Synthesis of Spirolactones Substituted at the Benzylic Position: Studies Toward the Formation of Manumycin Structural Analogs

By

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## Abstract

This study was designed to create a series of spirolactone compounds produced through an oxidative spiroannulation reaction, each with a different substituent at the benzylic position. The effect, if any, on the diastereoselectivity of the spiroannulation reaction caused by the benzylic substitution would then be determined by <sup>1</sup>H-NMR. Several synthetic methodologies were employed in attempts to produce these compounds but only a single compound was successfully produced in 27% yield in 5 steps. This compound had a hydroxyl function at the benzylic position and showed total enantioselectivity in the spiroannulation reaction. Several unique properties of the intermediate molecules created in these studies were discovered while attempting to synthesize the target molecules.

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#### **Chapter 1: Introduction**

## **1.1 Manumycin Compounds**

The production of new, and more effective antibiotic molecules has become a task of great importance in recent years.<sup>1-6</sup> New strains of pathogenic microbes which are resistant to many antibiotics which are currently available can result in serious infections that cannot be treated effectively, often leading to the death of the patient.<sup>1</sup> With the number of antibiotic resistant microbes on the rise, research into new antibiotic compounds is of increasing importance.<sup>1-6</sup>

The Manumycin family of compounds shows promise to be a highly effective class of antibiotic. Manumycin A is a secondary metabolite found in *Streptomyces parvulus* and was first isolated in 1963.<sup>7,8</sup> The isolation and characterization of many other members of the Manumycin family of compounds from other bacterium of the Steptomyces genera has come in subsequent years.<sup>8</sup> The quantity of Manumycin compounds that can be isolated from any of these bacterium is low, and always involves the death of the source organism.<sup>8</sup> Thus, to obtain pharmaceutically useful amounts of these compounds, a synthetic approach must be used. Figure 1 shows the structural similarity of the target compound **2** of this research and the C<sub>7</sub>N subunit **1** found in the majority of the compounds in the Manumycin family. As shown in Figure 1 further transformations of **2** should lead to **3** which is closely related to the C<sub>7</sub>N subunit.



Figure 1: Structural similarity of the  $C_7N$  subunit to a target molecule of this study and a possible structural analog of  $C_7N$  that could be produced from that target molecule.

The Manumycin family consists of many compounds, all of which share a common structural motif.<sup>7</sup> They normally contain two side-chains of varying length attached to a core skeleton.<sup>7,8</sup> The side-chain portions are relatively simple in their structure, while the core group is quite complex. The core group, called the C<sub>7</sub>N subunit, can be considered a highly functionalized cyclohexene ring.<sup>7,8</sup> This ring contains an alkene, a ketone, and a pure chiral centre marked with an asterix in Scheme 1along with other functional groups which vary depending on which specific member of the Manumycin group it is. While many of the functional groups found in the C<sub>7</sub>N subunit are relatively easy to produce by common synthetic methods, obtaining the pure chiral center has proven to be the most difficult aspect of the total synthesis. The biosynthetic pathway by which many Manumycin derivatives are naturally synthesized has been characterized.<sup>7</sup> Total synthesis of a few members of the Manumycin family, and analog compounds have been achieved.<sup>4,6,7-18</sup> Taylor and coworkers at the University of York have successfully synthesized Manumycin A, B, C, and Alisamycin among other natural products and a number of analogues of other Manumycin compounds as shown in Figure 2.<sup>9-13</sup>



Figure 2: Synthesis of Manimycin A by Taylor et al.<sup>9</sup>

Manumycin A is of great clinical interest because it is known to have activity as an inhibitor of the RAS farnesyltransferase, a protein involved with inflammation and in many types of cancer.<sup>7</sup> This inhibition activity makes Manumycin A a strong candidate molecule for use as a possible anti-inflammatory or anticancer drug.

# **1.2 Chirality of Biologically Active Molecules**

Chirality, or the 'handedness' of a molecule is extremely important to its function.<sup>19</sup> Nowhere is this truer than of molecules which are biologically active in the human body.<sup>19-25</sup> The main structural components of the human body, amino acids and carbohydrates, both contain many pure chiral centers.<sup>19</sup> These chiral centers must be in the correct orientation so that the molecule is active in the body.<sup>19</sup> If a molecule has the wrong chirality it can be inactive in the organism or have deleterious effects.<sup>19-25</sup>



Figure 3: *R*- and *S*-2-amino butane, a simple enantiomeric pair illustrating the "handedness" of a molecule.

The specific orientation of chiral molecules is denoted by the Cahn-Ingold-Prelog naming system based on the 4 substituents bound to the chiral carbon. A molecule which contains a pure chiral center, R or S only, will be optically active. Optical activity refers to a chiral molecules ability to rotate the plane of polarized light in a specific direction. Molecules can either rotate polarized light in the dextrorotatory or levorotatory, clockwise and counter clockwise direction respectively. Molecules which give a dextrorotatory rotation are denoted as the (+) stereoisomer while molecules which give the levorotatory rotation are denoted as the (-) stereoisomer.<sup>26</sup>

The two forms of stereoisomer are enantiomers and diastereomers. A pair of enantiomers represents two molecules that are non-superimposible mirror images of each other while diastereomers are molecules which are non-mirror images of one another. Any molecule which contains at least one chiral carbon, can contain  $2^n$  different stereoisomers where 'n' is the number of chiral centers in the molecule. If only 1 chiral carbon exists in a molecule only 2 stereoisomers are possible and these would be enantiomers as shown in Figure 3. In molecules which contain more than 1 chiral carbon more stereoisomers are possible. A molecule containing a chiral carbon will always have an enantiomer but only molecules with more than one chiral carbon will be able to have diastereomers.<sup>26</sup> As shown in Figure 4, 3-amino cyclohexanol contains 2 chiral centers and thus 4 stereoisomers are possible. Molecules **5**/7, **5**/8,

6/7, and 6/8 as each pair differs by a single stereocenter producing compounds, non-mirror images of each other.



Figure 4: 3-amino cyclohexanol, a molecule with two chiral centers and 4 possible stereoisomers.

Biologically active chiral molecules produced in a living organism are constructed with the help of enzymes. Enzymes are large biomolecules that help catalyze and control chemical reactions. Enzymes involved in the production of chiral biomolecules have very specific binding pockets that allow for molecules to enter only in specific orientations. Once in the active site, the molecule is held in place through a number of specific intermolecular interactions. While the molecule is in this orientation only one enantiomer can be produced as only one side of the molecule is oriented towards the reactive site of the enzyme.<sup>19</sup> When the production of chiral molecules is attempted outside of an organism via organic synthesis, other means must be employed to produce pure chiral centers as the rigorous control present in an enzyme is not available.

Reactions that produce only one stereocenter are called stereoselective reactions. To make a reaction stereoselective a feature of the substrate, reactant or the environment in which the reaction takes place must bias the formation of the stereocenter.<sup>26</sup> This can be done by using a single enantiomer as a starting material, using a chiral reagent which reacts to produce only one of the possible enantiomers, or by performing the reaction in a chiral medium which prevents the formation of unwanted stereocenters. It is also possible to control the formation of a stereocenter

by altering the nature of the compound or reagents used so that the formation of one chiral center is favoured over another.<sup>26-35</sup>

#### 1.3 Review of Research: Stereoselectivity of Spiroannulation Reactions

An annulation reaction involves the formation of a cyclic structure from an acyclic starting material. A spirocompound is a compound which has two ring structures linked through a single shared carbon, or spirocarbon. The spiroannulation reaction involves the reaction of a nucleophilic atom attached to a carbon chain which is also attached to a ring structure. As shown in Scheme 1 the mechanism of spiroannulation involves the use of lead tetraaceteate, or another oxidizing agent, which complexes with the phenolic oxygen. This complexation with the phenolic oxygen alters the electronic nature of the aromatic ring making the future spirocarbon, indicated with an (\*) in Scheme 1, more electrophilic. The carbon chain folds on itself adding to the electrophilic carbon. This addition then causes the aromatic structure of the ring to be lost, creating a cyclohexadiene bearing a spirocenter. The spirocarbon geometry is changed from a

planar structure to a tetrahedral one.



Scheme 1: Simplified mechanism of spiroannulation using lead tetraacetate

In an uncontrolled reaction the nucleophile attacks from either the *re* or the *si* face of the ring indiscriminately and produces an equal proportion of stereocenters. The top and bottom face of the molecule are denoted as *re* or *si*. These names are derived from the prochiral nature of the carbon and the orientation of the groups attached to it as shown in Figure 5. The *re* face is the side of a planar molecule on which the groups attached to a carbon are observed to be in decreasing order of priority using the Cahn-Ingold-Prelog priority rules in a clockwise direction. The *si* face is the face on which the groups are seen to be attached in decreasing order of priority

in a counterclockwise direction. Attack at a *re* or *si* face does not correlate to the production of the *R* or *S* center being made in the product.<sup>26</sup>

When the chain folds during this reaction it is able to attack from either the re or si face as shown in Figure 5. The directionality of this attack is what results in the formation of the specific chiral center at the spiroatom. The orientation of this chiral center is now fixed in either the R or S configuration depending on directionality from with the oxygen attacked the new spirocarbon.<sup>36</sup>



a: attack to the si face (from top of page). b: attack to the re face (from back of page) Figure 5: Possible mode of attack of the nucleophilic oxygen from either the *re* or *si* face.

When a chiral compound is produced without some measure of control the undesired stereocenter is produced along with the desired one. One must then isolate and discard the unwanted compound from the reaction mixture before further steps can be taken. This can be extremely difficult, time consuming, expensive and is wasteful.

In an attempt to control the formation of this stereocenter several previous studies have been undertaken.<sup>36-48</sup> An investigation of the effect that the electronic nature of the phenol ring on the spiroannulation reaction was done by creating a phenol derivative with a nitro functional group at the 3 position of the aromatic ring.<sup>36</sup> This phenol derivative was derived from (L)-3-Nitro-Tyrosine. With this strong electron withdrawing group in place the oxidative spiroannulation reaction did not produce any of the spiroproduct. The 3 position substituent was then modified to an electron donating substituent and it was found that the spiroannulation reaction could be carried out with excellent yields, demonstrating that an electron donating functionality is important in the formation of the spirocompound as shown in Figure 6.<sup>36</sup>

A different study found that the presence of a strong electron donating group, such as oxymethyl, ortho to the phenolic hydroxyl group gave the highest ratio of stereoselection at the spirocarbon in the spiroannulation reaction as well as a higher chemical yield.<sup>38-40</sup> The location of the electron donating group was also found to significantly affect the diastereoselectivity of the reaction.<sup>38,39</sup> In compounds where the oxymethyl group was placed at the 2 position on the ring rather than on the 3 position, stereoselectivity dropped from 81/19 to a 50/50 mixture of diastereomers as shown in Figure 5.<sup>38</sup> This result is believed to be due to the stabilization of the carbocation produced during the reaction.<sup>38,39</sup> This cation, called a phenoxenium ion, is stabilized during the intermediate steps of the reaction.<sup>38</sup> This stabilization also accounts for the greater overall yield of spiroannulation reactions done on phenolic derivatives which bear an electron donating group at position 3 and the inability of the oxidative spiroannulation reaction to take place on compounds bearing electron withdrawing groups at the 3 position.<sup>38,39</sup>



Figure 6: Effect on diastereroselectivity and yield of spiroannulation as a result of functionality at the 2 and 3 positions.

