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# Synthesis of Bromo Eugenol Derivatives with Molecular Bromine

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Abstract

The bromination of eugenol using molecular bromine ($Br_2$) has been widely reported. However, the outcomes have been inconsistent, and as a result, the specific steps of the bromination process have not been definitively established. This research aims to synthesize various derivatives of bromo eugenol, incorporating bromine atoms either in the alkene group, the aromatic ring, or both. The synthetic approaches employed include (1) direct bromination of eugenol using 1.2, 2.4, and 3.6 equivalents (equiv) of $Br_2$ in chloroform, (2) bromination of eugenyl benzoate with 2.4 equiv of $Br_2$ in chloroform, and (3) debromination of the 1,2-dibromide functionality in selected bromination products using an excess of zinc in ethanol. The bromination steps of eugenol were then proposed based on the composition of the products obtained. Alkene bromination of eugenol predominated with 1.2 equiv of $Br_2$, followed by aromatic bromination with excess $Br_2$ (2.4 and 3.6 equiv). Aromatic substitution primarily occurred at position 6 (ortho to the hydroxyl group) and subsequently at position 5 (para to the methoxy group). Based on these results, we propose that the bromination of eugenol with $Br_2$ proceeds initially through electrophilic addition to the alkene group, followed by electrophilic substitution on the aromatic ring. Protection of the phenol as a benzoyl ester shifted the regioselectivity of the first aromatic bromination from position 6 to 5. Furthermore, the 1,2-dibromide group has been successfully removed by zinc, resulting in derivatives containing bromine atoms only at the aromatic ring. This is by far the first comprehensive report on the bromination of eugenol with $Br_2$ and the first one reporting the bromination of alkene as the main route of bromination with a nearly equimolar amount of $Br_2$.

## 1. Introduction

Indonesia is the largest clove producer, reaching 73% of world production in 2022 [1]. Eugenol (4-allyl-2-methoxyphenol) (**1**) is the main compound (45–90%) in clove oil [2]. Compound **1** has various bioactivities, including as an antioxidant and antimicrobial [3]. Through modification of alkene, ether, phenol, and aromatic ring functional groups, various complex natural products have been successfully synthesized from **1** [4, 5, 6, 7]. Aromatic bromination is one form of modification that is widely reported, including the reagent *N*-bromosuccinimide [8], 4,4-dibromo-3-methylpyrazole-5-one [9], a mixture of $O_2$, HBr, and $Cu(OAc)_2$ [10], as well as 1,3-dibromo-5,5-dimethylhydantoin [11].

Molecular bromine ($Br_2$) is widely favored as a bromination reagent due to its accessibility and manageable handling [12]. Several studies have used $Br_2$ for the bromination of compound 1; however, reported outcomes to diverge particularly when employing 1 equivalent (equiv) of $Br_2$ (Figure 1). According to Frankforter and Lando [13], $Br_2$ initiated aromatic bromination, with the released HBr gas subsequently adding to the alkene. de Souza *et al.* [14] have documented simultaneous bromination of both the alkene and the aromatic ring. In contrast, Nicholas [15] contended that alkene bromination occurred more rapidly than ring bromination. Desmurs *et al.* [16] reported selective bromination of the alkene group but with low yield. Conversely, recent studies have also reported exclusive bromination of the aromatic ring [17].

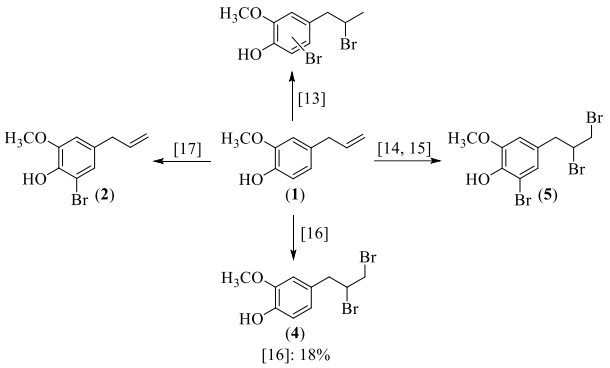


**Figure 1**. The main product of eugenol (**1**) bromination with **1** equiv of $Br_2$ from previous research

Based on these results, the precise sequence of bromination stages for compound **1** with $Br_2$ remains uncertain, specifically whether bromination initiates first on the alkene, the aromatic ring, or if both processes occur simultaneously. Therefore, this research aims to synthesize various bromo eugenol derivatives containing bromine atoms in the alkene group, aromatic ring, or both. The synthetic methods involved (1) direct bromination of eugenol with 1.2, 2.4, and 3.6 equivalents (equiv) of $Br_2$ in chloroform, (2) bromination of eugenyl benzoate with 2.4 equiv of $Br_2$ in chloroform, and (3) debromination of the 1,2-dibromide group from some bromination products with an excess of zinc in ethanol. The bromination steps of **1** are then proposed based on the composition of products obtained.

