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Synthesis Strategy of Cinnamaldehyde Derivate Compound from Cinnamon Bark Oil (*Cinnamomum burmanii*) to 2-hydroxycinnamaldehyde

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Abstract

Cinnamaldehyde is the major secondary metabolite of Cinnamon (*Cinnamomum burmanii*) that has various benefits in medical fields. One of the cinnamaldehyde derivatives, 2-Hydroxycinnamaldehyde (HC), has been shown to have good anticancer activity. In contrast to its activity, the synthesis method of HC from pure cinnamaldehyde has not been studied before. This research studies the synthesis of HC with a semisynthetic approach from the natural ingredient cinnamaldehyde. This study was initiated by purifying cinnamaldehyde from cinnamon bark oil with the salting method using a saturated sodium bisulfite solution. Cinnamaldehyde is converted into HC through the synthesis design in three-reaction steps, including nitration using nitric acid-acetic acid anhydride at 0-5 °C, reduction in mild condition by reflux using NH_4Cl-Fe in methanol-water solution, and diazotation-hydrolysis using $NaNO_2$-HCl at 5 °C. Optimization of the synthesis was evaluated to get the best method according to yield and characterized using TLC, UV-Vis, FTIR, and GC-MS/LC-MS. The isolated CD has a purity of up to 100% with a yield of about 36%. The 2-nitrocinnamaldehyde (NC) product from nitration was analyzed with ethanol and n-hexane (1:1) Rf = 0.84 and showed high purity with a 26% yield. The reduction product 2-aminocinnamaldehyde (Rf = 0.48) and 2-hydroxycinamaldehyde (Rf = 0.19) as a product from diazotation-hydrolysis obtained in moderate yield.

Keywords: 2-hydroxycinnamaldehyde, cinnamaldehyde, hydrolysis, nitration, reduction.

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1. INTRODUCTION

The major component of Cinnamon oil is Cinnamaldehyde (CD), with a content of 65-80% in *Cinnamomum burmanii* species (Prakash et al., 2012). Several studies have reported that CD is one of the chemical compounds with the best biological activity among other compounds contained in cinnamon oil (Suryanti et al., 2018). Its activities are antibacterial, antioxidant, antifungal, and anticancer (Al-Fekaiki et al., 2017; Herdwiani et al., 2014; Larasati & Meiyanto, 2018). In addition, the CD has been reported to play a role in inhibiting tumor cell proliferation and inhibiting apoptosis of several cancer cells, including breast, colon, and leukemia cancers (Hong et al., 2016; Zhang et al., 2011).

The technique used to isolate CD from cinnamon bark essential oil was column chromatography with dichloromethane and n-hexane as solvents. The method is quite simple, with the purity of CD obtained only reaching 71.36% (Wasia et al., 2017). However, with the salting method using sodium bisulfite, the purity of the isolated CD was better, which was about 88%, with the yield reaching 27%. The procedure is divided into two main stages: salt formation and hydrolysis to CD (Etika et al., 2018; Ngurah et al., 2018).

CD (3-phenyl-2-propanol) has an aromatic ring skeleton of benzene and propenal substituent, playing an essential role in synthesizing its derivatives. Molecular conditions like this have enormous potential to be modified to increase their activity as

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medicinal raw materials (Suryanti et al., 2018). Among the CD-derived compounds modified at the base skeleton of the benzene ring, the compound 2-hydroxycinamaldehyde (HC) have the best bioactivity in various field as an anti-fungal (Shreaz et al., 2016), antibacterial (Momtaz et al., 2018), antitumor (Lee et al., 2013), anticancer (Hwang et al., 2011; Larasati & Meiyanto, 2018), and many other benefits. HC was obtained from the isolation of natural ingredients from cinnamon bark oil (Kwon et al., 1996). Based on its wide bioactivity, one way to fulfill the needs of HC is by synthesis.

The previous HC synthesis used non-natural materials, with a condensation reaction between 2-hydroxybenzaldehyde and vinyl acetate with base K_2CO_3 (yield 34%), but also provided coumarin as by-products and other unknown by-products (Kim et al., 2004). In contrast to the previous method, in this study, a semisynthetic stage was carried out by rationalizing the synthesis of HC from the basic ingredient of CD. Natural ingredients are used in the synthesis because they have common side effects, the product is renewable, so it is abundant, and is considered safer in terms of impurities. A three-step synthesis shown in Figure 1 was used based on the Functional Group Interconversion (FGI) retrosynthetic approach. In addition, modifications to the aromatic ring in the ortho-position give good bioactivity (Gan et al., 2009). The compound 2-nitrocinnamaldehyde (NC) obtained from one of the reaction steps (Figure 1) is known to have bioactivity to inhibit Cyclin-Dependent Kinase 4/Cyclin D1 (Jeong et al., 2000). Thus, each step was optimized for reagents and reaction times in detail to produce alternative methods to form products with optimum yields. The product produced in each stage is monitored with TLC to determine product formation and then analyzed by FTIR to identify possible structures based on the rationalization of the termination approach. To fulfill the need for medicinal compounds from natural ingredients and based on the benefits possessed of the HC compound, the following is a study of the steps for synthesizing CD from natural materials to produce HC.