Compounds which had an electron withdrawing group at position 3 were found to be unreactive to typical spiroannulation reaction conditions. The strong electron withdrawing groups interfere with the formation of the spiroproduct, presumably by destabilizing the carbocation formed during the reaction. Without the stabilization created by an electron donating group at the 3 position it is impossible for the reaction to proceed.<sup>36</sup>

Further attempts to control the spiroannulation reaction were carried out using several different oxidizing reagents.<sup>38</sup> These reagents included lead tetraacetate (LTA), phenyliodine diacetate (PIDA), and phenyliodinetrifluoroacetate (PIFA). PIDA and PIFA are both hypervalent iodine reagents which have been used in multiple studies as oxidants to initiate the spiroannulation reaction while LTA is a heavy metal based reagent that is used less frequently

due to its toxicity.<sup>36-38,46-50</sup> It has been found that the chemical yield of spiroannulations carried out on phenolic derivatives is increased with LTA as the oxidant.<sup>37,38</sup> The reactions carried out with LTA as the oxidant were found to produce approximately double the chemical yield as those carried out using PIFA as the oxidizing agent.<sup>38</sup> Studies carried out to determine the best oxidant for the spiroannulation reaction were done with compounds similar to, and including those found in Figure 6.

The effect of introducing a group near the nucleophilic atom which acts to sterically hinder the folding of the carbon chain being spiroannulated has also been investigated.<sup>37,49</sup> The stereoselectivity of the spiroannulation reaction was also studied and showed increasingly better results as the size of the substituent near the nucleophilic atom increased. It has been found that a methyl group adjacent to the nucleophilic atom on the alkyl chain gave very poor diastereoselectivity. Furthermore, it was found that increasing the size of the methyl group to and isopropyl or tertiary butyl group improved the stereoselectivity to 7:3 and 8:2 respectively as shown in Figure 7. <sup>37,38,47-49</sup>



Figure 7: Steric effect of alkyl groups near the nucleophile.

Additional research undertaken has found that the size of the electron donating group does not positively affect the diastereoselectivity of the spiroannulation reaction. It was found however, that the larger the group ortho to the phenolic oxygen the lower the diastereoselectivity was in the spirocompound produced. When the ortho position was substituted with an oxyethyl group the diastereoselectivity was found to be 74/26. When this oxyethyl group was replaced with the much larger oxymethylcyclohexyl group the diastereoselectivity dropped to 65/35. The negative effect on diastereoselectivity caused by the presence of a large group at the ortho position shows that diastereoselectivity of the spiroannulation reaction is more related to the group adjacent the nucleophilic atom and less to the steric interactions of the electron donating group ortho to the phenolic oxygen with the alkyl chain.<sup>37</sup>

From the previous research done regarding the stereoselectivity of the spiroannulation reaction it can be seen that steric factors near the nucleophile involved in the spiroannulation reaction of simple phenols create a greater effect on the diastereoselectivity of the reaction than does the electronic nature of the ring. The electronic nature and substitution pattern of the aromatic ring do however play a role in the chemical yield, and to a lesser extent, the stereoselctivity of the spiroannulation reaction.

Both hypervalent iodine species and tetravalent lead species have been used extensively in the past as reagents in oxidative spiroannulation reactions and other types of reactions.<sup>51-61</sup> The most commonly utilized hypervalent iodine species for spiroannulation reactions are PIDA, and PIFA, but many other I(III) and I(V) species used in many cyclization and oxidation reactions have been developed. Hypervalent iodine species can be extensively manipulated in their structure allowing for them to show high chemoselectivity and stereoselectivity. This specificity is largely due to the alkyl, or other groups which are attached to the iodine atom. Since many hypervalent iodine species can be made *in situ*, often from highly stable precursors, the structural diversity of hypervalent iodine reagents is vast.<sup>61</sup>

Hypervalent iodine species have gained popularity in recent years as they are a more environmentally sound alternative to oxidants which contain toxic heavy metals such as lead, chromium, or mercury.<sup>61</sup> Iodine based reagents are also generally more stable, less toxic, and easier to handle than heavy metal reagents.<sup>51,58,59</sup> In addition to being more environmentally sound in terms of production and disposal, hypervalent iodine species often function catalytically in many oxidation reactions where as many heavy metal reagents are generally used stoichiometrically. Because of their catalytic behaviour, a much smaller amount of hypervalent iodine reagent is often required than the corresponding heavy metal oxidant to carry out the same transformation.<sup>51-61</sup>

LTA is a heavy metal based reagent that is used less frequently due, in part, to its toxicity. LTA is immediately toxic to the mucus membranes of the body as well as exhibiting highly toxic long term effects associated with heavy metal poisoning.<sup>50</sup> PIFA and PIDA do not have the same chemical dangers that LTA does. In previous research it has been shown that LTA produces higher chemical yields, better diastereoselectivity than PIFA or PIDA in most cases.<sup>36-40</sup> Further, spiroproducts that are isolated from reactions with LTA are more easily than those produced by either PIFA or PIDA.<sup>36-40</sup> It was found that the decomposition products of PIFA and PIDA formed after the spiroannulation reaction made purification of the desired spirocompounds extremely difficult.<sup>36,37,40</sup> Long column chromatography purifications often led to the loss of product in the process of purifying it.<sup>36,40</sup> Furthermore, it was found that many spirocompounds were sensitive to exposure to silica, breaking down before they could be isolated and characterized.<sup>40</sup>

In recent years the use of LTA and other lead based oxidants have led to many new compounds being synthesized as well as shorter methods of producing a wide range of compounds. LTA has been used in the production of compounds ranging from large natural products, as well as in the regio and stereoselective modifications of many compounds. The ability for the lead to be removed by chelation and filtration has proved valuable in the production of many compounds which are sensitive to more rigorous purification steps.<sup>62-70</sup>

# 1.4 Reactivity and Stability of the Functional Group Located on the Benzylic Carbon

Once functionalized to the carbonyl oxidation state the benzylic position is stabilized through a resonance form which is available due to its conjugation to the aromatic ring.<sup>26</sup> The resonance forms of a benzylic carbonyl diminishes the natural dipole found between the carbonyl oxygen and the carbonyl carbon. Some double bond character is imparted to the carbonyl carbon as the carbonyl oxygen takes up an alkoxide ion resonance form similar to an enolate ion as shown in Figure 8. The addition of electron donating groups to the aromatic ring increases the number of available resonance contributors and thus, the stability of the resonance forms in which the carbonyl carbon is in an enolate like state.<sup>26</sup>



Figure 8: Some resonance contributors of a benzylic carbonyl

The effects of the reduced carbonyl dipole are less evident in benzylic aldehydes due to the inherent instability of the terminal alkene that would be produced in an enolate like resonance form. The addition of strong nucleophiles such as Grignard reagents to benzylic aldehydes shows a lower than expected yield; in many cases less than 60%. However, reactions of benzylic ketones and Grignard type reagents show even lower chemical yields despite the use of much higher energy reaction conditions than are usually utilized with Grignard conditions.<sup>71</sup> Typically, a Grignard reaction must be cooled before and during the addition of a Grignard reagent. The cooling of the reaction mixture is commonly needed so that the energy given off by the reaction does not cause the reaction solvent to boil or ignite. Grignard, and other strong reagents, often require additional precautions to be taken when used in organic reactions so that these highly exothermic and rapid reactions can be carried out safely. Grignard reactions are generally carried out in a flame dried flask that has been purged with an inert gas like nitrogen or argon so that uncontrolled side reactions can not occur. In the case of additions to benzylic carbonyls, heating of the reaction mixture for long periods of time is often required to achieve only moderate yields.<sup>71</sup> In contrast, most Grignard reactions carried out on aliphatic carbonyls occur in near quantitative yields with very short reaction times.<sup>26</sup>

In the case of benzylic aldehydes on electron rich rings, a unique type of reaction has been observed. While attempting to produce a number of arylalkanols Sinha *et al.* found an unexpected side product when performing Grignard type additions to benzylic aldehydes.<sup>72</sup> Rather than the single addition of an ethyl group to the carbonyl, a double addition occurred resulting in the formation of a tertiary alcohol, rather that the expected secondary alcohol as shown in Figure 9. Through a series of experiments it was determined that once the secondary alcohol had formed, a Cannizaro type reaction took place which transformed the secondary alcohol into the corresponding secondary ketone.<sup>18</sup> Due to a large excess of Grignard reagent present, the high temperature, and long reaction time, a small amount of the tertiary alcohol was found to be formed (4-12%).<sup>72</sup>

The Cannizaro reaction involves the release of a hydride from the carbonyl carbon. In the Sinha study, this hydride would be the hydrogen atom which was originally present on the benzylic aldehyde. Hydride species are extremely poor leaving groups and are not commonly expelled. For this hydride to have been expelled, the resulting carbonyl would need to be highly stabilized so that the reaction would be energetically favourable. Secondly a good hydride acceptor must be located near by so that the electrons on the hydride can be quickly taken up into a bonding interaction and not remain as a very high energy hydride ion. The low yield of the side product in the experiments carried out by the Sinha's group indicate that the release of hydride from these compounds is not the most energetically favoured reaction, but the activation energy gap is low enough to allow the reaction to proceed in small amounts.<sup>72</sup>

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Shinha's study also found that the substitution pattern of the aromatic ring played a role in how much of the tertiary alcohol was formed. It was observed that the size of the alkyl group being added to the aldehydes had an effect on the amount of side reaction products formed. Compounds with oxymethyl or other electron donating groups at the ortho, meta, and para positions gave the highest yields of tertiary alcohol when treated with ethylmagnesium bromide. Aromatic structures with fewer substituents gave generally lower yields of the tertiary alcohol. When methylmagnesium bromide was used in place of ethylmagnesium bromide no side product was detected at all. From these results it appears that the secondary alcohol created when methyl magnesium bromide was added to the aldehyde was unable to expel a hydride atom. It is also evident that the number and positions of substituents altered the ability of the Cannizaro type reaction to take place.<sup>72</sup> Greater electron density in the aromatic ring helped the Canizaro reaction to proceed.<sup>72</sup>

#### 1.5 Spirocompounds as Inhibitors to Gene Splicing

In a recent study it was found that small, relatively simple spirocompounds acted as inhibitors of the pre-messenger ribonucleic acid (pre-mRNA) processing in yeast cells. The processing of pre-mRNA in yeast cells, as in all eukaryotes, is carried out by the spliceosome. The spliceosome is a highly specific set of proteins, short nucleic acids, and other biomolecules, including small nuclear ribonucleoproteins (snRNPs), which allow eukaryotic cells to splice premRNA in a highly specific way so that it can be exported from the cells nucleus and used to create proteins in the cells ribosomes. The splicing process involves many steps including site specific recognition on the pre-mRNA chain, protein/mRNA binding, protein/protein binding, the cleavage, folding and ligation of the RNA strand. This process is critical to an organisms survival and has been widely studied. Despite the large volume of research concerning the splicing process many aspects are still poorly understood.<sup>73</sup>

The study involving spirocompounds was carried out using small molecules with structures as shown in Figure 10 which were introduced to live yeast cultures. These cultures were grown in a medium containing <sup>32</sup>P labelled actin pre-mRNA which was incorporated into the yeast cells and spliced using the natural cellular splicing machinery. The study screened a wide range of spirocompounds to determine their ability to inhibit the splicing process. Along with the spirocompounds a number of aminoglycoside antibiotics, two protein kinase inhibitors, and a number of precursor molecules to the spirocompounds which did not contain a spirocenter were screened in the yeast splicing assay.<sup>73</sup>

Figure 10: General structure of spirocompounds found to have inhibitory effects on premRNA splicing and processing into mRNA in yeast cells.<sup>73</sup>