## 2. Experimental

### 2.1. Tools

The tools used included a dropping funnel, rotary evaporator, thin-layer chromatography plate (TLC, silica gel 60 $F_{254}$), column chromatography (CC) columns with diameters of 2 cm and 1 cm, 2- and 3-neck flasks, and a set of glassware. The instrument used was a Bruker-Avance Neo 500 MHz ($^1$H) and 125 MHz ($^{13}$C) NMR spectrometer in the Integrated Laboratory and Research Center, University of Indonesia.

### 2.2. Materials

The chemicals were obtained from Merck (Darmstadt, Germany), such as bromine ($Br_2$), chloroform ($CHCl_3$), sodium hydroxide (NaOH), benzoyl chloride (BzCl), acetic acid (AcOH), ethanol (EtOH), zinc (Zn), silica gel 60 (0.2–0.5 mm) and silica gel 60 (0.063–0.200 mm) for CC. Eugenol (**1**) was obtained from PT Indesso Aroma, Cileungsi, Bogor Regency. The technical materials used were $Na_2SO_4$ and technical solvents, including n-hexane, dichloromethane (DCM), ethyl acetate, and acetone. The technical solvent was distilled once before use.

### 2.3. Eugenol Bromination

The bromination procedure was adapted from Huang *et al.* [18]. Five mmol (0.82 g) of eugenol (**1**) was dissolved in 10 mL of $CHCl_3$ in an ice bath, then a solution of 0.31 mL (1.2 equiv) of $Br_2$ in 30 mL of $CHCl_3$ was dropped slowly (15 drops per minute) while stirring. After dripping, the mixture was stirred for 15 minutes in an ice bath and then for 18 hours at room temperature. The mixture was concentrated and then purified with CC. Bromination with 2.4 and 3.6 equiv of $Br_2$ had the same steps, but the amounts of $Br_2$ and $CHCl_3$ were adjusted to obtain the same concentration. The crude product of bromination with 1.2 equiv $Br_2$ was purified with *n*-hexane-EtOAc (99:1) eluent to elute remaining **1**, followed by *n*-hexane-EtOAc (49:1) to elute a mixture of compounds **2** and **3**, then with *n*-hexane-EtOAc (4:1) to elute compound **4**. Compound **4** was obtained as two fractions, namely **4a** and **4b**. Meanwhile, crude bromination products with 2.4 and 3.6 equiv $Br_2$ were purified with *n*-hexane-EtOAc (39:1) to elute compound **5**, followed by *n*-hexane-EtOAc (9:1) to elute compounds **6** and **7**. The NMR analysis of these products is as follows:

A mixture of **4-allyl-2-bromo-6-methoxyphenol** (**2**) and **4-allyl-5-bromo-2-methoxyphenol** (**3**): Yellowish liquid, $R_f$ = 0.36 in *n*-hexane-EtOAc 9:1. The signals related to compound **2** are $^1$H-NMR (500 MHz, $CDCl_3$) δ 6.92 (d, 1H, *J* = 1.7 Hz, H-5), 6.63 (d, 1H, *J* = 1.7 Hz, H-3), 5.93–5.87 (m, 1H, H-2'), 5.80 (s, 1H, OH), 5.12–5.07 (m, 2H, H-3'), 3.88 (s, 3H, $OCH_3$), 3.29 (d, 2H, *J* = 6.7 Hz, H-1'). $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 147.2 (C-6), 141.4 (C-1), 137.1 (C-2'), 132.9 (C-4), 124.5 (C-3), 116.4 (C-3'), 110.6 (C-5), 108.2 (C-2), 56.4 ($OCH_3$), 39.6 (C-1'). The signals related to compound **3** are $^1$H-NMR (500 MHz, $CDCl_3$) δ 7.11 (s, 1H, H-6), 6.70 (s, 1H, H-3), 5.97–5.94 (m, 1H, H-2'), 5.53 (s, 1H, OH), 5.07–5.04 (m, 2H, H-3'), 3.89 (s, 3H, $OCH_3$), 3.42 (dt, 2H, *J* = 6.4, 1.4 Hz, H-1'). $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 146.2 (C-2), 144.8 (C-1), 136.2 (C-2'), 130.7 (C-4), 118.6 (C-5), 116.4 (C-6), 114.9 (C-3'), 112.4 (C-3), 56.2 ($OCH_3$), 39.9 (C-1').