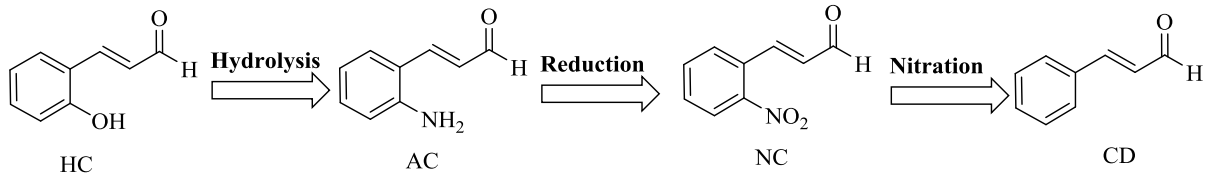


Figure 1. Retrosynthetic analysis from HC to CD

2. MATERIALS AND METHODS

Materials

Chemicals $NaHSO_3$ (39%) (Merck), HNO_3 (65%), acetic acid (CH_3COOH), NaOH, HCl, Fe powder were purchased from p.a (Merck), acetic acid anhydride p.a (Ajax finechem) and solvents Ethanol ethyl acetate p.a (Merck), dichloromethane (DCM), tetrahydrofuran (THF) p.a (Merck) with free of interfering impurities. Cinnamon bark oil was obtained from PT. Lansida from the distillation of cinnamon bark (*Cinnamomum burmanii*) obtained from the Yogyakarta area.

Isolation of CD from Cinnamon Bark Oil

Isolation of CD from cinnamon bark oil was carried out by adding $NaHSO_3$ solution into cinnamon oil (1:1) or until no more precipitate. Furthermore, the precipitate was filtered and washed with ethanol until the solid was white. The precipitate obtained was put in a round bottom flask and added 5% HCl. The mixture is refluxed for 1 hour or until all the precipitate is dissolved. Then the oil phase is separated from the water using a separating funnel and dried with anhydrous $MgSO_4$. Commercial Cinnamaldehyde (CCD) (98%) was used to compare CD isolate in TLC. Based on the synthesis strategy CD shown in Figure 1, there is three steps synthesis method in general.

Synthesis 2-Nitrocinnamaldehyde (NC) (Nitration)

The procedure adopted the Ngurah *et al*., (2018) method, with a lower nitric acid concentration (65%). Into 11 g of CD, 45 mL of acetic anhydride was added, and then 3.6 mL of nitric acid was added and stirred at a temperature of 0-5 oC. Next, glacial acetic acid (5 mL) was added to the mixture and stirred for 3-4 hours. The reaction was stopped, and

the mixture was incubated at room temperature. The mixture is then added with 20% HCl until it no longer forms a yellow precipitate. Then, the precipitate was separated and recrystallized with ethanol. Finally, the precipitate was separated and rinsed with ethanol until a yellowish-white precipitate was formed.

***Synthesis 2-Aminocinnamaldehyde* (AC) (Reduction)**

The procedure adopted the previously done method by Méndez et al. (2017) and has been modified. NC (2.8 mmol) was mixed with Fe powder (18.2 mmol) and NH_4Cl catalysts. The mixture was heated in an inert gas system (N2 gas) for 2 hours in a mixture of ethanol and water (ethanol: water = 9:1). The reaction product was filtered to separate the remaining solid Fe and rinsed with ethanol. The organic phase was extracted by adding saturated $NaHCO_3$. The organic phase obtained was dried with anhydrous $MgSO_4$, and the solvent was evaporated. Finally, the product obtained was separated by column chromatography.

***Synthesis 2-Hydroxycinnamaldehyde* (HC) (Diazotation and Hydrolysis)**

The procedure method used Taniguchi et al., (2009) method, which has been modified. First, AC (5 mmol) was mixed with concentrated H_2SO_4 (30 mmol) until dissolved. Then at a temperature of 5 °C, 1.1 mmol of $NaNO_2$ was added and stirred for 1 hour. After that, the mixture is poured into a container filled with water and THF, refluxed, and then extracted using ethyl acetate. Finally, the organic phase was dried with $MgSO_4$, then evaporated to obtain solid HC. The product obtained was separated by column chromatography.

