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A recently isolated natural compound, Petaslignolide A, from the leaves of *Petasites japonicas*, has shown to be an effective neuroprotecting agent because of its antioxidant and anti-seizure activity. Recent studies have shown that the anti-seizure activity is dependent upon a metabolite of the natural product, 9-hydroxypinoresinol. Thus, the first total biomimetic synthesis was proposed to obtain 9-hydroxypinoresinol while employing metal-free organocatalysis. The synthesis utilizes the known Sonogashira Coupling reaction followed by hydrogenation using Lindlar's catalyst, epoxidation with *m*CPBA then ending with the highly complex step of metal-free organocatalysis to obtain 9-hydroxypinoresinol. Preliminary research in the use of metal-free organocatalysis approach were unsuccessful, thus a revised biomimetic synthesis was proposed. Previous reactions yielding the epoxide is further tosylated followed by coupling with 1-phenyl-3-butene-1-ol utilizing alkylation conditions. Further oxidation of the alkene using ozonolysis conditions then ends with metal-free organocatalysis. This revised synthesis provides promise to understanding the structure-activity relationship of the analogs to 9-hydroxypinoresinol and in turn, elucidating the mechanism of activity. The first total synthesis of 9-hydroxypinoresinol will allow the creation of a class of new novel anti-epileptic pharmaceuticals.

APPROACHES TOWARDS THE BIOMIMETIC SYNTHESIS OF 9-HYDROXYPINORESINOL ANALOGS: A STEPPING POINT IN THE DEVELOPMENT OF A NEW ANTI-SEIZURE DRUG

by

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of the Requirements for the Degree
Master of Science

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2013

Approved by

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Committee Chair

APPROVAL PAGE

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Committee Members ____________________________

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Date of Final Oral Examination

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CHAPTER I

BACKGROUND

I. A Natural Products and Drug Discovery[1-15]

Research in the chemical and biological make up of natural compounds is continually growing for the purpose of advancing knowledge in the realm of medicinal cures, environmental benefits, aiding of chemical research and economic demands. Natural products as the source for drug discovery are increasingly attractive to pharmaceutical companies due to the vast number of compounds that have been shown to be biologically active.[1] Before pharmaceutical companies started, people relied solely on plants and animals for food and medicine. Reports of traditional medicine systems start dating back to 2900-2600 BCE where in Mesopotamia, the people used oils such as cedar, cypress, liquorice, myrrh, and poppy juice for medicinal purposes. Traditional Chinese medicine has reports dating back to 1100 BCE where they document using 52 prescriptions and through the years increase to 850 drugs around 659 CE. Indian medicine starts reporting at 1000 BCE with using around 516 drugs for medicinal purposes. Greeks and Romans report using herbs as drugs dating back to 460-377 BCE. [9]It is in this time of Hippocrates, who is considered the "father of medicine", where they report using 400 drugs which were all plant-based mixtures. All those previous reports are using the natural compound obtained from the biological source.[9] It wasn't until much

later that chemists started looking into the biosynthesis and mechanism of action of those natural products.

In the time frame of 1803-1805, European chemists revolutionized drug discovery development by looking further into the pharmacology of different compounds.[9] Looking at alkaloids in particular, plant-derived alkaloids became of interest when morphine was isolated from the opium plant in 1817. Isolation of other well-known plant compounds such as caffeine in 1819, quinine in 1820 and codeine in 1833 were considered the start of pharmacology research into plants. Antibacterial agents such as penicillin and streptomycin were isolated toward the end of World War II in the 1940's. While amphotericin B was isolated 1950 as an antifungal agent. Nucleosides were found in 1950 that derivation was possible for differing antiviral agents. Antitumor agents were discovered in 1950, and came from pure microbial sourced compounds or modified microbial sourced compounds.[9] For a long time, plant compounds were used in many different medicine sources because of their exceptional biological specificity and "ready to use" availability.[17] Although, now plant compounds are targeted as starting reagents/ structural base for the synthesis of other compounds.[9]

According to a recent review, in the last 15 years research by pharmaceutical companies into natural products has declined. In particular, between 2001 and 2008, the number of natural products that were being looked into for possible drugs declined by 30%.[1] One of the main reasons for that decline was due to a higher demand for "blockbuster" drugs that produce strong benefit to cost ratios.[1] Pharmaceutical companies

have always had the paradigm “one drug-one target-one disease”[9] so there is not just a demand for the “blockbuster” drugs but for any drug which can be made quickly and bring profit. From the perspective of drug companies, the incentives push research towards quick development to get into the revenue stream as early as possible. Even if the impact of more long term natural product research has strong benefits from a societal perspective it struggles to align with the incentives pharmaceutical companies face because it is “not very amenable to rapid high-throughput screening (HTS).”[1]

The process of going from the natural product to a possible pharmaceutical drug, includes obtaining the biological resource, screening of the biological activity, structural analysis, design of structure-related analogs and ending with large scale production of the drug.[1,5] The process can be prolonged during screening of the natural product extracts against other compound libraries because there are thousands of structures in the database.[13,15] Moreover, the process can be drawn-out when access to the resources, such as plants, microorganisms and algae are limited. The demand for a total synthesis is due to the lack of resources and allows for an easier approach to obtaining the compound. Furthermore, a synthesis could provide structures of analogs from the natural product that are unavailable in the isolation process. In the process of designing a drug, a synthesis aids in the research of understanding the biological mechanism as well as adds another resource in validating the structure of the natural product.

I. B Natural Products Classification[2-14]

Natural products are split into two main categories: primary metabolites and secondary metabolites. Primary metabolites are present in all cells and are directly used in the metabolism and reproduction of cells. Known primary metabolites include amino acids, nucleic acids, carbohydrates and sugars. Secondary metabolites are defined as compounds that affect the primary metabolites and other organisms which vary between species.[2] The secondary metabolites are of interest and are classified into five main classes. These classes are based on structural differences determined by their biosynthesis: polyketides, terpenoids/steroids, phenylpropanoid compounds, alkaloids and a few special carbohydrates. The class of phenylpropanoid compounds contains coumarins, lignans, flavanones, anthocyanins, flavones, isoflavanoids, stillbenes and lignins.[6] The compound of interest, 9-hydroxypinoresinol (Figure 1) is classified as a lignan.

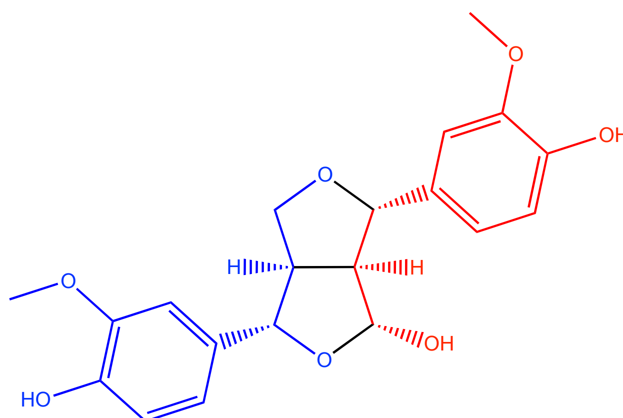


Figure 1. 9-hyroxypinoresinol

Lignans are described as a dimer of two phenylpropanoids (derivatives of phenylalanine) linked together by their central atoms which bear the side chain for each. The lignan class can be further split into many subclasses: furofurans, tetrahydrofurans, dibenzylbutanes, dibenzocyclooctadienes, etc.[6] Specifically, furofurans are considered to be one of the largest subclasses of natural product classification.[5,6] Since they are derivatives of phenylalanine, which is an amino acid, there is a biosynthesis for each furofuran lignan. A generalized biosynthesis starts with oxidative coupling of two phenylpropanoid compounds (ex. confieryl alcohol) by free-radicals (Figure 2).[12,14] Following the radical dimerisation, which builds the bridge of the two central rings, the radical intermediates are internally "trapped or captured" by the dirigent protein. The dirigent protein formulates the stereochemistry so the synthesis occurs in a regio- and enantioselective manner to give the furofuran structure (ex. (+/-) pinoresinol). [5,6,10,11,12]

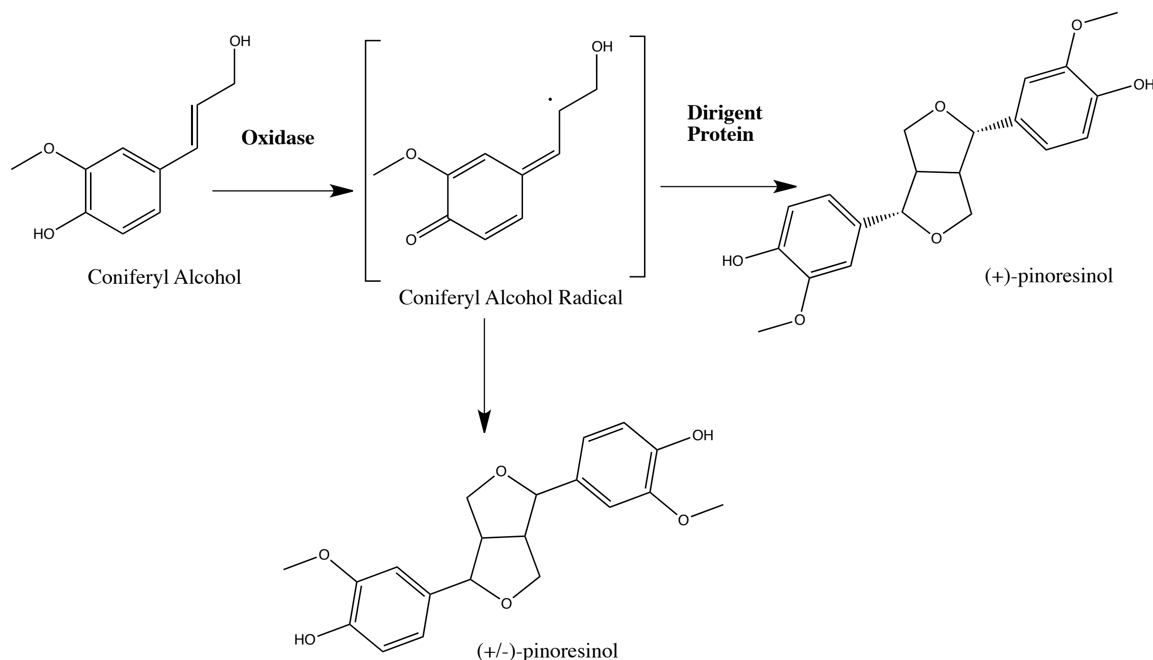


Figure 2. Generalized Biosynthetic Pathway of Lignans. Dirigent is Latin for "dirigere: to guide or align".[14] The dirigent protein serves as a common name since it can vary among different plants depending upon the enantioselectivity of the natural product.

The previously described biosynthesis (Figure 2) seems to be the consensus found in literature but there are other view points. A second example includes a route proposed by Dr. Mitchell Croatt which starts with oxidation of coniferyl alcohol to yield the coniferyl alcohol radical intermediate (Figure 3). Instead of oxidative coupling of two coniferyl alcohol intermediates (Figure 2), rather one radical intermediate attacks the alkene of an unoxidized coniferyl alcohol molecule and produces a benzylic radical. Now the compound is a dimer of two coniferyl alcohol compounds. The benzylic radical is then oxidized to form a cation and the alcohol of the first coniferyl alcohol molecule (blue) nucleophilically attacks the cation and forms the first tetrahydrofuran ring. In the

final step, the alcohol of the second coniferyl alcohol (brown) attacks the alkene and completes the second tetrahydrofuran ring to yield (+/-)-pinoresinol.