**4-(2,3-Dibromopropyl)-2-methoxyphenol** (**4a**): Light yellow liquid, $R_f$ = 0.48 in *n*-hexane-EtOAc 4:1. $^1$H- NMR (500 MHz, $CDCl_3$) δ 6.88 (d, 1H, *J* = 7.8 Hz, H-6), 6.81–6.77 (m, 2H, H-3 and H-5), 5.60 (s, 1H, OH), 4.37–4.30 (m, 1H, H-2'), 3.90 (s, 3H, $OCH_3$), 3.80 (dd, 1H, *J* = 10.4, 4.1 Hz, H-3'), 3.61 (dd, 1H, *J* = 10.4, 8.9 Hz, H-3'), 3.39 (dd, 1H, *J* = 14.6, 5.0 Hz, H-1'), 3.10 (dd, 1H, *J* = 14.6, 7.3 Hz, H-1'). $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 146.5 (C-2), 144.9 (C-1), 128.6 (C-4), 122.5 (C-5), 114.5 (C-6), 112.2 (C- 3), 56.1 ($OCH_3$), 52.9 (C-2'), 41.7 (C-1'), 36.2 (C-3').

**4-(2,3-Dibromopropyl)-2-methoxyphenol** (**4b**): Brownish liquid, $R_f$ = 0.43 in *n*-hexane-EtOAc 4:1. $^1$H- NMR (500 MHz, $CDCl_3$) δ 6.90 (d, 1H, *J* = 8.7 Hz, H-6), 6.75–6.71 (m, 2H, H-3 and H-5), 5.60 (s, 1H, OH), 3.90 (s, 3H, $OCH_3$), 3.76 (dd, 2H, *J* = 10.3, 6.8 Hz, H-3'), 3.69 (dd, 2H, *J* = 10.3, 6.3 Hz, H-1'), 3.29 (qi, 1H, *J* = 6,5 Hz, H-2'). $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 146.7 (C-2), 145.4 (C-1), 131.6 (C-4), 120.4 (C-5), 114.7 (C-6), 110.3 (C-3), 56.1 ($OCH_3$), 48.8 (C-2'), 35.9 (C-1' and C-3').

**2-Bromo-4-(2,3-dibromopropyl)-6-methoxyphenol** (**5**): Thick brown liquid, $R_f$ = 0.44 in *n*- hexane-EtOAc 4:1. $^1$H-NMR (500 MHz, $CDCl_3$) δ 7.03 (d, 1H, *J* = 1.6 Hz, H-3), 6.76 (d, 1H, *J* = 1.6 Hz, H-5), 5.87 (s, 1H, OH), 4.34–4.27 (m, 1H, H-2'), 3.91 (s, 3H, $OCH_3$), 3.82 (dd, 1H, *J* = 10.5, 4.1 Hz, H-3'), 3.60 (dd, 1H, *J* = 10.2, 9.4 Hz, H-3'), 3.39 (dd, 1H, *J* = 14.6, 4.5 Hz, H-1'), 3.04 (dd, 1H, *J* = 14.7, 7.7 Hz, H-1'). $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 147.1 (C-6), 142.4 (C-1), 129.5 (C-4), 125.6 (C-3), 111.5 (C- 5), 108.2 (C-3), 56.5 ($OCH_3$), 52.2 (C-2'), 41.3 (C-1'), 35.9 (C-3').