Characterization

Cinnamon Oil, CD isolated, and the synthesized product were analyzed by Thin Layer Chromatography (TLC). TLC plate used silica gel 60 GF_{254} Aluminum (size 10x3 cm). The eluent used in TLC analysis on CD isolation and nitration product is ethanol and hexane (95:5), at reductions used ethanol and hexane (1:1), and in the hydrolysis used n-hexane: ethyl acetate: dichloromethane (DCM) (5:4:1). The chromatographic spots were detected by exposure to 254 nm UV light. A double beam UV-Vis spectrophotometer carried out UV-Vis analysis at a 200-500 nm wavelength (SHIMADZU 1600 series). FT-IR analysis with KBr pellets with Perkin Elmer FT-IR spectrometer. GC-MS analysis was carried out by gas chromatography (GC, Agilent 7890B) and mass spectrometer (MS, Agilent 5977B). The inlet temperature was 200 °C. Helium gas flow 54.087 mL/minutes, with initial temperature column oven temperature (150 °C, 1 minute; ramp to 300 °C at 10 °C/minutes).

3. RESULTS AND DISCUSSION

Identification of Cinnamon Oil

Cinnamon oil from the bark of cinnamon (*Cinnamomum burmanii*) has a yellow-brown liquid appearance, with a specific gravity of 1.021 (25 °C) and a refractive index of 1.598 (25 °C). Six TLC spots shown in Table 1 were analyzed from Cinnamon oil, indicated as the number of components that make up Cinnamon Oil, with the most significant TLC spot shown at Retention Factor (Rf) = 0.73. According to the most significant spots area on TLC, the concentration of component cinnamon oil characterization with GC-MS was shown in Figure 2. CD (74.78%) with a Retention time (R. Time) of 9.827 minutes is the most significant component, so the main component of Cinnamon oil used in this research is CD. The other compound, such as citronellol (3.9%), alpha-copaene (5.36%), trans-caryophyllene (1.83%), and delta-cadinene (1.01%), are only a small part of cinnamon oil.

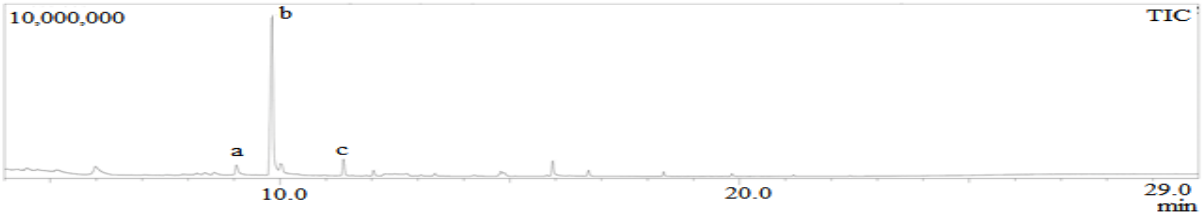


Figure 2. Total ionic chromatogram GC-MS analysis results of cinnamon oil (*Cinnamomum burmanii*). The peak compounds are (**a**) citronellol; (**b**) cinnamaldehyde; (**c**) alpha-copaene

Isolation of CD

CD isolation from Cinnamon oil by salting method rapidly occurs when adding sodium bisulfite solution to CD, making the Cinnamaldehyde bisulfite salt turn yellowish-white due to unwanted components trapped between the precipitates. This research carried out the repeated washing method with ethanol on the Cinnamaldehyde bisulfite salt until the salt precipitate was white. The salting reaction produces a yellow liquid that yielded about 36.96%, lower than previously reported studies by Ngurah et al., (2018), with a yield of 86.70%. However, the purity in this research is better than the previous research. The result of the TLC analysis of the CD isolation product is similar to that of commercial cinnamaldehyde (CCD) (Table 1).

The isolation results were a yellow liquid with a specific gravity of 1.0506 g/ml (26 °C) and a refractive index measured by a refractometer with 1.616 (22.68 °C). Then the isolated product was analyzed by FTIR, and the essential functional groups contained in the analysis are shown in Figure 3. C=O vibrations from the carbonyl at a wavenumber of 1667 cm^{-1} and double C-H bond vibration at wavenumber 2782 cm^{-1} and 2815 cm^{-1} indicate the presence of an aldehyde group. In addition, the CD has a monosubstituted benzene structure typical of citronellal compounds, shown around the 1500 cm^{-1} region.