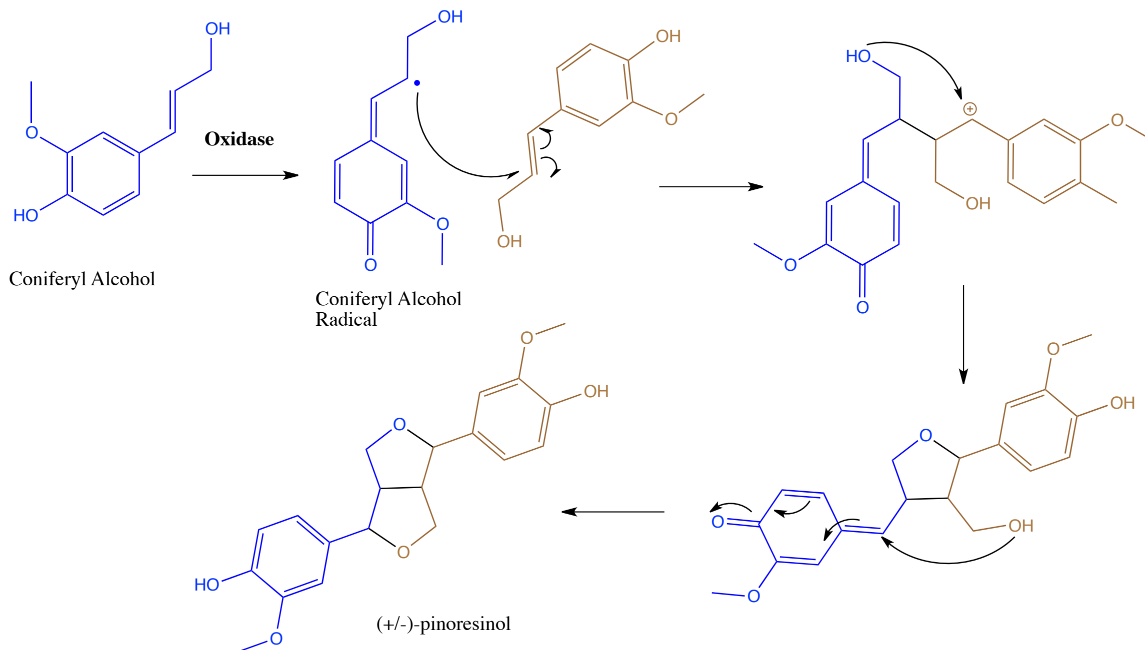


Figure 3. A second route to describe the Biosynthetic Pathway of Lignans

Looking further into the structural diversity of the furofuran lignans, some known furofurans will be discussed based upon their structural differences/commonalities in comparison to 9-hydroxypinoresinol. Pinoresinol, (+)-sesamin and (+)-eudesmin structures are as shown in Figure 4 as examples of furofuran lignans. Pinoresinol is the closest structure to 9-hydroxypinoresinol (Figure 1), only lacking the hydroxy group at the C9 position. It is found in the plant *Forsythia europaea* as the (+) form while the (-) form is found in *Daphne tangutica*.[5] (+)-Pinoresinol is found to be an antinociceptive agent which acts when painful stimuli is introduced by reducing the sensitivity.[13]

Sesame seeds come from *Sesamum indicum* and contain (+)-sesamin.[5,13] In comparing the structures, sesamin differs in the substituents on the phenyl rings, having dioxolane rings and also lacking the hydroxy group at the C9 position. Sesamin is known as an antitubercular agent which is used in the treatment of tuberculosis.[13] Tuberculosis is an infectious bacteria-related disease which affects the lungs and sometimes other parts of the body. Eudesmin is found in the plant *Araucaria angustifolia* and is known to be a neuroprotective compound by inhibiting tumor necrosis factor-α production and T-cell proliferation.[5,10,13]

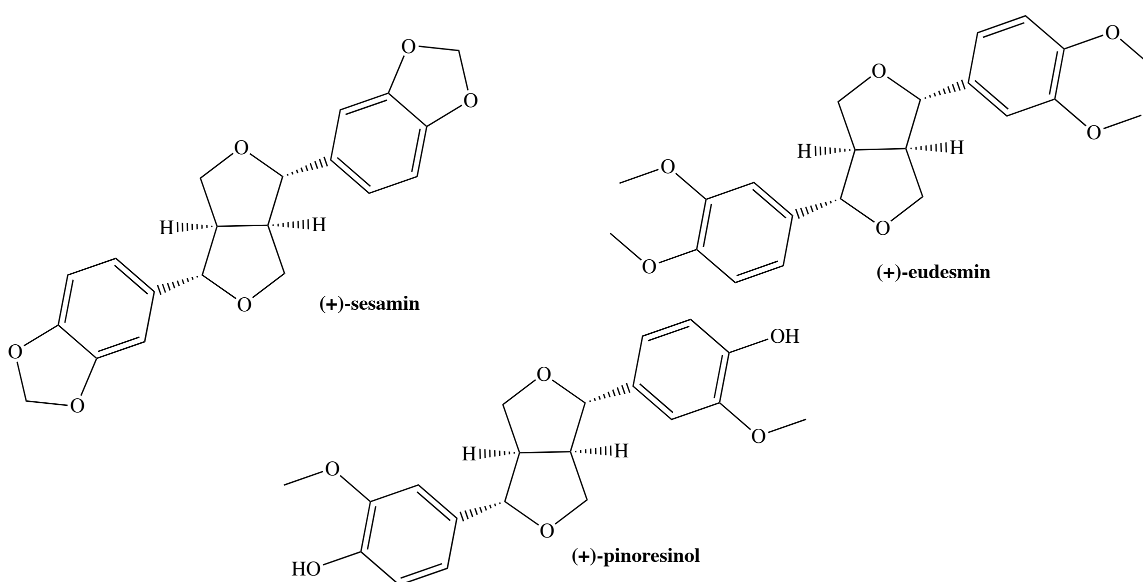


Figure 4. The structures of (+)-pinoresinol, (+)-eudesmin and (+)-sesamin

Many previous syntheses are known for all three of the compounds.[3,4,10] Andrew Pelter and his group show two very different routes to achieve pinoresinol, sesamin, eudesmin and other structurally unique lignans (Figure 5). The first route is an overall six

step synthesis producing the isomeric lignans via their corresponding dioxo-diesters.[8] The second route is considered the first "unambiguous synthesis" because it does not contain ring-opening intermediates which are common to previous syntheses. The synthesis is only two steps starting with oxidative coupling of ferulic acid derivatives with aqueous Iron (III) chloride to yield the dilactones. Further reduction of the dilactones with DIBAL yields the corresponding lignans.[7]

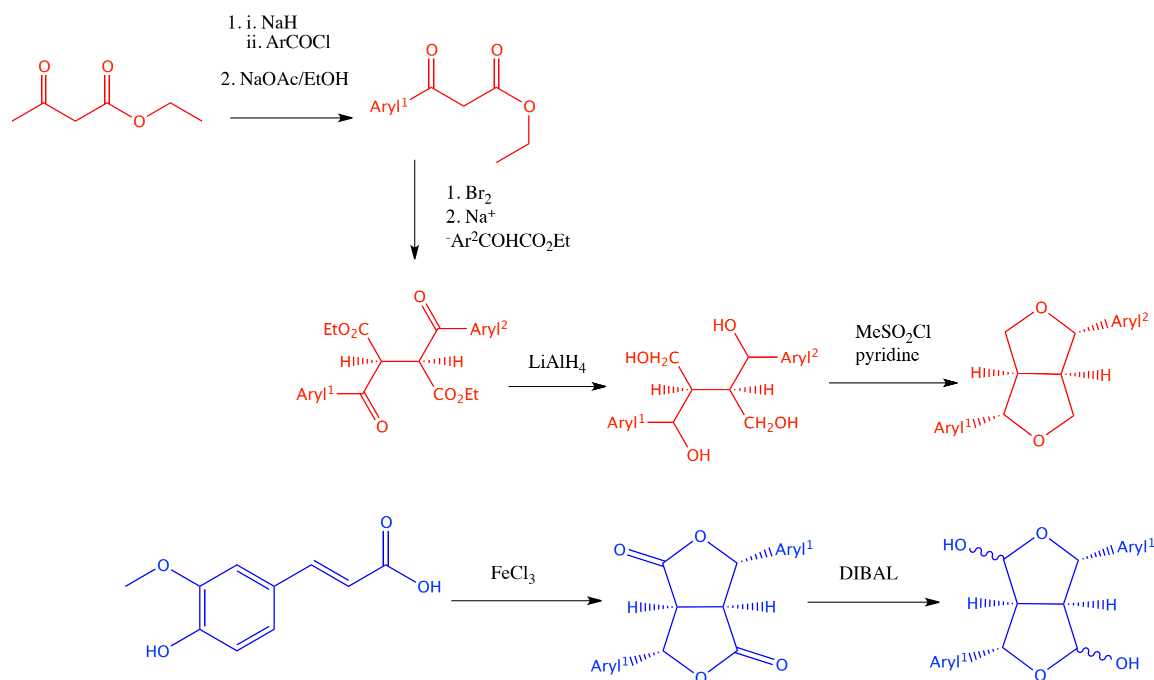


Figure 5. Andrew Pelter *et al.* routes to obtaining furofuran lignans. First route is in red and the second route is in blue.

I. C Background & Significance of Petaslignolide A[18-25]

Petaslignolide A was isolated from the leaves of *Petasites japonicas* which are native to Japan and Korea.[19] Originally, the plant served a wide variety of purposes in traditional oriental medicine such as treatment for asthma, oxidative stress and stomach ulcers.[19] Research on the Petasite plants has been ongoing for many years during which time many different compounds have been isolated with varying biological activity and molecular structure. An example is from *Petasites formosanus*, which contains *S*-Petasin, a sesquiterpene that is effective for use in treating hypertension.[13] Compounds in the extracts from the leaves of *Petasites japonicas* have been identified as polyphenolic due to the large number of (-OH) groups and aromatic rings present in the structure as shown in Figure 6.[18] Another term in the literature used to describe the structure of this type of compound is a lignan.

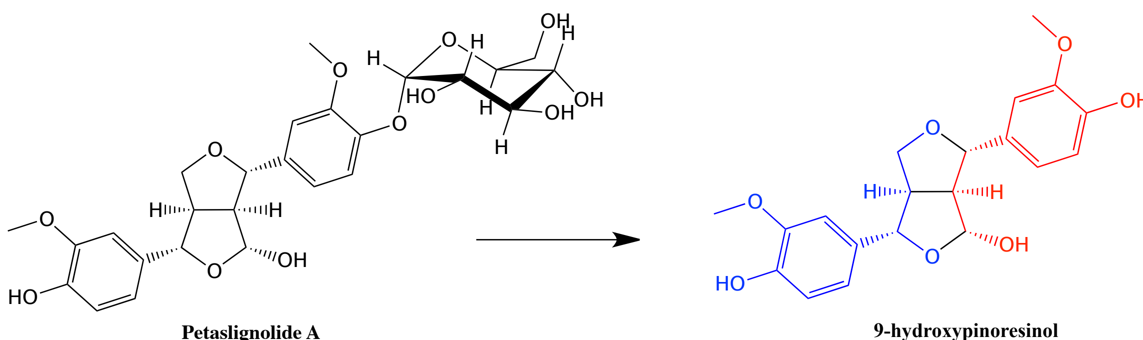


Figure 6. The structures of Petaslignolide A and 9-hydroxypinoresinol. Isolation yield from Petasites japonicas leaves of Petaslignolide A was 88 mg from 1.5 kg (0.0059%). Enzymatic deglycosylation with naringinase yields 9-hydroxypinoresinol with a purity of >90%.

Since the discovery of Petaslignolide A in 2005[19], which labeled the compound with antioxidant and anti-seizure activities, biological studies have been preformed to fully understand the mechanism of action. Originally, Petaslignolide A showed effective antioxidant activity in the DPPH radical scavenging activity, *in vitro* as well as *in vivo* against kainic acid neurotoxicity in mice. Results indicated that the antioxidant/anti-seizure activity was dependent upon the structural changes that take place during metabolism, in vivo, during which the glucose moiety was removed to yield 9-hydroxypinoresinol. Kainic acid is a central nervous system excitotoxin which produces seizures and sometimes can lead to neuronal death.

In 2007, the following report[21], antioxidant studies, *in vitro*, such as DPPH radical scavenging assays and Low density lipoproteins (LDL) incubated with Cu^{2+} were tested using the metabolized analog, 9-hydroxypinoresinol. Neuroprotection action using kainic acid induced neurotoxicity, *in vivo* were tested using 9-hydroxypinoresinol and Petaslignolide A. Antioxidant activity results indicated 9-hydroxypinoresinol was 4-fold more potent at preventing oxidation of the low density lipoproteins. Also, was 4.5-fold more effective at removing the oxidant radicals in the DPPH radical scavenging assays. Results of the neuroprotective action against kainic acid indicated 9-hydroxypinoresinol was more effective at delaying the onset time of the seizure, after kainic acid injection, than in comparison to Petaslignolide A. Mice were injected intraperitoneally with 9-hydroxypinoresinol, at different intervals of 2 hours, 24 hours and 3 days, prior to intraperitoneal injection of kainic acid. At every time interval, the onset time of the

seizure was increased, comparing to the control mice with no 9-hydroxypinoresinol. Longer pre-treatment, or multiple administrations, of 9-hydroxypinoresinol showed to further increase the onset time of the seizure in comparison to the single administration. An example of a single administration (30 mg/kg) at 24 hours before kainic acid injection, showed the time at which the seizure occurred was 22.0 ± 2.2 minutes. Multiple administrations (20 mg/kg) over 3 days before kainic acid injection, showed the time at which the seizure occurred was increased to 28.4 ± 3.1 minutes. These results indicate the build up of 9-hydroxypinoresinol in the body is important for more neuroprotective action to be seen. The effective dose of 9-hydroxypinoresinol was 10-20 mg/kg which is shown to be more efficient in comparison to reseratrol, curcumin, and naringenin. The metabolic pathway of 9-hydroxypinoresinol, *in vivo*, was unclear and obtaining structure-related analogs could help in determining the neuroprotective mechanism of action.