**Table 1**. The yield of bromination products of eugenol (**1**) with 1.2, 2.4, and 3.6 equiv $Br_2$

| $Br_2$ equivalent | Yield (%) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **4a** | **4b** | **4a + 4b** | **2 + 3** | **5** | **6** | **7** | **6 + 7** |
| 1.2 | 39 | 38 | 6 | 7 | - | - | - | - |
| 1.2 | 40 | 39 | 8 | 4 | - | - | - | - |
| 2.4 | - | - | - | - | 50 | 29 | - | - |
| 2.4 | - | - | - | - | 50 | 33 | - | - |
| 3.6 | - | - | - | - | 1.2 | 72 | 5 | 2 |
| 3.6 | - | - | - | - | - | 67 | 5 | 3 |

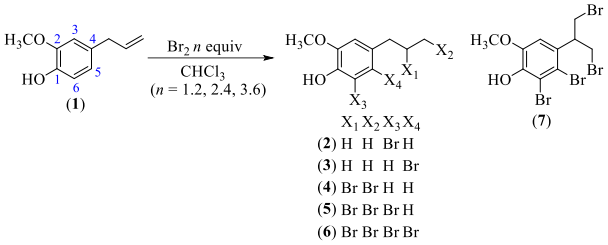


**Figure 2**. Bromination product of eugenol (**1**) with variations of $Br_2$ equivalent in $CHCl_3$

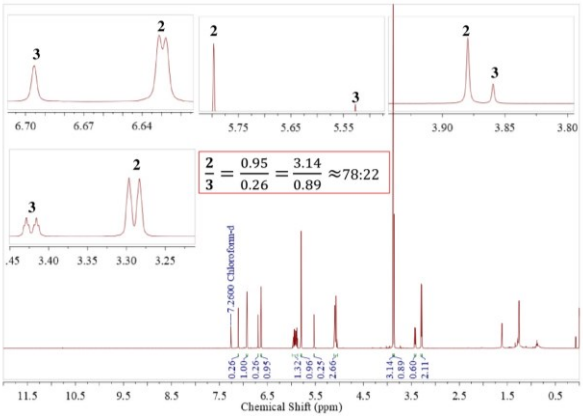


**Figure 3**. $^1$H-NMR analysis of a mixture of compounds **2** and **3**

**2,3-Dibromo-4-(2,3-dibromopropyl)-6-methoxyphenol** (**6**): White powder, $R_f$ = 0.39 in *n*- hexane-EtOAc 4:1. $^1$H-NMR (500 MHz, $CDCl_3$) δ 6.86 (s, 1H, H-5), 6.07 (s, 1H, OH), 4.54–4.48 (m, 1H, H-2'), 3.92 (s, 3H, $OCH_3$), 3.86 (dd, 1H, *J* = 10.8, 4.1 Hz, H-3'), 3.74 (dd, 1H, *J* = 10.7, 7.6 Hz, H-3'), 3.72 (dd, 1H, *J* =14.4, 5.0 Hz, H-1'), 3.11 (dd, 1H, *J* =14.5, 9.1 Hz, H-1'). $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 145.9 (C-6), 143.8 (C-1), 129.7 (C-4), 118.1 (C-3), 113.3 (C-5), 112.5 (C-2), 56.7 ($OCH_3$), 51.0 (C-2'), 44.8 (C-1'), 37.3 (C-3').

**2,3-Dibromo-4-(1,3-dibromopropan-2-yl)-6-methoxyphenol** (**7**): White powder, $R_f$ = 0.34 in *n*- hexane-EtOAc 4:1. $^1$H-NMR (500 MHz, $CDCl_3$) δ 6.78 (s, 1H, H-5), 6.13 (s, 1H, OH), 4.03–3.98 (qi, 1H, H-1'), 3.93 (s, 3H, $OCH_3$), 3.77 (d, 4H, *J* = 6.1 Hz, H-2'). $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 146.0 (C-6), 144.1 (C-1), 131.1 (C-4), 113.2 (C-3), 112.8 (C-2), 109.5 (C-5), 56.7 ($OCH_3$), 51.0 (C-1'), 34.8 (C-2').

## 2.4. Bromination of Eugenyl Benzoate

To complete the aromatic bromination product in another position, eugenol (**1**) was benzoylated, then the product was brominated, and subsequently, the ester group was hydrolyzed. Benzoylation of **1** was carried out by modifying the method of de Morais *et al.* [19]. To a solution of 5 mmol **1** in 4.4 mL of cold 5% (w/v) NaOH, 0.70 mL (1.2 equiv) of BzCl was slowly added. The mixture was allowed to react for 3 hours at room temperature. The solid eugenyl benzoate (**8**) formed during the reaction was vacuum-filtered and rinsed with cold distilled water, then dried overnight in an oven with circulating air at 40–45°C and weighed.

