# Mechanisms and characteristic properties for some reactions of eugenol

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**Abstract:** Various reactions are described in this work. Regiospecificity and regioselectivity of reactions are discussed. Some mechanisms and pathways of processes are also proposed. The eugenol derivatives syntheses are obtained by specific reactions using simple reagents or optically active catalysts.

**Keywords:** Eugenol, Bromination reaction, Nitration reaction, Dimerization reaction, Inclusion compound, Epoxidation reaction.

## 1. Introduction

Eugenol is a derivative of phenol and an essential compound in nature. It is extracted from essential oils; mainly the clove oils [1-4]. It has many activities: antiseptic, analgesic, fungicide, bactericide, insecticide, anti-carcinogenic, anti-allergic, anti-oxidant, anti-inflammatory, etc… [5-7]. Eugenol is characterized by low solubility in water and high stability. So, it exists in many natural products and is involved in various organic syntheses. Eugenol is characterized by several reactions relating to its acid-base characteristic [8, 9], electrophilic and nucleophilic properties [10]. The main reactions are: nucleophilic reactions of oxygen [11, 12], electrophilic substitution reactions of the aromatic ring [13], addition reaction and Dies-Alder reactions [14]. In the present work, we report mechanisms and characteristics properties for some reactions of eugenol.

## 2. Eugenol derivatives by reactions on the aromatic ring

### *2.1. Bromination reaction*

Because the bromination of eugenol **1** occurs preferentially on the olefinic side chain, Nicholas has realized the selective aromatic bromination using a protecting group C=C double bond: cyclopentadienyliron dicarbonyl ($Fp^+$). So, the presence of $Fp^+$ in the medium allows blocking the double bound in allylic chain (compound **2**) and the electrophilic aromatic substitution proceeds selectively on the *ortho* position (compound **3**) (Figure. 1) [15]. Finally, the 6-bromoeugenol **4** is easily deprotected with sodium iodide (NaI) in acetone.

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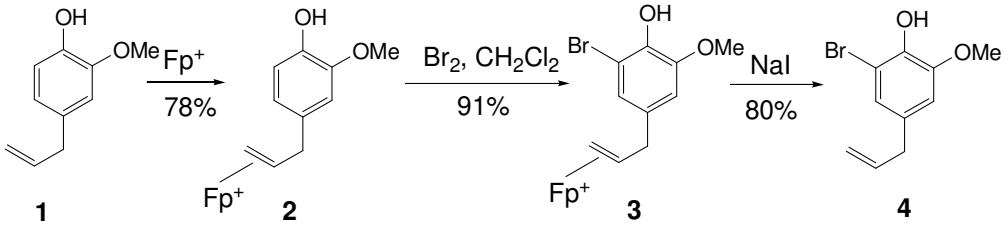
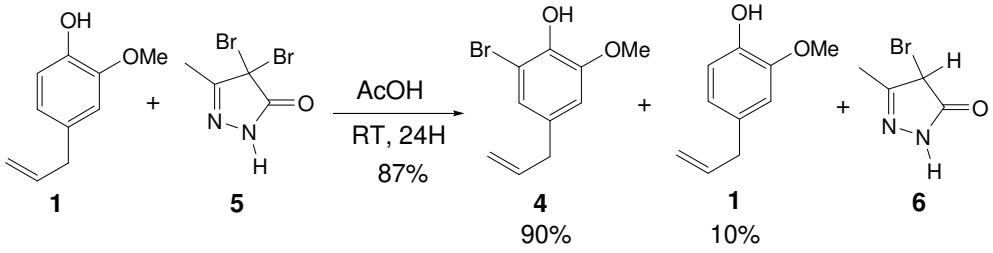


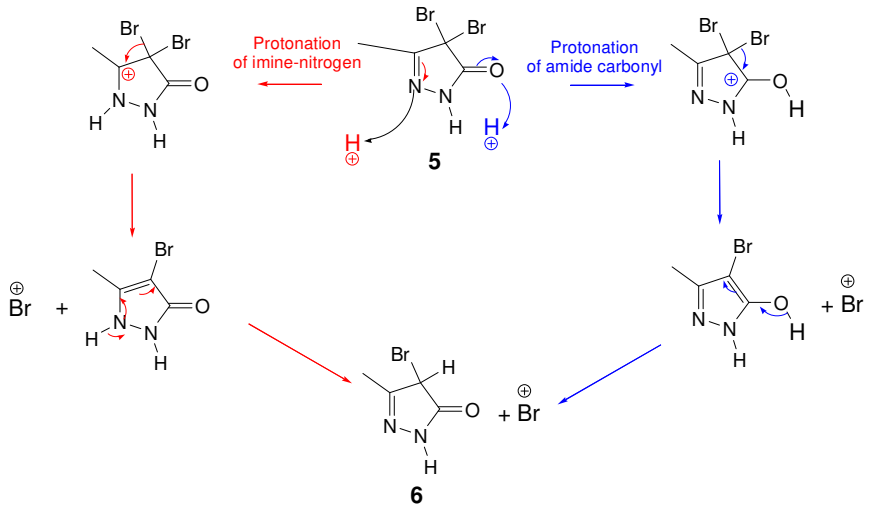

**Figureure 1:** Selective bromination reaction of eugenol in presence of $FP^+$ protecting group [15].

The 6-bromoeugenol **4** was also obtained by the selective and regiochemical reaction using the 4,4-dibromo-3-methylpyrazol-5-one **5** as an efficient monobromination agent (Figureure 2) [16].




**Figureure 2:** Monobromination reaction of eugenol [16].

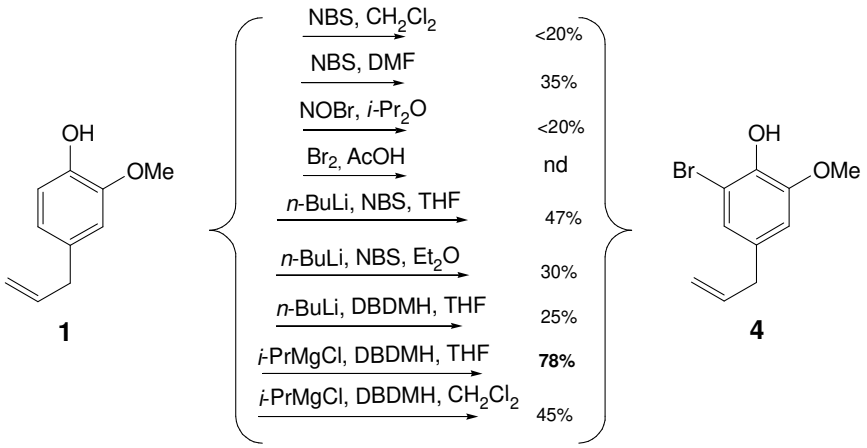
Because the reaction occurred in acetic acid medium, authors supposed that the protonation of **5** (imine-nitrogen or amide carbonyl) can polarize and weaken the C-Br bond. So, the 4,4-dibromo-3-methylpyrazol-5-one **5** becomes as a compound with an electrophilic bromine. We propose the mechanism for protonation of **5** (Figureure 3).




**Figureure 3:** Proposed pathways for protonation of **5**.

Furthermore, authors have studied the chemoselective *ortho*-bromination of eugenol in different medium to synthesis the obovatol (Figureure 4) [17]. The following bromination agents: *N*-bromosuccinimide (NBS), sodium hypobromite (NaOBr) and bromine ($Br_2$) were unsuccessful to provide the desired product **4.** However, the uses of bases with an electrophiles: n-butyllithium (n-BuLi) in presence of *N*-bromosuccinimide (NBS) or isopropylmagnesium chloride (*i*-PrMgCl) in presence of 1,3-dibromo-5,5-

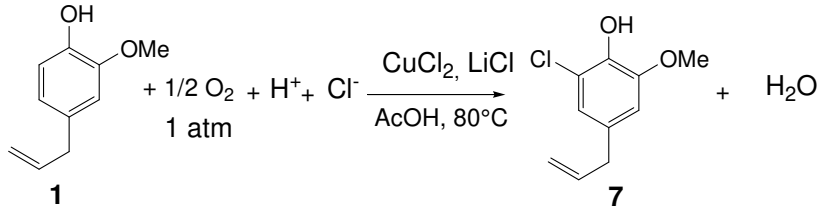
dimethylhydantoin (DBDMH) gave the final product with good yield. The best result was obtained with isopropylmagnesium chloride (*i*-PrMgCl) in THF as solvent (78% yield) (Figureure 4) [17].