Table 1. Comparison of thin-layer chromatography (with eluent Ethanol: n-hexane = 95:5) Cinnamon oil, CCD, and CD Isolation. The largest TLC spot area are shown in bold

TLC Spot	R_f Cinnamon Oil	R_f CCD	R_f CD
1	0.95	0.98	0.98
2	0.89	-	-
3	**0.73**	**0.72**	**0.72**
4	0.42	-	-
5	0.23	-	-
4	0.14	0.13	0.12

The isolated pure CD was confirmed by GC-MS, which showed two peaks in the TIC (Figure 4), but in mass spectra indicated a similar compound. The mass spectra analysis from peaks 1 (Figure 5) and 2 show a similar base peak of 131 m/z, as a value resulting from losing one H atomic radical from molecular weight 132 from CD, with a similarity index (SI) value ≥ 95. (Table 2). However, the first peak had a smaller retention time (R. time), so it was indicated that the compound was cis-cinnamaldehyde which has a lower boiling point (246 °C) with a concentration of 2.57%. On the other hand, the second peak with a larger R. time value indicates a trans-cinnamaldehyde compound (250-252 °C) with a concentration of about 97.43% as the isomer of the first peak. The isolated components are CD compounds with 100% purity.

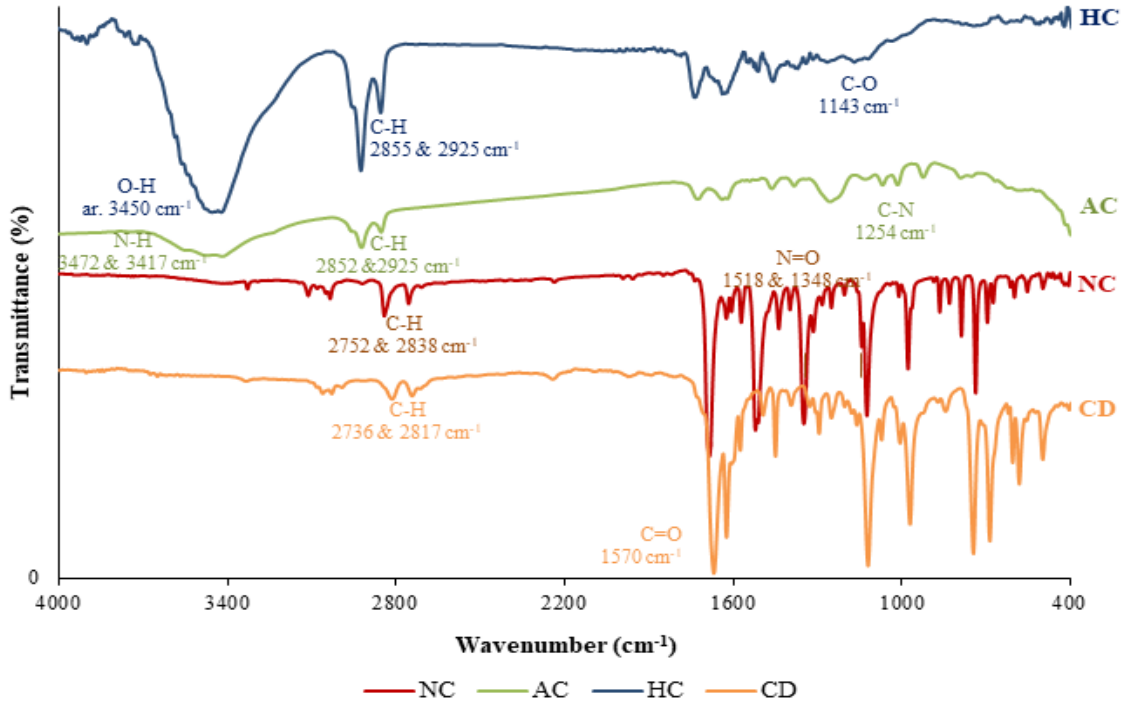


Figure 3. Comparison of the FTIR spectrum of the product isolation, nitration, reduction and hydrolysis