Product **8** was completely dissolved in 10 mL $CHCl_3$ and stirred in an ice bath for 15 minutes. A solution of 0.61 mL $Br_2$ (2.4 equiv) in 60 mL $CHCl_3$ was then dripped slowly (15 drops/minute). The remaining procedure was as in bromination **1** [18]. The bromination product was then purified using CC with *n*-hexane-EtOAc 9:1 eluent to obtain compound **9**, namely 5-bromo-4-(2,3-dibromopropyl)-2-methoxyphenyl benzoate [20].

Compound **9** was then acid-hydrolyzed by modifying the method of de Souza *et al.* [14]. One mmol of **9** was dissolved in 10 mL of AcOH, then 0.3 mL of 65% $H_2SO_4$ was added to the solution and refluxed for 18–24 hours (monitored using TLC). The mixture was then diluted with 10–15 mL of distilled water and extracted with DCM. The organic layer was then neutralized with saturated $NaHCO_3$ and rinsed with distilled water. After drying with $Na_2SO_4$, this organic layer was concentrated using a rotary evaporator and purified with CC. Compound **10**, a hydrolysis product, will be eluted in *n*-hexane-EtOAc 9:1.

**5-Bromo-4-(2,3-dibromopropyl)-2-methoxyphenol** (**10**): Yellowish liquid, $R_f$ = 0.46 in *n*- hexane-EtOAc 17:3. $^1$H-NMR (500 MHz, $CDCl_3$) δ 7.11 (s, 1H, H-6), 6.82 (s, 1H, H-3), 5.64 (s, 1H, OH), 4.52–4.46 (m, 1H, H-2), 3.89 (s, 3H, $OCH_3$), 3.84 (dd, 1H, *J* = 10.8, 4.2 Hz, H-3'), 3.74 (dd, 1H, *J* = 10.8, 7.3 Hz, H-3'), 3.59 (dd, 1H, *J* = 14.4, 5.3 Hz, H-1'), 3.04 (dd, 1H *J* = 14.4, 8.8 Hz, H- 1'). $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 145.9 (C-2), 145.6 (C- 1), 128.2 (C-4), 118.0 (C-6), 115.0 (C-5), 114.0 (C-3), 56.3 ($OCH_3$), 51.5 (C-2'), 43.0 (C-1'), 37.4 (C-3').

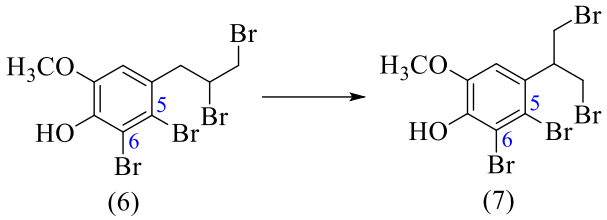


**Figure 4**. Change of compound **6** to compound **7**

### 2.5. Debromination of Compounds 5, 6, and 10

Compounds **5**, **6**, and **10** are bromination products of both the alkene and ring. To obtain bromination products at only the aromatic ring, the 1,2-dibromide groups in the three compounds were debrominated. The debromination procedure was adapted from de Souza *et al.* [14]. A 0.25 mmol of compound **5** was dissolved in 5 mL of EtOH, and then 0.12 g of Zn (7.5 equiv) was added and refluxed at a temperature of 70–80°C for 2 hours. After 2 hours, the mixture was filtered. The filtrate was diluted with distilled water and then extracted with DCM. The organic layer was separated, dried with anhydrous $Na_2SO_4$, and concentrated using a rotary evaporator.

The same treatment was also used for debromination of compounds **6** and **10**. Debromination of 0.25 mmol of compound **5** was also carried out with 12.5 equiv of Zn and 1 mmol of compound **6** with 10 equiv of Zn. Debromination of compounds **5** and **10** produces compounds **2** and **3**, respectively. Meanwhile, the debromination products of compound **6** still need CC purification with *n*-hexane-EtOAc (49:1) as the eluent to isolate compound **11**.

**4-Allyl-2-bromo-6-methoxyphenol** (**2**): Yellow liquid, $R_f$ = 0.54 in *n*-hexane-EtOAc 4:1. $^1$H-NMR (500 MHz, $CDCl_3$) δ 6.92 (d, 1H, *J* = 1.7 Hz, H-3), 6.62 (d, 1H, *J* = 1.6 Hz, H-5), 5.95–5.86 (m, 1H, H-2'), 5.83 (s, 1H, OH), 5.11–5.06 (m, 2H, H-3'), 3.87 (s, 3H, $OCH_3$), 3.29 (d, 2H, *J* = 6.7 Hz, H-1'). $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 147.1 (C-6), 141.3 (C-1), 137.1 (C-2'), 132.8 (C-4), 124.4 (C-3), 116.3 (C- 3'), 110.5 (C-5), 108.1 (C-2), 56.3 ($OCH_3$), 39.6 (C-1').