I. D Biomimetic Synthesis

A biomimetic synthesis was proposed to obtain 9-hydroxypinoresinol, and through structural modification of defined R-groups, obtain other analogs. Developing a synthesis would help provide a way to elucidate the mechanism of activity and create a class of new novel anti-epileptic pharmaceuticals. Retrosynthetically, the synthetic plan proposes that 9-hydroxypinoresinol can be made in only a few steps. Metal-free organocatalysis would be employed in the final step to combine the epoxide and an α, β-unsaturated aldehyde to form two tetrahydrofuran rings which are the core structure of 9-hydroxypinoresinol (Figure 7).

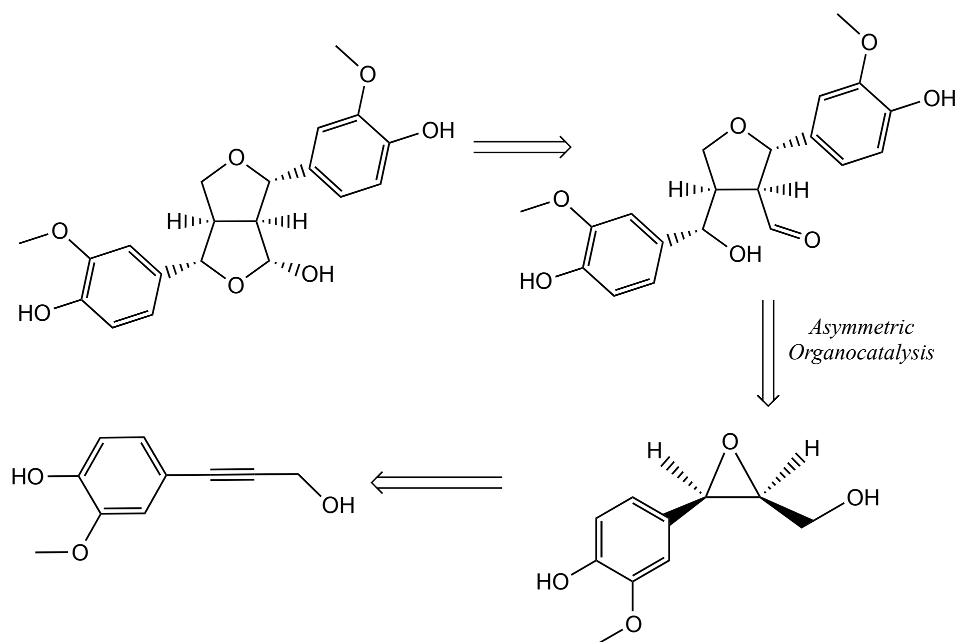


Figure 7. Retrosynthetic Design

I. E Organocatalysis and Proposed Mechanism[26-31]

Organocatalysis is of growing interest in organic chemistry, particularly in the synthesis of natural products and other chiral compounds in an enantioselective fashion. One of the main reasons it is of growing interest is because the catalysts are amino-acid derived, usually L-proline, and contain no inorganic metals. Metal-free catalysts can be less harmful, produce less toxic waste and be less expensive compared to organomettalic catalysts commonly used in organic synthesis. Popularity has grown due to the demand of enantiomerically pure drug compounds. Mechanistic properties of the organocatalysts vary depending on the substituents on the catalyst and substrates in the reaction conditions. Some known ways that the catalyst can act is as a Lewis acid/base (iminuim/

enamine) or as a Brønsted acid/ base. In the proposed retrosynthetic pathway, (Figure 7) the last step of the reaction goes through an organocatalyzed "iminuim-enamine" mechanism.[31]

The proposed "iminium-enamine" mechanism starts out with the organocatalyst **1** replacing the carbonyl oxygen of the aldehyde **2** and generating an iminium species **3** (Figure 8). The kinetics of the first step is very fast and in equilibrium with the starting reagents. The second step follows with a nucleophillic addition of the primary alcohol **4** to the electrophillic β-carbon **3** which generates an enamine species. The alcohol group in compound **4** is a reasonably good nucleophile and we propose equilibrium will proceed to the next step. After enamine species **5** is formed, the now nucleophillic α-carbon attacks the epoxide which opens it and concurrently forms the first tetrahydrofuran ring in **6**. Hydrolysis of the second iminium species **6** results in regeneration of the catalyst **1**. Hemi-acetal formation in **7**, from the alcohol to the aldehyde would yield the second tetrahydrofuran ring in **8**.

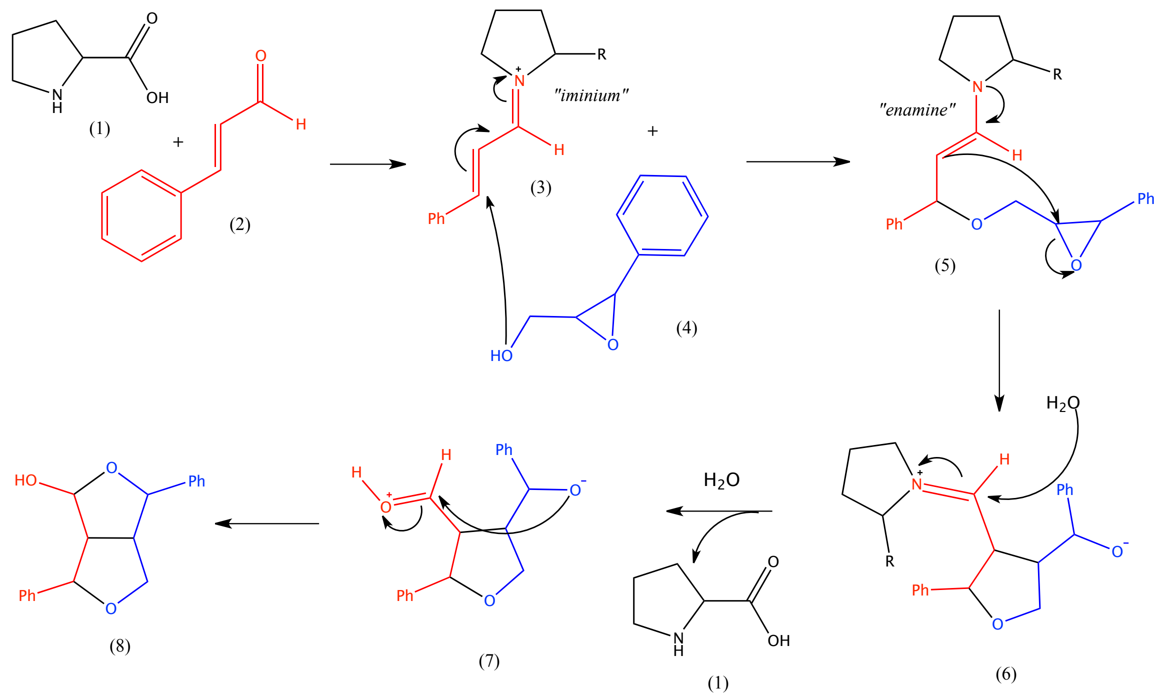


Figure 8. Proposed Organocatalysis Mechanism

In the scope of the proposed mechanism, it is also possible that after the enamine species is formed, the following mechanistic steps are highly kinetically controlled. This hypothesis is based on reactions that will be discussed in the results which show the time required for the reaction is not affected, even when temperature is increased. In accordance with this hypothesis and the proposed mechanism of action, various characterization techniques such as ^{1}H NMR and ^{13}C NMR will be used to help verify the mechanism and validate the structure.

CHAPTER II

EXPERIMENTAL

All reagents are commercially available and characterization by NMR was recorded on the Bruker AVANCE DRX 300 and JEOL ECA 500 MHz spectrometer at room temperature. For all the reaction procedures, optimum conditions are indicated after various trials of differing solvents, temperatures and reaction times were employed. Thin layer chromatography (TLC) in 50% EtOAC: 50% Hexane with vanillin staining was used in all procedures to determine completion of the reaction.

II. A 4-(3-hydroxyprop-1-yn-1-yl)-2-methoxyphenol[25]

In a 25 mL flask, $Pd(PPh_3)Cl_2$ (52.1 mg, 0.0742 mmol, 0.0251 eq.) and CuI (20.8 mg, 0.101 mmol, 0.0350 eq.) were added to a solution of 4-bromo-2-methoxyphenol (623.8 mg, 3.07 mmol, 1 eq.) in NEt_3 (5 mL). After stirring for a few minutes, propargyl alcohol (0.300 mL, 5.12 mmol, 1.6 eq.) was slowly added to the solution. The solution was allowed to stir at 80°C for 3 hours. The catalyst was filtered over a celite pad and concentrated under vacuum. Yield: 30% as an orange oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.06 (s, 1 H), 2.68 (d, *J* = 6.4 Hz, 1 H), 3.89 (s, 3 H) 4.29 (d, *J* = 2.5 Hz, 2 H), 6.80 (d, *J* = 8.3 Hz, 1 H), 6.96 - 7.02 (m, 2 H).

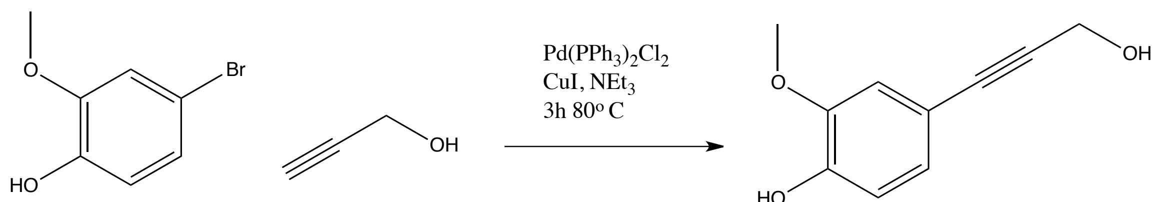


Figure 9. Sonogashira Coupling Reaction

II. B (*Z*)-3-phenyl-2-propen-1-ol[22,23]

In a 10 mL round bottomed flask, Lindlar's catalyst (101.4 mg, 0.905 mmol, 0.25 eq.) followed by quinoline (42 μL, 0.355 mmol, 0.1 eq.) was added to the solution of 3-phenylpropargyl alcohol (498.2 mg, 3.76 mmol, 1 eq.) in MeOH (5 mL) and placed under a hydrogen atmosphere. The reaction was stirred for 4 hours at room temperature. The catalyst was filtered off through a Celite pad two times and the resultant solution was concentrated under vacuum. Spectra was confirmed to be (*Z*)-3-phenyl-2-propene-1-ol in comparison to literature data. Yield: 95% as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.29 (br s, 1 H), 4.48 (d, *J* = 1.0 Hz, 2 H), 5.82 - 5.98 (m, 1 H), 6.58 (d, *J* = 11.7 Hz, 1 H), 7.19 - 7.24 (m, 1 H), 7.26 - 7.40 (m, 3 H), 7.41 - 7.50 (m, 1 H).

