The Design and Synthesis of Novel Chiral Z-Nitrones with Applications towards the Syntheses of Enantiomerically Pure 4-Hydroxy Amino Acids

by

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Dissertation submitted in partial fulfillment of
the requirements for the degree of Doctor
of Philosophy in the Department of
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2009

ABSTRACT

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Abstract

A number of 4-hydroxy amino acids have been synthesized via 1,3-dipolar cycloadditions of novel Z-nitrones and substituted olefins. Three achiral nitrones were synthesized in pursuit of a conformationally stable yet reactive Z-nitrone. The carboisopropoxynitrone was determined to be the best synthon in cycloadditions that favored a Z-nitrone oriented transition state. Solvent studies were performed for cycloaddition reactions and it was determined that polar solvents lead to "Z-derived" isoxazolidines whereas non-polar solvents primarily afford "E-derived" isoxazolidines. The incorporation of $MgBr_2 \cdot OEt_2$ to the reaction further enhanced the selectivity of the cycloaddition reaction in favor of "Z-derived" intermediates.

Chiral carboisopropoxynitrone derivatives were also realized and used in reactions with chiral olefins to afford optically active 4-hydroxy amino acids after several steps. (2R,4R)-4-hydroxyl-4-methylglutamic acid and (2R-4R)-monatin were both synthesized in high purity from corresponding optically active olefins and Z-nitrone. Furthermore, the (2S,4S) enantiomers of both amino acids could be synthesized via enantiomers of the chiral nitrone and olefins.

To Mom and Dad,

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1. Introduction

1.1 γ-hydroxyl-α-amino Acid Natural Products

Most biology text books define amino acids as the building blocks of life. Although only a handful of these amino acids are considered common substituents of proteins, thousands of uncommon amino acids exist in various forms of plants and life.[1] Furthermore, an ever growing number of these uncommon amino acids have been found to exhibit biological activity. The biological properties of these amino acids varies immensely depending on molecular make-up of such compounds. One specific niche of these biologically active amino acids includes the γ-hydroxy-α-amino acid motif. This subgroup of amino acids includes compounds such as isoleucines, 4-hydroxy glutamic acids, lycoperdic acid, and a natural sweetner substitute known as monatin (Figure 1).

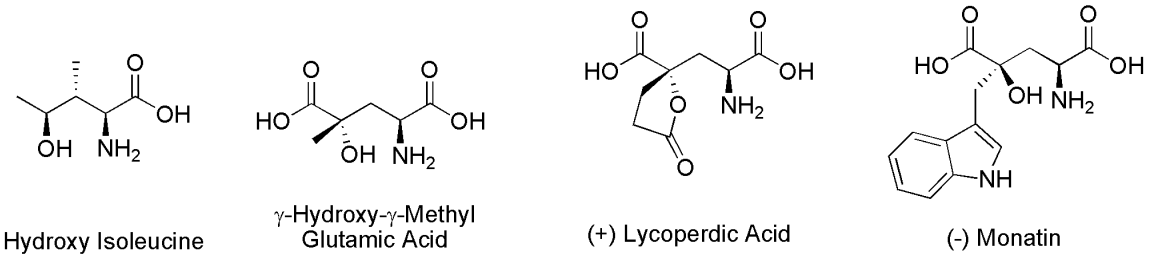


Figure 1: Natural Product Amino Acids

An important aspect of biologically significant amino acids is inherent within the stereochemistry of such molecules. Although the vast majority of these materials are of the L-stereochemical series (usually S- at the α-carbon), the relative stereochemistry between the α-NH_2 group and the γ-OH group can be either syn or anti as depicted in

Figure 2. The relative stereochemistry between these two substituents can have a significant impact on the biological properties. For instance, two stereoisomers of hydoxyisoleucine have been reported to possess drastically different biological properties. (2S,3S,4R) 4-hydroxyisoleucine was isolated from the flowers of the *Quararibea funebris* tree in southeastern Mexico.[2] The Zapotec tribes in Mexico used this plant as a cough remedy in addition to controlling menstrual disorders and psychological fears. On the other hand, the (2S,3R,4S) hydroxyisoleucine stereoisomer, isolated from the seeds of fenugreek *Trigonelle foenum-graecum Leguminosae*, was found to possess insulinotropic properties (Figure 2.).[3, 4]

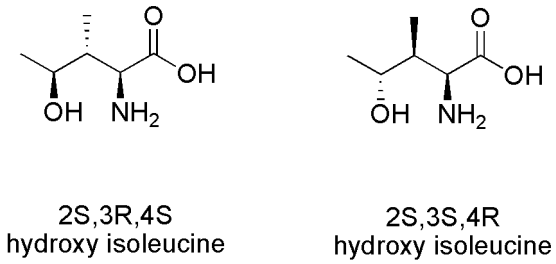


Figure 2: Hydoxyisoleucine Diastereomers

Therefore, inherent within this γ-hydroxy-α-amino acid subgroup is the fact that four sets of enantiomeric pairs can exist, all of which have the potential to possess different biological properties. Specifically, the functionality at the C-2, C-3, and C-4 carbons highlights the stereochemical potential for these amino acids. Not surprisingly, efforts towards synthesizing amino acids stereoisomers have been explored throughout recent years.

As previously mentioned, most biologically significant amino acids are of the L-series as illustrated in Figures 1 and 2. Two significant stereoisomers of γ-hydroxyisoleucine (Figure 2) were discussed earlier. Both members of the L-series of γ-methyl-γ-hydroxyglutamic acid (2S,4S) and (2S,4R) (Figure 1) are naturally occuring compounds found in *Ledenbergia roseoaena* and *Pandanus veichii* respectively.[5, 6] Interestingly, both of these L-series acids co-occur in *Phyllitis scolopendrium*.[5, 6]

Finally, (+)-lycoperdic acid (Figure 1) was isolated from the mushroom *Lycoperdon perlatum* in 1978.[7] The structure of this compound is quite similar to that of the 4-hydroxy-4-methyl glutamic acids so it is expected to have similar activity towards the glutamate receptor in the mammalian central nervous system.

One of the most recently studied 4-hydroxy glutamic acid derivatives is (2S,4S)-4-hydroxy-4-(indol-3-ylmethyl)glutamic acid.[8-11] This compound, monatin, was isolated from the roots of *Schlerochiton ilicifolius*, a spiny-leaved hardwood shrub found in South Africa and first elucidated by Ackerman and co-workers.[11] Heightened interest in this compound centers on the intense sweetness of the molecule, reportedly upwards of 1200 times sweeter than a 5% solution of sucrose.[11] Furthermore, Ackerman reported the major contributing stereoisomer was the 2S,4S isomer which they elucidated based on nOe experiements and the Clough-Lutz-Jirgenson rule.[12, 13] This rule states that addition of an acid to an aqueous solution of an L-α-amino acid will change the specific rotation to shift towards a more positive value, and vice versa in the case of a D-α-amino acid[14].

Recently, Bassoli discovered interesting results that conflict with Ackerman's original proposal that the 2S,4S isomer is both the major product and largest contributor to the level of sweetness. Among other things, his research determined the 2R,4R stereoisomer was the sweetest of the four potential isomers based a taste trial that analyzed the four isomers.[8]

The discrepancy between Ackerman's and Bassoli's results may have something to do with the manner in which the compounds were isolated. Ackerman's original proposal for the 2S,4S stereoisomers existence came after a series of extractions and purifications of the plant itself.[11] As a result, there exists the possibility that the isolation techniques proposed by Ackerman may actually have indirectly screened the other monatin stereoisomers in the process. Further evidence from Bassoli suggests this may be the case. Bassoli's research regarding the stereochemistry of a monatin extraction sample revealed the presence of all four stereoisomers being present.[8] This conclusion is surprising to say the least, since nature is often selective towards a specific isomer. Nevertheless, Bassoli has shown the existence of all four stereoisomers in the monatin extract sample as analyzed by chiral HPLC, however, whether the stereoisomers are present in the plant itself or the result of racemization/epimerization during the extraction process is not yet determined. Further investigations into the stereochemical analysis of monatin are painfully slow since the monatin extract is extremely difficult to obtain.[8]

γ-hydroxy-α-amino acids are also prevalent in much larger molecules such as trinems and the nikkomycins (Figure 3). The nikkomycins[15, 16] are a group of antibiotics produced by *Streptomyces tendae* and *S. cacaoi ssp. Asoensis*. Three specific nikkomycins of the 2S,3S,4S moiety are nikkomycin B, nikkomycin B_x, and nikkomycin J. These compounds are potent chitin synthetase inhibitors that exhibit antifungicidal, insecticidal, and acaricidal activities.[17]

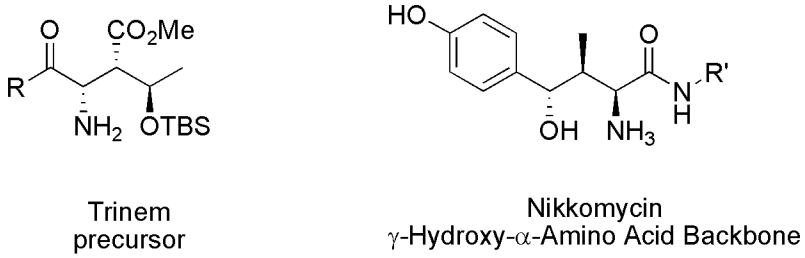


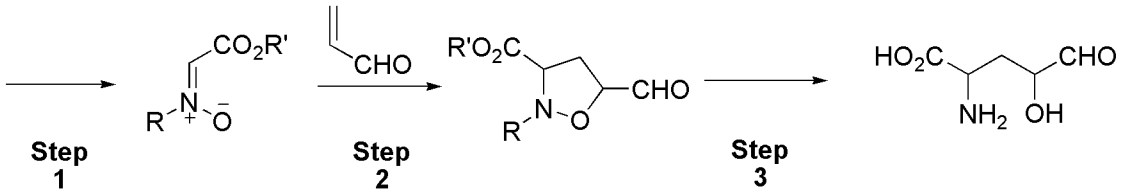
Figure 3: Natural Product Amino Acid Precursors

Trinems are a class of β-lactam antibiotics that were discovered by the Biondi group that have proven useful in treating infections.[18] They are known to be effective against both Gram positive and Gram negative bacteria strains. They have shown considerable promise in the treatment of infections caused by penicillin-resistant bacteria strains. The basic structure of this class of compounds incorporates a tricyclic ring system often containing heteroatoms (Figure 3). Although the structure of trinems is quite complex, Murahashi and others[19, 20] have reported their syntheses from the amino acid precursor shown above.[21]

1.2 1,3-Dipolar Cycloadditions

γ-hydroxy-α-amino acids have been synthesized in a number of different ways (see Section 1.6). One method that has arguably received the most attention is that of 1,3-dipoloar cycloadditions between dipoles and dipolarophiles.[22-24] Specifically, cycloadditions between azomethine oxides, otherwise known as nitrones, and substituted olefins were shown to be effective synthons in the synthetic pursuit of these amino acids. The synthetic approach towards the syntheses of these amino acids can be broken down into three key steps: synthesis of a suitable nitrone, 1,3-dipolar cycloaddition with a dipolarophile, and the subsequent ring-opening of the resultant heterocycle (Scheme 1).

Scheme 1: Three Steps to γ-Hydroxyl-α-Amino Acids



As a result, cycloaddition reactions between a nitrone and substituted olefin are quite powerful based on the remarkable potential of these reactions to produce up to three stereocenters at the C-2, C-3, and C-4 positions of the cycloadduct, often with significant regiochemical and stereochemical control based on established tendencies that will be discussed subsequently (Scheme 2).

Scheme 2: Potential Isoxazolidine Stereocenters

There are two main issues to address when predicting formation of an isoxazolidine ring through 1,3-dipolar cycloaddition reactions. The first of these issues is the regiochemistry of the cycloaddition reaction. That is, will substituents on the alkene dipolarophile be found at the 4 or 5 position of the isoxazolidine product. The second issue relates to the stereochemistry of the reaction product, both relative and absolute.

With regard to the former issue, regiochemistry, reliable predictions can be made based on frontier molecular orbital theory (FMO). Originally advanced by Fukui,[25] and later adapted for 1,3-dipolar cycloaddition reactions by Sustmann,[26] FMO reliably predicts the regiochemical outcome of cycloaddition reactions based on the electronic characteristics of the two reacting partners.

Sustmann suggested that three situations could operate with cycloaddition reactions (Figure 4).[26] The Diels-Alder reaction is often classified as a Type I interaction whereby the HOMO-diene interacts with the LUMO-dienophile. Furthermore, a Type III interaction is often associated with the ozonolysis reaction. However, Type II situations occur in most nitrone-olefin reactions where both the HOMO-nitrone:LUMO-dipolarophile and LUMO-nitrone:HOMO-dipolarophile can have an impact as to how the 1,3-dipoalar cycloaddition reactions proceed. In other words, generally, both

electron-rich and electron-deficient dipolarophiles enhance the reactivity in 1,3-dipolar cycloadditions.

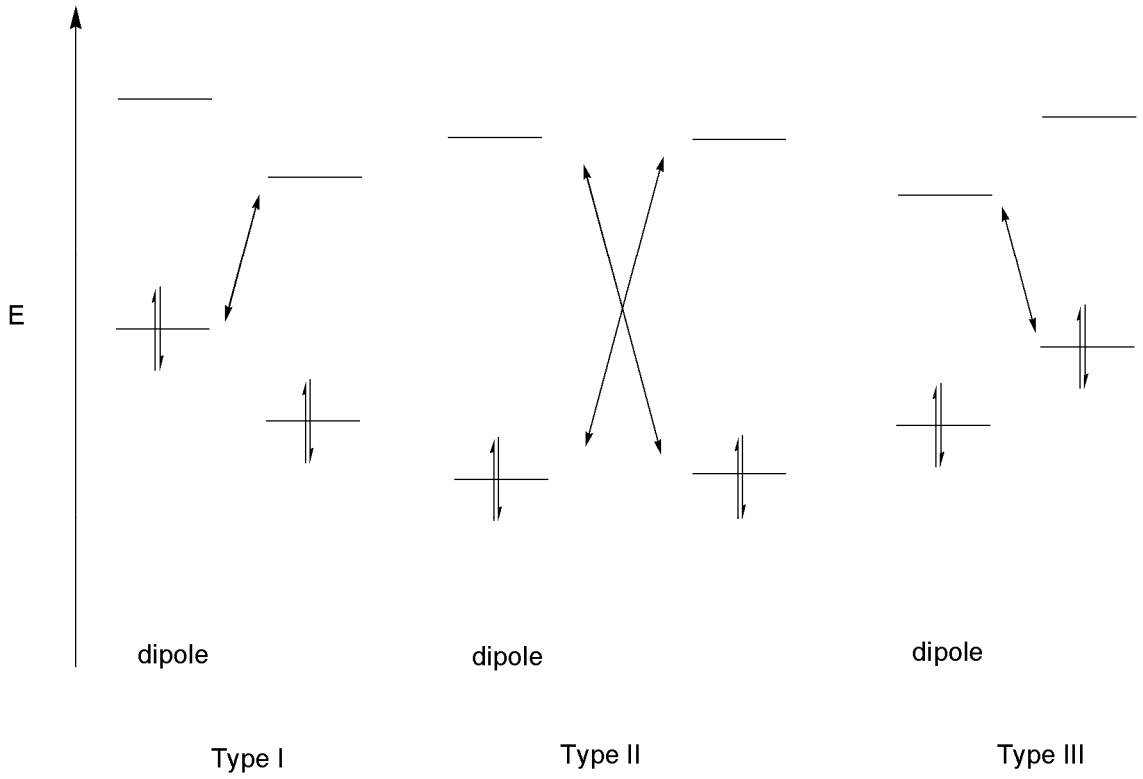
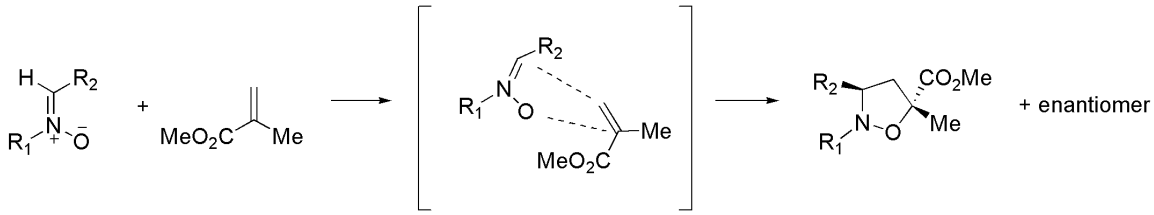


Figure 4: Sustmann's Type I-III 1,3-dipolarcycloadditions

An interesting observation made regarding C-alkyl nitrones versus C-acyl nitrones is that C-acyl nitrones have been shown to be much more reactive than their C-alkyl counterparts.[27] FMO theory explained this characteristic by recognizing that the HOMO-dipole is at a higher energy state in C-acyl nitrones. Furthermore, the corresponding LUMO-dipole is better stabilized. As a result, both the [LUMO-dipole and HOMO-dipolarophile] and [HOMO-dipole and LUMO-dipolarophile] interactions are much closer in energy, thus promoting greater reactivity.

With regard to the issue of relative and absolute stereochemistry for these 1,3-dipolar cycloaddition reactions, there are some general trends that have been discovered that allow for reliable predictions to be made regarding the manner in which the nitrone and olefin are oriented in the transition state. Electron withdrawing substituents predominantly adopt an endo position with respect to the N-O oxide of the nitrone in the transition state whereas electron rich substituents prefer an exo orientation. The theory used to explain these observations is concurrent with common Diels-Alder reactions where secondary orbital overlap with electron deficient substituents help to stabilize these substituents endo with respect to the nitrone functionality. Scheme 3 involving methyl methacrylate best illustrates both the regiochemical and relative stereochemical aspects of these cycloadditions

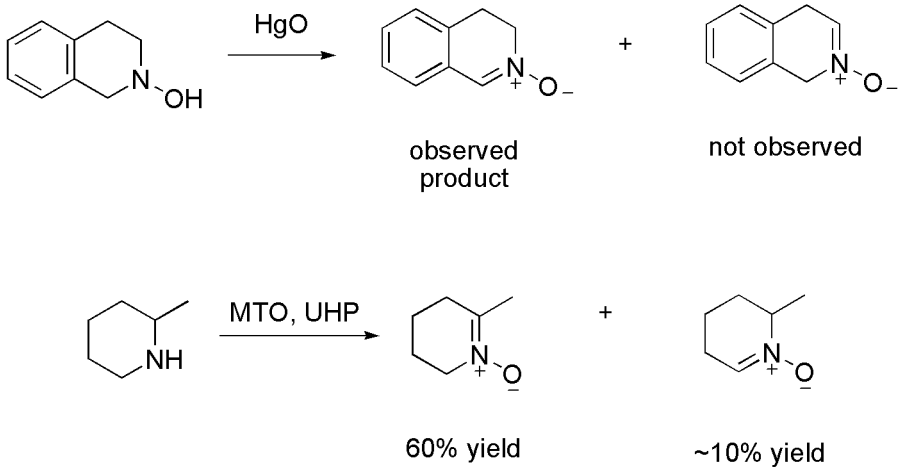
Scheme 3: Heterocycles via 1,3-dipolar Cycloadditions



1.3 History of Nitrones

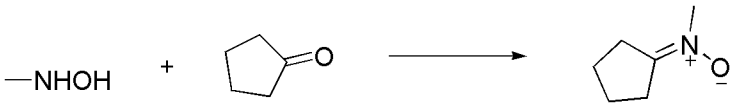
The term nitrone is a contraction of the term nitrogen ketone.[28, 29] Although nitrones can undergo nucleophilic attack, the major utility of nitrones in synthetic applications is based on the aforementioned 1,3-dipolar cycloaddition reactions. Various procedures for synthesizing nitrones have been reported.

Scheme 4: Synthetic Approaches for the Syntheses of Nitrones

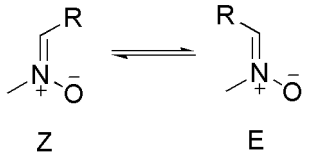


One such method proceeds through the oxidation of N,N-disubstituted hydroxylamines using oxidizing agents such as HgO[30, 31] or methyl trioxorhenium with urea hydrogen-peroxidase (MTO-UHP).[32] Another method involves the oxidation of a secondary amine. Both of these oxidation approaches have the potential to make two different nitrones (with respect to the C=N bond) when starting with an unsymmetrical hydroxylamine or amine (Scheme 4). Although one nitrone isomer often predominates, the potential exists for the synthesis of a mixture of nitrones. Another more controllable method for synthesizing nitrones involves the condensation of a hydroxylamine a ketone or an aldehyde which always leads to the same nitrone regioisomer (Scheme 5).

Scheme 5: Condensation Reaction to Afford Nitrones



Both cyclic and acyclic nitrones can be prepared. With acyclic nitrones, however, there is the possibility of E- and/or Z- stereoisomers. With alkyl substituents, the energy barrier between the two isomers is typically between the 28-35 kcal/mol range.[33] This means that a pure nitrone stereoisomer would be expected to be configurationally stable under the conditions of most cycloaddition reactions. With C-acyl nitrones, however, the energy barrier is considerably lower (18-20 kcal/mol).[33] This suggests the nitrone isomers should be capable of E/Z isomerization even at room temperature in solution (Figure 5). Because of this, acyclic C-acyl nitrones would be expected to undergo cycloaddition reactions involving both the Z- and E- stereoisomers, with the consequent increase in product stereochemical complexity.



R = alkyl or acyl

Figure 5: Ismerization of C-alkyl and C-acyl Nitrones

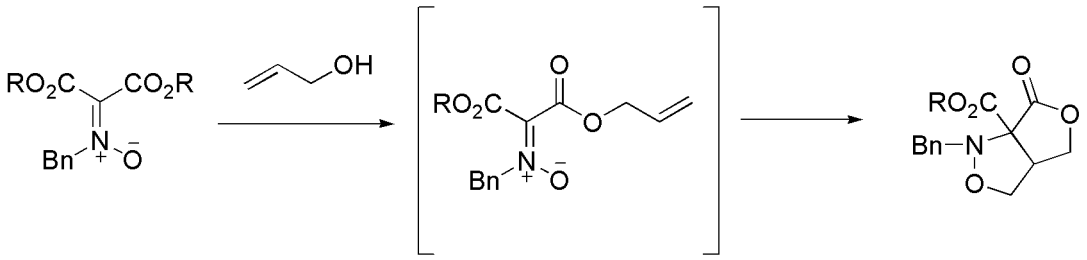
The relatively facile interconversions of such acyclic nitrones has deterred their use in cycloaddition reactions that focus on stereoselective syntheses. However, some researchers such as Inouye have reported a solvent effect directly related to the rates of isomerization and equilibration for these nitrones. Inouye studied the solvent effects of C_6D_6, $CDCl_3$, and CD_3SOCD_3 in regard to various acyclic nitrones.[34] His results were

interesting in that he determined E-nitrones predominate in nonpolar solvents whereas Z-nitrones are the major isomers found in polar solvents. Inouye also proposed that crystalline nitrones existed as the Z-isomer only, and that the isomerization occurred only when dissolved.

The fact that acyclic nitrones isomerize is certainly problematic in 1,3-dipolar cycloadditions when mixtures of diastereomers are formed. This issue is further compounded when one considers E-nitrones are much more reactive than the corresponding Z-nitrone isomer under most conditions. This effect is most likely due to greater steric interactions in the transition state when Z-nitrones are involved compared to the E-nitrone.

One approach that addressed the E/Z-isomerization of acyclic nitrones focused on the syntheses of α,α-dialkoxycarbonylnitrones by groups such as Tamura (Scheme 6).[35, 36] Their work had shown the relative stereochemistry of the heterocyclic product could be controlled by allowing only one side of the nitrone to react with the dipolarophile via the intramolecular cycloaddition. Even when the E-carbonyl substituent of the nitrone had undergone transesterification, the resultant olefin was unable to adopt the necessary position to undergo the intramolecular cycloaddition. However, one drawback to this research hinged on the disubstituted carbon of the original nitrone which greatly reduced the scope of such cycloadditions to reactions that favored a 1,1-dialkoxycarbonyl motif.

Scheme 6: Tamura's Intramolecular Cycloaddition



Another approach to isolating a specific nitrone isomer was through cyclic nitrones. Examples of such nitrones are Ali's nitrone[37, 38] **I** and Katagari's nitrone[39] **II** shown in Figure 6. The cyclic nitrones are important in that isomerization is prevented by the covalent ring incorporated within the nitrone itself in both cases.

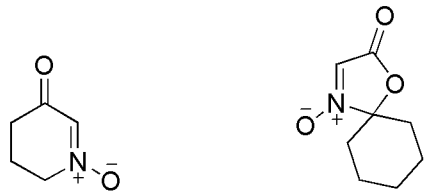


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Figure 6: Cyclic E-Nitrones

1.4 Chiral Nitrones

FMO theory as applied to 1,3-dipolar cycloadditions has been shown to be useful in predicting the regiochemical and relative stereochemical of a range of cycloaddition reactions. However, absolute stereochemical control of such cycloadditions is dependent on facial selectivity. That is, in the case of nitrone cycloadditions for a given planar nitrone 1,3-dipole under the FMO constraints described previously, optically active products will arise only if one nitrone face is sterically more available than the other.

Facial selectivy of these cycloadditions can be influenced in a number of ways. For instance, the incorporation of chiral auxiliaries within the nitrone, dipolarophile, or both can greatly influence the manner in which these cycloadditions occur. One of the first nitrones synthesized that addressed this issue was made by in the Baldwin group by Dr. Paul Greenspan and his racemic nitrones[40] **III** where the R-substituents were various alkyl chains (Figure 8). The utility of such a nitrone was further supported by work done by Harwood[41] regarding azomethine ylides that closely resembled Greenspan's nitrone. Additionally, Katagiri's chiral nitrone **IV** (Figure 7) was another example of a chiral cyclic nitrone that could be used in facially selective cycloaddition reactions.

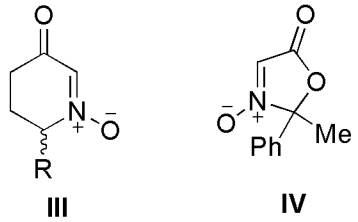


Figure 7: Chiral Cyclic E-Nitrones

Cyclic E-nitrone **V**, concurrently developed by both the Baldwin and Tamura groups, had a number of structural advantages for applications towards the syntheses of optically active γ-Hydroxy-α-Amino acids (Figure 8). For instance, the 5-phenyl substituent promoted facial selectivity in the cycloaddition reaction. Additionally, the C-acyl feature of nitrone **V** could be hydrolyzed to form the carboxylic acid inherent within α-amino acids. Furthermore, the Baldwin group also developed nitrone **VI**, which was a nitrone adaptation of Seebach's imidazolidinone.[42, 43]

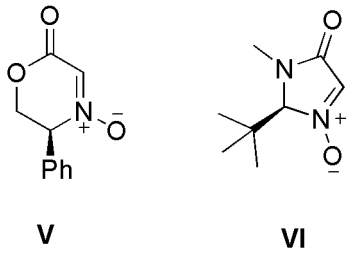
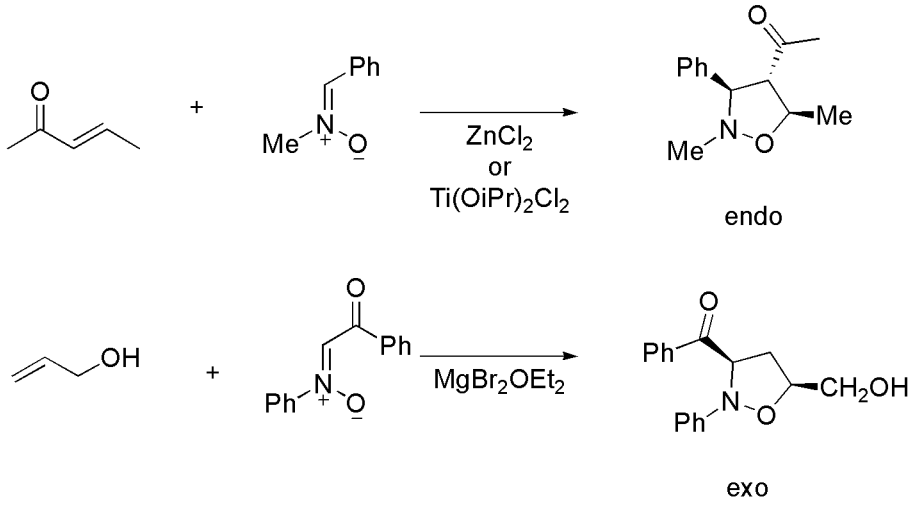


Figure 8: Baldwin's Chiral Cyclic E-Nitrones

1.5 Lewis Acid Catalysis

As previously explained, the formation of heterocycles via 1,3-dipolar cycloadditions using cyclic nitrones has had well documented success. Furthermore, the cycloaddition step has been further enhanced through the incorporation of Lewis acids into the reaction mixture. Lewis acids have been shown to chelate the nitrones and assist in the heterocycle formation. Molecules such as $MgBr_2 \cdot OEt_2$, ZnI_2, and titanium Lewis acids such as $TiCl_4$ and $Ti(OiPr)_2Cl_2$ have been explored as potential catalysts for 1,3-dipolarcycloadditions. The Kanemasa group has shown that certain Lewis acids such as $ZnCl_2$ and $Ti(OiPr)_2Cl_2$ can catalyze 1,3-dipolar cycloadditions that lead to endo-derived isoxazolidines with respect to the substituted olefin, while metal catalysts such as $MgBr_2OEt_2$ and $ZnBr_2$ promote exo-derived isoxazolidines (Scheme 7).[44-46] The Tamura group further expanded on this research by using $MgBr_2 \cdot OEt_2$ as a Lewis acid catalyst in cycloaddition reactions with Baldwin's chiral nitrone and allylic alcohols.[47]

Scheme 7: Kanemasa's Metal-assisted Cycloadditions

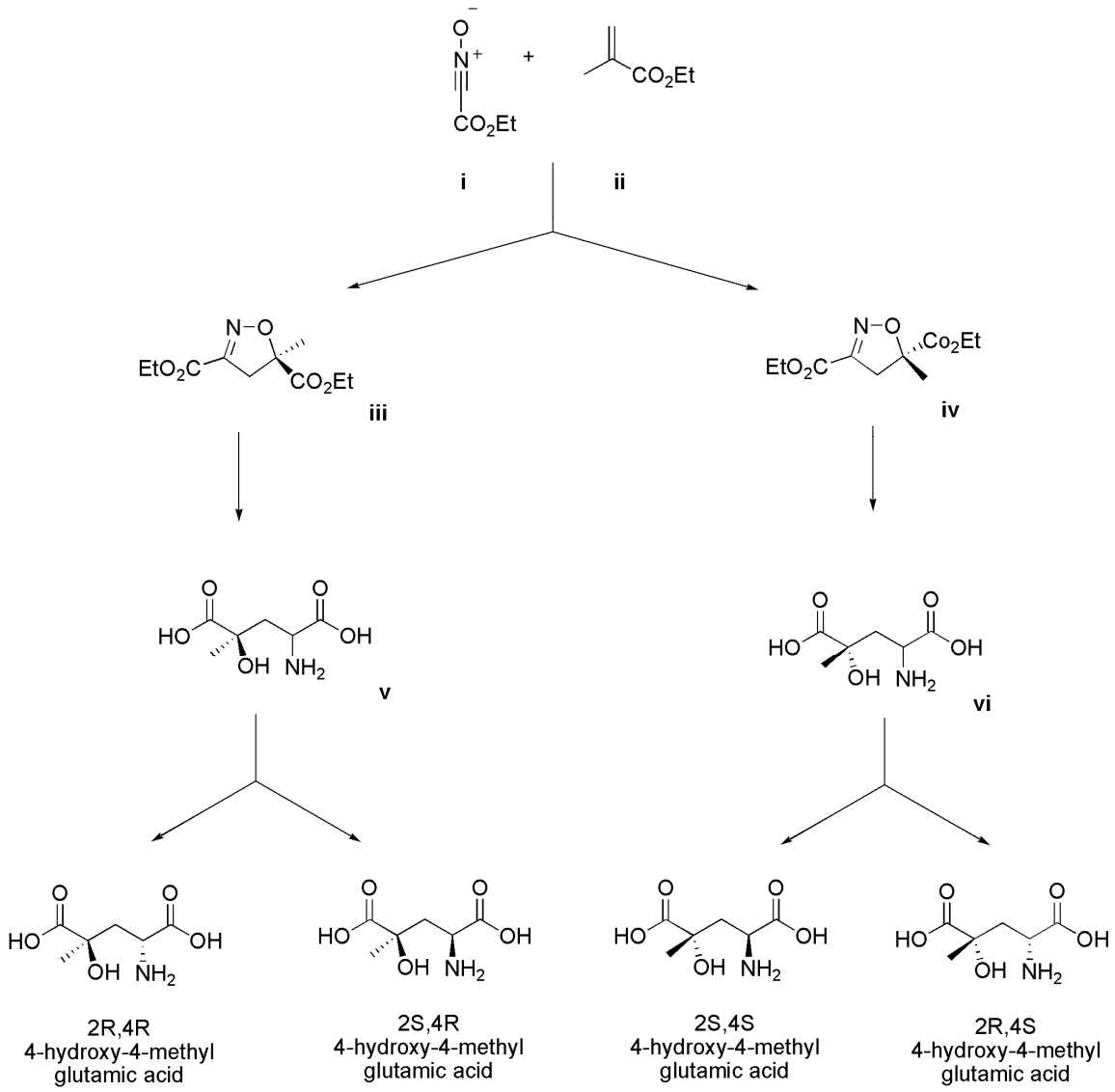


1.6 4-Hydroxy Amino Acid Synthetic Routes

In recent years, researchers have reported a range of synthetic routes to γ-hydroxy-α-amino acid natural products. For instance, 1,3-dipolar cycloaddition reactions between nitrile oxides and substituted olefins have been explored.[6, 8, 48] In some cases, alkylation reactions were the preferred pathways.[9, 10, 49] Examples of these reactions will be discussed in this section.

With regard to syntheses using nitrle oxides, the Bolte group[6] has synthesized both of the naturally occurring 2S-glutamic acids (along with the two unnatural amino acids) beginning with the cycloaddition reaction of nitrile oxide **i** and ethyl methacrylate to afford isoxazolines **iii** and **iv**, which were reduced before being subjected to diastereomeric resolution using enzymatic hydrolysis of Aspergillus oryzae protease to afford ~18% 2S,4R and ~11% 2S,4S total yield (Scheme 8).