**Figureure 4:** Monobromination reaction of eugenol in different medium [17].

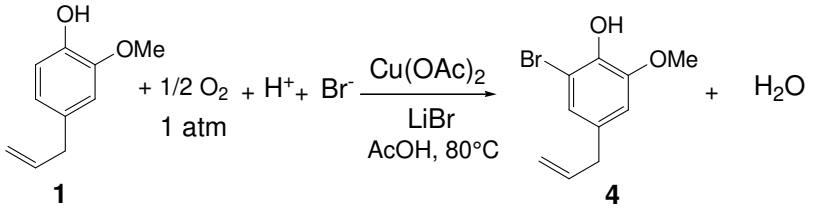
*2.2. Oxyhalogenation reaction*

The aerobic oxychlorination reaction of eugenol **1** is catalyzed by copper (II) dichloride ($CuCl_2$) in the presence of lithium chloride (LiCl) (Figure. 5) [18, 19]. The resulted product was the 6-chloroeugenol **7**.




**Figureure 5:** Oxychlorination reaction of eugenol [18, 19].

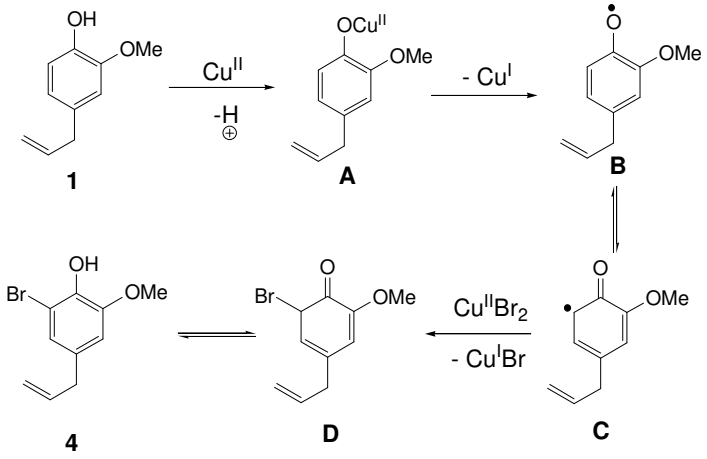
The oxidative bromination of eugenol **1** has occurred in the presence of lithium bromide (LiBr) and copper acetate ($Cu(AcO_2)$) under molecular oxygen. The need to use dioxygen is to avoid precipitation of copper(I) bromide (CuBr) and to re-oxide the Cu(I) (Figureure 6) [20].




**Figureure 6:** Oxybromination reaction of eugenol [20].

For the oxyhalogenation and specially the oxybromination, the authors have proposed the mechanism shown in Figureure 7. First, they suggest the formation of a copper (II) alcolate complex **A** by

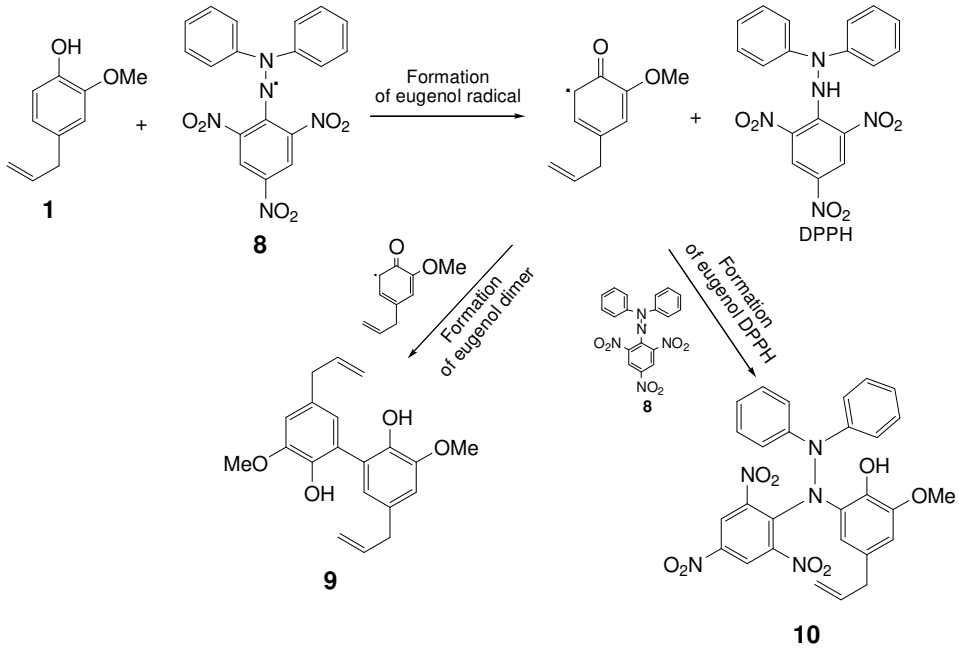
oxidation of eugenol **1** with copper(II) in presence of dioxygen. Then, the radical **B** is obtained by reduction of copper (II). The tautomer radical **C** reacts with $CuBr_2$ and brominated product **D** is obtained. Finely, tautomerization gives 6-bromoeugenol **4** [20].




**Figureure 7:** Proposed mechanism of oxybromination reaction of eugenol [20].

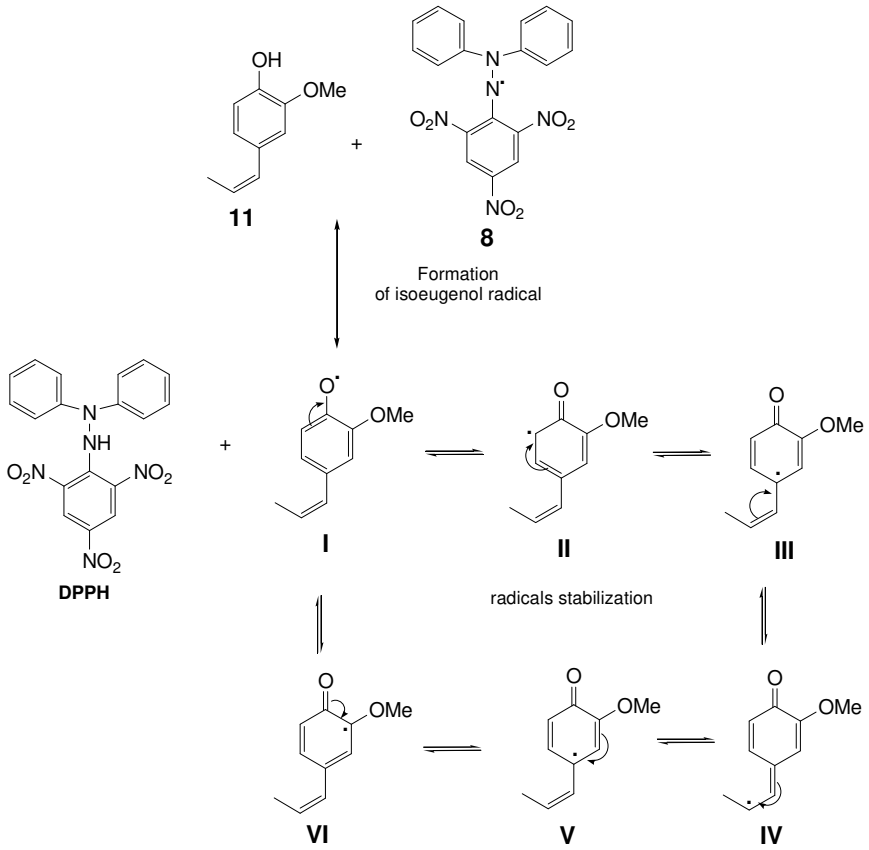
*2.3. Reactions with DPPH*

Authors have shown that the reaction of eugenol **1** on 2,2-dophenyl-1-picrylhydrazyl radical (DPPH$^{\bullet}$) **8** in a specific stoichiometry condition gives eugenol dimer **9** and eugenol DPPH compound **10** (Figureure 8) [21].