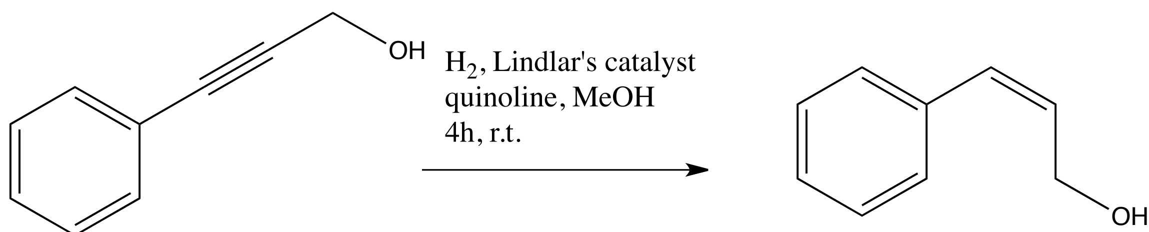


Figure 10. Hydrogenation Reaction

II. C *cis*-3-phenyl-2-oxiranemethanol[24]

To a stirred solution of 3-phenyl-2-propen-1-ol (225.9 mg, 1.68 mmol, 1 eq.) in THF (2.5 mL) in a 10 mL round bottom flask, *m*CPBA (387.7 mg, 2.25 mmol, 1.1 eq.) was added followed by an equivalent amount of THF (2.5 mL) until mCPBA was observed to have completely dissolved. The reaction was stirred at room temperature under argon for 24 hours until completion of the reaction as indicated by TLC. The reaction was quenched by the addition of an aqueous solution of $Na_2S_2O_3$ and allowed to stir for an additional 30 min. After the additional stirring, the solution was washed with saturated sodium bicarbonate, brine and DI water followed by extraction of the aqueous layers with ethyl acetate. The organic layers were dried over sodium sulfate, filtered and concentrated under vacuum. Purification by chromatography, on silica gel with EtOAc/ Hexane (1:1) as the eluent, was completed two times. Spectra was confirmed to be the *cis*-epoxide 3-phenyl-2-oxiranemethanol in comparison to literature spectra. Yield: 35% as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.10 (br s, 1 H), 3.41 - 3.61 (m, 2 H), 4.21 (d, J = 3.9 Hz, 2 H), 7.18 - 7.25 (m, 1 H), 7.29 - 7.43 (m, 4 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 57.2 (s, 1 C), 58.85 (s, 1 C), 60.5 (s, 1 C), 126.3 (s, 1 C), 128.0 (s, 2 C), 128.4 (s, 2 C), 134.7 (s, 1 C).

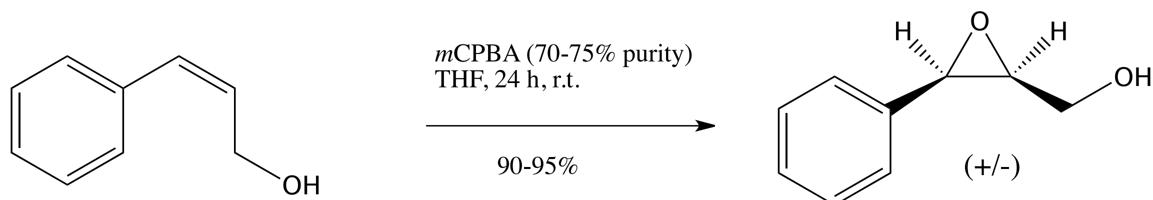


Figure 11. Epoxidation Reaction

For the organocatalytic reaction, various reaction conditions were tested using different catalysts (Catalysts I, II, III), temperatures, solvents, acid/base additives and time lengths. The experimental procedure for each of the varying reactions serves as a general guideline for set up and reagent equivalents. Based on the change in conditions, the general procedure was altered. All reactions were monitored by TLC in 50% EtOAc: 50% hexane with vanillin staining.

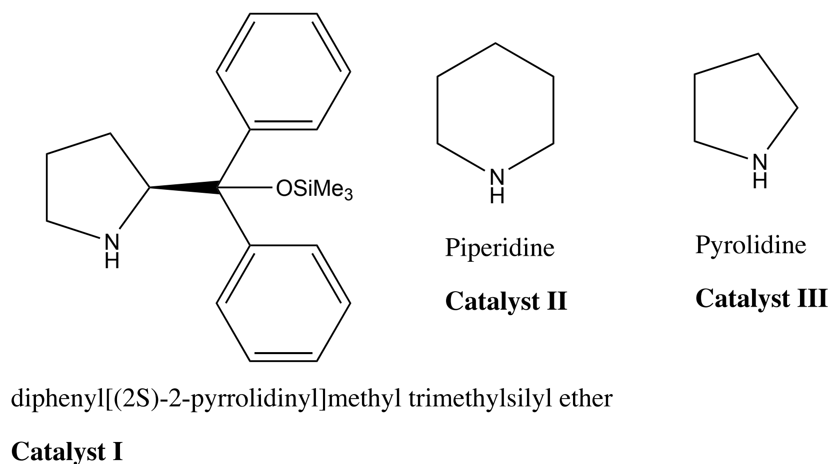


Figure 12. Structures of the varying catalysts for the organocatalysis reaction

II. D 9-hydroxypinoresinol analog (31) using Catalyst I

In a 10 mL round bottomed flask, 3-phenyl-2-oxiranemethanol (20 mg, 0.133 mmol, 1 eq.) and *trans*-cinnamaldehyde (25 μL, 0.199 mmol, 1.5 eq.) in the solvent (0.6 mL, 0.25 M) were allowed to stir for a few minutes following addition of Catalyst I (4 μL, 0.0133 mmol, 0.1 eq.). After further stirring of the reaction for a few minutes, acetic acid (0.8 μL, 0.0133 mmol, 0.1 eq.) was added. The reaction was allowed to stir at room temperature under argon until TLC indicated the starting epoxide was gone. The reaction was quenched with brine and allowed to stir for 10 min. After stirring, the solution was washed with excess brine and deionized water followed by extraction of the aqueous layers with EtOAc. The combined organic layers were dried over sodium sulfate, filtered and concentrated under vacuum. Purification was attempted by chromatography on silica gel with EtOAc/Hexane (1:1) as the eluent but the product was not obtained.

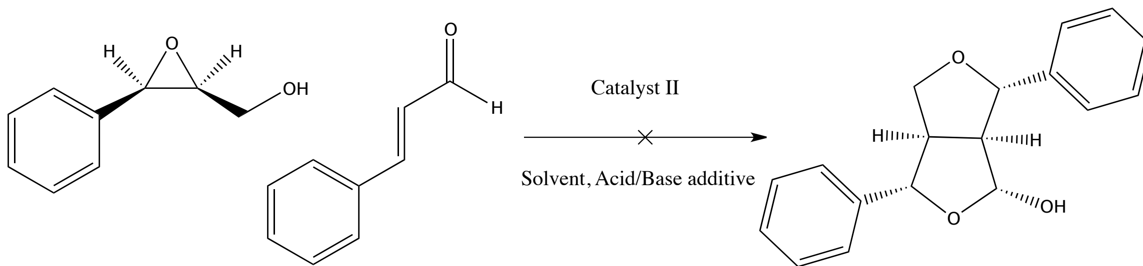


Figure 13. Catalyst I with 3-phenyl-2-oxiranemethanol and *trans*-cinnamaldehyde

II. E 9-hydroxypinoresinol analog (31) using Catalyst II

In a 10 mL round bottom flask, a solution of 3-phenyl-2-oxiranemethanol (20mg, 0.133 mmol, 1 eq.) and *trans*-cinnamaldehyde (25 μL, 0.199 mmol, 1.5 eq.) in piperdine (0.6 mL, 6.07 mmol, 45 eq.) were allowed to stir at room temperature under argon until TLC indicated the starting epoxide was completely gone. The reaction was then concentrated under vacuum to yield a thick orange oil. Purification was attempted by chromatography on silica gel with EtOAc/Hexane (1:1) as the eluent but the product was not obtained.

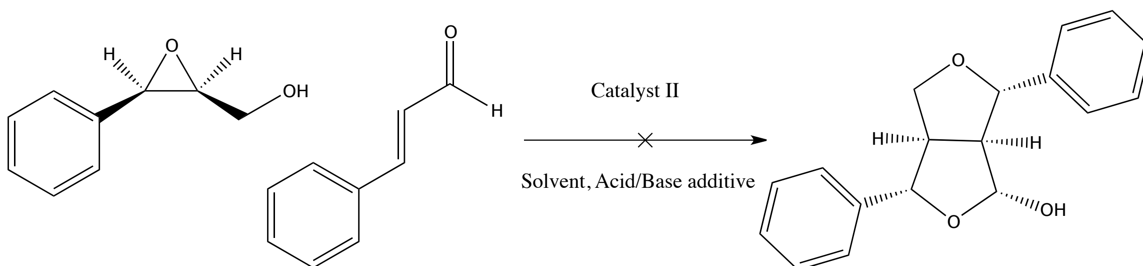


Figure 14. Catalyst II with 3-phenyl-2-oxiranemethanol and *trans*-cinnamaldehye

II. F 9-hydroxypinoresinol analog (26) using Catalyst II

The same procedure was employed as shown in II. E but with a different aldehyde reagent and catalyst.

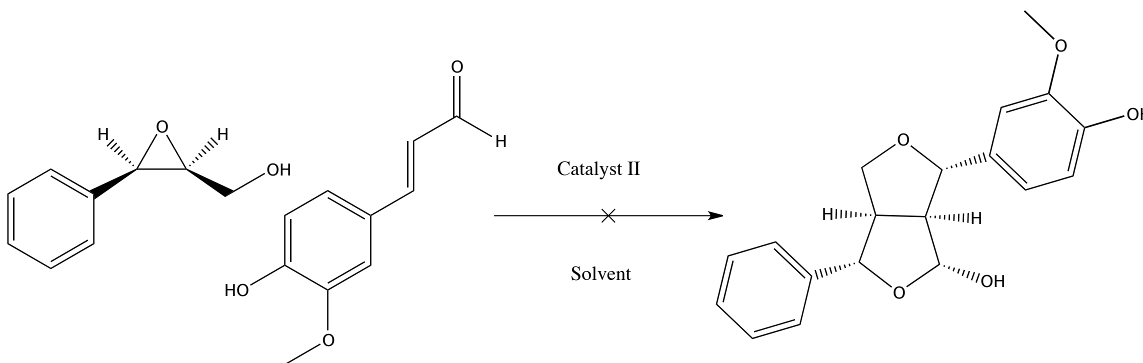


Figure 15. Catalyst II with 3-phenyl-2-oxiranemethanol and 4-hydroxy-3-methoxycinnamaldehyde

II. G 9-hydroxypinoresinol analog (26) using Catalyst II or III

In a 10 mL round bottom flask, a solution of 3-phenyl-2-oxiranemethanol (21.8 mg, 0.145 mmol, 1 eq.), 4-hydroxy-3-methoxycinnamaldehyde (36.5 mg, 0.205 mmol, 1.5 eq.) and catalyst II or III (0.5 mL, 5.76 mmol, 40 eq.) in $CDCl_3$ (4 mL) was allowed to stir at room temperature for 5-10 min then immediately characterized by ^{1}H and ^{13}C. NMR spectra were recorded at 5 min, 10 min and 25 min. Purification was attempted by chromatography on silica gel with EtOAc/Hexane (1:1) as the eluent but the product was not obtained.

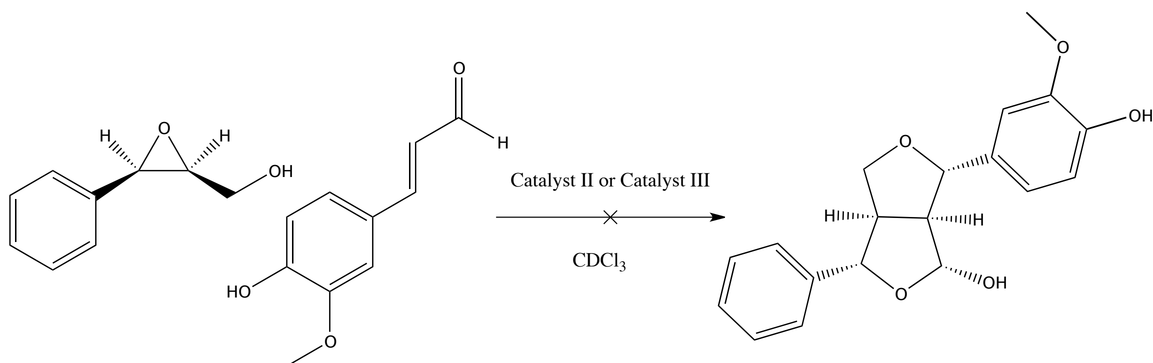


Figure 16. Catalyst II or Catalyst III with 3-phenyl-2-oxiranemethanol and 4-hydroxy-3-methoxycinnamaldehyde

II. H (3-phenyloxiran-2-yl)methyl 4-methylbenzenesulfonate[12]

In a 10 mL round bottom flask a solution of 3-phenyl-2-oxiranemethanol (19.38 mg, 0.129 mmol, 1 eq.) and *p*-toluenesulfonyl chloride (26.31 mg, 0.138 mmol, 1 eq.) in pyridine (0.140 mL, 1.74 mmol, 13.4 eq.) was allowed to stir at -15°C for 48 h. Temperature was controlled through the use of a CRYOTROL apparatus in an isopropanol bath. Due to the large staining of pyridine with vanillin, potassium permanganate stain was used instead for TLC. After 48 h, the reaction was quenched with excess aqueous ammonium chloride and the *p*-toluenesulfonyl chloride was filtered off. The solution was washed with deionized H_2O and extracted with DCM (3x). The combined organic layers were dried over sodium sulfate, filtered and concentrated under vacuum. Purification by chromatography on silica gel with EtOAc/Hexane (1:1) as the eluent was attempted. Yield 71% as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.44 (s, 3 H) 3.42 - 3.58 (m, 2 H) 3.82 - 3.90 (m, 2 H) 7.15 - 7.18 (m, 5 H) 7.26 - 7.37 (m, 4 H).