**4-Allyl-5-bromo-2-methoxyphenol** (**3**): White solid, $R_f$ = 0.53 in *n*-hexane-EtOAc 17:3. $^1$H-NMR (500 MHz, $CDCl_3$) δ 7.11 (s, 1H, H-6), 6.70 (s, 1H, H-3), 5.98–5.90 (m, 1H, H-2'), 5.55 (s, 1H, OH), 5.12–5.04 (m, 2H, H- 3'), 3.86 (s, 3H, $OCH_3$), 3.42 (dt, 2H, *J* = 6.4, 1,4 Hz, H- 1'). $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 146.1 (C-2), 144.7 (C- 1), 136.2 (C-2'), 130.7 (C-4), 118.5 (C-5), 116.4 (C-6), 114.9 (C-3'), 112.3 (C-3), 56.1 ($OCH_3$), 39.9 (C-1').

**4-Allyl-2,3-dibromo-6-methoxyphenol** (**11**): Brown liquid. $R_f$ = 0.48 in *n*-hexane-EtOAc 4:1. $^1$H-NMR (500 MHz, $CDCl_3$) δ 6.72 (s, 1H, H-5), 5.99 (s, 1H, OH), 5.97–5.88 (m, 1H, H-2'), 5.12 (dq, 1H, *J* = 10.1, 1.4 Hz, H- 3'), 5.07 (dq, 1H, *J* = 17.1, 1.6 Hz, H-3'), 3.89 (s, 3H, $OCH_3$), 3.52 (d, 2H, *J* = 6.4 Hz, H-1'). $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 146.1 (C-6), 142.8 (C-1), 135.6 (C-2'), 132.3 (C-4), 117.8 (C-3'), 116.8 (C-3), 112.3 (C-5), 111.4 (C-2), 56.5 ($OCH_3$), 41.8 (C-1').

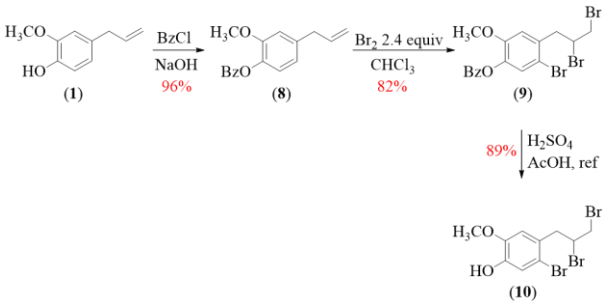


**Figure 5**. Synthesis of **10** through benzoylation, bromination, and hydrolysis of **1**

## 3. Results and Discussion

Bromination of eugenol (**1**) with 1.2–3.6 equiv of $Br_2$ in $CHCl_3$ produces six products: compounds **2**–**7** (Figure 2). Table 1 shows the yield of each compound. Bromination with 1.2 equiv of $Br_2$ produced compound **4**, a product of bromine addition to alkenes, as the main product. Apart from that, compounds **2** and **3**, products of bromine substitution at the aromatic ring, were also produced as minor products in the form of a mixture that was inseparable from CC.

Compound **4** was isolated as 2 fractions with different $R_f$ values, named **4a** and **4b**. Fraction **4a** is a yellow liquid, while fraction **4b** is a brownish liquid with $R_f$ of 0.48 and 0.43, respectively, in *n*-hexane-EtOAc (4:1). Based on the NMR spectra, both fractions have the same structure, namely 4-(2,3-dibromopropyl)-2-methoxyphenol. Different $^1$H and $^{13}$C NMR signals result from the 2,3-dibromopropyl side chain. Compound **4a** has a more complex splitting pattern of the diastereotopic protons: two double doublets (dd) at 3.10 and 3.39 ppm for H-1' along with two dd at 3.61 and 3.80 ppm for H-3', all with different coupling constants (*J*).