**Figureure 8:** Reaction eugenol **1** and DPPH$^{\bullet}$ **8** [21].

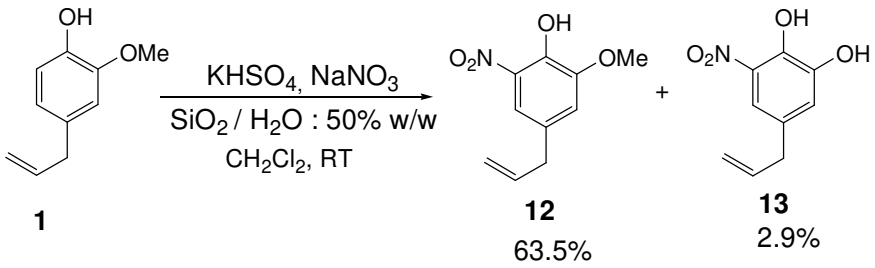
The situation changes with isoeugenol **11**. The radical isoeugenolO• **I** is stabilized by the aromatic ring and the vinyl group in the *para* position. So, the reaction between isoeugenol **11** and DPPH• **8** becomes reversible (Figureure 9) [21].




**Figureure 9:** Reversible reaction between isoeugenol **11** and DPPH• **8** [21].

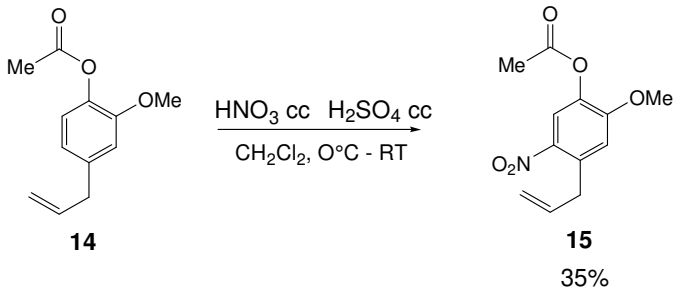
*2.4. Nitration reaction*

The simultaneous action of potassium hydrogen sulphate ($KHSO_4$), sodium nitrate ($NaNO_3$) and wet silica ($SiO_2$) on eugenol **1** at room temperature (RT) has given the *ortho* isomer of nitroeugenol **12** as main product. During the reaction, the 5-allyl-2-hydroxy-3-nitrophenol **13** is also obtained by loss of OMe protecting group (Figureure 10) [22, 23].



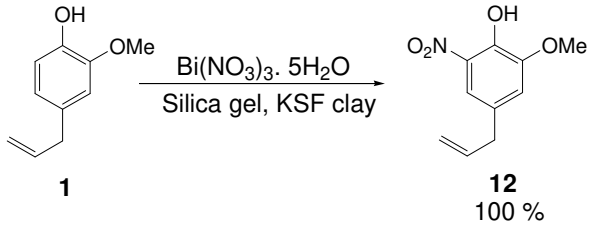

**Figureure 10:** Nitration of eugenol **1** in presence of $NaNO_3$ and wet $SiO_2$ [22, 23].

The nitration of eugenyl acetate **14** was accomplished differently than eugenol **1**. So, the authors have used a sulphonitric mixture (Figureure 11) [22, 23].



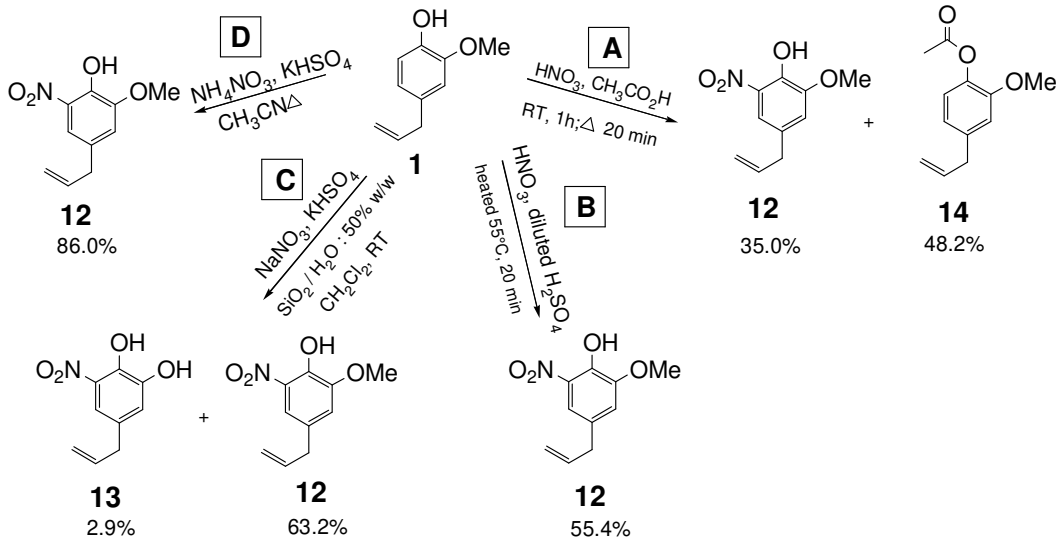

**Figureure 11:** Nitration of eugenyl acetate [22, 23].

A selective nitration reaction was occurred with bismuth nitrate pentahydrate ($Bi(NO_3)_3.5H_2O$) in presence of solid surfaces. The best results were obtained when using silica gel ($SiO_2$), KSF clay (montmorillonite), Dean-Stark water separator and microwave (Figureure 12) [24].



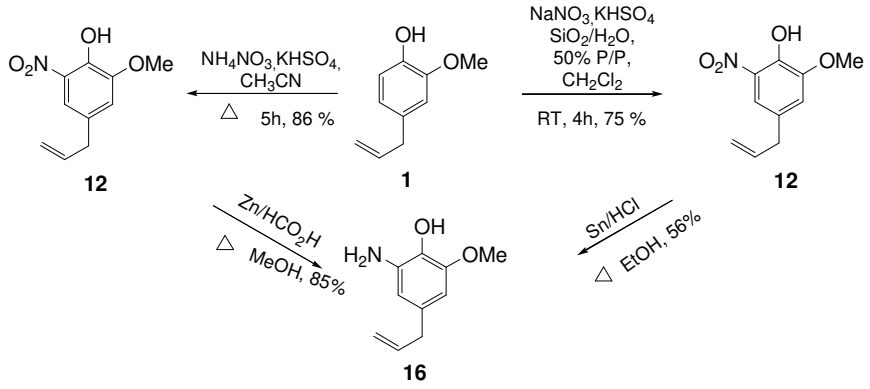

**Figureure 12:** Nitration reaction using $Bi(NO_3)_3.5H_2O$ [24].

Another group of authors has reported a regiospecific nitration of eugenol **1** with different medium. With method **A**, they obtained a very low yield because a competitive reaction occurred when acetic acid was used as a catalyst due to the formation of eugenyl acetate **14**. In order to eliminate the esterification reaction, method **B** was used (in dilute sulfuric acid as a catalyst), but still gives a low yield. Method **C** gave also two products (**12** and **13**). So, they performed the reaction by the replacement of concentrated nitric acid with ammonium nitrate ($NH_4NO_3$) and sulfuric acid with $KHSO_4$ (Method **D**). Then, the mixture was refluxed in acetonitrile ($CH_3CN$) and gave high yield of 5-allyl-2-hydroxy-3-nitrophenol **12** (Figureure 13) [25].



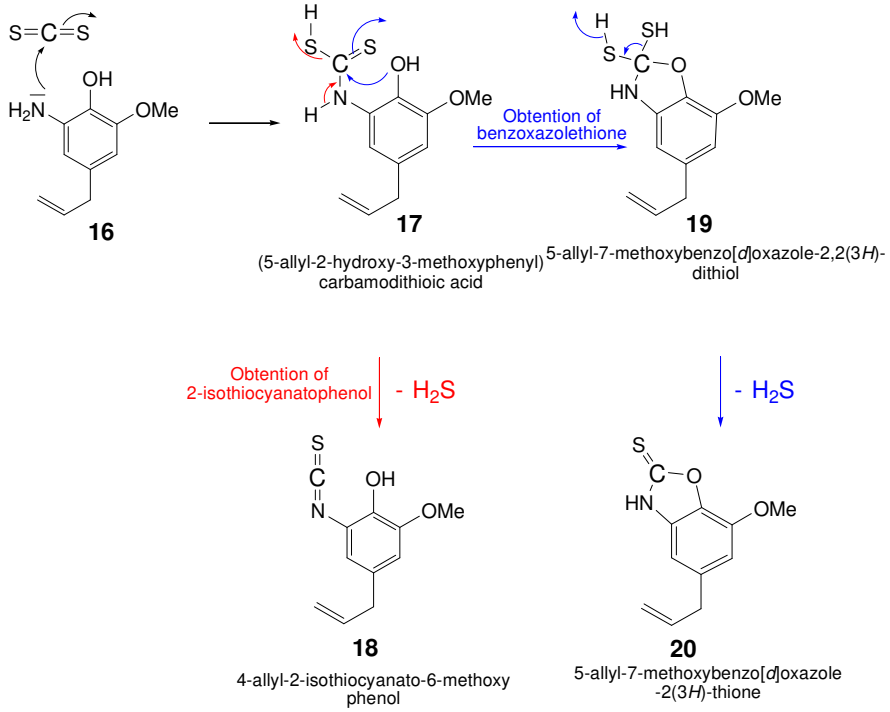

**Figureure 13:** Regiospecific nitration of eugenol **1** in different medium [25].

Sudarma et al. have prepared nitro eugenol **12** by the same method cited above [22, 23, 25]. For 4-allyl-2-methoxy-6-aminophenol **16,** they used a specific reduction reaction of nitro eugenol **12** using tin powder and concentrated hydrochloric acid in ethanolic solution. This product was obtained with moderate yield (56%) (Figureure 14) [26].



