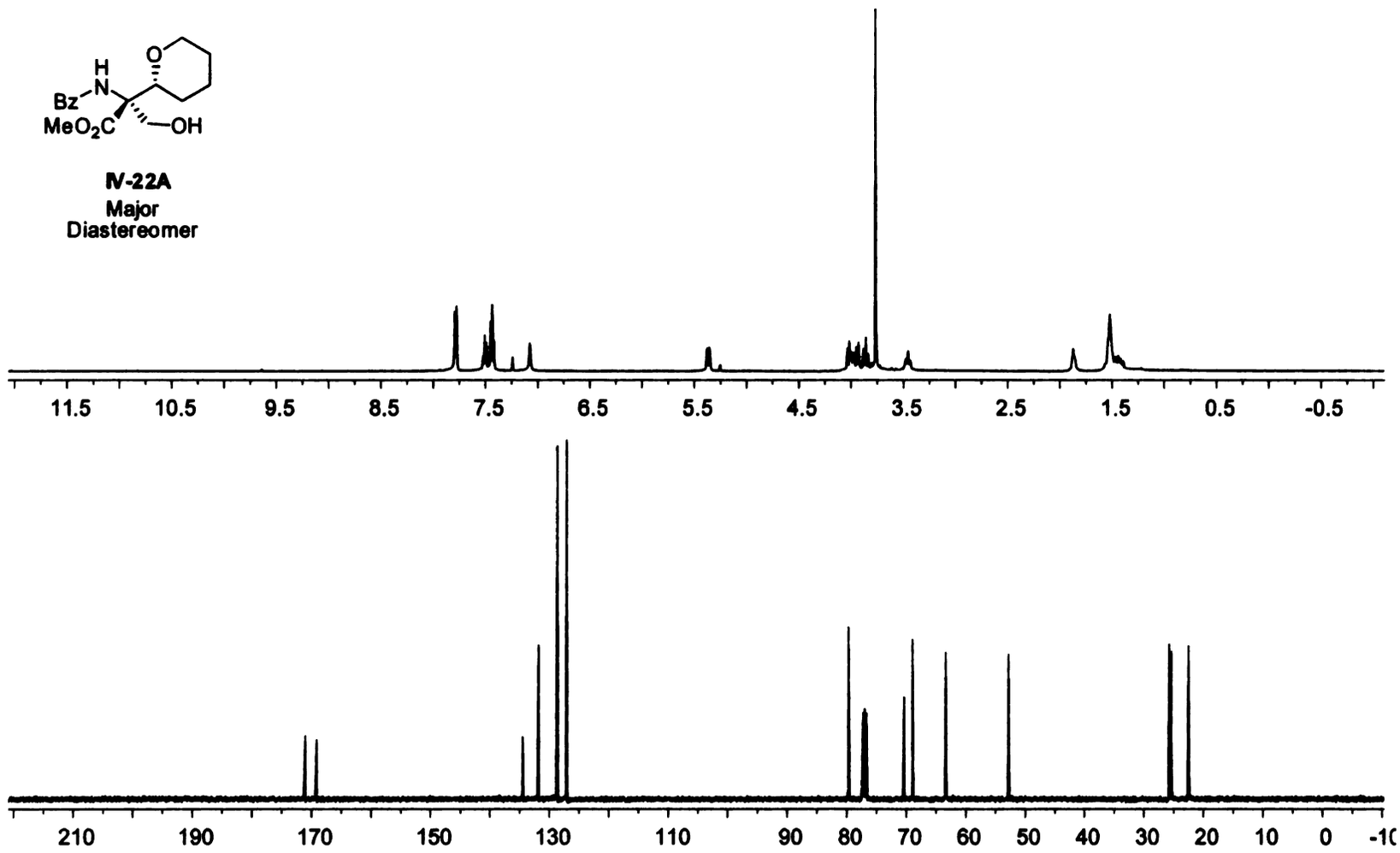


Figure IV-6. NMR spectra of compound **IV-22A.**

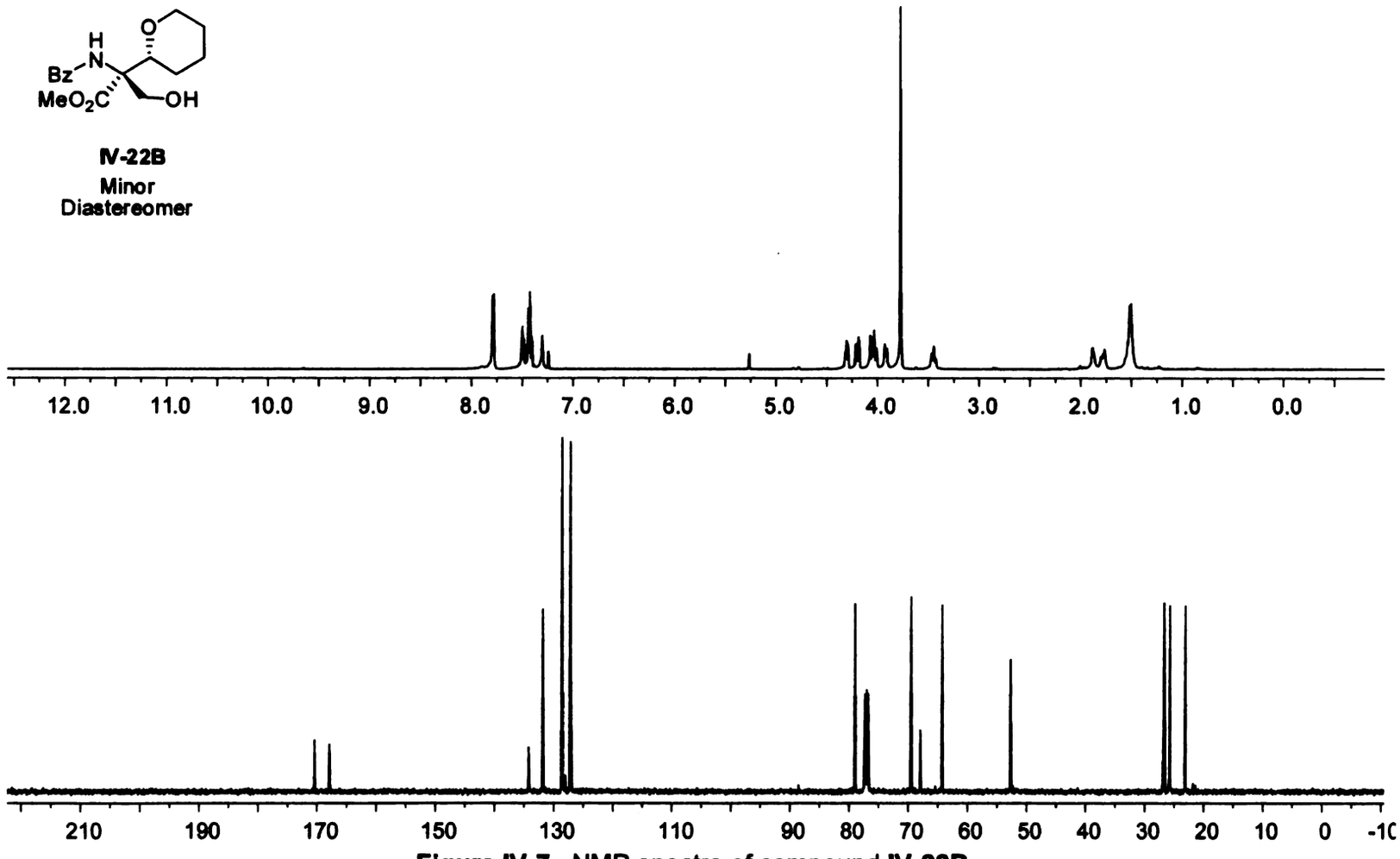