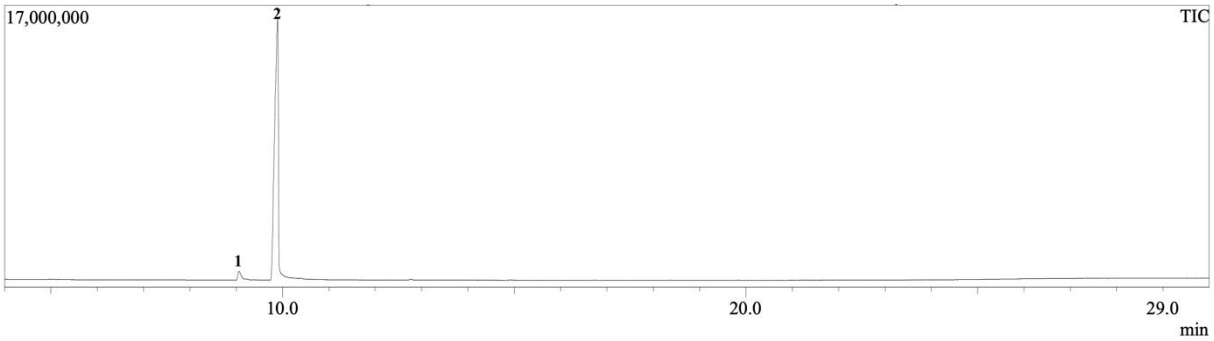
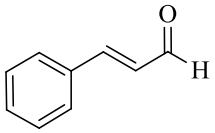


Figure 4. Total ionic chromatogram (TIC) from isolated cinnamaldehyde

Table 2. Components of Isolation of CD from Cinnamon Oil with GC-MS. Base peak are shown in bold

Peak	R. Time	%Area	Compound	SI	m/z	Structure
1	9.058	2.57	Cinnamaldehyde	95	51, 63, 77, 91, 103, 115, **131**	
2	9.892	97.43	Cinnamaldehyde	96	51, 63, 77, 91, 103, 115, **131**	

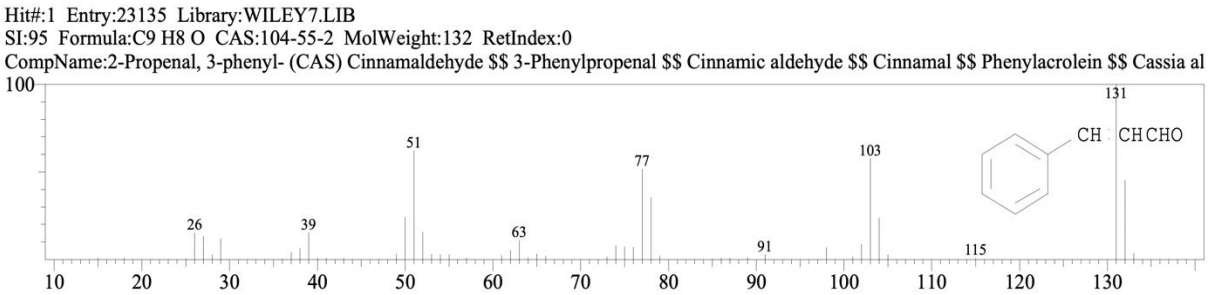


Figure 5. Mass Spectra GC-MS analysis results of Cinnamaldehyde

The synthesis of NC

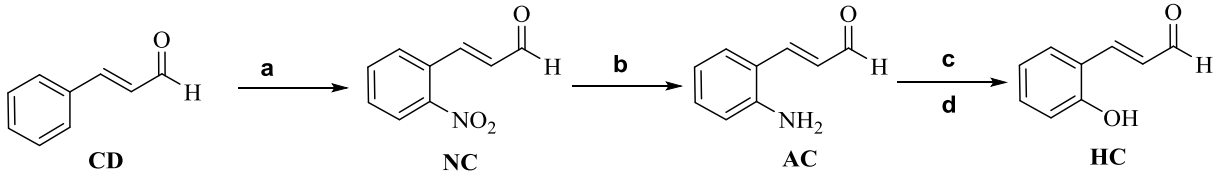


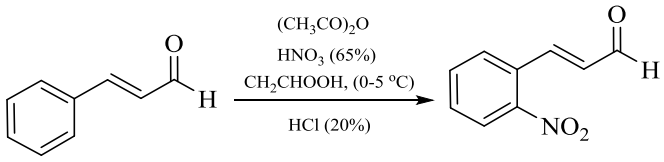
Figure 6. Reagents and conditions: (**a**) conc. HNO_3 (65%), conc. $(CH_3CO)_2O$ (97%), conc. CH_3COOH, temp. 0-5 ^oC; (**b**) Fe powder, NH_4Cl/ethanol, reflux in N_2 atmosphere; (**c**) H_2SO_4, $NaNO_2$ add in 5 ^oC, reflux 1h; (**d**) THF/H_2O reflux