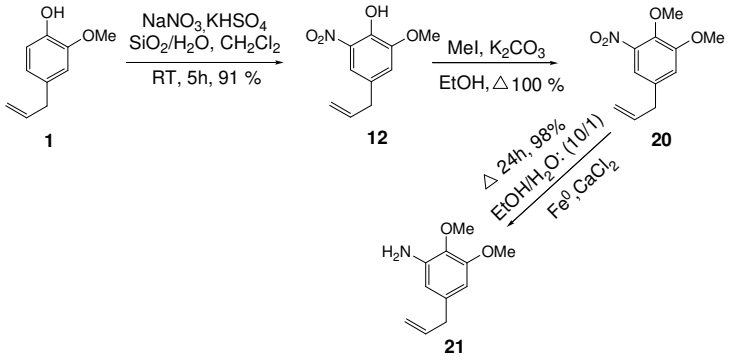

**Figureure 14:** Nitration and amination reactions of eugenol **1** [26, 27].

After, the same group has obtained compound **16** in high yield (85%) using zinc powder and formic acid in methanol. The action of carbon disulfide on amino-eugenol produced: phenylcarbamodithioic acid (**17**) (5.36%), 2-isothiocyanatophenol (**18**) (4.28%), and particularly 5-allyl-7-methoxybenzo[d]oxazole-2(3H)-thione (**20**) (32.70%). The reaction of cyclization from compound **17** via the intermediate **19** gave compound **20** with loss of $H_2S$. We also proposed that removal of $H_2S$ from compound **17** could lead to compound **18** (Figureure 15) [27].




**Figureure 15:** Proposed pathways for formation of isothiocyanate derivatives [27].

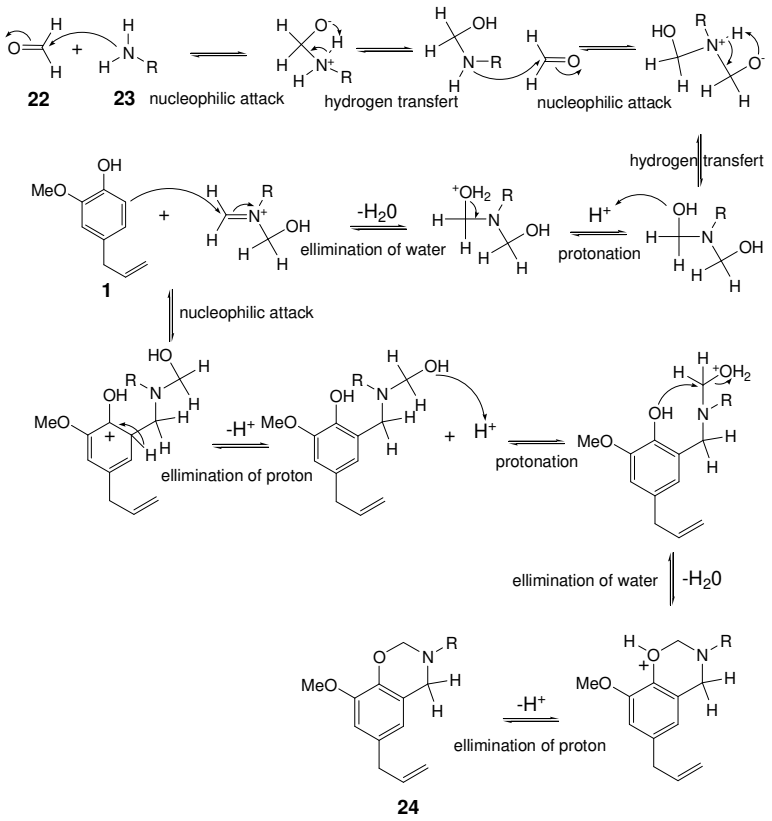
Kaufman et al. have used the Sudarma nitration efficient method to provide *o*-nitroeugenol **12** which underwent an *O*-methylation protection reaction in order to obtain an aminoeugenol derivative **21** (Figureure 16) [28].



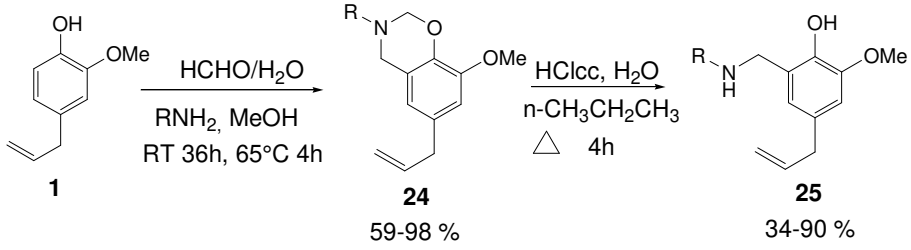

**Figureure 16:** Regiospecific amination of eugenol **1** [28].

*2.5. Mannich reaction*

The condensation of eugenol **1** with formaldehyde solution **22** and primary amine **23** (alkyl and aromatic) gives the oxazine rings. So, here Mannich reaction consists on one pot reaction between three compounds: eugenol **1**, formaldehyde **22** and amine **23**. Thus, the following mechanism is proposed (Figure. 17). The result was 1,3-benzoxazines **24**. Then, the hydrolysis of 1,3-benzoxazines **24** allowed the aminomethyl derivatives **25** (Figureure 18) [29].




**Figureure 17:** Proposed mechanism for obtention of 1,3-benzoxazines **24**.

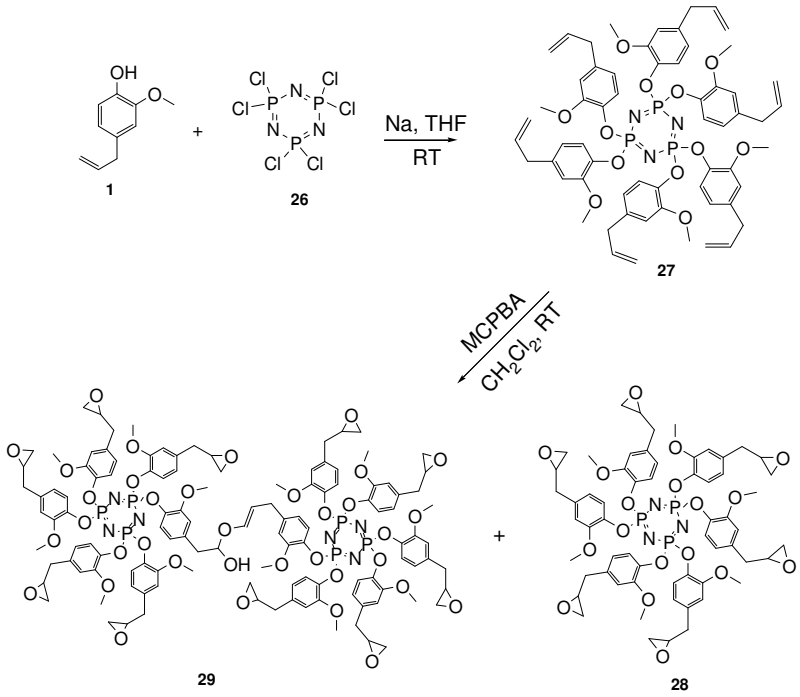



**Figureure 18:** Hydrolysis of 1,3-benzoxazines **25** [29].

## 3. Eugenol derivatives by modifications on the double bond

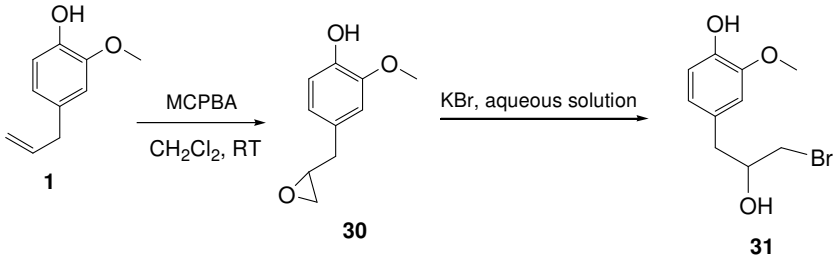
### *3.1. Epoxidation reaction*

The condensation reaction between eugenol **1** and hexachlorocyclotriphosphazene (HCP) **26** in presence of metallic sodium at room temperature gave hexakis(4-allyl-2-methoxyphenoxy)cyclotriphosphazene (HEP) **27**. This resulted product was subjected to the epoxidation reaction. The mass spectrum analysis of HEP epoxide **28** shown that correspond to a mixture of monomer epoxide **28** and dimer epoxide **29** products in a molar ratio 2:1 (Figureure 19) [30].