Figure IV-7. NMR spectra of compound **IV-22B.**

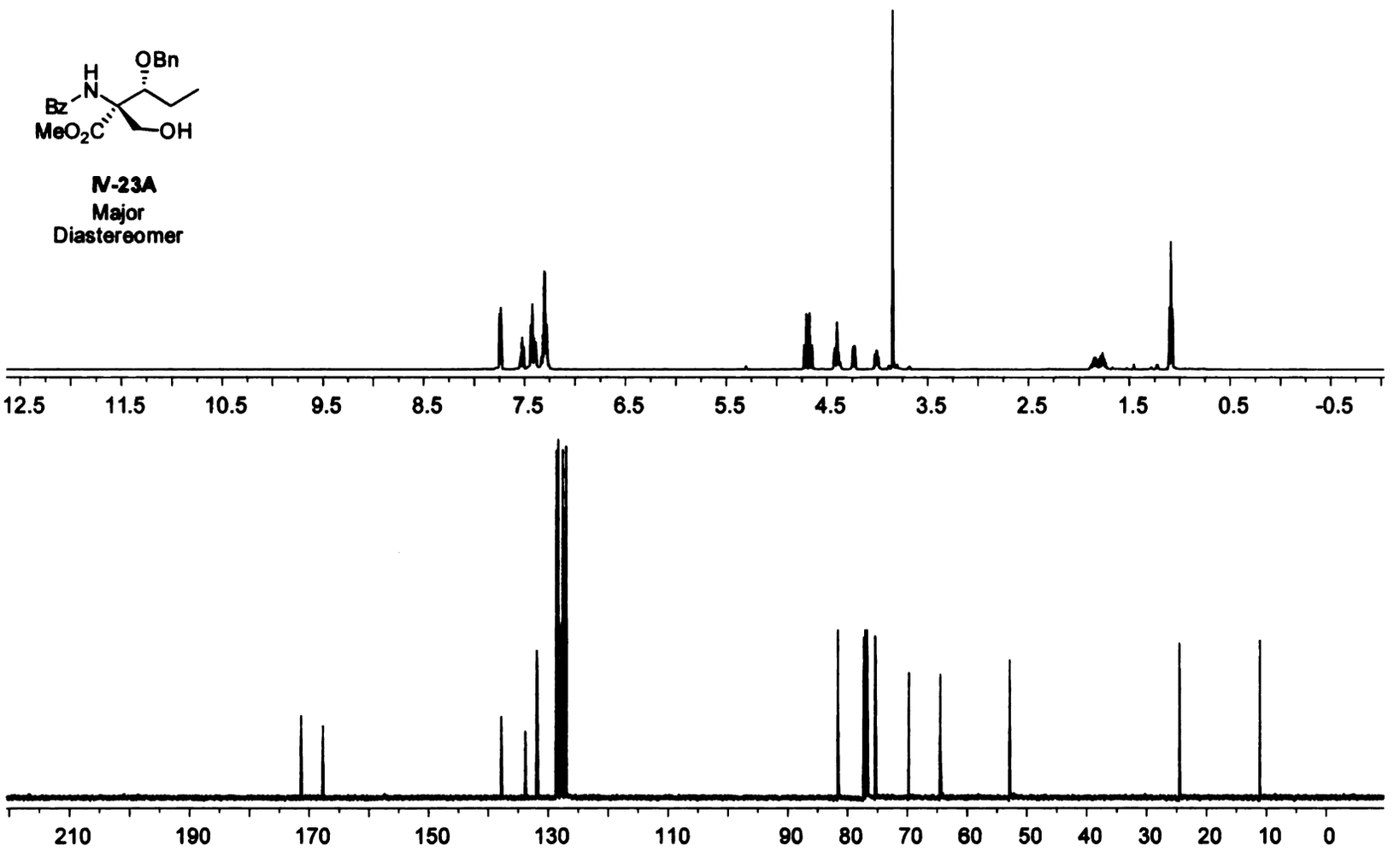