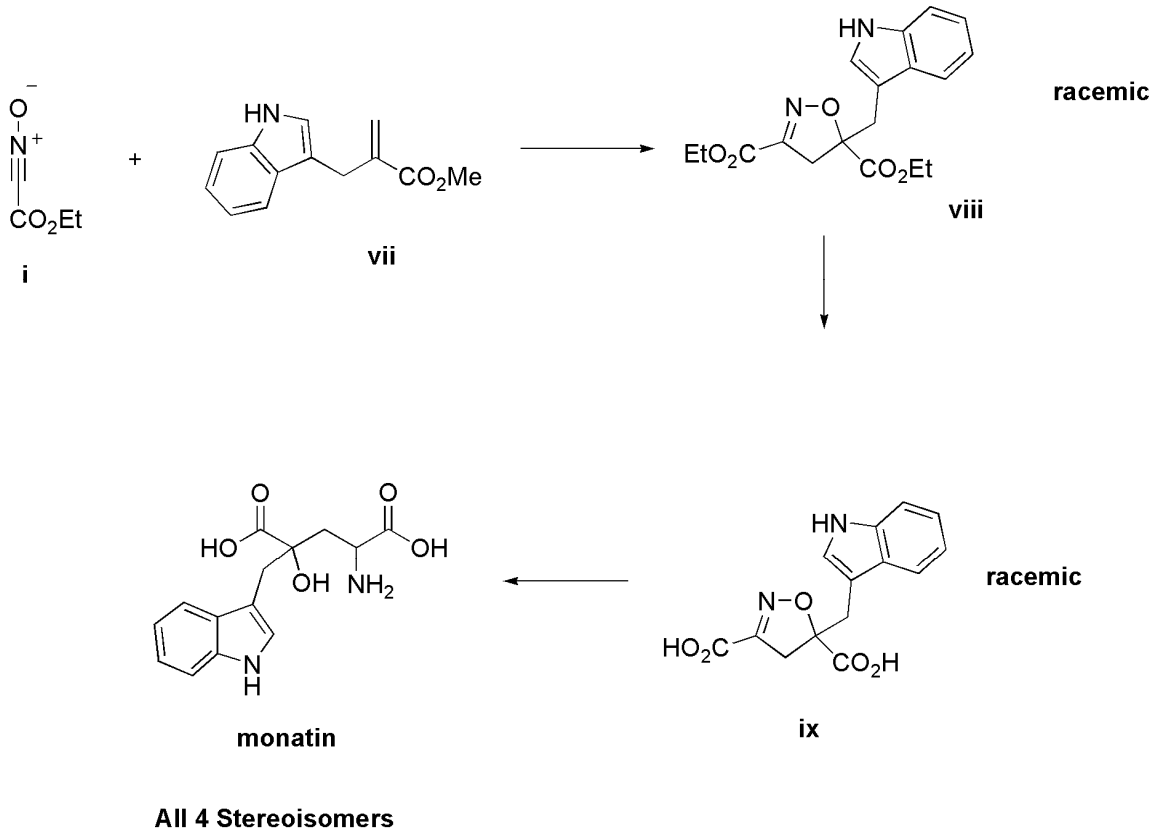
Scheme 8: Bolte's Synthesis of 4-hydroxyl-4-methyl glutamic acid Isomers



Similar to Bolte's research which utilized nitrile oxides, Holzapfel[48] reported the first racemic synthesis of monatin in the early 1990's. His approach began with the 1,3-dipolar cycloaddition reaction between nitrile oxide **i** and indolyl-

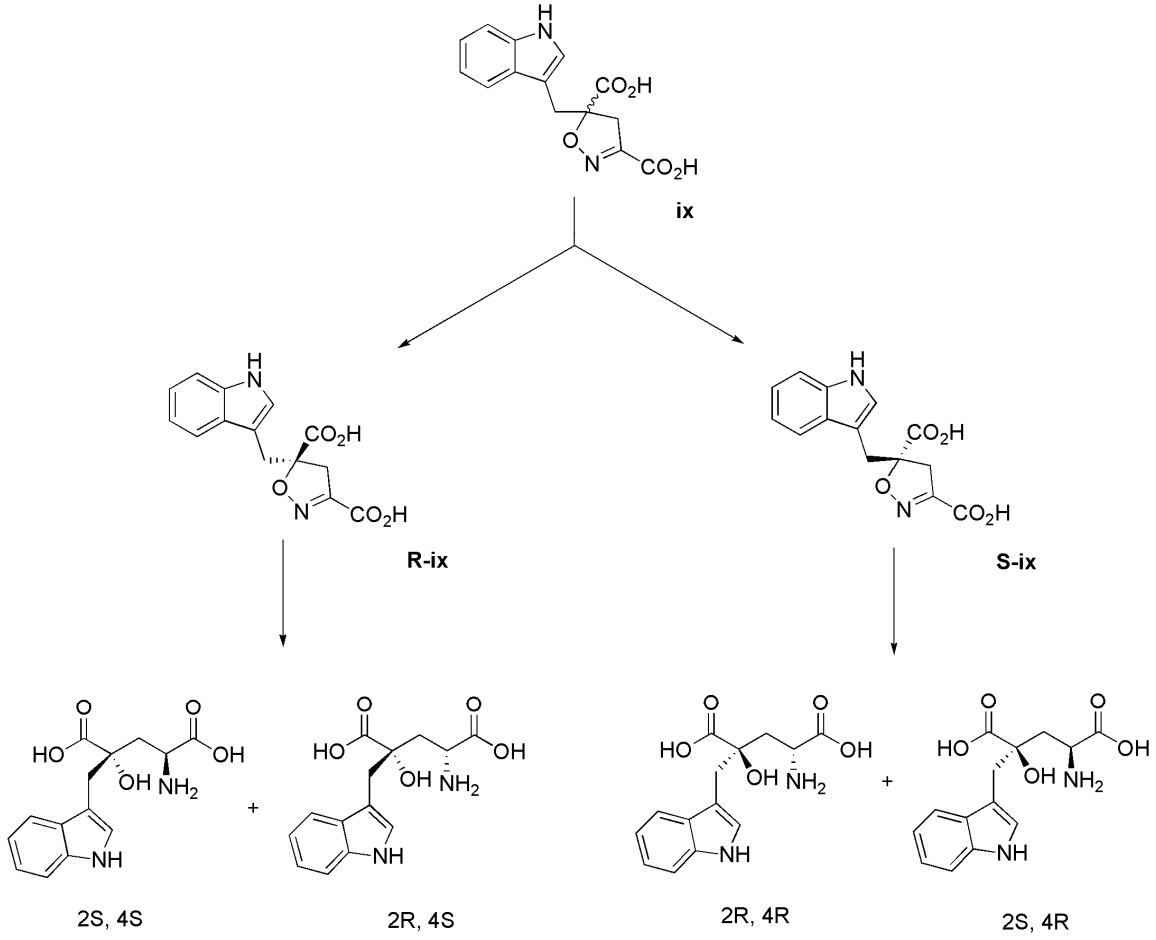
substituted olefin **vii** to afford enantiomeric pair of isoxazolines **viii**. Subsequent manipulations afforded all four monatin stereoisomers (Scheme 9).

Scheme 9: Holzapfel's Synthesis of Monatin



The Bassoli group reported[8] the syntheses of four monatin stereoisomers via resolution of a racemic isoxazoline **ix** using proteases from Aspergyllus oryzae to assist in isolating the enantiomeric pair of isoxazolines **R-ix** and **S-ix**. Hydrogenolysis of the isoxazolines afforded the two pairs (2S,4S-2R,4S and 2R,4R-2S,4R) of monatin diastereomers which were separated by RP-HPLC (Scheme 10).

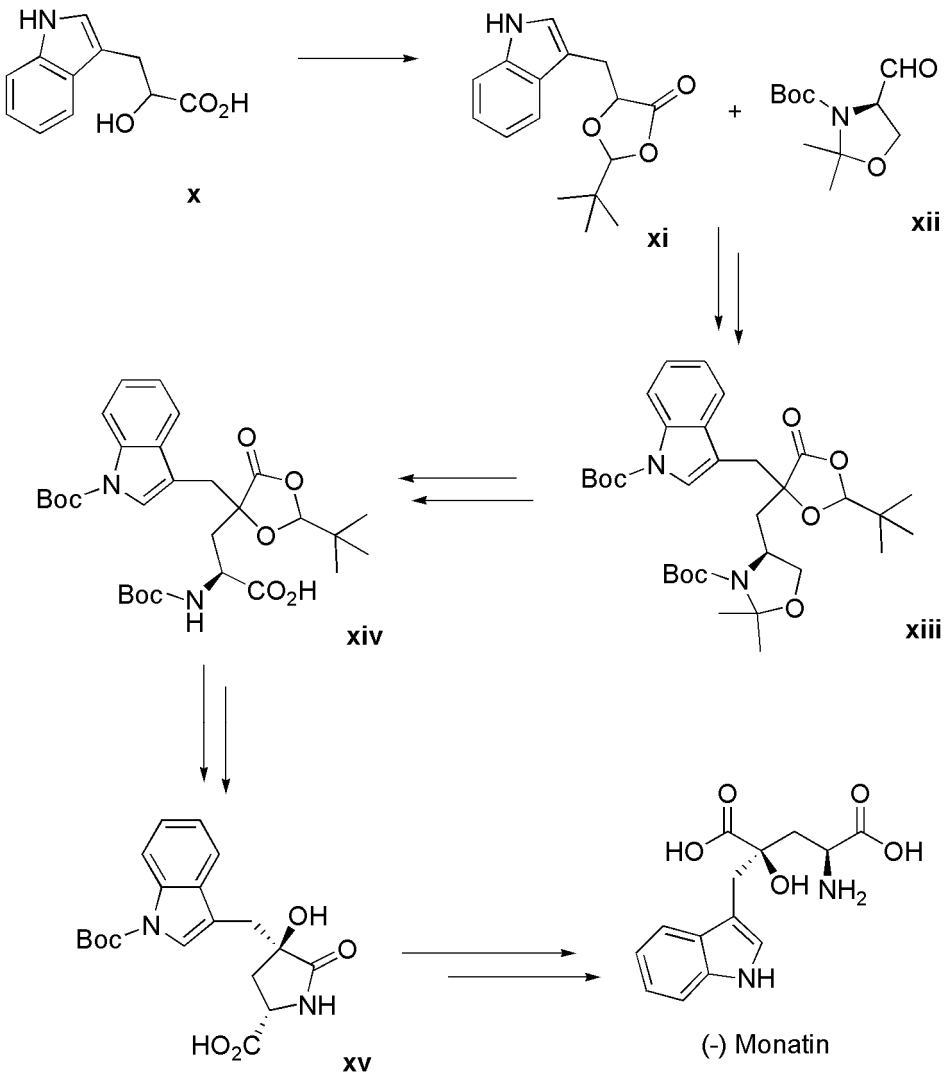
Scheme 10: Bassoli's Synthetic Approach to Monatin Isomers



Another synthetic approach towards the syntheses of γ-hydroxy-α-Amino acid natural products is through alkylation rections as alluded to above. These pathways generally include the use of chiral reactants in the pursuit of optically active target molecules such as in Goodman's[9, 49] and Coelho's[10] separate syntheses of monatin, which will be discussed here. Goodman's synthesis began with a modified alkylation reported by Seebach that consisted of commercially available racemic indolelactic acid **x** with pivalaldehyde (Scheme 11). Condensation of cis-dioxolanone **xi** with Garner

aldehyde **xii** followed by Barton deoxygenation afforded compound **xiii**. Selective deprotection of the pivalidene group afforded the β-amino alcohol mixture of diastereomers **xiv** which were oxidized to the corresponding carboxylic acids with PDC. The diastereomers were then converted to their corresponding lactams **xv**. Basic hydrolysis of the lactams produced the 2S,4S and 2R,4S amino acid isomers in two steps with a 52% and 48% yield, respectively.

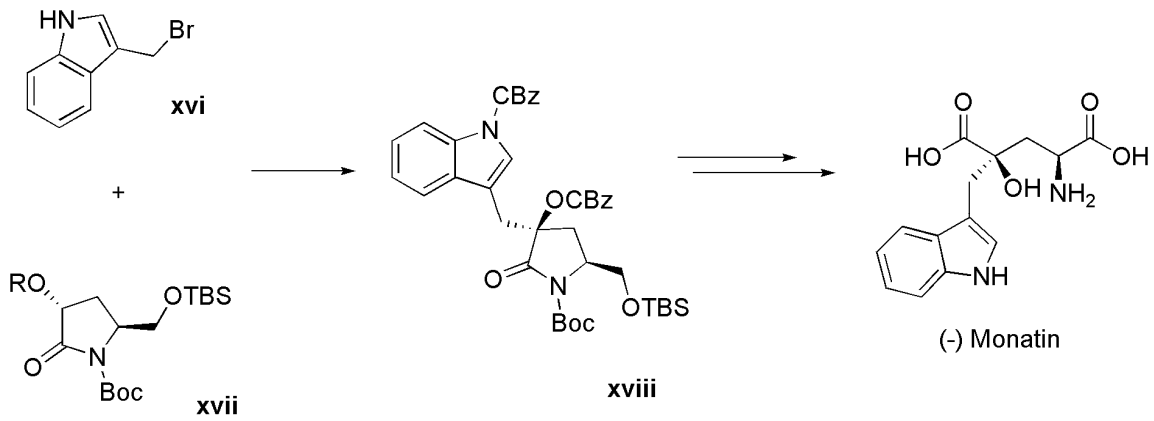
Scheme 11: Goodman's Synthesis of (-) Monatin



The Coelho group[10] proposed an alternate way to synthesize a N-Boc-N′-Boc lactam derivative through a highly diastereoselective formation of a quaternary center in a pyroglutamate derivative (Scheme 12). Starting with a L-pyroglutamic acid derivative **xvii**, Coelho formed the corresponding enolate and coupled it with an indole-derived

electrophile to afford lactam **xviii**. Basic hydrolysis followed by Jones oxidation afforded monatin in ~63% yield after two steps from the lactam (Scheme 12).

Scheme 12: Coelho's Synthesis of (-) Monatin

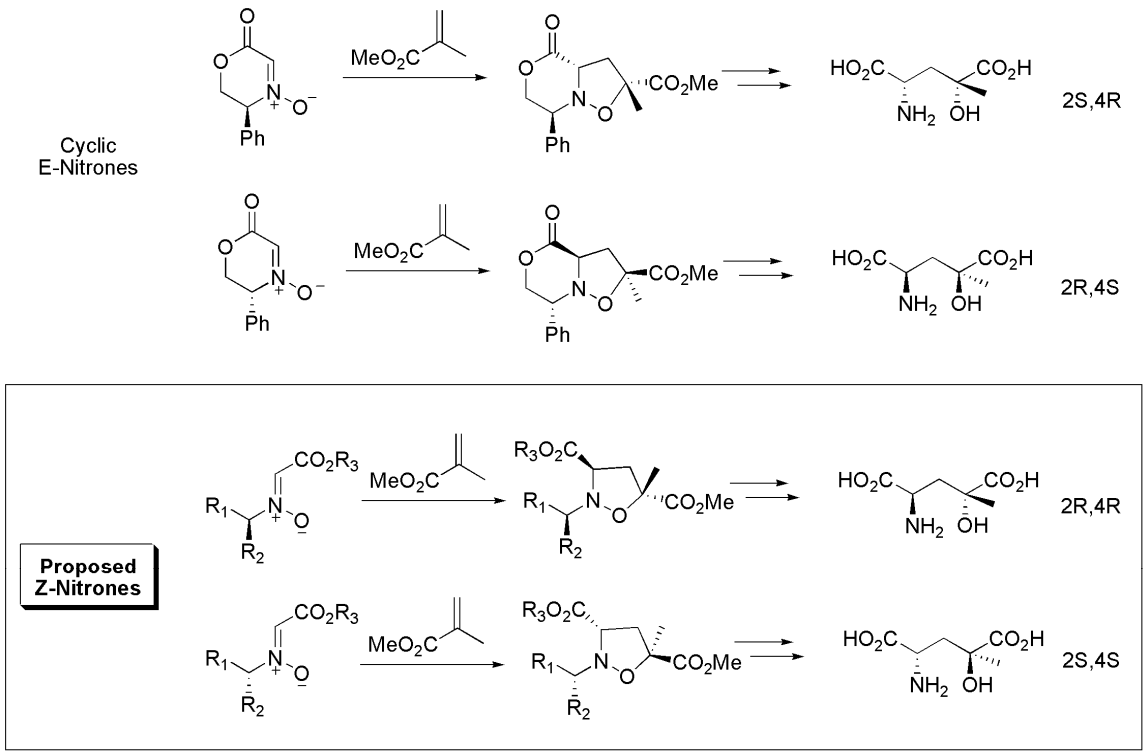


As illustrated in Schemes 8-12, γ-hydroxy-α-amino acids have been synthesized via in various ways. Synthetic routes through isoxazoline cycloadducts have been reported, however the synthetic utility of such reactions is limited by the formation of a mixture of stereoisomers. On the other hand, synthesizing these natural product amino acids through alkylation reactions and subsequent manipulations often requires optically active starting materials (which can be difficult to acquire in addition to the high costs often associated with such reagents). As a result, another synthetic approach toward these γ-hydroxy-α-amino acids has been explored, which is based on 1,3-dipolar cycloaddition reactions between nitrones and olefins.[47, 50]

1.7 Background of the Project

As discussed in Section 1.6, total syntheses of 4-hydroxy amino acids have been reported using a number of synthetic techniques. However, the synthetic designs towards the syntheses and isolation of enantiomerically pure 4-hydroxy amino acids were limited by reactions that produced a mixture of stereoisomers rather than enantiomerically pure products. The Baldwin group and others addressed this concern through applications of a chiral E-cyclic nitrone in cycloadditions that led to single isoxazolidine stereoisomers that were further manipulated to afford single amino acid stereoisomers[50]. Unfortunately, the application of such chiral E-cyclic nitrones was only viable if the relative stereochemistry of the -NH_2 and –OH substituents were anti. Therefore, a syn NH_2/OH relationship would require a Z-nitrone (Scheme 13).

Scheme 13: E- and Z-Nitrones and the Resulting Heterocycles Comparison



2. Results and Discussion

The goal of this research project was to develop a Z-nitrone for applications toward the syntheses of γ-hydroxy-α-amino acid stereoisomers that are unavailable via cyclic E-nitrones previously developed. The preliminary investigation was set up to design stable achiral Z-nitrones. In order to synthesize enantiomerically pure amino acids, the synthesis and isolation of Z-nitrones was of utmost importance. Two concepts were investigated in the pursuit of a reliable Z-nitrone motif as shown in Figure 9. One approach set out to study the potential intramolecular hydrogen-bonding stabilization effects of a C-carboxy acid nitrone. The other approach relied on a steric argument via bulky substituents attached to the carbonyl carbon of the nitrone with the expectation that a large enough substituent could drive the nitrone isomerization equilibrium towards the Z-nitrone conformation.

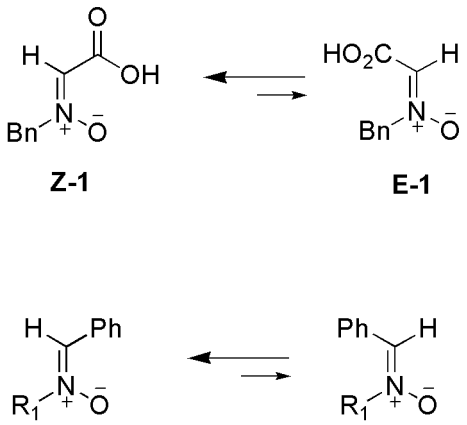
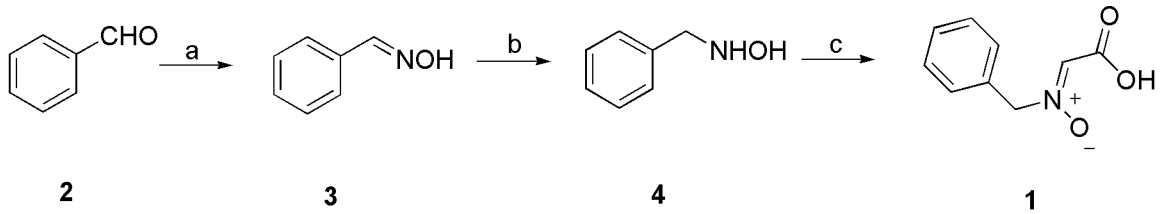


Figure 9: Proposed Nitrones

2.1 Carboxy Acid Nitrone 1

The synthetic design of this aldonitrone was proposed through a condensation reaction between hydroxylamine and an aldehyde. Specifically, combining benzyl hydroxylamine **4** and glyoxalic acid in methylene chloride while stirring at r.t. for 5h afforded acylnitrone **1** in nearly 80% yield (Scheme 14).[51] Glyoxalic acid was commercially available and benzyl hydroxylamine **4** was synthesized in two steps (combined yield of 93%) that began with a Schiff-base condensation of benzaldehyde **2** with hydroxylamine hydrochloride followed by reduction of oxime **3** to afford hydroxylamine **4**.

Scheme 14: Synthesis of Nitrone 1



a- 8M NaOH, NH_2OHHCl; b- $NaBH_3CN$, 2M HCl-MeOH; c- Glyoxalic acid, DCM

Spectroscopic studies were used to analyze nitrone **1** in order to determine the general structure of the synthesized nitrone. In general, Inouye reported[34] that ^1H NMR analysis could be used to differentiate between E- and Z-N-benzyl acylnitrones. He concluded that in $CDCl_3$ the benzylic protons of Z-acylnitrones had chemical shifts in the 4.8-5.0ppm range. On the other hand, E-aldonitrone benzylic protons were assigned

to peaks in the 5.7-5.8ppm range. Furthermore, the vinylic proton of a Z-aldonitrone had chemical shifts ~0.1ppm further upfield than the corresponding E-aldonitrone isomer: 7.1ppm to 7.2ppm respectively. The ^{1}H NMR analysis of nitrone **1** revealed a single nitrone isomer as evidenced by a single vinylic peak and a single benzylic peak (Figure 10). Furthermore, the chemical shifts of the N-benzylic and vinylic hydrogens coincided with the trends reported by Inouye for Z- aldonitrones. ^{1}H NMR analysis offered convincing evidence that supported the original hypothesis that a carboxylic acid moiety could sufficiently serve to stabilize the aldonitrone as a pure Z-isomer.

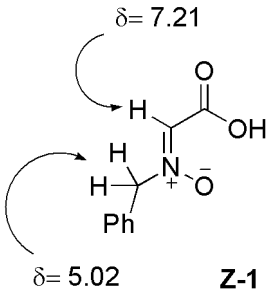


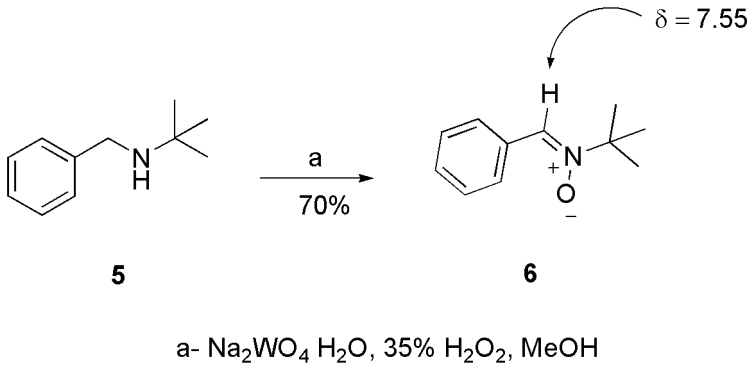
Figure 10: ^{1}H NMR studies for Nitrone 1

2.2 C-Phenyl Nitrones

In continued pursuit of a different stable Z-nitrone (or synthetic equivalent), C-aryl nitrones **6** and **10** were investigated. At first glance, C-aryl nitrones appear to lack the same functionality as the C-acyl nitrones in route towards the synthesis of amino acids. However, there is precedent for conversion of phenyl substituents to carboxylic acids via a ruthenium-catalyzed oxidation.[52, 53] As a result, the synthesis of a C-aryl nitrone could serve as a suitable precursor in the syntheses of amino acids via

isoxazolidine intermediates. The premise for this investigation was based on the hypothesis that steric interactions between the N-*t*-butyl and C-aryl substituents would inhibit the isomerization of this nitrone from its Z- to E-isomer. Phenyl nitrone **6** was synthesized in a 85% yield via an oxidation of the secondary amine **5** using $NaWO_4$ and hydrogen peroxide (Scheme 15).[54]

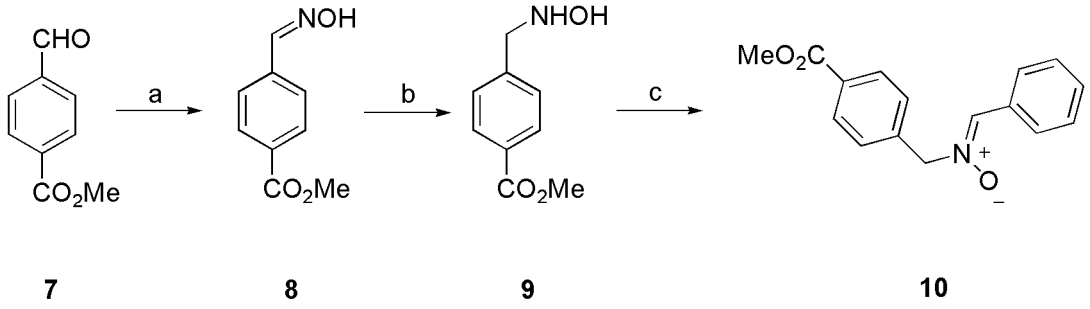
Scheme 15: Oxidation of 2^0 Amine to Nitrone 6



Additionally, nitrone **10** was synthesized which incorporated a carboxymethyl substituent. The motive behind this substituent change was two-fold. It would be ideal to have an easily removable protecting group attached to the nitrogen of the nitrone which the benzyl substituent provides via hydrogenation. Furthermore, the benzyl substituent presented the option to incorporate chirality at methylene carbon, which in turn could be used as a reactant in diastereoselective cycloadditions. Lastly, the p-CO_2Me functional group had been reported to not undergo ruthenium-catalyzed oxidation like unsubstitued phenyl substituents. Therefore, selective oxidation of the

phenyl substituent could be performed in the conversion of isoxazolidine intermediate to its corresponding amino acid.

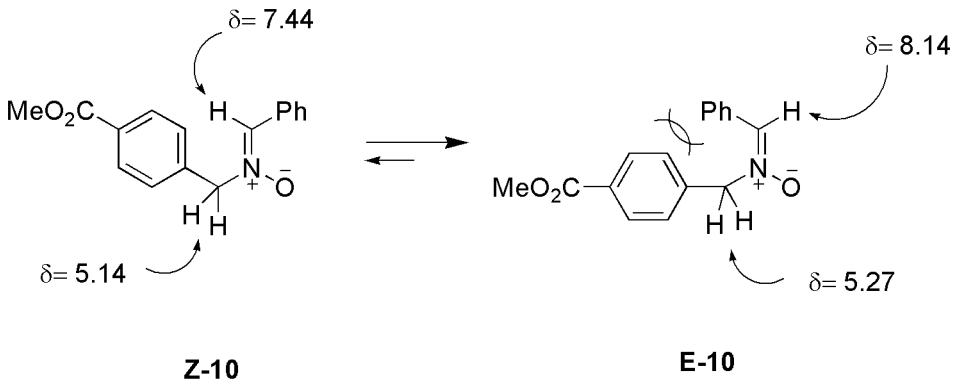
Scheme 16: Synthesis of Nitrone 10



a- NH_2OH HCl, $NaHCO_3$, MeOH; b- $NaBH_3CN$, 2N HCl-MeOH; c- Benzaldehyde, DCM

Nitrone **10** was synthesized in three steps (Scheme 16) starting with the condensation of **7** with NH_2OHHCl to afford oxime **8**. Selective reduction of oxime **8** with $NaBH_3CN$ afforded hydroxylamine **9** which was reacted with benzaldehyde to afford nitrone **10**. ^1H NMR analysis of nitrone **10** reveaed a mixture of nitrones was present in a ~3:1 Z/E-nitrone ratio. Apparently, the N-benzyl protecting group was not large enough to prevent the nitrone from isomerizing between the Z- and E-conformations (Scheme 17). It was decided at this point that nitrone **10** would be an unsuitable candidate for cycloaddition reactions.

Scheme 17: ^{1}H NMR studies of E/Z-Nitrone 10

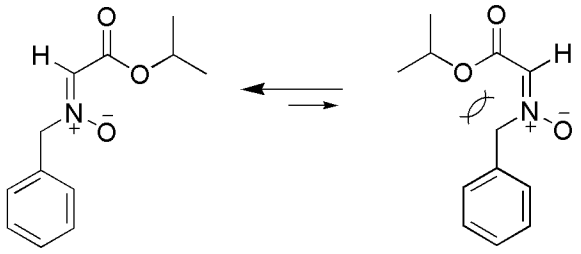


2.3 Carboxy Ester Nitrones

In addition to aldonitrones with a carboxylic acid functional group, ester-derived aldonitrones were also synthesized following a similar approach. Although the ester group would not have the advantage of the stabilizing hydrogen bond noted for the free acid, it was hypothesized that the steric bulk of a large alkyl ester would destabilize the E-nitrone configuration relative to the desired Z-nitrone.

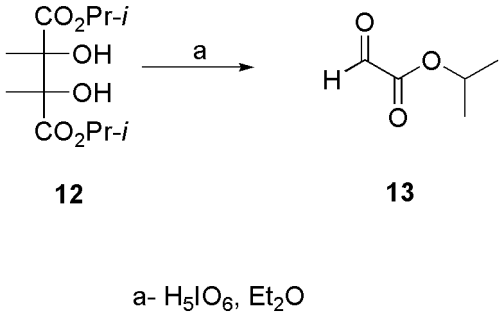
However, the motive behind ester functionality no longer centered on a hydrogen-bonding effect since the acidic hydrogen was replaced with an alkyl substituent. Rather, ester-derived aldonitrones were hypothesized as suitable Z-specific nitrone candidates based on a steric argument. Specifically, highly branched esters such as *i*-Pr and *t*-Bu esters were proposed to be ideal substituents in regards to destabilizing the E-nitrone configuration (Scheme 18).

Scheme 18: Nitrone 11 Isomerization Potential



The first ester-derived nitrone investigated was nitrone **11**. Nitrone **11** was synthesized via condensation between hydroxylamine **4** and isopropylglyoxylate **13**. Aldehyde **13** was synthesized via periodic acid oxidation[55] of diisopropyl tartrate **12**. The oxidation was carried out at 0 °C while stirring for 2h to yield aldehyde **13** in 95% yield (Scheme 19).

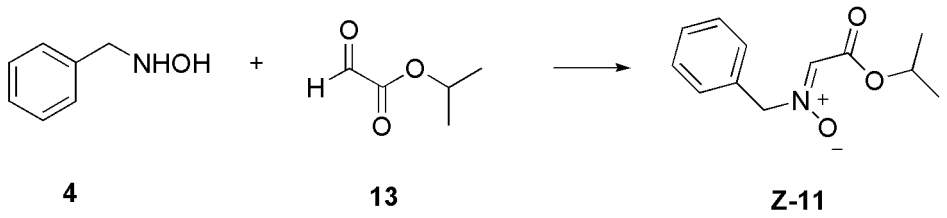
Scheme 19: Oxidation of Diisopropyl Tartrate to Isopropyl Glyoxylate 13



Following the same procedure as Scheme 15-step d, the condensation reaction between aldehyde **13** and benzylhydroxylamine **4** in methylene chloride gave nitrone **11** in 75% yield after stirring at room temperature for 5h (Scheme 20). The resulting nitrone was again analyzed by ^{1}H NMR to determine the respective ratios of the E/Z-nitrones

present. ^{1}H NMR analysis of nitrone **11** showed both nitrones had been synthesized. The chemical shifts of the N-benzylic and vinylic protons associated nitrone isomer **E-11** and **Z-11** followed the trends discussed earlier for carboxylic acid nitrone **1**.

Scheme 20: Synthesis of Nitrone 11



These results are drastically different than the observations made with respect to the carboxylic acid-derived nitrone. First impressions of these ester-derived nitrones had shown them to be poor candidates in the search for Z-specific nitrones, however a thorough investigation into what inhibited the Z-nitrone from forming exclusively was performed.

This investigation was facilitated by the observation that preparing the nitrone in a H_2O/EtOH solvent mixture rather than CH_2Cl_2 afforded crystalline nitrone **Z-11** that was essentially the pure isomer. A thorough understanding of the solvent effects with respect to E/Z nitrone isomerizations led to a modification of the original condensation procedure. Since equilibrium favored E-aldonitrones in non-polar solvents such as methylene chloride, a polar solvent mixture composed of 50:50 ethanol:water was chosen in order to promote selective formation of the Z-aldonitrone. Interestingly, the condensation reaction appeared to proceed much faster as evidenced by the formation

and precipitation of a white solid in this polar solvent mixture after a mere thirty minutes while stirring at room temperature. The reaction vessel was allowed to stir an additional two hours to allow for completion of the reaction. Filtration of the white solid afforded crude nitrone **11** in 93% yield. ^{1}H NMR analysis in $CDCl_3$ showed a 5:1 ratio of what was believed to be **Z-11** to **E-11** based on the corresponding vinyl and benzylic proton chemical shifts, however the isomeric ratio was improved upon through via recrystallization of the crude nitrone in warm ethanol to ultimately afford a nitrone isomeric ratio greater than 20:1 in favor of **Z-11**. The $CDCl_3$ dissolved nitrone was set aside and then analyzed by ^{1}H NMR again one hour later in order to qualitatively observe any further isomerization between the E/Z isomers. Not surprisingly, the Z-nitrone isomerized in the non-polar deuterated-solvent afford a 1.5:1 ratio that favored nitrone **E-11**. Subsequent ^{1}H NMR studies were conducted after two hours and twenty-four hours, however, the nitrone appeared to reach equilibrium sometime between the first and second hour in $CDCl_3$, with the nitrone ratios stabilizing at a 1.9:1 ratio favoring **E-11** in that time frame. Deuterated solvents with high dielectric constants such as d_4-methanol and d_6-dimethy sulfoxide were also used in these qualitative isomerization studies whereby the equilibrium ratio favored **Z-11**. Furthermore, the ratio of **Z-11** to **E-11** exceeded 4:1 even after twenty-four hours of dissolution in the polar solvents. Therefore, polar solvents not only affect the equilibrated nitrone isomeric ratios but also decrease the rate of such isomerizations.