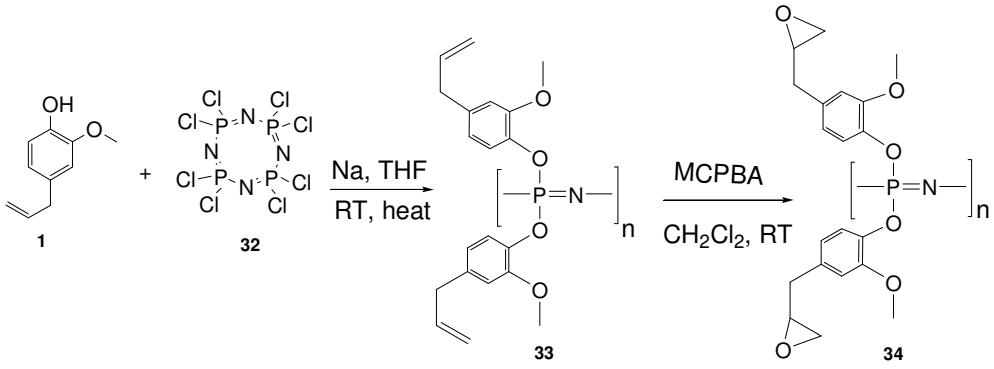

**Figureure 19:** Synthesis of HEP epoxides **28** and **29** [30].

The epoxide-eugenol **30** was prepared by the oxidizing agent *meta*-chloroperbenzoic acid (MCPBA). The nucleophilic reaction between the bromide and the heterocyclic oxide produces its cleavage to the bromo-alcohol compound **31** using an aqueous solution of potassium bromide (KBr) (Figureure 20) [31].




**Figureure 20:** Synthesis of eugenol epoxide **30** [31].

In order to prepare eugenol oligomer derivatives (OEP) **33**, the authors used the action of octachlorocyclotetraphosphazene (OCP) **32** on eugenol **1** in presence of metallic sodium (Na). Next, the epoxidation was conducted in presence of MCPBA to give octakis(4-glycydyl-2-methoxyphenoxy)cyclotetraphosphazene (EOEP) **34** (Figureure 21) [32].




**Figureure 21:** Synthesis of eugenol epoxide **34** [32].

The synthesis of eugenol epoxy **37** was realized in three steps from the starting eugenol **1**. First, the acetyl eugenol **14** was prepared by classical esterification reaction, and then compound **14** was oxidized into acetyl eugenol oxide **35** using MCPBA. Last, authors have used the Nouailhas et al. method's which is relative to the *O*-glycidylation reaction [33]. This consist of: i) a nucleophilic substitution ($SN_2$) between phenolate ion (derived from oxide **35** and epichloridrin **36** in a strong basic medium, ii) then followed by closing reaction to obtain the eugenol epoxy **37** (Figureure 22) [34].

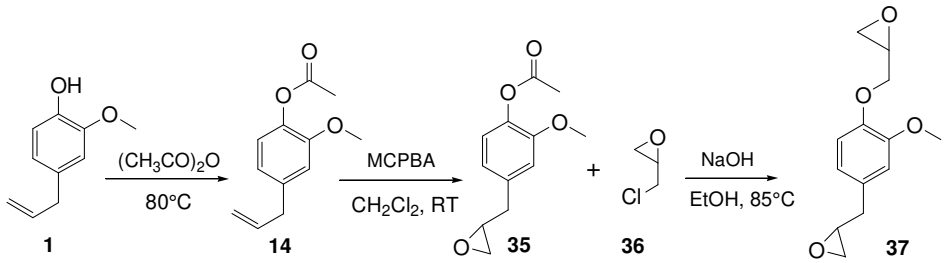
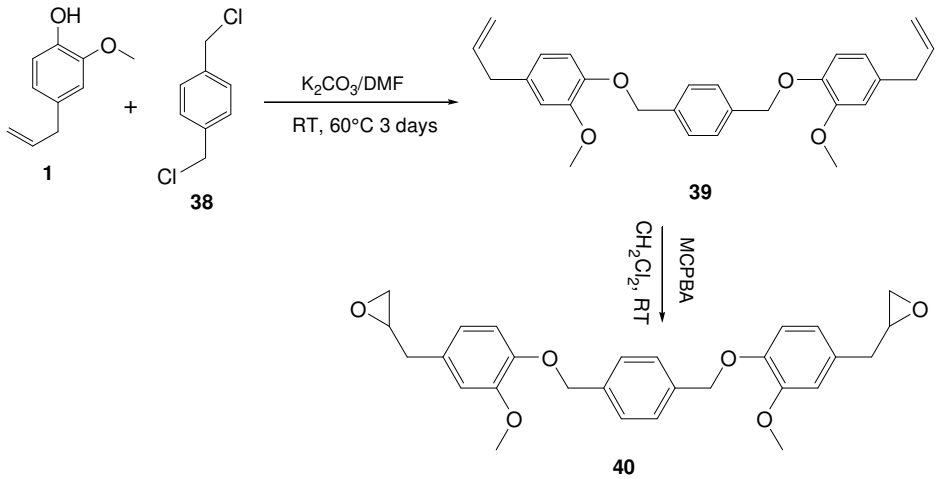



**Figure. 22:** Syntheses of acetyl eugenol oxide **35** and eugenol epoxy **37** [34].

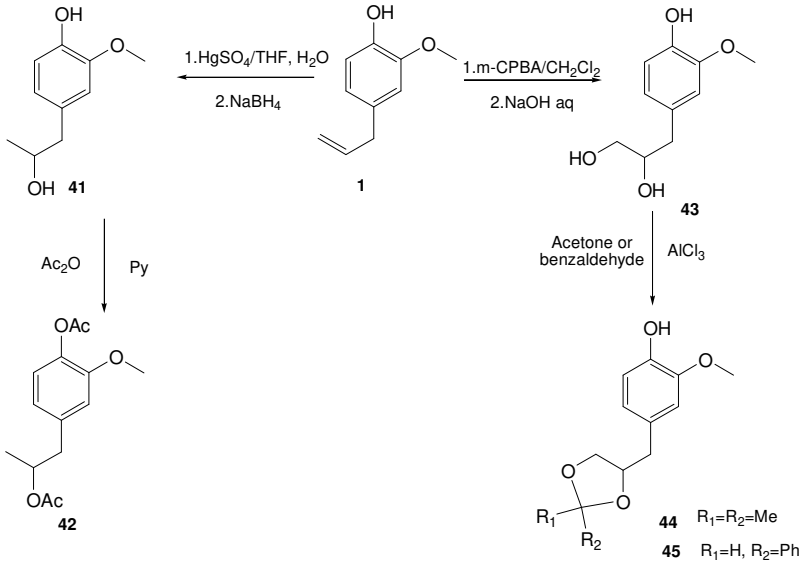
The authors have prepared a novel eugenol epoxy resin DEU-EP **40** by simple reactions (Figureure. 23) [35]. First, they used the Williamson etherification reaction between α,α'-dichloro-p-xylene **38** and eugenol **1** and obtained the DEU: 1,4-bis((4-allyl-2-methoxyphenoxy)methyl)benzene **39**. Then classical epoxidation on strand vinylic yields the novel epoxy resin: 2-(4-(4-((2-methoxy-4-(oxiranylmethyl)phenoxy)methyl)benzyloxy)-3-methoxybenzyl)oxirane **40**.



