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OXADIAZINONES AS CHIRAL AUXILIARIES: CHIRAL TEMPLATES FOR
ASYMMETRIC CONJUGATE ADDITION IN THE SYNTHESIS
OF (*R*)-(+)-TOLTERODINE

FATIMA OLAYEMI OBE

171 Pages

The stereoselective formation of carbon-carbon bonds through the process of conjugate addition has proven to be a very important methodology in synthetic organic chemistry. In this context, oxadiazinones are chiral auxiliaries that have been applied in the asymmetric aldol addition reaction to synthesize valuable synthetic fragments such as the aldol side chain of the multi-drug resistance medicinal agent, hapalosin. This thesis describes efforts that were directed towards employing oxadiazinones as chiral scaffolds for the process of asymmetric conjugate addition with the ultimate objective of using this methodology in the preparation of medicinal agents such as Tolterodine. Preliminary efforts focused on using an *N*₄-*p*-methoxybenzyl substituted oxadiazinone to achieve these goals. This oxadiazinone was acylated with *trans*-cinnamic acid via the Steglich reaction with 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) and catalytic *N,N*-dimethylamino pyridine (DMAP). This substrate was then reacted with a Normant reagent, a mixture of the Grignard reagent, methylmagnesium bromide and copper (I) bromide-dimethylsulfide complex. The diastereoselectivity of the conjugate addition product was determined by analysis of the 500 MHz ¹H NMR spectrum to be no greater than 3:1, a value unsuitable for meaningful asymmetric synthesis. This observation was in contrast to higher stereoselectivities observed in the asymmetric aldol reaction with *Ephedra* based oxadiazinones

where ratios of 95:5 are commonly observed. To resolve this issue, a new series of oxadiazinones were designed, namely N₄-isopropylloxadiazinone and N₄-*p*-diphenylmethyloxadiazinone. The observed diastereoselectivity of the asymmetric conjugate addition for the N₄-isopropylloxadiazinone was lower. This reinforced the idea that the diastereoselectivity was being influenced by the conformational dynamics of the ring system and not just the N₄-substituent. This thesis will describe the chemistry that has been accomplished to this point and make projections for future efforts in the synthesis of the medicinally valuable target compound, tolterodine (Detrol).

KEYWORDS: Chiral Auxiliaries; oxadiazinones; Acylation; Asymmetric; Conjugate Addition; Tolterodine

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FATIMA OLAYEMI OBE

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

MASTER OF SCIENCE

Department of Chemistry

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2020

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OF (*R*)-(+)-TOLTERODINE

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CHAPTER I: INTRODUCTION

The term chirality comes from the Greek word “*kheir*-, hand” which implies “handedness”.¹ Chiral molecules have the ability to exist in right- and left-hand forms and are categorized under a broad class of isomers known as stereoisomers. Stereoisomers are molecules with the same molecular and structural formulae but differ in the spatial arrangement of the atoms. This isomerism is a result of the presence of an atom, often a carbon atom, in the molecule, that is connected to four unique substituents. Such atoms are called chiral centers or stereocenters. If two stereoisomeric molecules are mirror images of each other and are not superimposable, they are referred to as enantiomers. However, if the stereoisomeric molecules cannot be related by a mirror plane, they are known as diastereomers. Enantiomers and diastereomers have major differences. While enantiomers may have one or more chiral centers, diastereomers that possess chirality must have at least two chiral centers. In addition, although enantiomers rotate plane polarized light in equal magnitude but opposite directions, they exhibit the same physical and chemical properties. In contrast, diastereomers usually differ in their physical and chemical properties, a characteristic exploited in this thesis project. Because enantiomers have identical enthalpies and entropies from when they arise from chemical reactions, they are usually obtained in equal amounts and this mixture is called a “racemic mixture”.² Based on how the four unique substituents are arranged in space around the chiral centers of each enantiomer, they are described as either *R*-isomer or *S*-isomer.

The importance of selectively synthesizing one enantiomer over the other in a biologically active molecule cannot be overemphasized. Due to identical composition and functional groups, enantiomers may exhibit similar chemical and physical properties, yet, they

may differ in their medicinal efficacy in biological environments.³ This is directly linked with the ability of naturally occurring biomolecules such as enzymes to discriminate between different enantiomers due to the intrinsic chirality of enzymes.⁴ In fact, most biomolecules that make up our body systems are chiral in nature (Figure 1).⁵ For instance, proteins are composed of α -amino acids, most of which are chiral in nature. These biomolecules make up receptors in the human body and these receptors could be highly stereoselective.

Figure 1. Chirality and biomolecules.

As a result, a particular enantiomeric molecule may strongly interact with a biological receptor while the other enantiomer may only have a weak interaction (Figure 2).⁶ The implication of this is that one enantiomer of a drug may be effective in treating a certain disease while the other enantiomer may be weakly therapeutic, inactive, or toxic. In such cases, the active enantiomer is known as a *eutomer* while the inactive enantiomer is known as a *distomer*.

Figure 2. Enantioselectivity of biological receptors.

There are numerous examples of drugs that fall into this category (Figure 3); Albuterol is a block buster drug that is sold as a racemic mixture and used in anti-asthmatic inhalant. The (*R*)-isomer is the major active ingredient of the drug while the (*S*)-Albuterol (**1**) is significantly less effective.⁷ Another example is an antidepressant drug sold under the trade name Zoloft (**2**) which belongs to a group of compounds known as the aminotetralins.⁸ The (*1R,4S*)-enantiomer of Zoloft is the eutomer while the (*1S,4R*)-enantiomer has no activity against depression. In the same vein, (*R*)-penicillamine (**3**) is an antidote against metal poisoning while the opposite enantiomer is capable of causing total blindness.⁹

Figure 3. Examples of eutomers (pharmacologically active enantiomers).

The fact that stereochemistry has a direct influence on the potency and sometimes, on the toxicity of the drugs,¹⁰ makes it important to consider the pharmacological effects of drugs in their two enantiomerically pure forms and as the racemic mixture. Consequently, the topic under discussion possesses high relevance in the pharmaceutical industry.

Of all the cases of different side effects associated with the use of a drug as a racemic mixture ever reported, the most catastrophic of all is the thalidomide incident which occurred in the 1950s.^{11,12} Thalidomide (Figure 4) was a drug synthesized by a German pharmaceutical company known as Grünenthal Chemie in the 1950s. The drug was primarily distributed in Germany, Australia and Canada and was reported further distributed in more than 46 countries. The drug was administered to pregnant women with the sole aim of suppressing morning sickness. It was ultimately discovered that those women who took thalidomide gave birth to deformed babies. Some babies were born with deformed arms and legs, some had deformed faces while some were too deformed to survive. About 2,000 deaths were recorded as a result of thalidomide and more than 10,000 deformed babies were reported.¹³

Figure 4. The (*S*)-enantiomer (left) and the (*R*)-enantiomer of thalidomide.

Nearly two decades after the onset of the thalidomide tragedy, researchers unraveled the mystery behind the incident.^{14a} It was noted that the drug was sold as a racemic mixture of the (*R*)- and (*S*)-enantiomers as illustrated in Figure 4. The (*R*)-enantiomer (**4b**) has a sedative effect, relieving pregnant women of morning sickness while the (*S*)-enantiomer (**4a**) is a teratogen that interferes with fetal development. It was initially thought that the individual enantiomers could be separated so that there could still be therapeutic value for pregnant women dealing with morning sickness. Unfortunately, the (*R*)- and (*S*)-enantiomers interconvert *in vivo* thereby making the separation of enantiomers of no practical value (Scheme 1).^{14b}

Scheme 1. Racemization of Thalidomide in a biological environment.

A study conducted in Brazil in 2016 and reported in the *European Journal of Medical Genetics* showed that thalidomide children are still being born yearly.^{14c} Even though the World Health Organization (WHO) initially withdrew the drug from the market, its sale was later allowed due to its effectiveness in treating other diseases such as leprosy. It was proposed by the authors that the availability of thalidomide to pregnant women in Brazil trying to manage leprosy symptoms led to the birth of numerous deformed children in 2016.

Thalidomide is a paramount example of the importance of molecular chirality in pharmaceutical agents. Even though there is no value in isolating the individual enantiomers, it is

an important lesson in the differing levels of biological activity of enantiomers. Reactions that are designed to selectively form one enantiomer over the other are collectively known as stereoselective reactions. Such reactions can be further described as being *asymmetric reactions* or *asymmetric syntheses*.

Asymmetric synthesis involves inducing chirality into a substrate, preferentially forming one stereoisomer over the other; this process is formally known as asymmetric induction. One way of achieving asymmetric synthesis is through the use of compounds known as chiral auxiliaries. Chiral auxiliaries are organic compounds with pre-existing fixed chiral centers. They therefore assist in preferentially establishing the stereochemistry of a new chiral center in molecules. As such, the usage of chiral auxiliaries has been proven to be an effective tool in controlling asymmetry in a wide variety of reactions.¹⁵ Beyond this, the stereoselective formation of carbon-carbon bonds through the process of asymmetric conjugate addition has proven to be a very important methodology in synthetic organic chemistry.¹⁶⁻¹⁸ The use of chiral auxiliaries to guide the stereoselective bond formation has continued to be a reliable methodology for obtaining products in high diastereoselectivity (Figure 5).

Koga's lactam (**6**) was one of the first chiral auxiliaries successfully used in the process of asymmetric conjugate addition.¹⁹ The diastereoselectivities for this process were high, but the chiral auxiliary did not offer the practicality of ease of preparation. This auxiliary would be followed by the more successful application of Oppolzer's sultam (**7**).²⁰⁻²⁴ The sultam is based on the D-camphor template and has proven to be applicable in a variety of conjugate addition applications. Another chiral auxiliary that has been employed for the process of asymmetric conjugate addition is Chiacchio and Romeo's bicyclic sultam (**8**).²⁵ While not as employed to the

same degree as Oppolzer's sultam, the bicyclic sultam template was still successful in its applications.

Figure 5. Chiral auxiliaries for diastereoselective conjugate addition reactions.

Badía and coworkers²⁶⁻²⁹ developed a more practical chiral auxiliary based on using Myers' (1*S*,2*S*)-pseudoephedrine (**9**)^{30a,b} template as a chiral template for asymmetric conjugate addition. While this chiral template has proven to be very useful, the dominant chiral auxiliary that has been employed in chiral auxiliary mediated asymmetric conjugate additions is the Evans' oxazolidinone (**10**).³¹⁻³⁸ The Evans' auxiliary has proven to be the most versatile of all of the auxiliaries presented here. While catalytic asymmetric conjugate addition methods are continuing to increase in their applications, the Evans' oxazolidinone remains as a viable option to achieve asymmetric synthetic ends. In this context, in 2019, Ortiz and coworkers^{39,40} were able to synthesize a series of gamma-amino acids by this methodology (Scheme 2).

Scheme 2. The Ortiz asymmetric application of the Evans' oxazolidinone.

Also, Takayama and coworkers employed the Evans' oxazolidinone in the synthesis of the *Lycopodium* alkaloid Lycopoclavamine-A via an asymmetric conjugate addition (Scheme 3).⁴¹

Scheme 3. The Takayama asymmetric application of the Evans' oxazolidinone.

The most commonly used of the Evans' chiral auxiliary are derived from naturally occurring compounds such as L-phenylalanine (**18**) and L-valine (**20**) and some unnatural α -amino acids such as L-phenylglycine (**19**), L-*tert*-leucine (**21**) and modified L-serine (**22**) (Figure

6). The use of the Evans' chiral auxiliary in asymmetric synthesis follows a general pathway of acylation and conjugate addition reactions (Scheme 4).³¹⁻³⁶ For the oxazolidinones, the C₄-position is the stereochemical controlling element.

Figure 6. Various amino acids source for the Evans' oxazolidinones formation.

Scheme 4. General pathway for asymmetric synthesis using the Evans' oxazolidinones.

Several researchers have carried out structural modifications on the Evans' five-membered-ring oxazolidinone by varying the substituent at the C₄-position with the goal of achieving an improved diastereoselectivities (Figure 7).⁴²⁻⁴⁸

Figure 7. Structural modifications to the Evans' chiral auxiliary.

Some of the structural modifications include the introduction of diphenyl methyl group by Sibi and coworkers (**29**), introduction of a polymer backbone by Abell *et al.* (**31**), introduction of sulfur analog by Crimmins *et al.* (**32**), conversion into a bicyclic structure by de Parrodi *et al.* (**33**) and so on. However, the original Evans' oxazolidinone developed in the early 1980s (**18**) has withstood the test of time as it was recently used by Williams and coworkers in their synthesis of *Baulamycin A* recently published in the *Journal of Organic Chemistry* in January 2020.⁴⁹

The successful application of the Evans' auxiliary in numerous conjugate addition applications served as the impetus for the proposed research described herein. There was an interest in conducting asymmetric conjugate addition reactions, but it was decided to take a different route other than modifying the classical oxazolidinones. This led us to a six-membered ring class of compounds known as the oxadiazinones (**34**). In this context, oxadiazinones are chiral auxiliaries that are structurally related to the Evans' oxazolidinone as aza-homologs. Oxadiazinones represent a class of heterocycles that were first prepared by the Dow Chemical Company in a research program led by Trepanier and coworkers^{50,51} in the 1960s. The goal of synthesizing the oxadiazinones by Dow was not for it to be used as a chiral auxiliary. Rather, it was meant to serve as a therapeutic agent. It was tested against Parkinson disease and some cardiovascular diseases, of which in both cases, it was found ineffective. As a result, literature references concerning the *Ephedra* based oxadiazinones became sparse from the chemical literature for about two decades. Not until the late 1990s when it was employed by Husson and coworkers in diastereoselective alkylations (**35**)⁵² and asymmetric dipolar cycloadditions (**36**)^{53,54} (Figure 8).

Figure 8. Examples of chiral oxadiazinones.

Our research group first utilized the oxadiazinones as chiral auxiliaries in the early 2000s where they were applied as chiral auxiliaries in the asymmetric aldol addition reaction (Scheme

5).^{55,56} The success of the asymmetric induction in the oxadiazinone mediated aldol reaction is believed to be due to the stereogenic N₄-nitrogen which serves at the stereochemical control element guiding the reaction.

Scheme 5. Oxadiazinones in the asymmetric aldol addition reaction.

This is partially based on the fact that the observed diastereoselectivities for the asymmetric aldol reaction ranges from 3:1 to 99:1 when the N₄-substituent is a methyl group, and ranges from 10:1 to 99:1 when the N₄-substituent is a much larger isopropyl group. The conformation and the configuration of the N₄-nitrogen is a result of chiral relay where stereochemical information is relayed from the C₅ and C₆ positions of the oxadiazinone ring system. An X-ray crystal structure for aldol adduct (Figure 9) was obtained and serves to suggest that it is the N₄-position that directs the stereochemistry of the aldol process.

Figure 9. Chiral relay in oxadiazinone mediated asymmetric aldol reactions: X-ray crystal structure.

The high diastereoselectivity achieved with the oxadiazinones in the asymmetric aldol addition reaction suggested that this chiral auxiliary could be employed as well as chiral templates in asymmetric conjugate addition reactions. Thus, the proposed research would follow the same reaction pathway as the oxazolidinones of Evans' in the use of oxadiazinones as chiral auxiliaries (Scheme 6). Should the oxadiazinone-guided asymmetric conjugate addition reaction be successful, then it will be employed as a chiral template in the synthesis of the medicinal agent tolterodine.

Scheme 6. General pathway of conjugate addition reaction with the oxazolidinone and proposed conjugate addition pathway with the oxadiazinones.

Tolterodine (**45**) (Figure 10) is a medicinal agent distributed under the trade name Detrol and sold by Pfizer, Inc. It belongs to a class of drugs known as antispasmodics used in countering involuntary contraction of muscles. Tolterodine is specifically used in the treatment of overactive bladder. It helps in relaxing the muscles in the bladder and thereby improves the patient's ability to control urination. It helps in reducing urine leakage, feelings of frequent urination and ultimately prevent frequent bathroom visits.^{57,58}

Figure 10. Tolterodine

Tolterodine (Detrol), **45**

It is proposed that tolterodine will be synthesized following the general pathway of acylation using the Steglich reaction (Figure 11). This will involve the acylation of the heterocycle (**34**) with *trans*-cinnamic acid to obtain the acylated oxadiazinone (**43**) followed by conjugate addition reaction with a Normant reagent (copper bromide dimethyl sulfide and 2-benzyloxy-5-methyl phenylmagnesium bromide, **46**) to create the conjugate addition product (**47**) with a new chiral center. This will then be subjected to hydrolysis to cleave off the chiral auxiliary and obtained the carboxylic acid (**48**). The carboxylic acid can then be taken through the Steglich reaction with diisopropylamine to obtain the intermediate **49** which will then be reduced and deprotected to obtain the tolterodine (**45**).

Scheme 7. Proposed pathway for tolterodine synthesis using the oxadiazinones as chiral templates.