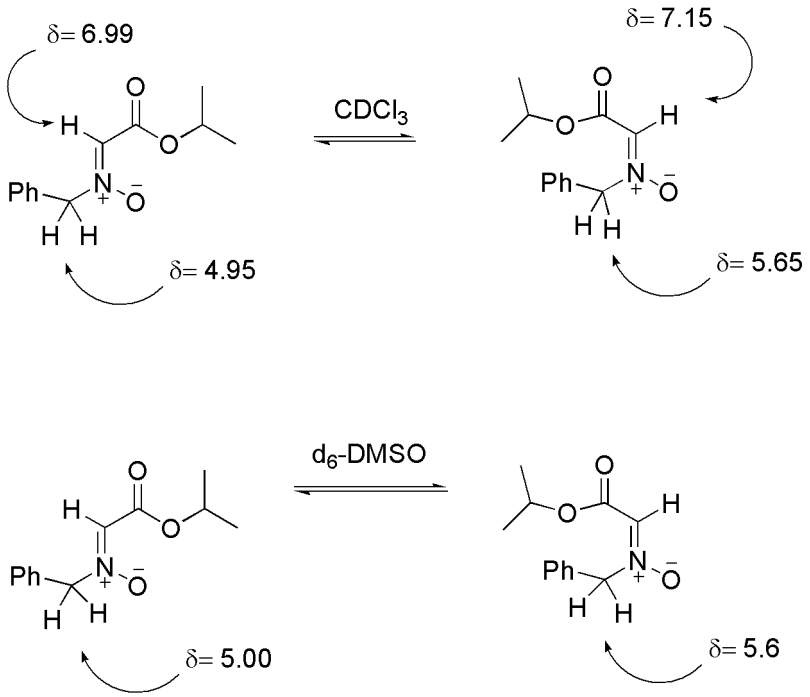


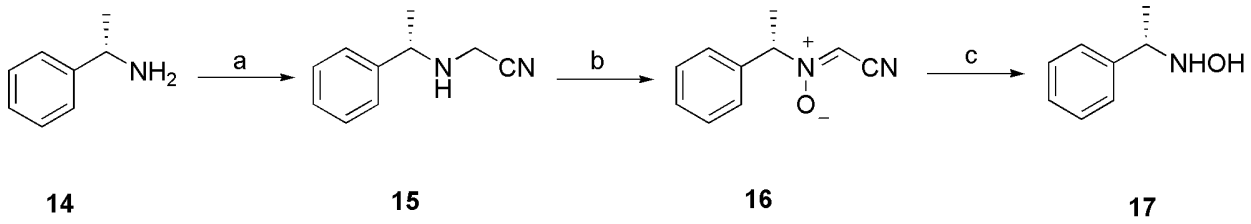
Figure 11: ^{1}H NMR studies of Nitrone 11 in $CDCl_3$ and d_6-DMSO

The original Z/E-nitrone isomeric ratio of 5:1 was improved by a careful recrystallization of the crude nitrone from warm ethanol to afford exclusively **Z-11** in a 79% yield within the limits of the ^{1}H NMR analysis. As a result, it was concluded that the white solid that precipitated from the solvent mixture from the condensation reaction was the Z-nitrone, and only after dissolution in non-polar solvents such as chloroform or methylene chloride was nitrone isomerization observed. The polarity of the solvent is believed to have a direct effect on the interactions between the acyl oxygen and oxide of the nitrone. Highly polar solvents help to minimize the electronic interactions between these two oxygen atoms, and as a result, the nitrone is stable as the Z-isomer.

2.4 Chiral Carboxy Nitrones

The application of chiral nitrones towards the syntheses of optically pure amino acids has been well documented in recent years primarily in instances where cyclic E-nitrones were used.[47, 50] Incorporating the aspect of chirality within our new acyclic Z-nitrones seemed to be the next logical step. The N-benzyl substituent is a good position at which to include an element of chirality because the N-benzyl protecting group can be easily cleaved under catalytic hydrogenation conditions. With this in mind, exchanging one of the benzylic hydrogens with an alkyl substituent will accomplish the conversion of an achiral N-benzyl substituent to a chiral N-α-methylbenzyl group. Chiral nitrone **18** was synthesized via a condensation reaction between glyoxalic acid and S-2-phenyl ethyl hydroxylamine **17** (Scheme 22).[56] However, the synthesis of hydroxylamine **17** could not be made enantiomerically pure via the reaction conditions from Scheme 15. In order to synthesize the hydroxylamine precursors a different synthetic route was pursued (Scheme 21).[56]

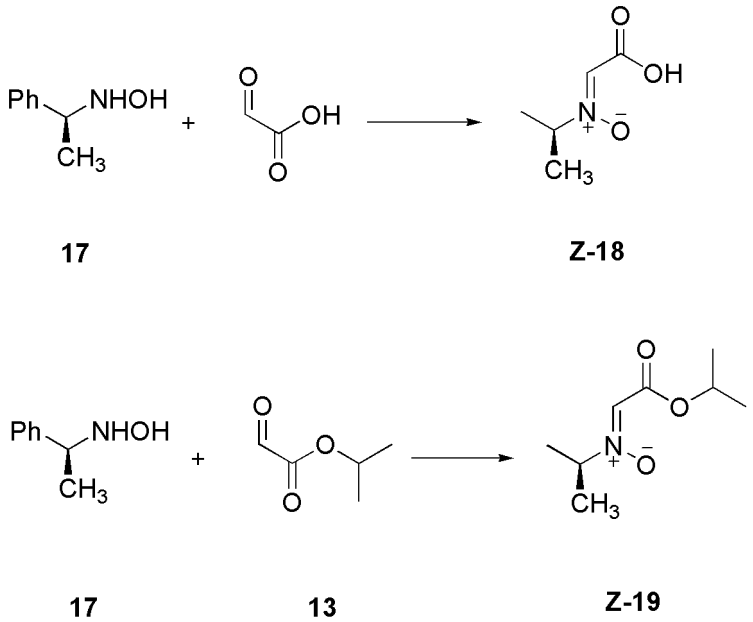
Scheme 21: Synthesis of Chiral Hydroxylamine 17



a- K_2CO_3, $ClCH_2CN$, MeCN; b- *m*-CPBA, DCM; c- NH_2OH HCl, MeOH

The alternate route began with commericially available S-2-phenylethylamine **17** in a substitution reaction with chloroacetonitrile. The secondary amine **15** was then oxidized with *meta*-chloroperbenzoic acid to afford nitrone **16** which was then reacted with hydroxylamine hydrochloride to give S-2-phenylethyl hydroxylamine **17** in a carbonyl exchange reaction. S-Nitrone **19** was synthesized via condensation of isopropyl glyoxylate **13** and hydroxylamine **17** in a 50/50 ethanol/water mixture (Scheme 22), the product precipitating from the reaction mixture as described earlier.

Scheme 22: Syntheses of Chiral Nitrones 18 + 19



A single isomer was observed by ^{1}H NMR analysis of nitrone **18** (Figure 12) as was expected with the carboxylic acid proton hydrogen-bonding to the nitrone oxide. ^{1}H NMR analysis confirmed that ester nitrone **Z-19** had been synthesized exclusively based on the observance of a single vinylic proton (Figure 13). Furthermore, the resulting

equilibration of **Z-19** to **E-19** in deuterated solvents proceeded even slower than in the achiral versions, which was expected due to the extra steric bulk associated with the α-methyl substituent present in the chiral nitrone.

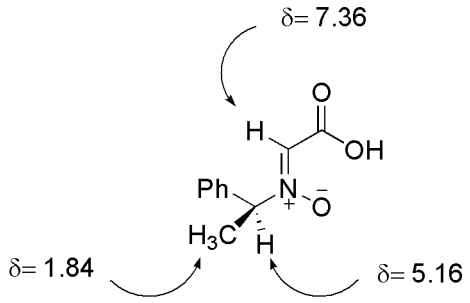


Figure 12: ^{1}H NMR analysis of Nitrone 18 in $CDCl_3$

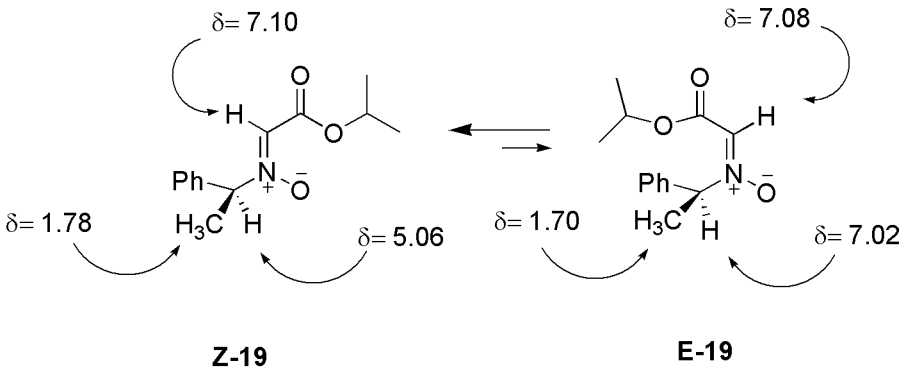
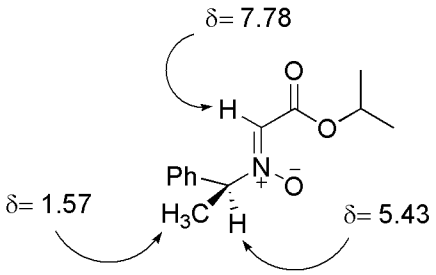


Figure 13: ^{1}H NMR analysis of Nitrone 19 in $CDCl_3$

Interestingly, a ^{1}H NMR spectrum was obtained for nitrone **19** in D_6-DMSO which revealed only a single isomer (Figure 14). This nitrone did not isomerize even after twenty four hours in the polar deuterated solvent, which further supported the Z-nitrone stabilizing effects of polar solvents.



Z-19

Figure 14: ^{1}H NMR analysis of Nitrone 19 in d_6-DMSO

Finally, X-ray crystallography was used to determine that the Z-nitrone was the result of an ethanol recrystallization of the largely crude product (Figure 15). As a result, chiral nitrone **Z-19** has significant promise for use in enantioselective total synthesis.

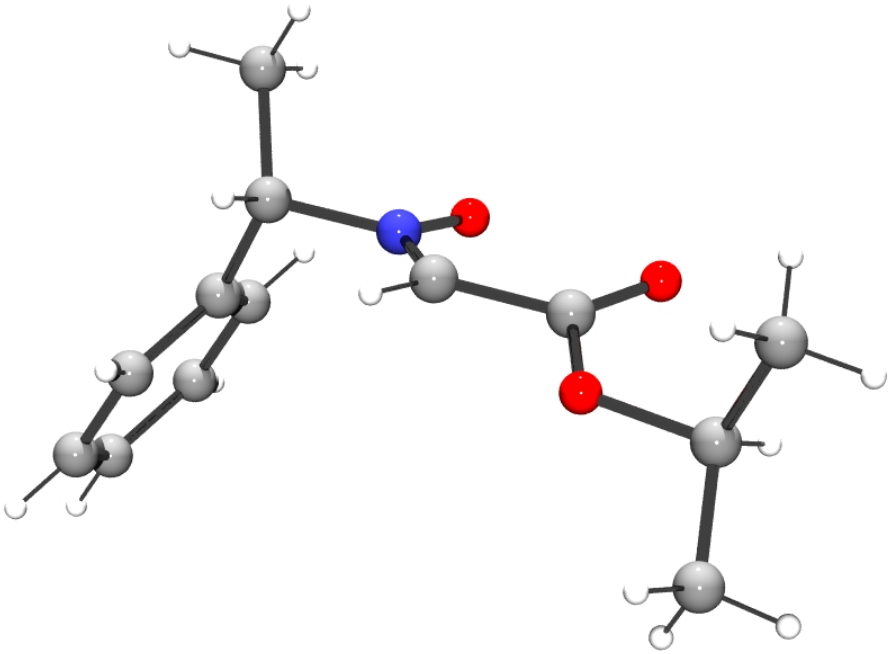


Figure 15: X-ray Crystallographic Structure of Nitrone Z-19

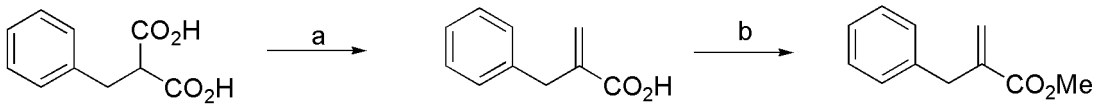
3. Dipolar Cycloadditions

Substituted olefins are used as reaction partners with nitrones for 1,3-dipolar cycloaddition reactions. A number of olefins are commercially available such as methyl methacrylate, cis/trans-butene, etc. However, most biologically active 4-hydroxy amino acids possess functional groups at the C-4 position that correspond to substituted olefins that are not commercially available. Presented here are the syntheses of several of these compounds.

3.1 Olefins of Interest

Olefin **22** is an interesting alkene in that it can be readily synthesized. It is similar in structure to indolylmethyl methacrylates **26** and **27**, the alkenes needed for the synthesis of monatin. Therefore, an investigation into the cycloaddition reactivity of Z-nitrones **1** and **11** with olefin **22** should provide useful comparisons for later studies.

Scheme 23: Synthesis of Alkene 22



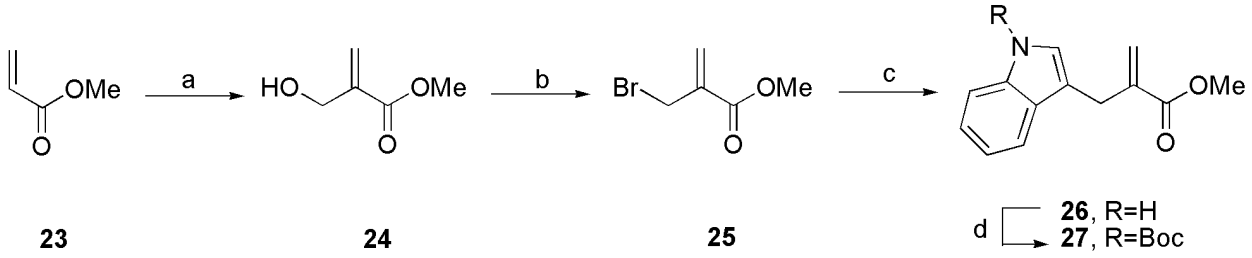
20 **21** **22**

a- 37% Formalin, $HNEt_2$; b- TMS-CH_2N_2, 3:2 Toluene:MeOH

The synthetic approach used to make benzyl methacrylate started with the synthesis of 2-benzyl acrylic acid **21** by reacting benzyl malonic acid **20** with

formaldehyde in diethylamine.[57] Acrylic acid derivative **21** was converted into methyl ester **22** via esterification with trimethylsilyl-diazomethane (Scheme 23).[58]

Scheme 24: Syntheses of Indole Alkene 26 and N-Boc-Indole Alkene 27



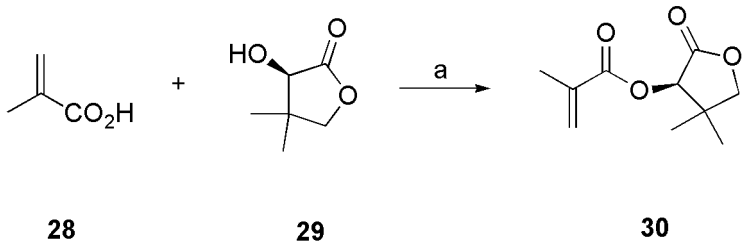
a- Paraformaldehyde, DABCO; b- PBr_3, Et_2O; c- Indole, 3M MeMgBr, THF; d- Boc_2O, DMAP, MeCN

Indolyl methyl methacrylate **26** was synthesized in three steps (Scheme 24) that began with the Baylis-Hillman reaction between formaldehyde and methylacrylate **23** in the presence of DABCO in a sealed tube at high temperature.[59] The product of this reaction was shown to be a 2:1 mixture of dimerized ether and the desired 2-hydroxylmethyl methacrylate. Various reaction conditions[60, 61] were tried to increase the yield of the desired alcohol product **24**, and the optimized conditions were found to involve using a 50/50 solvent mixture of water and dioxane. Under these conditions, the yield of the desired of alcohol product **24** synthesized was doubled, making the overall synthetic design more favorable. Bromination of alcohol **24** using PBr_3 afford bromide **25**. Indolyl alkene **26** was then synthesized via a substitution reaction between indole and bromide **25**. Conversion of indolyl alkene **26** to N-Boc protected indolyl alkene **27**

offered another derivative that could be advantageous in subsequent reactions for use in the synthesis of monatin.

Optically active olefins were synthesized to be used with several achiral and chiral nitrones discussed earlier. R-pantolactone alcohol **29** made for a good candidate[62] in this regard since both enantiomers are commercially available in addition to the fact that the substituent was rather large and could conceivably promote facial selectivity in the cycloaddition reaction step, especially when an optically active nitrone such as 2-phenylethyl nitrone was used with the optically active olefin causing a double diastereoselection effect. For instance, the R-pantolactone-derived acrylate **30** was synthesized via coupling methacrylic acid **28** and R-pantolactone alcohol **29** using DCC/DMAP coupling conditions (Scheme 25).

Scheme 25: Synthesis of Chiral Alkene 30

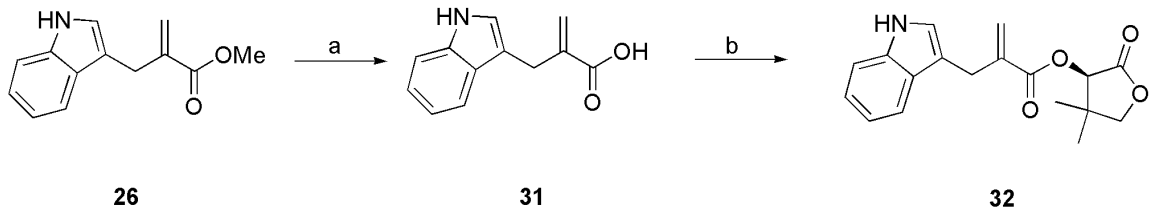


a- DCC, DMAP, DCM

The optically active R-pantolactone-derived indolylmethyl acrylate olefin was synthesized in two steps that started with the careful hydrolysis of the indolylmethyl methacrylate **26** to afford indolylmethyl acrylic acid **31.** The careful hydrolysis was

achieved using a 9:1 solvent mixture of methylene chloride:methanol. The coupling of acrylic acid **31** with R-pantolactone alcohol **29** in the presence of DCC/DMAP afforded enantiomerically pure olefin **32** (Scheme 26).

Scheme 26: Synthesis of Chiral Alkene 32



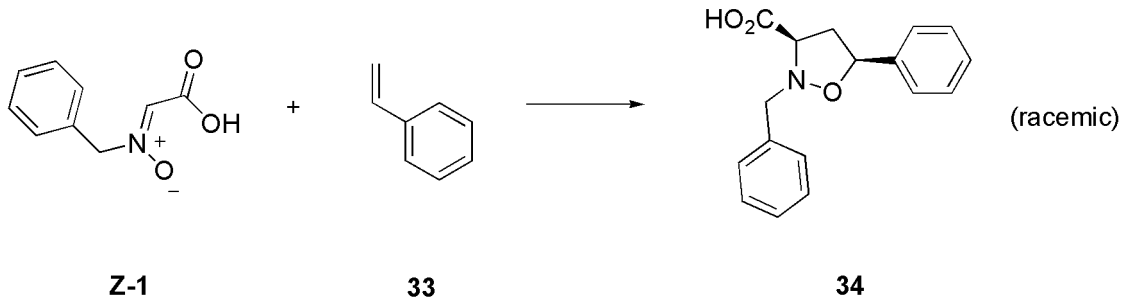
a- 2N NaOH, 9:1 DCM:MeOH; b- R-Pantolactone, DCC, DMAP, DCM

3.2 CO_2H-Nitrone Cycloadditions

For the work described herin, the 1,3-dipolar cycloaddition reaction between a nitrone and olefin is the critical step towards the synthesis of γ-hydroxy-α-amino acids and is the featured reaction of this work. This single step controls the relative stereochemistry found at the C-2 and C-4 carbons in the amino acids when 1,1-disubstituted olefins are used in addition to the stereochemistry found at the C-3 carbon when 1,2 disubstituted olefins are used. Furthermore, the absolute stereochemistry at the C-2 and C-4 carbons can also be set during this reaction when optically active nitrones and olefins are used in the cycloaddition reaction. Therefore, it was of utmost importance to develop reaction conditions that optimized the overall selectivity of this reaction process.

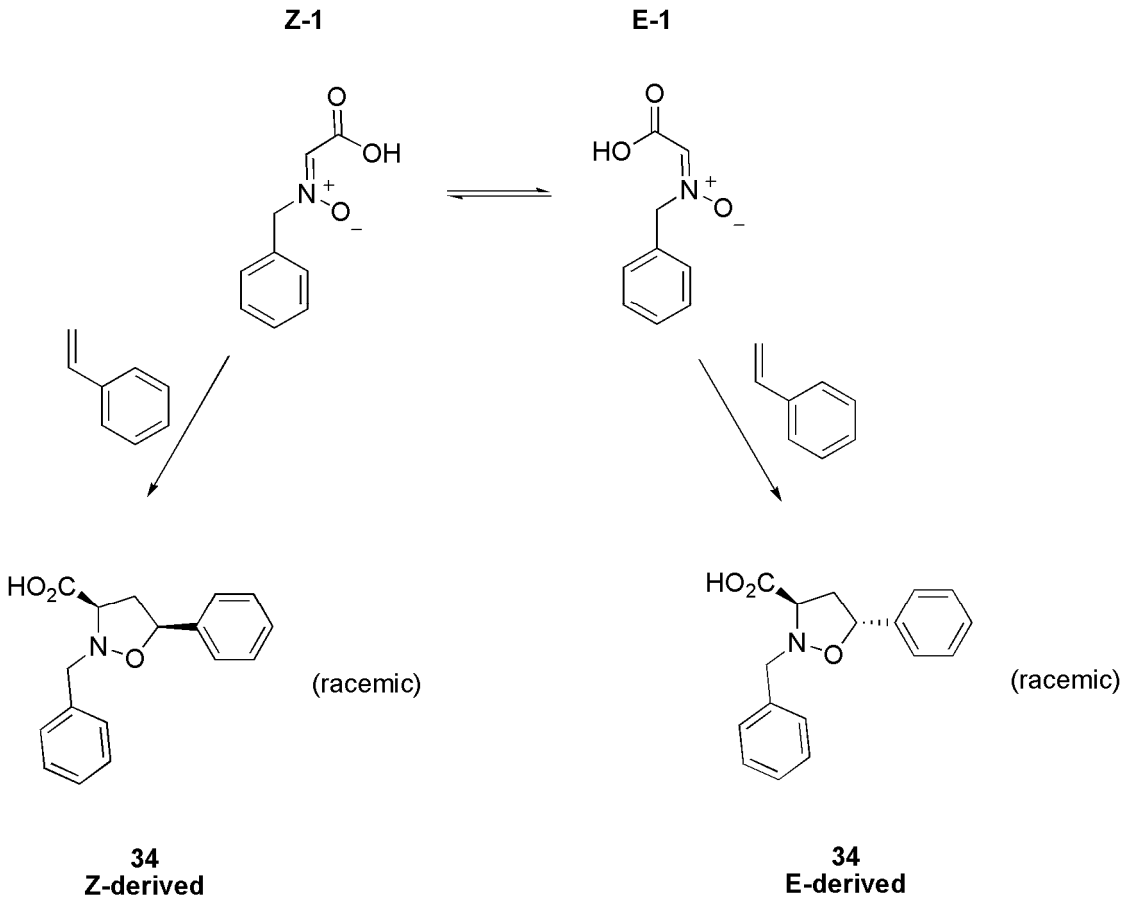
Investigation into the nature of these cycloadditions began with achiral nitrones and olefins to better understand the relative stereochemistry of these reactions before deciphering the absolute stereochemistry when optically active starting materials were employed. The carboxylic acid nitrone **1** was the first candidate investigated for these cycloadditions since the Z-isomer was stabilized by the hydrogen-bonding type interaction between the acidic proton of the carboxylic acid and the oxide of the nitrone.

Scheme 27: Cycloaddition Reaction between Nitrone 1 and Styrene



The first cycloaddition experiment paired carboxylic acid nitrone **1** with styrene **33** (Scheme 27).[63] Since FMO theory predicted the olefin would react with the nitrone to afford a syn product as the major isomer, only a single isoxazolidine isomer should have been synthesized in this reaction. However, ^{1}H NMR analysis of crude product **34** determined that two isoxazolidine diastereomers were synthesized in roughly a 15:1 diastereomeric ratio based ^{1}H NMR integration (Scheme 28).

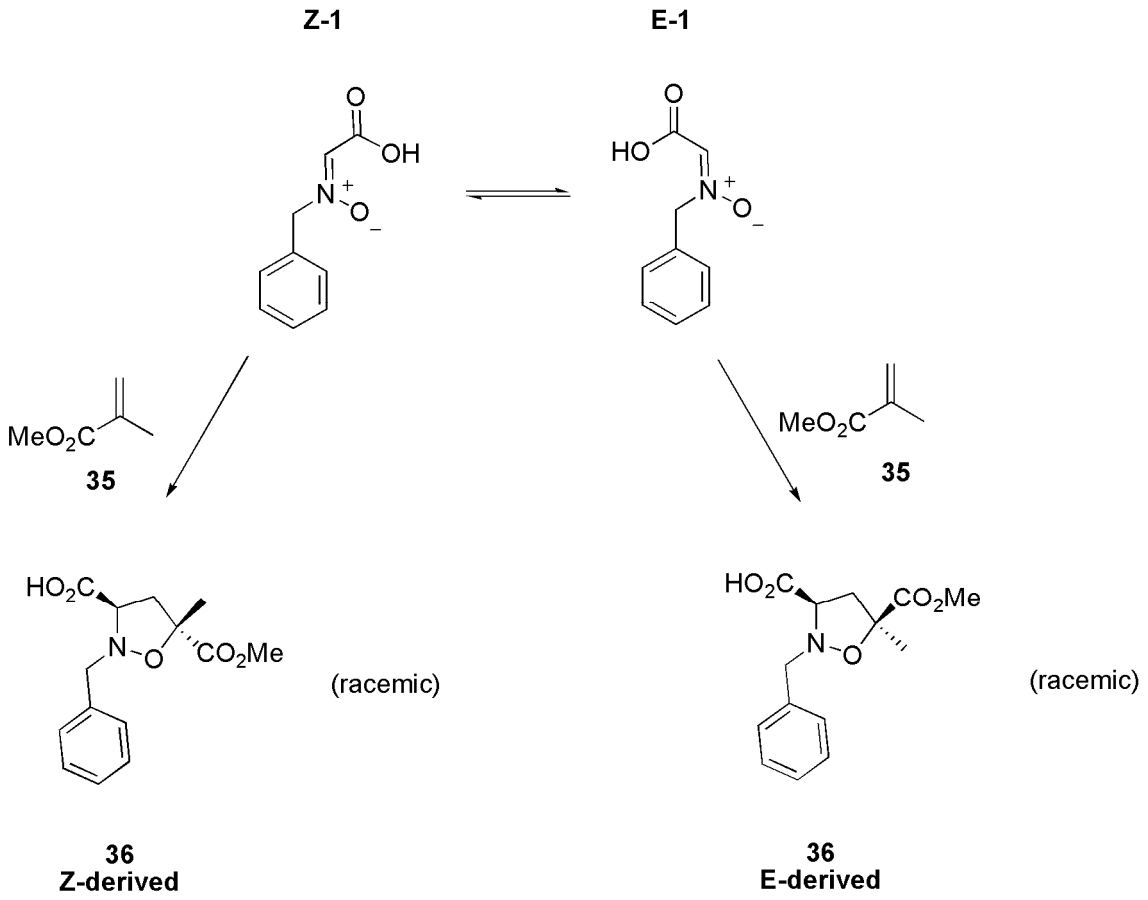
Scheme 28: Proposed Pathway for the Mixture of Isoxazolidine 34 Products



This observation of two products meant that one of two things had happened during the cycloaddition; either the olefin was competing between an endo and exo transition state or the nitrone was isomerizing between its corresponding E- and Z-isomer (or a combination of the two). Previous cycloaddition reactions between styrene and the cyclic E-nitrone reported by the Baldwin group demonstrated a preference for one isoxazolidine major product in nearly 10:1 ratio.[50] Based on our previous results with styrene cycloadditions E/Z isomerization would seem to be the more likely source

of the small amount of the minor diastereomer, however, competition between the endo/exo transition state may also contribute to the diastereomeric product mixture.

Scheme 29: Proposed Pathway for the Syntheses of Isoxazolidine 36



Methyl methacrylate **35** was then reacted with nitrone **1** to afford isoxazolidine **36** en route to the total synthesis of γ-hydroxyl-γ-methylglutamic acid (Scheme 29). Even with excess methyl methacrylate, this cycloaddition was a much slower reaction than with styrene. After four days up to half of the original unreacted nitrone remained with methyl methacrylate while the styrene reaction was complete in less than 48 hours. The reaction was allowed to stir an additional two days for a total of six days, all the while

maintaining a temperature of 23 °C. ^{1}H NMR analysis of the crude reaction product revealed a pair of diastereomers which were assumed to have resulted from the E/Z isomerization of the nitrone during the extended reaction time. The diastereomeric ratio was determined to be about 6:1 based on ^{1}H NMR integration, however the relative stereochemistry of the isoxazolidine could not be determined by ^{1}H NMR analysis so it remained unclear as to which isoxazolidine product was the major isomer. This uncertainty will be addressed in Chapter 4. Another attempt at this cycloaddition involved changing the solvent from chloroform to methanol. ^{1}H NMR analysis of the products from this reaction again revealed a mixture of two diastereomers, however the relative ratios between the isoxazolidines changed from 6:1 to 3:1. One possible explanation for this decrease in stereoselectivity is that the basic methanol solvent interrupts, or at least weakens the hydrogen bond between the acid proton and nitrone oxygen. If this was the effect that in fact took place during the reaction, then the drop in diastereomeric excess could be attributed to an increase in isoxazoldine product via a transition state that included more of the E-nitrone. Therefore, it was hypothesized that major isoxazolidine isomer in each case was the result of a cycloaddition between the olefin and **Z-1**.

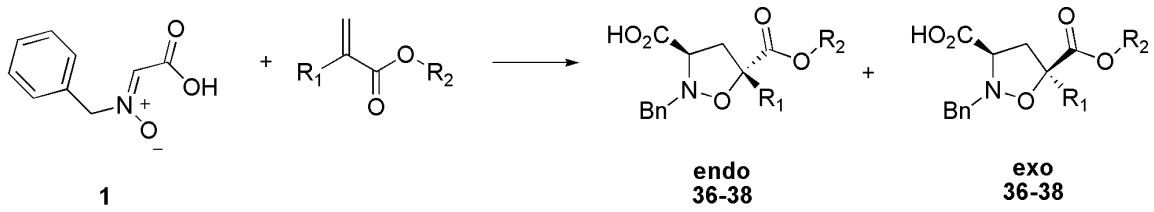


Table 1: Analysis of Isoxazolidine Ratios in Reactions between Nitrone 1 and Various Alkenes in chloroform

Reaction	Alkene	Isoxazolidine	Endo:Exo
Entry 1	R1 = Me, R2 = Me	36	6:1
Entry 2	R1 = Bn, R2 = Me	37	4:1
Entry 3	R1 = CH2-Indole, R2 = Me	38	2:1

A select group of acrylate-derived olefins were used in reactions with this carboxylic acid nitrone in order to determine the scope of possibilities for this nitrone with respect to an isoxazolidine precursor to Monatin (Table 1). Although isoxazolidines **37** and **38** were synthesized, the endo:exo distribution was less selective, the reactions proceeded slower, and the isoxazolidine yields were lower than the synthesis of isoxazolidine **36**.

In further studies, olefins such as methyl crotonate, Z-2-butene, and E-2-butene were also used in cycloaddition reactions with nitrone **1**. The cycloaddition between nitrone **1** and methyl crotonate proceeded even more slowly than the reaction with methyl methacrylate and, therefore, nothing of value could be determined. Furthermore, the cycloaddition reactions with the 2-butene isomers failed to produce more than ten

percent isoxazolidine product even after fourteen days of stirring at room temperature. The lack of reactivity between this nitrone and butenes could be explained by the fact that these olefins are electron rich and thus were not favorable candidates when paired with the nitrone. However the lack of reactivity between this nitrone and methyl crotonate was surprising and not consistent with its reactivity when exposed to cyclic E-nitrone as reported by the Baldwin group.[50] In one attempt to increase the overall isoxazolidine yields for cycloadditions with nitrone **1**, the reaction conditions were altered by increasing the temperature of the reaction vessels. Unfortunately, no presence of isoxazolidine products was ever observed by ^{1}H NMR analysis. It was believed that the nitrone itself decomposed as a result of the increased temperature of the reaction. Because no isoxazolidine products were observed in several reactions, these high temperature cycloaddition reactions were abandoned.

In addition to the unsuccessful thermal reactions described above, two additional approaches to improving the cycloaddition reactions were explored: microwave irradiation and Lewis acid catalysis. With regard to microwave irradiation,[64] various conditions were used that ranged from wattages from 100W to 250W and reaction times between five minutes to 30 minutes. Methyl methacrylate was the olefin used in these trial reactions for reasons previously described. It was determined that the vast range of conditions used to promote faster reactions between this nitrone and olefin had no effect at increasing the reactivity of this reaction. Although microwave irradiation has been

reported to be effective in some cycloaddition reactions,[64] the conditions tried in the present reaction proved to be ineffective.

An attempt at using a Lewis acid to accelerate these cycloadditions was also studied. $MgBr_2OEt_2$ had been reported as a potential candidate in this regard[44, 46, 47]. Cycloaddition reactions between carboxylic acid nitrone **1** and methyl methacrylate in the presence of $MgBr_2OEt_2$ were studied. In one reaction, a catalytic amount of the Lewis acid was added and in the other experiment, a stoichiometric equilavent of $MgBr_2OEt_2$ was used. Once again, ^1H NMR analysis revealed no increased reactivity or stereoselectivity when the Lewis acid was used. It is possible, however, that this lack of reactivity was related to the insolubility of the Lewis acid catalyst in the apolar solvent reaction medium.

3.3 Cycloadditions with Carboxy Isopropyl Nitrone

With the lack of reactivity observed when using carboxylic acid nitrone **1**, isopropyl ester-derived nitrone **11** was next investigated. The first experiment performed was a reaction between nitrone **11** and methyl methacrylate **35.** The cycloadditions were performed in different solvents of varying dielectric constants (Table 2). There appeared to be a direct relationship between the solvent polarity and the diastereomeric ratio of isoxazolidine products. Cycloadditions in polar solvents such as acetonitrile (MeCN) and dimethylsulfoxide (DMSO) favored the formation of **endo-39**

isoxazolidines by ratios upwards of 10:1. Conversely, non-polar solvents such as 1,4-dioxane and chloroform greatly reduced the ratio of **endo-39** to its **exo-39** diastereomer.