**Figureure. 23:** Synthesis of eugenol epoxide **40** [35].

*3.2. Hydroxylation reaction*

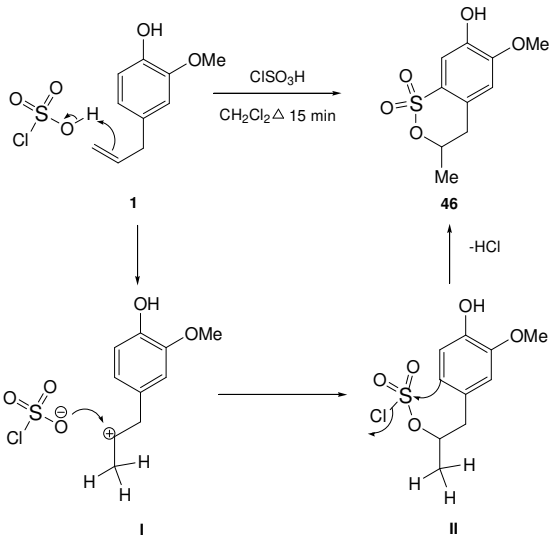
Da Silva et al. chemically modified the double bond of eugenol to increase the antioxidant effect of new eugenol derivatives. First, authors have realized the monohydroxylation reaction. The action of aqueous mercury sulfate solution on eugenol **1** in THF followed by addition of a solution of sodium borohydride ($NaBH_4$) gave compound **41** in moderate yield (35%). Then using m-CPBA, they obtained the 4-(2,3-dihydroxypropyl)-2-methoxyphenol **43** which has used to prepare different 1,3-dioxolane phenol derivatives **44** and **45** in good yield (62%) [36]. Compounds **41, 43, 44** and **45** shown higher $IC_{50}$ values than eugenol because of their specific structures. Furthermore, the hydrophilicity for **41** and **43** is high due to additional hydroxyl groups (Figureure. 24) [36].




**Figureure. 24:** Hydroxylation reactions of eugenol [36].

*3.3. Markovnikov addition*

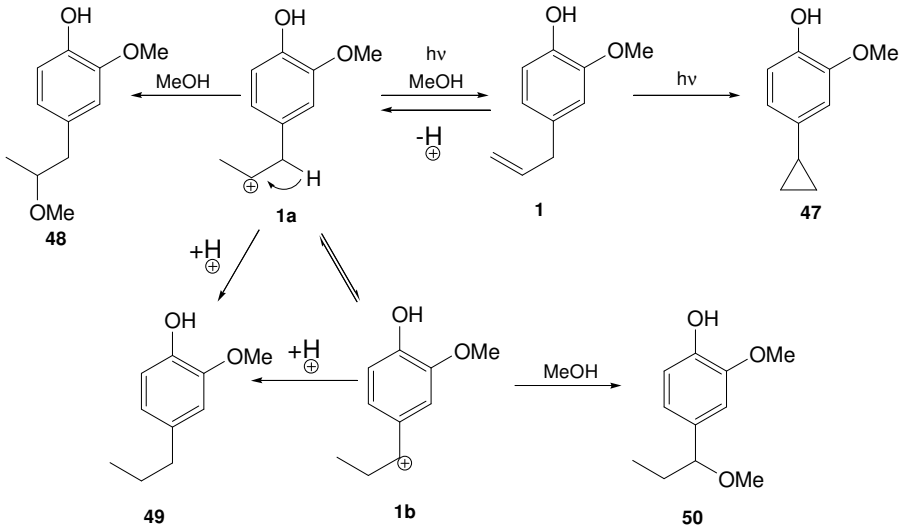
Authors have used the regionspeficific Markovnikov reaction to prepare the cyclic sulfonic ester **46.** The hydrogen atom from chlorosulfuric acid is added to the double bond of allyl group in eugenol **1**. A positive charge on the second carbon results forming a carbocation intermediate **I.** Then, chlorosulfuric ion attacks the carbocation and creates a more stable intermediate **II**. Finally, cyclisation leads the sulfonic ester **46** by elimination of HCl (Figureure. 25) [37].




**Figureure. 25:** Proposed mechanism for the formation of cyclic sulfonic ester **46** [37].

*3.4. Photochemical Reaction*

Mihara and Shibamoto have obtained new phenol derivatives using photochemical irradiation of eugenol **1**. The cyclopropane derivative **47** results by 1,2 aryl migration. The others products are result of methanol addition products (**48** and **50**). Authors have confirmed by the mass spectra that synthesis of compound **49** occurs under ionic process through carbocation intermediates **1a** and **1b** (Figureure. 26) [38].



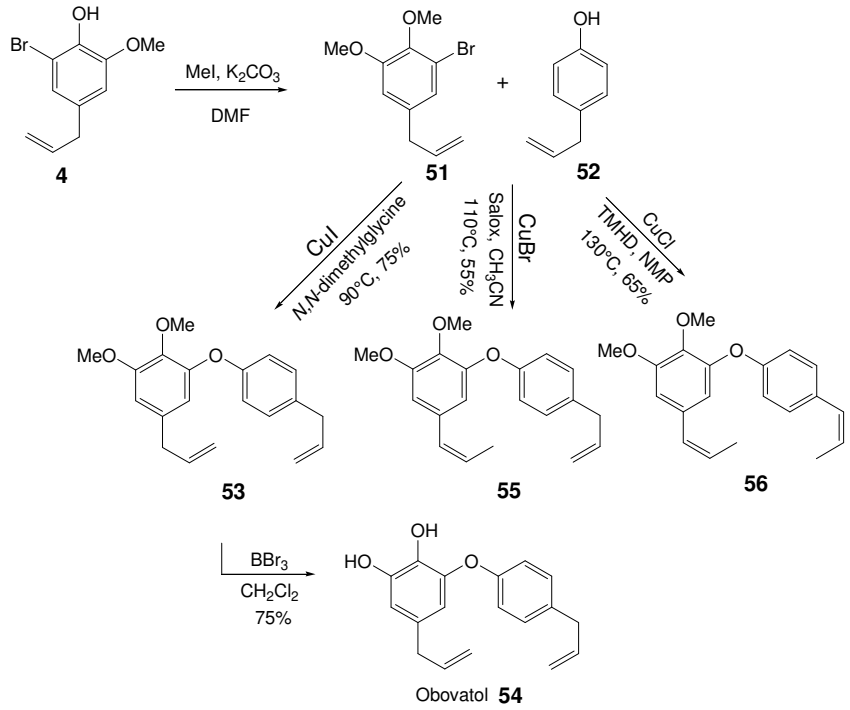

**Figureure. 26:** Proposed mechanism for the formation of irradiated eugenol derivatives [38].

## 4. Eugenol derivatives by modifications on the hydroxyl group

*4.1. Etherification reaction*

The diaryl ether compound: Obovatol **54** was prepared by Ullmann coupling reaction between the *ortho*-bromophenol **51** and *p*-allylphenol **52**. The experimental conditions are chosen to ovoid the olefin

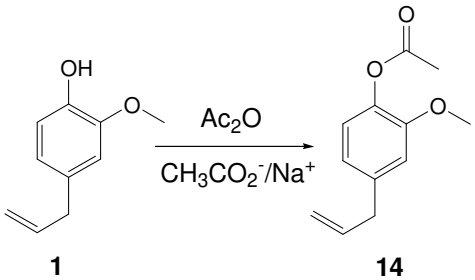
migration in the desired product **53**. So, they used CuI as catalyst, *N,N*-dimethylglycine as ligand and dioxane as solvent at 90°C. The followed step was the demethylation reaction using boron tribromide ($BBr_3$) to have compound **54**. Unfortunately, when changing catalyst (CuBr), ligand (Salox: salicylaldoxime) and solvent (acetonitrile), the mono-migration occurred easily in product **55**. Under high temperature (130°C) and high basic condition (*N*-methy-2-pyrrolidone), the terminal olefins migrated to the stable internal olefins (compound **56**) (Figureure. 27) [17].




**Figureure. 27:** Synthesis of obovatol **54** from 6-bromoeugenol **4** [17].

*4.2. Esterification reaction*

Eugenyl acetate **14** was synthesized from essential oil (extracted from *Syzygium aromaticum L*) and commercial eugenol **1** with good yields. The crystal structure of this compound was realized by powder X-ray diffraction (Figureure. 28) [39].




**Figureure. 28:** Obtention of eugenyl acetate **14** [39].

Laroque et al. have used a heterogeneous catalysis in solvent-free reactions for the synthesis of eugenyl acetate **14**. The esterification reaction was realized using the molecular sieve catalyst 4Å and

Amberlite XAD-16. The results were highest conversion of eugenol **1** to eugenyl acetate **14** (90 to 98 %) (Figureure. 29) [40].