After incubation of the yeast cultures with the labelled actin pre-mRNA and each of the individual molecules of interest, it was found that spirocompounds were able to inhibit the spliceosomes function while the nonspiro precursor compounds did not effect the gene splicing process. It was also found that only the spirocompounds which contained a lactone ring

connected to the spirocarbon were able to inhibit spliceosome activity. The extent of inhibition caused by each compound was determined by identifying the concentration at which 50% of the maximal inhibition was obtained (IC<sub>50</sub>). The spirocompounds tested produced IC<sub>50</sub> concentrations ranging from 0.7mM to 3.0mM using compound G<sub>12</sub> and compound G<sub>14</sub> respectively. Although these concentrations are higher than those of the commercial antibiotics tested, such as Neomycin which has an IC<sub>50</sub> = 0.08mM, they indicate that the spirocompounds do show significant levels of inhibition. The spirolactone compounds were further tested using the yeast cultures to determine which stage of the splicing process they were interrupting. After analysis of the yeast spliceosome on a non-denaturing gel it was found that some of the spirolactone compounds allowed for the B complex, containing the U4, U5, and U6 snRNPs to form while other spirocompounds allowed for both the A and B complexs to form and a single spirocompound allowed for the formation of neither spliceosome complex. Neither of the commercial antibiotics tested allowed either of the spliceosome complexs to form.<sup>73</sup>

This type of spliceosome complex binding inhibition has the potential to be a very valuable tool in further study of the spliceosome. These small spirolactones provide a method for spliceosome researchers to allow the B complex to form and study its structure while inhibiting the majority of the A complex from forming. Further study into these types of compounds could lead to the development of a spirolactone compound that completely inhibits the formation of the A complex giving researchers an even better tool for study into the structural configuration and operation of the spliceosome.<sup>73</sup>

## **1.6 Objective:**

An investigation of the effect of substitution near the spiro atom would appears to be a natural next step in the understanding of this reaction and how diastereoselectivity of the oxidative spiroannulation step can be controlled. The objectives of this study were to synthesise a variety of phenolic derivatives differing by the substitution pattern at the benzylic carbon; carry out the spiroannulation of these compounds producing novel spirocompounds; determine the effect, if any, of the varying substitution has on the diastereoselectivity of the spiroannulation.

In order to reach these objectives a short synthesis using vanillin (4-hydroxy-3methoxybenzaldehyde) as a starting material was designed. Vanillin was chosen as the starting material as it is inexpensive and has the necessary substituents at the correct positions to anticipate high chemical yields and higher diastereoselectivity than results previously published.<sup>36-40,46-49</sup>

#### **Chapter 2: Results and Discussion:**

#### 2.1 Reactions in the alcohol oxidation state

My original idea was to synthesize compounds 15a/15b via a short synthesis giving the spirocompounds where an oxymethyl substituent is found on the benzylic carbon as shown in Scheme 2. Assuming success in this synthesis I had planned to replace the oxymethyl substituent with a larger one to determine the effect on diastereoselectivity of the spiroannulation reaction. The replacement of the oxymethyl group would have been fairly easy to perform as it would only require the slight modification of step C in Scheme 2. The initial synthetic route to produce compounds of this general structure is shown in Scheme 2. First, the protection of the phenolic alcohol of 4-hydroxy-3-methoxy benzaldehyde (9) was required in order to avoid unwanted reactions with this alcohol in future steps, namely deprotonation or unwanted alkylation. This was carried out via known procedures<sup>40</sup> [NaOH, NaI, benzyl chloride, acetonitrile, reflux] and afforded 10 in 94% yield. This compound showed an expanded aromatic signal in the <sup>1</sup>H-NMR spectrum along with a new singlet peak at 5.24ppm which together, integrated for 7 protons indicating the successful addition of the benzyl protecting group. Alkylation of 10 via the addition of allyl magnesium bromide under inert conditions gave 11 in 91% yield. Compound 11 was not separated into its enantiomers and was assumed to be racemic as were all the compounds produced from 11. This reaction required 3 hours reaction time and heating to reflux in THF in order to afford this yield. The <sup>1</sup>H-NMR spectrum showed that the addition of the Grignard reagent was successful as a multiplet at 5.8ppm as well as a triplet at 4.6ppm indicating the addition of the allyl group were observed. The loss of the aldehyde signal at 9.8ppm confirmed that this reaction was successful and the desired product was produced.

Compound **11** was then used in several different reactions in attempts and functionalize the benzylic alcohol. Initially, sodium hydride was used to deprotonate the alcohol and the resulting alkoxide ion was reacted with methyl iodine to produce **12**. The <sup>1</sup>H NMR spectrum of the product of this reaction showed the addition of singlet at 3.1ppm which integrated for 3 protons indicating that the addition of a methyl group to the benzylic oxygen was indeed successful.



Scheme 2: Initial synthetic scheme to produce spirocompounds **15a** and **15b**. [A: NaOH, benzyl chloride B: allyl magnesium bromide C: sodium hydride, methyl iodide D: 1: borane-THF, 2: NaOH,  $H_2O_2 E: H_2$ , Pd/C F: LTA acetone 0 C]

Anti-Markovnikov hydration of **12** afforded the terminal alcohol **13** in 88% yield. The absence of the multiplet signal at 5.83ppm in the <sup>1</sup>H-NMR spectrum of **13** confirmed that the double bond had reacted as expected and the presence of a hydroxyl group (3403cm<sup>-1</sup>) was confirmed by IR spectroscopy. The absence of a doublet around 1.5ppm to 2.0ppm strongly

suggested that the reaction proceeded as expected via an anti-Markovnikov addition producing the primary alcohol as the presence of a doublet signal would indicate a terminal methyl group. Deprotection of the phenolic alcohol was then required so that a spiroannulation reaction could be carried out. This deprotection was first attempted using hydrogen gas and palladium on carbon as a catalyst. The desired product **14** was not produced; instead the hydrogenation of **13** yielded the triol **16** as shown in Figure 11. This was evident in the <sup>1</sup>H-NMR spectrum by the loss of the signals associated with the methyl ether (4.45ppm) and signals associated with the benzylic methylene (5.07ppm). This result was unexpected as the benzyl functional group is known to be highly labile under hydrogenation conditions while the methyl ether is known to be more stable. Further experimentation with hydrogen gas at lower pressure and with a decreased amount of catalytic palladium revealed that the removal of the benzyl protecting group was impossible without the removal of the methyl ether as well.

The benzyl protecting group is also known to be labile when treated with aqueous acids. Compound 13 was therefore mixed with hydrochloric acid at high temperatures (80-100  $\degree$ C) in order to remove the benzyl protecting group. Again the triol 16 was formed. Subsequently, many attempts to selectively remove the benzyl protecting group while retaining the methyl ether with aqueous acids also failed to produce the desired product resulting in only the triol 16 being produced. These aqueous acids included hydrochloric acid, sulphuric acid, and nitric acid ranging from 0.5% v/v to 15% v/v. Eventually it was found that 2.5% HCl<sub>(aq)</sub> would cleave the methyl ether leaving the benzyl protecting group intact. This was carried out at room temperature over 15 minutes with gentle stirring and produced the unwanted compound 17. At lower concentrations of acid no reaction was observed on 13 and at greater concentrations both the benzyl and methyl ethers would be cleaved. After this discovery the benzyl protecting group was abandoned in this synthetic scheme and a more labile protecting group was utilized.



Figure 11: Deprotection of the phenolic oxygen of 13 by hydrogenation, aqueous acid or Lewis acid cleavage resulting in two unwanted compounds, 16 or 17.

As shown in Scheme 3, the methoxyethoxymethyl (MEM) protecting group was added to 9 in place of the benzyl protecting group producing 18 in 87% yield in hopes that the MEM ether would be cleaved preferentially over the methyl ether in a subsequent step. This procedure was carried out using solid sodium hydroxide and MEM chloride in acetonitrile. <sup>1</sup>H-NMR of the crude sample revealed the addition of new peaks consistent with published structures indicating that the MEM ether was introduced to the phenolic hydroxyl. Compound 18 was then used to prepare compound 21 via the same reaction steps as was used to transform 10 into 13 in Scheme 2. The removal of the MEM ether was attempted using dilute aqueous acids, as was done in attempts to remove the benzyl protecting group previously, as well as aqueous Lewis acids such as titanium tetrachloride and zinc dichloride. All procedures attempting to remove the MEM ether formed the triol 16 or preferentially cleaved the methyl ether, neither of these results were useful to the intended synthesis. Protection with the methoxymethyl (MOM) ether was then preformed on 9 and the production of 22 was achieved in similarly good yields to the procedure utilizing the MEM ether, as shown in Scheme 3. The MOM ether is well known as an extremely labile hydroxyl protecting group that can be removed easily. This protecting group is often utilized in the synthesis of compounds which bear highly sensitive functional groups. After synthesizing 25 deprotection was attempted. Unfortunately all attempts to remove the MOM ether also produced either the triol 16, or cleavage of the methyl ether preferentially over the MOM group. Attempts to remove the MOM ether were carried out using the same methodology as with the MEM ether. It was found experimentally that approximately the same concentration of aqueous mineral acids or Lewis acids would remove the methyl ether from 21 or 25 while not cleaving the MEM or MOM ethers. This result contradicted existing literature about this protecting group.<sup>20</sup>



Scheme 3: Production of compounds 21 and 25, to be used in place of 13 for the production of spirocompounds 15a and 15b as per Scheme 2. A: NaOH, MEM-chloride. B: NaOH, MOM-chloride.

A literature survey of many studies utilizing the benzyl, MEM, and MOM ethers as hydroxyl protecting groups showed that all of these groups should have been more labile under the deprotection conditions used than methyl ethers. The lack of published research showing that benzylic ethers are more labile than phenolic ethers may be a result of issues associated with their synthesis.

It is very likely that the highly electron rich nature of the phenol ring in the compounds of this study resulted in the benzylic carbon being more highly stabilized than compounds published heretofore. The high degree of resonance stabilization available to a carbocation forming at the benzylic position made the benzylic methyl ether significantly more labile than the hydroxyl protecting groups employed. The addition of electron donating groups to the aromatic ring allows for additional resonance structures to be formed when a carbocation is present. These additional resonance forms give a carbocation forming on compound **13** exceptional stability. When exposed to aqueous acids the oxygen of the methyl ether could protonate by obtaining a labile proton from the solution. This protonation would create an oxonium ion that could easily depart from **13** in a  $S_n$ 1 type manner creating a benzylic carbocation. The charge of this carbocation could then be delocalized through the phenol  $\pi$  system until a water molecule would add producing compound **16** as illustrated in Figure 12.



Figure 12: Possible mechanism for the transformation of compound 13 to 17

Substitution of the benzylic alcohol was abandoned and the spiroannulation of **16** was carried out using LTA as shown in Figure 13 which produced **26** in a 27% yield after purification by column chromatography over silica using 50:50 ethyl acetate:hexane as the eluent. A portion of the <sup>1</sup>H-NMR spectrum of **26** is highlighted in Figure 14 below. The <sup>1</sup>H-NMR spectrum of **26** showed a doublet signal with peaks centered around 6.29ppm with a J-coupling constant of 9.92Hz. This doublet corresponds to the proton at position 10 being split by the proton at position 11. A second doublet is observed around 5.72ppm with a J-coupling value of 2.67Hz which corresponds to the proton at position 7 being split weakly by the proton at position 11. A doublet of doublets is observed around 6.95ppm which corresponds to the proton at position 11. This proton is split by the proton at position 10 with a J-coupling of 9.92Hz to a doublet which is split again by the proton at position 7 with a weaker J-coupling value of approximately 3Hz. The

combinations of the observed peaks in the <sup>1</sup>H-NMR spectrum of **26**, and the lack of any additional peaks corresponding to a second diastereomer, strongly suggest that a single compound has been produced.