Figure IV-8. NMR spectra of compound **IV-23A.**

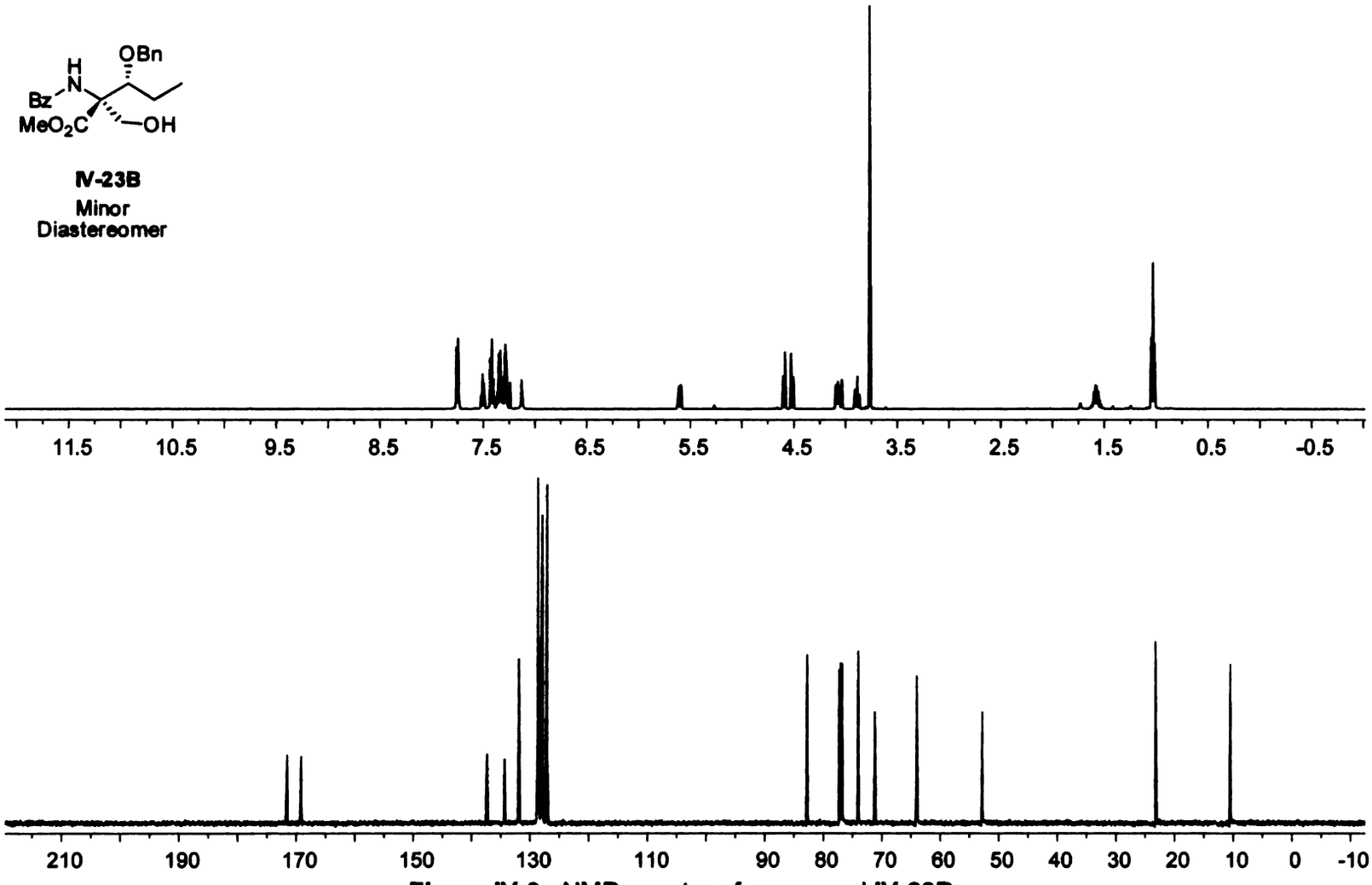


Figure IV-9. NMR spectra of compound **IV-23B.**