Scheme 30: Synthesis of Isoxazolidines 39

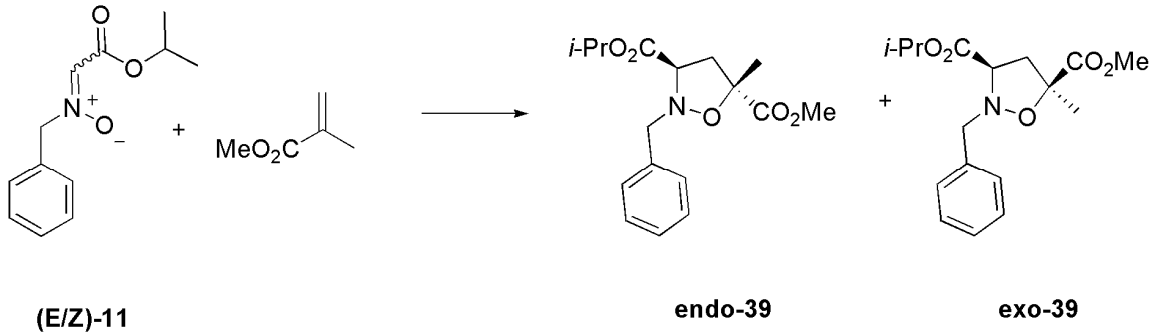
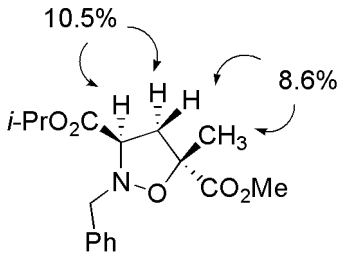


Table 2: Solvent Effect Studies

Solvent	Dielectric Constant ε	endo:exo
Dioxane	2.2	3:1
Chloroform	4.8	3:1
methanol	33	7:1
acetonitrile	38	10:1
dimethylsulfoxide	47	12:1

The results presented in this table demonstrate the important role that solvents have in controlling cycloadditions between acyclic nitrones and substituted olefins. As an interesting side note, when the reaction was performed in the absence of solvent, the product ratio was still a respectable 10:1. As shown in the table, the best solvent for these cycloadditions was dimethylsulfoxide which yielded roughly a 12:1 ratio of

isoxazolidine products. In order to determine which isoxazolidine product was the major isomer, the major isoxazolidine was analyzed via NOE experiments.



endo-39

Figure 16: NOE Analysis of the Major Isoxazolidine Product

Since the desired isoxazolidine product would be formed through a reaction with nitrone as its Z-isomer, the relationship between the isopropyl ester of the nitrone and the methyl ester of the olefin would be *anti* with respect to each other on the isoxazolidine ring. NOE experiments confirmed the diester relationship by studying the methylene protons within the isoxazolidine ring. The fact that one of the methylene protons enhanced only the single methine proton within the ring, along with the fact that the other methylene proton enhanced only the other methine proton within the ring, demonstrated that the methine protons at C-2 and C-4 were anti to one another (Figure 16). Therefore, the ester substituents geminal to these methine protons were proven to be anti to each other as well, as predicted based on earlier arguments.

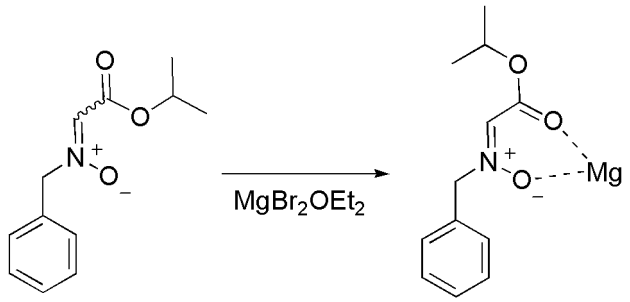
In order to increase the diastereomeric ratios of the isoxazolidine products, various Lewis acids were added to the reactions. These included $MgBr_2{\cdot}OEt_2$, $ZnBr_2$, and $Ti(OiPr)_4$, each of which was studied as a potential catalyst and/or chelator in order to

accelerate the cycloaddition reactions, with the ultimate goal of increasing diastereomeric ratios for the isoxazolidine products. It was believed that accelerating the reaction rates would minimize **Z-11** from isomerizing to **E-11** and thus maximize formation of the endo-derived isoxazolidine **endo-39**.

The Lewis acid experiment began with $MgBr_2$. Similar to the carboxylic acid nitrone, it was determined that $MgBr_2{\cdot}OEt_2$ had no effect when the solvent for the reaction was acetonitrile. It was believed that $MgBr_2{\cdot}OEt_2$ was ineffective due to its insolubility in this solvent. Therefore it was decided that a different solvent, one which $MgBr_2{\cdot}OEt_2$ was soluble, would offer an opportunity for a successful $MgBr_2{\cdot}OEt_2$ experiment. Methanol was selected and the cycloaddition was performed under standard conditions. Gratifyingly, it appeared that soluble $MgBr_2{\cdot}OEt_2$ did, in fact, enhance the diastereomeric ratios of isoxazolidines in favor of the desired product. The increase in diastereomeric ratios went from 10:1 in methanol alone to approximately 15:1 in methanol containing 1.1 eq $MgBr_2{\cdot}OEt_2$. Additional experiments that studied the role that $MgBr_2{\cdot}OEt_2$ played in the enhanced selectivity were performed. It was found that decreasing the amount of $MgBr_2{\cdot}OEt_2$ to 10% produced a smaller diastereomeric ratio. Moreover, 2eq (200 mole %) did not lead to any further diastereomeric enhancement over that obtained with 110 mole % catalyst. Therefore, this experiment suggests that $MgBr_2{\cdot}OEt_2$ is operating as a chelator to stabilize the Z-nitrone rather than as an actual reaction catalyst (Scheme 31). To further support this claim, thin layer chromatography

was used to monitor the cycloaddition reaction rates for both the presence of $MgBr_2 \cdot OEt_2$ and its absence. Interestingly, the reaction where $MgBr_2 \cdot OEt_2$ was absent actually proceeded faster than the reaction that included 1.1 eq of $MgBr_2 \cdot OEt_2$ based on TLC spot intensity. The presence of $MgBr_2 \cdot OEt_2$ slowed the reaction rate of these cycloadditions and as a result would have impaired the selectivity of the cycloaddition if not for $MgBr_2 \cdot OEt_2$ serving as a Z-nitrone chelator that diminished the tendency to isomerizes.

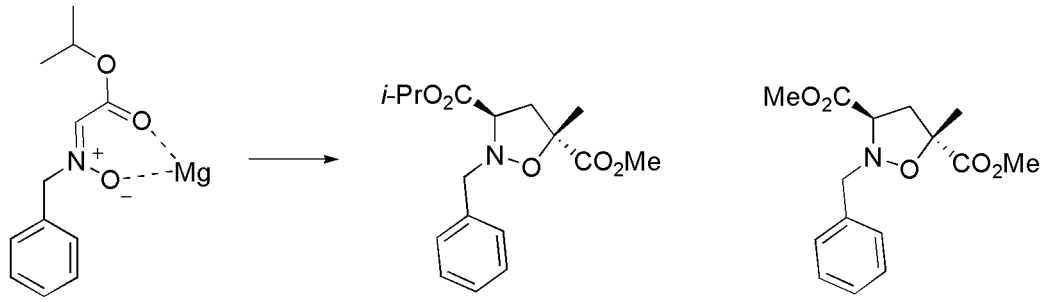
Scheme 31: Proposed $MgBr_2 \cdot OEt_2$ Chelation to Nitrone 11



(E/Z)-11 **Z-11**

An interesting observation from the ^{1}H NMR analysis of these $MgBr_2 \cdot OEt_2$-mediated cycloadditions showed that when this reaction was performed in a 50:50 mixture of MeCN:MeOH, the isopropyl ester of the nitrone was prone to undergo transesterification with the alcohol solvent. ^{1}H NMR analysis revealed that only the nitrone ester was prone to transesterification and not the ester on the olefin. This effect led to a mixture of isoxazolidines that consisted of both **endo/exo-39** as well as **endo/exo-40** (Scheme 32). Because the ester is ultimately lost in the subsequent isoxazolidine manipulations, this transesterification creates no real problems.

Scheme 32: Transesterification in the Presence of $MgBr_2OEt_2$



chelated Z-11 **39** **40**

Microwave irradiation was used in an attempt to further enhance the isoxazolidine diastereomeric ratios of cycloaddition reactions with carboxy ester nitrones. The parameters chosen were similar to those used in the carboxylic acid nitrone microwave irradiated reactions. Interestingly, microwave irradiation appeared to accelerate the cycloaddition reactions more than 100 fold. These cycloaddition reactions proceeded to completion within three minutes whereas the same cycloaddition reaction performed at room temperature in the absence of microwave irradiation proceeded to completion only after 8 or more hours. Furthermore, only a single isoxazolidine product was observed from the microwave irradiated cycloaddition reaction based on ^{1}H NMR analysis. Although this information was promising, closer analysis of the ^{1}H NMR for the microwave irradiated isoxazolidine products showed subtle changes in chemical shifts between the thermal and microwave irradiated isoxazolidines. This suggested that another reaction pathway might be operating, although the matter was not pursued further.

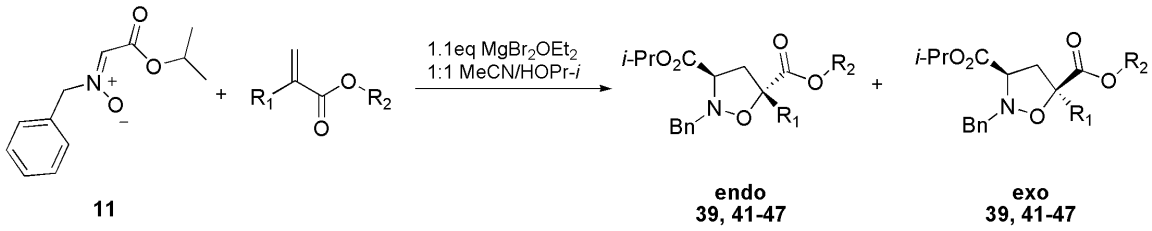
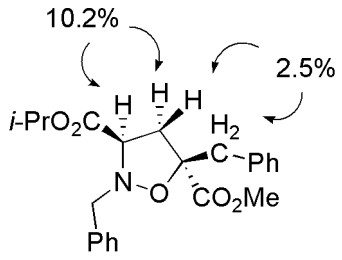


Table 3: Analysis of Isoxazolidine Ratios in Reactions between Nitrone 11 and Various Alkenes

Reaction	Alkene	Isoxazolidine	Endo:Exo
Entry 1	R1 = Me R2 = Me	39	20:1
Entry 2	R1 = Me R2 = Bn	41	15:1
Entry 3	R1 = Bn R2 = Me	42	15:1
Entry 4	R1 = CH2-Indole R2 = Me	43	2.5:1
Entry 5	R1 = CH2-N-Boc-Indole R2 = Me	44	2.5:1
Entry 6	R1 = CH2OH R2 = Me	45	1:0
Entry 7	R1 = CH2OMOM R2 = Me	46	10:1
Entry 8	R1 = CH2Br R2 = Me	47	1:1

Various other olefins were also studied for their reactivity with the isopropyl ester nitrone **11**. A cycloaddition reaction between isopropyl ester nitrone and methyl-2-benzylacrylate **22** (Table 3, Entry 3) showed high diastereoselective ratios on par with methyl methacrylate. The conditions optimized through the methylmethacrylate studies

proved useful again with respect to methyl-2-benzylacrylate **22**. Additionally, these results had shown that the same reaction conditions could be used for a cycloaddition reaction between isopropyl ester nitrone and indolylmethyl methacrylate to afford the isoxazolidine intermediate required for monatin. To confirm the relationship between the isopropyl ester of the nitrone and the methyl ester of the olefin, NOE experiments were performed on the benzylmethacrylate-derived isoxazolidine major diastereomer (Figure 17). Fortunately, the major isoxazolidine isomer was shown to possess the *anti* relationship between the ester functional group, consistent with the earlier conclusion that these reactions were proceeding through Z-nitrone **11**.



endo-42

Figure 17: NOE Analysis of Isoxazolidine 42

The big question regarding the utility of the isopropyl ester nitrone had to do with its reactivity with indolylmethyl methacrylate **26** (Table 3, Entry 4). The favorable reaction of this nitrone with benzyl methacrylate demonstrated the potential for this olefin with similar electronic properties to react comparably. Unfortunately, the cycloaddition reaction proceeded to give only a 2.5:1 isoxazolidine ratio in a 50:50 MeCN:HOPr-*i* solvent mixture based on ^{1}H NMR analysis. The realization that this

cycloaddition produced the worst product distribution with respect to the diastereomeric ratio was disheartening. The only favorable observation that resulted from this experiment had to do with the NOE analysis which showed the major isoxazolidine isomer was the anti-relationship between the isopropyl ester and methyl ester (Figure 18).

endo-43 **exo-43**

Figure 18: NOE Analysis of Isoxazolidine 43

The opportunity existed to optimize the reaction conditions for indolylmethyl methacrylate. This problem was solved by changing the solvent mixture of the cycloaddition reaction from a 50:50 mixture of MeCN:*i*-PrOH to a 50:50 mixture of MeCN:MeOH. The exchange of isopropanol for methanol meant that transesterification of the ester attached to the nitrone would occur and thus lead to two additional isoxazolidines with methyl esters attached to the C-2 carbon of the ring. However, this transesterification would not limit the scope of these cycloadditions because the esters are hydrolyzed in the subsequent steps leading to the amino acid target molecules.

Interestingly, the cycloaddition reactions between isopropylester and indolylmethyl methacrylate that were performed in the 50:50 methanol:acetonitrile

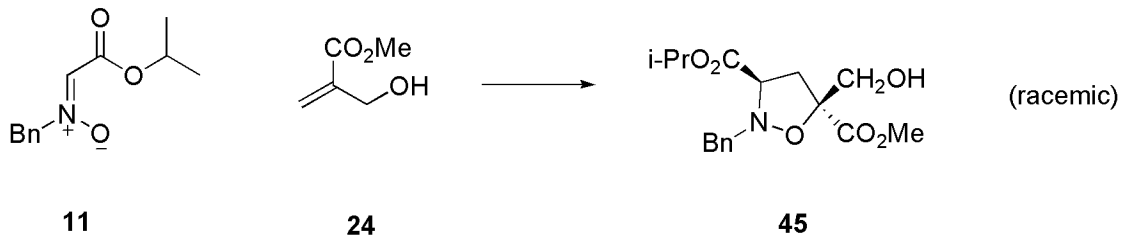
mixture primarily afforded two isoxazolidines that had been determined to be the anti ester isoxazolidines of the methyl ester and isopropyl ester respectively. Further analysis revealed the combined product ratios to be roughly 15:1 in favor of the combination of **endo-43-O*i*Pr** and **endo-43-OMe** compared to the pair of **exo-43-OR** products when a 5:1 alkene:nitrone ratio was used. Interestingly, when the alkene:nitrone ratio was dropped to 2:1, the product ratio still favored the endo isoxazolidine by tenfold. Not surprisingly, when a 1:1 alkene:nitrone reactant ratio observed, the isoxaolidine ratio dropped to ~2:1 favoring the endo product.

Interestingly, the cycloaddition reaction with E-2-butene did not afford any noticeable isoxazolidine product even after allowing the reaction to stir for more than two weeks. It was believed that the electron rich dipolarophile interfered with its reactivity when paired with the electron rich nitrone. Furthermore, methyl crotonate did not exhibit similar isoxazolidine ratios compared to its isomer, methyl methacrylate. The isoxazolidine diastereomeric ratios for reactions with methyl crotonate were approximately 1:1 as opposed to the nearly 20:1 ratio in the case of methyl methacrylate. This observation came as quite a surprise due to the similarity between the two corresponding olefins. An investigation into the odd reactivity of methyl crotonate was not pursued.

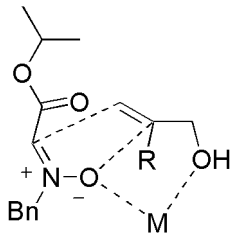
Cycloadditions between isopropyl nitrone **11** and a number of methyl methacrylate derivatives were also studied following the same optimized reaction

conditions mentioned above. 2-Hydroxymethyl methacrylate **24** reacted remarkably well with the nitrone to afford the endo product (with respect to the olefin ester) exclusively (Scheme 33) (Table 3, Entry 6). The formation of a single diastereomer in this reaction did not come as a surprise based on earlier work done by Kanemasa[46] and Tamura[47] in cycloadditions with allylic alcohols.

Scheme 33: Synthesis of Isoxazolidine 45



It seems likely that in the formation of **45**, the hydroxyl functional group coordinated to the $MgBr_2$ molecule to promote an exo transition state with respect to the alcohol (Figure 20). Considering the effect with the electron withdrawing aspect of the methyl ester of the olefin preferring an endo position, the combined effects of the ester and alcohol moieties would compliment one another to promote a very selective cycloaddition reaction.



TS-45

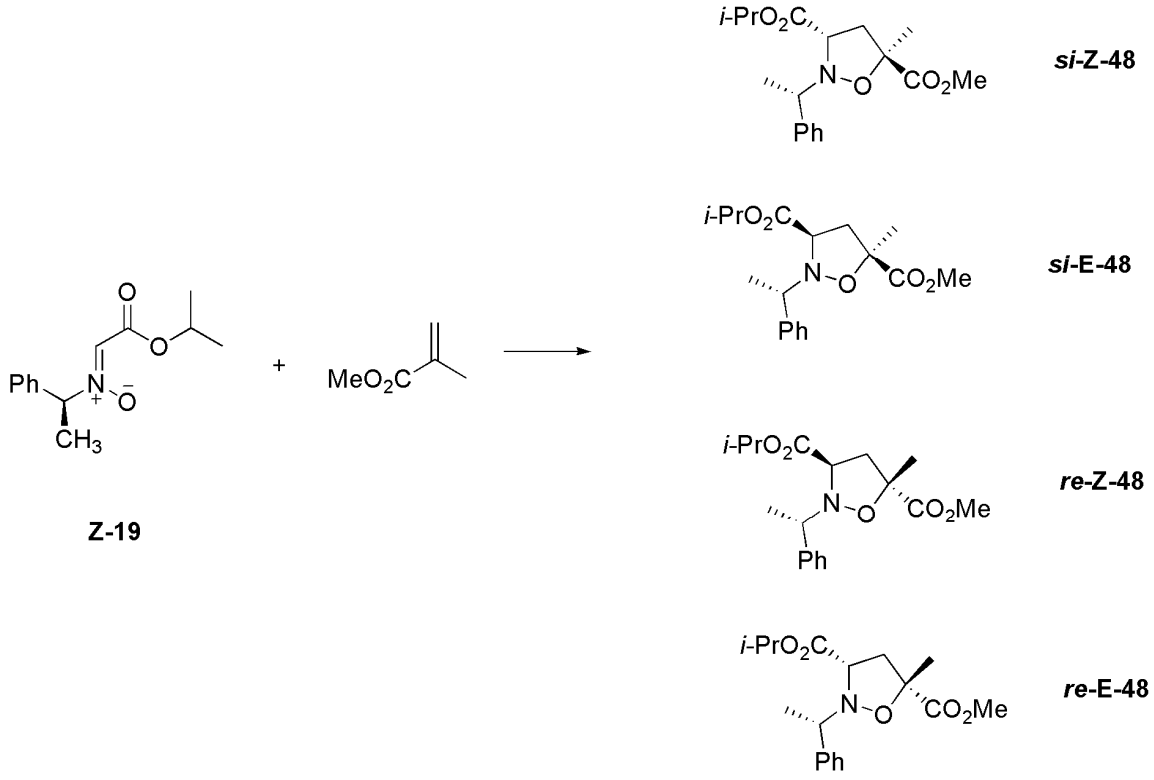
Figure 19: Proposed Metal-chelation Effects Between Nitrone 11 and Olefin 24

Another cycloaddition was performed with a MOM-protected derivative of olefin **24** (Table 3, Entry 7). The intent of this experiment was to confirm the beneficial effect proposed between the alcohol substituent and the Lewis acid described above. As predicted, the isoxazolidine products diastereomeric ratio of 10:1 was smaller when the MOM ether olefin was used which further supports the claim that hydroxyl substituent coordinated with the Lewis acid and promoted the endo transition state with respect to the alcohol. Interestingly, the 2-bromomethyl methacrylate did not show the same level of selectivity that was observed with either the hydroxyl or MOM-ether methacrylate derivatives (Table 3, Entry 8).

3.4 Cycloadditions with Chiral Z-Nitrones

With a better understanding regarding the nature of cycloadditions with nitrone **11**, reactions between chiral nitrone **19** and olefins were investigated using the optimized conditions developed previously (2-5 equivalents of olefin, 1.1 equivalents $MgBr_2{\cdot}OEt_2$, 50:50 MeOH:MeCN).

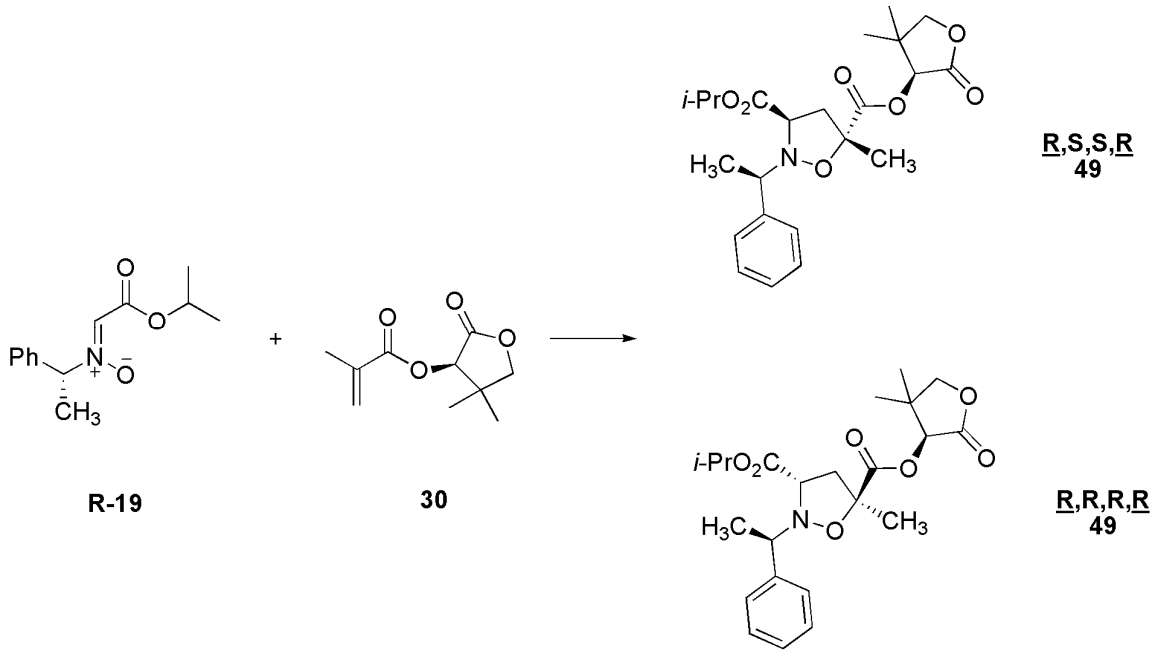
Scheme 34: Possible Isoxazolidines Formed in the Cycloaddition between Chiral Nitrone 19 and Methylmethacrylate



^{1}H NMR analysis of the isoxazolidine products generated in the reaction between nitrone **19** and methylmethacrylate **35** revealed the presence of three distinguishable isoxazolidine diastereomers in an approximate ratio of 5:5:1. In addition to the stereochemical issues discussed previously (E/Z –nitrone isomerization and endo/exo preference of the alkene CO_2Me group), reactions with chiral nitrone **Z-19** had the additional feature of re/si nitrone facial selectivity. Taken together, one would now expect as many as four diastereomeric products (Scheme 34). Assuming that the alkene ester always reacts with an endo preference, the final product distribution will be the result of Z/E-nitrone isomerization and re/si nitrone facial selectivity, the latter being

governed by the chiral α-methyl benzyl substituent. The fact that three major isoxazolidine products were observed was disheartening, although the final analysis regarding the utility of this chiral nitrone could not be fully explored until later when paired with an optically active olefin in order to determine the extent of a double diastereoselection effect between the two chiral reactants.

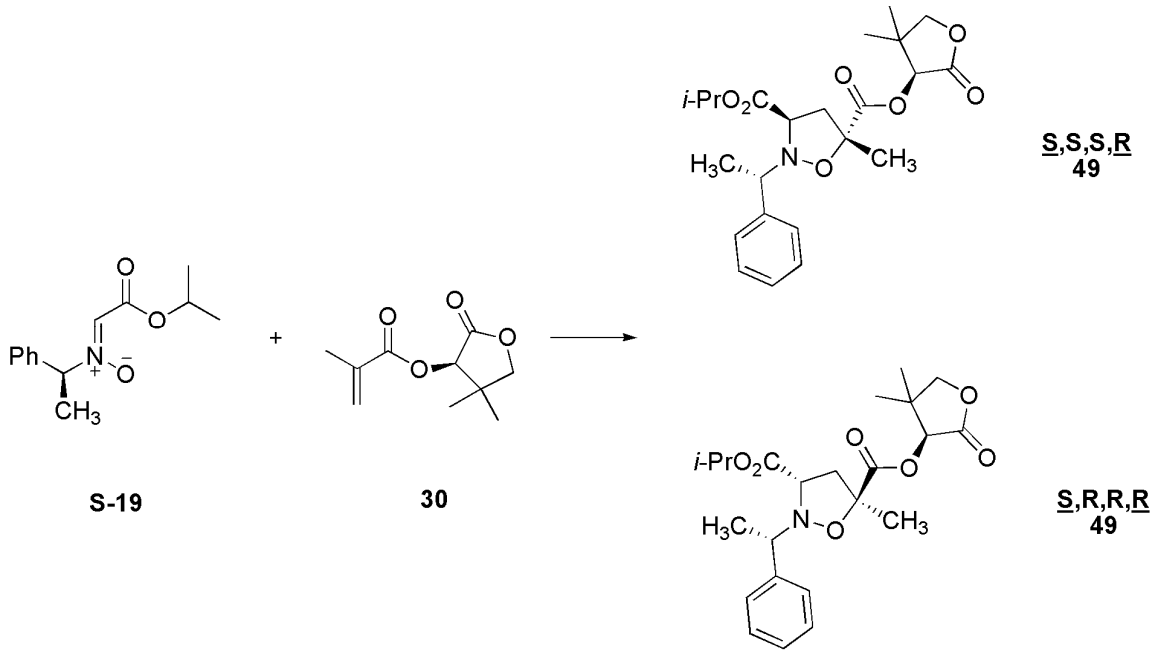
Scheme 35: Isoxazolidine Products Formed in the Cycloaddition Reaction Between R-Nitrone 19 and Chiral Alkene R-30



R-pantolactone-derived methyl methacrylate **30** was reacted with R- α -methylbenzyl nitrone **R-19** in order to study the double diastereomer effect. Two major isoxazolidine diastereomers were isolated from this reaction in roughly a 1:1 ratio. It was determined by ^{1}H NMR that the major isoxazolidines synthesized in this reaction were the R,S,S,R and R,R,R,R diastereomers seen in Scheme 35 (where the underlined R/S

refer to the chiral auxiliaries). This meant that the cycloaddition proceeded primarily through the Z-nitrone isomer and minimal Z- to E- isomerization occurred. Although this reaction was not selective towards a single diastereomer, the fact that this reaction proceeded almost exclusively through the Z isomer was promising.

Scheme 36: Isoxazolidine Products Formed in the Cycloaddition Reaction Between S-Nitrone 19 and Chiral Alkene R-30



The chiral nitrone enantiomer, S-α-methylbenzyl nitrone was also reacted with R-pantolactone-derived methyl methacrylate **30** and the results of this reaction showed a 10-15:1 ratio of isoxazolidine diastereomers **49** (Scheme 36). When compared to the cycloaddition with R-α-methylbenzyl nitrone, both isoxazolidines matched up so that it was determined the only difference in using the R or S nitrone was in the product ratios.

Furthermore, the fact that a single isoxazolidine was made in 85% yield was very promising regarding the utility of these chiral nitrones and olefins because these chiral reactants could lead to amino acids with high enantiomeric excess based on this one reaction using chiral nitrones and olefins.

The relative and absolute stereochemistry of the major isoxazolidine isomer was determined by X-ray crystallography to be **S,R,R,R-49** diastereomer (Figure 20). Therefore, the **S-19** and R-pantolactone olefin **30** would lead to the R,R amino acid after the chiral auxiliaries were removed.

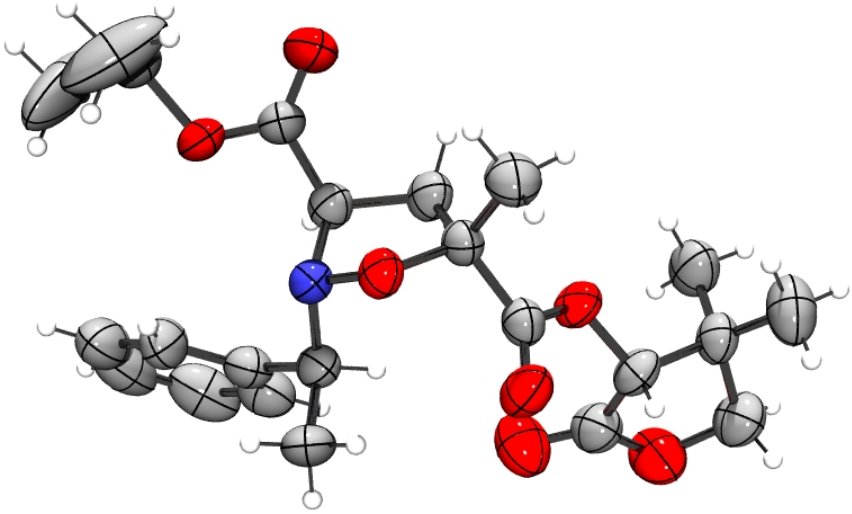
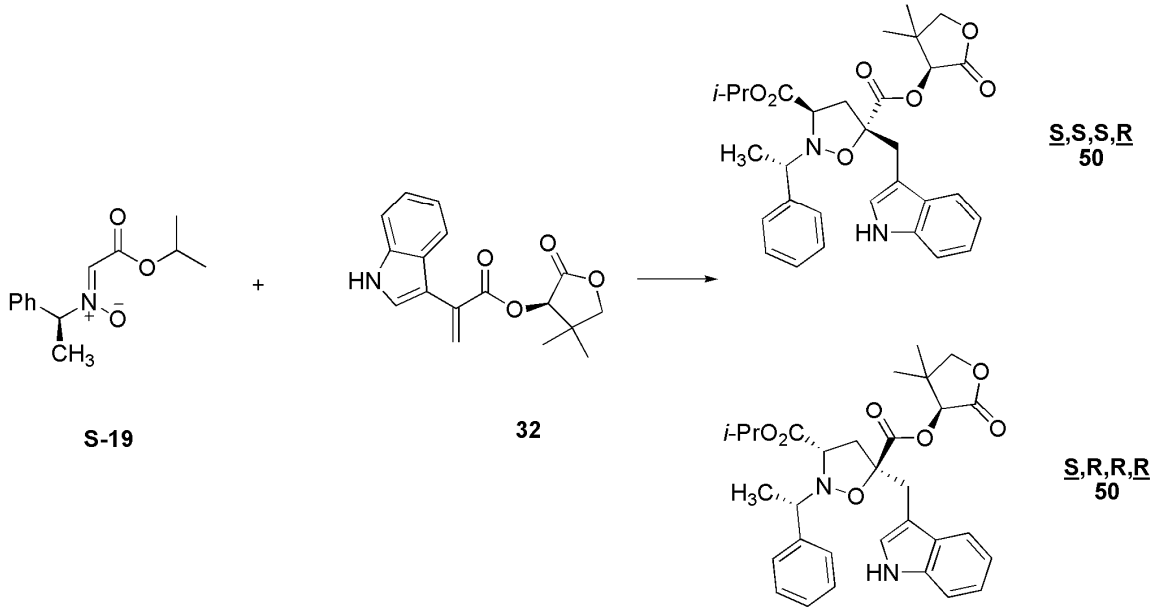


Figure 20: X-ray Crystallography Structure of Isoxazolidine 49

Nitrone **19** was also reacted with the R-pantolactone derived indolylmethyl methacrylate **32**. The S-nitrone was paired with the R-olefin for reasons explained in Scheme 36. Additionally, the solvent mixture composed of 50:50 methanol:acetonitrile was used to promote the cycloaddition with the Z-nitrone. However, this solvent mixture increased the potential number of isoxazolidine products that would be formed from this reaction due to the previously observed transesterification that had taken place in other reactions that involved this solvent combination. As a result, four isoxazolidine diastereomers with a methyl ester at the C-2 carbon of the ring could be synthesized in addition to the four isoxazolidines with the isopropyl ester still attached at the C-2 atom. ^{1}H NMR analysis revealed only two major isoxazolidine products were synthesized from this reaction and after isolation, spectroscopic evidence suggests that these isoxazolidines were the methyl ester and isopropyl ester of the S,R,R,R diastereomers **50** Scheme 37). Therefore it was determined that this was a highly stereoselective reaction that could lead to the R,R monatin isomer in high enantiomeric excess.

Scheme 37: Isoxazolidine Products Formed in the Cycloaddition Reaction Between S-Nitrone 19 and Chiral Alkene R-32

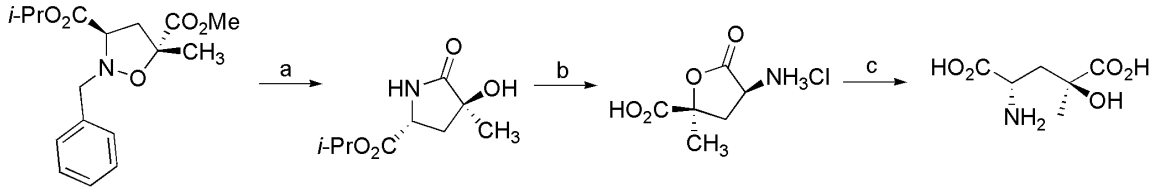


4. Progress towards Natural Product 4-Hydroxyl Amino Acids

4.1 γ-hydroxyl-γ-methyl-α-amino glutamic acid

The conversion of isoxazolidines to their corresponding amino acids could be achieved in two or three steps. These procedures include the hydrogenolysis of the isoxazolidine N-O bond, acidic hydrolysis of the resultant lactam to afford its respective lactone, and finally the basic hydrolysis. This sequence is illustrated in Scheme 38 using cycloadduct **endo-39** as a model substrate.

Scheme 38: Three Step Conversion of Isoxazolidines to γ-hydroxyl-α-amino Acids



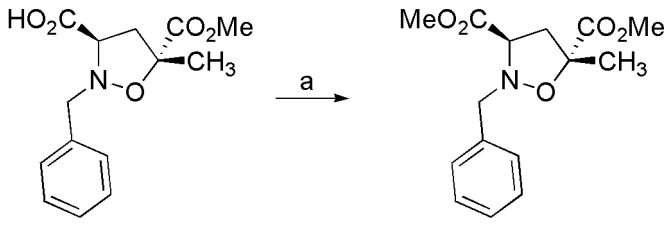
endo-39 **51** **52** **53**

a- H_2, $Pd(OH)_2$/C, MeOH; b- 6N HCl; c- 1N NaOH

Direct hydrogenolysis of the C-2 carboxylic acid nitrone was attempted on a Parr shaker at 60 psi, however these conditions were shown ineffective and neither the lactam nor the isoxazolidine reactant were recovered. It was believed that the carboxylic acid interfered with the reduction and so the acid was converted to the methyl ester. Although there are a number of ways to synthesize methyl esters from carboxylic acids, it was determined that chemically stable and commercially available trimethylsilyl

diazomethane[58] was the most suitable methylating reagent due to it being a fast reaction in addition to affording quantitative conversion to isoxazolidine **40** (Scheme 39).