In summary, this chapter has presented the importance of molecular chirality in bioactive molecules, and why it is important that medicinal agents are carefully evaluated for the properties of their enantiomers and racemic mixtures. Oxazolidinones have also been discussed as the mostly used chiral auxiliary in asymmetric synthesis to date. Likewise, the use of oxadiazinones as structurally novel chiral auxiliaries in the asymmetric aldol addition reaction have been discussed. The goal of this research is to apply these oxadiazinones in the synthesis of the medicinal agent tolterodine (Detrol), through asymmetric conjugate addition reaction.

CHAPTER II: OXADIAZINONES AS CHIRAL AUXILIARIES IN ASYMMETRIC CONJUGATE ADDITION REACTIONS

Introduction

As stated in Chapter I, the oxadiazinones have proven to be effective tools for conducting chiral auxiliary-directed asymmetric aldol addition reactions. The oxadiazinones that have been employed have relied primarily on the N₄-substituent as the stereochemical control element leading to the observed diastereoselection in the asymmetric aldol addition reaction. This chapter explores the use of the chiral oxadiazinones in the process of asymmetric conjugate addition reactions (Figure 11). The oxadiazinones that will be presented in this chapter will also feature this N₄-substituent as a key element of variation in the pursuit of the best possible diastereoselectivities (Figure 11).

Figure 11. Proposed oxadiazinone mediated asymmetric conjugate addition pathway.

Results and Discussion

Ephedrine based oxadiazinones, synthesis, acylation and asymmetric conjugate addition

The conjugate addition project began with the same ephedrine based oxadiazinone that launched the asymmetric aldol addition project that was described in Chapter 1. The (1*R*,2*S*)-ephedrine based oxadiazinone (**34**) was synthesized in a three-step reaction: N-nitrosation, lithium aluminum hydride reduction, and cyclization (Scheme 8). The (1*R*,2*S*)-ephedrine (**52**) starting material was reacted with sodium nitrite (NaNO₂) in the presence of aqueous hydrochloric acid (HCl, 3M) and tetrahydrofuran (THF) to give the N-nitrosamine target (**53a** and **53b**) as a mixture of *E*- and *Z*-diastereomers in a yield of 95%. The (1*R*,2*S*)-ephedrine based N-nitrosamine thus obtained was reacted with the reducing agent lithium aluminum hydride (LiAlH₄) using THF as solvent. This afforded the (1*R*,2*S*)-ephedrine based hydrazine (**54**) in a 93% yield. The hydrazine product was immediately taken through a cyclization reaction with carbonyldiimidazole (CDI) (**55**) in the presence of THF to give the target (1*R*,2*S*)-ephedrine based oxadiazinone (**34**) as a white solid in a 74% yield.

Scheme 8. Synthesis of (1*R*,2*S*)-ephedrine based oxadiazinone **25**.

The mechanisms of these reactions are shown in Schemes 9-11. The N-nitrosation follows the standard pathway for the N-nitrosation of a secondary amine in which nitrous acid is generated *in situ* and reacted with the ephedrine substrate (Scheme 9). The lithium aluminum hydride reduction involves the formation of hydrogen gas as the initial step with subsequent attack of the hydride on the nitrosamine functional group (Scheme 10). The process ultimately yielded the desired ephedrine-based hydrazine. The hydrazine in turn reacted with carbonyldiimidazole through a series of nucleophilic addition/elimination pathways to form the target ephedrine based oxadiazinone.⁵⁹

Scheme 9. The N-nitrosation reaction mechanism for the formation of compound **53**.

Nitrous acid formation

N-Nitrosation

Scheme 10. The lithium aluminum hydride reduction reaction mechanism for the formation of compound **54**.

Scheme 11. The cyclization reaction mechanism for the formation of compound **34**.

The (1*R*,2*S*)-ephedrine based oxadiazinone (**34**) thus obtained was acylated following the method of Steglich and coworkers,⁶⁰ in which the heterocycle was reacted with *trans*-cinnamic acid (**56**) in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) (**57**), and 4-(dimethylamino)pyridine (DMAP) catalyst (**58**) to afford the N₃-cinnamoyloxadiazinone (**43**) in a 71% yield after chromatography purification (Scheme 12). With this material in hand, the asymmetric conjugate addition reaction was carried out using the Normant conditions.^{61,62} Thus, the acylated oxadiazinone (**43**) was treated with a mixture of methylmagnesium bromide and copper bromide-dimethylsulfide complex to yield the conjugate addition product in a 65% isolated chemical yield after chromatographic purification. The reaction mechanisms for the acylation and conjugate addition reactions are shown in Schemes 13 and 14, respectively.

Scheme 12. Acylation and conjugate addition with the (1*R*,2*S*)-ephedrine based oxadiazinone for the formation of compound **59**.

Scheme 13. Mechanism of reaction for the oxadiazinone acylation for the formation of compound **43**.

Scheme 14. Mechanism of reaction for the asymmetric conjugate addition reactions^{63,64} leading to the formation of compound **59**.

This reaction generated a mixture of diastereomeric products (**59a** and **59b**) in a ratio of 5.1:1 in favor of the major diastereomer as determined by 500 MHz ^1H NMR spectroscopy (Figure 12). The major diastereomer was tentatively assigned as the (*R*)-diastereomer (**59a**) based on the stereochemical orientation of the N_4 -methyl group.

Figure 12. 500 MHz ^1H NMR spectrum of the conjugate addition product of (1*R*,2*S*)-ephedrine based oxadiazinone.

Stereochemistry determination of (1R,2S)-ephedrine conjugate addition product through classical resolution

The stereochemistry of the diastereomeric products of the conjugate addition reaction with the (1R,2S)-ephedrine based oxadiazinone was determined through the use of classical resolution (Scheme 15).^{65,66} This was accomplished by reacting 5.24 grams of racemic mixture of a commercially sourced 3-phenylbutyric acid (**60a** and **60b**) with an enantiomerically pure chiral amine, (S)-(-)-phenylethylamine (**61**). This reaction generated a mixture of diastereomeric carboxylate salts (**62a** and **62b**). The generated salts, being diastereomers, differ in their physical and chemical properties. Hence, one of the salts was very soluble in ethanol-water solution while the other salt readily formed fine long needles of white crystals. The crystals were recovered by vacuum filtration and subjected to a second recrystallization using ethanol and water.

The salt (**62b**) obtained from this process was subjected to extraction using aqueous hydrochloric acid (1M) and diethyl ether which aided the recovery of the single diastereomer of the phenyl butyric acid in a 48% isolated recovered yield. (Scheme 16). The optical rotation of the recovered acid was determined by polarimetric analysis to be $[\alpha]_D = +43^\circ$ (75% ee). From the known compound (**60a** and **60b**), the (R)-isomer has a known optical rotation of -57° while the S-isomer has an optical rotation of $+57^\circ$. This suggests that the recovered carboxylic acid was the S-enantiomer of the butyric acid and that the salt that initially came out of the ethanol-water solution was the (S-amine, S-carboxylic acid)-diastereomer (**62b**).

Scheme 15. Stereochemistry determination by classical resolution.

Scheme 16. Stereochemistry determination: polarimetric analysis.

The (*S*)-(+)-3-phenylbutyric acid (**60a**) obtained from the classical resolution was acylated with the (1*R*,2*S*)-ephedrine based oxadiazinone (**34**) using the Steglich reaction conditions (Scheme 17). The acylated product (**63**) obtained was then analyzed by 500 MHz ^1H NMR spectroscopy. The obtained spectrum (Figure 13) was then compared with the 500 MHz ^1H NMR spectrum obtained from the initial ephedrine based oxadiazinone directed conjugate addition reaction (Figure 14).

Scheme 17. Stereochemistry determination: Steglich reaction with the recovered butyric acid.

Figure 13. 500 MHz ^1H NMR spectrum of the product of Steglich reaction between the (1*R*,2*S*)-ephedrine based oxadiazinone and (*S*)-(+)-3-phenylbutyric acid (**60a**).

Figure 14. 500 MHz ^1H NMR spectrum of the conjugate addition product of (1*R*,2*S*)-ephedrine based oxadiazinone.

From the results obtained from the classical resolution, it became clear that the (*S*)-isomer was the major isomer! This was contrary to the initial prediction that the (*R*)-isomer was the major isomer. It then became essential to consider what could be the reason behind the *S*-isomer's domination in this reaction.

Rationale to why the (S)-diastereomer was observed as the major isomer

Following the classical resolution results, a rationalization of the stereochemical outcome had to be made as the observed result was diametrically opposed to the predicted result. It is proposed that if the N₃-acyl side chain is held in place as seen (**65**), then the (*R*)-isomer is expected to be the dominant isomer. However, if there is a flexibility around the α -carbon, such that the acyl side chain is rotated downward as shown (**64**), then the (*S*)-isomer becomes the dominant isomer. There may be other potential transition states that give rise to the observed stereochemical outcome. Ultimately, the diastereoselectivity observed for this system (5.1:1) is below the desired diastereoselectivity ratio desired for this work. As such, another family of the *Ephedra* alkaloid, namely (1*S*,2*S*)-pseudoephedrine, was considered.

Scheme 18. Rationale for the observed stereoselectivity in the ephedrine-based system.

In a bid to improve the diastereoselectivity of the oxadiazinones in asymmetric conjugate addition reaction, the (1*S*,2*S*)-pseudoephedrine based oxadiazinone (**70**) was also examined. This oxadiazinone was synthesized by reacting the (1*S*,2*S*)-pseudoephedrine substrate (**67**) with sodium nitrite in the presence of hydrochloric acid (3M) and tetrahydrofuran (THF) to give the N-nitrosamine diastereomers (**68a** and **68b**) in near quantitative yield of 97%. The N-nitrosamine product was then reacted with LiAlH₄ in the presence of THF to afford the hydrazine (**69**) with a near quantitative yield of 99%. The hydrazine was, in turn, reacted with carbonyldiimidazole to give the (1*S*,2*S*)-pseudoephedrine based heterocycle (**70**) in a 74% yield (Scheme 19).

Scheme 19. Synthesis of the (1*S*,2*S*)-pseudoephedrine based oxadiazinone **70**.

With the pseudoephedrine heterocycle (**70**) in hand, a Steglich reaction (Scheme 20) was conducted in which *trans*-cinnamic acid was coupled with the heterocycle using the coupling agent EDC and DMAP catalyst to afford the corresponding N₃-*trans*-cinnamoyloxadiazinone (**71**) in a 59% yield after chromatography purification.

Scheme 20. Acylation of the (1*S*,2*S*)-pseudoephedrine based oxadiazinone.

The purified N₃-*trans*-cinnamoyloxadiazinone (**71**) was then subjected to Normant-Grignard addition reaction (Scheme 21) to yield the corresponding N₃-(3-methyl hydrocinnamoyl) oxadiazinone as a mixture of diastereomers (**72a** and **72b**) in a 79% yield after chromatography.

Scheme 21. Asymmetric conjugation addition with the (1*S*,2*S*)-pseudoephedrine-N₃-cinnamoyloxadiazinone.

The diastereoselection ratio was determined by the use of 500 MHz ¹H NMR spectroscopy (Figure 15) to be 3.4:1, with the *R*-isomer (**72a**) assigned as the major diastereomer tentatively.

Figure 15. 500 MHz ^1H NMR spectrum of the conjugate addition product of (1*S*,2*S*)-pseudoephedrine system.

Apart from lower diastereoselectivity observed relative to the (1*R*,2*S*)-ephedrine system, there was also a line broadening of one of the diagnostic peaks in the 500 MHz ^1H NMR spectrum of the pseudoephedrine based oxadiazinone directed conjugate addition products (**72a**, **b**) (Figure 14). This led to a follow-up investigation of the starting material (**71**) for this reaction. A ^{13}C NMR spectral analysis was carried out on the acylated starting material for both the (1*R*,2*S*)-ephedrine based oxadiazinone (**43**) and the (1*S*,2*S*)-pseudoephedrine based oxadiazinone (**71**). The spectra obtained for the two compounds (Figure 16), suggested that the ephedrine-based compound (**43**) is conformationally rigid while the pseudoephedrine-based system (**71**) in

conformationally flexible, which could be the reason for the lower diastereoselectivity observed in relation to the ephedrine-based system.

Figure 16. 125 MHz ^{13}C NMR spectra comparing the conformational rigidity of the ephedrine based oxadiazinone (**43**, top) and the pseudoephedrine based oxadiazinone (**71**, bottom) systems.

As a result of the low diastereoselectivity and the conformational flexibilities exhibited by the pseudoephedrine-based system, another member of the *Ephedra* family, the (1*R*,2*S*)-norephedrine based N₄-*para*-methoxybenzyloxadiazinone was also considered. It was projected that the larger group at the N₄-position would significantly improve the diastereoselectivity of the oxadiazinone.

In pursuit of an improved diastereoselectivity in the asymmetric conjugate addition synthesis, a norephedrine based oxadiazinone (**73**) was also employed (Figure 17). In this case, the N₄-substituent (stereochemical control element) would be a *para*-methoxybenzyl (PMB) group, a group that was believed would aid in improving diastereoselectivity due to its larger steric demand compared to the N₄-methyl group. This *para*-methoxy-benzyl- substituted oxadiazinone was synthesized from the (1*R*,2*S*)-norephedrine precursor (**74**) (Figure 18).

Figure 17. The *Ephedra* based oxadiazinones.

Figure 18. The *Ephedra* alkaloids as the key starting materials for the formation of the oxadiazinones.

The synthesis follows similar reaction pathway as the ephedrine and pseudoephedrine-based systems (Scheme 22). However, prior to the N-nitrosation reaction, the (1*R*,2*S*)-norephedrine was subjected to reductive amination with *para*-methoxybenzaldehyde (**74**) in the presence of ethanol absolute to introduce the -PMB group. The reaction was later brought to completion through the addition of sodium borohydride (NaBH₄) as shown the reaction mechanism (Scheme 23) leading to the formation of the amino alcohol (**75**). Without further purification, the α-amino alcohol was immediately converted to the corresponding N-nitrosamine (**76**) in a 95% yield through reaction with sodium nitrite in the presence of aqueous HCl (3M) and THF. With the N-nitrosamine in hand, a lithium aluminum hydride (LiAlH₄) reduction was carried out using THF as the solvent. This led to the isolation of the corresponding hydrazine (**77**) in a 90% yield. The hydrazine was then reacted with carbonyldiimidazole using THF as solvent. This yielded the (1*R*,2*S*)-norephedrine based N₄-*p*-methoxybenzyl oxadiazinone (**73**) in a 47% yield.

Scheme 22. Synthesis of the (1*R*,2*S*)-norephedrine-N₄-*p*-methoxybenzyl oxadiazinone, **73**

Scheme 23. Reductive amination reaction mechanism for the formation of N₄-*p*-methoxybenzyl amino alcohol, **75**.

To determine if the steric volume of the incoming group would have an impact on the diastereoselectivities of the conjugate addition reactions, the *para*-methoxybenzyl oxadiazinone (**73**) was taken through two different acylation pathways (Scheme 24). In the first reaction (Scheme 24a), the heterocycle was acylated with *trans*-cinnamic acid using the Steglich reaction conditions to give the (1*R*,2*S*)-norephedrine based N₄-*p*-methoxybenzyl-N₃-cinnamoyl oxadiazinone (**78**) in an 80% yield. In this case, methyl magnesium bromide (CH_3MgBr) would be employed as the Grignard reagent for the conjugate addition reaction. In the second reaction pathway (Scheme 24b), on the other hand, the heterocycle was acylated with *trans*-crotonylchloride (**79**) in the presence of sodium hydride (NaH) base and THF to yield the (1*R*,2*S*)-norephedrine based N₄-*p*-methoxybenzyl-N₃-crotonyl oxadiazinone (**80**) in a 51% yield.

Here, the conjugate addition reaction would be conducted using phenyl magnesium bromide (PhMgBr) as the Grignard reagent.

Scheme 24. Acylation reactions with the (1*R*,2*S*)-norephedrine based oxadiazinone using (a) *trans* cinnamic acid and (b) *trans*-crotonyl chloride, for the formation of the acylated products **78** and **80**.

With the acylated products in hand, the (1*R*,2*S*)-norephedrine based N₄-*p*-methoxybenzyl-N₃-cinnamoyl oxadiazinone (**78**) was taken through asymmetric conjugate addition reaction (Scheme 25) using copper bromide dimethyl sulfide (CuBr • S(CH₃)₂) and methyl magnesium bromide (CH₃MgBr) (the Normant reagent) to give the conjugate addition product (**81**) as a mixture of diastereomers (**81a** & **81b**) in a 62% yield. In this case, a methyl group was added to the unsaturated side chain to create a new chiral center.

Scheme 25. Asymmetric conjugation addition in the formation of compound **81**.

Scheme 26. Asymmetric conjugate addition in the formation of compound **82**.