Figure 13: Formation of 26 from 16 with LTA in acetone.

Previous studies into small spirocompounds with similar structure to **26** have reported additional peaks in the <sup>1</sup>H-NMR spectrum which correspond to the production of a mixture of diastereomers.<sup>36,37,46,47</sup> The spiroannulation to produce **26** was repeated using both PIFA and PIDA as oxidants which resulted in compound **26** in 4% and 9% yields respectively with no change to the diastereoselectivity observed. A clean spectrum of **26** produced with PIFA or PIDA could not be obtained as the repeated chromatography steps appear to result in the degradation of the product.



Figure 14: Portion of the <sup>1</sup>H-NMR spectrum of spiroether 26.

The selectivity observed in the formation of **26** was not expected at the outset of this study as all previous attempts to control the diastereoselectivity of spiroannulation have yielded mixtures of diastereomers.<sup>36,37,46,47</sup> This study is the first in which the benzylic carbon on the alkyl chain has been modified and the first to focus on 6 membered rings rather than 5 member rings. Therefore, it is logical to assume that, it is these two modifications which bring diastereoselectivity to this reaction.



Figure 15: 6 member transition state leading to the two enantiomers 26a and 26b

The 6 member transition state would resemble that of a "chair" like state of cyclohexane as shown in Figure 15. This transition state would be most energetically stable if the benzylic hydroxyl were positioned in a pseudoequatorial orientation. This orientation of the hydroxyl group would also allow for the antibonding  $\sigma^*$  orbital of the carbon-oxygen bond to overlap into the area of space where the nucleophile would engage the electrophilic carbon. This hyperconjugation effect would lower the energy level of the nucleophiles addition to the forming spirocarbon. Assuming the orientation of the hydroxyl to be equatorial, and that the hydroxyl function exists in as a racemic mixture there are 4 possible reactions that could occur. A *re* face attack by a chain bearing either the *R* or *S* hydroxyl, or the *si* attack by the chain bearing either the R or S hydroxyl.

Molecular modeling reveals that the S hydroxyl would favour a transition state where the hydroxyl is equatorial and the nucleophile approaches the ring from the re face so that the nucleophiles path is furthest away from the electron rich alkene which is substituted with the oxymethyl group. The R hydroxyl would favour a transition state where the hydroxyl is again equatorial and the nucleophile must attack from the si face to avoid the electron rich alkene. These two cyclization reactions would result in enantiomers, compounds **26a** and **26b** in Figure 16. These two compounds would be indistinguishable from one another by NMR, TLC, mass spectrometry or other methods.



Figure 16: The enantiomeric pair of products from the spiroannulation of 16.

It is highly unlikely that the spiroannulation of **16** would give only a single compound given the racemic nature of **16**, the non-chiral reaction conditions employed, and knowledge gained from previous research into molecules of similar structure to **26**.<sup>36,37,46,47</sup> It is much more likely to hypothesize that the reaction gives an equal mixture of enantiomers that can not be isolated from each other. This prediction matches very well with the observed spectrum of
compound 26. From all data available it is logical to conclude that the production of 26a and26b proceeds with enantioselectivity producing a mixture of enantiomers.

## 2.2 Reactions in the Carbonyl oxidation state

At this stage of the study it was decided that the benzylic ether would be too labile to continue to work with and an alternative synthetic scheme was devised to produce the desired target compounds. Scheme 4 outlines this new approach. Oxidation of the benzylic hydroxyl on 11 would produce the ketone 27. From this ketone it was expected that carbon or nitrogen functionalities could be obtained in acceptable yields.



Scheme 4: Oxidation of the benzylic alcohol to the corresponding carbonyl and synthesis to create a spiroproducts via a Wittig reaction or reductive amination. A: Jones Reagent, 1h. B: ethyltriphenylphosphine ylide. C: 1: borane-THF/cyclohexene 2:  $H_2O_2$ , NaOH 3:  $H_2$ , Pd/C 4: LTA, acetone 0°C D: alkyl amine,  $H_2SO_4$  E: LTA, acetone 0°C

The oxidation of **13** using Jones Reagent [chromic acid/sulphuric acid in acetone] afforded the ketone **27** in 92% yield. The loss of the single proton signal at 4.7ppm in <sup>1</sup>H-NMR and the loss of some splitting in the multiplet around 5.8ppm showed that the benzylic proton had been removed and the oxidation successful. The Wittig reaction was then attempted on the ketone using three different triphenylphosphine ylides bearing either a methyl, ethyl, or benzyl substituents. These reactions were carried out using well established methodologies for Wittig additions. The methyl and ethyl triphenylphosphine species were deprotonated with butyllithium while the benzyl triphenylphosphine reagent was deprontonate with solid sodium hydroxide. Despite attempting these reactions in THF, DMF, CH<sub>2</sub>Cl<sub>2</sub>, CHCl<sub>3</sub>, and acetonitrile at temperatures ranging from -10°C to reflux for each solvent, no product was isolated from any of these reactions. The reaction of **27** with benzyl triphenylphosphine was also attempted in a solvent free manner. This methodology involved the solid state mixing of finely ground sodium hydroxide pellets, benzyl triphenylphosphine and **27** in a reaction flask being heated in a boiling water bath for 5 hours. Again no product was isolated from the reaction, only starting material was recovered.

Reductive amination was attempted on 27 to create an amine at the benzylic position. Ketone 27 was mixed with large excesses of propylamine, tertiary butylamine, or cyclohexylamine with a small amount of concentrated sulphuric acid. The reaction was dissolved in cyclohexanol and distilled continuously until 175mL of distillate was collected. Cyclohexanol was chosen as the solvent for these reactions as it forms a low boiling point azeotrope with water and is thus an effective method of removing the water that is produced in the formation of an imine. Water must be removed from this reaction as its presence will cleave an imine and produce the original ketone and amine. Unfortunately the imine could not be successfully isolated after the azeotropic distillation. A non isolatable imine intermediate in this type of reaction is not uncommon so a second attempt at these reactions was undertaken. In this series of reactions the reducing agent was added to the reaction mixture immediately following distillation. Both sodium cyanoborohydride and sodium borohydride in methanol were utilized independently as reducing agents in these reactions. Again, no product was isolated from these reactions; only starting materials were recovered. After the inactivity of the benzylic ketone was observed, a second alternative synthesis was devised to utilise stronger reagents in attempts to produce the desired target molecule. Scheme 5 shows this new approach.



Scheme 5: Attempted synthesis to produce **36a** and **36b** from **10**. A: methyl magnesium bromide B: Jones Reagent C: **38**,  $Mg_{(S)}$ , ethyl ether D: 1:  $H_2SO_4$ ,  $H_2O$ ,  $90^{\circ}C$  2:  $H_2$ , Pd/C F: LTA, acetone G: benzyl chloride, NaOH.

From aldehyde 10, methyl magnesium bromide was added to form the alcohol 32. This reaction was successful as indicated by loss of the aldehyde peak at 9.8ppm and the addition of a doublet at 1.5ppm, which integrated for three protons, as well as a quartet observed at 4.8ppm corresponding to the benzylic proton in <sup>1</sup>H-NMR spectrum of 32. This reaction proceeded with an optimized yield of 96%. Oxidation of 32 was accomplished with Jones reagent to 33 in 93% yield. The <sup>1</sup>H-NMR spectrum of this compound showed a shift in the methyl signal from 1.5ppm to 2.5ppm and the change of this signal from a doublet to a singlet. The alkyl bromide 38 was then reacted with 33 in diethyl ether under inert conditions in the presence of cleaned magnesium metal. Despite multiple attempts at temperatures ranging from -10°C to reflux and the addition of solid iodine to the reaction as a catalyst, the Grignard addition to ketone 33 was not achieved.

After observation of the apparent inactivity of the benzylic ketone to the above reaction conditions, the Knovenegal condensation reaction was attempted. This modified aldol condensation can be allowed to react for long periods of time at high temperatures. It was hoped that the high energy and long reaction time available while utilizing a Knovenegal condensation would allow the formation of **42a** and **42b** from **33** via the method outlined in Scheme 6. Compound **33** was dissolved in pyridine and the reaction mixture was allowed to reflux for 11 days with the addition of 4 equivalents of malonic acid and 4.5 equivalents of finely ground sodium hydroxide every 24 hours. This reaction was followed by TLC and one new spot appeared after 6 days of reaction. After the full 11 days this new spot had become stronger on TLC and the reaction was stopped. Isolation of the new compound by column chromatography was carried out however the identity of the new compound could not be established. <sup>1</sup>H-NMR of

this compound revealed it was most likely a self reaction product of malonic acid polymerizing to a large extent. This compound was not fully characterized.



Scheme 6: Potential synthesis from **33** utilizing the Knovenegal condensation to create the spiroethers **42a** and **42b**. A: pyridine/piperidine, malonic acid NaOH. B: 1: NaH 2: H<sub>2</sub> Pd/C C: LTA, acetone.

The Knovenegal condensation was then attempted using diethyl malonate in place of malonic acid. This reaction was carried out for 5 days at reflux with the addition of 2.5eq of diethyl malonate every 24 hours. Pyridine was used as both the solvent and the base to drive this reaction along with a small amount of piperidine. TLC of the reaction mixture showed no new spots and work up of the reaction also revealed no new product.

The lack of reactivity of these benzylic carbonyls is most likely due to the additional electron density imparted to the carbonyl carbon due to its proximity to the highly electron dense aromatic system. The phenols  $\pi$  system is able to give the carbonyl carbon an alkene resonance state that can be well stabilized throughout the  $\pi$  system in a manner similar to how a carbocation can be stabilized in the phenol ring. The success of reactions like the Wittig reaction, reductive amination, Grignard type additions, and many other reactions that could be attempted on this carbonyl all depend on the natural dipole of the carbonyl function to make the carbon electrophilic. In the case of compounds with the general structure of **33**, it appears logical to assume from these experiments that the natural carbonyl dipole has been greatly reduced. A

large reduction in the magnitude of the dipole moment away from the carbonyl carbon would make it much less electrophilic and thus, much less reactive to the reactions outlined in this chapter. Compound **33** could adopt resonance forms similar to those shown in Figure 8. These resonance forms would diminish the natural dipole of the carbonyl by stabilizing the alkoxide ion produced from resonance delocalization of the carbonyl  $\pi$  bond.

To test this rational **33** was treated with 6eq of methyl magnesium bromide and stirred at reflux in THF for 3 hours. The work up of this reaction showed only a yield of 58% of the resulting tertiary alcohol as shown in Figure 17. It was also noted that neutralization of this reaction after 3 hours was highly exothermic and caused a large amount of foam indicating a large amount of the methyl magnesium bromide still remained in the reaction flask. The yield of these reactions is low for a Grignard type addition particularly considering the reaction time, temperature, and the large excess of reagent used. This reaction's low yield shows that exceptionally harsh conditions such as these are not sufficient to drive reactions with these electron rich benzylic ketones to completion with a high yield. By comparison, a Grignard reaction carried out on a ketone that is not part of a conjugated system, for example **43** in Figure 17, will proceed rapidly with near quantitative yields. These types of reactions are generally exothermic and go to completion in less than 30 minutes.



Figure 17: Comparison of Grignard reaction on compound **33** versus a common aliphatic ketone **43**.

## 2.3 Reactions Involving the Addition of Halogens

After repeated attempts to introduce functionality to the benzylic carbon with alkyl, oxygen, or nitrogen groups, halogenation of this position was attempted. A halogen atom attached to the benzylic position would give a relatively large, highly electron rich substituent that could influence the spiroannulation reaction through steric interaction with the carbon chain to which it was attached or through a stereoelectronic effect. The addition of chlorine, bromine, or iodine atoms was attempted though a number of different methodologies outlined in Scheme 7.