Scheme 39: Esterification of Isoxazolidine 36 to Isoxazolidine 40

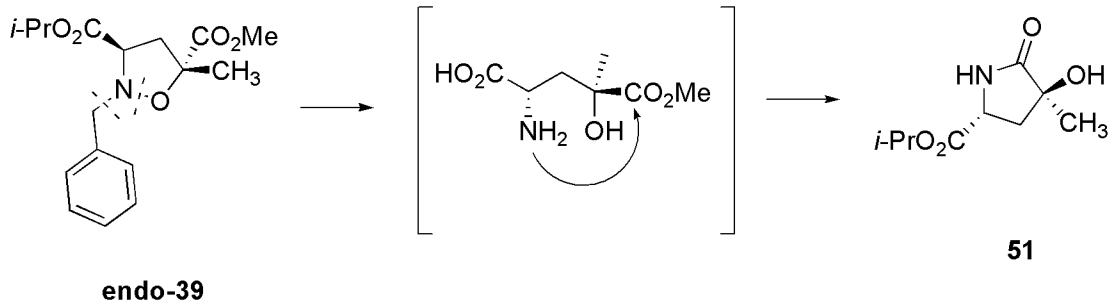


36 **40**

a- TMS-diazomethane, 3:2 Tol:MeOH

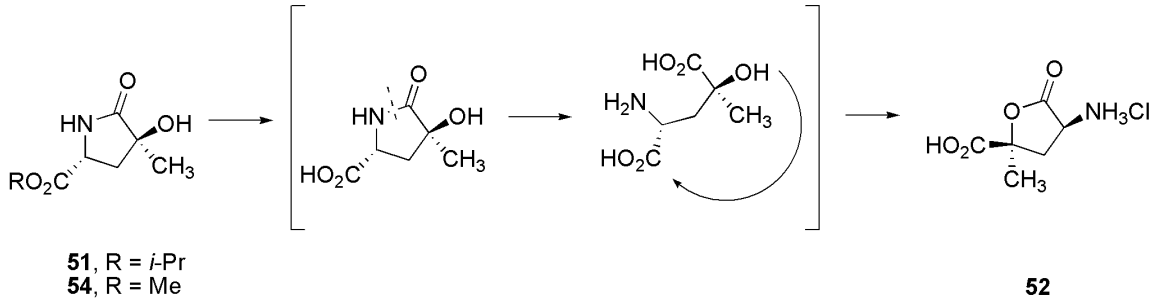
The first step in converting these isoxazolidine rings into the corresponding amino acids involved cleavage of the N-O bond. Various reagents were available to perform this task, including Zn/HOAc,[65, 66], SmI_2,[67, 68] and $Mo(CO)_6$[69, 70] among others.[71-73] As expected, hydrogenolysis of the isoxazolidine cleaved the N-O bond in addition to cleaving the N-benzyl substituent. A range of reaction conditions was examined in this regard, however the optimal conditions were determined to be 1 atm of H_2 with Pearlman's catalyst ($Pd(OH)_2$ in methanol shaken on a Parr shaker for 5-24 hours depending on the isoxazolidine[47] (Scheme 40).

Scheme 40: Hydrogenolysis of Isoxazolidine to Afford Lactam 51



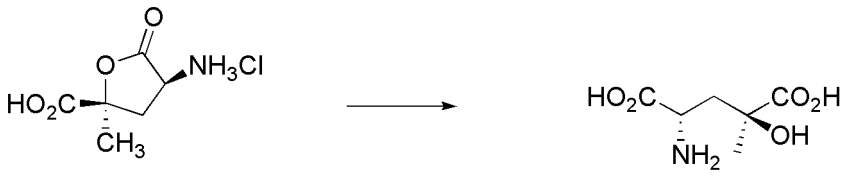
Both lactams **51** (from Scheme 40) and **54** were hydrolyzed under the acidic conditions of 6N HCl at reflux (Scheme 41). Acidic hydrolysis essentially did three things to the lactam. For instance, the esters were hydrolyzed to their corresponding carboxylic acids, the lactam was hydrolyzed to its corresponding ammonium chloride salt and carboxylic acid. Lastly, the 4-hydroxy substituent was involved in an intramolecular esterification that afforded a 5-membered lactone. These reactions were confirmed by ^{1}H NMR and IR analyses. NMR analysis revealed the disappearance of the isopropyl substituent and the IR showed a shift in the carbonyl stretch from 1690cm^{-1} to 1760cm^{-1} which was comparable to values for structurally similar lactams and lactones, respectively.

Scheme 41: Acidic Hydrolysis of Lactams to Afford Lactone 52



The final step towards the synthesis of 4-hydroxy amino acids required basic hydrolysis of the lactone with 1N NaOH to the open chain and afford the disodium salt. Careful acidification of the disodium salt to pH~4-5 yielded 4-hydroxy amino acid **53** (Scheme 42).

Scheme 42: Basic Hydrolysis of Lactones to Afford Target 4-Hydroxyl-2-Amino Acids



52 **53**

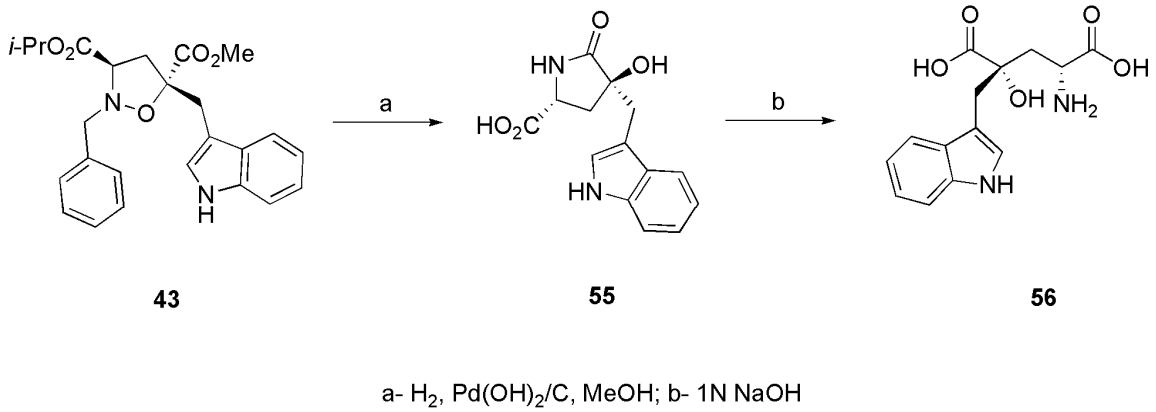
4.2 Monatin

The conversion of racemic indole isoxazolidine **43** to racemic monatin proved to be more problematic. The hydrogenolysis proceeded as expected to afford lactam **55**. Interestingly, it was observed that the isopropyl ester hydrolyzed in D_2O. The resultant carboxylic acid was believed to be the same intermediate as that proposed by Goodman[9, 49] in his pursuit of monatin, although there was a discrepancy in the chemical shifts between Goodman's reported lactam and lactam **55** as synthesized from isoxazolidine **43** in Scheme 44. The ^{1}H NMR chemical shift variations could be explained by the fact that lactam **55** was analyzed in d_6-DMSO with a trace amount of D_2O. Since d_6-DMSO and D_2O often affect protons differently in ^{1}H NMR analysis, it was accepted that a mixture of these solvents would produce chemical shifts that may not match with Goodman's analysis. Furthermore, there is no evidence that suggests that the

hydrogenolysis conditions used in the synthesis of lactam **55** would adversely affect its stereochemistry, and since the stereochemical characterization of isoxazolidine **43** had already been confirmed by NOE analysis (Figure 19), there was no reason to doubt that lactam **55** had been synthesized.

Attempts at the acid catalyzed hydrolysis of lactam **55** to its corresponding lactone were unsuccessful, although the reaction was only performed on a very small sample of lactam. ^{1}H NMR analysis of the product after this reaction showed the disappearance of the indole protons. Interestingly, a similar observation had been reported by Goodman.[9] Therefore, a simple basic hydrolysis of the carboxylic acid should afford racemic Monatin (Scheme 43).

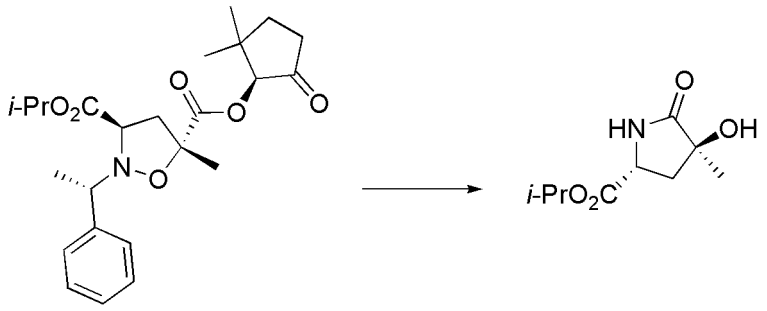
Scheme 43: Two Step Conversion of Isoxazolidine 43 to Afford Racemic Monatin



Schemes 38 and 43 illustrate the syntheses of racemic 4-hydroxyl glutamic acid and racemic monatin. In order to synthesize enantiomerically pure isomers of these 4-hydroxy amino acids required the conversion of optically active isoxazolidines **49** and **50**. These isoxazolidines were hydrogenolyzed under the same conditions described

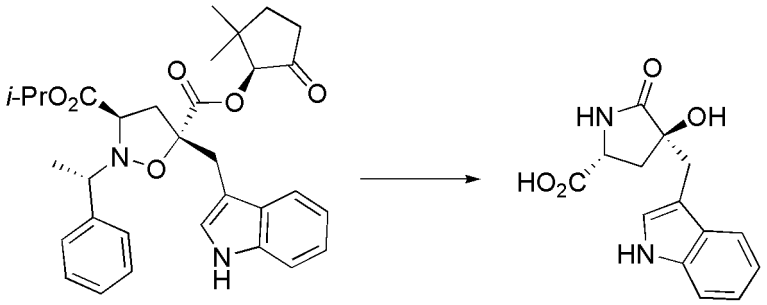
earlier to afford lactam **51** from isoxazolidine **49** (Scheme 44) and lactam **55** from isoxazolidine **50** (Scheme 45).

Scheme 44: Hydrogenolysis of Enantiomerically Pure Isoxazolidine 49 to Lactam 51



49 **51**

Scheme 45: Hydrogenolysis of Enantiomerically Pure Isoxazolidine 50 to Lactam 55



50 **55**

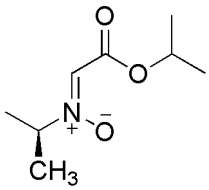
5. Conclusions

The synthesis of stable Z-nitrones **11** and **19** have been realized. Furthermore, 1,3-dipolar cycloaddition reaction conditions that proceed through the Z-nitrone isomer have been optimized for these nitrones through the use of polar solvents. Manipulations of the isoxazolidines have led to the syntheses of biologically relevant γ-hydroxyl-α-amino acids in high purity as shown in the total syntheses of 4-hydroxyl-4-methyl-glutamic acid **53** and monatin.

The methodology behind cycloadditions with optically active nitrone **19** can be used in the syntheses of other γ-hydroxyl-α-amino acids by using different substituted dipolarophiles.

6. Crystallographic Data

Chiral Nitrone 19



Z-19

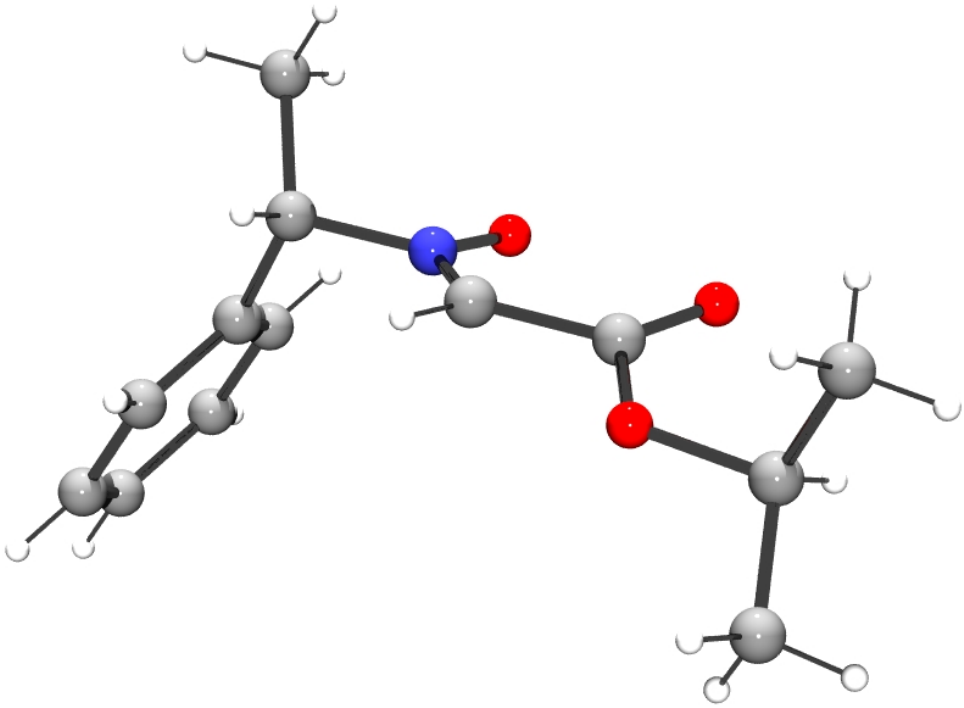


Table 1. Crystal data and structure refinement for Nitrone **19**

Identification code	md32	
Empirical formula	C13 H17 N O3	
Formula weight	235.28	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 5.0665(6) Å	α= 90°.
	b = 10.3232(12) Å	β= 90°.
	c = 25.509(3) Å	γ = 90°.
Volume	1334.2(3) $Å^3$	
Z	4	
Density (calculated)	1.171 Mg/m^3	
Absorption coefficient	0.083 mm^{-1}	
F(000)	504	
Crystal size	0.16 x 0.09 x 0.04 mm^3	
Crystal color and habit	colourlessneedle	
Diffractometer	Bruker SMART Apex II	
Theta range for data collection	1.60 to 23.89°.	
Index ranges	-5<=h<=5, -11<=k<=11, -29<=l<=29	
Reflections collected	14400	
Independent reflections	1225 [R(int) = 0.0939]	
Observed reflections (I > 2sigma(I))	733	
Completeness to theta = 23.89°	98.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9967 and 0.9868	
Solution method	SHELXS-97 (Sheldrick, 1990)	
Refinement method	SHELXL-97 (Sheldrick, 1997)	
Data / restraints / parameters	1225 / 0 / 166	
Goodness-of-fit on F^2	1.244	
Final R indices [I>2sigma(I)]	R1 = 0.0602, wR2 = 0.1541	
R indices (all data)	R1 = 0.1142, wR2 = 0.1868	
Absolute structure parameter	-10(10)	
Largest diff. peak and hole	0.220 and -0.161 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **19**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N(1)	3043(10)	4558(4)	1105(2)	65(1)
O(1)	5551(10)	4672(4)	1076(2)	95(1)
O(3)	1662(8)	1894(4)	1889(1)	80(1)
O(2)	5469(10)	2947(5)	1899(2)	105(2)
C(1)	1293(18)	3710(4)	67(2)	118(7)
C(2)	1522(19)	3291(5)	-449(2)	117(6)
C(3)	2230(15)	4161(6)	-841(2)	110(2)
C(4)	2711(19)	5451(6)	-716(2)	117(6)
C(5)	2482(17)	5870(4)	-200(2)	104(5)
C(6)	1773(11)	5000(5)	191(1)	66(2)
C(1A)	-428(10)	4521(8)	-65(2)	134(8)
C(2A)	-239(12)	4116(9)	-584(2)	161(10)
C(3A)	2159(15)	4201(6)	-846(1)	110(2)
C(4A)	4367(12)	4690(8)	-590(2)	100(5)
C(5A)	4177(10)	5095(8)	-72(2)	96(5)
C(6A)	1779(11)	5010(5)	191(1)	66(2)
C(7)	1508(12)	5439(5)	757(2)	70(2)
C(8)	2339(19)	6816(7)	863(2)	115(3)
C(9)	1842(12)	3717(5)	1398(2)	64(1)
C(10)	3230(13)	2851(6)	1755(2)	67(2)
C(11)	2632(13)	929(6)	2266(2)	92(2)
C(12)	1360(20)	-312(8)	2121(4)	176(5)
C(13)	2090(20)	1356(8)	2800(3)	154(4)

Table 3. Bond lengths [Å] and angles [°] for md32.

N(1)-O(1)	1.278(6)	C(3A)-H(3A)	0.9300
N(1)-C(9)	1.297(6)	C(4A)-C(5A)	1.3899
N(1)-C(7)	1.489(6)	C(4A)-H(4A)	0.9300
O(3)-C(10)	1.313(7)	C(5A)-C(6A)	1.3901
O(3)-C(11)	1.469(6)	C(5A)-H(5A)	0.9300
O(2)-C(10)	1.197(6)	C(6A)-C(7)	1.518(6)
C(1)-C(2)	1.3900	C(7)-C(8)	1.507(9)
C(1)-C(6)	1.3900	C(7)-H(7)	0.9800
C(1)-H(1)	0.9300	C(8)-H(8A)	0.9600
C(2)-C(3)	1.3900	C(8)-H(8B)	0.9600
C(2)-H(2)	0.9300	C(8)-H(8C)	0.9600
C(3)-C(4)	1.3900	C(9)-C(10)	1.456(7)
C(3)-H(3)	0.9300	C(9)-H(9)	0.9300
C(4)-C(5)	1.3900	C(11)-C(13)	1.459(10)
C(4)-H(4)	0.9300	C(11)-C(12)	1.479(9)
C(5)-C(6)	1.3900	C(11)-H(11)	0.9800
C(5)-H(5)	0.9300	C(12)-H(12A)	0.9600
C(1A)-C(6A)	1.3898	C(12)-H(12B)	0.9600
C(1A)-C(2A)	1.3904	C(12)-H(12C)	0.9600
C(1A)-H(1A)	0.9300	C(13)-H(13A)	0.9600
C(2A)-C(3A)	1.3899	C(13)-H(13B)	0.9600
C(2A)-H(2A)	0.9300	C(13)-H(13C)	0.9600
C(3A)-C(4A)	1.3899		

O(1)-N(1)-C(9)	124.1(5)	C(2)-C(3)-C(4)	120.0
O(1)-N(1)-C(7)	115.4(5)	C(2)-C(3)-H(3)	120.0
C(9)-N(1)-C(7)	120.4(5)	C(4)-C(3)-H(3)	120.0
C(10)-O(3)-C(11)	118.6(5)	C(5)-C(4)-C(3)	120.0
C(2)-C(1)-C(6)	120.0	C(5)-C(4)-H(4)	120.0
C(2)-C(1)-H(1)	120.0	C(3)-C(4)-H(4)	120.0
C(6)-C(1)-H(1)	120.0	C(4)-C(5)-C(6)	120.0
C(1)-C(2)-C(3)	120.0	C(4)-C(5)-H(5)	120.0
C(1)-C(2)-H(2)	120.0	C(6)-C(5)-H(5)	120.0
C(3)-C(2)-H(2)	120.0	C(5)-C(6)-C(1)	120.0

C(6A)-C(1A)-C(2A)	120.0	C(7)-C(8)-H(8C)	109.5
C(6A)-C(1A)-H(1A)	120.0	H(8A)-C(8)-H(8C)	109.5
C(2A)-C(1A)-H(1A)	120.0	H(8B)-C(8)-H(8C)	109.5
C(3A)-C(2A)-C(1A)	120.0	N(1)-C(9)-C(10)	123.0(6)
C(3A)-C(2A)-H(2A)	120.0	N(1)-C(9)-H(9)	118.5
C(1A)-C(2A)-H(2A)	120.0	C(10)-C(9)-H(9)	118.5
C(2A)-C(3A)-C(4A)	120.0	O(2)-C(10)-O(3)	123.7(6)
C(2A)-C(3A)-H(3A)	120.0	O(2)-C(10)-C(9)	126.8(6)
C(4A)-C(3A)-H(3A)	120.0	O(3)-C(10)-C(9)	109.4(5)
C(3A)-C(4A)-C(5A)	120.0	C(13)-C(11)-O(3)	110.1(6)
C(3A)-C(4A)-H(4A)	120.0	C(13)-C(11)-C(12)	114.4(7)
C(5A)-C(4A)-H(4A)	120.0	O(3)-C(11)-C(12)	106.2(5)
C(4A)-C(5A)-C(6A)	120.0	C(13)-C(11)-H(11)	108.6
C(4A)-C(5A)-H(5A)	120.0	O(3)-C(11)-H(11)	108.6
C(6A)-C(5A)-H(5A)	120.0	C(12)-C(11)-H(11)	108.6
C(1A)-C(6A)-C(5A)	120.0	C(11)-C(12)-H(12A)	109.5
C(1A)-C(6A)-C(7)	118.7(4)	C(11)-C(12)-H(12B)	109.5
C(5A)-C(6A)-C(7)	121.3(4)	H(12A)-C(12)-H(12B)	109.5
N(1)-C(7)-C(8)	108.8(5)	C(11)-C(12)-H(12C)	109.5
N(1)-C(7)-C(6A)	110.0(4)	H(12A)-C(12)-H(12C)	109.5
C(8)-C(7)-C(6A)	114.9(4)	H(12B)-C(12)-H(12C)	109.5
N(1)-C(7)-H(7)	107.6	C(11)-C(13)-H(13A)	109.5
C(8)-C(7)-H(7)	107.6	C(11)-C(13)-H(13B)	109.5
C(6A)-C(7)-H(7)	107.6	H(13A)-C(13)-H(13B)	109.5
C(7)-C(8)-H(8A)	109.5	C(11)-C(13)-H(13C)	109.5
C(7)-C(8)-H(8B)	109.5	H(13A)-C(13)-H(13C)	109.5
H(8A)-C(8)-H(8B)	109.5	H(13B)-C(13)-H(13C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2$x 10^3)for md32. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}	
N(1)59(3)	75(3)	61(3)	-1(2)	3(2)	-3(2)	
O(1)58(3)	127(4)	99(3)	12(3)	6(2)	-19(2)	
O(3)69(3)	85(3)	88(3)	29(2)	-12(2)	0(2)	
O(2)79(3)	124(4)	111(3)	22(3)	-40(3)	-12(3)	
C(1)220(20)	83(9)	50(7)	4(6)	-5(11)	-39(12)	
C(2)198(19)	80(9)	74(9)	4(7)	-25(11)	1(12)	
C(3)113(6)	140(7)	77(5)	-24(5)	-7(4)	-4(6)	
C(4)133(14)	152(14)	65(8)	-3(9)	22(9)	-55(13)	
C(5)161(15)	86(9)	65(8)	-1(7)	16(9)	-64(11)	
C(6)66(4)	73(4)	60(3)	5(3)	8(3)	-4(3)	
C(1A)	94(11)	230(20)	76(10)	-17(11)	3(8)	-68(14)
C(2A)	170(19)	250(30)	59(10)	-27(12)	11(11)	-109(19)
C(3A)	113(6)	140(7)	77(5)	-24(5)	-7(4)	-4(6)
C(4A)	80(9)	160(15)	59(9)	21(9)	6(7)	29(10)
C(5A)	77(9)	151(13)	61(9)	4(8)	-15(7)	-1(11)
C(6A)	66(4)	73(4)	60(3)	5(3)	8(3)	-4(3)
C(7)75(4)	68(4)	66(3)	8(3)	10(3)	8(3)	
C(8)182(7)	81(4)	84(4)	-5(3)	19(5)	-8(6)	
C(9)59(3)	75(3)	57(3)	3(3)	4(3)	-6(3)	
C(10)59(4)	79(4)	64(3)	-1(3)	-4(3)	5(4)	
C(11)96(5)	102(5)	76(4)	31(3)	-20(3)	14(5)	
C(12)242(12)	95(6)	191(8)	48(6)	-118(9)	-12(8)	
C(13)229(11)	153(7)	81(5)	45(5)	3(6)	33(8)	

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for md32.

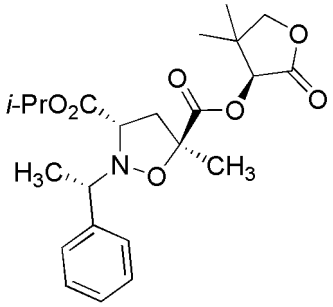
	x	y	z	U(eq)
H(1)	819	3128	328	142
H(2)	1200	2428	-533	141
H(3)	2383	3881	-1186	132
H(4)	3185	6033	-978	140
H(5)	2804	6733	-117	125
H(1A)	-2033	4464	111	160
H(2A)	-1716	3789	-755	193
H(3A)	2286	3930	-1193	132
H(4A)	5971	4747	-766	120
H(5A)	5654	5422	99	115
H(7)	-357	5360	854	84
H(8A)	2069	7012	1227	173
H(8B)	1306	7394	652	173
H(8C)	4174	6917	779	173
H(9)	12	3664	1379	76
H(11)	4545	840	2222	110
H(12A)	1838	-536	1769	264
H(12B)	-517	-225	2147	264
H(12C)	1952	-981	2356	264
H(13A)	3000	2157	2865	232
H(13B)	2701	711	3043	232
H(13C)	231	1482	2844	232

Table 6. Torsion angles [°] for md32.

C(6)-C(1)-C(2)-C(3)	0.0
C(1)-C(2)-C(3)-C(4)	0.0
C(2)-C(3)-C(4)-C(5)	0.0
C(3)-C(4)-C(5)-C(6)	0.0
C(4)-C(5)-C(6)-C(1)	0.0
C(2)-C(1)-C(6)-C(5)	0.0
C(6A)-C(1A)-C(2A)-C(3A)	0.0
C(1A)-C(2A)-C(3A)-C(4A)	0.0
C(2A)-C(3A)-C(4A)-C(5A)	0.0
C(3A)-C(4A)-C(5A)-C(6A)	0.0
C(2A)-C(1A)-C(6A)-C(5A)	0.0
C(2A)-C(1A)-C(6A)-C(7)	-179.8(4)
C(4A)-C(5A)-C(6A)-C(1A)	0.0
C(4A)-C(5A)-C(6A)-C(7)	179.8(5)
O(1)-N(1)-C(7)-C(8)	-54.8(6)
C(9)-N(1)-C(7)-C(8)	127.4(6)
O(1)-N(1)-C(7)-C(6A)	71.8(6)
C(9)-N(1)-C(7)-C(6A)	-105.9(5)
C(1A)-C(6A)-C(7)-N(1)	112.4(6)
C(5A)-C(6A)-C(7)-N(1)	-67.4(6)
C(1A)-C(6A)-C(7)-C(8)	-124.4(7)
C(5A)-C(6A)-C(7)-C(8)	55.8(8)
O(1)-N(1)-C(9)-C(10)	3.9(8)
C(7)-N(1)-C(9)-C(10)	-178.6(4)
C(11)-O(3)-C(10)-O(2)	4.4(8)
C(11)-O(3)-C(10)-C(9)	-177.6(5)
N(1)-C(9)-C(10)-O(2)	15.0(9)
N(1)-C(9)-C(10)-O(3)	-163.0(5)
C(10)-O(3)-C(11)-C(13)	87.5(7)
C(10)-O(3)-C(11)-C(12)	-148.1(7)

Symmetry transformations used to generate equivalent atoms:

Optically Active Isoxazolidine 49



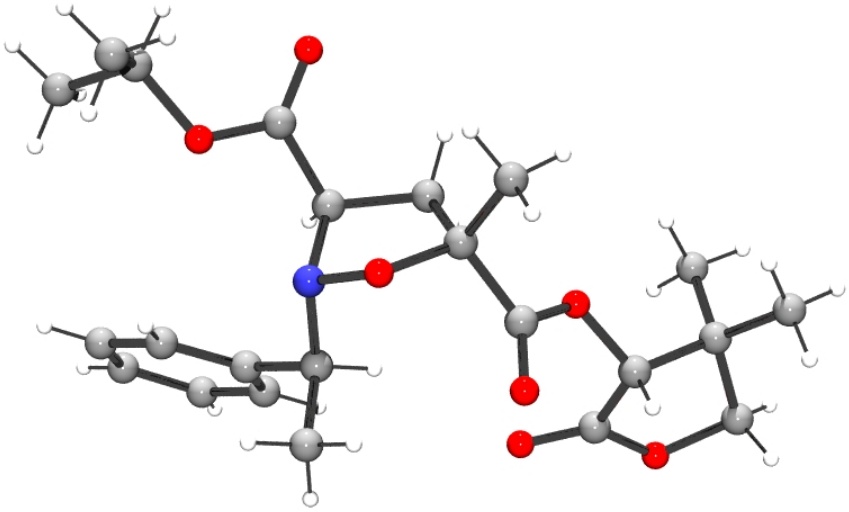


Table 1. Crystal data and structure refinement for Isoxazolidine **49**

Identification code	Isoxazolidine **56**	
Empirical formula	C23 H31 N O7	
Formula weight	433.49	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 10.5221(12) Å	α= 90°.
	b = 9.0685(11) Å	β= 95.082(7)°.
	c = 12.5980(14) Å	γ = 90°.
Volume	1197.4(2) $Å^3$	
Z	2	
Density (calculated)	1.202 Mg/m^3	
Absorption coefficient	0.089 mm^{-1}	
F(000)	464	
Crystal size	0.20 x 0.06 x 0.04 mm^3	
Crystal color and habit	colourlessneedle	
Diffractometer	Bruker SMART Apex II	
Theta range for data collection	1.62 to 23.45°.	
Index ranges	-11<=h<=11, -9<=k<=10, -14<=l<=14	
Reflections collected	15962	
Independent reflections	3379 [R(int) = 0.0712]	
Observed reflections (I > 2sigma(I))	2170	
Completeness to theta = 23.45°	97.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9965 and 0.9405	
Solution method	SHELXS-97 (Sheldrick, 1990)	
Refinement method	SHELXL-97 (Sheldrick, 1997)	
Data / restraints / parameters	3379 / 1 / 280	
Goodness-of-fit on F^2	0.997	
Final R indices [I>2sigma(I)]	R1 = 0.0446, wR2 = 0.0938	
R indices (all data)	R1 = 0.0943, wR2 = 0.1168	
Absolute structure parameter	0.0(15)	
Largest diff. peak and hole	0.126 and -0.142 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for s1. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	-7886(3)	-250(3)	-2233(3)	104(1)
O(2)	-7758(2)	-2415(3)	-1440(2)	77(1)
O(3)	-4593(2)	-1390(3)	-950(2)	53(1)
O(4)	-2072(3)	-880(3)	-1300(2)	69(1)
O(5)	-2693(2)	344(3)	-2795(2)	57(1)
O(6)	-1700(3)	-2187(4)	-3761(2)	92(1)
O(7)	-334(3)	-656(3)	-4440(2)	88(1)
N(1)	-5236(3)	-2554(3)	-1569(2)	51(1)
C(1)	-4752(5)	-5082(5)	-3696(4)	80(1)
C(2)	-5439(6)	-6173(6)	-4268(4)	97(2)
C(3)	-6429(6)	-6843(6)	-3853(6)	100(2)
C(4)	-6739(5)	-6480(6)	-2869(5)	90(2)
C(5)	-6054(4)	-5427(4)	-2290(4)	75(1)
C(6)	-5056(4)	-4702(4)	-2696(3)	60(1)
C(7)	-4311(3)	-3527(4)	-2041(3)	56(1)
C(8)	-3423(4)	-4219(4)	-1160(3)	72(1)
C(9)	-6024(3)	-1717(4)	-2373(3)	52(1)
C(10)	-7315(4)	-1351(4)	-1999(3)	58(1)
C(11)	-9079(4)	-2358(5)	-1173(4)	71(1)
C(12)	-9085(5)	-2192(10)	-23(5)	159(3)
C(13)	-9646(5)	-3757(9)	-1579(7)	182(4)
C(14)	-5243(3)	-374(4)	-2627(3)	58(1)
C(15)	-4284(3)	-210(4)	-1651(3)	48(1)
C(16)	-4424(4)	1222(5)	-1049(3)	73(1)
C(17)	-2901(4)	-337(4)	-1872(3)	51(1)
C(18)	-1422(3)	310(4)	-3105(3)	55(1)
C(19)	-1201(4)	-999(5)	-3763(3)	69(1)
C(20)	16(4)	898(5)	-4295(4)	76(1)
C(21)	-1101(4)	1602(4)	-3801(3)	57(1)
C(22)	-709(5)	2979(5)	-3171(4)	90(2)
C(23)	-2180(4)	1919(5)	-4646(4)	81(1)

Table 3. Bond lengths [Å] and angles [°] for s1.