Likewise, the (1*R*,2*S*)-norephedrine- N_4 -*p*-methoxybenzyl- N_3 -crotonyloxadiazinone (**80**) was subjected to an asymmetric conjugate addition reaction (Scheme 26) using copper bromide dimethyl sulfide ($\text{CuBr} \cdot \text{S}(\text{CH}_3)_2$) and phenyl magnesium bromide (PhMgBr) to give the conjugate addition product (**82**) as a mixture of diastereomers (**82a** and **82b**) in a 52% yield. Here, the incoming group added to the unsaturated side chain was the more sterically demanding phenyl group. Both conjugate addition products (**81** and **82**) were analyzed by 500 MHz proton NMR spectroscopy.

The (1*R*,2*S*)-norephedrine- N_4 -*p*-methoxybenzyl- N_3 -(3-phenylbutanoyl) (**81**) gave a diastereomeric ratio of 2.9:1 in favor of the major diastereomer (Figure 19). The (1*R*,2*S*)-norephedrine based N_4 -*p*-methoxybenzyl- N_3 -(3-phenylbutanoyl) (**82**) also gave a diastereomeric ratio of 2.9:1 in favor of the major diastereomer (Figure 20). This implies that the steric volume of the incoming group has no direct impact on the stereoselectivities of the asymmetric conjugate addition reactions.

Figure 19. 500 MHz ^1H NMR spectrum of the (1*R*,2*S*)-norephedrine based N_4 -*p*-methoxybenzyl- N_3 -(3-phenylbutanoyl) oxadiazinone (**81**).

Figure 20. 500 MHz ^1H NMR spectrum of the (1*R*,2*S*)-norephedrine based N_4 -*p*-methoxybenzyl- N_3 -(3-phenylbutanoyl) oxadiazinone (**82**).

Based on the stereochemical orientation of the N₄-*p*-methoxybenzyl group (the stereochemical control element), the (*R*)-isomer (**81a**) was assigned the major diastereomer in the case of the cinnamoyl system while the (*S*)-isomer (**82a**) was assigned the major diastereomer in the case of the crotonyl system.

*Stereochemistry determination of (1*R*,2*S*)-norephedrine conjugate addition product through hydrolysis*

To establish the stereochemical orientation of the major and minor isomers of the norephedrine system, the addition product (**81**) was subjected to oxidative hydrolysis using ceric ammonium nitrate (Ce(NH₄)₂(NO₃)₆ and acetonitrile (CH₃CN) in an aqueous medium to recover the acyl side chain of the conjugate addition products (Scheme 27).

Scheme 27. The norephedrine stereochemistry determination by hydrolysis and polarimetric analysis.

The phenyl butyric acid side chain (**84**) was isolated from this reaction in a 22% yield after chromatography purification. The recovered acid was then taken through polarimetric analysis giving an optical rotation of +22° (39% ee), suggesting that the (*S*)-isomer is also the major isomer in this case, contrary to the predicted *R*-isomer.

Rationale for the low diastereoselectivities and stereochemical orientation of the major isomer

As stated earlier, just as in the case of the ephedrine based oxadiazinone (**59**), the major isomer for the norephedrine-based system turned out to be the (*S*)-isomer as against the (*R*)-isomer which was predicted based on the stereochemical orientation of the N₄-*para*-methoxybenzyl group. To rationalize this observation, the acylated starting material (**78**) was analyzed by 125 MHz ¹³C NMR (Figure 21). The analysis suggested that the acylated starting material is conformationally rigid. This was evident in the distinct peaks present in the alkyl carbon region of the spectrum contrary to peaks distortions observed in this region in the pseudoephedrine-based system.

Figure 21. Investigation of conformational rigidity of the norephedrine based system by 125 MHz ^{13}C NMR.

This observation suggested that the pyramidal inversion observed in the case of the pseudoephedrine (Figure 16) is not relevant in the case of this norephedrine-based oxadiazinone. The explanation that could possibly be given for the low diastereoselectivity observed for this system therefore, is a possible conformational flexibility of the acyl side chain in the molecule (Figure 22).

Figure 22. Rationale for the observed stereoselectivity in the norephedrine based system.

In Figure 22 above, if the intermediate **78c** was predominantly formed, the *R*-isomer (**81a**) would be the major isomer. On the other hand, if the intermediate **78d** was predominantly formed, then the *S*-isomer (**81b**) would be expected to be the major isomer. However, there is a possibility of both intermediates competing with each other and forming in almost equal amounts. If this is the situation, then the observed low diastereoselectivity is unavoidable.

More efforts towards increasing the diastereoselectivity of the conjugate addition: The N₄-para-methoxybenzyloxadiazinone from L-phenyl alaninol, synthesis and application

Following the attempts made to obtain high diastereoselectivities in the asymmetric conjugate additions from the *Ephedra*-based oxadiazinones, a new oxadiazinone, the N₄-para-methoxybenzyloxadiazin-2-one (**89**) was also considered (Scheme 28). In this new system, L-phenylalaninol (**85**) was employed as the precursor for the oxadiazinone synthesis in place of the norephedrine (**74**). Based on the low diastereoselectivities obtained from the *para*-methoxybenzyl norephedrine-based oxadiazinone (**73**), a more sterically demanding group was envisioned as a good candidate to be considered as the stereochemical control element (N₄-substituent) (Figure 23). Unfortunately, the (1*R*,2*S*)-norephedrine could not be used to accomplish this purpose.

Figure 23. Comparison between the norephedrine and the L-phenylalaninol based oxadiazinones.

This is because of the scarcity and high cost associated with this compound.⁶⁷ As a result, L-phenylalaninol (**85**), a compound derived from the natural α -amino acid L-phenylalanine, was employed as an alternative precursor for the synthesis of the new oxadiazinones. Before proceeding to the isopropyl-substituted heterocycle, a derivative of the *para*-methoxybenzyl (PMB) substituted oxadiazinone (**73**), the L-phenylalaninol-based-N₄-PMB oxadiazinone (**89**), was synthesized using the L-phenylalaninol starting material. The synthesis began with the reductive amination of the amino acid derivative L-phenylalaninol (**85**) with *para*-anisaldehyde in the presence of ethanol (100%) (Scheme 28).

The reaction afforded the amino alcohol N₄-*para*-methoxybenzyl L-phenyl alaninol (**86**) in a 78% yield. The N₄-*para*-methoxybenzyl L-phenylalaninol product was then taken through N-nitrosation reaction using sodium nitrite, an aqueous solution of HCl (3M), and tetrahydrofuran which resulted in the target N-nitrosamine (**89**) in a 65% yield. Without further purification, the N-nitrosamine was subjected to LiAlH₄ reduction in the presence of tetrahydrofuran to yield the target beta-hydroxy hydrazine (**88**) in a 31% yield. The hydrazine product thus obtained was then dissolved in tetrahydrofuran and subjected to a cyclization reaction via the coupling agent carbonyl diimidazole (**55**). This reaction afforded the N₄-*para*-methoxybenzyloxadiazin-2-one (**89**) in a 35% yield after chromatography purification.

Scheme 28. Synthesis of the L-phenylalanine based N₄-*para*-methoxybenzyl-oxadiazin-2-one, **89**.

Acylation and asymmetric conjugate addition with L-phenylalaninol-N₄-para-methoxybenzyl-oxadiazinone

The L-phenylalaninol based N₄-*para*-methoxybenzyloxadiazinone (**89**) thus obtained was subjected to an acylation reaction (Scheme 29) using *trans*-cinnamic acid (**56**) in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) (**57**) coupling agent and 4-dimethylaminopyridine (DMAP) catalyst (**58**). The L-phenylalaninol-N₄-*para*-methoxybenzyl-N₃-cinnamoyl oxadiazinone (**90**) product obtained in this process was purified by column

chromatography in a 65:35, hexane: ethyl acetate solvent system, which resulted in a 71% yield of the target product.

Scheme 29. Acylation of the L-phenylalanine based N₄-*para*-methoxybenzyl-oxadiazinone, **89**.

The pure N₄-*para*-methoxybenzyl-N₃-cinnamoyl oxadiazinone (**90**) obtained from the Steglich reaction above was analyzed by 500 MHz ¹H NMR and 125 ¹³C NMR spectroscopy. The analysis of these spectra revealed that some of the signals were significantly broadened which suggested that this compound is conformationally flexible. Nonetheless, for the sake of experimentation, the acylated product was subjected to an asymmetric conjugate addition reaction (Scheme 30).

Scheme 30: Asymmetric conjugate addition reaction with the N₄-*para*-methoxybenzyl-N₃-cinnamoyl oxadiazinone **91**.

The conjugate addition reaction was carried out in the presence of methyl magnesium bromide, copper bromide (Normant reagent), tetrahydrofuran (THF) and dimethyl sulfide (DMS). The corresponding N₃-(3-phenylbutanoyl)- N₄-*para*-methoxybenzyl oxadiazinone target was obtained and purified by flash column chromatography, leading to the isolation of the target molecule as a mixture of diastereomers (**91a** and **91b**) in an unoptimized yield of 9.8%. From the analysis of the 500 MHz ¹H NMR spectrum of the conjugate addition product, significant line broadening was observed in multiple signals. This was indicative of conformational flexibility observed in the conjugate addition products. It was not possible to determine the reaction diastereoselectivity under these circumstances. This observation suggested that this system is not a good candidate for the asymmetry conjugate addition reaction. Hence, no further analysis was conducted on the reaction mixture.

Initial attempts to increase the diastereoselectivity of the conjugate addition: The L-phenylalaninol-N₄-isopropyl oxadiazinone synthesis and application

While the results from the asymmetric conjugate addition using the *Ephedra*-based oxadiazinones resulted in a diastereoselectivity of 5:1, there was still an interest in pursuing the development of an optimal chiral oxadiazinone template. It was proposed that the N₄-*p*-methoxybenzyl group did not provide enough steric volume to influence the conjugate addition. Based on the limitation of the N₄-*p*-methoxybenzyl system to generate the desired level of diastereoselection, a new oxadiazinone was envisioned wherein the N₄-substituent would be more sterically demanding. To this end, a new oxadiazinone bearing an N₄-isopropyl group was proposed in the place of the former N₄-*p*-methoxybenzyl substituent (Figure 24).

Figure 24. Increasing the steric demand of the N₄-substituent.

Unfortunately, the proposed oxadiazinone (**92**) could not be prepared, as the chiral beta-amino alcohol template, (1*R*,2*S*)-norephedrine (**74**), was no longer commercially available from the only United States supplier, Sigma-Aldrich chemical (Merck KGaS)⁶⁷, as noted earlier. To circumvent this problem, beta-amino alcohols sourced from commonly available alpha-amino

acids were selected as the new chiral template (Figure 25). Thus, L-phenylalaninol (**85**) was employed in the newly proposed oxadiazinone (**94**). This new oxadiazinone would have the benefit of being sourced from an inexpensive, commonly available chiral starting material and offer a larger steric volume at the N₄-position, and potentially lead to higher diastereoselection in the asymmetric conjugate addition process.

Figure 25. The design of a new L-phenylalaninol based N₄-isopropyloxadiazinone.

Synthesis of the L-phenyl alaninol based N₄-isopropyloxadiazinone

The synthesis of this oxadiazinone began with the reductive amination^{68,69} of commercially available L-phenylalaninol (**85**) with reagent grade acetone in the presence of acetic acid and sodium triacetoxyborohydride (Scheme 31). This process afforded the target N₄-isopropyl-L-phenyl-alaninol (**94c**) in 44% yield. The N₄-isopropyl-L-phenylalaninol was then subjected to an N-nitrosation reaction in the presence of sodium nitrite, an aqueous solution of HCl (3M), and tetrahydrofuran.^{70,71} This reaction resulted in a near quantitative isolation of the N-nitrosamine product (**94d**) as a mixture of diastereomers with a percentage yield of 94%. At this stage, the N-nitrosamine needed to be reduced to the hydrazine (**94f**). Our research group

had used lithium aluminum hydride (LiAlH_4)⁷²⁻⁷⁴ to accomplish this task, but we wanted to pursue a reduction pathway that was more efficient and less dangerous. Thus, without further purification, the N-nitrosamine was reduced using the method of Kandasamy and coworkers,⁷⁵ in which the N-nitrosamine was reacted with formamidine sulfinic acid (**94e**) in the presence of an aqueous solution of sodium hydroxide (1M) and methanol. This process yielded the desired hydrazine product (**95**) in 84% yield.

Scheme 31. Synthesis of the L-phenylalaninol based N_4 -isopropylloxadiazinone.

A potential reaction mechanism for this transformation is illustrated in Scheme 32. The overall reaction mechanism is divided into two stages. The first stage involves the decomposition of the formamidine sulfinic acid (**94e**) to give urea (**95b**) and ultimately, sulfoxylic acid (**95e**). In

the second stage, the sulfoxylic acid reduces the nitrosamine by a process of nucleophilic addition and elimination of sulfur dioxide in two independent steps.

Scheme 32. Mechanism for the formamidine sulfinic acid reduction of N-nitrosamine **58**.

The hydrazine (**95**) thus obtained, without further purification, was then reacted with carbonyl diimidazole for 18 hours to induce cyclization as described in the method developed by Husson and coworkers⁵³ to obtain the target N₄-isopropylloxadiazinone (**94**). The crude product

was then subjected to column chromatography purification in a 50:50 hexanes: ethyl acetate solvent system, resulting in an isolated chemical yield of 77%.

Acylation and asymmetric conjugate addition with the N₄-isopropylloxadiazinone

The pure heterocycle (**94**) obtained from the cyclization reaction was taken through acylation reaction using the two pathways of *trans*-cinnamic acid and crotonyl chloride. The acylation reaction with *trans*-cinnamic acid was carried out in the presence of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) coupling agent, 4-dimethylaminopyridine (DMAP) catalyst and anhydrous dichloromethane (Scheme 33) to yield the cinnamoyl acylated oxadiazinone (**96**) in a 30% yield after chromatography purification in a 75:25 hexanes: ethyl acetate solvent system. The N₃-crotonyl variation was prepared by reacting the heterocycle (**94**) with *trans*-crotonyl chloride in the presence of sodium hydride and anhydrous dichloromethane (Scheme 34). The process yielded the acylated heterocycle (**97**) in an unoptimized yield of 18% after chromatography purification (75:25 hexanes: ethyl acetate).

Scheme 33. Synthesis of N₄-isopropyl-N₃-cinnamoyloxadiazinone.

Scheme 34. Synthesis N₄-isopropyl-N₃-crotonyloxadiaxinone.

The N₄-isopropyl-N₃-cinnamoyloxadiaxinone (**96**) was further subjected to a conjugate addition reaction (Scheme 35) reaction using Normant reagent (methyl magnesium bromide and copper (I) bromide dimethyl sulfite complex) in the presence of tetrahydrofuran. The target N₃-(3-methylcinnamoyl)- N₄-isopropyl oxadiazinone (**98**) was isolated as a mixture of diastereomers (**98a** & **98b**) in a 47% yield after chromatography purification (85:15 hexanes: ethyl acetate).

Scheme 35. Synthesis of the N₃-(3-methylcinnamoyl)- N₄-isopropyl oxadiazinone (**98**)

Upon analysis of the crude product with 500 MHz ¹H NMR, These products yielded an integration ratio of 1.5:1 in favor of the major diastereomer (Figure 26).

Figure 26. 500 MHz ^1H NMR spectrum of the N_4 -isopropyl- N_3 -(3-methylcinnamoyl) oxadiazinone diastereomers (**98a** & **98b**) conjugate addition product.

Following the same reaction procedure as the cinnamoyl derivative, the N_3 -crotonyl- N_4 -isopropyl oxadiazinone (**97**) was reacted with methyl magnesium bromide and copper (I) bromide dimethyl sulfite complex in the presence of tetrahydrofuran (Scheme 36) to yield the target N_3 -(3-phenylbutanoyl)- N_4 -isopropyl oxadiazinone (**99**) as a mixture of diastereomers (**99a** & **99b**) in a 70% yield after chromatography purification (85:15 hexanes: ethyl acetate).

Scheme 36. Synthesis of the N₃-(3-phenylbutanoyl)- N₄-isopropyl oxadiazinone (**75a & 75b**)

The crude conjugate addition product was analyzed with 500 MHz ¹H NMR and a diastereomeric ratio of 1.6:1 was observed in favor of the major isomer (Figure 27).

Figure 27. 500 MHz ¹H NMR spectrum of the N₄-isopropyl-N₃-(3-phenylbutanoyl) oxadiazinone (**99a & 99b**) diastereomers.

The low diastereoselectivity observed for the N₄-isopropyl system was not what was expected. This set us thinking on what could be responsible for such outcome and it was again reasoned that this could be as a result of flexibilities around the N₃-position of the acylated starting material (Figure 28) as seen in the case of the *para*-methoxybenzyl (PMB) systems.

Figure 28. Potential alteration of configuration in the conjugate addition starting material for the isopropyl system.

It was proposed that the steric volume of the isopropyl group caused the acyl side chain to adopt another orientation. At this point, the reaction condition for the asymmetric aldol addition reaction (the use of titanium reagent)^{76,77} was considered a possible solution to the flexibility problem. Hence, the isopropyl oxadiazinone was taken through some titanium chemistry, believing that complexing the material with metal compound such as titanium tetrachloride (TiCl₄) would hold the structure in place and give the reaction a better diastereoselectivities (Figure 29).