Scheme 7: Synthesis of phenol derivatives bearing halide substituents at the benzylic position. A: thionyl chloride or dibromotriphenylphosphine B: chlorotrimethylsilane, LiBr (or NaI)

Initially the transformation of the benzylic alcohol of **11** to the corresponding chlorine using thionyl chloride was attempted. This was conducted under inert condition in a flask connected to a two stage gas trap consisting of two 500mL Erlyenmyer flasks full of water with interconnecting tubing that forced any gas from the reaction through both volumes of water before it was allowed to escape. Alcohol **11** was mixed with 3 equivalents of thionyl chloride in dichloromethane at room temperature for 6 hours. The reaction was then quenched by the slow addition of water which produced sulphur dioxide gas which was collected in the gas trap. The reaction mixture was extracted and only starting material was isolated. The reaction was repeated and water was replaced as the quenching agent with 100% ethanol denatured with methanol. This was done to ensure that the final aqueous quenching did not allow for the halide to depart through a  $S_n$ 1 type reaction with the water. Again, only starting material was recovered. The next attempt to introduce a halide function to the benzylic position was carried out using chlorotrimethylsilane and lithium bromide or sodium iodide to transform 11 into the corresponding bromide or iodide species. In accordance with the published method<sup>74</sup> of these reactions 2.5 equivalents of chlorotrimethylsilane and 2 equivalents of lithium bromide or sodium iodide were refluxed overnight in distilled dichloromethane under an inert atmosphere. The reaction mixture was extracted and the product isolated using well dried glassware and solvents. Only starting material was recovered from these attempts, thus the reactions were repeated and allowed to react 3 days before work up. Again, only the starting material was recovered.

Attempts to substitute a bromine on compound 11 was carried out using bromine and triphenylphosphine as shown in Figure 18. Liquid bromine was mixed with triphenylphosphine in dichloromethane to form dibromotriphenylphosphine which was mixed with 11 at room temperature,  $-10^{\circ}$ C and reflux separately. None of these attempts generated the desired product.



Figure 18: Attempted addition of bromine to compound 11 to produce alkyl bromide 49. A= Br<sub>2</sub>, triphenylphosphine

After the failure of these reactions to introduce a halide to the benzylic position further literature surveys revealed an additional methodology that may allow for the synthesis of a compound with the desired functionality. Using Ferulic acid as a starting material it is theoretically possible to produce the desired halide compounds through two different routes. As shown in Scheme 8, the addition of hydrobromic acid (HBr) directly to the alkene of Ferulic acid should produce the monobrominated acid 51 which could be spiroannulated to 52a and 52b. Alternately Ferulic acid could be hydrogenated to 53 and bromine introduced via a radical addition from either n-bromosuccinimide or molecular bromine.



Scheme 8: Attempted addition of HBr to Ferulic acid and the addition of HBr via a radical addition to 53 to produce 51. A= HBr in acetic acid.  $B=H_2 Pd/C C=Br_2$ , Uv light or heat. D= LTA acetone

The direct addition of HBr was carried out with a freshly prepared solution of 0.25 molar Br<sub>2</sub> in glacial acetic acid. This solution was added to Ferulic acid which was dissolved in glacial acetic acid and the reaction was self indicating of completion by the loss of the distinct red color of bromine. Once the reaction was observed to be complete the product was isolated and analysed by <sup>1</sup>H-NMR. Oddly, the expected product, **51**, was not found to be present. <sup>1</sup>H-NMR revealed that the bromine atom from HBr had added onto the aromatic ring producing compound **54** as shown in Figure 19. <sup>1</sup>H-NMR revealed a reduction in the integration of the aromatic region by one proton and the pair of doublets indicative of the double bond was still present, though shifted downfield slightly. DEPT-45 NMR of **54** showed that the signal from the carbon ortho to the alkyl group was absent suggesting that the bromine had been added to the ring meta to the phenolic oxygen and ortho to the oxymethyl group as shown in Figure 19.



Figure 19: The addition of HBr to Ferulic Acid resulted in the unexpected production of 54.

Addition of halides to an aromatic system under non-catalyzed conditions has been reported previously in the literature.<sup>75,76</sup> It has been found that bromine can be added to an activated benzene system using acidic or basic conditions.<sup>76</sup> The available literature, however, does not make reference to this addition taking place in the presence of an alkene which does not react. In the case of **54** the alkene conjugated between the aromatic ring and the carboxylic acid does not take up an equivalent of HBr as expected. Until further studies are conducted on this type of reaction and a definitive mechanism cannot be proposed, it can be concluded that the alkene function must be rendered unreactive. A mechanism for this reaction must involve, as a first step, the inactivation of the nucleophilic nature of the alkene. This could be achieved through a resonance shift of the alkenes  $\pi$  electrons; perhaps by the protonation of the alkene from the acidic reaction solution. A mechanism involving the protonation of the alkene would be a possible mechanism for this bromination would allow rapid protonation. As shown in Figure 20, a possible mechanism for this bromination would require the removal of a proton from the phenol ring and the ejection of hydride as a terminal step. H<sub>b</sub> as shown in Figure 20,

could be removed by the acetate anion, or other anion present in solution, but  $H_a$  would then be released as a hydride into solution in order to produce **54**. This hydride would then quickly react with a free proton in solution to become  $H_2$  gas. The production of hydride is, energetically, extremely unfavoured but, in this reaction, provides a relatively simple mechanism to explain the observed results. In this reaction, the addition of HBr to Ferulic acid dissolved in acetic acid I observed large amount of bubbles very rapidly being released from the reaction mixture. The gas released by this bubbling process was collected and found to be highly flammable. The production of a flammable gas other than hydrogen is extremely unlikely in this reaction. While the mechanism in Figure 20 has not been proven with any certainty, the fact that a flammable gas appeared to be produced from the reaction suggests that this mechanism is at least plausible.



Ferulic acid

Figure 20: Possible mechanism for the addition of bromine to the aromatic ring of Ferulic acid and not to the alkene present in Ferulic acid.

The failure to produce a benzylic halogen from either the benzylic alcohol or the benzylic carbonyl can be explained with the same rationals used in Sections 2.1 and 2.2. The electronic nature of the aromatic ring results in the benzylic alcohol and carbonyl to be unreactive to available reaction conditions.

#### **Chapter 3: Conclusion and Future Studies**

#### 3.1 Concluding Remarks:

The reactivity of the benzylic position created many unexpected issues in the attempts to create phenol derivates substituted at this position. The only successful synthesis was that of the hydroxyl functionalized compound 26. <sup>1</sup>H-NMR of this compound revealed that the hydroxyl group at the benzylic carbon of 26 biased the sprioannulation reaction to produce the enantiomers 26a and 26b. These compounds could not be isolated from each other or characterized individually so their structure remains theoretical at this point in time. The <sup>1</sup>H-NMR spectrum of 26 supports the hypothesis that an enantiomeric pair of compounds was formed as discussed above.

The highly labile nature of substituents linked to this benzylic hydroxyl made addition, substitution, or modifications, of this position impossible. The oxidation of this hydroxyl function to the carbonyl created a compound that was so unreactive to available methodologies that no products could be isolated from any attempts to functionalize the carbonyl. The high electron density of the carbonyl carbon, due to its location in the conjugated aromatic/carbonyl system, made it impossible to alter in this study.

While most attempts to functionalize the benzylic position of the compounds presented in this thesis were unsuccessful, at least one was not entirely fruitless. A new example of electrophilic bromination of aromatic systems was observed in which an alkene conjugated to the aromatic system was protected from the bromination condition due to its highly conjugated nature. This discovery warrants more study to determine the reaction mechanism, and its usefulness in further synthesis.

## 3.2 Future Studies:

Future studies of compound **26** could be carried out to attempt and separate the enantiomers.. This could be carried out by functionalizing the hydroxyl with a chiral auxiliary to produce a pair of diastereomers which could be isolated. The chiral auxiliary could then be cleaved from the compound to produce enantiomerically pure product. Due to the highly labile nature of groups added to the hydroxyl function this plan may prove extremely difficult. The sensitivity of the lactone ring in **26** would also add further difficulty to that study as many condition to cleave a chiral auxiliary, for example a chiral ester, would also likely open the lactone ring.

A second future study into the spiroannulation reaction could focus on forming a physical linkage between the benzylic hydroxyl, and a hydroxyl at the 2 position on the aromatic ring as shown in Figure 21. This linkage could 'lock' the aliphatic chain in place and cause an effect on the spiroannulation reaction.



Figure 21: Possible structure of a compound linked between the spiroring and the alkene carbon through an acetal.

Further studies could also be undertaken with regards to the reaction mechanism of the electrophilic bromination reaction which is presented in section **2.3** of this thesis. Analytical experiments to detect hydrogen gas production could be done to determine the validity of a mechanism in which hydride is released. From these results further studies could be undertaken to determine the exact mechanism by which bromine is added to the aromatic ring and not the

alkene. The validity of the possible mechanism presented in Figure 20 could be tested by utilizing Ferulic acid with labelled protons at various positions. If the proton attached to the double bond nearer to the carboxylic acid, as shown in Figure 22, were replaced with deuterium it would be possible to examine the validity of the mechanism shown in Figure 20. With this position deuterated it would not be detectable on <sup>1</sup>H-NMR. Once the reaction was carried out it would be expected that approximately 50% of the deuterium would be expelled as hydride and replaced with a proton, detectable by <sup>1</sup>H-NMR. If <sup>1</sup>H-NMR of the products from the bromination of the deuterated Ferulic acid revealed an increase in integration equivalent to 0.5 of a proton it would strengthen the case for the mechanism presented. If the results were not as expected, a new mechanism would need to be devised and tested.



Figure 22: Mechanism of a deuterated Ferulic acid producing two brominated products: one <sup>1</sup>H-NMR silent, one <sup>1</sup>H-NMR detectable.

#### **Chapter 4: Experimental Procedures:**

Solvents and commercial purchased compounds were used without purification. Melting points were determined on a hot stage instrument and are uncorrected. Infrared (IR) were recorded on a Perkin Elmer System 2000 FTIR with compounds placed on KBr plates as a film. Mass spectra (m/z) were obtained utilizing a Hewlett Packard 5989 B mass spectrometer with a 5890 Series II Gas Chromatograph. <sup>1</sup>H-NMR (300.13 MHz) and <sup>13</sup>C-NMR (75.47 MHz) spectra were obtained with a Bruker AMX300 spectrometer. All samples were dissolved in deuterated chloroform with an internal standard of tetramethylsilane (TMS) and expressed in parts per million. All reactions done under "inert conditions" were carried out in an oven dried flask sealed with a rubber septum and connected to a continuous flow of dry nitrogen gas for the duration of the reaction unless otherwise stated.

**4-benzyloxy-3-methoxy-benzaldehyde (10):** 1.315g (8.65mmol) of vanillin was mixed with 2.174g (15.7mmol) of K<sub>2</sub>CO<sub>3</sub> and 2.113g (16.7mmol) of benzyl chloride in acetonitrile (25mL) and stirred at reflux overnight. The reaction mixture was then acidified to pH = 1 with HCl (50% v/v) and extracted with 3x20mL EtOAc. The organic fractions were combined and washed with 10mL of brine and then dried over magnesium sulphate and the solvent was removed under reduced pressure. Recrystallization was preformed from a solution of 95:5 EtOAc:hexanes which afforded 1.968g (94%) of pale yellow crystal.