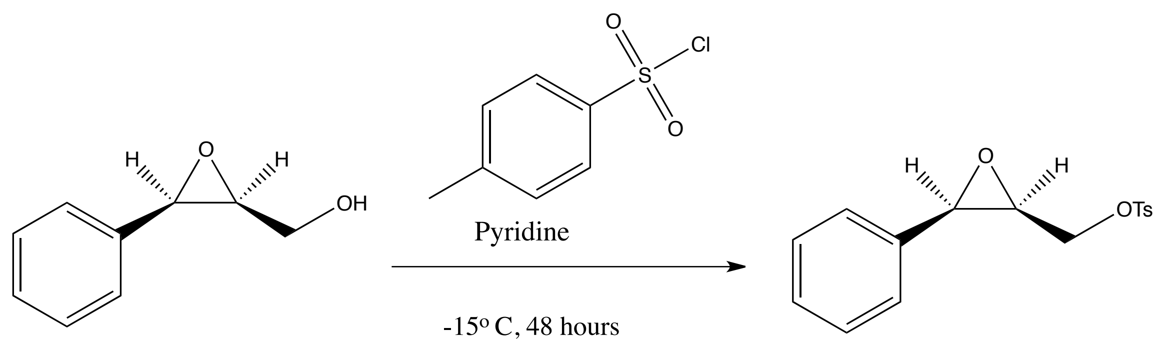


Figure 17. Tosylation Reaction

CHAPTER III

RESULTS AND DISCUSSION

III. A Original Biomimetic Synthesis Design

In the first step of the synthesis, the Sonogashira coupling reaction is used to couple propargyl alcohol (**2**) with 4-bromo-2-methoxyphenol (**1**) in order to achieve **3** which contains the appropriate substituents as shown in the desired parent compound (Figure 18). Steps two and three employ the previously described hydrogenation (Figure 10) and epoxidation reactions (Figure 11) to obtain the derivative of 3-phenyl-2-oxiranemethanol (**5**) to be used in the final step. The final step of the synthesis demonstrates high complexity because it utilizes a metal-free organocatalyst that is proposed to proceed through "iminium-enamine" catalysis (Figure 8), to form the final product.

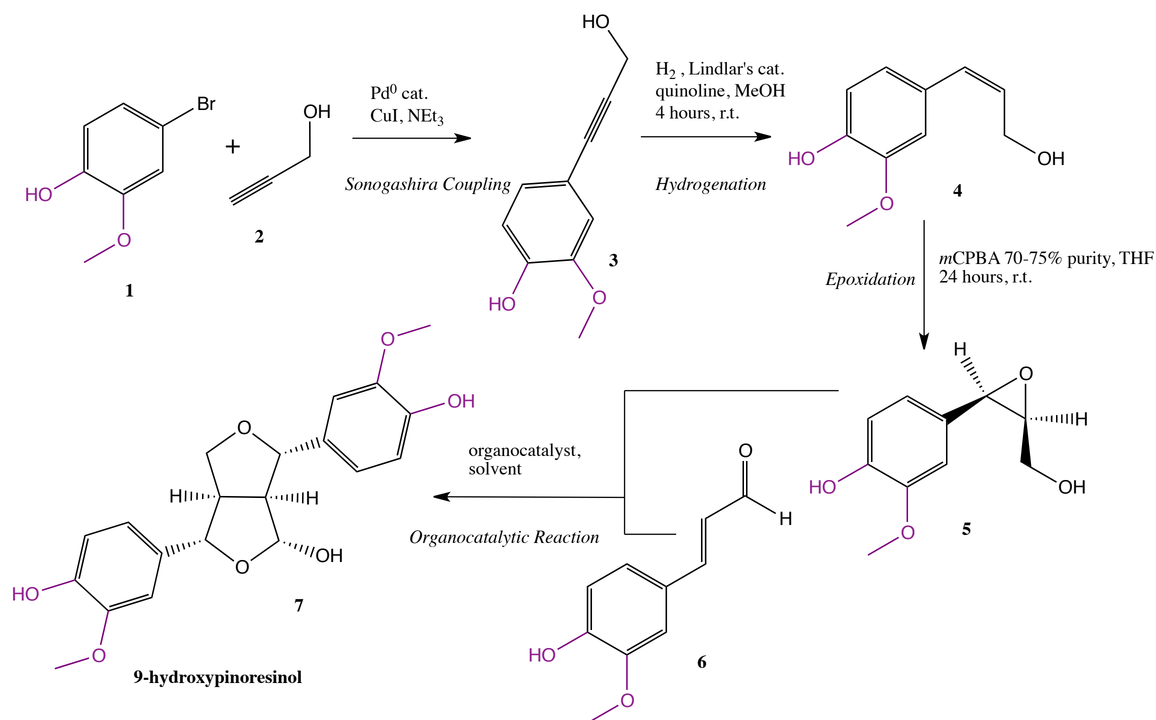


Figure 18. Original Synthetic Design

III. B Sonogashira Coupling Reaction

In the first step of the synthetic route the well-known Sonogashira coupling reaction is used to couple propargyl alcohol with 4-bromo-2-methoxyphenol in order to achieve the appropriate substituents as shown in the desired parent compound. Many reactions were attempted but were not easily reproducible possibly due to impurities in the starting materials. Proceeding on with the substrate in the subsequent steps was not attempted due to insufficient material.

Sonogashira coupling is defined through the use of a Pd^0 catalyst and a Cu^I co-catalyst to couple terminal alkynes with aryl halides. The mechanism, as shown in Figure

19, starts first with Pd^0 catalyst undergoing oxidative addition into the aryl bromide compound. In addition, deprotonation of the terminal alkyne and addition of the copper (I) iodide co-catalyst results in creation of the "Cu-acetylide species". Trans-metallation between the "Pd-halide species" and the "Cu-alkyne species" followed by reductive elimination, completes the coupling.

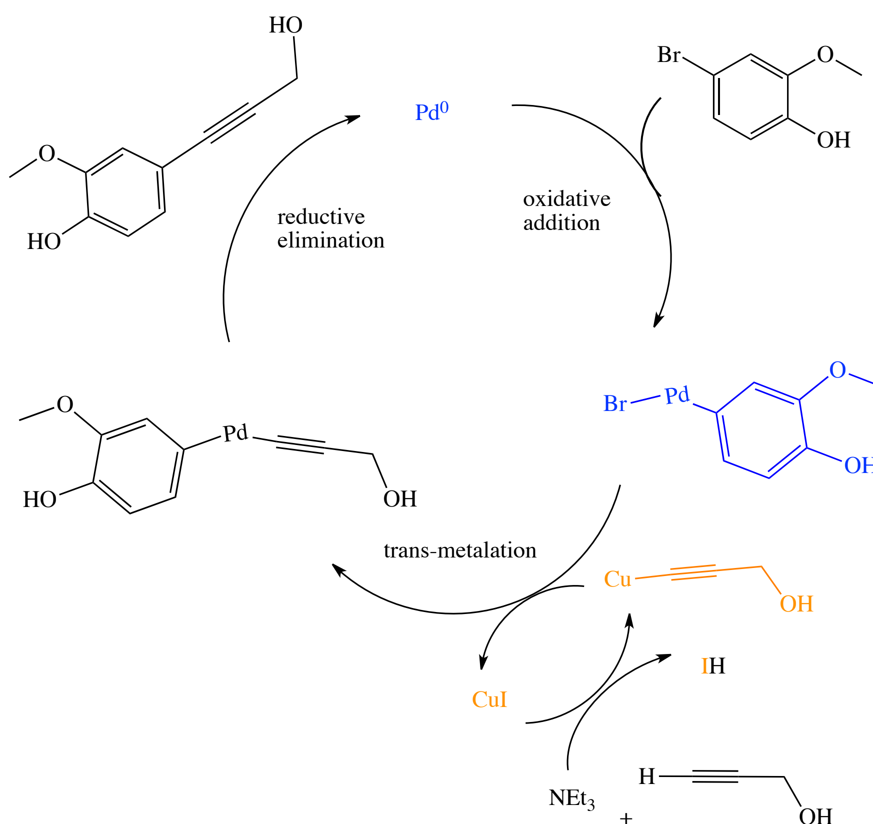


Figure 19. Sonogashira Coupling Mechanism

III. C Hydrogenation Reaction

The following steps of the synthesis (Steps 2-4) were established using a derivative of 9-hydroxypinoresinol. This approach was used in order to determine the optimum conditions in a quick timeline using low-cost reagents.

As stated previously, 3-phenylpropargyl alcohol was partially hydrogenated, to give the *cis*-alkene. Normal hydrogenation of an alkyne will give the alkane product through the use of Pd/C but using Lindlar's catalyst (Pd/C "poisoned" with Pb) allowed the reaction to stop at the alkene. Monitoring by TLC was simplified with the alkyne and alkene each staining a different color with vanillin. The alkyne stained green while the alkene stained purple. The reaction was very successful with high percent yields so purification was not needed and could be easily scaled up from milligrams to 2 grams scale.

III. D Epoxidation Reaction

As stated previously (*Z*)-3-phenyl-2-propen-1-ol was oxidized to yield the *cis* epoxide, *cis*-3-phenyl-2-oxiranemethanol, using *m*CPBA. After a few attempts, it was discovered that one of the *m*CPBA reagent bottles had been reduced and was not working in the reaction. The percent yields were generally good but ranged from 35% to 85%. The reaction was easily scaled up to a 2 gram scale. It was seen that upon scaling up, more basic washing was needed in order to completely remove the *m*CPBA or 3-chlorobenzoic acid. Monitoring by TLC was simplified with the alkene and epoxide each staining different colors with vanillin. The alkene stained purple while the epoxide stained

turquoise. TLC indicated the alkene and epoxide co-spotted in the same area, so purification by column chromatography was difficult. After purification was completed, ^{1}H NMR indicated separation was achieved thus the epoxide was ready to move on with the last step.

Epoxidation of an alkene and *m*CPBA (*meta*-chloroperoxybenzoic acid) proceeds through a concerted mechanism in which the alkene acts as the nucleophile and mCPBA is the electrophile. Hydrogen bonding between the hydrogen on the -OH and the carbonyl oxygen makes the -OH oxygen more electrophilic thus attracting the alkene resulting in the formation of an epoxide and 3-chlorobenzoic acid.

III. E Organocatalysis Reaction

Catalyst I (diphenyl 2-pyrrolidinyl methyl trimethylsilyl ether), is well known throughout organocatalysis literature and, when used, often gives successful results. Upon comparing the literature to this project, our reaction showed its uniqueness because there is no literature reference indicating use of an epoxide in this type of organocatalysis reaction. Catalyst II (piperidine) and III (pyrrolidine) are common cyclic amine sources, so it was proposed they would react similarly and serve as a possible catalyst. All experimental ^{1}H NMR and ^{13}C NMR were compared to the original paper by Min *et al*.[19] in which ^{1}H and ^{13}C NMR peak data are given for 9-hydroxypinoresinol.

In trial one, as seen in Table 1 using the known Catalyst I, many reaction conditions were tested under varying solvents, (toluene, H_2O, MeOH, THF, $CHCl_3$) and temperatures (r.t., 50°C) with reaction times varying from one week to three weeks.