The respective signals in compound **4b** are only one dd at 3.69 ppm for H-1' and one dd at 3.76 ppm for H-3', both with similar *J*. Conversely, two carbon signals in **4a** (41.7 ppm for C-1' and 36.2 ppm for C-3') is simplified into one signal at 35.9 ppm in **4b**. These indicate that the diastereotopic protons are getting more chemically equivalent at **4b** than **4a**. This is also evidenced by a quintet multiplicity of H-2' at **4b** versus a more complex multiplet at **4a**. Therefore, we expect **4a** and **4b** to be different conformers at the side chain, but further study is still needed to confirm their stereochemistry.

The results of this study show that bromination of **1** with 1.2 equiv of $Br_2$ starts predominantly (85%) in the alkene group. As shown in Figure 1, the formation of compound **4** as the main product of bromination of **1** has not been reported with 1 equiv of $Br_2$. The formation of **4** was only reported by Desmurs *et al.* [16], with a yield of only 18%. The formation of **4** as the main product in this study aligns with the easier way for bromine to add alkenes rather than substitute aromatic rings [21].

**Table 2**. Debromination yield of compounds 5, 6, and 10

| Zn equivalent | Yield (%) | | |
|---|---|---|---|
| | 2 from 5 | 11 from 6 | 3 from 10 |
| 7.5 | 83 | 45 | 96 |
| 7.5 | 93 | 43 | 83 |
| 10 | – | 40 | – |
| 12.5 | 71 | – | – |

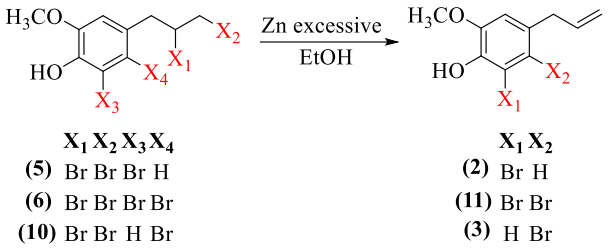


**Figure 6**. Debromination reaction scheme

A mixture of compounds **2** and **3** was also produced as a by-product (approximately 6%). These two compounds are a pair of positional isomers of 6-bromo and 5-bromo, which both produce $R_f$ = 0.36 in the eluent *n*-hexane-EtOAc 9:1. The integration analysis of the 1H NMR spectrum revealed a composition of approximately 78% for compound 2 and 22% for compound 3 (Figure 3). Compound 2 was recently reported by Ahmed *et al.* [17] without the inclusion of compound 3. Aromatic bromination without prior alkene bromination is made possible by the highly active aromatic ring of **1,** which binds 3 activating groups (phenol, methoxy, allyl). Generally, specific bromination reagents are used to obtain compound **2** [9, 10, 11].

When $Br_2$ is added in excess (2.4 and 3.6 equiv), bromination continues on the aromatic ring of **4**. Aromatic bromination takes place first at position 6 (*ortho* against the hydroxyl group) to form compound **5**, followed by a second bromination at position 5 (*para* against the methoxy group) to form compound **6**. As shown in Table 1, bromination with 2.4 equiv of $Br_2$ produces **5** as the main product (50%) and **6** as an additional product (31%). When the $Br_2$ equivalent is higher (3.6 equiv), only a small amount of **5** remains and **6** practically becomes the main product (69%). Interestingly, 5% of compound **7** was also produced, which is thought to be a rearrangement product of **6** (Figure 4).

Similar rearrangements have been reported in the dibromides of the compounds safrole [22] and estragole [23], as well as their derivatives [24]. However, this is the only study that reported rearrangement in tetrabromide compounds. The first bromination at position 6 is in line with the stronger activating properties of the phenol group [21], directing the bromination to the *ortho* position relative to the group. Two doublet signals at 6.76 and 7.03 ppm confirmed this bromination position with a *meta*-coupling constant value of 1.6 Hz. After the second bromination at position 5, these two signals change to a singlet signal at 6.86 ppm.