<sup>1</sup>**H-NMR: CDCl<sub>3</sub> δ** 3.94 (s, 3H, OCH<sub>3</sub>), 5.26 (s, 2H, OCH<sub>2</sub>), 7.01 (d, 1H, J=8.4Hz, CH, C5), 7.48 (m, 7H, Ar), 9.82 (s, 1H, CHO)

<sup>13</sup>C-NMR: CDCl<sub>3</sub> δ 23.8, 38, 80.0, 94.2, 94.9, 94.9, 96.1, 96.5, 96.5, 96.5, 158.9

**IR:(neat)** 1682 cm<sup>-1</sup>

**MS: M<sup>+</sup>** 241

**mp:** 62.4-64.8°C

1-[4-(benzyloxy)-3-methoxyphenyl]but-3-en-1-ol (11): 116mg (0.470mmol) of 10 was dissolved in 5ml of anhydrous THF under inert atmosphere and mixed with allyl magnesium bromide (0.05mL, 2.0M in THF, 0.709mmol) was added. The reaction was stirred at reflux for 2 hours. The reaction was then cooled to room temperature and 5mL of water was added to quench the reaction. The reaction mixture was then extracted with 3x10mL EtOAc and the organic fractions were combined before being washed with 10mL of brine. The mixture was then dried over magnesium sulphate and the solvent removed under reduced pressure. 130mg of yellow oil isolated. Chromatography using 15% EtOAc in Hexane as eluent afforded 124mg (91%) of off white solid. <sup>1</sup>H-NMR: CDCl<sub>3</sub> δ 3.88 (s, 3H, OCH<sub>3</sub>), 4.71 (m, 2H, CH<sub>2</sub>), 5.28 (s, 3H, OCH<sub>2</sub>,CH), 5.31 (s, 1H,OH exchangeable with D<sub>2</sub>O), 5.83 (m, 1H, CH, C3), 6.76 (m, 2H, CH, C5,C6), 6.92 (s, 2H, CH, C4), 7.48 (m, 6H, aromatic)

<sup>13</sup>C-NMR: CDCl<sub>3</sub> δ 11.3, 23.8, 38.8, 40.6, 82.0, 85.1, 85.3, 94.5, 94.5, 95.1, 96.1, 96.3, 96.3, 102.3

**IR: (neat)** 3401 cm<sup>-1</sup>

**MS: M**<sup>+</sup> decomposed

**mp:** 57.6-61.0°C

**1-benzyloxy-2-methoxy-4-(1-methoxybut-3-en-1-yl)benzene (12):** 162mg (0.570mmol) of **11** was dissolved in 15mL of dry THF under inert atmosphere and mixed with 26mg (1.08mmol) of NaH (60% dispersed in mineral oil) and stirred for 30 minutes. 117mg (0.825mmol) of methyl iodide was then added to the solution which was allowed to stir at room temperature for 90 minutes. The reaction was then neutralized with HCl (10% v/v) and immediately extracted with 3x10mL EtOAc. The reaction mixture was then washed with 10mL of brine before being dried over magnesium sulphate and then solvent was removed under reduced pressure. 157mg (92%) of yellow oil isolated.

<sup>1</sup>H-NMR: CDCl<sub>3</sub> δ 3.72 (s, 3H, OCH<sub>3</sub>), 4.07 (t, 2H, J=6.9Hz, CH<sub>2</sub>), 4.45 (s, 3H, OCH<sub>3</sub> aliphatic), 4.76 (t, 1H, J=11.0Hz, CH), 5.07 (s, 2H, OCH<sub>2</sub>), 5.65 (m, 1H, CH, C10), 6.73 (m, 2H, CH<sub>2</sub>, C11), 6.91 (m, 2H, CH, C5,C6,), 7.43 (m, 6H, CH, C2, aromatic [Bz])
<sup>13</sup>C-NMR: CDCl<sub>3</sub> δ 11.3, 23.8, 24.2, 39.6, 50.6, 81.1, 81.1, 85.0, 85.1, 87.3, 96.1, 97.2, 97.3,

97.8, 102.3

**IR: (neat)** 2250 cm<sup>-1</sup>

MS: M<sup>+</sup> decomposed

**4-[4-(benzyloxy)-3-methoxyphenyl]-4-methoxybutan-1-ol (13):** 134mg (0.449mmol) of **12** was dissolved in 10mL of dry THF under inert atmosphere in an ice bath and mixed with 0.71mL (8.5mmol) of 1M BH<sub>3</sub>-THF solution and stirred for 1 hour. Then 0.95mL (23.7mmol) of 1M NaOH solution and 1.95mL(6.3mmol) of  $H_2O_2$  (30% v/v) were added and the reaction was allowed to stir overnight at room temperature. The reaction mixture was then extracted with 3x15mL of EtOAc and the organic fractions were combined before being washed with 2x10mL of brine and then being dried over magnesium sulphate. The solvent removed under reduced pressure and 208mg of brown oil was isolated. Column chromatography using 30:70 EtOAc:hexane as eluent afforded 125mg (88%) of grey oil.

<sup>1</sup>H-NMR: CDCl<sub>3</sub> δ 1.72 (m, 4H, CH<sub>2</sub>, C2, C3), 3.22 (s, 3H, OCH<sub>3</sub>), 3.65 (t, 1H, J=5.7Hz, CH-OH), 3.91 (s, 3H, OCH<sub>3</sub> aliphatic), 4.11 (m, 2H, CH<sub>2</sub>-OH), 4.15 (s, 1H, OH, exchanges with D<sub>2</sub>O), 5.18 (s, 2H, OCH<sub>2</sub>), 6.73 (m, 1H, CH, C5), 6.85 (m, 2H, CH, C9, C10), 7.38 (m, 5H, aromatic [Bz])

<sup>13</sup>C-NMR: CDCl<sub>3</sub> δ 8.1, 22.3, 25.7, 52.8, 59.0, 65.0, 67.8, 110.6, 114.2, 115.6, 123.7, 123.7, 124.4, 125.0, 125.0

**IR: (neat)** 3403 cm<sup>-1</sup>

**MS: M<sup>+</sup> 316** 

1-(4-hydroxy-3-methoxyphenyl)butane-1,4-diol (16): 111mg (0.367mmol) of 13 was dissolved in 15mL of THF and mixed with 31mg of 5% Pd/C. The mixture was then placed under 22psi of  $H_2$  gas for 12 hours with constant agitation in a sealed vessel. The reaction mixture was then filtered though Celite washing with acetone and the filtrate was collected. The solvent was removed under reduced pressure to yield 74mg (96%) of brown oil. <sup>1</sup>H-NMR: CDCl<sub>3</sub> δ 1.81 (m, 2H, CH<sub>2</sub>), 2.03 (m, 2H, CH<sub>2</sub>), 2.29 (m, 2H, CH<sub>2</sub>), 3.91 (s, 3H, OCH<sub>3</sub>), 3.95 (s, 1H, OH, exchanges with D<sub>2</sub>O), 4.11 (t, 2H, J=6.8Hz, CH-OH), 6.86 (m, 3H, CH, C6, C9, C10)

<sup>13</sup>C-NMR: CDCl<sub>3</sub> δ 24.3, 31.1, 57.4, 64.7, 75.3, 104.6, 110.1, 115.8

IR: (neat) 3428 cm<sup>-1</sup>

**MS:** M<sup>+</sup> decomposed

1-[4-(benzyloxy)-3-methoxyphenyl]butane-1,4-diol (17): 54mg (0.181mmol) of compound 13 was dissolved in 25mL of 2.5% HCl(aq) and stirred for 30 minutes at room temperature. The reaction mixture was then extracted with 3x10mL EtOAc. The organic fractions were combined together and washed with 5mL of brine before being dried over magnesium sulphate. The solvent was then removed under reduced pressure and 42mg(81%) of clear oil was obtained.

<sup>1</sup>**H-NMR: CDCl<sub>3</sub> δ** 1.74 (m, 2H, CH<sub>2</sub>), 1.84 (m, 2H, CH<sub>2</sub>), 3.68 (m, 2H, CH<sub>2</sub>), 3.96 (s, 3H,

OCH<sub>3</sub>), 4.69 (t, 1H, J=6.8Hz, CH-OH), 5.26 (s, 2H, OCH<sub>2</sub>), 6.91 (m, 2H, CH, C9, C10), 7.02 (s,

1H, CH, C6), 7.44 (m, 5H, aromatic [Bz])

<sup>13</sup>C-NMR: CDCl<sub>3</sub> δ 23.4, 26.3, 34.7, 35.2, 38.5, 51.1, 81.3, 89.8, 89.9, 90.7, 91.9, 91.9, 94.3, 98.0

IR: (neat) 3426 cm<sup>-1</sup>

MS: M<sup>+</sup> decomposed

**3-methoxy-4-[2-(methoxyethoxy)methoxy]benzaldehyde (18):** 518mg (3.40mmol) of vanillin was mixed with 733mg of  $K_2CO_3$  (5.3mmol) and 0.52mL (4.2mmol) of MEM-Cl and refluxed in 30mL of acetonitrile for 20 hours following the reaction by TLC (20% ethyl acetate: hexanes) until complete. Then 10mL of 5% HCl<sub>(aq)</sub> was added to the reaction mixture and stirred for 5 minutes. The reaction mixture was then extracted with 3x15mL EtOAc and the organic fractions

were combined and washed with 10mL of brine before being dried over magnesium sulphate.

The solvent was then removed under reduced pressure to yield 702mg (87%) of clear oil.

<sup>1</sup>H-NMR: CDCl<sub>3</sub> δ 3.26 (s, 3H, OCH<sub>3</sub>), 3.41 (t, 2H, J=6.1Hz, OCH<sub>2</sub> remote), 3.64 (t, 2H,

J=6.1Hz, OCH<sub>2</sub>), 3.77 (s, 3H, OCH<sub>3</sub>), 5.37 (s, 2H, OCH<sub>2</sub>-O), 7.18 (m, 1H, CH, C2), 7.38 (m, 2H,

CH, C5, C6 ), 9.76 (s, 1H, CHO)

<sup>13</sup>C-NMR: CDCl<sub>3</sub> δ 23.7, 26.1, 36.4, 39.7, 61.2, 2.7, 82.8, 93.6, 158.7

**IR: (neat)** 1684 cm<sup>-1</sup>

MS: M<sup>+</sup> decomposed

## 1-{3-methoxy-4-[(2-methoxyethoxy)methoxy]phenyl}but-3-en-1-ol (19): 117mg

(0.488mmol) of **18** was dissolved in 10mL of dry THF under inert conditions and 84mg of allyl magnesium bromide bromide (2.0M in THF, 0.579mmol) was added and stirred for 2 hours. The reaction was quenched with 10mL of water and extracted with 3x15mL EtOAc. The organic fractions were combined and washed with 10mL of brine before being dried over magnesium sulphate. The solvent was then removed under reduced pressure to yield 131mg (96%) of yellow solid.