Results of those various trials indicate that neither solvent nor heat had a major effect on the progression of the reaction. Acid/base additives such as acetic acid and sodium acetate were added to change the conditions of the solution, based on the proposed mechanism, but results indicated the desired product was not obtained. Analysis of the NMR results show only starting materials (Figure 20). Due to the unsuccessful results, piperidine was tried as another catalyst.

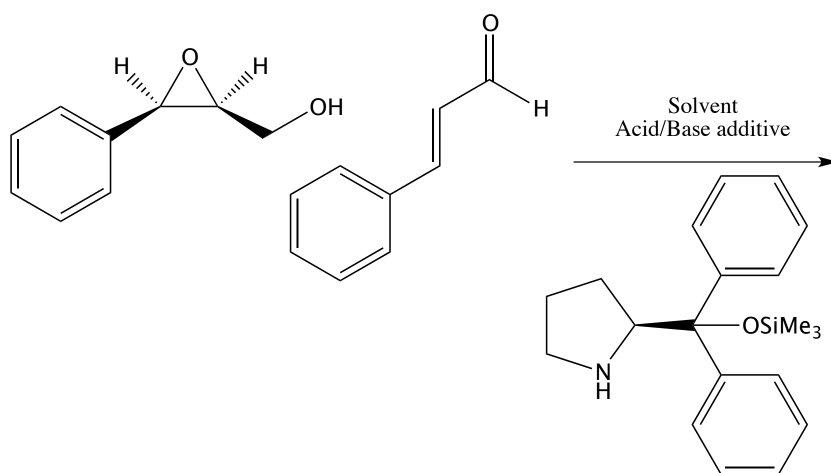


Figure 20. Substrates used in Trial 1

Table 1. Trial 1: varying reaction conditions with Catalyst I

Entry	Solvent--Additive	Temperature [°C]	Reaction Time [days]	Results
1	Toluene/H_2O--NaOAc	r.t.	8	No reaction
2	Toluene/H_2O--NaOAc	50	23	No reaction
3	MeOH/H_2O--NaOAc	r.t to 50	15	No reaction
4	MeOH	r.t.	15	No reaction
5	MeOH--Acetic Acid	r.t.	7	No reaction
6	THF--NaOAc	50	12	No reaction
7	$CHCl_3$--NaOAc	r.t.	12	No reaction

In trial 2, as seen in Table 2, piperidine (Catalyst II) was used (Figure 21). In this trial, piperidine served as both the catalyst and solvent thus varying temperature and presence of acid/base additive was attempted. Results indicated that for the piperidine reactions in which an additive (acid/base) was present, there was no presence of the desired product being formed, only starting material remained. On the other hand, the piperidine reaction without an additive showed a possibility of product formation, but it was very hard to analyze the crude reaction by ^{1}H NMR. Attempt at column chromatography only yielded the product decomposing and recovering starting materials. Since the reactions indicated that neither solvent nor temperature had an effect, the next attempt was to change the aldehyde source.

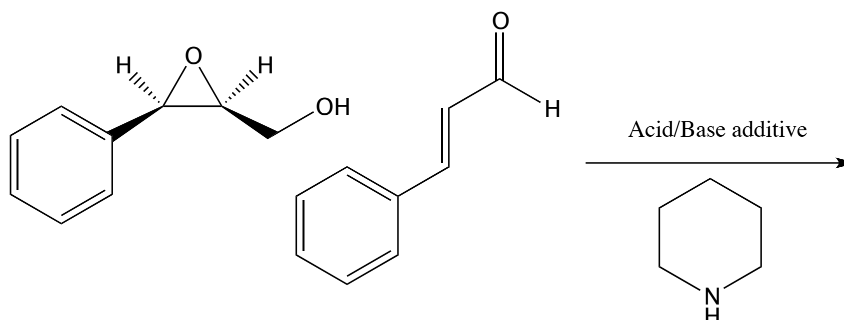


Figure 21. Substrates used in Trial 2

Table 2. Trial 2: varying reaction conditions with Catalyst II and *trans*-cinnamaldehyde

Entry	Solvent--Additive	Temperature [°C]	Reaction Time [days]	Results
1	Piperidine--NaOAc	r.t. to 50	11-13	No reaction
2	Piperidine--Acetic Acid	r.t.	3-51	No reaction
3	Piperidine	100	4	Decomposition
4	Benzene	reflux	1	No reaction

A cinnamaldehyde derivative, 4-hydroxy-3-methoxycinnamaldehyde, was chosen because it had the appropriate aryl groups which match the desired product. It can be theorized that the electron-donating effect of those groups could possibly change the outcome of the reaction. In trial 3, Catalyst II was tested with 4-hydroxy-3-methoxycinnamaldehyde (Figure 22). As seen in Table 3, various solvents and

temperatures were screened with each having varying reaction times. Crude ^{1}H NMR indicated a reaction was taking place, different from trial 2, but still not the desired product formation. Purification by chromatography was attempted to discover other possible products, but was unsuccessful with decomposition and recovery of starting materials. Each of the reactions were concentrated under vacuum before obtaining an ^{1}H NMR and being placed on the column, which could have played a role in the reason for decomposition.

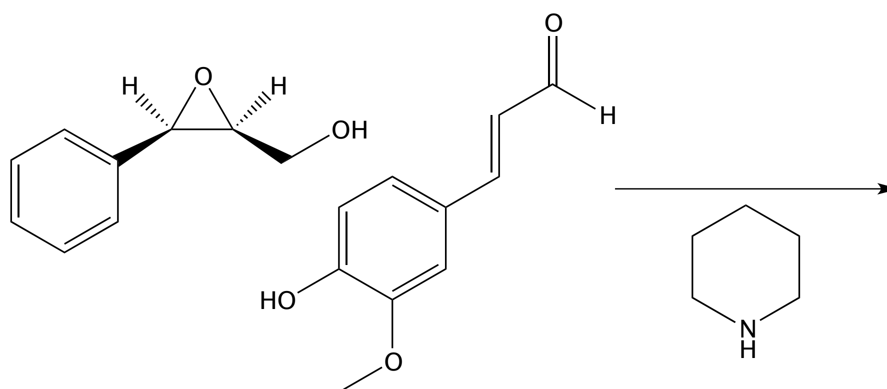


Figure 22. Substrates used in Trial 3

Table 3. Trial 3: varying reaction conditions with Catalyst II and 4-hydroxy-3-methoxycinnamaldehyde

Entry	Solvent	Temperature [°C]	Reaction Time [days]	Results
1	MeOH	r.t	7	Decomposition
2	THF	85-90 to r.t.	17-21	Decomposition
3	Acetonitrile	85	10	Decomposition

Even though the previous trials were unsuccessful in obtaining the desired product formation, ^{1}H NMR still showed possible product formation other than what was intended. In order to look further into the possible products, trial 4 employs $CDCl_3$ as the solvent and all reactions were run at room temperature (Figure 23). Trial 3 showed more promise than trial 2 with possible product formation in solution, thus the decision to continue using 4-hydroxy-3-methoxycinnamaldehyde as the aldehyde source seemed logical. Catalyst II and Catalyst III were both used in order to continue investigating new catalyst sources. In trial 4, ^{1}H NMR was obtained at 5, 10 and 25 minutes and ^{13}C NMR was obtained at 25 minutes. The ^{1}H NMR showed changes in chemical shifts over time but the ^{13}C NMR indicated no change in the chemical shift of the starting material. Some of the ^{1}H NMR showed an absence of the alkene peaks resultant from the aldehyde source which were positive results, but after immediate column purification there were only starting materials. 2D NMR was obtained but the results were inconclusive due to the low concentration and poor ^{1}H and ^{13}C NMR data.

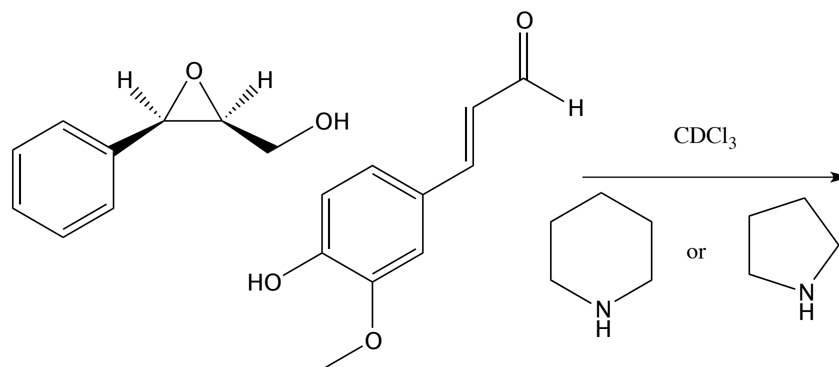


Figure 23. Substrates used in Trial 4

In summary of trials 1, 2, 3 and 4, Catalyst I showed no results regardless of solvent or temperature. Catalyst II and III gave promising results of possibly confirming the proposed mechanism, independent of temperature. All attempts at isolation of the product were unsuccessful. After many unsuccessful reactions were run this step of the synthesis was finally put aside and a new synthesis was developed.

III. F Revised Biomimetic Synthesis Design

The revised synthesis (Figure 24) remains the same as the original design (Figure 18) in the beginning with employing hydrogenation and epoxidation reactions to yield *cis*-3-phenyl-2-oxiranemethanol (**5**) to be used in the subsequent steps. Step three introduces a tosylation reaction in which a tosyl group replaces the hydrogen on the terminal alcohol to serve as a better leaving group for the following step. The next two steps were designed to build part of the compound that is based off the pathway of the proposed mechanism. Alkylation reaction serves to couple the tosylated epoxide **11**, with commercially available 1-phenyl-3-butene-1-ol **9**, together to form the coupled product,

12. The terminal alkene on **12** is then oxidized to the aldehyde under ozonolysis conditions to form **13**. The resultant compound **13**, mimics the final intermediate in the proposed mechanism, so the final step again employed the organocatalytic reaction in order to achieve a derivative of 9-hydroxypinoresinol.

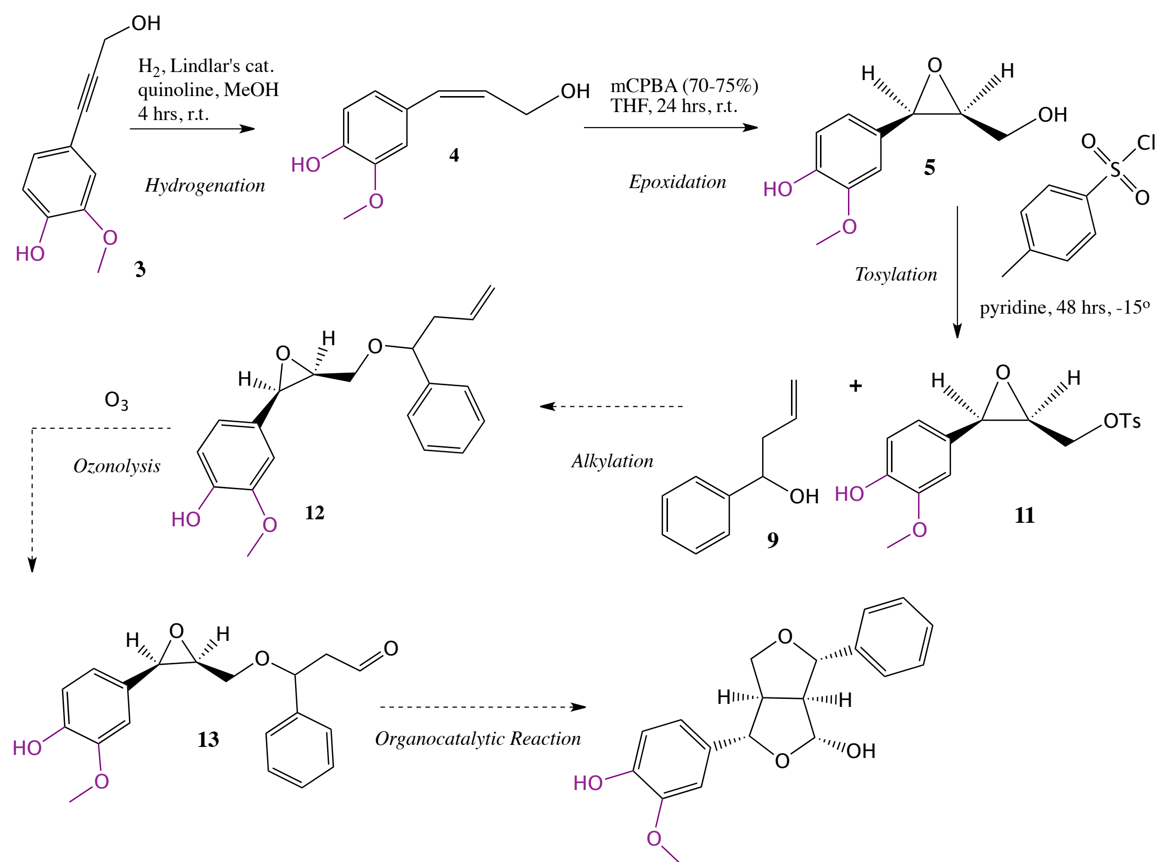


Figure 24. Revised Synthetic Design

III. G Tosylation Reaction

As stated previously, tosyl chloride was used to tosylate *cis*-3-phenyl-2-oxiranemethanol. Analysis by proton NMR was hard due to the small reaction scale and

possible impurities in the epoxide starting material. Although, in comparison to literature data the spectra indicated that the reaction was successful. This route will be explored by future researchers.