Our approach with retrosynthetic analysis of HC from CD is shown in the schematic Figure 4. The rational disconnection approach is carried out from HC through 3 primary synthesis steps. First, the hydrolysis process assumes the NH_2 group can be replaced by hydroxyl (-OH) by forming a diazonium salt. Second, The AC product is assumed to be obtained through the reduction step of NC by replacing the NO_2 group with NH_2. Furthermore, the last NC was obtained by substituting the nitro group with hydrogen attached to the aromatic ring through the nitration step of CD. Based on the strategy used to obtain CD derivative products, the first stage is the formation of NC through nitration. Generally, the nitration of aromatic compounds produces ortho- and para-substituted groups. The nitration strategy carried out by the influence of the propenal group was carried out using nitric acid, glacial acetic acid, and anhydrous acetic acid. The general reaction conditions are shown in Figure 6a, which results in an ortho-product trend, with no para-product being formed (Robert & Bellis, 1953). Theoretically, acetic acid in this reaction is an initiator for forming nitronium ions which are then stabilized by

acetic anhydride anions (Bak & Smallridge, 2004). The nitration reaction generally uses nitric acid with a high concentration (99%). In this case, the use of nitric acid with a concentration that tends to be lower (65%) affects the formation of the product. Variations in incubation time affect the amount of yield in optimizing the formation of NC products. Each variation showed a single spot in TLC analysis, as shown in Table 3.

Based on Table 3 data, it is shown that the optimum condition occurs when the incubation reaction time is four days, and the number of moles of HNO_3 reacted is twice the number of moles of CD with the highest percent yield, which is around 49.94%. The %Yield value is greater than that reported by Robert and Bellis (1953), which is around 36-46%, although the number of moles of nitric acid and the optimum time tend to be larger than the previously reported reaction, which is for two days incubation time with a ratio CD: HNO_3 = 1:1. Based on these data, it can also be seen that NC products cannot be formed with a mole ratio of CD: HNO_3 = 1:3. It can be caused by the effect of anions on aromatic nitration with acetyl nitrate. The excess ionic liquid acts as a solvent, reducing the nitrate concentration in the system (Lu et al., 2013).

Table 3. Optimization of the nitration reaction through incubation time (1-4) and number of moles of reagent (5-8) and TLC analysis results



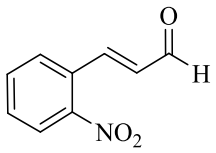
CD **NC**

Entry no.	CD (mol)	Conc. HNO_3 (mol)	Incubation time (Day)	Yield (%)	Rf Product (EtOH:Hexane = 95:5)
1	0.08	0.08	2	12.88	0.47
2	0.08	0.08	4	23.27	0.47
3	0.08	0.08	6	25.95	0.47
4	0.08	0.08	8	21.48	0.47
5	0.08	0.08	4	25.95	0.47
6	0.08	0.12	4	27.1	0.53
7	0.08	0.16	4	49.94	0.52
8	0.08	0.24	4	-	-

The results of TLC analysis for each variation in incubation time and amount of HNO_3 showed a single spot with an Rf value shown in Table 3. The Rf value in that single spot was different from the Rf value in CD, showing a different compound was created, with further characterization with FT-IR (Figure 3, NC with red line). The absorption was identified as a group function of NC at wavenumber 1683 cm^{-1} as the spectrum of stretching C=O carbonyl indicates the presence of an aldehyde group, which is strengthened by the presence of double absorption, which is the vibration of the C-H bond at wavenumbers 2782 cm^{-1} and 2815 cm^{-1}. Two strong symmetrical peaks at 1348 cm^{-1} and 1518 cm^{-1} as the N=O stretching nitro group spectrum are amplified with a strong peak at 1123 cm^{-1} as the spectrum of the C-N stretching, indicating the formation of nitro substituents in the product.

The results of the GC-MS analysis in Table 4 show the single spot found in the TLC results of the nitration product NC. The mass spectra analysis from the single peak from the nitration step shown in Figure 7 showed a base peak of 77 m/z as a positive ion fragment of benzene and the presence of atomic molecular mass radicals of NC, which lost one H radical m/z at 177 indicating that the compound is NC. The single point base indicates that the compound has a purity of 100%, which indicates the synthesis method of acetic anhydride and nitric acid reacted with cinnamaldehyde to react specifically.