<sup>1</sup>H-NMR: CDCl<sub>3</sub> δ 3.26 (s, 3H, OCH<sub>3</sub>), 3.44 (t, 2H, J=6.1Hz OCH<sub>2</sub>, remote), 3.74 (broad s, 5H, OCH<sub>2</sub>, OCH<sub>3</sub>), 4.53 (t, 2H, J=4.7Hz, CH<sub>2</sub>), 5.06 (m, 1H, CH-OH), 5.07 (s, 1H, OH, exchanges with D<sub>2</sub>O), 5.26 (s, 2H, O-CH<sub>2</sub>-O), 5.73 (m, 1H, CH, C3), 6.73 (m, 2H, CH<sub>2</sub>, C4), 6.78 (s, 1H, CH, C6), 7.03 (m, 2H, CH, C9, C10)

<sup>13</sup>C-NMR: CDCl<sub>3</sub> δ 23.6, 26.3, 27.1, 29.7, 29.9, 37.1, 41.9, 81.5, 82.1, 84.9, 92.0, 94.5 IR: (neat) 3398 cm<sup>-1</sup>, 2251 cm<sup>-1</sup>

MS: M<sup>+</sup> decomposed

mp: 217.3-221.8°C

**2-methoxy-4-(1-methoxybut-3-en-1-yl)-1-[(2-methoxyethoxy)methoxy]benzene (20):** 87mg (0.362mmol) of **19** was mixed with 16mg of NaH (60% dispersed in mineral oil, 0.4mmol) and 255mg (1.81mmol) of methyl iodine was then added to the solution which was allowed to stir at room temperature for 90 minutes. The reaction was then neutralized with HCl (10% v/v) and immediately extracted with 3x10mL EtOAc and washed with 10mL of brine. The organic fractions were then combined, dried over magnesium sulphate and solvent removed under reduced pressure. 84mg (92%) of yellow oil was isolated.

<sup>1</sup>**H-NMR: CDCl<sub>3</sub> δ** 3.26 (s, 3H, OCH<sub>3</sub>), 3.34 (s, 3H, OCH<sub>3</sub>), 3.58 (t, 2H, J=10.1Hz OCH<sub>2</sub>), 3.86 (s, 5H, OCH<sub>2</sub>, OCH<sub>3</sub>), 4.14 (m, 2H, CH<sub>2</sub>), 4.98 (t, 1H, J=9.7Hz CH-OH), 5.02 (s, 1H, OH, exchanges with D<sub>2</sub>O), 5.33 (s, 2H, OCH<sub>2</sub>-O), 5.76 (m, 1H, alkene), 6.78 (d, 2H, J=8.2Hz, alkene), 6.71 (s, 1H, Ar), 7.16 (m, 2H, Ar)

<sup>13</sup>C-NMR: CDCl<sub>3</sub> δ 23.8, 26.3, 26.9, 29.7, 29.9, 37.5, 42.5, 66.3, 81.2, 82.3, 84.9, 91.9, 95.3 IR: (neat) 2248 cm<sup>-1</sup>

**MS:**  $M^+$  decomposed

**2-methoxy-4-(1-methoxybut-3-en-1-yl)-1-[(2-methoxyethoxy)methoxy]benzene (21):** 102mg (0.362mmol) of **20** was mixed with 0.68mL (8.1mmol) of 1.0M BH<sub>3</sub>-THF solution at 0°C and allowed to stir for 1 hour. Then 0.85mL (21.3mmol) of 1.0M NaOH solution and 1.74mL (15mmol) of 30% H<sub>2</sub>O<sub>2</sub> were added and the reaction mixture was allowed to stir overnight at room temperature. The reaction mixture was then extracted with 3x15mL of EtOAc and the organic fractions were combined. The organic fractions were then washed with 10mL of brine before being dried over magnesium sulphate. The solvent was removed under reduced pressure and 95mg (88%) of yellow oil was recovered.

<sup>1</sup>H-NMR: CDCl<sub>3</sub> δ 1.52-1.88 (m, 4H, CH<sub>2</sub>), 3.16 (s, 3H, OCH<sub>3</sub>), 3.38 (s, 3H, OCH<sub>3</sub>), 3.67 (m, 3H, CH<sub>2</sub>, OH, integration looses 1H with D<sub>2</sub>O), 3.91 (s, 5H, OCH<sub>2</sub>, OCH<sub>3</sub>), 4.21 (t, J=5.8Hz, 1H, CH-OH), 5.37 (s, 2H, OCH<sub>2</sub>-O), 6.82 (m, 2H, Ar), 7.18 (m, 1H, Ar)
<sup>13</sup>C-NMR: CDCl<sub>3</sub> δ 12.4, 23.7, 26.4, 26.8, 29.8, 37.5, 38.1, 42.4, 66.4, 81.2, 84.8, 91.6
IR: (neat) 3397 cm<sup>-1</sup>

MS: M<sup>+</sup> decomposed

**3-methoxy-4-(methoxymethoxy)benzaldehyde (22):** 521 mg (4.770 mmol) of vanillin was mixed with 725mg of K<sub>2</sub>CO<sub>3</sub> (5.25mmol) and 0.53mL of MOM-Cl (6.58mmol)) in 25mL of acetonitrile. The reaction mixture was heated to reflux for 18 hours, followed by TLC (20% ethyl acetate: hexane) until complete. After cooling to room temperature 10mL 5% HCl added to the reaction mixture which was stirred for 5 min. The reaction mixture was then extracted with 3x15mL EtOAc and the organic fractions were combined before being washed with 10mL of brine. The organic fractions were then dried over magnesium sulphate and the solvent removed under reduced pressure. 603mg (90%) of brown solid was recovered and used without further purification.

<sup>1</sup>**H-NMR: CDCl<sub>3</sub> δ** 3.41 (s, 3H, OCH<sub>3</sub>), 3.95 (s, 3H OCH<sub>3</sub>), 5.42 (s, 2H, CH<sub>2</sub>), 6.85 (m, 2H, Ar), 7.23 (d, 1H, Ar)

<sup>13</sup>C-NMR: CDCl<sub>3</sub> δ 23.2, 24.1, 62.0, 80.1, 82.1, 94.1, 158.9

IR: (neat) 1688 cm<sup>-1</sup>

**MS:** M<sup>+</sup> 196

**1-[3-methoxy-4-(methoxymethoxy)phenyl]but-3-en-1-ol (23):** 497mg (2.536mmol) of **22** was mixed with 0.2mL of allyl magnesium chloride (2.0M in THF, 2.75mmol) under inert conditions in a dry flask. The reaction mixture was heated to reflux and stirred overnight. The reaction

mixture was quenched by the addition of 5mL of water. The reaction was then extracted with 3x15mL of EtOAc and the organic fractions were combined before being washed with 10mL of brine. The organic fractions were then dried over magnesium sulphate and the solvent was removed under reduced pressure. 567mg (94%) of yellow solid was recovered.

<sup>1</sup>H-NMR: CDCl<sub>3</sub> δ 2.57 (m, 2H, CH<sub>2</sub>), 3.51 (s, 3H, OCH<sub>3</sub>), 3.97 (s, 3H, OCH<sub>3</sub>), 4.67 (t, 1H, J=6.2Hz, CH), 5.21 (s, 1H, OH, exchanges with D<sub>2</sub>O), 5.26 (s, 2H, CH<sub>2</sub>), 5.88 (m, 1H, alkene), 6.91 (d, 1H, J=8.4Hz, alkene), 7.06 (s, 2H, Ar), 7.17 (d, 1H, J=8.4Hz, alkene), 7.31 (s, 1H, alkene)

<sup>13</sup>C-NMR: CDCl<sub>3</sub> δ 11.7, 23.4, 24.2, 40.8, 64.3, 83.1, 83.2, 85.4, 102.5

**IR: (neat)** 3403 cm<sup>-1</sup>,2254 cm<sup>-1</sup>

**MS: M<sup>+</sup> 238** 

**mp:** 68.3-71.2 °C

2-methoxy-4-(1-methoxybut-3-en-1-yl)-1-(methoxyethoxy)benzene (24): 79mg (0.403mmol) of 23 was mixed with 61mg of NaH (60% dispersed in mineral oil, 15.3mmol) and 284mg (2.0mmol) of methyl iodine in 10mL of THF and allowed to stir for 3 hours. The reaction was then quenched by the addition of 2mL of water and the reaction mixture was extracted with 3x10mL of EtOAc. The organic fractions were combined and washed with 10mL of brine before being dried over magnesium sulphate. The solvent was removed under reduced pressure and 76mg (91%) of yellow solid was recovered.

<sup>1</sup>**H-NMR: CDCl<sub>3</sub> δ** 2.53 (m, 2H, CH<sub>2</sub>), 3.27 (s, 3H, OCH<sub>3</sub>), 3.52 (s, 3H, OCH<sub>3</sub>), 3.91 (s, 3H, OCH<sub>3</sub>), 4.72 (t, 1H, J=11.3Hz, CH), 5.31 (s, 2H, OCH<sub>2</sub>), 5.82 (m, 1H, alkene), 6.71 (m, 2H, alkene), 6.97 (s, 1H, Ar), 7.18 (d, 2H, Ar)

<sup>13</sup>C-NMR: CDCl<sub>3</sub> δ 11.4, 23.6, 24.2, 40.8, 63.0, 83.5, 83.5, 86.3, 86.4, 102.7

**IR: (neat)** 2253 cm<sup>-1</sup>

MS: M<sup>+</sup> decomposed

mp: 118.3-121.1 °C

#### 4-methoxy-4-[3-methoxy-4-(methoxymethoxy)phenyl]butan-1-ol (25): 51mg (0.202mmol) of

24 was mixed with 0.32mL (.228mmol) of 1.0M BH<sub>3</sub>-THF solution at O°C under inert conditions and stirred for 1 hour. Then 0.43mL (10.7mmol) of 1.0M NaOH solution and 0.88mL (7.76mmol) of 30% H<sub>2</sub>O<sub>2</sub> were added and the reaction mixture was allowed to stir overnight at room temperature. The reaction was then extracted with 3x15mL of EtOAc and the organic fractions were combined before being dried over magnesium sulphate. The solvent was then removed under reduced pressure and 47mg (86%) of yellow oil was recovered.

<sup>1</sup>H-NMR: CDCl<sub>3</sub> δ 1.51-1.87 (m, 4H, CH<sub>2</sub>), 3.21 (s, 3H, OCH<sub>3</sub>), 3.52 (s, 3H, OCH<sub>3</sub>), 3.92 (s, 3H OCH<sub>3</sub>), 5.27 (s, 2H, OCH<sub>2</sub>), 6.78 (m, 1H, Ar), 6.81 (s, 1H, Ar), 7.18 (m, 1H, Ar)
<sup>13</sup>C-NMR: CDCl<sub>3</sub> δ 7.65, 21.6, 22.8, 23.3, 25.6, 36.2, 50.0, 88.9, 109.5, 110.4, 112.9
IR: (neat) 3411 cm<sup>-1</sup>

MS: M<sup>+</sup> decomposed

**5-hydroxy-8-methoxy-1-oxaspiro[5,5]undeca-7,10-diene-9-one (26):** 51mg (0.240mmol) of **16** was dissolved in 10mL of acetone at 0°C and 319mg (0.72mmol) of lead tetraacetate was added. The reaction was stirred overnight and allowed to warm to room temperature. The reaction mixture was then filtered through Celite with acetone and the filtrate was collected. The solvent was removed under reduced pressure and the resulting solid was redissolved in a 10mL of acetone. 13 drops of ethylene glycol was added to the solution and was stirred overnight. The solution was then filtered through Celite and the filtrate was collected. The solvent was removed under reduced pressure and the solution and was stirred overnight. The solution was then filtered through Celite and the filtrate was collected. The solvent was removed under reduced pressure and the solution and was stirred overnight. The solution was then filtered through Celite and the filtrate was collected. The solvent was removed under reduced pressure and the solution and was stirred overnight. The solution was then filtered through Celite and the filtrate was collected. The solvent was removed under reduced pressure and 87mg of black solid was isolated. Column chromatography was

preformed on the black solid with 50% ethyl acetate: hexanes as the eluant and 13mg (27%) of brown oil was isolated.