III. H Alkylation and Ozonolysis Reactions

The alkylation mechanism of the tosylated epoxide **11**, with 1-phenyl-3-butene-1-ol **9**, starts with deprotonation of the alcohol group on **9** resulting in anion formation which then attacks the electrophilic carbon containing the tosylate group. The tosylate group leaves and results in toluene sulfonate and the compound **12** (Figure 25).

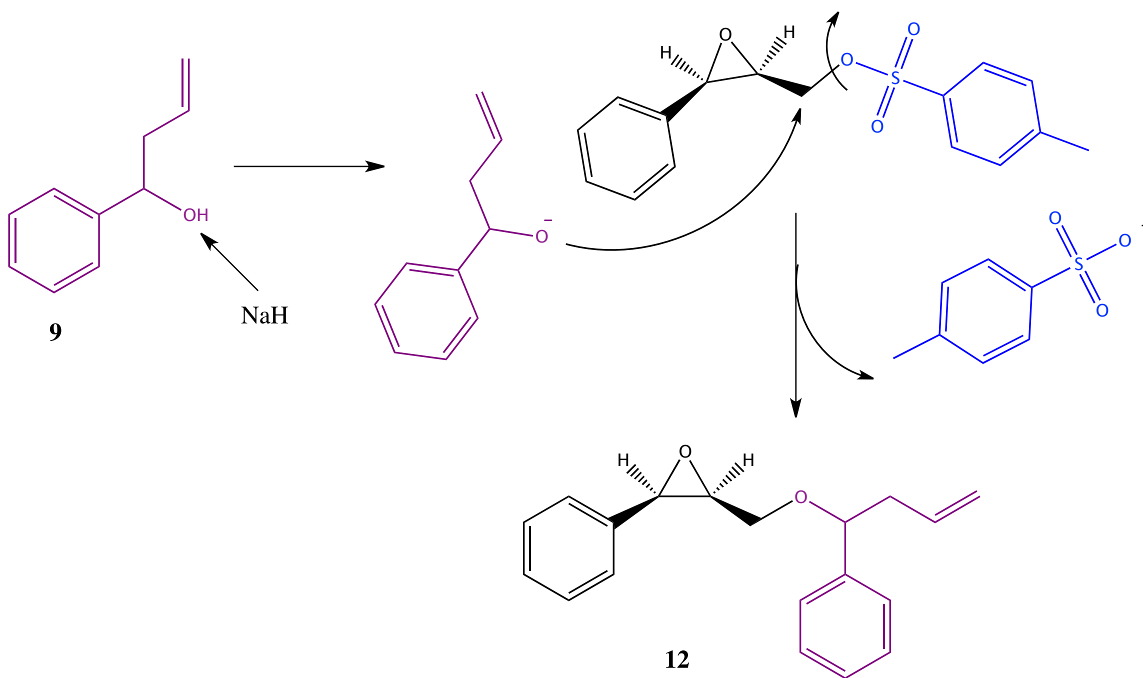


Figure 25. Alkylation Mechanism

Ozonolysis of **12** will be used to oxidize the alkene to the aldehyde to give compound **13** which will be subjected to the final organocatalysis step. The mechanism of the reaction undergoes 1,3-dipolar cyloaddition between O_3 and the terminal alkene resulting in 5-membered ring called a molozonide. Retro-1,3-cycloaddition happens immediately due to the unstable molozonide, to give an aldehyde and a carbonyl oxide. The two products then recombine through a 1,3-dipolar cycloaddition to form a second ozonide. Reductive cleavage of the ozonide by CH_3SCH_3 yields the aldehyde of **13**, and a second aldehyde (Figure 26).

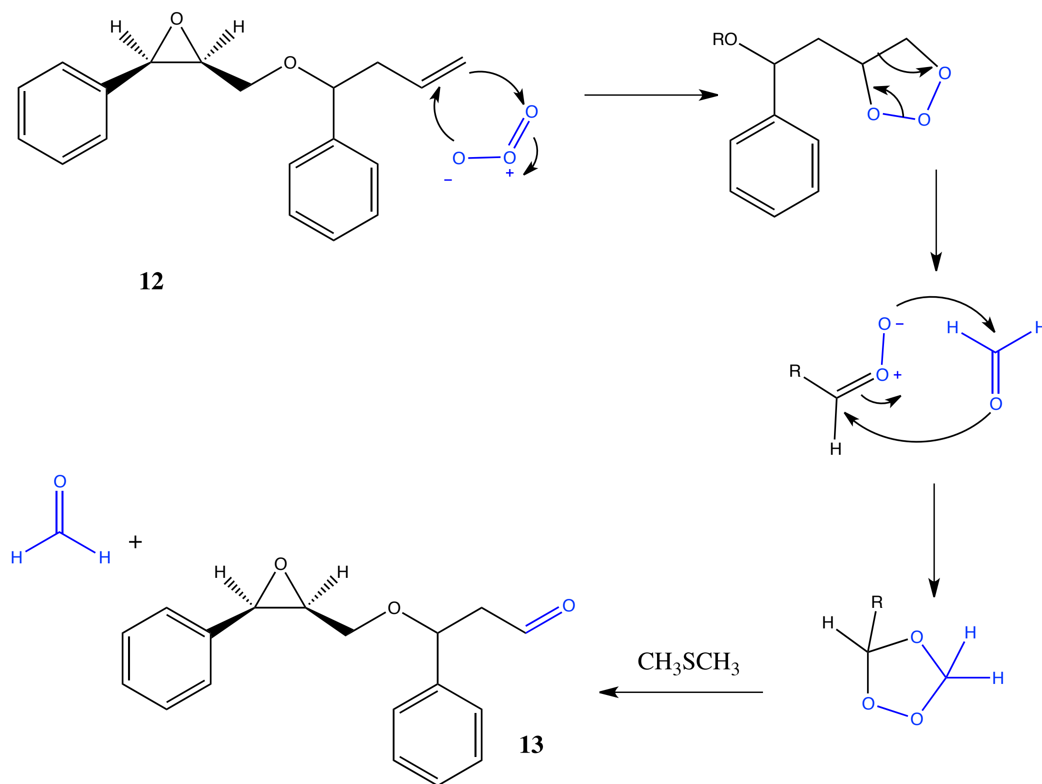


Figure 26. Ozonolysis Mechanism

In the revised synthesis (Figure 24), the last two steps needed to make compound **13**, were not attempted. If the project is carried on further in the research group, the reactions could be attempted using the previously made tosylated epoxide compound **11** with the commercially available compound, 1-phenyl-3-butene-1-ol **9**.

III. I Analog Diversification

If future researchers continue this project and successfully synthesize 9-hydroxypinoresinol, then the next step in the process of natural products to drugs will be structure-related analog diversification. Further use of the revised synthesis will be used to modify the substituents of aryl groups to obtain a class of structurally-diverse analogs which may potentially posses the same or better anti-seizure activity.

As shown in Table 4, only compounds **19** and **5,** from the proposed synthesis (Figure 7), are needed to be altered at specific positions (R-R^3) to obtain a class of twelve different analogs. The derivatives of reagents **19** (**19-23**) and **5** (**5, 7,** & **25**) were chosen based on the analog products being structurally different/unique, possessing the same bio-functionality as 9-hydroxypinoresinol and being easily accessible through commercial availability.

Table 4. List of structural analogs

R^2 and R^3 Possibilities		R and R^1 Possibilities	
R^1, R, O, H, H, OH, R^3, R^2 **2**	O, H, R^1, R **5**	O, H **7**	O, H, HO **25**
H_3CO, Br, HO **19**	R = OH $R^1 = OCH_3$ $R^2 = OH$ $R^3 = OCH_3$ **2**	R = H $R^1 = H$ $R^2 = OH$ $R^3 = OCH_3$ **30**	R = OH $R^1 = H$ $R^2 = OH$ $R^3 = OCH_3$ **35**
Br **21**	R = OH $R^1 = OCH_3$ $R^2 = H$ $R^3 = H$ **26**	R = H $R^1 = H$ $R^2 = H$ $R^3 = H$ **31**	R = OH $R^1 = H$ $R^2 = H$ $R^3 = H$ **36**
H_3CO, Br, H_3CO **22**	R = OH $R^1 = OCH_3$ $R^2 = OCH_3$ $R^3 = OCH_3$ **27**	R = H $R^1 = H$ $R^2 = OCH_3$ $R^3 = OCH_3$ **32**	R = OH $R^1 = H$ $R^2 = OCH_3$ $R^3 = OCH_3$ **37**
O, Br **23**	R = OH $R^1 = OCH_3$ $R^2 = H$ $R^3 =$ O **28**	R = H $R^1 = H$ $R^2 = H$ $R^3 =$ O **33**	R = OH $R^1 = H$ $R^2 = H$ $R^3 =$ O **38**
Br, O **24**	R = OH $R^1 = OCH_3$ $R^2 =$ O $R^3 = H$ **29**	R = H $R^1 = H$ $R^2 =$ O $R^3 = H$ **34**	R = OH $R^1 = H$ $R^2 =$ O $R^3 = H$ **39**

Upon comparison of the various derivatives of the aryl halide source, changes are shown in all compounds (**21-24**) in whether or not the alcohol, on the R^2 position, plays a significant role for biological activity. Starting with **21** as the first derivative would be beneficial because it is already similar to the preliminary data as well as there are no substituents in both the R^2 and R^3 positions. Due to this, **21** could serve as a good control, along with **19,** when comparing the other derivative compounds **22** and **23**. Compound **22** is of interest because it is similar to **19** but only slightly different in the replacement of the alcohol group with a methoxy-group. Structural differences in the size and position of the oxygen substituent are seen in **23** and **24**; comparing the R^2 position (**22** & **24**) versus the R^3 position (**23**). This will be significant when looking at the reaction reactivity and overall biological activity of the other analogs.

Upon comparison of the derivatives of the aldehyde source, only two compounds (**7**, **25**) are shown due to the lack of commercial availability and similar structure relationship. Changes in the R and R^1 positions are seen in the presence of no substituents in both (**7**), and the presence of the alcohol group only in the R position along with no substituent in the R^1 position (**25**). These two derivatives (**7**, **25**), along with **5**, will provide evidence to what literature has already stated, indicating the alcohol group in the R position (**5**, **25**) is needed for the biological activity.[19,21] Therefore, if biological testing against kainic acid is performed on these analogs, then it is hypothesized that **26-29** and **35-39** should possess some, if not potentially improved, biological activity in comparison to the parent compound **2**.

CHAPTER IV

CONCLUSION

The first total synthesis of 9-hydroxypinoresinol was proposed consisting of known organic reactions with a highly complex step utilizing metal-free organocatalysis to form the two tetrahydrofuran rings of the core structure thus achieving the desired product in only four steps. After the synthesis was attempted, steps 1-3 were successfully completed but unsuccessful organocatalysis results indicated the need for a revised synthesis. The revised synthesis was designed to add onto the original design by pre-building a part of the compound which mimicked the proposed organocatalytic pathway. The revised synthesis was only increased to seven steps in comparison to four steps from the original synthesis. All of the reagents were commercially available and are easily altered through the aryl groups to obtain a class of structurally-diverse analogs. This synthesis could serve as a tool for further understanding the chemical, structural and biological properties of the compound as well as facilitate the progression of understanding the importance of 9-hydroxypinoresinol for future drug discovery leads as an anti-seizure drug.

REFERENCES

Natural Products and Drug Discovery Papers

[1] Li, J.;Vederas, J.C. *Science* **2009**, *325*, 161.