O(1)-C(10)	1.189(4)	C(9)-H(9A)	0.9800
O(2)-C(10)	1.305(4)	C(11)-C(12)	1.457(6)
O(2)-C(11)	1.459(4)	C(11)-C(13)	1.474(7)
O(3)-C(15)	1.443(4)	C(11)-H(11A)	0.9800
O(3)-N(1)	1.445(3)	C(12)-H(12A)	0.9600
O(4)-C(17)	1.188(4)	C(12)-H(12B)	0.9600
O(5)-C(17)	1.351(4)	C(12)-H(12C)	0.9600
O(5)-C(18)	1.426(4)	C(13)-H(13A)	0.9600
O(6)-C(19)	1.199(5)	C(13)-H(13B)	0.9600
O(7)-C(19)	1.340(5)	C(13)-H(13C)	0.9600
O(7)-C(20)	1.463(5)	C(14)-C(15)	1.528(5)
N(1)-C(9)	1.464(4)	C(14)-H(14A)	0.9700
N(1)-C(7)	1.477(4)	C(14)-H(14B)	0.9700
C(1)-C(6)	1.371(5)	C(15)-C(17)	1.509(5)
C(1)-C(2)	1.389(7)	C(15)-C(16)	1.517(5)
C(1)-H(1A)	0.9300	C(16)-H(16A)	0.9600
C(2)-C(3)	1.351(7)	C(16)-H(16B)	0.9600
C(2)-H(2A)	0.9300	C(16)-H(16C)	0.9600
C(3)-C(4)	1.351(7)	C(18)-C(19)	1.477(6)
C(3)-H(3A)	0.9300	C(18)-C(21)	1.519(5)
C(4)-C(5)	1.367(6)	C(18)-H(18A)	0.9800
C(4)-H(4A)	0.9300	C(20)-C(21)	1.519(5)
C(5)-C(6)	1.375(5)	C(20)-H(20A)	0.9700
C(5)-H(5A)	0.9300	C(20)-H(20B)	0.9700
C(6)-C(7)	1.521(5)	C(21)-C(23)	1.514(5)
C(7)-C(8)	1.522(5)	C(21)-C(22)	1.517(6)
C(7)-H(7A)	0.9800	C(22)-H(22A)	0.9600
C(8)-H(8A)	0.9600	C(22)-H(22B)	0.9600
C(8)-H(8B)	0.9600	C(22)-H(22C)	0.9600
C(8)-H(8C)	0.9600	C(23)-H(23A)	0.9600
C(9)-C(14)	1.519(5)	C(23)-H(23B)	0.9600
C(9)-C(10)	1.513(5)	C(23)-H(23C)	0.9600
C(10)-O(2)-C(11)	119.4(3)	C(15)-O(3)-N(1)	109.4(2)

C(17)-O(5)-C(18)	117.0(3)
C(19)-O(7)-C(20)	108.8(3)
O(3)-N(1)-C(9)	101.8(2)
O(3)-N(1)-C(7)	111.1(2)
C(9)-N(1)-C(7)	112.6(3)
C(6)-C(1)-C(2)	120.2(5)
C(6)-C(1)-H(1A)	119.9
C(2)-C(1)-H(1A)	119.9
C(3)-C(2)-C(1)	120.2(5)
C(3)-C(2)-H(2A)	119.9
C(1)-C(2)-H(2A)	119.9
C(2)-C(3)-C(4)	120.2(6)
C(2)-C(3)-H(3A)	119.9
C(4)-C(3)-H(3A)	119.9
C(3)-C(4)-C(5)	120.0(5)
C(3)-C(4)-H(4A)	120.0
C(5)-C(4)-H(4A)	120.0
C(4)-C(5)-C(6)	121.3(5)
C(4)-C(5)-H(5A)	119.3
C(6)-C(5)-H(5A)	119.3
C(1)-C(6)-C(5)	118.0(4)
C(1)-C(6)-C(7)	121.5(4)
C(5)-C(6)-C(7)	120.5(4)
N(1)-C(7)-C(8)	109.7(3)
N(1)-C(7)-C(6)	108.1(3)
C(8)-C(7)-C(6)	111.1(3)
N(1)-C(7)-H(7A)	109.3
C(8)-C(7)-H(7A)	109.3
C(6)-C(7)-H(7A)	109.3
C(7)-C(8)-H(8A)	109.5
C(7)-C(8)-H(8B)	109.5
H(8A)-C(8)-H(8B)	109.5
C(7)-C(8)-H(8C)	109.5
H(8A)-C(8)-H(8C)	109.5
H(8B)-C(8)-H(8C)	109.5
N(1)-C(9)-C(14)	106.1(3)
N(1)-C(9)-C(10)	111.6(3)
C(14)-C(9)-C(10)	114.0(3)
N(1)-C(9)-H(9A)	108.3
C(14)-C(9)-H(9A)	108.3
C(10)-C(9)-H(9A)	108.3
O(1)-C(10)-O(2)	123.9(4)
O(1)-C(10)-C(9)	123.7(4)
O(2)-C(10)-C(9)	112.3(3)
C(12)-C(11)-O(2)	108.7(4)
C(12)-C(11)-C(13)	113.3(6)
O(2)-C(11)-C(13)	104.7(4)
C(12)-C(11)-H(11A)	110.0
O(2)-C(11)-H(11A)	110.0
C(13)-C(11)-H(11A)	110.0
C(11)-C(12)-H(12A)	109.5
C(11)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	109.5
C(11)-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12C)	109.5
H(12B)-C(12)-H(12C)	109.5
C(11)-C(13)-H(13A)	109.5
C(11)-C(13)-H(13B)	109.5
H(13A)-C(13)-H(13B)	109.5
C(11)-C(13)-H(13C)	109.5
H(13A)-C(13)-H(13C)	109.5
H(13B)-C(13)-H(13C)	109.5
C(9)-C(14)-C(15)	103.9(3)
C(9)-C(14)-H(14A)	111.0
C(15)-C(14)-H(14A)	111.0
C(9)-C(14)-H(14B)	111.0
C(15)-C(14)-H(14B)	111.0
H(14A)-C(14)-H(14B)	109.0
O(3)-C(15)-C(17)	109.2(3)
O(3)-C(15)-C(16)	106.9(3)
C(17)-C(15)-C(16)	107.2(3)
O(3)-C(15)-C(14)	104.6(3)

C(17)-C(15)-C(14)	115.0(3)
C(16)-C(15)-C(14)	113.5(3)
C(15)-C(16)-H(16A)	109.5
C(15)-C(16)-H(16B)	109.5
H(16A)-C(16)-H(16B)	109.5
C(15)-C(16)-H(16C)	109.5
H(16A)-C(16)-H(16C)	109.5
H(16B)-C(16)-H(16C)	109.5
O(4)-C(17)-O(5)	123.0(3)
O(4)-C(17)-C(15)	126.0(3)
O(5)-C(17)-C(15)	110.9(3)
O(5)-C(18)-C(19)	111.7(3)
O(5)-C(18)-C(21)	113.8(3)
C(19)-C(18)-C(21)	104.0(3)
O(5)-C(18)-H(18A)	109.1
C(19)-C(18)-H(18A)	109.1
C(21)-C(18)-H(18A)	109.1
O(6)-C(19)-O(7)	122.2(4)
O(6)-C(19)-C(18)	129.1(4)
O(7)-C(19)-C(18)	108.7(4)
O(7)-C(20)-C(21)	105.1(3)
O(7)-C(20)-H(20A)	110.7
C(21)-C(20)-H(20A)	110.7
O(7)-C(20)-H(20B)	110.7
C(21)-C(20)-H(20B)	110.7
H(20A)-C(20)-H(20B)	108.8
C(23)-C(21)-C(18)	111.2(3)
C(23)-C(21)-C(20)	110.6(3)
C(18)-C(21)-C(20)	97.6(3)
C(23)-C(21)-C(22)	111.3(4)
C(18)-C(21)-C(22)	113.4(3)
C(20)-C(21)-C(22)	112.1(3)
C(21)-C(22)-H(22A)	109.5
C(21)-C(22)-H(22B)	109.5
H(22A)-C(22)-H(22B)	109.5
C(21)-C(22)-H(22C)	109.5
H(22A)-C(22)-H(22C)	109.5
H(22B)-C(22)-H(22C)	109.5
C(21)-C(23)-H(23A)	109.5
C(21)-C(23)-H(23B)	109.5
H(23A)-C(23)-H(23B)	109.5
C(21)-C(23)-H(23C)	109.5
H(23A)-C(23)-H(23C)	109.5
H(23B)-C(23)-H(23C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2$x 10^3)for s1. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)69(2)	75(2)	173(3)	52(2)	33(2)	23(2)
O(2)41(2)	73(2)	122(3)	34(2)	25(2)	11(1)
O(3)53(2)	59(2)	48(1)	7(1)	11(1)	-4(1)
O(4)52(2)	89(2)	67(2)	20(2)	6(2)	-3(2)
O(5)46(2)	71(2)	58(2)	12(1)	19(1)	3(1)
O(6)118(3)	72(2)	92(2)	-6(2)	31(2)	-5(2)
O(7)98(2)	79(2)	94(2)	1(2)	49(2)	11(2)
N(1)45(2)	50(2)	58(2)	4(2)	9(2)	1(2)
C(1)95(4)	74(3)	70(3)	8(3)	12(3)	15(3)
C(2)141(5)	82(4)	64(3)	-6(3)	-9(4)	26(4)
C(3)117(5)	59(3)	116(5)	-4(3)	-37(4)	9(3)
C(4)76(3)	67(3)	123(5)	-2(3)	-2(3)	3(3)
C(5)71(3)	55(3)	100(4)	-8(3)	12(3)	-5(2)
C(6)59(3)	51(2)	72(3)	6(2)	8(2)	11(2)
C(7)49(2)	54(2)	68(3)	11(2)	18(2)	5(2)
C(8)50(3)	62(3)	103(3)	9(2)	4(2)	13(2)
C(9)48(2)	56(2)	50(2)	6(2)	4(2)	-1(2)
C(10)44(2)	54(3)	76(3)	5(2)	4(2)	4(2)
C(11)39(2)	74(3)	102(4)	18(3)	15(2)	5(2)
C(12)72(4)	289(10)	118(5)	-60(6)	17(4)	27(5)
C(13)68(4)	180(7)	304(10)	-115(7)	52(5)	-48(4)
C(14)54(3)	64(2)	57(3)	12(2)	11(2)	-2(2)
C(15)50(2)	46(2)	51(2)	7(2)	11(2)	-1(2)
C(16)76(3)	63(3)	81(3)	-6(2)	25(2)	5(2)
C(17)55(3)	46(2)	53(2)	1(2)	11(2)	-4(2)
C(18)44(2)	70(3)	54(2)	0(2)	17(2)	0(2)
C(19)66(3)	74(3)	68(3)	8(2)	19(2)	5(2)
C(20)68(3)	87(4)	78(3)	6(2)	31(2)	-3(2)
C(21)59(3)	60(3)	56(2)	2(2)	18(2)	-10(2)

C(22)106(4)	77(3)	91(3)	-11(3)	32(3)	-28(3)
C(23)77(3)	84(3)	82(3)	24(2)	8(3)	-7(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for s1.

	x	y	z	U(eq)
H(1A)	-4084	-4607	-3992	95
H(2A)	-5216	-6444	-4939	116
H(3A)	-6899	-7556	-4247	120
H(4A)	-7419	-6946	-2584	107
H(5A)	-6267	-5196	-1609	90
H(7A)	-3808	-2946	-2508	67
H(8A)	-2963	-3456	-761	108
H(8B)	-2830	-4861	-1469	108
H(8C)	-3915	-4776	-694	108
H(9A)	-6158	-2322	-3018	62
H(11A)	-9521	-1524	-1537	85
H(12A)	-8714	-1260	191	239
H(12B)	-8598	-2974	328	239
H(12C)	-9947	-2233	168	239
H(13A)	-9625	-3797	-2339	273
H(13B)	-10514	-3817	-1404	273
H(13C)	-9169	-4569	-1258	273
H(14A)	-5779	494	-2725	70
H(14B)	-4812	-533	-3267	70
H(16A)	-3798	1257	-447	109
H(16B)	-5263	1273	-807	109
H(16C)	-4300	2040	-1512	109
H(18A)	-821	294	-2465	66
H(20A)	143	1354	-4974	91
H(20B)	794	996	-3827	91

H(22A)	-531	3757	-3653	135
H(22B)	40	2775	-2704	135
H(22C)	-1390	3276	-2758	135
H(23A)	-1954	2739	-5073	121
H(23B)	-2939	2152	-4310	121
H(23C)	-2332	1067	-5091	121

Table 6. Torsion angles [°] for s1.

C(15)-O(3)-N(1)-C(9)	-37.6(3)
C(15)-O(3)-N(1)-C(7)	82.5(3)
C(6)-C(1)-C(2)-C(3)	1.5(7)
C(1)-C(2)-C(3)-C(4)	-1.5(8)
C(2)-C(3)-C(4)-C(5)	0.3(8)
C(3)-C(4)-C(5)-C(6)	1.0(7)
C(2)-C(1)-C(6)-C(5)	-0.3(6)
C(2)-C(1)-C(6)-C(7)	179.1(4)
C(4)-C(5)-C(6)-C(1)	-1.0(6)
C(4)-C(5)-C(6)-C(7)	179.6(4)
O(3)-N(1)-C(7)-C(8)	59.8(4)
C(9)-N(1)-C(7)-C(8)	173.3(3)
O(3)-N(1)-C(7)-C(6)	-178.9(3)
C(9)-N(1)-C(7)-C(6)	-65.4(4)
C(1)-C(6)-C(7)-N(1)	135.1(4)
C(5)-C(6)-C(7)-N(1)	-45.6(5)
C(1)-C(6)-C(7)-C(8)	-104.6(4)
C(5)-C(6)-C(7)-C(8)	74.8(4)
O(3)-N(1)-C(9)-C(14)	35.6(3)
C(7)-N(1)-C(9)-C(14)	-83.5(3)
O(3)-N(1)-C(9)-C(10)	-89.2(3)
C(7)-N(1)-C(9)-C(10)	151.8(3)
C(11)-O(2)-C(10)-O(1)	7.0(6)
C(11)-O(2)-C(10)-C(9)	-169.5(4)
N(1)-C(9)-C(10)-O(1)	146.7(4)
C(14)-C(9)-C(10)-O(1)	26.5(6)
N(1)-C(9)-C(10)-O(2)	-36.8(4)
C(14)-C(9)-C(10)-O(2)	-157.0(3)
C(10)-O(2)-C(11)-C(12)	-114.0(5)
C(10)-O(2)-C(11)-C(13)	124.5(5)
N(1)-C(9)-C(14)-C(15)	-21.7(4)

C(10)-C(9)-C(14)-C(15)	101.6(3)
N(1)-O(3)-C(15)-C(17)	-99.6(3)
N(1)-O(3)-C(15)-C(16)	144.7(3)
N(1)-O(3)-C(15)-C(14)	24.0(3)
C(9)-C(14)-C(15)-O(3)	-0.9(3)
C(9)-C(14)-C(15)-C(17)	118.9(3)
C(9)-C(14)-C(15)-C(16)	-117.1(3)
C(18)-O(5)-C(17)-O(4)	3.9(5)
C(18)-O(5)-C(17)-C(15)	-179.9(3)
O(3)-C(15)-C(17)-O(4)	-27.2(5)
C(16)-C(15)-C(17)-O(4)	88.3(4)
C(14)-C(15)-C(17)-O(4)	-144.4(4)
O(3)-C(15)-C(17)-O(5)	156.7(3)
C(16)-C(15)-C(17)-O(5)	-87.7(4)
C(14)-C(15)-C(17)-O(5)	39.6(4)
C(17)-O(5)-C(18)-C(19)	89.5(4)
C(17)-O(5)-C(18)-C(21)	-153.1(3)
C(20)-O(7)-C(19)-O(6)	175.8(4)
C(20)-O(7)-C(19)-C(18)	-2.3(5)
O(5)-C(18)-C(19)-O(6)	-28.3(6)
C(21)-C(18)-C(19)-O(6)	-151.5(5)
O(5)-C(18)-C(19)-O(7)	149.6(3)
C(21)-C(18)-C(19)-O(7)	26.5(4)
C(19)-O(7)-C(20)-C(21)	-22.8(5)
O(5)-C(18)-C(21)-C(23)	-43.4(4)
C(19)-C(18)-C(21)-C(23)	78.3(4)
O(5)-C(18)-C(21)-C(20)	-159.0(3)
C(19)-C(18)-C(21)-C(20)	-37.3(4)
O(5)-C(18)-C(21)-C(22)	82.9(4)
C(19)-C(18)-C(21)-C(22)	-155.4(4)
O(7)-C(20)-C(21)-C(23)	-79.8(4)
O(7)-C(20)-C(21)-C(18)	36.3(4)
O(7)-C(20)-C(21)-C(22)	155.4(4)

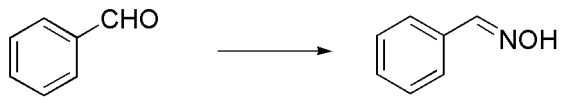
Symmetry transformations used to generate equivalent atoms:

7. Experimental

General Experimental Details: 1D NMR spectra were obtained usinga Varian Unity INOVA-400 spectrometer. In $CDCl_3$, the references was set to 7.24ppm, and in D_2O, references were set to 4..79ppm. Coupling constants are reported in the delta (ppm) scale. 2D NMR data was collected using a Varian INOVA-500 spectrometer. Infrared spectra were studied using a Nicolet Avatar 360 FT-IR spectrometer.

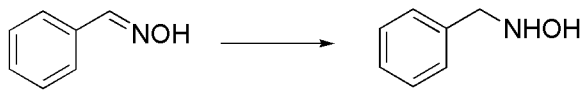
Compounds were purified using flash chromatography[74] on Silica Gel (230-400 mesh). Commercially available reagents and solvents were used as purchased.

Synthesis of Benzaldahyde oxime **(2)**



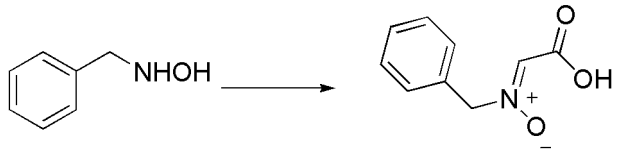
An 8M solution was prepared by dissolving 4.79g NaOH in 15mL H_2O. 4.25mL of benzaldehyde was added to the basic solution along with 3.37g NH_2OHHCl while stirring at r.t. for 30min. The solution was acidified with 10% aqueous HCl to pH 10. The product was extracted with 3-25mL aliquots of methylene chloride. The organic layer was dried with Na_2SO_4 and placed on the high vac to remove residue water to afford 96% yield of oxime.

Synthesis of N-benzylhydroxylamine **(3)**



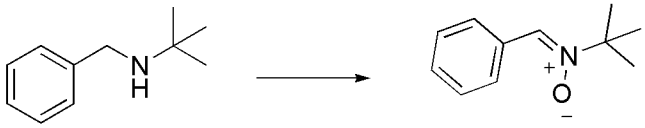
3.88g of oxime (32.1 mmole) was added to a solution of 1.34g $NaBH_3CN$ dissolved in 30mL MeOH. Methyl Orange was added as an indicator. The solution was then acidified with either a 6N HCl-MeOH or 2N HCl-MeOH solution in order to maintain a pink-colored solution. The solution was stirred for 2h at r.t. After 2h, the MeOH was removed via rotary evaporation. The aqueous solution was then dissolved in an additional 30mL H_2O and 6M KOH was added until the solution was at pH 9. The product was extracted with 3-30mL aliquots of methyle chloride. The combined organic layers were dried with Na_2SO_4 and the organic solvent was removed via rotary evaporation and then placed on a high vac to afford the hydroxylamine in 97% yield. 1H NMR (400 MHz, CDCl3) δ 7.39 – 7.17 (m, 6H), 3.91 (s, 2H), 3.36 (d, *J* = 0.7 Hz, 1H). 13C NMR (101 MHz, CDCl3) δ 136.98, 130.08, 129.47, 128.71, 128.52, 127.90, 127.10, 77.62, 77.50, 77.30, 76.98, 58.29.

Synthesis of (Z)-N-(carboxymethylene)(phenyl)methanamine oxide **(1)**



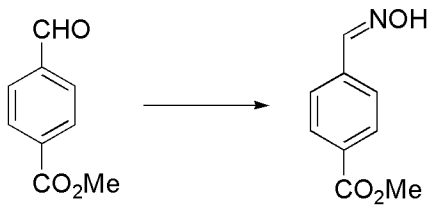
3.06g hydroxylamine (24.9 mmole) and 2.29g glyoxalic acid were dissolved in 30mL of methylene chloride. The solution was stirred at r.t. for 5h. An additional 40mL methylene chloride was added to the solution. The organic layer was then washed with 60mL H_2O. 2-30mL aliquots of methylene chloride were added to wash the aqueos layer. The combined organic layers were dried with Na_2SO_4 and then rotory evaporated followed by further drying on a high vac to afford pure nitrone in 79% yield. 1H NMR (400 MHz, cd3od) δ 7.63 (d, *J* = 3.5 Hz, 1H), 7.51 – 7.30 (m, 5H), 5.04 (d, *J* = 3.2 Hz, 2H).

Synthesis of (Z)-N-benzylidene-2-methylpropan-2-amine oxide **(6)**



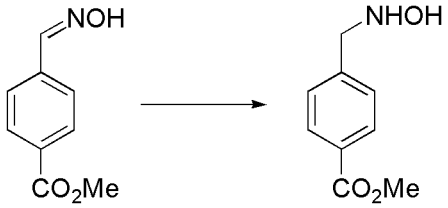
0.73mL N-*t*-Butyl-N-Benzylamine (4.0mmole), 0.066g $Na_2WO_4H_2O$ (0.2mmole), and 10mL MeOH were stirred in a roundbottom flask at 0 C. 1.45g 35% H_2O_2 (15mmole) were added dropwise to the solution at 0 C and then allowed to warm to r.t. while stirring for 3h. The methanol was rotovapped and the aqeous layer was extracted three times with methylene chloride. The combined organic layers were washed with sat. NaCl and then dried with Na_2SO_4. The organic solvent was rotovapped and the product was dried on high vac. 1H NMR (400 MHz, CDCl3) δ 8.27 (dd, *J* = 6.7, 3.1 Hz, 2H), 7.59 (s, 1H), 7.49 – 7.34 (m, 3H), 1.61 (t, *J* = 1.5 Hz, 9H). 13C NMR (101 MHz, CDCl3) δ 130.82, 129.41, 128.65, 77.46, 77.14, 76.83, 28.42.

Synthesis of methyl 4-((hydroxyimino)methyl)benzoate **(8)**



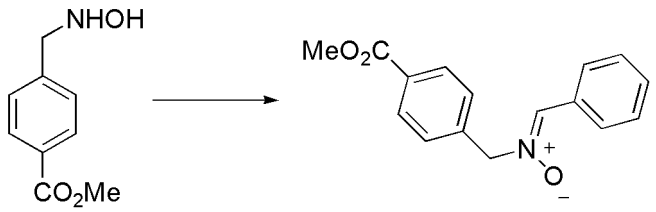
2.56g Benzaldehyde (15.6mmole) was dissolved in 25mL MeOH. 1.25g NH_2OH HCl was dissolved in 35mL H_2O. 2.35g $NaHCO_3$ was added to the aqueous layer at 0 C and then allowed to stir at r.t. for 30min. The benzaldehyde solution was added to the aqueous solution and stirred for 6h. The MeOH was rotovapped and the product was extracted with 3 aliquots of diethyl ether. The combined ethereal layers were dried with Na_2SO_4, rotovapped, and then placed on high vac to afford 2.55g oxime (91%). 1H NMR (400 MHz, CDCl3) δ 8.34 (s, 1H), 8.16 (s, 1H), 8.03 (d, *J* = 8.2 Hz, 2H), 7.68 – 7.56 (m, 2H), 3.97 – 3.82 (m, 3H). 13C NMR (101 MHz, CDCl3) δ 149.69, 130.17, 127.07, 77.51, 77.20, 76.88, 52.47.

Synthesis of methyl 4-((hydroxyamino)methyl)benzoate **(9)**



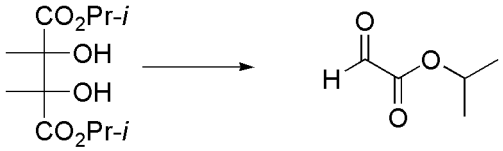
1.0g oxime (2.79mmole) was added to a solution of 0.117g $NaBH_3CN$ (1.86mmole) in 15mL MeOH. Methyl orange (indicator) was added to the solution. Aliquots of 2N methanolic HCl was added to the solution in order to maintain a pink colored solution. The mixture was allowed to stir for 2h and then the MeOH was rotovapped. The remaining residue was dissolved in H_2O and 2M KOH was added to reach pH 9. The product was extracted from the aqueous layer by extraction with 3-25mL portions of methylene chloride. The combined organic layers were dried with Na_2SO_4, rotovapped, and placed on high vac. 1H NMR (400 MHz, CDCl3) δ 8.13 (s, 1H), 8.01 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 8.5 Hz, 2H), 4.10 (s, 1H), 3.90 (d, *J* = 0.5 Hz, 4H), 3.88 (d, *J* = 0.4 Hz, 2H).

Synthesis of (Z)-N-benzylidene(4-(methoxycarbonyl)phenyl)methanamine oxide **(10)**



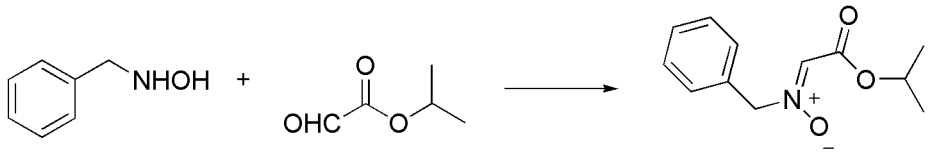
0.008g Hydroxylamine (0.044mmole) and 0.005mL benzaldehyde (1equiv.) were dissolved in 2mL methylene chloride. The solution was stirred at r.t. overnight. The solvent was rotovapped to afford 0.01g nitrone (84%). 1H NMR (400 MHz, CDCl3) δ 8.20 (dd, *J* = 6.6, 3.2 Hz, 2H), 8.06 (dd, *J* = 13.0, 4.4 Hz, 3H), 7.55 (d, *J* = 8.1 Hz, 3H), 7.41 (ddd, *J* = 9.6, 6.8, 4.4 Hz, 5H), 5.14 (s, 2H), 3.89 (t, *J* = 1.5 Hz, 3H). 13C NMR (101 MHz, CDCl3) δ 166.75, 138.18, 135.71, 133.50, 131.13, 130.86, 130.38, 130.26, 130.21, 129.22, 129.09, 128.76, 128.57, 77.55, 77.24, 76.92, 70.77, 52.46.

Synthesis of isopropyl 2-oxoacetate **(14)**



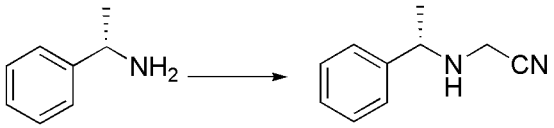
1.8mL of diisopropyl tartrate (8.5 mmole) was dissolved in 15mL Et_2O and cooled to 0 C. 1.85g H_5IO_6 was added in small portions over a 30min period. The solution was allowed to warm to r.t. while stirring for 2h. The solution was then filtered and the solid residue was washed with 2-25mL aliquots of Et_2O. The combined organic layers were dried with Na_2SO_4 and then rotovapped followed by placement on a high vac to afford the aldehyde in 95% yield. 1H NMR (400 MHz, CDCl3) δ 5.17 – 5.04 (m, 1H), 1.28 – 1.21 (m, 6H).

Synthesis of (Z)-N-(2-isopropoxy-2-oxoethylidene)(phenyl)methanamine oxide **(15)**



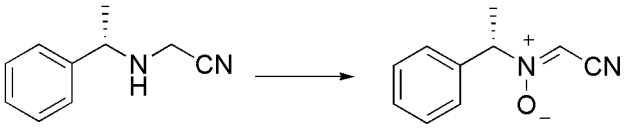
1.02g Hydroxylamine (69.4mmole) and 1.11g isopropylglyoxylate (1equiv.) were dissolved in 9mL of 50:50 EtOH:H_2O. The mixture was stirred for 5h at r.t. After 5h the product precipitated out of solution. The solid was filtered and dried on a high vac. The crude nitrone product was recrystallized by dissolving it in warm EtOH and H_2O to afford 78% pure Z-nitrone. 1H NMR (400 MHz, CDCl3) δ 7.41 (s, 4H), 7.01 (s, 1H), 5.09 (s, 1H), 4.96 (s, 2H), 1.37 – 1.06 (m, 6H).

Synthesis of (S)-2-(1-phenylethylamino)acetonitrile **(17)**



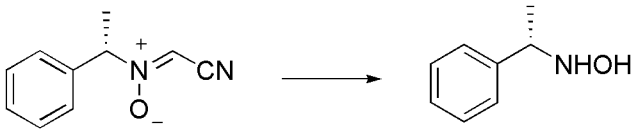
4mL S-2-phenyl-ethylamine (31mmole) was dissolved in 150mL MeCN. 8.55g K_2CO_3 and 2.95mL $ClCH_2CN$ were added to the solution and stirred at 60 C for 24h. The suspension was then filtered through Celite and the filtrate was concentrated on a rotory evaporator. The crude product was purified via column chromatography using 3:1 hexanes:EtOAc to afford 95% pure product. 1H NMR (400 MHz, CDCl3) δ 7.44 – 7.12 (m, 5H), 3.98 (q, *J* = 6.5 Hz, 1H), 3.51 (dd, *J* = 17.5, 1.1 Hz, 1H), 3.21 (dd, *J* = 17.5, 1.1 Hz, 1H), 1.74 (s, 1H), 1.35 (dd, *J* = 6.5, 1.0 Hz, 3H). 13C NMR (101 MHz, CDCl3) δ 128.96, 127.94, 127.08, 77.54, 77.22, 76.90, 56.98, 35.24, 31.13, 24.16.

Synthesis of (S,Z)-N-(cyanomethylene)-1-phenylethanamine oxide **(18)**



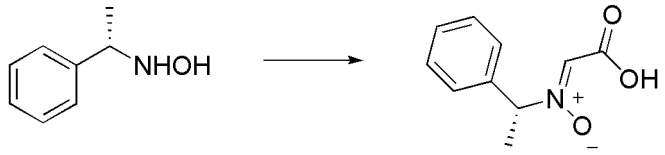
2.87g amine (17.9mmole) was dissolved in 80mL methylene chloride. 9.72g *m*-CPBA (2equiv.) was added to the solution in several portions at 0 C. The suspension was stirred at 0 C for 1h. Aqueous $Na_2S_2O_3$ and sat. $NaHCO_3$ were added to the solution and stirred an additional 30min at 0 C in order to quench the reaction. The mixture was extracted with three portions of 50mL methylene chloride. The combined organic layers were dried with Na_2SO_4 and concentrated via rotory evaporation to afford 76% nitrone product.

Synthesis of (S)-N-(1-phenylethyl)hydroxylamine **(19)**



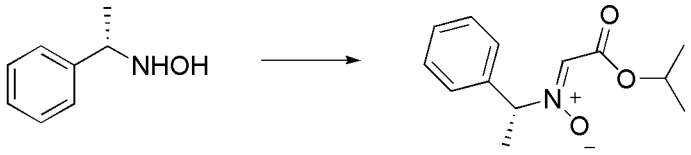
3.05g nitrone (17.5mmole) was dissolved in 90mL MeOH. 6.09g NH_2OH HCl was added to the mixture and stirred at 60 C for 2h. The solution was diluted with 150mL methylene chloride and filtered through a pad of Celite. The filtrate was concentrated via rotory evaporation and then partitioned between sat. $NaHCO_3$ and chloroform. The organic layer was extracted and the aqueous layer was further extracted twice more with 30mL portions of chloroform. The combined organic layers were dried with Na_2SO_4 and concentrated via rotory evaporation to afford S-hydroxylamine in 94% yield. 1H NMR (400 MHz, CDCl3) δ 7.43 – 7.20 (m, 6H), 4.11 (q, *J* = 6.6 Hz, 1H), 1.39 (d, *J* = 6.7 Hz, 3H).

Synthesis of (R,Z)-N-(carboxymethylene)-1-phenylethanamine oxide **(20)**



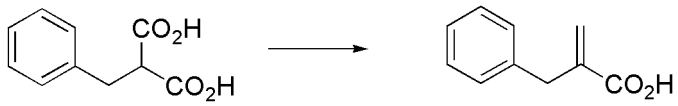
0.40g glyoxalic acid monohydrate (4.4 mmole) and 0.85g S-2-phenyl-hydroxylamine (1equiv.) were dissolved in 10mL DCM. The mixture was allowed to stir at r.t. for 5h. An additional 25mL DCM was added to the solution. The organic layer was then washed with 30mL H_2O. 2-30mL aliquots of methylene chloride were added to wash the aqueos layer. The combined organic layers were dried with Na_2SO_4 and then concentrated via rotory evaporated followed by drying on a high vac to afford chiral nitrone in 72% yield. 1H NMR (400 MHz, CDCl3) δ 7.33 – 7.23 (m, 2H), 5.22 (s, 1H), 5.00 (q, *J* = 6.8 Hz, 1H), 1.58 (d, *J* = 6.8 Hz, 3H). 13C NMR (101 MHz, CDCl3) δ 169.64, 154.38, 137.08, 129.45, 127.77, 114.07, 77.47, 77.35, 77.15, 76.83, 66.42, 57.40, 18.81.

Synthesis of (R,Z)-N-(2-isopropoxy-2-oxoethylidene)-1-phenylethanamine oxide **(21)**



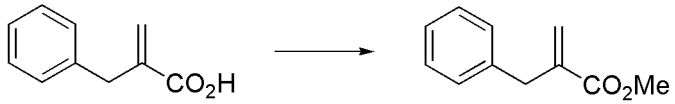
0.60g isopropyl glyoxylate and 0.70g S-2-phenyl-hydroxylamine (1equiv.) were dissolved in 5mL of a 50:50 mixture of EtOH:H_2O. The mixture was allowed to stir at r.t. overnight. The suspension was then filtered and the solid was dried on a high vac to afford pure S-nitrone in 68% yield. 1H NMR (400 MHz, cd3od) δ 7.66 (s, 1H), 7.60 – 7.05 (m, 5H), 5.38 (q, *J* = 6.8 Hz, 1H), 5.06 (dt, *J* = 12.5, 6.3 Hz, 1H), 4.85 (s, 1H), 3.35 – 3.27 (m, 1H), 1.75 (d, *J* = 6.8 Hz, 3H), 1.30 – 1.21 (m, 6H).

Synthesis of 2-benzylacrylic acid **(22)**



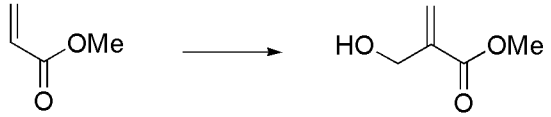
3.4g of the diacid (17.5 mmole), 7.41mL 37% Formalin, and 1.80mL $HNEt_2$ were added to a roundbottom flask and stirred at r.t. for 3h. The solution was then stirred an additional 2h at 100 C. After reflux, the solution was cooled to r.t. and diluted with 40mL $CHCl_3$. 50mL $NaHCO_3$ was added to the organic solution and the chloroform was extracted. The aqueous layer acidified to pH 1 and extracted with 3-30mL $CHCl_3$. The combined organic layers were dried with Na_2SO_4 and rotovapped followed by further drying on a high vac. 1H NMR (400 MHz, CDCl3) δ 9.47 (s, 1H), 7.53 – 6.96 (m, 5H), 6.28 (s, 1H), 5.70 – 5.24 (m, 1H), 3.62 (d, *J* = 19.8 Hz, 2H).

Synthesis of methyl 2-benzylacrylate **(23)**



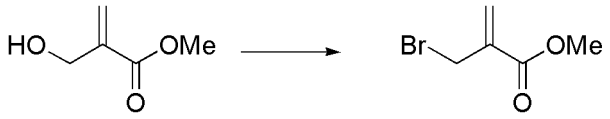
2.0g of acid (12 mmole) was dissolved in 40mL of a 3:2 solution of toluene:methanol. 9.1mL TMS-diazomethane (1.5 equiv.) was added dropwise to the solution at r.t. over a 30min period. The solution was allowed to stir at r.t. an additional 2h before the reaction was quenched with a drop of glacial acetic acid. The solution was rotovapped and dried on a high vac. 1H NMR (400 MHz, CDCl3) δ 7.33 – 7.09 (m, 5H), 6.22 (d, *J* = 0.8 Hz, 1H), 5.50 – 5.37 (m, 1H), 3.71 (t, *J* = 2.3 Hz, 3H), 3.62 (s, 2H).

Synthesis of methyl 2-(hydroxymethyl)acrylate **(26)**



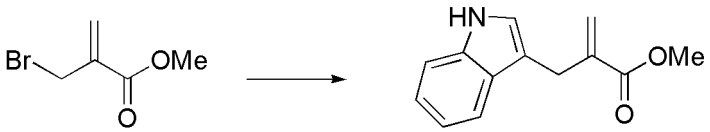
2.1mL methylacrylate (23 mmole), 1.05g paraformaldehyde, and 0.13g DABCO were added to a pressure tube and stirred in a closed system for 4h at 95 C. The solution was then cooled to r.t. followed by extraction with 3-30mL aliquots of Et_2O. The organic layers were dried with Na_2SO_4 and rotovapped followed by further drying on a high vac. The crude product was chromatographed (2:1 Hexanes:ethyl acetate). 1H NMR (400 MHz, CDCl3) δ 6.21 – 6.15 (m, 1H), 5.78 (dd, *J* = 1.7, 1.2 Hz, 1H), 4.26 – 4.21 (m, 2H), 3.70 (dd, *J* = 2.7, 1.6 Hz, 3H), 2.97 (s, 1H). 13C NMR (101 MHz, CDCl3) δ 166.78, 139.41, 125.61, 77.47, 77.15, 76.83, 62.00, 51.90.