Figure 29. Proposed solution to the configuration flexibility of the isopropyl system.

On this basis, the N₃-cinnamoyl-N₄-isopropylloxadiaxinone starting material (**94**) was taken through three separate conjugate addition reactions using titanium tetrachloride (TiCl_4), titanium (IV) isopropoxide ($\text{Ti}(\text{OiPr})_4$) and methylmagnesium bromide. In the first reaction with TiCl_4 , the acylated heterocycle was reacted with methyl magnesium bromide and TiCl_4 at $-78\text{ }^\circ\text{C}$ in the presence of tetrahydrofuran (Scheme 36A). The second reaction followed the same protocol but in this case, the TiCl_4 was replaced with $\text{Ti}(\text{OiPr})_4$ (Scheme 36B). The third reaction was conducted at $-10\text{ }^\circ\text{C}$ using only methyl magnesium bromide (Scheme 37C). The proton NMR for the first and third reactions showed some evidence of endocyclic nucleophilic attack on the heterocycle rather than conjugate addition, resulting in ring opening and formation of hydrazines and carboxylic acids while the second reaction gave some addition products that could not be identified by proton NMR analysis.

Scheme 37. Observation from the 500 MHz ^1H NMR spectra of the metal complexing reactions with the N_4 -isopropyl- N_3 -(3-phenylbutanoyl) oxadiazinone.

Further attempts to increase the diastereoselectivity of the conjugate addition:

*The L-phenylalaninol- N_4 -diphenylmethyloxadiazinone and the
L-phenylalaninol- N_4 -(1,3-diphenyl-2 propyl) oxadiazinone*

Having examined the *Ephedra*-based oxadiazinones, the N_4 -*para*-methoxybenzyl substituted oxadiazinones and the N_4 -isopropyl substituted oxadiazinone and the diastereoselectivities in all cases were lower than the desired diastereoselectivity (99:1 or

greater), more oxadiazinone derivatives, the L-phenylalaninol- N_4 -(1,3-diphenyl-2 propyl) oxadiazinone (**101**) and the L-phenylalaninol- N_4 -diphenylmethyl oxadiazinone (**102**) (Figure 30) will be synthesized and applied in the asymmetric conjugate addition reactions to determine if a better diastereoselectivity can be obtained through these new systems.

Figure 30. Proposed design improvement of the N_4 -substituted oxadiazinone.

A proposed reaction pathway to the synthesis of these new oxadiazinones are described below.

*Proposed attempt to increase the diastereoselectivity of the conjugate addition: the
 N_4 -1,3-diphenyl-2-propyloxadiazinone*

In a bid to improve the diastereoselectivity over the N_4 -position of the oxadiazinone, a new ring system will be pursued. This new system involves the replacement of the isopropyl group at the N_4 -position with the much larger 1,3-diphenyl-2-propyl group (Figure 31).

Figure 31. Structural comparison between the N₄-isopropyl and the N₄-1,3-diphenyl-2-propyl oxadiazinones.

The synthesis of this system will be accomplished by reacting the L-phenylalaninol (**85**) starting material with 1,3-diphenylpropan-2-one (**103**) in the presence of sodium triacetoxyborohydride and acetic acid (Scheme 38) to obtain the amino alcohol N₄-(1,3-diphenyl-2-propyl)-L-phenyl-alaninol (**104**) which will then be subjected to N-nitrosation reaction using sodium nitrite and an aqueous solution of HCl (3M) using THF solvent to obtain N-nitrosamine (**105**). The N-nitrosamine can then be subjected to reduction reaction in the presence of formamidinesulfinic acid (**94a**), an aqueous solution of sodium hydroxide (1M), and methanol. This will be immediately followed with the cyclization of the hydrazine in the presence of carbonyl diimidazole (**55**) and tetrahydrofuran to obtain the N₄-1,3-diphenyl-2-propyloxadiazinone.

Scheme 38. Proposed synthesis of the L-phenyl alaninol based N₄-1,3-diphenyl-2-propyloxadiazinone.

Proposed acylation and asymmetric conjugate addition with the N₄-1,3-diphenyl-2-propyloxadiazinone

The N₄-1,3-diphenyl-2-propyl heterocycle obtained from the above process will be taken through the Steglich and crotonyl acylation reactions (Scheme 39). The acylated product will in turn be subjected to the conjugate addition reactions (Scheme 40). The conjugate addition products that will be obtained will then be analyzed by proton NMR to determine the stereoselectivities of the new cyclic system.

Scheme 39. Proposed Steglich reaction (top) and crotonyl acylation of the N₄-1,3-diphenyl-2-propyloxadiazinone.

Scheme 40. Proposed asymmetric conjugation addition with the N₄-1,3-diphenyl-2-propyloxadiazinone.

A few reactions have been conducted with the L-phenylalaninol-N₄-(1,3-diphenyl-2-propyl) oxadiazinone (**101**) which were not very successful. The system is still under study to determine the best reaction conditions for the oxadiazinone synthesis.

Proposed attempt to increase the diastereoselectivity of the conjugate addition:

N₄-diphenylmethyloxadiazinone

The next oxadiazinone that will be examined is the L-phenylalaninol-N₄-diphenylmethyl oxadiazinone (**102**). In this system, the N₄-substituent will be the much larger diphenylmethyl group (Figure 32). As a matter of fact, work has already begun on the synthesis of this oxadiazinone. The first three reactions (reductive amination, reduction and nitrosation) have been successfully conducted (Scheme 41).

Figure 32. Structural comparison between the N₄-1,3-diphenyl-2-propyl oxadiazinones (**101**) and the N₄-diphenylmethyl oxadiazinones (**102**).

Scheme 41. Synthesis of the N₄-diphenylmethyl oxadiazinones (**102**).

The synthesis began with the reaction of the L-phenylalaninol (**85**) starting material with benzophenone imine (**111**) in the presence of anhydrous dichloromethane. The target benzophenone imine of phenylalaninol (**112**) was obtained as a yellow solid in a 97% yield after recrystallization. This was followed by reduction of the benzophenone imine of phenylalaninol using sodium borohydride in the presence of methanol and tetrahydrofuran which yielded the reduced amino alcohol (**113**) in a near quantitative yield of 97%. The next step was the N-nitrosation of the benzophenone imine of phenylalaninol; however, there was a concern that the substrate would undergo acid catalyzed deprotection of the diphenyl methyl group under the standard conditions of N-nitrosation (sodium nitrite/hydrochloric acid). To this end, the substrate was reacted with *tert*-butyl nitrite (**116**)⁷⁸ (Scheme 42) to circumvent the direct use of an acidic solution.

Scheme 42. Attempted N-nitrosation of *N*-diphenylmethyl-L-phenylalaninol.

Unfortunately, the use of *tert*-butyl nitrite failed to successfully cause the N-nitrosation of the *N*-diphenylmethyl-L-phenylalaninol substrate. This was evident from the complexity of the 500 MHz ^1H NMR spectrum of the crude reaction mixture and from the analysis of the thin layer chromatography plate that suggested the presence of starting material, the N-nitrosation products, and other unidentified byproducts. To resolve this problem, sodium nitrite (NaNO_2) and aqueous hydrochloric acid (HCl) (the original reaction conditions) were reconsidered. Thus, the starting material was dissolved in THF and hydrochloric acid and reacted with sodium nitrite (Scheme 43). We were gratified to learn that the N-nitrosation reaction was more successful under these new conditions. This process resulted in the formation of the target product (**114**) in conjunction with benzophenone through some deprotection/oxidation pathway. The product was isolated as a mixture of diastereomers (**114a** & **114b**) in a 94% yield.

Scheme 43. N-nitrosation of *N*-diphenylmethyl-L-phenylalaninol with sodium nitrite and hydrochloric acid.

The N-nitrosamine (**114**) obtained in this process will be subjected to reduction reaction using the formamidine sulfinic acid (**94a**) reaction conditions to obtain the N_4 -diphenylmethyl substituted hydrazine (**115**) which will be immediately followed with cyclization in the presence of carbonyl diimidazole (**55**) and tetrahydrofuran to obtain the N_4 -1,3-diphenylmethyl oxadiazinone (**102**).

CHAPTER III: CONCLUSION AND FUTURE DIRECTIONS

In search of a suitable chiral template for the synthesis of the medicinal agent tolterodine via asymmetric conjugate addition, a series of heterocycles known as oxadiazinones were synthesized. These compounds were then applied in asymmetric conjugate addition reactions and analyzed.

First, three members of the *Ephedra* alkaloids, namely (1*R*,2*S*)-ephedrine; (1*S*,2*S*)-pseudoephedrine and (1*R*,2*S*)-norephedrine were employed in the synthesis of the corresponding oxadiazinones. This was followed by the use of α -amino acid, L-phenyl alaninol, as a precursor for the synthesis of the oxadiazinones.

Of the three members of the *Ephedra* alkaloid family, the ephedrine-based oxadiazinone yielded the highest diastereoselectivity when subjected to asymmetric conjugate addition reaction conditions. In contrast, the pseudoephedrine based oxadiazinone displayed a significant line broadening of diagnostic peaks in both ^1H NMR and ^{13}C NMR spectra of the acylated product, an indication that the molecule is conformationally flexible. This kind of line broadening was also observed in one of the L-phenylalaninol based systems.

It was projected that having a more sterically demanding substituent at the N₄-position (the stereochemical controlling element) of the oxadiazinones would help in improving the diastereoselectivity. However, the observed result was that the diastereoselectivity of the asymmetric conjugation decreased. Upon replacing the methyl group at the N₄-positions of the ephedrine and pseudoephedrine oxadiazinones with *para*-methoxy benzyl (PMB) and isopropyl groups in L-phenyl alaninol based oxadiazinones, a subsequent decrease in diastereoselectivity was observed. This implies that, as the steric bulk increases, diastereoselectivity decreases. This

was reasoned to be due to structural flexibility due to the steric hinderance constituted by the bulkiness of the N₄-substituent.

Complexing the acylated heterocycles with a transition metal in order to improve the compounds' conformational rigidity was considered a possible remedy. Titanium tetrachloride and titanium isopropoxide were used as the complexing agents. However, the results observed showed no indication of asymmetric conjugate addition. Metals other than titanium may ultimately give a different result.

In terms of future works, other metals will be considered in achieving conformational rigidity of the acylated substrates. Also, the conjugate addition products will be taken through hydrolysis in order to recover the chiral carboxylic acid side chains which will thereafter be employed in the synthesis of the medicinal agent tolterodine.

Overall, the oxadiazinones have proven to be a viable chiral template in aldol addition reaction and has shown potentials in conjugate addition. These compounds will be further developed to obtain an improved diastereoselectivity of the system.

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<https://www.sigmaaldrich.com/catalog/search?term=%281R%2C2S%29-norephedrine&interface=All&N=0&mode=match%20partialmax&lang=en®ion=US&focus=product>
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APPENDIX A: EXPERIMENTALS

General Remarks: Chemical reagents and solvents were purchased from commercial vendors and used without further purification. All reactions were conducted in flame-dried or oven dried glassware under a nitrogen atmosphere. Solvents were removed by rotary evaporation and further dried by a Welch DryFast mechanical pump. All ^1H and ^{13}C NMR spectra were recorded in deuterated chloroform (CDCl_3) using an NMR spectrometer operating at 500 and 400 MHz for ^1H NMR and operating at 125 and 100 MHz for ^{13}C NMR. Chemical shifts were reported in parts per million (δ scale) and coupling constant (J values) are listed in Hertz (Hz). Tetramethylsilane (TMS) was used as internal standard ($\delta = 0$ ppm). Major isomers were reported except otherwise stated. OH and NH peaks were reported except when not observed. Infrared spectra were reported in reciprocal centimeters (cm^{-1}) and were measured in nujol mull, regular chloroform or as a neat liquid. Melting points were recorded on a Mel-Temp apparatus and were uncorrected. All polarimetric experiments were carried out using a Jasco P-2000 polarimeter.

N-nitrosamine of (1*R*,2*S*)-Ephedrine (53): The (1*R*,2*S*)- ephedrine substrate (**52**) (20.00 g, 121.0 mmol) was placed in a 250 mL round bottom flask and dissolved in tetrahydrofuran (THF) (40 mL). This was followed with the addition of an aqueous hydrochloric acid (51 mL, 2.74 M, 139 mmol) and sodium nitrite (9.60 g, 139 mmol) and the reaction was left stirring for 24 h. The mixture was then made basic through dilution with saturated aqueous solution of NaHCO₃ and then extracted with ethyl acetate (75 mL) followed by brine wash. The organic product was dried with MgSO₄, filtered under gravity and solvents-removed under reduced pressure to yield 22.21 g (95%) of the target molecule as a yellow solid: MP: 92-94 °C. ¹H NMR (CDCl₃): δ = 1.47 (d, *J* = 7.0 Hz, 3H), 2.40 (bs, 1H), 2.96 (s, 3H), 4.69 (quintet, *J* = 7.0 Hz, 1H), 5.07 (d, *J* = 5.1 Hz, 1H), 7.35-7.37 (m, 5H). ¹³C NMR (CDCl₃): δ = 13.4, 31.4, 65.3, 74.6, 126.4, 128.4, 128.8, 141.0. IR (KBr): 3374, 2983, 1452 cm⁻¹.

(1R,2S)-2-methylamino-*N*-amino-1-phenyl-1-propanol (54): The reducing agent lithium aluminum hydride (LiAlH₄) (12.3 g, 325 mmol) and the solvent tetrahydrofuran (THF) (300 mL) were placed in a flame-dried, nitrogen-purged, 5 L, 3-neck round bottom flask set up with an addition funnel and a condenser. The mixture was then heated under reflux. This was followed with the addition of the nitrosamine substrate (**53**) (21.0 g, 108 mmol) which was pre-dissolved in THF. The addition was carried out via the addition funnel over a period of 30 min. The reaction mixture was thereafter maintained under reflux for another 5 hrs. after which it was cooled to room temperature. Once at room temperature, NaOH (6M) was carefully added to the reaction vessel to consume any unreacted LiAlH₄. The reaction was then extracted with ethyl acetate (150 mL) and washed with brine (100 mL). The recovered organic product was then dried with MgSO₄, filtered under gravity and solvents-removed under reduced pressure to yield 18.0 g (93%) of the target molecule as a yellow viscous oil: ¹H NMR (CDCl₃): δ = 0.83 (d, *J* = 6.7 Hz, 3H), 2.59 (s, 3H), 2.76 (dq, *J* = 6.7, 1.5 Hz, 1H), 5.21 (s, 1H), 7.21-7.39 (m, 5H). IR (KBr): 2978, 1619, 1046 cm⁻¹.

(5R,6S)-4,5-Dimethyl-6-phenyl-1,3,4-oxadiazin-2-one (34): The (1R,2S) hydrazine substrate (**54**) (14.3 g, 79.4 mmol) was placed in a flame-dried, nitrogen-purged 500 mL round bottom flask and dissolved in THF (200 mL). To the solution was added *p*-toluene sulfonic acid monohydrate (15.1 g, 87.4 mmol) followed with the addition of 1,1-carbonyldiimidazole (14.2 g, 87.4 mmol). The resulting mixture was heated under reflux for three hours after which it was cooled to room temperature, followed with addition of an aqueous solution of sodium bicarbonate (50 mL). The reaction was then extracted with ethyl acetate (50 mL) and washed with brine (50 mL). The recovered organic product was dried with MgSO₄, filtered under gravity and solvents-removed by rotary evaporation to yield 12.1 g (74%) of the target molecule as a white solid: MP: 118-120 °C. ¹H NMR (CDCl₃): δ = 1.02 (d, *J* = 7.0 Hz, 3H), 3.03 (s, 3H), 3.44 (dq, *J* = 4.3, 7.0 Hz, 1H), 6.05 (d, *J* = 4.3 Hz, 1H), 7.13-7.15 (m, 1H), 7.24-7.26 (m, 2H), 7.29-7.30 (m, 2H). ¹³C NMR: δ = 11.7, 46.6, 57.0, 74.2, 125.3, 128.0, 128.6, 136.2, 152.2. IR (KBr): 3228, 2943, 1686 cm⁻¹. ESI HRMS for C₁₁H₁₄N₂NaO₂⁺: calcd (M + Na⁺) 229.0947, found 229.0950.