[2] Hanson, J.R. *Natural Products: The Secondary Metabolites*; Royal Society of Chemistry Publishing: Cambridge, **2003**.

[3] Reviews: Ward, R.S. *Nat. Prod. Rep*. **1999**, *16*, 75.

[4] Reviews: Whiting, D.A. *Nat. Prod. Rep*. **1990**, *7*, 349.

[5] Barton, D.; Nakanishi, K.; Meth-Cohn, O. *Comprehensive Natural Products Chemistry Vol.1* Elsevier: Amsterdam, **1999**.

[6] Raphael, R.A.; Tamm, C.; Shamma, M. *Dictionary of Natural Products Vol.7* Chapman & Hall: Cambridge, **1994**.

[7] Pelter, A.; Ward, R. S.; Watson, D.J.; Jack, I.R. *J. Chem. Soc. Perkin Trans*. **1982**, *1*, 175.

[8] Pelter, A.; Ward, R.S.; Watson, D.J.; Jack, I.R. *J. Chem. Soc. Perkin Trans*. **1982**, *1*, 183.

[9] Buss, A.D.; Butler, M.S. *Natural Products Chemistry for Drug Discovery* Royal Society of Chemistry Publishing: Cambridge, **2010**.

[10] Brown, R.; Swain, N.A. *Synthesis* **2004**, *6*, 811.

[11] Hearon, W.M.; MacGregor, W.S. *Chemical Reviews* **1955**, *55*, 957.

[12] Halls, S.; Lewis, N. *Biochemistry* **2002**, *41*, 9455.

[13] *Dictionary of Natural Products DataBase*. CHEMnetBASE, CRC Press.

[14] Shih, C.; Huang, T.; *Evid. Based Complement Alternat. Med.* **2011**, *2011,*132,374.

[15] Butler, M.S. *J. Nat. Prod.* **2004**, *67*, 2141.

[16] Harvey, A. *Drug Discov. Today* **2008**, *13*, 894.

[17] Malik, N.N. *Drug Discov. Today*, **2008**, *13*, 909.

Petaslignolide A and synthesis papers

[18] Kim, Y.C. *Arch. Pharm. Res.* **2010***, 33*, 1611.

[19] Min, B-S; Sok, D.-E.; Lee, H.-K.; Cui, H.S.; Kim, M.R. *Arch. Pharm. Res.* **2005**, *28*, 1023.

[20] Sok, D.-E.; Cui, H.S.; Kim, M.R. *Recent Pat. Food. Nutr. Agric.* **2009**, *1*, 87.

[21] Cui, H.S.; Sok, D.-E.;Min, B.S.; Kim, M.R. *J. Pharm. Pharmacol.* **2007**, *59,* 521.

[22] Lindlar, H.; Dubuis, R. *Org. Syn.* **1973,** *5,* 880.

[23] Kim, I.S.; Dong, G.R.; Jung, Y.H. *J. Org. Chem.* **2007,** *72,* 5,424.

[24] Waldemar, A.; Wirth, T. *Acc. Chem. Res.* **1999,** *32,* 703.

[25] Chang, K.-H.; *Dalton Trans.* **2004,** 1731.

Organocatalysis papers

[26] Anwar, S.; Chang, H-J; Chen, H. *Org. Let.* **2011**, *13*, 2200.

[27] Lathrop, S.P.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 13628.

[28] J.-C. Chung *Tetrahedron Lett.* **2006**, *47*, 6433.

[29] Dondoni, A.; Massi, A. *Angew. Chem. Int. Ed. Engl.* **2008**, *47*, 4638.

[30] Dalko, P.I.; Moisan, L. *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 3726.

[31] Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3,* 719.

Revised Synthesis Papers:

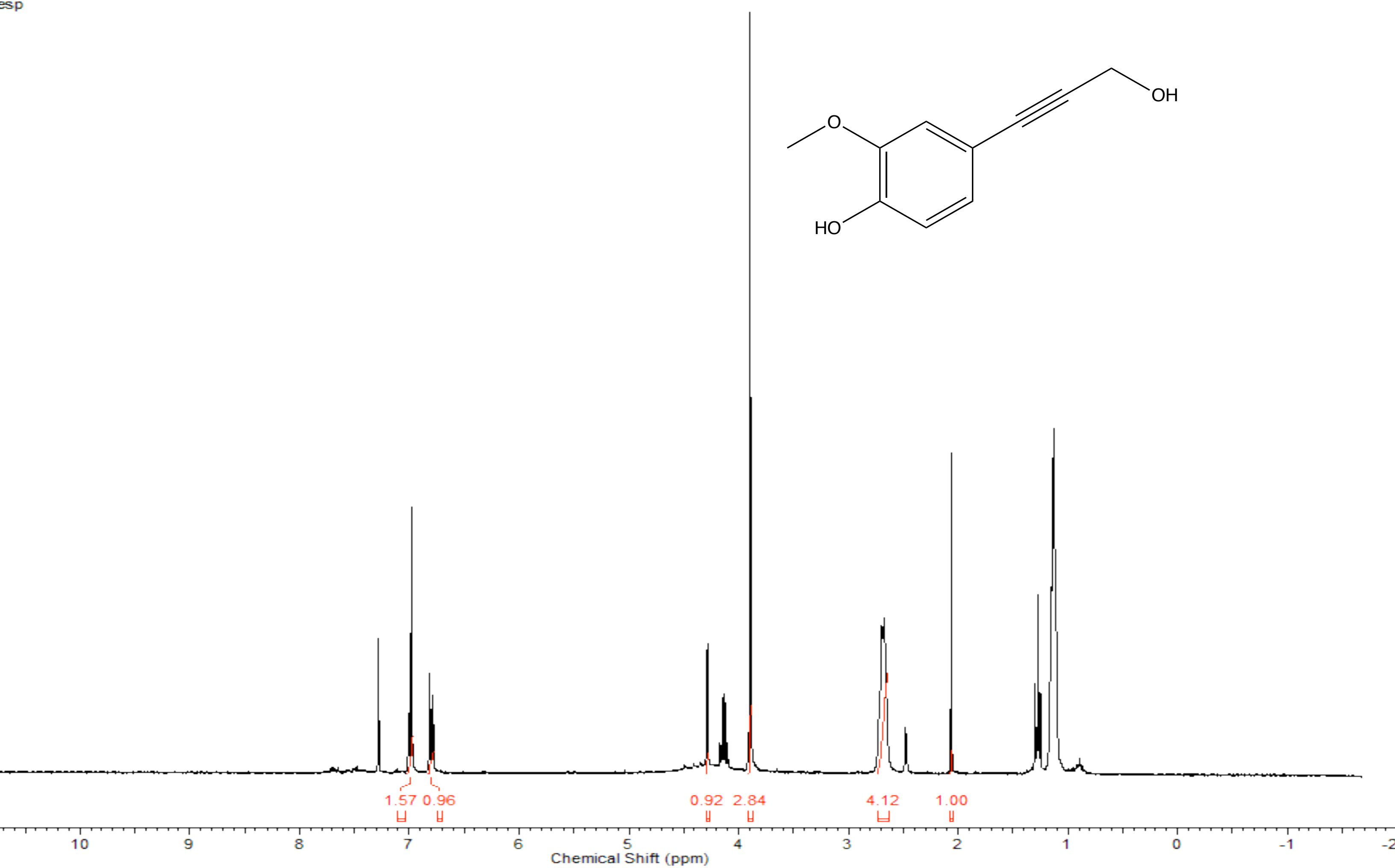
[32] Brunner, H.; Sichender, A. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 718.

[33] Shinagawa, Y.; Inoue, T.; Katsushima, T.; Hashimoto, H.; et.al *ACS Med. Chem. Lett.* **2011**, *2*, 238.

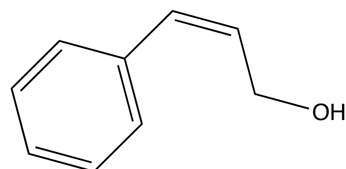
APPENDIX A

NMR SPECTRA OF COMPOUNDS

Sonogashira Coupling Reaction: ^{1}H NMR



Hydrogenation Reaction: ^{1}H NMR



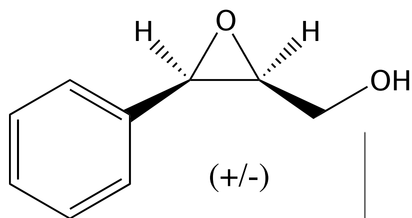
LN-24_2.001 (1).ESP

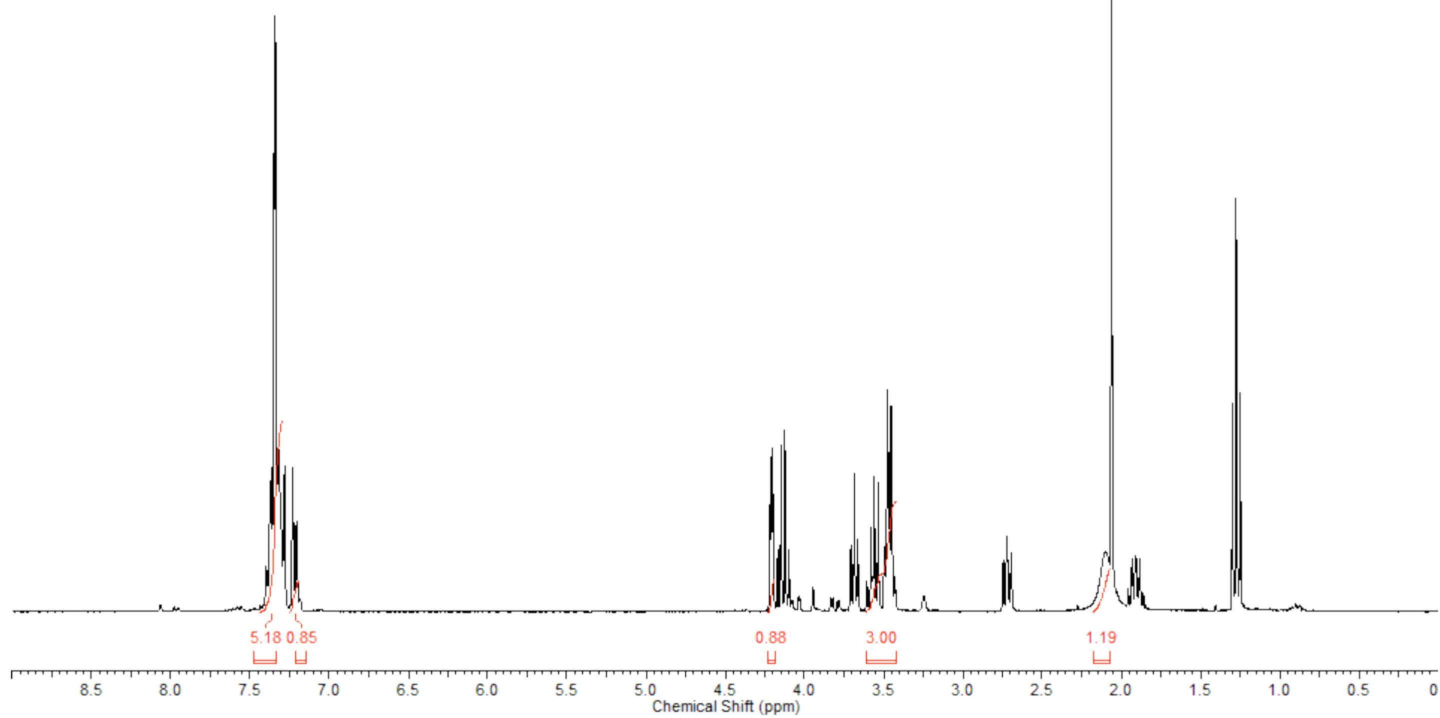
2.95 6.56 1.83 3.27 1.92 1.67

8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0

Chemical Shift (ppm)

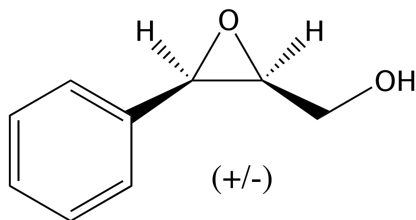
Epoxidation Reaction: ^{1}H NMR





Epoxidation Reaction: ^{13}C NMR

LN-153 CARBON J COUPLING.ESP



192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0

Chemical Shift (ppm)

Tosylation Reaction: ^{1}H NMR