<sup>1</sup>**H-NMR: CDCl<sub>3</sub> δ** 0.76-0.98 (m, 4H), 2.43 (t, 2H, J=10.3Hz, CH<sub>2</sub>), 2.87 (t, CH<sub>2</sub>-O, J=12.1Hz), 3.76 (s, 4H, OCH<sub>3</sub>, OH), 4.81 (s, 1H, CH-O), 5.71(d, 1H, J=3Hz, CH, H<sub>7</sub>), 6.30 (d, 1H, CH, J= 9Hz, 3Hz, H<sub>10</sub>), 6.84 (dd, 1H, CH, J=3Hz, H<sub>11</sub>),

<sup>13</sup>C-NMR: CDCl<sub>3</sub> δ 25.4, 25.6, 57.8, 59.7, 63.7, 124.0, 126.2, 128.9,

**IR: (neat)** 3347 cm<sup>-1</sup>, 1646 cm<sup>-1</sup>

**MS: M<sup>+</sup> 166** 

1-[4-(benzyloxy)-3-methoxyphenyl]but-3-en-1-one (27): 112mg (0.394mmol) of 11 was dissolved in 5mL diethyl ether and mixed with 10mL of 10% Na<sub>2</sub>Cr<sub>2</sub>O<sub>7</sub> in 5% H<sub>2</sub>SO<sub>4</sub> and stirred at room temperature for 3.5 hours. The reaction mixture was then extracted with 5x20mL diethyl ether and the organic fractions were combined before being washed with 4x20mL water, 3x15mL saturated NaHCO<sub>3</sub>, and 10mL brine. The organic fractions were then dried over magnesium sulphate before the solvent was removed under reduced pressure. 111mg of clear oil (99%) was recovered and used without further purification.

<sup>1</sup>**H-NMR: CDCl<sub>3</sub> δ** 3.77 (m, 2H, CH<sub>2</sub>), 3.98 (s, 3H, OCH<sub>3</sub>), 5.08 (s, 1H, OH, exchanges with D<sub>2</sub>O), 5.17 (s, 2H, OCH<sub>2</sub>), 6.12 (m, 1H, alkene), 6.94 (d, 2H, J=8.3Hz, alkene), 7.54 (m, 8H, Ar[Bz])

<sup>13</sup>C-NMR: CDCl<sub>3</sub> δ 9.6, 22.3, 37.0, 77.6, 78.7, 85.0, 88.9, 93.4, 93.6, 93.6, 95.0, 96.1, 110.7 IR: (neat) 1680 cm<sup>-1</sup>, 2251 cm<sup>-1</sup>

**MS: M<sup>+</sup> 281** 

1-[4-(benzyloxy)-3-methoxyphenyl]ethanol (32): 453mg (1.812mmol) of 10 was dissolved in 10mL of THF under inert atmosphere and mixed with 334mg (2.80mmol) of methyl magnesium

bromide and stirred at reflux for 5 hours. The reaction was then quenched by the addition of 10mL of water and extracted with 3x15mL of EtOAc. The organic fractions were then combined and washed with 10mL of brine before being dried over magnesium sulphate. The solvent was removed under reduced pressure and 309mg (64%) clear oil was recovered.

<sup>1</sup>**H-NMR: CDCl<sub>3</sub> δ** 1.47 (d, 3H, J=10.6Hz, CH<sub>3</sub>), 3.98 (s, 3H, OCH<sub>3</sub>), 4.87 (q, 1H, J=10.4Hz, CH), 5.18 (s, 2H, OCH<sub>2</sub>), 5.19 (s, 1H, OH, exchanges with D<sub>2</sub>O), 6.89 (m, 2H, Ar), 7.02 (s, 1H, Ar), 7.47 (m, 5H, Ar[Bz])

<sup>13</sup>C-NMR: CDCl<sub>3</sub> δ 23.6, 38.5, 38.6, 39.7, 81.3, 85.1, 94.9, 94.9, 94.9, 95.4, 97.3, 97.3IR: (neat) 3388 cm<sup>-1</sup>

**MS: M<sup>+</sup> 257** 

1-[4-(benzyloxy)-3-methoxyphenyl]ethanone (33): 108mg (0.4186mmol) of 32 was dissolved in 10mL diethyl ether and mixed with 15mL of 10% Na<sub>2</sub>Cr2O7 in 5% H<sub>2</sub>SO<sub>4</sub> and stirred at room temperature for 3.5 hours. The reaction mixture was then extracted with 5x20mL diethyl ether and the organic fractions were collected before being washed with 4x20mL of water, 3x15mL of saturated NaHCO<sub>3</sub>, and 10mL of brine. The organic fractions were then combined and dried over magnesium sulphate and the solvent was removed under reduced pressure. 105mg (98%) of brown solid was recovered.

<sup>1</sup>H-NMR: CDCl<sub>3</sub> δ 2.51 (s, 3H, CH<sub>3</sub>), 3.91 (s, 3H, OCH<sub>3</sub>), 5.23 (s, 2H, OCH<sub>2</sub>), 6.97 (m, 2H, Ar), 7.52 (m, 1H, Ar, 5H, Ar[Bz])
<sup>13</sup>C-NMR: CDCl<sub>3</sub> δ 22.6, 36.9, 37.3, 78.6, 79.1, 89.1, 93.7, 93.7, 94.6, 95.2, 95.2
IR: (neat) 1658 cm<sup>-1</sup>
MS: M<sup>+</sup> 256
mp: 78.5-81.8 <sup>C</sup>

### (2E)-3-(2-bromo-4-hydroxy-3-methoxyphenyl)prop-2-enoic acid (54): To 103mg

(0.531mmol) of Ferulic acid dissolved in 10:1 glacial acetic acid:dichloromethane, freshly prepared 0.25M HBr in acetic acid was added dropwise until reaction was persistently red in colour (approx. 12mL). The reaction was allowed to stir at room temperature for 15 minutes and was then extracted with 3x10mL of dichloromethane. The organic fractions were then combined and dried over magnesium sulphate before the solvent was removed under reduced pressure resulting in 0.128g (88%) white solid.

<sup>1</sup>H-NMR: CDCl<sub>3</sub>  $\delta$  3.92 (s, 3H, OCH3), 5.97 (s, 1H, OH, exchanges with D<sub>2</sub>0), 6.68 (d, 1H, alkene, J= 14Hz), 6.74 (m, 1H, CH Ar), 6.99 (d, 1H, alkene, J=14Hz), 7.07 (m, 1H, CH Ar) <sup>13</sup>C-NMR: CDCl<sub>3</sub>  $\delta$  37.8, 80.4, 81.0, 89.6, 113.3

**IR: (neat)** 3441 cm<sup>-1</sup>, 2258 cm<sup>-1</sup>

**MS: M<sup>+</sup> 273** 

mp: greater than 230°C, limit of available apparatus.

# Appendix 1: NMR Spectrum of Compounds



<sup>1</sup>H-NMR of 4-benzyloxy-3-methoxy-benzaldehyde



<sup>13</sup>C-NMR of 4-benzyloxy-3-methoxy-benzaldehyde



<sup>1</sup>H-NMR of 1-[4-(benzyloxy)-3-methoxyphenyl]but-3-en-1-ol



<sup>13</sup>C-NMR of 1-[4-(benzyloxy)-3-methoxyphenyl]but-3-en-1-ol



<sup>1</sup>H-NMR of 1-benzyloxy-2-methoxy-4-(1-methoxybut-3-en-1-yl)benzene



<sup>13</sup>C-NMR of 1-benzyloxy-2-methoxy-4-(1-methoxybut-3-en-1-yl)benzene



<sup>1</sup>H-NMR of 4-[4-(benzyloxy)-3-methoxyphenyl]-4-methoxybutan-1-ol


<sup>13</sup>C-NMR of 4-[4-(benzyloxy)-3-methoxyphenyl]-4-methoxybutan-1-ol



<sup>1</sup>H-NMR of 1-(4-hydroxy-3-methoxyphenyl)butane-1,4-diol



loib-4, l-hydroxy-3-methoxyphenyl)butane-1, loib



<sup>1</sup>H-NMR of 1-[4-(benzyloxy)-3-methoxyphenyl]buatane-1,4-diol



<sup>13</sup>C-NMR of 1-[4-(benzyloxy)-3-methoxyphenyl]buatane-1,4-diol



<sup>1</sup>H-NMR of 3-methoxy-4-[2-(methoxyethoxy)methoxy]benzaldehyde



<sup>13</sup>C-NMR of 3-methoxy-4-[2-(methoxyethoxy)methoxy]benzaldehyde



<sup>1</sup>H-NMR of 1-{3-methoxy-4-[(2-methoxyethoxy)methoxy]phenyl}but-3-en-1-ol



<sup>13</sup>C-NMR of 1-{3-methoxy-4-[(2-methoxyethoxy)methoxy]phenyl}but-3-en-1-ol



<sup>1</sup>H-NMR of 2-methoxy-4-(1-methoxybut-3-en-1-yl)-1-[(2-methoxyethoxy)methoxy]benzene



<sup>13</sup>C-NMR of 2-methoxy-4-(1-methoxybut-3-en-1-yl)-1-[(2-methoxyethoxy)methoxy]benzene



<sup>1</sup>H-NMR of 2-methoxy-4-(1-methoxybut-3-en-1-yl)-1-[(2-methoxyethoxy)methoxy]benzene



<sup>13</sup>C-NMR of 2-methoxy-4-(1-methoxybut-3-en-1-yl)-1-[(2-methoxyethoxy)methoxy]benzene



<sup>1</sup>H-NMR of 3-methoxy-4-(methoxymethoxy)benzaldehyde



<sup>13</sup>C-NMR of 3-methoxy-4-(methoxymethoxy)benzaldehyde



<sup>1</sup>H-NMR of 1-[3-methoxy-4-(methoxymethoxy)phenyl]but-3-en-1-ol



<sup>13</sup>C-NMR of 1-[3-methoxy-4-(methoxymethoxy)phenyl]but-3-en-1-ol



<sup>1</sup>H-NMR of 2-methoxy-4-(1-methoxybut-3-en-1-yl)-1-(methoxymethoxy)benzene



<sup>13</sup>C-NMR of 2-methoxy-4-(1-methoxybut-3-en-1-yl)-1-(methoxymethoxy)benzene



<sup>1</sup>H-NMR of 4-methoxy-4-[3-methoxy-4-(methoxymethoxy)phenyl]butan-1-ol



<sup>13</sup>C-NMR of 4-methoxy-4-[3-methoxy-4-(methoxymethoxy)phenyl]butan-1-ol



<sup>1</sup>H-NMR of 5-hydroxy-8-methoxy-1-oxaspiro[5,5]undeca-7,10-diene-9-one



<sup>13</sup>C-NMR of 5-hydroxy-8-methoxy-1-oxaspiro[5,5]undeca-7,10-diene-9-one



<sup>1</sup>H-NMR of 1-[4-(benzyloxy)-3-methoxyphenyl]but-3-en-1-one



<sup>13</sup>C-NMR of 1-[4-(benzyloxy)-3-methoxyphenyl]but-3-en-1-one



<sup>1</sup>H-NMR of 1-[4-(benzyloxy)-3-methoxyphenyl]ethanol



<sup>13</sup>C-NMR of 1-[4-(benzyloxy)-3-methoxyphenyl]ethanol



<sup>1</sup>H-NMR of 1-[4-(benzyloxy)-3-methoxyphenyl]ethanone



<sup>13</sup>C-NMR of 1-[4-(benzyloxy)-3-methoxyphenyl]ethanone



<sup>1</sup>H-NMR of (2E)-3-(2-bromo-4-hydroxy-3-methoxyphenyl)prop-2-enoic acid



<sup>13</sup>C-NMR of (2E)-3-(2-bromo-4-hydroxy-3-methoxyphenyl)prop-2-enoic acid

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