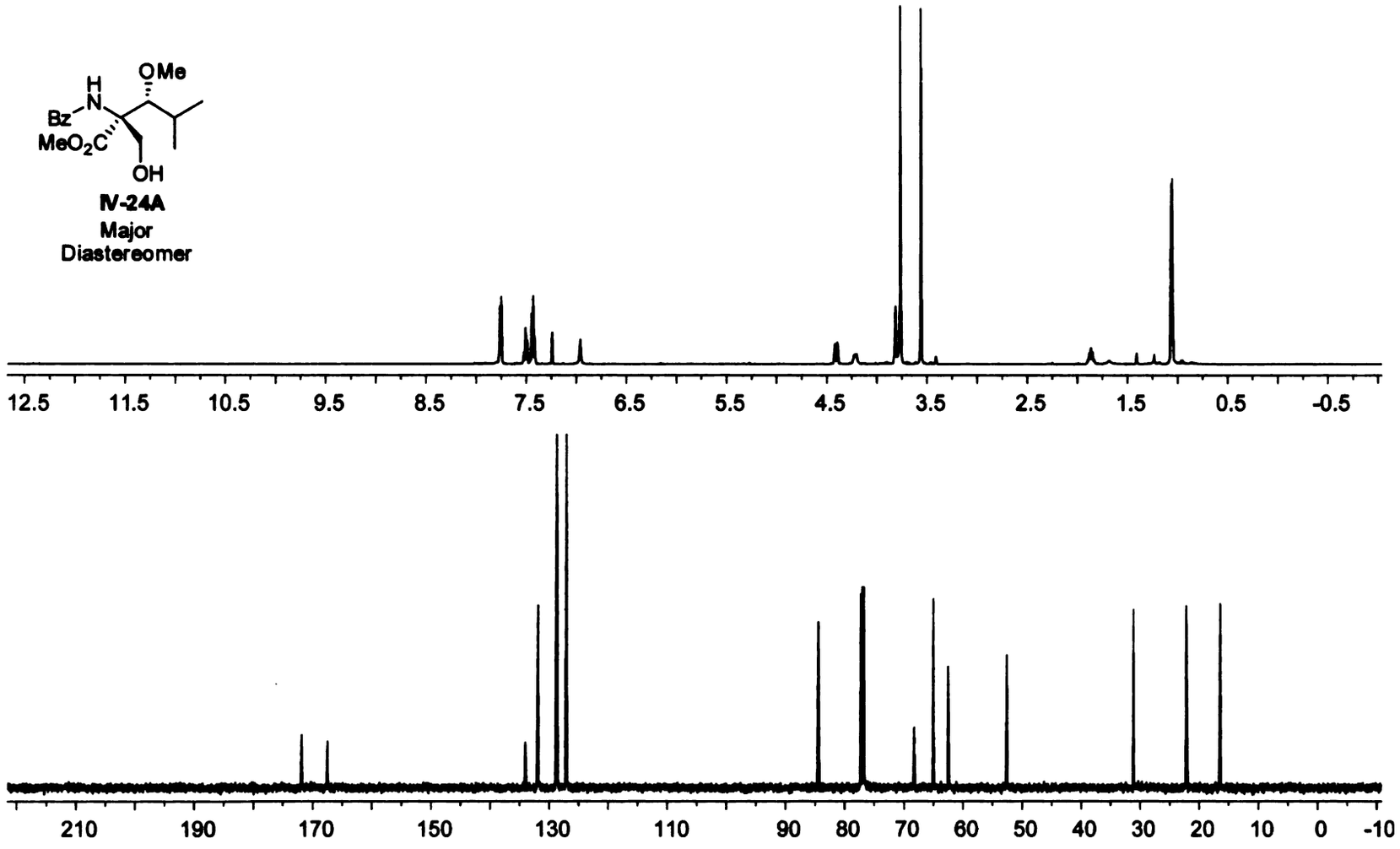


Figure IV-10. NMR spectra of compound **IV-24A.**