(5*S*,6*R*)-3-*trans*-Cinnamoyl-*N*₄-*p*-methoxybenzyl-4-methyl-6-phenyl-1,3,4-oxadiazinone

(43): To a flame dried, nitrogen purged 250 mL round bottom flask was added *trans*-cinnamic acid (1.29 g, 8.72 mmol) and dissolved in anhydrous dichloromethane (16 mL). This was followed with the addition of the coupling agent 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) (1.671 g, 8.72 mmol), the 4-dimethylaminopyridine (DMAP) catalyst (0.134 g, 1.09 mmol) and the oxadiazinone substrate (0.900 g, 4.36 mmol), sequentially and left stirring at room temperature for 16 hours. The reaction was then diluted with dichloromethane (80 mL) and washed with 1 M HCl (20 mL), 1M NaOH (20 mL) (twice) followed by brine (20 mL) wash. The organic layer thus recovered was dried over magnesium sulfate, gravity filtered, and solvent removed under reduced pressure. The crude product obtained was purified by flash column chromatography (hexane: ethyl acetate, 70:30) to yield the title compound (1.034 g, 71%) as a white solid: MP: 125-128 °C. ¹H NMR (CDCl₃): δ = 0.93 (d, *J* = 7.0 Hz, 3H), 3.08 (s, 3H), 3.48 (dq, *J* = 6.9, 4.6 Hz, 1H), 6.12 (d, *J* = 4.6 Hz, 1H), 7.34-7.38 (m, 3H), 7.41-7.45 (m, 5H), 7.61-7.64 (m, 3H), 7.88 (d, *J* = 15.6 Hz, 1H). ¹³C NMR (CDCl₃): δ = 12.7, 43.8, 56.9, 77.9, 119.0, 125.0, 128.2, 128.4, 128.7, 128.9, 130.5, 134.8, 135.8, 145.8, 148.1, 166.6. IR (CHCl₃): 1730, 1704, 1623, 1267, 1197, 724, 703 cm⁻¹. ESI HRMS for C₂₀H₂₀N₂NaO₃⁺: calcd (M + Na⁺) 359.1366, found 359.1366.

(5*S*,6*R*)-4-*para*-Methoxybenzyl-4-methyl-6-phenyl-3-(3'-phenylbutanoyl)-1,3,4-

oxadiazinone (59): To a 100 mL flame dried, nitrogen purged three-neck round bottomed flask was added copper bromide dimethyl sulfide complex (0.933 g 4.54 mmol), tetrahydrofuran (THF) (5 mL) by syringe and dimethyl sulfide solvent (5 mL) by syringe, one after the other. The reaction was then cooled to a temperature of -78 °C in a dry ice/ ethanol bath. Methyl magnesium bromide (1.51 mL, 4.54 mmol) was then carefully added to the solution by syringe and left to stir for 45 minutes at -78 °C. The N₃-cinnamoyloxadiazinone (**43**) substrate (0.509 g, 1.51 mmol) was dissolved in THF (6 mL) and then added by dropwise addition to the reaction vessel through an addition funnel. The reaction was left stirring for 17 hours while it gradually warmed up to room temperature. The reaction was then diluted with ethyl acetate (80 mL) and washed with 1M NaOH (20 mL), 1 M HCl (20 mL) and brine solution (20 mL). The recovered organic layer was dried with magnesium sulfate, filtered under gravity and solvent removed under high vacuum. The crude product obtained was purified by flash column chromatography (Hexane: ethyl acetate, 70:30) to yield 0.348 g (65%) of the titled compound as a colorless viscous oil. Only the major isomer is reported: ¹H NMR (CDCl₃): δ = 0.79 (d, *J* = 7.0 Hz, 3H), 1.32 (d, *J* = 6.8 Hz, 3H), 2.82 (s, 3H), 3.11 (dd, *J* = 7.6, 16.4 Hz, 1H), 3.27-3.49 (m, 3H), 5.99 (d, *J* = 4.4 Hz, 1H), 7.15-7.20 (m, 1H), 7.25-7.29 (m, 6H), 7.31-7.34 (m, 1H), 7.37-7.41 (m, 2H). ¹³C NMR (CDCl₃): δ = 12.4, 21.8, 36.2, 43.3, 45.9, 56.8, 124.9, 126.3, 127.1, 128.2, 128.4, 128.7, 135.7, 146.0, 148.4, 172.6. IR (CHCl₃): 1778, 1724, 1257, 1137, 744, 700 cm⁻¹. ESI HRMS for C₂₁H₂₄N₂NaO₃⁺: calcd (M + Na⁺) 375.1679, found 375.1678.

60a

(S)-(+)-3-Phenylbutanoic acid (60a): To a racemic mixture of (*S*)-(+)-3-Phenylbutanoic acid (**60a**) and (*R*)-(+)-3-Phenylbutanoic acid (**60b**) (5.24 g, 31.9 mmol) in a 250 mL beaker was added the chiral amine (*S*)-(-)-1-phenylethylamine (**61**) (3.90 g, 31.9 mmol), ethanol (100%) (13 mL) and deionized water (15 mL). The mixture was stirred gently until a homogeneous solution was obtained. The solution was then left to stand at room temperature for about 15 minutes to allow the formation of the carboxylate diastereomeric crystal salt (**62b**). The crystals formed (4.16 g) was recovered by vacuum filtration. The recovered crystals were subjected to second recrystallization by dissolution in ethanol and deionized water solution (15 mL each) by means of heating and spinning at 50 °C on a rotary evaporator. The homogenous solution was allowed to stand at room temperature till crystals were reformed. The crystals (3.15 g) were again collected by vacuum filtration. The carboxylate salt was then extracted with diethyl ether (80 mL) and aqueous hydrochloric acid (1M) (50 mL) to yield 1.26 g (48%) of the (*S*)-(+)-3-Phenylbutanoic acid (**60a**) as a colorless liquid. ¹H NMR (CDCl₃): δ = 1.30 (d, *J* = 6.9 Hz, 3H), 2.58 (dd, *J* = 8.3, 15.6 Hz, 1H), 2.67 (dd, *J* = 6.9, 15.6 Hz, 1H), 3.27 (sxt, *J* = 7.5, 14.7 Hz, 1H), 7.19-7.23 (m, 3H), 7.29-7.32 (m, 2H); ¹³C NMR (CDCl₃): δ = 21.9, 36.2, 42.7, 126.5, 126.7, 128.6, 145.5, 178.9; IR (neat): 2970, 1706, 1296, 763, 700 cm⁻¹ ESI HRMS for C₁₁H₁₄N₂NaO₂⁺: calcd (M + Na⁺) 187.0730, found 187.0730.

N-nitrosamine of (1S,2S)-pseudoephedrine (68): The (1S,2S)-pseudoephedrine substrate (20.00 g, 121.0 mmol) was placed in a 250 mL round bottom flask together with Tetrahydrofuran (THF) (50 mL). This was followed with the addition of an aqueous hydrochloric acid (50.8 mL, 2.74 M, 139 mmol) and sodium nitrite (9.60 g, 139 mmol) and the reaction was left stirring for 24h. The mixture was then made basic through dilution with saturated aqueous solution of NaHCO₃ and then extracted with ethyl acetate (75 mL) followed by brine wash (25 mL). The organic product was dried with MgSO₄, filtered under gravity and solvents-removed under reduced pressure to yield 22.9 g (97%) of the target molecule as a yellow solid after recrystallization (EtOAc-hexanes, 1:1): MP: 85-86 °C. ¹H NMR (CDCl₃): δ = 1.29 (d, *J* = 6.6 Hz, 3H), 2.44 (bs, 1H), 3.07 (s, 3H), 4.75-4.86 (m, 2H), 7.32-7.41 (m, 5H). ¹³C NMR (CDCl₃): δ = 16.0, 30.2, 65.1, 76.4, 126.8, 128.6, 128.9, 140.4. IR (KBr): 3480, 3032, 1465, 1268, 820, 721 cm⁻¹.

(1*S*,2*S*)-2-methylamino-*N*-amino-1-phenyl-1-propanol (69): The reducing agent lithium aluminum hydride (LiAlH₄) (13.4 g, 353 mmol) and the solvent tetrahydrofuran (THF) (400 mL) were placed in a flame-dried, nitrogen-purged, 5 L, 3-neck round bottom flask set up with an addition funnel and a condenser. The mixture was then heated under reflux. This was followed with the addition of the nitrosamine substrate (**68**) (22.9 g, 118 mmol) which was pre-dissolved in THF. The addition was carried out via the addition funnel over a period of 30 min. The reaction mixture was thereafter maintained under reflux for another 5 hrs. after which it was cooled to room temperature. Once at room temperature, NaOH (6M) was carefully added to the reaction vessel to consume any unreacted LiAlH₄. The reaction was then extracted with ethyl acetate (150 mL) and washed with brine (100 mL). The recovered organic product was then dried with MgSO₄, filtered under gravity and solvents-removed under reduced pressure to yield 21.1 g (99%) of the target molecule as a yellow viscous oil: ¹H NMR (CDCl₃): δ = 0.79 (d, *J* = 6.6 Hz, 3H), 2.58 (s, 3H), 2.63-2.69 (m, 1H), 4.42 (d, *J* = 9.2 Hz, 1H), 7.27-7.38 (m, 5H). IR (KBr): 3333, 2975, 754, 701 cm⁻¹.

(5*S*,6*S*)-4,5-Dimethyl-6-phenyl-1,3,4-oxadiazin-2-one (70): The (1*S*,2*S*) hydrazine substrate (**69**) (2.86 g, 15.9 mmol) was placed in a flame-dried, nitrogen-purged 100 mL round bottom flask and dissolved in THF (100 mL). To the solution was added *p*-toluene sulfonic acid monohydrate (3.02 g, 15.88 mmol) followed with the addition of 1,1-carbonyldiimidazole (3.09 g, 19.1 mmol). The resulting mixture was heated under reflux for three hours after which it was cooled to room temperature and an aqueous solution of sodium bicarbonate (50 mL) was added. The reaction was then extracted with ethyl acetate (50 mL) and washed with brine (50 mL). The recovered organic product was dried with MgSO₄, filtered under gravity and solvents-removed by rotary evaporation to yield 2.40 g (74%) of the target molecule as a white solid after chromatography purification: MP: 97-98 °C. [α]_D²³ +30.1° (THF). ¹H NMR (CDCl₃): δ = 0.96 (d, *J* = 6.8 Hz, 3H), 2.69 (s, 3H), 3.22 (dq, *J* = 6.8, 9.9 Hz, 1H), 5.25 (d, *J* = 9.9 Hz, 1H), 7.31-7.34 (m, 3H), 7.36-7.41 (m, 3H), 7.65 (s, 1H). ¹³C NMR (CDCl₃): δ = 14.3, 40.0, 58.8, 80.7, 127.1, 128.7, 129.0, 136.6, 153.0. IR (KBr): 3240, 1699, 755, 700 cm⁻¹.

(4*S*,5*S*)-3-*trans*-Cinnamoyl-4,5-dimethyl-6-phenyl-1,3,4-oxadiazinone (71): *trans*-Cinnamic acid (2.58 g, 17.4 mmol) was added to a flame dried, nitrogen purged 250 mL round bottom flask and dissolved in anhydrous dichloromethane (16 mL). This was followed with a sequential addition of the coupling agent 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) (3.34 g, 17.4 mmol), the 4-dimethylaminopyridine (DMAP) catalyst (0.268 g, 2.18 mmol) and the oxadiazinone substrate (1.80 g, 8.72 mmol). The reaction was then left stirring for 16 hours at room temperature after which the reaction was diluted with dichloromethane (80 mL) and washed with 1 M HCl (20 mL), 1M NaOH (20 mL) (twice) followed by brine (20 mL) wash. The organic layer thus recovered was dried over magnesium sulfate, gravity filtered, and solvent removed under reduced pressure. The crude product obtained was purified by flash column chromatography (hexane: ethyl acetate, 75:25) to yield the title compound (1.74 g, 59%) as a white fluffy solid. MP: 47-50 °C. ¹H NMR (CDCl₃): δ = 1.21 (d, *J* = 6.8 Hz, 3H), 2.91 (s, 3H), 3.42 (dq, *J* = 6.8, 10.4 Hz, 1H), 5.30 (d, *J* = 9.8 Hz, 1H), 7.36-7.38 (m, 2H), 7.42-7.45 (m, 6H), 7.53 (d, *J* = 15.7, 1H), 7.62-7.64 (m, 1H), 7.89 (d, *J* = 15.7 Hz, 1H). ¹³C NMR (CDCl₃): δ = 15.4, 38.7, 61.0, 84.1, 118.7, 126.9, 128.4, 128.9, 129.0, 129.3, 130.5, 134.8, 136.0, 145.8, 149.5, 165.8. IR (CHCl₃): 1704, 1626, 1577, 1204, 1128, 1045, 700, 666 cm⁻¹. ESI HRMS for C₂₀H₂₀N₂NaO₃⁺: calcd (M + Na⁺) 359.1366, found 359.1358.

(5*S*,6*R*)-4-*para*-Methoxybenzyl-4-methyl-6-phenyl-3-(3'-phenylbutanoyl)-1,3,4-

oxadiazinone (72): To a 100 mL flame dried, nitrogen purged three-neck round bottomed flask was added copper bromide dimethyl sulfide complex (1.00 g 4.87 mmol), tetrahydrofuran (THF) (5 mL) by syringe and dimethyl sulfide solvent (5 mL) by syringe, one after the other. The reaction was then cooled to a temperature of -78 °C in a dry ice/ ethanol bath. Methyl magnesium bromide (1.62 mL, 4.87 mmol) was then carefully added to the solution by syringe and left to stir for 45 minutes at -78 °C. The N₃-cinnamoyloxadiaxinone (**29**) substrate (0.546 g, 1.62 mmol) was dissolved in THF (6 mL) and then added by dropwise addition to the reaction vessel through an addition funnel. The reaction was left stirring for 17 hours while it gradually warmed up to room temperature. The reaction was then diluted with ethyl acetate (80 mL) and washed with 1M NaOH (20 mL), 1 M HCl (20 mL) and brine solution (20 mL). The recovered organic layer was dried with magnesium sulfate, filtered under gravity and solvent removed under high vacuum. The crude product obtained was purified by flash column chromatography (Hexane: ethyl acetate, 70:30) to yield 0.451 g (79%) of the titled compound as a colorless oil. ¹H NMR (CHCl₃): δ = 0.96 (d, *J* = 6.8 Hz, 3H), 1.29 (d, *J* = 6.9 Hz, 3H), 2.62 (s, 3H), 2.90-3.04 (m, 2H), 3.25-3.29 (dd, *J* = 7.7, 15.7 Hz, 1H), 3.35 (sxt, *J* = 7.1 Hz, 1H), 5.1 (bs, 1H), 7.13-7.18 (m, 4H), 7.21-7.24 (m, 3H), 7.31-7.33 (m, 3H). ¹³C NMR (CHCl₃): δ = 15.6, 22.0, 36.8, 36.9, 44.7, 45.1, 83.9, 126.5, 126.9, 127.1, 128.5, 128.6, 128.9, 129.3, 135.9, 145.9, 171.9. IR (neat): 1781, 1728,

1211, 1126, 760, 700 cm^{-1} . ESI HRMS for $\text{C}_{21}\text{H}_{24}\text{N}_2\text{NaO}_3^+$: calcd ($\text{M} + \text{Na}^+$) 375.1679, found 375.1673.

75

(1R,2S)-N-*para*-Methoxybenzyl-norephedrine (75): To a 1000 mL round bottom flask containing (1R,2S)-norephedrine (10.0 g, 66.1 mmol) was added *para*-anisaldehyde (8.8 mL, 72 mmol) and 100% methanol (100 mL) to make a solution. To the solution was added two scoops of MgSO₄ and stirred thoroughly, and the reaction mixture was stirred overnight. At which point NaBH₄ (3.77 g, 99.2 mmol) was added to the reaction and stirred for another for 2 hours, after which NaOH (50 mL, 1M) was added to the reaction mixture and stirred for 1 hour. After which most of the ethanol was removed *in vacuo* and the resulting slurry was reconstituted with 200 mL ethyl acetate and the organic layer was collected and washed with 50 mL deionized water, 50 mL brine, dried over MgSO₄, filtered and solvents removed *in vacuo*. The crude product was used without further purification in the next step.

***N*-((1*R*,2*S*)-2-*para*-Methoxybenzyl-*N*-nitrosamino)-1-phenyl-1-propanol (76):** To the 1000 mL round bottom flask containing crude protected (1*R*,2*S*)-norephedrine (**2.1**) was added, THF (80 mL) followed by aqueous solution of hydrochloric acid (2M, 50 mL, 100 mmol) and stirred to make a solution. To the solution was added NaNO₂ (4.6 g, 66.1 mmol) slowly in one portion and allowed to stir overnight. The reaction was then extracted in 200 mL ethyl acetate and washed with 50mL 1M HCl, 50 mL brine, dried over MgSO₄, filtered and solvent removed under high vacuum. The crude product obtained was purified by flash column chromatography (Hexane: ethyl acetate, 70:30) to give 18.9 g (96%) of the title compound (a mixture of diastereomers), as a yellow oil. ¹H NMR (CDCl₃): δ = 1.46 (d, *J* = 6.9 Hz, 3H), 3.79 (s, 3H), 4.26 (dq, *J* = 5.1, 6.9 Hz, 1H), 4.37 (d, *J* = 14.6 Hz, 1H), 4.76 (d, *J* = 14.6 Hz, 1H), 5.09 (d, *J* = 5.1 Hz, 1H), 6.81 (m, 2H), 6.90 (m, 2H), 6.97 (m, 2H). ¹³C NMR (CDCl₃): δ = 9.80, 15.2, 47.5, 55.36, 55.38, 59.4, 64.0, 65.0, 73.8, 76.8, 76.9, 77.2, 77.4, 114.0, 114.3, 114.5, 125.8, 126.39, 126.43, 128.1, 128.4, 128.6, 128.7, 129.6, 133.2, 141.0, 141.3, 159.3, 159.8.