Table 4. Results of GC-MS analysis of nitrated products

Peak	R. Time	%Area	Compound	SI	Structure
1	29.301	100	o-Nitrocinnamaldehyde (2-Nitrocinnamaldehyde)	80	

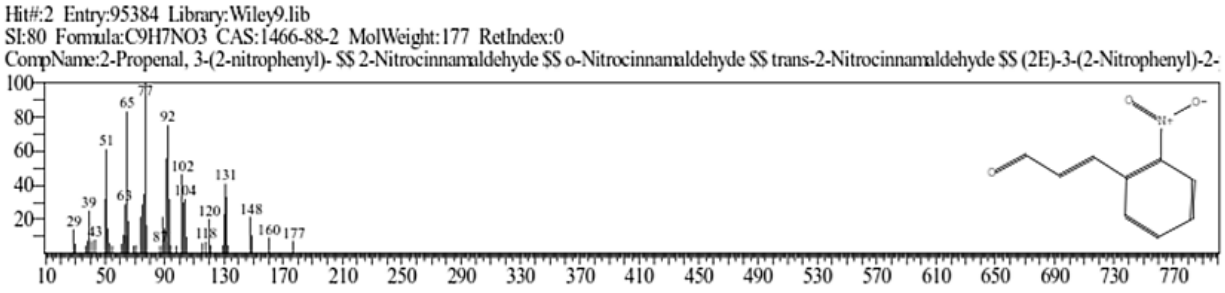


Figure 7. Mass Spectra GC-MS analysis results of NC

The Synthesis of AC

The second step in the strategy for synthesizing CD derivative compounds shown in Figure 6b is the reduction of NC to AC. The nitro group must generally compete with the unsaturated carbon and the aldehyde group to convert it to an amine group. The strategy NC reduction method can produce AS adopting method carried out by Méndez et al., (2017), which uses Nitrobenzaldehyde and reduced using reagents containing Fe and NH4Cl powder and heated for 2 hours. The reaction in dealing with reduction reactions to avoid unwanted side reactions is to use the reductant NH_4Cl to make the system more neutral, thereby reducing indications of the formation of by-products and reducing the concentration of H^+ ions in the system (Patil, 2015).

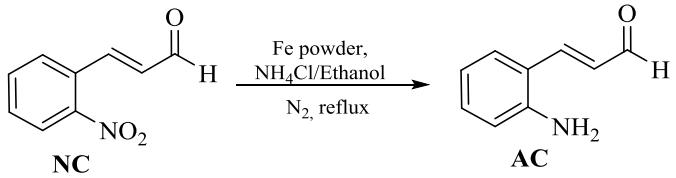
The synthesized product is separated from Fe at the end of the synthesis. The extracted product is dissolved in ethyl acetate solvent, resulting in a yellowish-brown and reddish-brown solid. The optimization of the reduction carried out is shown in Table 5. The optimum amount of NH_4Cl for the reaction was 3.4 mmol with the highest percent crude yield at 76.5%, while the optimization carried out on reaction time resulted in a less significant Yield value for the product. The results of the optimization of the AC product in the form of crude solids were then analyzed by TLC (Ethanol: n-hexane = 1:1), resulting in 2 stains where the first stain had the same R_f value as NC, which was around 0.84, indicating that there was still residual reactant, while the stain the second is assumed to be the product of reduction with an R_f value of about 0.48.

NC will be adsorbed on the surface of the Fe powder and release electrons. Fe, which donates electrons, so NH_4Cl, which H_2O will hydrolyze, produces protons H^+. Acid conditions are obtained from NH_4Cl, which is an acidic salt. NH_4Cl is obtained from the strong acid HCl and the weak base NH_3. NH_4Cl undergoes hydrolysis to produce H^+, which reduces NC to produce an amine pair in the product. The product purified by column chromatography was characterized using UV-Vis (Figure 8) and FT-IR with the comparison results shown in Figure 3 (AC in green line). The UV AC spectrum, shown in Figure 8, has two absorption peaks at wavelengths of 230 nm and 338 nm.

The structure of NC and AC shows the transitions -σ*, -π*, -π* and n-π*. Each spectrum has two peaks due to a transition in benzene. Benzene has three types of -π* absorption band, namely E band (200-230 nm), K band (200-230 nm), and B band (260 nm). Based on the UV-Vis analysis result, AC compounds have a larger wavelength (338 nm) than NC (248 nm). It indicates a bathochromic shift, a shift in wavelength to a longer one. The shift in wavelength becomes longer as the conjugate system gets longer. The shift in

wavelength is due to the different roles between the nitro and amine groups. The NO_2 group, an electron-withdrawing group, will attract electrons from the benzene ring, while the NH_2 group, an electron-donating group, will donate electrons to the benzene ring. When resonating, the NO_2 group, as an electron-withdrawing group, will attract electrons. A carbonyl group is also an electron-withdrawing group, so there is a competition for attracting electrons not to form a long conjugate system. The electrons from the benzene ring will be more attracted to the NO_2 group because NO_2 is stronger than the carbonyl group. At the same time, NH_2 is an electron booster, the lone pair on the N atom is used to push electrons that the conjugate system is longer. Therefore, the more extended conjugation system of AC causes the wavelength to be longer.