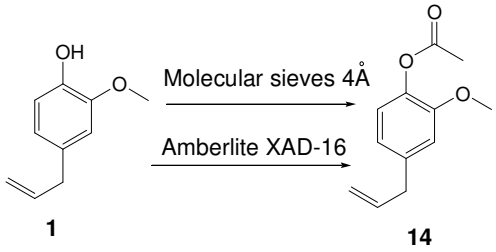



**Figure. 29:** Synthesis of eugenyl acetate **14** by molecular sieve and Amberlite XAD-16 [40].

Da Silva et al. have proposed two main methods of preparing other esters of eugenol **1**. The first uses different anhydrides (butanoic and hexanoic) in presence of pyridine at room temperature. All derivatives compounds **57** and **58** are obtained in high yields (respectively 72% and 60%). The second method uses carboxylic acids (benzoic and cinnamic) and ibuprofen in presence of 4-dimethylaminopyridine (DMAP) as catalyst and dicyclohexylcarbodiimide (DCC) as coupling agent. The resulting compounds (**59**, **60** and **61**) are also obtained in good yields (respectively 66%, 64% and 60%) (Figure. 30) [36].

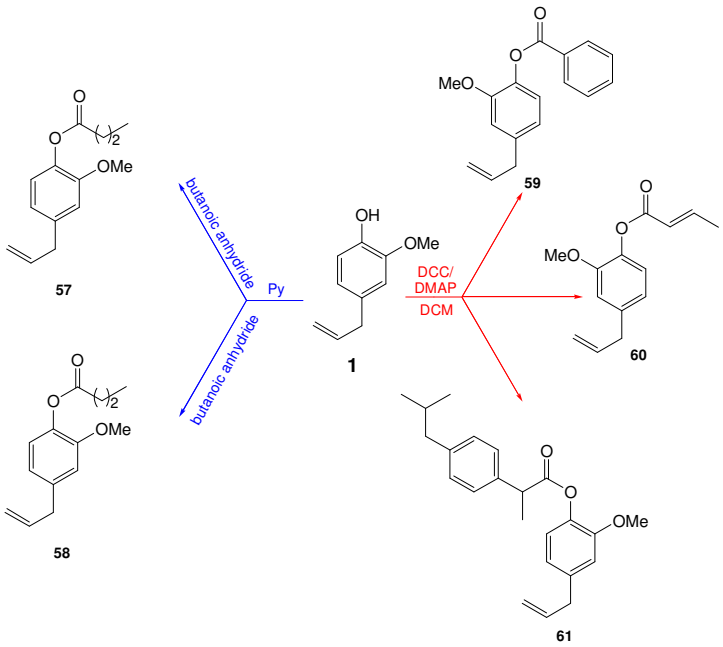



**Figure. 30:** Synthesis of esters' eugenol by two methods [36].

*4.3. Demethylation reaction*

In order to prepare hydroxychavicol **62**, the demethylation reaction of eugenol **1** was employed. Authors have performed this reaction using a homogeneous system by dissolving eugenol in $CH_2Cl_2$ and $AlCl_3$ in $CH_2Cl_2$-DMS. So, the demethylation mechanism occurs through a slow $SN_2$ processes and gives the intermediate **I**. The electron pair on the oxygen atom (in O-methoxy) resonates with the aromatic ring, thus lowering the chances of nucleophilic attack on the Al atom. The chloride ions attack the methyl and proton

groups respectively (with partial positive charges) and give the intermediate **II** (aluminum complex). To complete the demethylation step, cold HCl is added to decompose the latter complex (Figure. 31) [41].

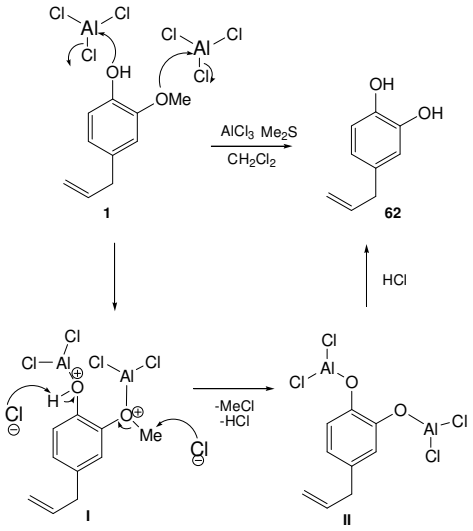



**Figure. 31:** Proposed demethylation mechanism of eugenol [41].

## 5. Dimerization reaction

Asano and Gisvold have obtained the dehydrodieugenol **63** by action of a solution of ammonium hydroxide ($NH_4OH$) and potassium ferricyanide $K_3Fe(CN)_6$ on eugenol **1** (Figure. 32) [42].

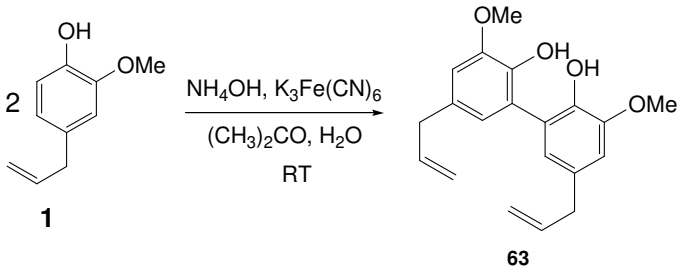



**Figure. 32:** Obtention of dehydrodieugenol **63** [42].

The dimerization of eugenol **1** in presence of CuCl(OH)/TMEDA (tetramethylethylenediamine) has given the dehydrodieugenol: 3,3'-dimethoxy-5,5'-di-2-propenyl-1-1'-biphenyl-2,2'-diol **63**. The reactivity on eugenol ring is located in positions C6 of aromatic. So, eugenol dimer **63** was obtained because of the presence of $Cu^{+2}$ which forms a complex and favors the cross-linking between *ortho* positions (Figure. 33) [43].

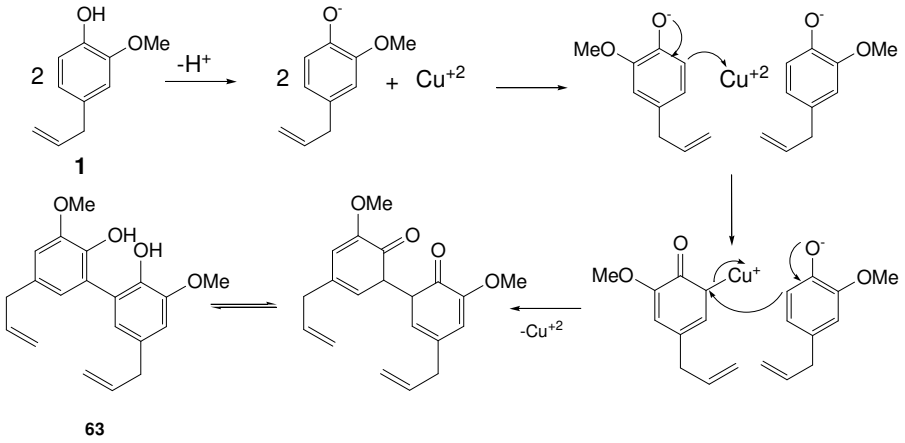



**Figure. 33:** Dimerization pathway reaction of eugenol **1** [43].

After, Delogu et al. have used dehydrodieugenol **63** to prepare the dibromo dimer **64** following the specific protocol. First, the biphenol is made to act with the base $K_2CO_3$ in dry DMF, and then $CH_3I$ is added to the reaction mixture at 50°C. Di-*O*-methyldehydrodieugenol **64** was obtained in good yield. Then, this last compound undergoes the action of benziltriethylammonium tribromide [BTEA.$Br_3$] as brominating agent. The reaction affords a mixture of three bromo diastereomers **65**. To regenerate the starting allyl chains, the debromination reaction was occurred in the presence of Zn (dust) in ethanol solution (at reflux). The 5,5'-diallyl-6,6'-dibromo-1,1'-biphenyl **66** was obtained in high yield (Figure. 34) [44].