77

(1*R*,2*S*)-2-(1-(*para*-Methoxybenzyl)hydrazinyl)-1-phenyl-1-propanol (77): To a 2000 mL flame dried, nitrogen purged three neck round bottom flask fitted with a pressure equalizing addition funnel and a water cooled reflux condenser, was added LiAlH₄ (4.60 g, 121mmol) followed by THF (300 mL) to give a dark gray suspension. Heat was applied and THF brought to reflux, at which point *N*-((1*R*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-(4-methoxybenzyl) nitrous amide **2.2** (18.1 g, 60.3 mmol) dissolved in THF (150 mL) was poured into the LiAlH₄-THF mixture dropwise from the addition funnel after which the reaction was stirred under reflux for 3 hours. By the end, the reaction mixture took the color of pea soup, at which point heat was removed and reaction allowed to cool to room temperature. The reaction was quenched with dropwise addition of 1M NaOH (100 mL) from addition funnel. Upon addition of NaOH heavy precipitate formation was observed. The precipitate was broken into a slurry and allowed to settle, the supernatant solution was decanted to a 1000 mL round bottom flask and most of the THF was removed under reduced pressure. The concentrated reaction mixture was reconstituted with 250 mL ethyl acetate and 70 mL 1M NaOH and the organic layer was separated, and the aqueous layer was back extracted with 100 mL ethyl acetate. The organic layers were combined, washed with 50 mL brine, dried with MgSO₄, filtered and the solvents removed *in vacuo*. To give the crude β-hydroxyhydrazine which went on to the cyclization step.

(5*S*,6*R*)-4-(*para*-Methoxybenzyl)-5-methyl-6-phenyl-1,3,4-oxadiazinone (73):

To a 1000 mL round bottom flask containing the crude hydrazine (**77**) (17.12 g, 59.80 mmol), was added dichloromethane (540 mL) and triethylamine (25.0 mL, 179 mmol) sequentially and the resulting solution was cooled in an ice bath. Triphosgene (5.860 g, 19.73 mmol) was then added to the cold solution and the reaction was allowed to stir for 16 hours at room temperature after which it was washed with 1 M HCl (50 mL) followed by brine wash (50 mL). The organic layer was dried over MgSO₄ solvent removed under reduced pressure. The crude product obtained was purified by flash column chromatography (hexanes: ethyl acetate, 70:30) to give the title compound as a yellow viscous oil in a 53% yield over two steps. ¹H NMR (CDCl₃): δ = 0.91 (d, *J* = 6.9 Hz, 3H), 3.25 (dq, *J* = 6.9 Hz, 3.0 Hz, 1H), 3.83 (s, 3H), 4.02 (d, *J* = 12.4 Hz, 1H), 4.15 (d, *J* = 12.4 Hz, 1H), 5.8 (d, *J* = 3.0 Hz, 1H), 6.40 (s, 1H), 6.87-6.96 (m, 2H), 7.28-7.34 (m, 5H), 7.35-7.42 (m, 2H). ¹³C NMR (CDCl₃): δ = 11.8, 53.9, 55.4, 62.3, 74.7, 114.3, 125.3, 127.6, 128.0, 128.6, 130.5, 136.5, 152.2, 159.6.

N₃-*trans*-Cinnamoyl-N₄-*p*-methoxybenzyl-4-methyl-6-phenyl-1,3,4-oxadiazinone (78): *trans*-

Cinnamic acid (0.807 g, 5.45 mmol) was added to a flame dried, nitrogen purged 250 mL round bottom flask and dissolved in anhydrous dichloromethane (16 mL). This was followed with a sequential addition of the coupling agent 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) (1.05 g, 5.45 mmol), the 4-dimethylaminopyridine (DMAP) catalyst (0.110 g, 0.90 mmol) and the oxadiazinone substrate (1.42 g, 4.54 mmol). The reaction was then left stirring for 16 hours at room temperature after which the reaction was diluted with dichloromethane (80 mL) and washed with 1 M HCl (20 mL), 1M NaOH (20 mL) (twice) followed by brine (20 mL) wash. The organic layer thus recovered was dried over magnesium sulfate, gravity filtered, and solvent removed under reduced pressure. The crude product obtained was purified by flash column chromatography (hexane: ethyl acetate, 80:20) to yield 1.14 g (80%) of the title compound as a white fluffy solid: MP: 57-61°C. ¹H NMR (CDCl₃): δ = 0.85 (d, *J* = 7.0 Hz, 3H) 3.47 (dq, *J* = 4.8, 7.0 Hz, 1H) 3.82 (s, 3H) 4.20 (d, *J* = 12.5 Hz, 1H) 4.39 (d, *J* = 12.5 Hz, 1H) 6.14 (d, *J* = 4.6 Hz, 1H) 6.94 (d, *J* = 8.6 Hz, 2H) 7.26 (d, *J* = 7.8 Hz, 2H) 7.33 (t, *J* = 7.3, 1H), 7.39 (d, *J* = 7.8, 2H) 7.41-7.43 (m, 3H), 7.47 (d, *J* = 8.6 Hz, 2H) 7.52 (d, *J* = 15.7 Hz, 1H) 7.59 (m, 2H) 7.78 (d, *J* = 15.7 Hz, 1H). ¹³C NMR (CDCl₃): δ = 12.5, 52.0, 55.3, 59.3, 78.0, 114.4, 119.1, 124.9, 127.0, 128.2, 128.4, 128.7, 128.8, 130.4, 130.7, 134.9, 135.9, 145.4, 148.2, 159.8, 166.8. IR (CHCl₃):

1760, 1727, 1615, 1247, 1216, 1136, 823, 736, 701 cm^{-1} . ESI-HRMS calcd for $\text{C}_{27}\text{H}_{26}\text{N}_2\text{NaO}_4$
($\text{M} + \text{Na}^+$): 465.1785. Found: 465.1779.

N₃-trans-Cinnamoyl-N₄-p-methoxybenzyl-4-methyl-6-phenyl-3-(3'-phenylbutanoyl)-1,3,4-oxadiazinone (81): To a flame dried, nitrogen purged three-neck 100 mL round bottomed flask was added copper bromide dimethyl sulfide complex (0.696 g, 3.39 mmol), tetrahydrofuran (THF) (5 mL) by syringe and dimethyl sulfide solvent (5 mL) by syringe, one after the other. The reaction was then cooled to a temperature of -78 °C using dry ice and ethanol. Methyl magnesium bromide (1.13 mL, 3.39 mmol) was then carefully added to the solution by syringe and left to stir for 45 minutes at -78 °C. The N₃-cinnamoyloxadiazinone (**x**) substrate (0.500 g, 1.13 mmol) was dissolved in THF (6 mL) and then added dropwise to the reaction vessel via addition funnel. The reaction was left stirring overnight, gradually warming up to room temperature. The reaction was then diluted with ethyl acetate (80 mL) and washed with 1M NaOH (20 mL), 1 M HCl (20 mL) and brine solution (20 mL). The recovered organic layer was dried with magnesium sulfate, filtered under gravity and solvent removed under high vacuum. The crude product obtained was purified by flash column chromatography (hexanes: ethyl acetate, 80:20) to yield 0.321 g (60%) of the titled compound as a yellow viscous oil. ¹H NMR (CDCl₃): δ = 0.61 (d, *J* = 7.0 Hz, 3H), 1.20 (d, *J* = 6.9 Hz, 3H), 2.95 (dd, *J* = 7.9, 16.7 Hz, 1H), 3.22-3.27 (m, 3H), 3.30-3.37 (m, 1H), 3.75 (s, 3H), 3.92 (d, *J* = 12.5 Hz, 1H), 4.01 (d, *J* = 12.5 Hz, 1H), 5.93 (d, *J* = 4.5 Hz, 1H), 6.82-6.85 (m, 2H), 7.07-7.11 (m, 3H), 7.17-7.20 (m, 5H), 7.25-7.28 (m, 2H), 7.32-7.34 (m, 2H). ¹³C NMR (CDCl₃): δ = 12.3, 21.9, 36.0, 45.6, 51.4, 55.3,

58.7, 77.9, 114.3, 124.8, 126.2, 127.0, 127.1, 128.1, 128.5, 128.7, 130.7, 135.9, 146.2, 148.4, 159.8, 172.6. ESI-HRMS calcd for $\text{C}_{28}\text{H}_{30}\text{N}_2\text{NaO}_4$ ($\text{M} + \text{Na}^+$): 481.2098. Found: 481.2090.

N₃-*trans*-Crotonyl-N₄-*p*-methoxybenzyl-4-methyl-6-phenyl-1,3,4-oxadiazinone (80): To a flame-dried nitrogen-purged 100 mL round bottom flask was added the oxadiazinone substrate (0.50 g, 1.6 mmol) which was dissolved in dimethylformamide (DMF) (8.00 mL). To the solution was added the sodium hydride base (0.077 g, 3.2 mmol). The reaction was allowed to stir for 10 minutes and the crotonyl chloride (0.17 mL, 1.8 mmol) was then added. The reaction was left stirring for 18 hours at room temperature, after which it was diluted with dichloromethane (50 mL) and washed with 1 M HCl (20 mL) and brine (20 mL). The organic layer thus recovered was dried over magnesium sulfate, gravity filtered, and solvent removed under reduced pressure. The titled compound was isolated as a yellow solid in a yield of 0.595 g (98%) after purification by flash column chromatography (hexanes: ethyl acetate, 80:20): MP: 54-56 °C. ¹H NMR (CDCl₃). δ = 0.77 (d, *J* = 6.9 Hz, 3H), 1.93 (dd, *J* = 1.4, 6.9 Hz, 3H), 3.38 (dq, *J* = 4.5, 7.0 Hz, 1H) 3.83 (s, 3H) 4.13 (d, *J* = 12.6 Hz, 1H) 4.31 (d, *J* = 12.6 Hz, 1H) 6.07 (d, *J* = 4.5 Hz, 1H) 6.92 (d, *J* = 8.5 Hz, 2H) 7.07 (dq, *J* = 7.5, 15.2 Hz, 1H) 7.20 (d, *J* = 7.5 Hz, 2H) 7.26-7.37 (m, 4H), 7.42 (d, *J* = 8.5 Hz, 2H). ¹³C NMR (CDCl₃): δ = 12.4, 18.5, 51.5, 55.3, 59.1, 77.9, 114.3, 123.6, 124.9, 127.0, 128.1, 128.7, 130.7, 135.9, 145.7, 148.2, 159.7, 166.6. IR (CHCl₃): 1762, 1725, 1639, 1248, 790, 823, 733 cm⁻¹. ESI-HRMS calcd for C₂₂H₂₄N₂NaO₄ (M + Na⁺): 403.1628. Found: 403.1622.

N₃-*trans*-Crotonyl-N₄-*p*-methoxybenzyl-4-methyl-6-phenyl-1,3,4-oxadiazinone (82): To a flame dried, nitrogen purged three-neck 100 mL round bottomed flask was added copper bromide dimethyl sulfide complex (0.580 g, 2.82 mmol), tetrahydrofuran (THF) (5 mL, by syringe) and dimethyl sulfide solvent (5 mL, by syringe), one after the other. The reaction was then cooled to a temperature of -78 °C using dry ice and ethanol. Methyl magnesium bromide (0.940 mL, 2.82 mmol) was then carefully added to the solution by syringe and left to stir for 45 minutes at -78 °C. The N₃-crotonyloxadiazinone (**80**) substrate (0.358 g, 0.940 mmol) was dissolved in THF (6 mL) and then added dropwisely to the reaction vessel via addition funnel. The reaction was left stirring for 17 hours while it gradually warmed up to room temperature. The reaction was then diluted with ethyl acetate (80 mL) and washed with 1M NaOH (20 mL), 1 M HCl (20 mL) and brine solution (20 mL). The recovered organic layer was dried with magnesium sulfate, filtered under gravity and solvent removed under high vacuum. The crude product obtained was purified by flash column chromatography (Hexane: ethyl acetate, 70:30) to yield 0.224g (52%) of the titled compound as a yellow viscous oil: (only the major isomer is reported) ¹H NMR (CDCl₃): δ = 0.58 (d, *J* = 7.0 Hz, 3H), 1.33 (d, *J* = 7.0 Hz, 3H), 3.17 (dd, *J* = 7.3, 16.7 Hz, 1H) 3.29-3.33 (m, 2H), 3.35-3.38 (sxt, *J* = 6.9 Hz, 1H), 3.85 (s, 3H), 4.07 (d, *J* = 12.4 Hz, 1H), 4.19 (d, *J* = 12.4 Hz, 1H), 6.05 (d, *J* = 4.6 Hz, 1H) 6.93-6.96 (m, 2H), 7.17-7.21 (m, 3H), 7.26-7.32 (m, 4H) 7.35-7.38 (m, 2H), 7.42-7.47 (m, 3H). ¹³C NMR (CDCl₃) δ = 12.2, 22.1, 36.2, 45.6, 51.2, 55.3, 58.6, 78.0, 114.3, 124.8, 126.3, 127.0, 128.1, 128.5, 128.7, 128.8,

130.6, 135.9, 146.1, 148.7, 159.7, 172.5. IR (CHCl₃): 1775, 1726, 1213, 1136, 850, 740, 700 cm⁻¹

¹. ESI-HRMS calcd for C₂₈H₃₀N₂NaO₄ (M + Na⁺): 481.2098. Found: 481.2100.

(S)-(+)-3-phenylbutyric acid (84): The N₃-(3-methylcinnamoyl)-N₄-para-methoxybenzyl oxadiazinone substrate (1.26 g, 2.74 mmol) was added together with acetonitrile (50 mL) into a 250 mL round bottom flask and homogenized by stirring. To the homogenized mixture was added Ceric ammonium nitrate (Ce(NH₄)₂NO₃) (7.53 g, 13.7 mmol) pre-dissolved in deionized water (50 mL). The reaction was left to stir for 3hrs. The mixture was thereafter put on rotary evaporator to get rid of the solvents. The concentrated solution was then extracted with diethyl ether (50 mL) and brine solution (30 mL). The recovered organic layer was treated with 1M NaOH (30 mL) and dried with MgSO₄. The aqueous layer was further treated with 3M HCl (30 mL) and extracted with diethyl ether (50 mL). The second organic product was washed with brine and also dried with MgSO₄. Both organic products were filtered under gravity and solvent removed under high vacuum. The second organic product contained the target molecule and was therefore taken through further purification by flash column chromatography (Hexanes-ethyl acetate, 80:20). This yielded the title compound (0.10 g, 22%) as a colorless oil: $[\alpha]^{23}_{\text{D}} +22$. ¹H NMR (CDCl₃): δ = 1.33 (d, J = 7.0 Hz, 3H), 2.58 (dd, J = 8.2, 15.5 Hz, 1H), 2.68 (dd, J = 6.8 Hz, 1H), 3.28 (sxt, J = 7.0 Hz, 1H), 7.19-7.23 (m, 3H), 7.29-7.32 (m, 2H). ¹³C NMR (CDCl₃): δ = 21.9, 36.2, 42.6, 126.5, 126.7, 128.6, 145.5, 178.5. IR (neat): 2970, 1706, 1296, 763, 700 cm⁻¹. ESI HRMS for C₁₁H₁₄N₂NaO₂⁺: calcd (M + Na⁺) 187.0730, found 187.0730.

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***N*-para-Methoxybenzyl-L-phenylalaninol (86):** To a 1000 mL round bottom flask containing L-phenylalaninol (15.678 g, 103.7 mmol) was added *para*-anisaldehyde (14.0 mL, 114 mmol) and 100% methanol (150 mL) to make a solution. To the solution was added two scoops of MgSO₄ and allowed to stir overnight. At which point NaBH₄ (5.90 g, 155.5 mmol) was added to the reaction and stirred for another for 2 hours, after which 50 mL 1M NaOH was added to the reaction mixture and stirred for 1 hour. Then most of the ethanol was removed *in vacuo* and the resulting slurry was reconstituted with 200 mL ethyl acetate and the organic layer was collected and washed with 50 mL DI water, 50 mL brine, dried over MgSO₄, filtered and solvents removed *in vacuo* to give a crude solid. The crude product was than recrystallized to give the title compound as white crystals in 90% yield. MP: 88-90 °C. ¹H NMR (CDCl₃): δ = 2.78 (dd, *J* = 6.8, 13.7 Hz, 1H), 2.84 (dd, *J* = 7.0, 13.7 Hz, 1H), 2.96-3.00 (m, 1H), 3.37 (dd, *J* = 5.4, 10.8 Hz, 1H), 3.66 (dd, *J* = 3.9, 10.8 Hz, 1H), 3.74 (s, 2H), 3.82 (s, 3H), 6.86 (d, *J* = 8.6 Hz, 2H), 7.15 (d, *J* = 8.6 Hz, 2H), 7.19 (d, *J* = 7.5 Hz, 2H), 7.24-7.28 (m, 1H), 7.30-7.34 (m, 2H). ¹³C NMR (CDCl₃): (one of the aromatic carbons was not observed potentially due to coincidental overlap) δ = 38.1, 50.6, 55.3, 59.5, 62.7, 113.9, 126.4, 128.6, 129.3, 132.2, 138.7, 158.8. IR (CHCl₃): 3288, 2900, 1608, 1248, 1177, 857, 746, 699 cm⁻¹. ESI-HRMS calcd for C₁₇H₂₂NO₂ (M + H⁺): 272.1645. Found: 272.1637.