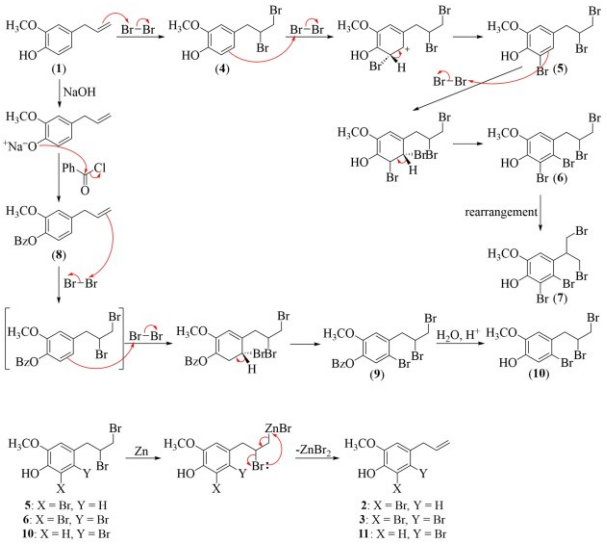


**Figure 7**. (a) Proposed bromination mechanism of eugenol (**1**) and eugenyl benzoate (b) proposed debromination mechanism of products **5**, **6**, and **10**

To obtain the first aromatic bromination product at position 5, bromination was carried out with 2.4 equiv of $Br_2$ at **1** after being protected as eugenyl benzoate (**8**). The bromination product (**9**) was then acid-hydrolyzed to deprotect the benzoyl group and produce compound **10** (Figure 5). Compound **10**, a positional isomer of **5**, was produced with an overall average yield of 70% from **1**. The yield of each reaction stage is given in Figure 5. The presence of two singlet signals at 6.82 and 7.11 ppm that indicate two *para* aromatic protons in the $^1$H NMR spectrum of **10** confirms that aromatic bromination occurs at position 5. Thus, there has been a shift in the regioselectivity of aromatic bromination from position 6 to position 5 with the addition of the benzoyl group. Similar regioselectivity shifts have been reported in the nitration of **1** protected with acetyl group [25, 26] as well as in the bromination of **1** protected with methyl group [18].

To obtain bromo eugenol derivatives containing bromine atoms only in the aromatic ring, we also carried out debromination of 1,2-dibromide groups from compounds **5**, **6**, and **10**, using excess zinc in ethanol. Debromination of compounds **5** and **10** produces pure compounds **2** and **3** (Figure 6). Debromination used 7.5 equiv of Zn in EtOH [14] and produced excellent yields, namely 88% for **2** and 90% for **3** (Table 2). Both products are obtained directly without CC purification. Compound **11** was also successfully obtained from the debromination of compound **6**, but with a low yield (44%). Adding Zn up

to 12.5 equiv in debromination of **5** and 10 equiv in debromination of **6** was ineffective and slightly reduced the yield (Table 2).

The low yield of **11** is partly caused by the formation of side products with an $R_f$ slightly above the target product, which needs to be purified with CC. The NMR spectra of **2**, **3**, and **11** resulting from the debromination show the appearance of a $^1$H signal at 5.0–6.0 ppm from the alkene $sp^2$ proton as well as $^{13}$C signals at 115–118 ppm and 136–138 ppm, which are typical for the terminal alkene group (–CH=CH$_2$). Thus, bromination of **1** with Br$_2$ can also produce aromatic bromination products through the debromination approach.

Overall, we proposed the bromination mechanism of **1** with Br$_2$ in chloroform, as shown in Figure 7. The electrophilic addition of **1** gives **4**, and the electrophilic substitution of **4** gives **5**, **6**, and **7**, respectively. Bromination of eugenyl benzoate **8** produces tribromide **9**, which gives 10 after acid-hydrolysis. Debromination of **5**, **6**, and **10** occurs through zinc insertion to form an organozinc halide, followed by a bimolecular 1,2-elimination of zinc bromide to form **2**, **3**, and **11** [27].

## 4. Conclusion

Based on this study, bromination of **1** with 1.2 equiv of Br$_2$ predominantly takes place in the alkene group, while with 2.4 and 3.6 equiv of Br$_2$, bromination occurs both on the alkene and the aromatic ring. Therefore, the bromination stage can be proposed to begin with electrophilic addition to the alkene, followed by electrophilic substitution of the aromatic ring. The first substitution occurs at position 6, then the second one at position 5. Adding a benzoyl ester protection group shifts the first substitution to position 5. Debromination of the 1,2-dibromide group has also been successfully carried out on the products containing bromine atoms at the alkene group and the aromatic ring. Overall, 8 bromination products were produced with good yields (40% to quantitative). Product **4** has bromine atoms in the alkene group, products **5**, **6**, **7**, and **10** contain bromine atoms at the aromatic ring, and products **2**, **3**, and **11** have bromine atoms in both the alkene group and the aromatic ring. The molecular structures of those products have been confirmed by NMR spectroscopy.

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