Synthesis of methyl 2-(bromomethyl)acrylate **(27)**



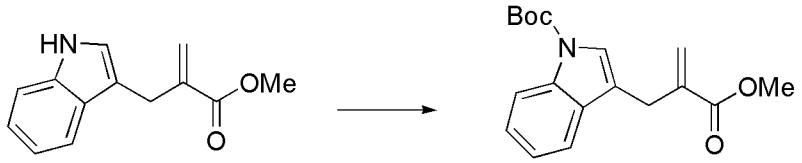
0.29mL PBr_3 was dissolved in 10mL dry Et_2O under N_2 at 0 C. 0.83g –OH (7.2 mmole) was dissolved in dry Et_2O and slowly added to the PBr_3 via cannulation. The solution was allowed to warm to r.t. while stirring overnight. The solution was then cooled to 0 C and the any unreacted PBr_3 was quenched with 30mL H_2=O. The solution was then extracted with 3-30mL portions of petroleum ether. The combined organic layers were dried with Na_2SO_4 and rotovapped followed by further drying on a high vac. 1H NMR (400 MHz, CDCl3) δ 6.31 – 6.26 (m, 1H), 5.96 – 5.89 (m, 1H), 4.15 – 4.10 (m, 2H), 3.77 (s, 3H).

Synthesis of methyl 2-((1H-indol-3-yl)methyl)acrylate **(28)**



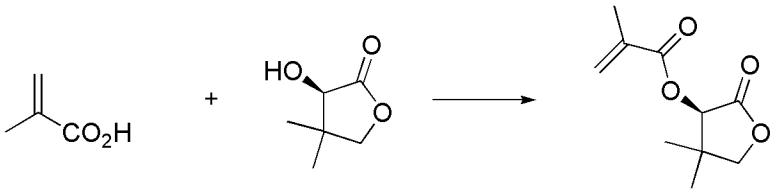
0.4g indole (3.41) was dissolved in 6mL dry THF and cooled to 0 C under N_2. 1.21mL 3M MeMgBr (1.1 equiv) was added dropwise to the indole solution and stirred at 0 C for 10min. 0.64g –Br (3.6 mmole) was dissolved in 7mL dry THF and then added via cannulation to the indole solution. The reaction was allowed to warm to r.t. while stirring an additional 1h followed by the addition of 30mL Et_2O. H_2O was added to the solution and the organic layer was extracted. The aqueous solution was extracted twice more with 30mL aliquots of methyle chloride. The organic layers were dried with Na_2SO_4 and rotovapped before being placed on a high vac. 1H NMR (400 MHz, CDCl3) δ 8.09 (s, 4H), 7.50 (d, *J* = 7.9 Hz, 10H), 7.32 (dd, *J* = 8.1, 0.8 Hz, 10H), 7.22 (d, *J* = 2.1 Hz, 2H), 7.20 – 7.02 (m, 24H), 6.99 (s, 11H), 6.17 (d, *J* = 0.6 Hz, 12H), 5.51 – 5.42 (m, 12H), 4.09 (qd, *J* = 7.1, 1.8 Hz, 27H), 3.81 – 3.67 (m, 66H), 2.03 (dd, *J* = 13.1, 7.3 Hz, 43H), 1.49 – 1.18 (m, 49H), 0.94 (s, 1H), 0.86 (d, *J* = 6.9 Hz, 2H).

Synthesis of tert-butyl 3-(2-(methoxycarbonyl)allyl)-1H-indole-1-carboxylate **(29)**



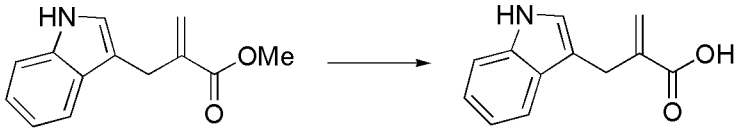
1.78g alkene (8.28mmole) was dissolved in 12mL MeCN. 1.9g Boc_2O was dissolved in 20mL MeCN and added to the alkene solution. 0.051g DMAP was added to the mixture which was stirred at r.t. for 1h. The mixture was concentrated via rotory evaporation and the crude product was chromatographed in an 8:1 mixture of hexanes:EtOAc. 1H NMR (400 MHz, CDCl3) δ 8.08 (s, 1H), 7.42 (dd, *J* = 7.8, 0.7 Hz, 1H), 7.38 (s, 1H), 7.32 – 7.24 (m, 1H), 7.21 – 7.13 (m, 1H), 6.21 (d, *J* = 1.1 Hz, 1H), 5.48 (d, *J* = 1.2 Hz, 1H), 3.75 (s, 4H), 3.69 (dd, *J* = 7.2, 0.6 Hz, 3H), 1.62 (d, *J* = 10.4 Hz, 13H).13C NMR (101 MHz, CDCl3) δ 188.02, 167.62, 138.49, 130.43, 126.44, 124.53, 124.20, 122.60, 119.45, 117.73, 115.44, 83.72, 77.52, 77.21, 76.89, 52.18, 28.41, 27.48.

Synthesis of (R)-4,4-dimethyl-2-oxo-tetrahydrofuran-3-yl methacrylate **(32)**



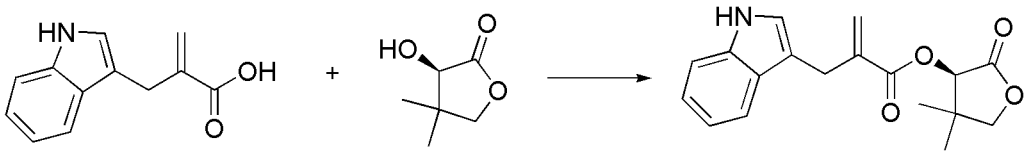
1.8mL acid (24 mmole) and 5.98g R-Pantolactone (2equiv.) were dissolved in 20mL dry methylene chloride. 0.138g DMAP was added and the solution was cooled to 0 C. 5.29g DCC (1.1 equiv.) was added to the solution and stirred for 20min at 0 C. The solution was then stirred overnight while warming to r.t. The solution was acidified with 2N HCl and extracted with 3-40mL aliquots of methylene chloride. The combined organic layers were dried with Na_2SO_4 and then rotovapped followed by further drying on a high vac.

Synthesis of 2-((1H-indol-3-yl)methyl)acrylic acid **(33)**



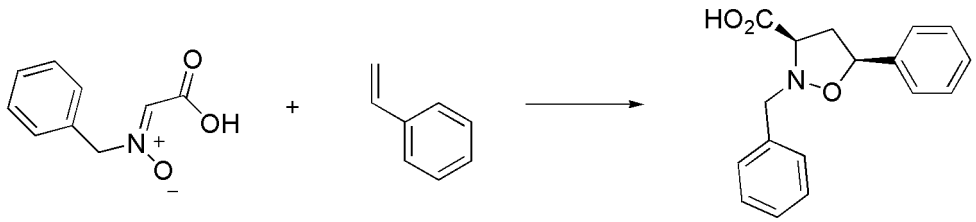
0.50g MeEster (2.3 mmole) waas dissolved in 11mL of 9:1 DCM:MeOH. 1.7mL 2N NaOH (1.5 equiv.) were added to the solution and stirred at r.t. overnight. The solvent was removed via rotorary evaporation and the product was further dried on a high vac. 1H NMR (400 MHz, CDCl3) δ 11.29 (s, 1H), 8.36 (s, 1H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.31 – 7.14 (m, 2H), 6.98 (d, *J* = 1.4 Hz, 1H), 6.42 (s, 1H), 5.65 (s, 1H), 3.95 – 3.79 (m, 2H). 13C NMR (101 MHz, CDCl3) δ 172.87, 172.20, 139.44, 136.76, 128.10, 127.52, 123.48, 122.15, 119.56, 119.24, 112.49, 111.66, 77.89, 77.57, 77.25, 61.02, 27.53, 21.29, 14.41. (W/ EtOAc)

Synthesis of (R)-4,4-dimethyl-2-oxo-tetrahydrofuran-3-yl 2-((1H-indol-3-yl)methyl)acrylate **(34)**



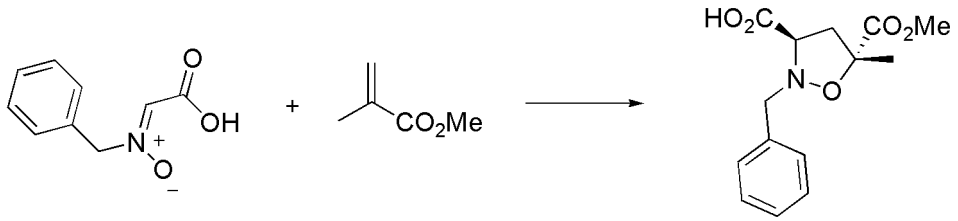
0.31g acid (1.5 mmole) and 0.40g R-Pantolactone (2equiv.) were dissolved in 5mL dry methylene chloride. 9mg DMAP was added and the solution was cooled to 0 C. 0.35g DCC was added to the cooled solution and stirred for 15min. The solution was allowed to warm to r.t. and stirred overnight. The crude product was chromatographed in a 3:1 hexanes:ethyl acetate mixture to afford 62% pure chiral ester. 1H NMR (400 MHz, cdcl3) δ 8.11 (s, 1H), 7.54 (d, *J* = 7.9 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.23 – 7.15 (m, 1H), 7.15 – 7.08 (m, 1H), 7.06 (d, *J* = 2.3 Hz, 1H), 6.33 (d, *J* = 1.0 Hz, 1H), 5.62 (d, *J* = 1.3 Hz, 1H), 5.44 (s, 1H), 4.02 (s, 2H), 3.82 (s, 2H), 1.17 (s, 3H), 1.04 (s, 3H).

Synthesis of (3R,5S)-2-benzyl-5-phenylisoxazolidine-3-carboxylic acid **(36)**



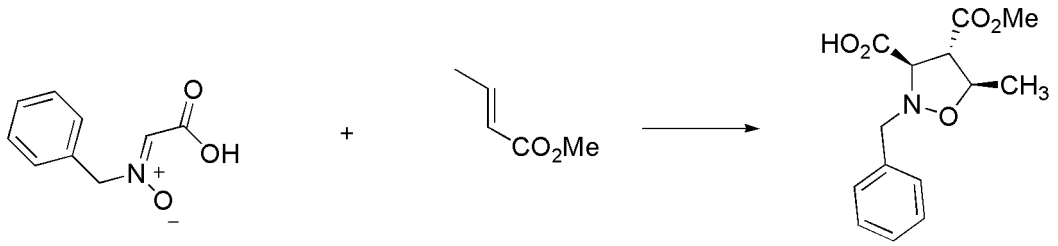
0.529g nitrone (2.96 mmole) and 1mL styrene were dissolved in 6mL chloroform and stirred at r.t. for 4h. The solvent was removed via rotory evaporation followed by further drying on a high vac. 91% pure isoxazolidine was collected.

Synthesis of (3R,5R)-2-benzyl-5-(methoxycarbonyl)-5-methylisoxazolidine-3-carboxylic acid **(37)**



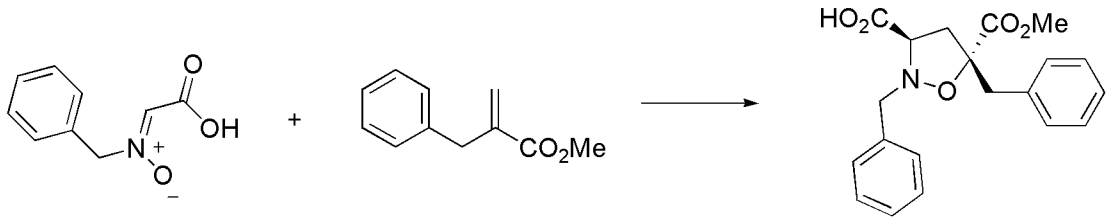
0.25g nitrone (1.4 mmole) and 0.75mL methylmethacylate (5 equiv.) were dissolved in 4mL chloroform and stirred at r.t. for 7 days. The solvent was rotovapped and the product was placed on a high vac. 1H NMR (400 MHz, CDCl3) δ 7.41 – 7.28 (m, 10H), 4.28 (d, *J* = 12.7 Hz, 1H), 3.91 (dd, *J* = 8.6, 3.4 Hz, 1H), 3.85 (d, *J* = 12.8 Hz, 1H), 3.81 – 3.75 (m, 3H), 3.23 (dd, *J* = 13.4, 8.6 Hz, 1H), 2.69 (dd, *J* = 13.3, 3.4 Hz, 1H), 1.47 (s, 3H).

Synthesis of (3R,4S,5R)-2-benzyl-4-(methoxycarbonyl)-5-methylisoxazolidine-3-carboxylic acid **(38)**



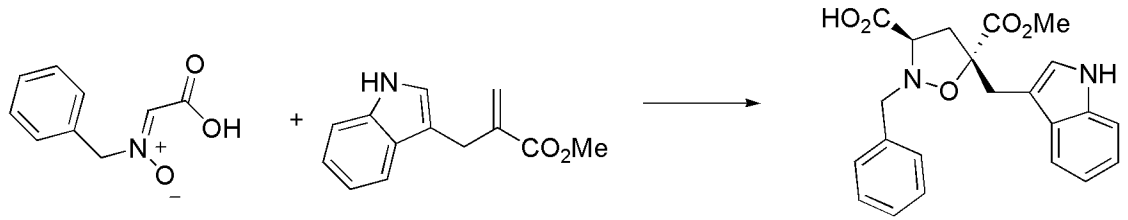
0.25g nitrone (1.4 mmole) and 0.75mL methylmethacylate (5 equiv.) were dissolved in 4mL chloroform and stirred at r.t. for 7 days. The solvent was rotovapped and the product was placed on a high vac. Product yield and ^{1}H NMR analysis was not determined due to the unreactive nature of this reaction.

Synthesis of (3R,5R)-2,5-dibenzyl-5-(methoxycarbonyl)isoxazolidine-3-carboxylic acid **(40)**



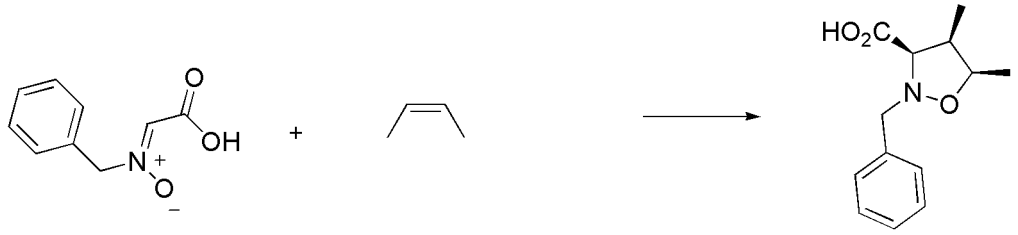
0.219g nitrone (1.23 mmole) and 0.26g benzylmethacrylate (1 equiv.) were dissolved in 5mL chloroform and stirred at r.t. for 10 days. The solvent was rotovapped and the product was placed on a high vac.

Synthesis of (3R,5R)-5-((1H-indol-3-yl)methyl)-2-benzyl-5-(methoxycarbonyl) isoxazolidine-3-carboxylic acid **(41)**



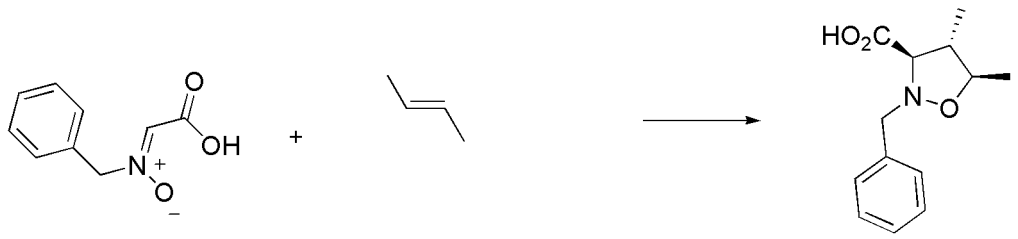
0.25g nitrone (1.4 mmole) and 0.60g indolylmethacrylate (2 equiv.) were dissolved in 5mL chloroform and stirred at r.t. for 7 days. The solvent was rotovapped and the product was placed on a high vac.

Synthesis of (3R,4R,5R)-2-benzyl-4,5-dimethylisoxazolidine-3-carboxylic acid **(42)**



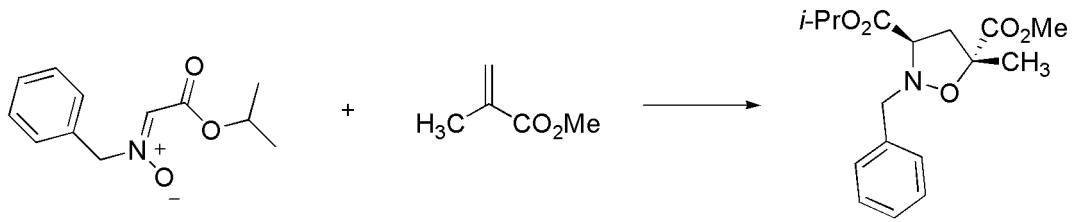
0.50g nitrone (2.8 mmole) were dissolved in 2mL chloroform in a pressure tube. The solution was cooled to -78 C in a dry ice:acetone bath and 1.5g *cic*-butene (10 equiz.) were bubbled in. The tube was sealed and stirred at r.t. for 7 days. The solution was concentrated via rotory evaporation and unreacted nitrone was recovered. Product yield and ^{1}H NMR analysis was not determined due to the unreactive nature of this reaction.

Synthesis of (3R,4S,5R)-2-benzyl-4,5-dimethylisoxazolidine-3-carboxylic acid **(43)**



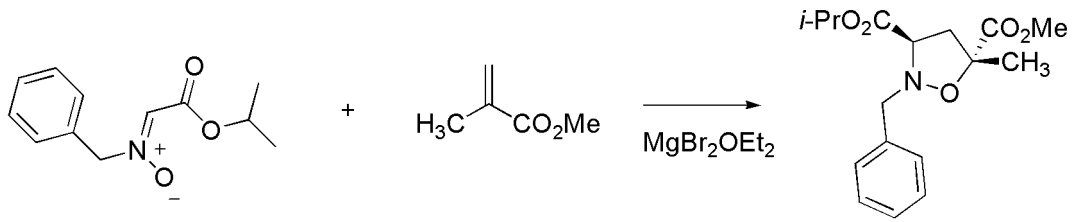
0.50g nitrone (2.8 mmole) were dissolved in 2mL chloroform in a pressure tube. The solution was cooled to -78 C in a dry ice:acetone bath and 1.5g *trans*-butene (10 equiz.) were bubbled in. The tube was sealed and stirred at r.t. for 7 days. The solution was concentrated via rotory evaporation and unreacted nitrone was recovered. Product yield and ^{1}H NMR analysis was not determined due to the unreactive nature of this reaction.

Synthesis of (3R,5R)-3-isopropyl 5-methyl 2-benzyl-5-methylisoxazolidine-3,5-dicarboxylate **(44)**



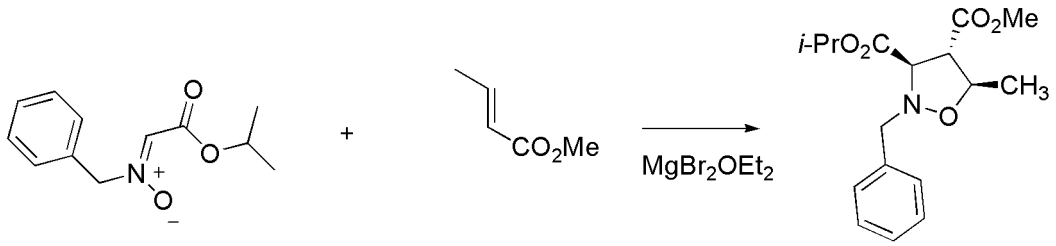
0.14g nitrone (0.633 mmole) and 0.15mL methylmethacrylate (1.25equiv.) were dissolved in 1.5mL of a 50:50 mixture of HOPr-*i*:MeCN. The mixture was stirred at r.t. for 18h. The solution was concentrated on a rotory evaporator to afford 0.16g isoxazolidine (79%). 1H NMR (400 MHz, CDCl3) δ 7.40 – 7.17 (m, 1H), 4.96 (dt, *J* = 12.5, 6.3 Hz, 0H), 4.21 (d, *J* = 13.5 Hz, 0H), 4.04 (d, *J* = 13.5 Hz, 0H), 3.78 – 3.68 (m, 1H), 3.02 (dd, *J* = 12.9, 7.8 Hz, 0H), 2.51 (dd, *J* = 12.9, 7.2 Hz, 0H), 1.54 (s, 1H), 1.23 – 1.14 (m, 1H).

Synthesis of (3R,5R)-3-isopropyl 5-methyl 2-benzyl-5-methylisoxazolidine-3,5-dicarboxylate **(44)** in the presence of $MgBr_2 \cdot OEt_2$



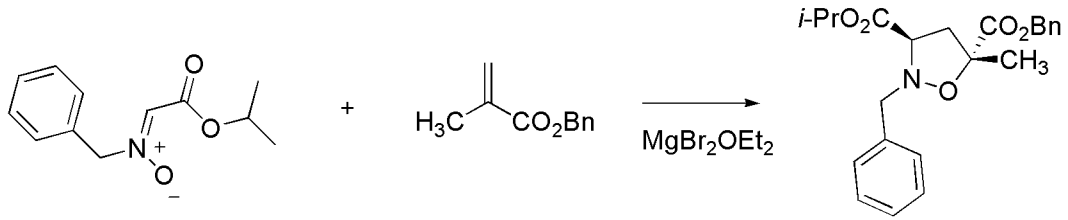
0.028g nitrone (0.13 mmole), 0.033g $MgBr_2OEt_2$ (1.1equiv.), and 0.06mL methylmethacrylate (5 equiv.) were dissolved in 0.3mL of a 50:50 mixture of MeOH:MeCN. The solution was stirred at r.t. for 18h. 3mL of methylene chloride were added and the solution was partitioned with 3mL H_2O. The organic layer was collected and the aqueous layer was washed twice more with 3mL portions of methylene chloride. The combined organic layers were dried with Na_2SO_4 and concentrated via rotory evaporation. The crude product was chromatographed in 4:1 Hexanes:EtOAc to afford 0.035g isoxazolidine (85%). 1H NMR (400 MHz, CDCl3) δ 7.40 – 7.17 (m, 1H), 4.96 (dt, *J* = 12.5, 6.3 Hz, 0H), 4.21 (d, *J* = 13.5 Hz, 0H), 4.04 (d, *J* = 13.5 Hz, 0H), 3.78 – 3.68 (m, 1H), 3.02 (dd, *J* = 12.9, 7.8 Hz, 0H), 2.51 (dd, *J* = 12.9, 7.2 Hz, 0H), 1.54 (s, 1H), 1.23 – 1.14 (m, 1H).

Synthesis of (3R,4S,5R)-3-isopropyl 4-methyl 2-benzyl-5-methylisoxazolidine-3,4-dicarboxylate **(46)**



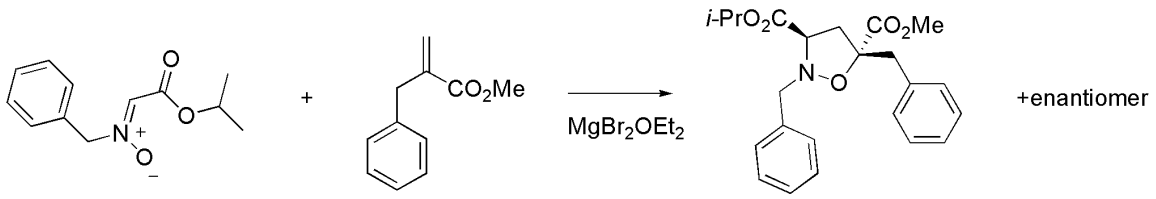
0.014g nitrone (0.063 mmole), 0.018g $MgBr_2OEt_2$ (1.1equiv.), and 0.03mL methylcrotonate (5 equiv.) were dissolved in 0.2mL of a 50:50 mixture of MeOH:MeCN. The solution was stirred at r.t. for 18h. 3mL of methylene chloride were added and the solution was partitioned with 3mL H_2O. The organic layer was collected and the aqueous layer was washed twice more with 3mL portions of methylene chloride. The combined organic layers were dried with Na_2SO_4 and concentrated via rotory evaporation.

Synthesis of (3R,5R)-5-benzyl 3-isopropyl 2-benzyl-5-methylisoxazolidine-3,5-dicarboxylate **(47)**



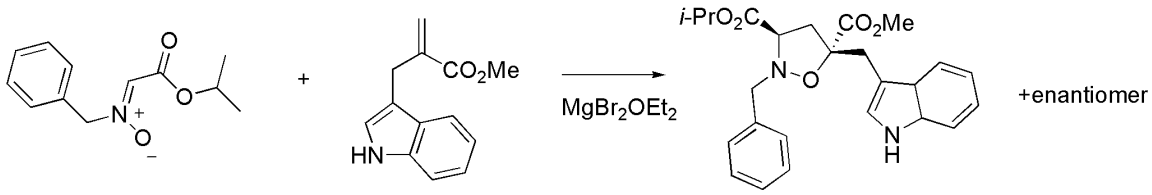
0.028g nitrone (0.13 mmole), 0.036g $MgBr_2OEt_2$ (1.1equiv.), and 0.10mL benzylmethacrylate (5 equiv.) were dissolved in 0.2mL of a 50:50 mixture of MeOH:MeCN. The solution was stirred at r.t. for 18h. 3mL of methylene chloride were added and the solution was partitioned with 3mL H_2O. The organic layer was collected and the aqueous layer was washed twice more with 3mL portions of methylene chloride. The combined organic layers were dried with Na_2SO_4 and concentrated via rotory evaporation.

Synthesis of (3R,5R)-3-isopropyl 5-methyl 2,5-dibenzylisoxazolidine-3,5-dicarboxylate **(48)**



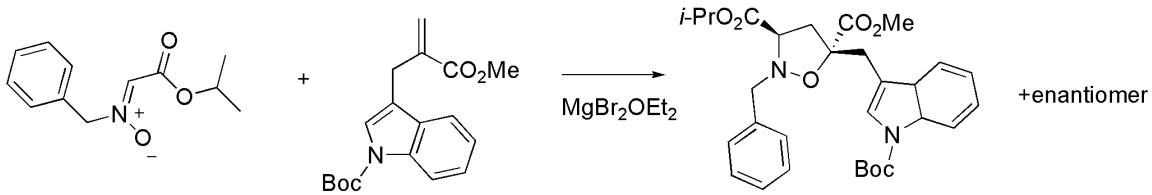
0.044g nitrone (0.2 mmole), 0.057g $MgBr_2OEt_2$ (1.1equiv.), and 0.07g 2-phenylmethyl methacrylate (2 equiv.) were dissolved in 0.5mL of a 50:50 mixture of *i*-PrOH:MeCN. The solution was stirred at r.t. for 18h. 3mL of methylene chloride were added and the solution was partitioned with 3mL H_2O. The organic layer was collected and the aqueous layer was washed twice more with 3mL portions of methylene chloride. The combined organic layers were dried with Na_2SO_4 and concentrated via rotory evaporation. The crude product was chromatographed in 9:1 Hexanes:EtOAc to afford 0.048g isoxazolidine (63%).

Synthesis of (3R,5R)-3-isopropyl 5-methyl 5-((1H-indol-3-yl)methyl)-2-benzylisoxazolidine-3,5-dicarboxylate **(49)**



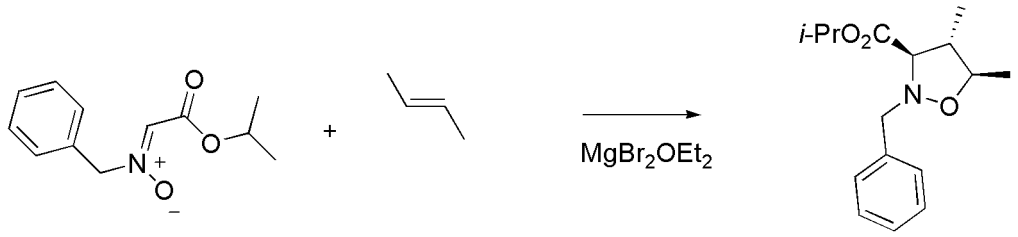
0.029g nitrone (0.13 mmole), 0.033g $MgBr_2OEt_2$ (1.1equiv.), and 0.14g indolylmethylmethacrylate (5 equiv.) were dissolved in 0.3mL of a 50:50 mixture of MeOH:MeCN. The solution was stirred at r.t. for 18h. 3mL of methylene chloride were added and the solution was partitioned with 3mL H_2O. The organic layer was collected and the aqueous layer was washed twice more with 3mL portions of methylene chloride. The combined organic layers were dried with Na_2SO_4 and concentrated via rotory evaporation. The crude product was chromatographed in 5:1 Hexanes:EtOAc to afford 0.032g of OPr-*i* and OMe isoxazolidines (55%).

Synthesis of (3R,5R)-3-isopropyl 5-methyl 2-benzyl-5-((1-(tert-butoxycarbonyl)-1H-indol-3-yl)methyl)isoxazolidine-3,5-dicarboxylate **(50)**



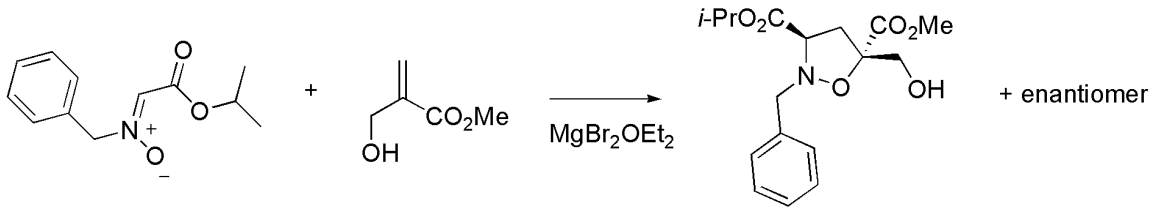
0.031g nitrone (0.13 mmole), 0.040g $MgBr_2OEt_2$ (1.1equiv.), and 0.083g N-Boc-indolylmethylmethacrylate (2 equiv.) were dissolved in 0.3mL of a 50:50 mixture of *i*-PrOH:MeCN. The solution was stirred at r.t. for 18h. 3mL of methylene chloride were added and the solution was partitioned with 3mL H_2O. The organic layer was collected and the aqueous layer was washed twice more with 3mL portions of methylene chloride. The combined organic layers were dried with Na_2SO_4 and concentrated via rotory evaporation. The crude product was chromatographed in 5:1 Hexanes:EtOAc to afford g of isoxazolidine (%). 1H NMR (400 MHz, CDCl3) δ 8.09 (d, *J* = 7.0 Hz, 6H), 7.46 – 7.12 (m, 47H), 5.05 – 4.94 (m, 1H), 4.26 (d, *J* = 13.5 Hz, 1H), 4.11 (d, *J* = 13.4 Hz, 1H), 3.59 (s, 6H), 3.35 (dd, *J* = 37.8, 14.6 Hz, 3H), 3.01 (dd, *J* = 12.9, 7.8 Hz, 2H), 2.77 (dd, *J* = 13.0, 7.9 Hz, 1H), 1.19 (d, *J* = 6.3 Hz, 12H).

Synthesis of (3R,4S,5R)-isopropyl 2-benzyl-4,5-dimethylisoxazolidine-3-carboxylate **(52)**



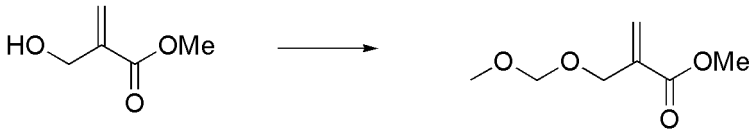
0.071g nitrone (0.32 mmole) were dissolved in 1.5mL MeCN in a pressure tube. The solution was cooled to -78 C in a dry ice:acetone bath and ~0.02g *cic*-butene (5 equiz.) were bubbled in. The tube was sealed and stirred at r.t. for 5 days. The solution was concentrated via rotory evaporation and unreacted nitrone was recovered. Product yield and ^{1}H NMR analysis was not determined due to the unreactive nature of this reaction.

Synthesis of (3R,5S)-3-isopropyl 5-methyl 2-benzyl-5-(hydroxymethyl)isoxazolidine-3,5-dicarboxylate **(53)**



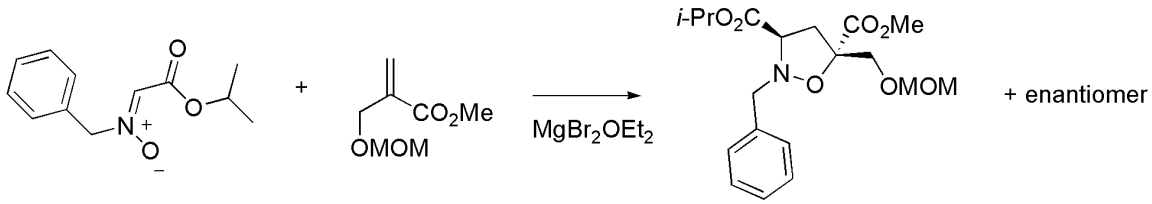
0.028g nitrone (0.13 mmole), 0.036g $MgBr_2OEt_2$ (1.1equiv.), and 0.06g 2-hydroxymethylmethacrylate (5 equiv.) were dissolved in 0.3mL of a 50:50 mixture of MeOH:MeCN. The solution was stirred at r.t. for 18h. 3mL of methylene chloride were added and the solution was partitioned with 3mL H_2O. The organic layer was collected and the aqueous layer was washed twice more with 3mL portions of methylene chloride. The combined organic layers were dried with Na_2SO_4 and concentrated via rotory evaporation. The crude product was chromatographed in 4:1 Hexanes:EtOAc to afford 0.035g isoxazolidine (85%). 1H NMR (400 MHz, CDCl3) δ 7.44 – 7.13 (m, 7H), 4.96 (dt, *J* = 12.5, 6.3 Hz, 1H), 4.10 (dd, *J* = 34.9, 13.5 Hz, 2H), 3.74 – 3.72 (m, 4H), 2.89 – 2.80 (m, 1H), 2.70 (dd, *J* = 13.2, 6.8 Hz, 1H), 1.27 – 1.09 (m, 7H).