(S)-N-(1-Hydroxy-3-phenyl-2-propanyl)-N-(4-methoxybenzyl)nitrous amide (87): To a 1000 mL round bottom flask containing *N-p*-methoxybenzyl-L-phenylalaninol (23.1 g, 85.1 mmol) was added THF (100 mL) and 2M HCl (64.0 mL, 128 mmol) to make a homogeneous solution. To the solution was added NaNO₂ (5.87 g, 85.1 mmol) in one portion which reacted exothermically. The reaction was stirred overnight. At which point the reaction was extracted with 200 mL ethyl acetate and the organic layer was washed with aqueous hydrochloric acid (1M HCl, 25 mL), brine (25 mL), dried over MgSO₄, filtered and solvents removed *in vacuo*. The crude material was then recrystallized to give the title compound as a yellow solid in 88% yield. MP: 79-81 °C. ¹H NMR (CDCl₃): δ = 3.13 (dd, *J* = 8.2, 13.8 Hz, 1H), 3.19 (dd, *J* = 6.9 13.8 Hz, 1H), 3.80 (s, 3H), 3.96 (d, *J* = 5.5 Hz, 2H), 4.31-4.36 (m, 1H), 4.41 (d, *J* = 14.6 Hz, 1H), 4.82 (d, 14.6 Hz, 1H), 6.80 (d, *J* = 8.6 Hz, 2H), 6.95 (d, *J* = 8.6 Hz, 2H), 7.10-7.11 (m, 2H), 7.24-7.30 (m, 3H). ¹³C NMR (CDCl₃): δ = 37.6, 47.9, 55.3, 64.2, 65.9, 114.2, 126.1, 126.9, 128.7, 129.1, 129.8, 137.1, 159.3. IR (CHCl₃): 3354, 1612, 1448, 1249, 1177, 1138, 837, 732, 701 cm⁻¹. ESI-HRMS calcd for C₁₇H₂₀N₂NaO₃ (M + Na⁺): 323.1366. Found: 323.1357.

(S)-2-(1-(4-Methoxybenzyl)hydrazinyl)-3-phenyl-1-propanol (88): To a 2000 mL flame dried, nitrogen purged, three neck round bottom flask fitted with a pressure equalizing addition funnel and a water cooled reflux condenser, was added LiAlH_4 (5.689 g, 149.9 mmol), and then was added THF (500 mL) to give a dark gray suspension. Heat was applied and THF brought to reflux, at which point *N*-nitrosamine (**87**) (22.5 g, 74.9 mmol) dissolved in THF (100 mL) was poured into the LiAlH_4 -THF mixture dropwise from the addition funnel. The reaction was stirred under reflux for 3 hours. By the end, the reaction mixture took the color of pea soup, at which point heat was removed and reaction allowed to cool to room temperature. The reaction was quenched with dropwise addition of 1M NaOH (100 mL) from addition funnel. Upon addition of NaOH heavy precipitate formation occurred. The precipitate was broken into a slurry and allowed to settle, the supernatant solution was then decanted to a 1,000 mL round bottom flask and pumped to remove most of the THF. The concentrated reaction mixture was reconstituted with 250 mL ethyl acetate and 70 mL 1M NaOH and the organic layer was separated, and the aqueous layer was back extracted with 100 mL ethyl acetate. The organic layers were combined, washed with 50 mL brine, dried with MgSO_4 , filtered and the solvents removed *in vacuo* to give the crude β -Hydroxy hydrazine which went on to the cyclization step.

(S)-5-Benzyl-4-(*para*-methoxybenzyl)-1,3,4-oxadiazinone (89): Tetrahydrofuran (THF) (20 mL) was added to the beta-hydroxyl hydrazine (21.124 g, 73.8 mmol) substrate in a flame dried nitrogen purged 250 mL round bottomed flask and left to homogenize at room temperature. Carbonyldiimidazole (CDI) (12.0 g, 73.8 mmol) was then added to the solution and left stirring for 18 hours at room temperature. Thereafter, the solution was subjected to rotary evaporation to remove the THF solvent and the resulting viscous oil was diluted with ethyl acetate (80 mL) and washed with 1 M HCl (15 mL) and brine solution (15 mL). The recovered organic layer was dried over MgSO₄, filtered under gravity and solvents-removed under reduced pressure. The crude product was purified by flash column chromatography (hexanes: Ethylacetate, 60:40) to yield 8.05 g (35 %) of the title compound as a yellow solid. MP: 111-112 °C. ¹H NMR (CDCl₃): δ = 2.89 (dd, *J* = 8.0, 13.9 Hz, 1H), 2.99 (dd, *J* = 7.4, 13.9 Hz, 1H), 3.17-3.21 (m, 1H), 3.19 (s, 3H), 3.83 (d, *J* = 12.8 Hz, 1H), 4.01 (d, *J* = 12.8 Hz, 1H), 4.17 (dd, *J* = 2.1, 11.5 Hz, 1H), 4.60 (dd, *J* = 3.4, 11.5 Hz, 1H), 6.82 (bs, 1H), 6.84 (d, *J* = 8.7 Hz, 2H), 7.11 (d, *J* = 8.7 Hz, 2H), 7.17 (d, *J* = 7.6 Hz, 2H), 7.25-7.33 (m, 3H). ¹³C NMR (CDCl₃): δ = 36.2, 55.2, 55.3, 61.7, 64.1, 114.1, 126.7, 127.4, 128.6, 129.3, 130.2, 137.5, 151.9, 159.4. IR (CHCl₃): 3235, 1718, 1242, 833, 772, 699 cm⁻¹. ESI-HRMS calcd for C₁₈H₂₀N₂NaO₃ (M + Na⁺): 335.1366. Found: 335.1358.

(S)-5-Benzyl-3-*trans*-crotonyl-4-(*para*-methoxybenzyl)-1,3,4-oxadiazinone (90): The oxadiazinone substrate (4.203 g, 13.46 mmol) was added to a flame dried, nitrogen purged 250 mL round bottom flask and dissolved in anhydrous dichloromethane (30 mL). To the solution was added *trans*-cinnamic acid (2.390 g, 16.20 mmol), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) (3.110 g, 16.20 mmol), and 4-dimethylaminopyridine (DMAP) catalyst (0.330 g, 2.700 mmol) sequentially. The reaction was allowed to stir for 18 hours at room temperature, after which it was diluted with dichloromethane (80 mL) and washed with 1 M HCl (20 mL), 1M NaOH (20 mL) followed by brine (20 mL) wash. The organic layer thus recovered was dried over magnesium sulfate, gravity filtered, and solvent removed under reduced pressure. The crude product obtained was purified by flash column chromatography (hexane: ethyl acetate, 65:35) to yield 4.221 g (71%) of the title compound as a yellow viscous oil. ^1H NMR: δ = 2.77 (dd, J = 6.0, 13.9 Hz, 1H), 2.86 (dd, J = 8.3, 13.9 Hz, 1H), 3.65 (bs, 1H), 3.71 (s, 3H), 3.87 (d, J = 12.5 Hz, 1H), 4.11 (d, J = 12.5 Hz, 1H), 4.16 (bs, 1H), 4.68 (dd, J = 6.2, 11.45 Hz, 1H), 6.76 (d, J = 8.2 Hz, 2H), 7.12 (m, 5H), 7.27-7.32 (m, 4H), 7.41 (bs, 5H), 7.62 (d, J = 14.8, 1H). ^{13}C NMR (CDCl_3): (one of the aromatic carbons was not observed potentially due to line broadening) δ = 37.7, 55.2, 58.2, 61.8, 68.3, 114.1, 117.7, 126.7, 126.9, 128.4, 128.7, 129.2,

130.3, 131.1, 134.8, 136.7, 144.9, 150.3, 159.6, 166.5. IR (CHCl₃): 1769, 1680, 1615, 831, 756, 701 cm⁻¹. ESI-HRMS calcd for C₂₇H₂₆N₂NaO₄ (M + Na⁺): 465.1785. Found: 465.1778.

N₃-(3-methylcinnamoyl)-N₄-para-methoxybenzyl oxadiazinone (91): To a 1000 mL flame-dried, nitrogen purged three-neck round bottomed flask was added copper bromide dimethyl sulfide complex (5.884 g, 28.62 mmol), tetrahydrofuran (THF) (27 mL, by syringe) and dimethyl sulfide solvent (27 mL by syringe), one after the other. The reaction was then cooled to a temperature of -78 °C. in a dry ice/ethanol bath. Methyl magnesium bromide (9.540 mL, 28.62 mmol) was then carefully added to the solution by syringe and left to stir for 45 minutes at -78 °C. The acylated heterocycle (4.221 g, 9.540 mmol) was dissolved in THF (30 mL) and then added by dropwise addition to the reaction vessel through an addition funnel. The reaction was left stirring for 15 hours while it gradually warmed up to room temperature. The reaction was then diluted with ethyl acetate (80 mL) and washed with 1M NaOH (20 mL), 1 M HCl (20 mL) and brine solution (20 mL). The recovered organic layer was dried with magnesium sulfate, filtered under gravity and solvent removed under high vacuum. The crude product obtained was purified by flash column chromatography (Hexane: ethyl acetate, 75:25) to yield 0.4291 g (9.8%) of the titled compound as a colorless oil: Significant peak broadening was observed in the ¹H NMR analysis of this compound, hence, no further analysis was conducted on it.

***N*-Isopropyl-L-phenylalaninol (94c):** A 1,000 mL round bottom flask was flame dried and nitrogen purged. L-Phenyl alaninol (15.1 g, 99.9 mmol) was added to the flask and dissolved in 1,2-dichloroethane (350 mL). To the solution was added reagent grade acetone (7.34 mL, 99.9 mmol), Sodium acetoxy borohydride ($\text{NaB(OAc)}_3\text{H}$) (29.67 g, 140 mmol) and acetic acid (6 mL), sequentially and stirred for about 22 hours at room temperature. The product was extracted with 6M NaOH (10 mL) and washed with brine. The organic product was dried over MgSO_4 , filtered under gravity and solvents-removed under reduced pressure to yield 8.43 g (44 %) of the target compound as a yellow oil. MP: 52-53 °C. ^1H NMR (CDCl_3): δ = 0.96 (d, J = 6.2 Hz, 3H), 1.02 (d, J = 6.2 Hz, 3H), 2.69 (dd, J = 7.2, 13.6 Hz, 1H), 2.75 (dd, J = 6.5, 13.5 Hz, 1H) 2.85 (sept, J = 6.2 Hz, 1H), 2.94-2.99 (m, 1H), 3.22 (dd, J = 5.9, 10.4 Hz, 1H), 3.54 (dd, J = 4.1, 10.4 Hz, 1H), 7.15-7.17 (m, 2H), 7.20-7.23 (m, 1H), 7.28-7.31 (m, 2H). ^{13}C NMR (CDCl_3): δ = 23.4, 38.5, 46.0, 57.3, 63.0, 126.4, 128.5, 129.2, 138.5. IR (neat): 2964, 1479, 1039 cm^{-1} . ESI-HRMS calcd for $\text{C}_{12}\text{H}_{21}\text{NO}$ ($\text{M} + \text{H}^+$): 194.1539. Found: 194.1540.

(S)-2-(N-Isopropyl-N-nitroso-amino)-3-phenyl-1-propanol (94d): To the *N*-isopropyl-L-phenylalaninol (8.43g, 43.6 mmol) starting material in a 1,000 mL round bottomed flask was added sodium nitrite (NaNO_2) (4.00 g, 58.0 mmol), 3M HCl (22 mL) and tetrahydrofuran (THF) (50 mL) and stirred for 18 hours at room temperature. The reaction was diluted with ethyl acetate (150 mL) and washed with brine. The organic product was dried over MgSO_4 , filtered under gravity and solvents-removed under reduced pressure to yield 9.15 g (94 %) of the target *N*-isopropyl-N-nitroso-L-phenylalaninol. Only the major isomer is described: ^1H NMR (CDCl_3): δ = 0.77 (*d*, J = 6.8 Hz, 3H), 1.12 (*d*, J = 6.8 Hz, 3H), 3.22 (*dd*, J = 8.0, 13.7 Hz, 1H), 3.33 (*dd*, J = 7.1, 13.7 Hz, 1H), 3.78 (*dd*, J = 3.9, 11.8 Hz, 1H), 3.90 (*dd*, J = 6.7, 11.8 Hz, 1H) 4.14-4.25 (*m*, 1H), 4.37 (*bs*, 1H), 5.05 (*sept*, J = 6.8 Hz, 1H), 7.17-7.27 (*m*, 3H), 7.30-7.34 (*m*, 2H). IR (CHCl_3): 3411, 3027, 1601, 1454, 1172, 744, 701 cm^{-1} . ESI-HRMS calcd for $\text{C}_{12}\text{H}_{18}\text{N}_2\text{O}_2$: 222.1368. Found: 222.1371.

(S)-2-(N-Amino-N-Isopropyl)amino-3-phenyl-1-propanol (95): To the N-isopropyl-N-nitroso-L-phenylalaninol (9.150 g, 41.16 mmol) starting material in a 1,000 mL round bottomed flask was added methanol (83 mL) and heated under reflux until temperature rises up to 50°C. The reaction was heated at 50°C for five minutes, aqueous NaOH (1M, 412 mL, 412 mmol) was then added. This was followed with the addition of formamidine sulfinic acid (22.25 g, 205.8 mmol) Still maintaining the temperature, and stirred for 5 hours. The product was extracted three times with dichloromethane (50 mL each). The resulting organic layers were combined and washed with brine (20 mL). The organic product was dried over MgSO₄, filtered under gravity and solvents-removed under reduced pressure to yield 7.226 g (84 %) of the target hydrazine which was initially an oil but turned a white solid upon refrigeration. MP: 59-61 °C. ¹H NMR (CDCl₃): δ = 1.13 (d, *J* = 6.3 Hz, 3H), 1.17 (d, *J* = 6.3 Hz, 3H), 2.74 (dd, *J* = 10.3, 13.1 Hz 1H), 2.83 (dd, *J* = 3.9, 13.1 Hz, 1H), 2.94 (sept, *J* = 6.3, 12.6 Hz, 1H), 3.05-3.10 (m, 1H), 3.53-3.58 (m, 2H), 7.17-7.21 (m, 3H), 7.26-7.29 (m, 2H). ¹³C NMR (CDCl₃): δ = 19.8, 20.9, 30.0, 55.3, 63.1, 126.1, 128.1, 129.2, 139.5.

(S)-5-Benzyl-4-Isopropyl-1,3,4-oxadiazinone (94): Tetrahydrofuran (THF) (90 mL) was added to the N₄-Isopropyl hydrazine (7.23 g, 34.7 mmol) starting material in a nitrogen purged 1 L round bottomed flask and left to homogenize at room temperature. Carbonyl diimidazole (CDI) (5.91 g, 36.5 mmol) was then added and left to stir for 18 hours at room temperature. The solution was subjected to rotary evaporation to remove the THF solvent and the resulting viscous oil was diluted with dichloromethane (120 mL) and washed with 1 M HCl (20 mL) and brine (20 mL). The recovered organic layer was dried over MgSO₄, filtered under gravity and solvents-removed under reduced pressure. The crude product was purified by flash column chromatography (hexanes: ethyl acetate, 50:50) to yield 6.28 g (77 %) of the N₄-isopropylloxadiazinone target as a light-yellow solid. MP: 90-91 °C. ¹H NMR (CDCl₃): δ = 1.02 (d, *J* = 6.2 Hz, 3H), 1.18 (d, *J* = 6.2 Hz, 3H) 2.84 (dd, *J* = 8.7, 13.9 Hz, 1H), 2.95 (dd, *J* = 6.6, 13.9 Hz, 1H) 3.02 (sxt, *J* = 6.2, 12.4 Hz, 1H), 3.30-3.33 (m, 1H), 4.08 (dd, *J* = 1.2, 11.5 Hz, 1H), 4.45 (dd, *J* = 3.5, 11.5 Hz, 1H) 6.84 (s, 1H), 7.21-7.25 (m, 3H), 7.29-7.32 (m, 2H). ¹³C NMR (CDCl₃): δ = 20.3, 20.4, 36.9, 53.1, 55.9, 64.3, 126.6, 128.6, 129.3, 138.0, 152.7. IR (CCl₄): 3514, 1702, 1093, 754 cm⁻¹. ESI-HRMS calcd for C₁₃H₁₈N₂NaO₂ (M + Na⁺): 257.1260. Found: 257.1252.