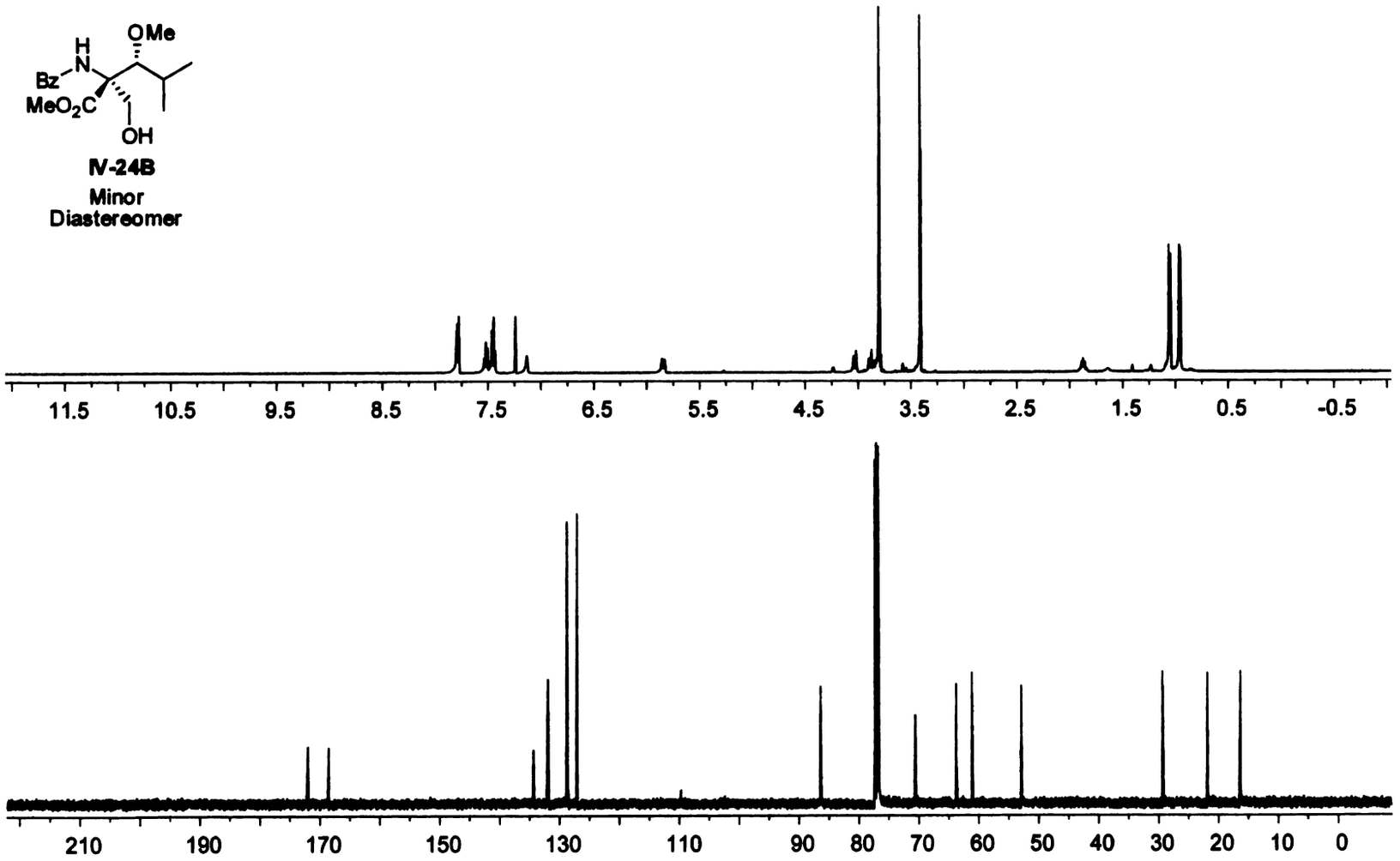
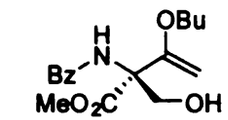


Figure IV-11. NMR spectra of compound **IV-24B.**



IV-25

Figure IV-12. NMR spectra of compound **IV-25.**

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