Synthesis of methyl 2-((methoxymethoxy)methyl)acrylate



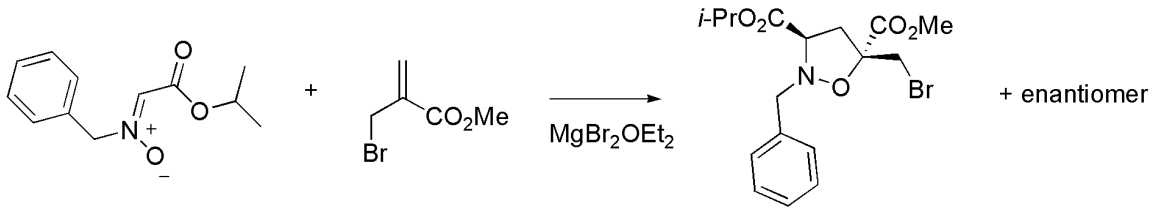
0.14g alcohol (1.2 mmole) was dissolved in 1.4mL dry DCM and cooled to 0 C. 1.62mL Hunig's Base (10.18 mmole) and 0.37mL MOMCl were added to the solution. The mixture was stirred for 50min at 0 C. 2mL 1M HCl were added and the reaction mixture was diluted with 20mL H_2O. The product was extracted with 3-10mL aliquots of DCM. The combined organic layers were dried with Na_2SO_4 and concentrated via rotory evaporation. 1H NMR (400 MHz, CDCl3) δ 6.27 – 6.19 (m, 1H), 5.85 – 5.75 (m, 1H), 4.59 (d, *J* = 0.5 Hz, 2H), 4.22 – 4.16 (m, 2H), 3.76 – 3.66 (m, 3H), 3.31 – 3.26 (m, 3H). 13C NMR (101 MHz, CDCl3) δ 166.33, 137.17, 126.42, 96.08, 77.58, 77.27, 76.95, 65.78, 55.45, 51.96.

Synthesis of (3R,5S)-3-isopropyl 5-methyl 2-benzyl-5-((methoxymethoxy)methyl) isoxazolidine-3,5-dicarboxylate **(54)**



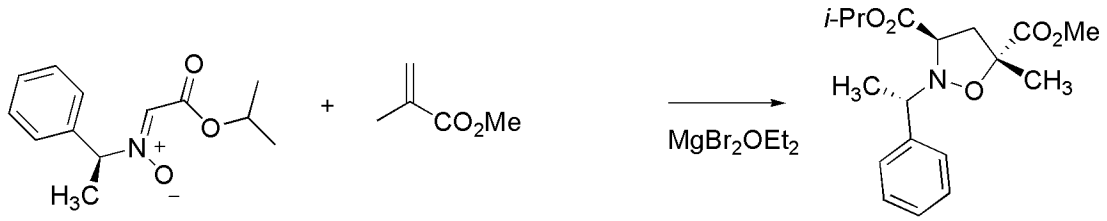
0.014g nitrone (0.31 mmole), 0.017g $MgBr_2OEt_2$ (1.1equiv.), and 0.05g 2-MOM (5eqzuiv.) were dissolved in 0.2mL of a 50:50 mixture of MeOH:MeCN. The solution was stirred at r.t. for 18h. 3mL of methylene chloride were added and the solution was partitioned with 3mL H_2O. The organic layer was collected and the aqueous layer was washed twice more with 3mL portions of methylene chloride. The combined organic layers were dried with Na_2SO_4 and concentrated via rotory evaporation to afford 0.084g isoxazolidine (48%). 1H NMR (400 MHz, CDCl3) δ 7.45 – 7.15 (m, 6H), 5.05 – 4.83 (m, 1H), 4.62 – 4.47 (m, 2H), 4.27 – 4.02 (m, 2H), 3.88 (d, *J* = 10.0 Hz, 1H), 3.81 – 3.71 (m, 5H), 3.64 (t, *J* = 7.7 Hz, 1H), 3.25 (t, *J* = 2.8 Hz, 3H), 2.91 (dd, *J* = 13.1, 8.0 Hz, 1H), 2.59 (dd, *J* = 13.2, 7.3 Hz, 1H), 1.24 – 1.11 (m, 8H). 13C NMR (101 MHz, CDCl3) δ 172.18, 169.08, 136.00, 129.54, 128.42, 127.77, 96.80, 84.87, 77.52, 77.20, 76.88, 70.15, 69.42, 66.22, 61.48, 55.48, 52.86, 39.19, 21.85.

Synthesis of (3R,5R)-3-isopropyl 5-methyl 2-benzyl-5-(bromomethyl)isoxazolidine-3,5-dicarboxylate **(55)**



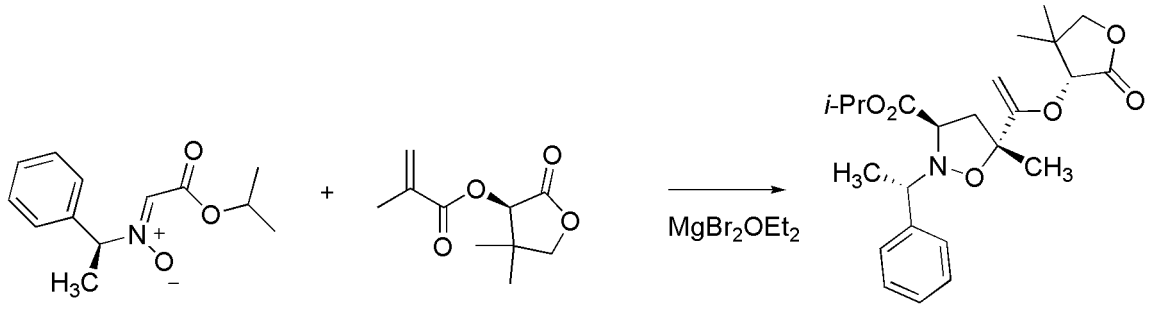
0.028g nitrone (0.127 mmole), 0.036g $MgBr_2OEt_2$ (1.1equiv.), and 0.07g 2-bromomethylmethacrylate (3 equiv.) were dissolved in 0.3mL of a 50:50 mixture of MeOH:MeCN. The solution was stirred at r.t. for 18h. 3mL of methylene chloride were added and the solution was partitioned with 3mL H_2O. The organic layer was collected and the aqueous layer was washed twice more with 3mL portions of methylene chloride. The combined organic layers were dried with Na_2SO_4 and concentrated via rotory evaporation. 1H NMR (400 MHz, CDCl3) δ 7.44 – 7.14 (m, 7H), 4.96 (dt, *J* = 12.5, 6.3 Hz, 1H), 4.28 (d, *J* = 14.3 Hz, 1H), 4.10 (d, *J* = 14.3 Hz, 1H), 3.82 – 3.71 (m, 4H), 3.62 – 3.44 (m, 4H), 3.13 (dd, *J* = 13.2, 7.8 Hz, 1H), 2.66 – 2.53 (m, 1H), 1.28 – 1.15 (m, 15H).

Synthesis of (3R,5R)-3-isopropyl 5-methyl 5-methyl-2-((S)-1-phenylethyl) isoxazolidine-3,5-dicarboxylate **(56)**



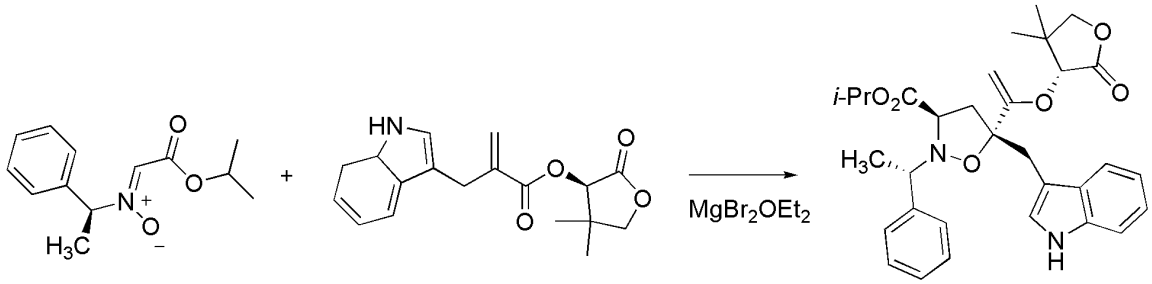
0.041g nitrone (0.17 mmole), 0.048g $MgBr_2OEt_2$ (1.1equiv.), and 0.08mL methylmethacrylate (5 equiv.) were dissolved in 0.5mL of a 50:50 mixture of MeOH:MeCN. The solution was stirred at r.t. for 18h. 3mL of methylene chloride were added and the solution was partitioned with 3mL H_2O. The organic layer was collected and the aqueous layer was washed twice more with 3mL portions of methylene chloride. The combined organic layers were dried with Na_2SO_4 and concentrated via rotory evaporation.

Synthesis of (3R,5R)-5-((R)-4,4-dimethyl-2-oxo-tetrahydrofuran-3-yl) 3-isopropyl 5-methyl-2-((S)-1-phenylethyl)isoxazolidine-3,5-dicarboxylate **(57)**



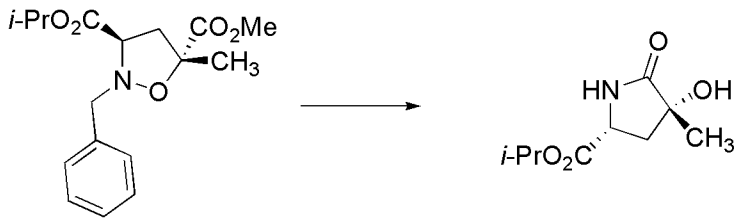
0.21g nitrone (1.9 mmole), 0.53g $MgBr_2OEt_2$ (1.1equiv.), and 0.75g R-alkene (2 equiv.) were dissolved in 4.4mL of a 50:50 mixture of MeOH:MeCN. The solution was stirred at r.t. for 18h. 10mL of methylene chloride were added and the solution was partitioned with 10mL H_2O. The organic layer was collected and the aqueous layer was washed twice more with 3mL portions of methylene chloride. The combined organic layers were dried with Na_2SO_4 and concentrated via rotory evaporation. 1H NMR (400 MHz, CDCl3) δ 7.24 (ddt, *J* = 11.1, 8.3, 4.4 Hz, 7H), 5.39 (d, *J* = 2.4 Hz, 1H), 4.88 – 4.73 (m, 1H), 4.11 – 3.97 (m, 2H), 3.90 (q, *J* = 6.3 Hz, 1H), 3.76 (dd, *J* = 8.1, 4.4 Hz, 1H), 3.13 (dd, *J* = 13.1, 8.1 Hz, 1H), 2.53 (dd, *J* = 13.1, 4.4 Hz, 1H), 1.57 – 1.45 (m, 4H), 1.27 – 1.17 (m, 4H), 1.14 (s, 3H), 1.10 (dd, *J* = 12.8, 6.3 Hz, 8H). 13C NMR (101 MHz, CDCl3) δ 171.98, 170.54, 142.26, 128.71, 128.05, 84.18, 77.53, 77.22, 76.90, 76.39, 76.04, 69.06, 67.00, 66.59, 41.12, 40.26, 24.17, 23.16, 22.57, 21.78, 20.11.

Synthesis of (3R,5R)-5-((R)-4,4-dimethyl-2-oxo-tetrahydrofuran-3-yl) 3-isopropyl 5-((1H-indol-3-yl)methyl)-2-((S)-1-phenylethyl)isoxazolidine-3,5-dicarboxylate **(58)**



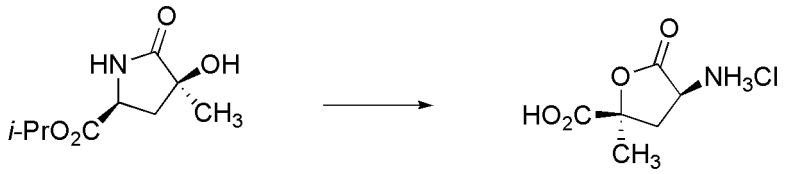
0.069g nitrone (0.29 mmole), 0.082g $MgBr_2OEt_2$ (1.1equiv.), and 0.86g R-alkene (3 equiv.) were dissolved in 0.8mL of a 50:50 mixture of MeOH:MeCN. The solution was stirred at r.t. for 18h. 3mL of methylene chloride were added and the solution was partitioned with 3mL H_2O. The organic layer was collected and the aqueous layer was washed twice more with 3mL portions of methylene chloride. The combined organic layers were dried with Na_2SO_4 and concentrated via rotory evaporation to afford 0.071g isoxazolidine (45%). 1H NMR (400 MHz, CDCl3) δ 8.23 (s, 1H), 7.59 (d, *J* = 7.9 Hz, 1H), 7.40 – 7.16 (m, 9H), 7.08 (dddd, *J* = 16.0, 7.9, 7.1, 1.1 Hz, 2H), 5.26 (s, 1H), 4.81 – 4.69 (m, 1H), 3.95 – 3.86 (m, 3H), 3.77 (dd, *J* = 8.1, 5.5 Hz, 1H), 3.55 – 3.45 (m, 1H), 3.40 (d, *J* = 14.8 Hz, 1H), 3.09 (dd, *J* = 13.2, 8.1 Hz, 1H), 2.78 (dd, *J* = 13.2, 5.5 Hz, 1H), 1.59 (d, *J* = 6.3 Hz, 4H), 1.11 – 1.00 (m, 9H), 0.86 – 0.75 (m, 4H), 0.69 (d, *J* = 18.5 Hz, 3H). 13C NMR (101 MHz, CDCl3) δ 172.77, 172.32, 170.76, 142.18, 136.01, 128.69, 128.30, 127.95, 124.41, 122.11, 119.71, 118.91, 111.30, 109.32, 88.06, 77.53, 77.21, 76.89, 76.50, 76.38, 75.91, 69.09, 67.24, 66.64, 40.55, 40.12, 32.96, 23.11, 22.67, 22.26, 21.79, 19.69, 18.97.

Synthesis of (2R,4R)-isopropyl 4-hydroxy-4-methyl-5-oxopyrrolidine-2-carboxylate **(59)**



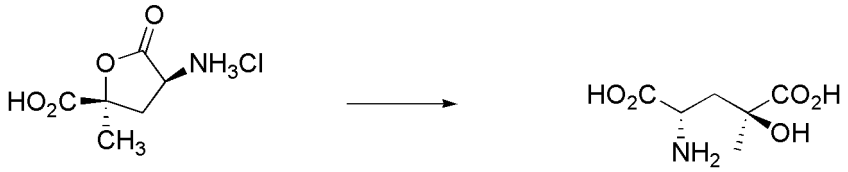
0.10g isoxazolidine (0.34 mmole) and 0.16g 20% $Pd(OH)_2/C$ were dissolved in 5mL MeOH. The solution was pressurized with H_2 gas at 15psi and shaken on a Parr shaker at r.t. for 18h. The solution was filtered through a pad of Celite and washed with excess MeOH. The filtrate was concentrated on a rotory evaporator and further dried via high vac to afford 0.04g lactam (67%).

Synthesis of (2S,4S)-4-(chloroamino)-2-methyl-5-oxo-tetrahydrofuran-2-carboxylic acid **(60)**



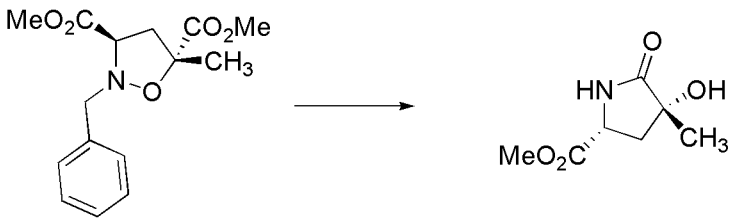
0.08g lactam (0.40mmole) was dissolved in 3mL 6N HCl and stirred at 110 C 18h.The solvent was removed via rotory evaporation to afford 0.068g of lactone (87%)

Synthesis of (2S,4S)-γ-hydroxyl glutamic acid **(61)**



0.068g lactone (0.35mmole) was dissolved in 3mL 1N NaOH and stirred at r.t 30min. The mixture was concentrated to afford 0.048g of 4-hydroxy-4-methyl-glutamic acid

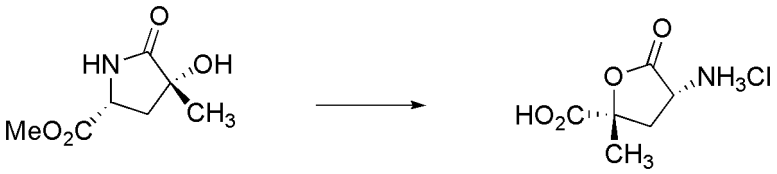
Synthesis of (2R,4R)-methyl 4-hydroxy-4-methyl-5-oxopyrrolidine-2-carboxylate **(62)**



0.10g isoxazolidine (0.34 mmole) and 0.16g 20% $Pd(OH)_2/C$ were dissolved in 5mL MeOH. The solution was pressurized with H_2 gas at 15psi and shaken on a Parr shaker at r.t. for 18h. The solution was filtered through a pad of Celite and washed with excess MeOH. The filtrate was concentrated on a rotory evaporator and further dried via high vac to afford 0.04g lactam (67%). 1H NMR (400 MHz, cd3od) δ 7.64 (d, *J* = 7.9 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.14 (s, 1H), 7.11 – 7.05 (m, 1H), 7.05 – 6.98 (m, 1H), 3.66 (d, *J* = 12.4 Hz, 3H), 3.40 – 3.27 (m, 4H), 3.23 (d, *J* = 14.1 Hz, 1H), 3.07 (d, *J* = 14.3 Hz, 1H), 2.70 (dd, *J* = 13.4, 8.2 Hz, 1H), 2.03 (dd, *J* = 13.3, 7.0 Hz, 1H).

Synthesis of (2R,4R)-4-(chloroamino)-2-methyl-5-oxo-tetrahydrofuran-2-carboxylic acid

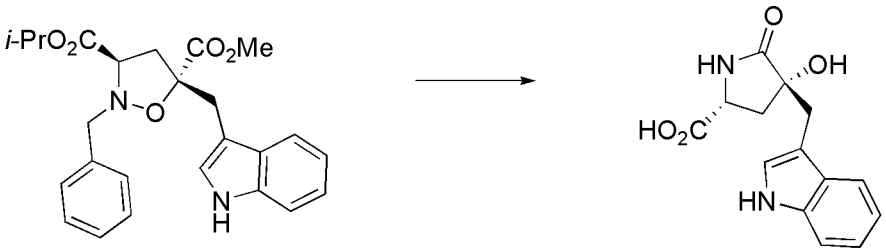
(60)



0.10g lactam (0.58 mmole) was dissolved in 5mL 6N HCl and stirred at 100 C for 18h.

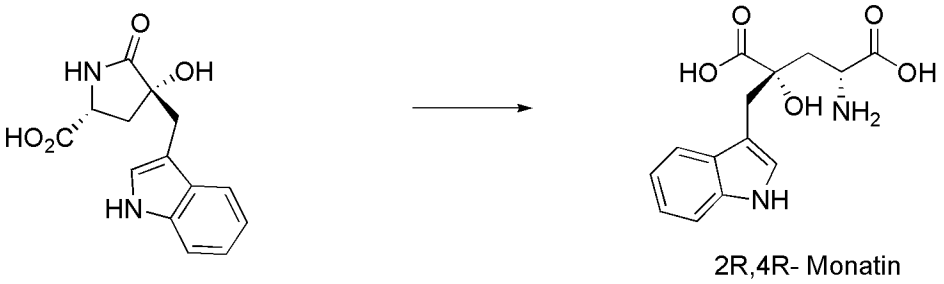
The mixture was lyophilized to afford lactone

Synthesis of (2R,4R)-4-((1H-indol-3-yl)methyl)-4-hydroxy-5-oxopyrrolidine-2-carboxylic acid **(63)**



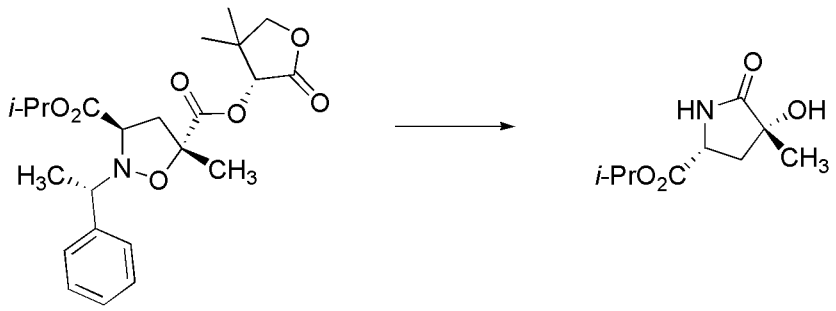
0.010g isoxazolidine (0.023mmole) and 9.5mg 20% $Pd(OH)_2/C$ were dissolved in 0.5mL MeOH. The solution was pressurized with H_2 gas at 15psi and shaken on a Parr shaker at r.t. for 18h. The solution was filtered through a pad of Celite and washed with excess MeOH. The filtrate was concentrated on a rotory evaporator. The oil was then diluted with 3mL THF and heated to 80 C for 4h. The product was concentrated again via rotory evaporation and further dried via high vac. 1H NMR (400 MHz, CDCl3) δ 8.36 (s, 0H), 7.60 (d, *J* = 7.4 Hz, 1H), 7.40 – 6.96 (m, 5H), 6.64 (s, 1H), 5.06 – 4.81 (m, 1H), 3.80 – 3.64 (m, 4H), 3.16 (dd, *J* = 24.6, 14.1 Hz, 2H), 2.62 (dd, *J* = 12.7, 8.0 Hz, 1H), 2.14 (dd, *J* = 13.3, 6.4 Hz, 1H), 1.23 – 1.08 (m, 7H).

Synthesis of (2R,4R)-Monatin **(64)**



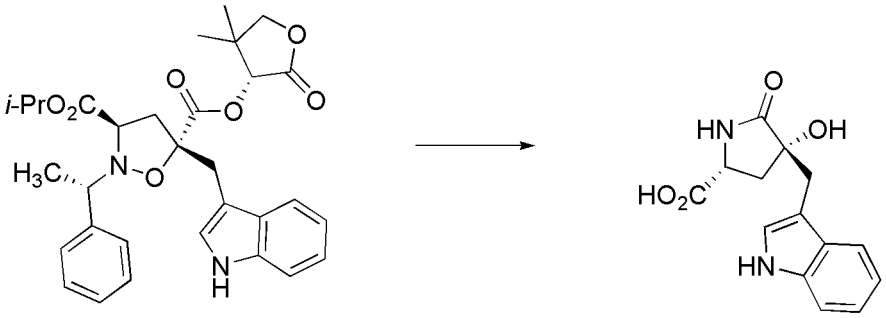
0.027g lactam (0.115 mmole) was dissolved in 5mL EtOH. 0.3mL 2N NaOH was added to the solution which was heated at 100 C for 3h. The solution was acidified to ~pH 4 and then concentrated (unsuccessfully).

Synthesis of (2R,4R)-isopropyl 4-hydroxy-4-methyl-5-oxopyrrolidine-2-carboxylate **(59)**



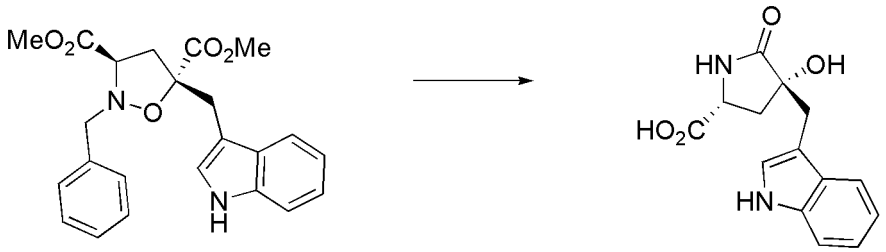
0.045 nitrone (0.11 mmole) and 47mg of 20% $Pd(OH)_2$ were dissolved in 3mL MeOH. The solution was pressurized with H_2 gas at 15psi and shaken on a Parr shaker at r.t. for 18h. The solution was filtered through a pad of Celite and washed with excess MeOH. The filtrate was concentrated on a rotory evaporator and the crude product was chromatographed with 1:1 Hexanes:EtOAc to afford 0.90g lactam (92%). 1H NMR (400 MHz, CDCl3) δ 6.72 (s, 1H), 5.04 (dd, *J* = 12.3, 6.3 Hz, 1H), 4.05 (s, 1H), 2.46 (dd, *J* = 12.9, 7.2 Hz, 1H), 2.25 (dd, *J* = 13.0, 6.6 Hz, 1H), 1.37 (d, *J* = 8.6 Hz, 3H), 1.23 (dd, *J* = 6.1, 1.7 Hz, 7H).

Synthesis of (2R,4R)-4-((1H-indol-3-yl)methyl)-4-hydroxy-5-oxopyrrolidine-2-carboxylic acid **(63)**



0.020 nitrone (0.046 mmole) and 20mg of 20% $Pd(OH)_2$ were dissolved in 0.5mL MeOH. The solution was pressurized with H_2 gas at 15psi and shaken on a Parr shaker at r.t. for 18h. The solution was filtered through a pad of Celite and washed with excess MeOH. The filtrate was concentrated on a rotory evaporator and the crude product was chromatographed with 4:1 Hexanes:EtOAc to afford 0.008g lactam (86%).

Synthesis of (2R,4S)-4-((1H-indol-3-yl)methyl)-4-hydroxy-5-oxopyrrolidine-2-carboxylic acid **(63)**



0.020 nitrone (0.046 mmole) and 20mg of 20% $Pd(OH)_2$ were dissolved in 0.5mL MeOH. The solution was pressurized with H_2 gas at 15psi and shaken on a Parr shaker at r.t. for 18h. The solution was filtered through a pad of Celite and washed with excess MeOH. The filtrate was concentrated on a rotory evaporator and the crude product was chromatographed with 4:1 Hexanes:EtOAc to afford 0.008g lactam (86%). 1H NMR (400 MHz, cdcl3) δ 8.27 (s, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.46 – 7.18 (m, 7H), 7.17 – 7.00 (m, 2H), 6.92 (d, *J* = 2.2 Hz, 1H), 4.26 (d, *J* = 13.1 Hz, 1H), 4.00 (d, *J* = 13.1 Hz, 1H), 3.77 (t, *J* = 7.4 Hz, 1H), 3.61 (s, 3H), 3.55 (s, 3H), 3.38 (q, *J* = 14.6 Hz, 2H), 3.07 (dd, *J* = 13.0, 8.1 Hz, 1H), 2.77 (dd, *J* = 13.0, 6.9 Hz, 1H).

References

[1] R. Williams, *Aldrichchimica Acta* **1992**, *25*, 11.

[2] A. G. Jamieson, A. Sutherland, C. L. Willis, *Organic & Biomolecular Chemistry* **2004**, *2*, 808.

[3] V. Rolland-Fulcrand, M. Rolland, M. L. Roumestant, J. Martinez, *European Journal of Organic Chemistry* **2004**, 873.

[4] Q. Wang, J. Quazzani, N. A. Sasaki, P. Potier, *European Journal of Organic Chemistry* **2002**, 834.

[5] V. Helaine, J. Bolte, *Tetrahedron-Asymmetry* **1998**, *9*, 3855.

[6] V. Helaine, J. Rossi, T. Gefflaut, S. Alaux, J. Bolte, *Advanced Synthesis & Catalysis* **2001**, *343*, 692.

[7] K. Makino, K. Shintani, T. Yamatake, O. Hara, K. Hatano, Y. Hamada, *Tetrahedron* **2002**, *58*, 9737.

[8] A. Bassoli, G. Borgonovo, G. Busnelli, G. Morini, M. G. B. Drew, *European Journal of Organic Chemistry* **2005**, 1652.

[9] K. Nakamura, T. J. Baker, M. Goodman, *Organic Letters* **2000**, *2*, 2967.

[10] D. D. Oliveira, F. Coelho, *Tetrahedron Letters* **2001**, *42*, 6793.

[11] R. Vleggaar, L. G. J. Ackerman, P. S. Steyn, *Journal of the Chemical Society-Perkin Transactions 1* **1992**, 3095.

[12] G. W. Clough, *Journal of the Chemical Society* **1918**, *113*, 526.

[13] O. Lutz, B. Jirgensons, *Berichte Der Deutschen Chemischen Gesellschaft* **1931**, *64*, 1221.

[14] W. J. Whelan, *Chemistry & Industry* **1965**, 124.

[15] W. A. Konig, K. P. Pfaff, H. H. Bartsch, H. Schmalle, H. Hagenmaier, *Liebigs Annalen Der Chemie* **1980**, 1728.

[16] J. Delzer, H. P. Fiedler, H. Muller, H. Zahner, R. Rathmann, K. Ernst, W. A. Konig, *Journal of Antibiotics* **1984**, *37*, 80.

[17] A. G. M. Barrett, S. A. Lebold, *Journal of Organic Chemistry* **1991**, *56*, 4875.

[18] S. Biondi, A. Pecunioso, F. Busi, S. A. Contini, D. Donati, M. Maffeis, D. A. Pizzi, L. Rossi, T. Rossi, F. M. Sabbatini, *Tetrahedron* **2000**, *56*, 5649.

[19] G. S.p.A., **1992**.

[20] Ciba-Geigy, *Eur. Patent Appl. 279781* **1988**.

[21] H. Ohtake, Y. Imada, S. Murahashi, *Journal of Organic Chemistry* **1999**, *64*, 3790.

[22] R. Huisgen, *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 633.

[23] N. W. Le Bel, J., *J. Am. Chem. Soc.* **1959**, *81*, 6334.

[24] C. M. Brown, K.; Rogers, A.; Tylor, C.; Wright, R., *Proc. Chem. Soc., London* **1960**, 254.

[25] K. Fukui, *Acc. Chem. Res.* **1971**, *4*, 57.

[26] R. Sustmann, *Tetrahedron Letters* **1971**, 2717.

[27] R. S. Huisgen, H.; Bruning, I.;, *Chem. Ber.* **1969**, *102*, 1102.

[28] L. Smith, *Chem. Rev.* **1938**, *23*, 193.

[29] J. M. Hamer, A., *Chem. Rev.* **1964**, *64*, 473.

[30] J. Thesing, H. Mayer, *Chemische Berichte-Recueil* **1956**, *89*, 2159.

[31] J. Thesing, H. Mayer, *Annalen Der Chemie-Justus Liebig* **1957**, *609*, 46.

[32] A. Goti, L. Nannelli, *Tetrahedron Letters* **1996**, *37*, 6025.

[33] R. Huisgen, *1,3-Dipolar Cycloaddition Chemistry* **1984**, *1*, 1.

[34] Y. Inouye, J. Hara, H. Kakisawa, *Chemistry Letters* **1980**, 1407.

[35] O. Tamura, N. Mita, N. Kusaka, H. Suzuki, M. Sakamoto, *Tetrahedron Letters* **1997**, *38*, 429.

[36] O. Tamura, T. Okabe, T. Yamaguchi, J. Kotani, K. Gotanda, M. Sakamoto, *Tetrahedron* **1995**, *51*, 119.

[37] S. A. Ali, M. I. M. Wazeer, *Journal of the Chemical Society-Perkin Transactions 2* **1986**, 1789.

[38] S. A. Ali, M. I. M. Wazeer, *Tetrahedron* **1988**, *44*, 187.

[39] N. Katagiri, H. Sato, A. Kurimoto, M. Okada, A. Yamada, C. Kaneko, *Journal of Organic Chemistry* **1994**, *59*, 8101.

[40] P. Greenspan, *Ph.D Dissertation*, Duke University **1989**.

[41] A. S. Anslow, L. M. Harwood, H. Phillips, D. Watkin, *Tetrahedron-Asymmetry* **1991**, *2*, 997.

[42] R. Naef, D. Seebach, *Helvetica Chimica Acta* **1985**, *68*, 135.

[43] R. Polt, D. Seebach, *Journal of the American Chemical Society* **1989**, *111*, 2622.

[44] S. Kanemasa, T. Uemura, E. Wada, *Tetrahedron Letters* **1992**, *33*, 7889.

[45] S. Kanemasa, T. Tsuruoka, E. Wada, *Tetrahedron Letters* **1993**, *34*, 87.

[46] S. Kanemasa, T. Tsuruoka, *Chemistry Letters* **1995**, 49.

[47] O. Tamura, T. Shiro, M. Ogasawara, A. Toyao, H. Ishibashi, *Journal of Organic Chemistry* **2005**, *70*, 4569.

[48] C. W. Holzapfel, K. Bischofberger, J. Olivier, *Synthetic Communications* **1994**, *24*, 3197.

[49] K. Nakamura, T. J. Baker, M. Goodman, *Organic Letters* **2000**, *2*, 4269.

[50] S. W. Baldwin, A. Long, **2004**, pp. 104.

[51] D. O. Keirs, K., *Heterocycles* **1989**, *28*, 841.

[52] U. L. Spitzer, D., *Can. J. Chem* **1975**, *53*, 2865.

[53] P. K. Carlsen, T.; Martin, V.; Sharpless, K.B., *J. Org. Chem.* **1981**, *46*, 3936.

[54] S. M. Murahashi, H.; Shiota, T.; Tsuda, T.; Watanabe, S., *J. Org. Chem.* **1990**, *55*, 1736.

[55] B. R. Haug, D., *Org. Lett.* **2004**, *6*, 4783.

[56] H. K. Tokuyama, T.; Fukuyama, T., *Organic Syntheses* **2003**, *80*, 207.

[57] D. V. Lu, R., *Bioorg. and Med. Chem. Lett.* **2007**, *17*, 5614.

[58] N. A. Hashimoto, T.; Shioiri, T., *Chem. Pharm. Bull.* **1981**, *29*, 1475.

[59] S. L. Drewes, G.; Roos, G., *Syn. Comm.* **1987**, *17*, 291.

[60] T. V. Turki, J.; Amri, H., *Tet. Lett.* **2005**, *46*, 3071.

[61] K. Sawamura, K. Yoshida, A. Suzuki, T. Motozaki, I. Kozawa, T. Hayamizu, R. Munakata, K. Takao, K. Tadano, *Journal of Organic Chemistry* **2007**, *72*, 6143.

[62] R. D. Larsen, E. G. Corley, P. Davis, P. J. Reider, E. J. J. Grabowski, *Journal of the American Chemical Society* **1989**, *111*, 7650.

[63] Y. Tokunaga, M. Ihara, K. Fukumoto, *Tetrahedron Letters* **1996**, *37*, 6157.

[64] B. Baruah, D. Prajapati, A. Boruah, J. S. Sandhu, *Synthetic Communications* **1997**, *27*, 2563.

[65] P. U. Wovkulich, M., *Tetrahedron* **1985**, *41*, 3455.

[66] Q. H. Zhao, F.; Romero, D., *J. Org. Chem.* **2002**, *67*, 3317.

[67] S. P. Desvergnes, S.; Vallee, Y., *J. Org. Chem.* **2005**, *70*, 1459.

[68] J. C. Revuelta, S.; Brandi, A., *Tet. Lett.* **2004**, *45*, 8375.

[69] D. S. Zhang, C.; Miller, M., *J. Org. Chem.* **1998**, *63*, 885.

[70] S. G. Cicchi, A.; Brandi, A.; Guarna, A.; Sarlo, F., *Tet. Lett.* **1990**, *31*, 3351.

[71] A. P. Dondoni, D., *Tetrahedron* **2003**, *59*, 4261.

[72] S. R. Cicchi, J.; Zanobini, A.; Betti, M.; Brandi, A., *Synlett.* **2003**, 2305.

[73] H. K. Iida, K.; Kibayashi, C., *J. Am. Chem. Soc.* **1986**, *108*, 4647.

[74] W. K. Still, M.; Mitra, A., *J. Org. Chem.* **1978**, *43*, 2923.

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