(S)-5-Benzyl-3-*trans*-cinnamoyl-4-isopropyl-1,3,4-oxadiazinone (96): To a flame-dried nitrogen-purged 500 mL round bottom flask was added the oxadiazinone substrate (3.360 g, 14.34mmol) which was dissolved in anhydrous dichloromethane (80.00 mL). To the solution was added *trans*-cinnamic acid (2.550 g, 17.21 mmol), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) (3.300 g, 17.21 mmol), and 4-dimethylaminopyridine (DMAP) catalyst (0.440 g, 3.585 mmol) sequentially. The reaction was allowed to stir for 18 hours at room temperature, after which it was diluted with dichloromethane (80 mL) and washed with 1 M HCl (20 mL), 1M NaOH (20 mL) followed by brine (20 mL) wash. The organic layer thus recovered was dried over magnesium sulfate, gravity filtered, and solvent removed under reduced pressure. The crude product obtained was purified by flash column chromatography (hexane: ethyl acetate, 75:25) to yield 1.564 g (30%) of the title compound as a yellow oil: IR (neat): 1780, 1674, 1623, 1285, 1226, 733, 702 cm^{-1} . The acylated product thus obtained was taken through the conjugate addition reaction without further analysis.

(S)-5-Benzyl-4-isopropyl-3-(3'-phenylbutanoyl)-1,3,4-oxadiazinone (98): To a 100 mL flame dried, nitrogen purged three-neck round bottomed flask was added copper bromide dimethyl sulfide complex (0.722 g, 3.51 mmol), tetrahydrofuran (THF) (4 mL, by syringe) and dimethyl sulfide solvent (4 mL, by syringe), one after the other. The reaction was then cooled to a temperature of -78 °C in a dry ice/ethanol bath. Methyl magnesium bromide (1.17 mL, 3.51 mmol) was then carefully added to the solution by syringe and left to stir for 45 minutes at -78 °C. The acylated heterocycle (0.426 g, 1.17 mmol) was dissolved in THF (4 mL) and then added by dropwise addition to the reaction vessel via an addition funnel. The reaction was left stirring for 15 hours while it gradually warmed up to room temperature. The reaction was then diluted with ethyl acetate (80 mL) and washed with 1M NaOH (20 mL), 1 M HCl (20 mL) and brine solution (20 mL). The recovered organic layer was dried with magnesium sulfate, filtered under gravity and solvent removed under high vacuum. The crude product obtained was purified by flash column chromatography (hexanes: ethyl acetate, 85:15) to yield 0.211 g (47%) of the titled compound as a colorless oil: ^1H NMR (CDCl_3): δ = 0.96 (app. t, J = 5.9 Hz, 6H), 1.36 (d, J = 7.0 Hz, 3H), 2.09 (dd, J = 7.8, 13.6 Hz, 1H), 2.47 (dd, J = 6.5, 13.6 Hz, 1H), 2.90-2.97 (m, 2H), 3.14-3.28 (m, 2H), 3.36-3.45 (m, 2H), 4.15 (dd, J = 7.0, 11.4 Hz, 1H), 7.15-7.31 (m, 10H). ^{13}C NMR (CDCl_3): δ = 19.6, 20.2, 22.3, 37.3, 39.1, 43.6, 56.9, 57.6, 68.1, 126.6, 126.8, 127.2, 128.5,

128.6, 129.3, 137.0, 145.8, 154.0, 172.0. IR (neat): 1789, 1731, 1604, 1289, 1218, 701, 667 cm^{-1} .

ESI-HRMS calcd for $\text{C}_{23}\text{H}_{28}\text{N}_2\text{NaO}_3$ ($\text{M} + \text{Na}^+$): 403.1992. Found: 403.1984.

(S)-5-Benzyl-3-*trans*-crotonyl-4-isopropyl-1,3,4-oxadiazinone (97): To a flame-dried nitrogen-purged 250 mL round bottom flask was added the oxadiazinone substrate (1.50 g, 6.40 mmol) which was dissolved in anhydrous dichloromethane (32.0 mL). To the solution was added the sodium hydride (0.310 g, 12.80 mmol). The reaction was allowed to stir for 10 minutes and the crotonyl chloride (0.64 mL, 6.7 mmol) was then added. The reaction was left stirring for 18 hours at room temperature, after which it was diluted with dichloromethane (50 mL) and washed with 1 M HCl (20 mL) and brine (20 mL). The organic layer thus recovered was dried over magnesium sulfate, gravity filtered, and solvent removed under reduced pressure. The title compound was isolated in a yield of 0.345 g (18%) after purification by flash column chromatography (hexanes: ethyl acetate, 75:25). ¹H NMR (CDCl₃): δ = 1.06 (d, *J* = 6.3 Hz, 6H), 1.95 (dd, *J* = 1.7, 6.9 Hz, 3H), 2.63 (dd, *J* = 7.8, 13.7 Hz, 1H), 2.91 (dd, *J* = 6.7, 13.7 Hz, 1H), 3.11 (p, *J* = 6.2 Hz, 1H), 3.65 (p, *J* = 7.3 Hz, 1H), 3.90 (dd, *J* = 7.7, 11.6 Hz, 1H), 4.40 (dd, *J* = 6.9, 11.6 Hz, 1H) 6.80 (dq, *J* = 1.6, 15.2 Hz, 1H), 7.16 (dq, *J* = 6.9, 15.2 Hz, 1H), 7.20-7.23 (m, 2H), 7.25-7.26 (m, 1H), 7.30-7.33 (m, 2H).

(S)-5-Benzyl-4-isopropyl-3-(3'-phenylbutanoyl)-1,3,4-oxadiazinone (99): To a 100 mL flame dried, nitrogen purged three-neck round bottomed flask was added copper bromide dimethyl sulfide complex (0.703 g, 3.42 mmol), tetrahydrofuran (THF) (4 mL) by syringe and dimethyl sulfide solvent (4 mL) by syringe, one after the other. The reaction was then cooled to a temperature of -78 °C in a dry ice/ethanol bath. Phenylmagnesium bromide (1.14 mL, 3.42 mmol) was then carefully added to the solution by syringe and left to stir for 45 minutes at -78 °C. The substrate (**97**) (0.345 g, 1.14 mmol) was dissolved in THF (4 mL) and then added by dropwise addition to the reaction vessel via an addition funnel. The reaction was left stirring for 15 hours while it gradually warmed up to room temperature. The reaction was then diluted with ethyl acetate (80 mL) and washed with 1M NaOH (20 mL), 1 M HCl (20 mL) and brine solution (20 mL). The recovered organic layer was dried with magnesium sulfate and filtered under gravity followed by the removal of the solvent under high vacuum. The crude product obtained was purified by flash column chromatography (hexanes: ethyl acetate, 85:15) to yield 0.306 g (70%) of the titled compound as a yellow oil. ¹H NMR (CDCl₃): δ = 0.96 (app. t, *J* = 5.8 Hz, 6H), 1.36 (d, *J* = 7.0 Hz, 3H), 2.09 (dd, *J* = 7.8, 13.5 Hz, 1H), 2.47 (dd, *J* = 6.4, 13.5 Hz, 1H), 2.89-3.03 (m, 2H), 3.14-3.28 (m, 2H), 3.36-3.69 (m, 2H), 4.15 (dd, *J* = 7.0, 11.5 Hz, 1H), 7.22-7.26 (m, 3H), 7.27-7.30 (m, 3H). ¹³C NMR (CDCl₃): δ = 19.6, 20.3, 21.8, 35.9, 39.1, 43.5, 57.2, 57.8, 68.0, 126.4, 126.9, 127.1, 128.5, 128.7, 129.2, 136.8, 145.9, 152.9, 172.5. IR (neat): 1786,

1724, 1604, 1218, 759, 701 cm^{-1} . ESI-HRMS calcd for $\text{C}_{23}\text{H}_{28}\text{N}_2\text{NaO}_3$ ($\text{M} + \text{Na}^+$): 403.1992.

Found: 403.1982.

Benzophenone imine of phenylalaninol (112): To a 1,000 mL, flame dried, nitrogen purged round bottom flask was added anhydrous dichloromethane (250 mL), Benzophenone imine (11.7 mL, 69.4 mmol) and L-Phenyl alaninol (10.0 g, 66.1 mmol) sequentially, and left to stir for 24 hours at room temperature. The reaction was then washed with brine (20 mL), dried over MgSO_4 , filtered under gravity and solvents-removed under high vacuum. The target benzophenone imine of phenylalaninol was isolated as a yellow solid which was recrystallized with ethyl acetate (30 mL) and hexane (2 mL). The pure yellow crystals were recovered by vacuum filtration and washed with hexanes and air-dried at room temperature. First and second seeds were obtained which yielded a total amount of 20.12 g (97 %) of the title compound as a white solid: MP: 121-124 °C; ^1H NMR (CDCl_3) : δ = 2.13 (s, 1H), 2.84 (dq, J = 5.4, 7.8 Hz, 2H), 3.66-3.71 (m, 2H), 3.77-3.91 (m, 1H), 6.64 (d, J = 7.1 Hz, 2H) 6.94-6.96 (m, 2H), 7.12-7.20 (m, 3H), 7.26-7.39 (m, 6H), 7.55-7.62 (m, 2H). ^{13}C NMR (CDCl_3): δ = 39.1, 39.8, 59.6, 65.5, 66.2, 70.5, 100.0, 125.8, 126.0, 126.3, 126.5, 127.4, 127.6, 127.8, 128.1, 128.2, 128.3, 128.6, 128.9, 129.8, 130.1, 136.7, 138.6, 138.9, 139.7, 144.6, 169.8. IR (CHCl_3): 3232, 1620, 1294, 732, 700 cm^{-1} . ESI-HRMS calcd for $\text{C}_{23}\text{H}_{28}\text{N}_2\text{NaO}_3$ ($\text{M} + \text{Na}^+$): 338.1515. Found: 338.1505.

L-N-diphenylmethyl phenylalaninol (113) : To a 250 mL flame dried, nitrogen purged round bottom flask was added Benzophenone imine of phenylalaninol (4.00 g, 12.7 mmol), tetrahydrofuran (THF) (20 mL), methanol (20 mL) and sodium borohydride (NaBH₄) (0.72 g, 19.0 mmol) sequentially, and left to stir for 1 hour at room temperature, after which the solution was placed on rotary evaporator to remove the methanol. The concentrated solution was then diluted with dichloromethane (80 mL) and washed with 1 M NaOH (20 mL) and brine (20 mL). The organic layer was dried over MgSO₄, filtered under gravity and solvents-removed under high vacuum to yield 3.89 g (97 %) of the title compound as a colorless viscous oil: ¹H NMR (CDCl₃): δ = 2.74 (dd, *J* = 6.0, 12.7 Hz, 1H), 2.82-2.91 (m, 2H), 3.34 (dd, *J* = 4.5, 10.7 Hz, 1H), 3.60 (dd, *J* = 3.4, 10.7 Hz, 1H) 4.92 (s, 1H), 7.07-7.14 (m, 4H), 7.17-7.25 (m, 5H), 7.27-7.33 (m, 6H). ¹³C NMR (CDCl₃): 38.4, 57.5, 63.1, 64.1, 126.4, 127.1, 127.17, 127.2, 127.4, 128.1, 128.6, 129.3, 129.8, 138.5, 143.58, 143.59. IR (CHCl₃): 3328, 1600, 1030, 745, 700 cm⁻¹.

N- N₄-diphenylmethyl-N₄-nitroso-L-phenyl-alaninol. (114): To the N₄-isopropyl-L-phenyl-alaninol (0.953 g, 3.00 mmol) starting material in a 1 L round bottomed flask was added Sodium nitrite (NaNO₂) (4.00 g, 58.0 mmol), 3M HCl (22 mL) and tetrahydrofuran (THF) (50 mL) and stirred for 18 hours at room temperature. The reaction was diluted with ethylacetate (150 mL) and washed with brine. The organic product was dried over MgSO₄, filtered under gravity and solvents-removed under reduced pressure to yield 9.15 g (94 %) of the titled compound as a yellow solid: 87-90 °C. ¹H NMR (CDCl₃): δ = 2.84 (dd, *J* = 4.9, 13.3 Hz, 1H), 3.23 (dd, *J* = 10.2, 13.3 Hz, 1H), 3.87 (dd, *J* = 5.2, 12.2 Hz, 1H) 3.96 (dd, *J* = 3.2, 12.2 Hz, 1H), 4.06-4.13 (m, 1H), 6.40 (s, 1H), 6.81-6.83 (m, 2H), 7.10-7.38 (m, 13H). ¹³C NMR (CDCl₃): (mixture of diastereomers), δ = 33.9, 38.8, 61.4, 63.7, 69.6, 76.8, 77.1, 77.4, 126.8, 126.9, 128.00, 128.05, 128.1, 128.2, 128.5, 128.6, 128.7, 128.73, 128.8, 128.83, 128.9, 129.1, 129.3, 129.9, 136.6, 137.1, 137.2, 138.9, 139.1; IR (CHCl₃): 3432, 3065, 1603, 1454, 1141, 733, 701 cm⁻¹. ESI-HRMS calcd for C₂₂H₂₂N₂NaO₂ (M + Na⁺): 369.1579. Found: 369.1570.

APPENDIX B: SELECTED NMR SPECTRA

500 MHz ^1H NMR spectrum of compound **34**

100 MHz ^{13}C NMR spectrum of compound **34**

500 MHz ^1H NMR spectrum of compound **43**

125 MHz ^{13}C NMR spectrum of compound **43**

500 MHz ^1H NMR spectrum of compound **59**

100 MHz ^{13}C NMR spectrum of compound **59**

500 MHz ^1H NMR spectrum of compound **60a**

125 MHz ^{13}C NMR spectrum of compound **60a**

500 MHz ^1H NMR spectrum of compound **70**

100 MHz ^{13}C NMR spectrum of compound **70**

500 MHz ^1H NMR spectrum of compound **71**

125 MHz ^{13}C NMR spectrum of compound **71** with line broadening

Chemical structure of compound 72 is shown. The structure is a 6-membered cyclic urea derivative with a methyl group on one nitrogen, a phenyl group on the adjacent carbon, and a 1-phenylpropan-2-yl group on the other nitrogen.

¹H NMR spectrum (CDCl₃) of compound 72. The spectrum shows peaks from 0 to 8 ppm. Key peaks are labeled:

- 2.9821, 3.9236, 4.3168, 0.8977, 0.9810, 1.0000, 1.0050, 3.0188, 3.0716, 2.9691, 1.2976, 1.2838, 0.9699, 0.9564, 5.0622, and a large aromatic multiplet between 7.1 and 7.4 ppm.

100 MHz ^{13}C NMR spectrum of compound **72** with line broadening

125 MHz ^{13}C NMR spectrum of compound **78**

500 MHz ^1H NMR spectrum of compound **81**

100 MHz ^{13}C NMR spectrum of compound **81**

500 MHz ^1H NMR spectrum of compound **80**

100 MHz ^{13}C NMR spectrum of compound **80**

500 MHz ^1H NMR spectrum of compound **82**

100 MHz ^{13}C NMR spectrum of compound **82**

500 MHz ^1H NMR spectrum of compound **84**

100 MHz ^{13}C NMR spectrum of compound **84**

500 MHz ^1H NMR spectrum of compound **86**

125 MHz ^{13}C NMR spectrum of compound **86**

500 MHz ^1H NMR spectrum of compound **87**

100 MHz ^{13}C NMR spectrum of compound **87**

500 MHz ^1H NMR spectrum of compound **89**

100 MHz ^{13}C NMR spectrum of compound **89**

500 MHz ^1H NMR spectrum of compound **90**

125 MHz ^{13}C NMR spectrum of compound **90** with line broadening

500 MHz ^1H NMR spectrum of compound **94c**

125 MHz ^{13}C NMR spectrum of compound **94c**

500 MHz ^1H NMR spectrum of compound **94d**

500 MHz ^1H NMR spectrum of compound **95**

100 MHz ^{13}C NMR spectrum of compound **95**

500 MHz ^1H NMR spectrum of compound **94**

125 MHz ^{13}C NMR spectrum of compound **94**

500 MHz ^1H NMR spectrum of compound **97**

500 MHz ^1H NMR spectrum of compound **98**

100 MHz ^{13}C NMR spectrum of compound **98**

500 MHz ^1H NMR spectrum of compound **99**

100 MHz ^{13}C NMR spectrum of compound **99**

500 MHz ^1H NMR spectrum of compound **112**

100 MHz ^{13}C NMR spectrum of compound **112**

500 MHz ^1H NMR spectrum of compound **113**

100 MHz ^{13}C NMR spectrum of compound **113**

500 MHz ^1H NMR spectrum of compound **114**

100 MHz ^{13}C NMR spectrum of compound **114**