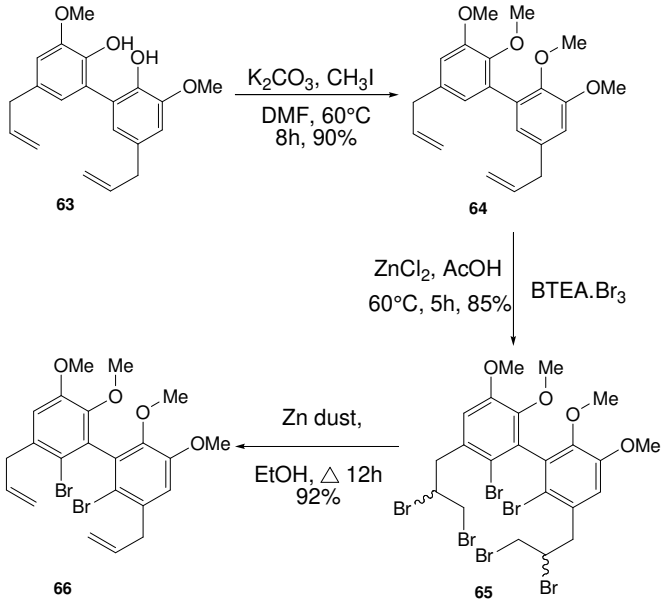



**Figure. 34:** Obtention of 5,5'-diallyl-6,6'-dibromo-1,1'-biphenyl **66** [44].

In order to separate the two atropo enantiomer (a*S*)-(-) and (a*R*)-(+), authors have used the (1*R*)-(-)-menthyl chloroformate **67** as chiral derivatizing agent. To the menthylcarbonate **68** was applied the bromination reaction followed by debromination reaction. So, the resolution of the obtained bromo-menthylcarbonate **69** was achieved by their solubility in diethyl ether at room temperature [44]. Later, the enantiomer (*S*)-*6,6'*-dibromo-dehydrodieugenol **72** has used as an efficient agent for the treatment of tumor cells: melanoma (Figure. 35) [45].

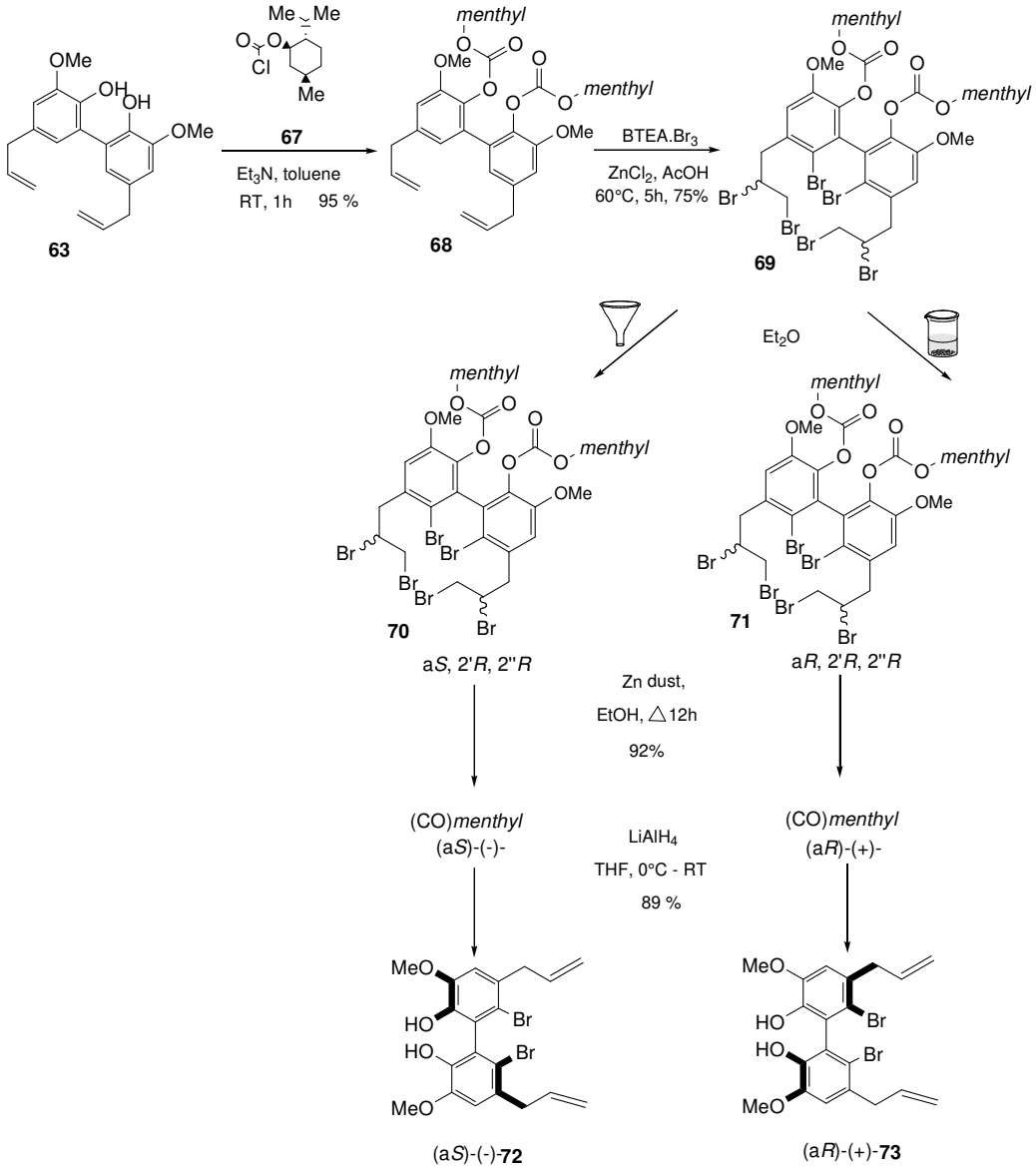



**Figure. 35:** Obtention of (*S*)-*6,6'*-dibromo-dehydrodieugenol **72** [45].

## 6. Inclusion compound

The authors have described the inclusion of eugenol **1** in β-cyclodextrin (β-CD) **74** and its antifungal activity. Therefore, they have shown that eugenol-β-cyclodextrin (β-CD-EU) **75** is an active agent with great potential in the controlled release against P. litchii (Figure. 36) [46].

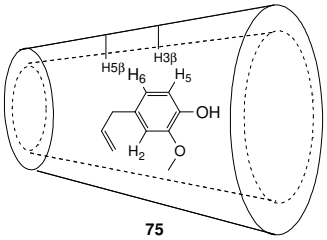



**Figure. 36:** Inclusion complex of eugenol-β-cyclodextrin **75** [46].

Because eugenol **1** is slightly soluble in water [47], the authors had the idea to use of inclusion complexes using a suitable host molecule [48]: cyclodextrins (CDs) [49]. The authors have found that the occupancy factor (o.f) of eugenol **1** and β-CD **74** is 1 and 0.5 respectively (Figure. 37) [48].

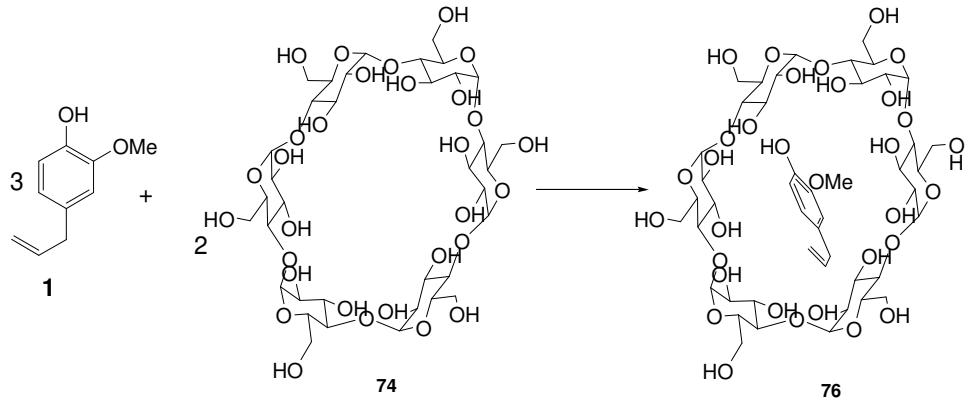



**Figure. 37:** Obtention of eugenol-β-cyclodextrin **76** [48].

## 3. Conclusion

The reactions discussed in this work describe some properties and mechanisms of organic synthesis for eugenol derivatives. Through these great organic reactions, carried out by conventional reactions and through reagents or optically active catalysts, we can understand the process of enantioselectivity. Also, the chemical transformation of abundant natural products, of simple structures, often enables efficient access to optically pure intermediates which can be used in the total synthesis of products with biological activities.

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