Table 5. Product optimization reduction



NC **AC**

Entry no.	NC (mmol)	Fe (mmol)	NH_4Cl (mmol)	Reaction time (h)	Yield* (%)
1	2.8	18.2	2.3	2	72.26
2	2.8	18.2	3.4	2	76.5
3	2.8	18.2	4.5	2	75.99
4	2.8	18.2	5.6	2	48.2
5	2.8	18.2	6.7	2	47.14
6	2.8	18.2	2.3	1	87.63
7	2.8	18.2	2.3	1.5	83.93
8	2.8	18.2	2.3	2	85.98
9	2.8	18.2	2.3	2.5	82.62
10	2.8	18.2	2.3	3	87.83
11	2.8	18.2	2.3	5	50.36

**Yield value of crude*

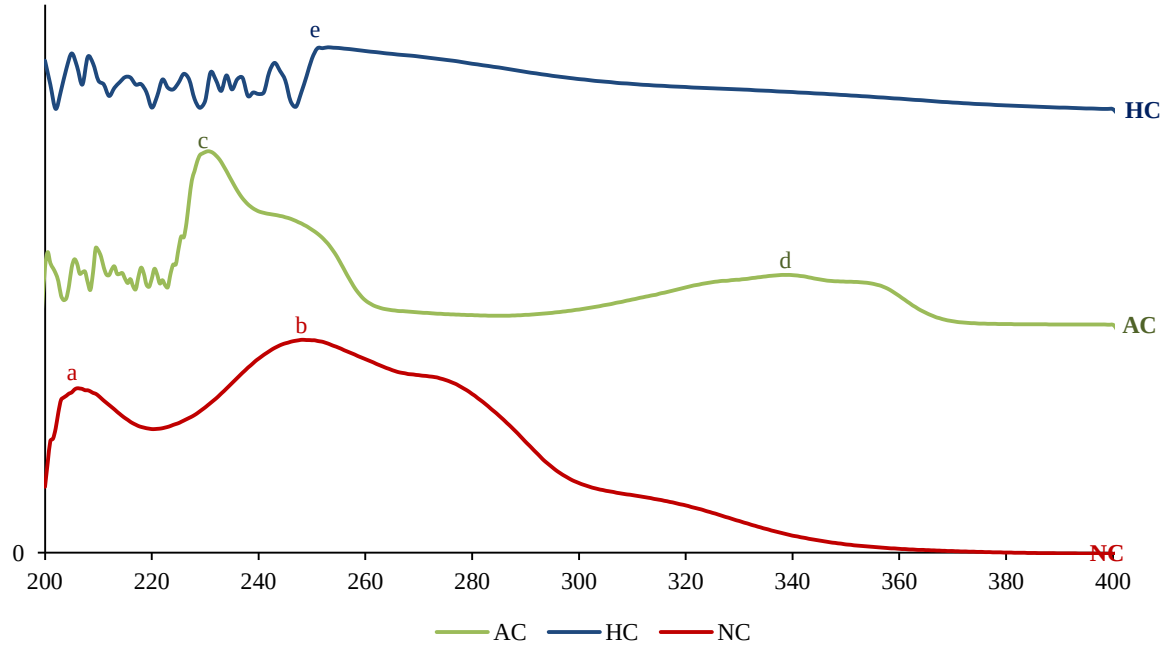


Figure 8. Comparison of the UV spectra of the product during the CD synthesis step. absorption peak of Nitration = (**a**) λ 206 nm and (**b**) λ 248 nm; Reduction = (**c**) λ 230 nm and (**d**) λ 338 nm; Hydrolysis = (**e**) λ 253 nm

The comparison FT-IR results are shown in Figure 3 to identify the functional groups of each stage product. The resulting reduction product (AC in green line) has a different absorption wavenumber from NC (in red line), so it is assumed that the product produced from the reduction process has a different structure from the nitrated product. The absorption present in the product was identified as a group nitro from NC at wavenumber at 1518 cm^{-1} and 1348 cm^{-1} as the N=O stretching group and a strong peak at 1123 cm-1 as the spectrum of the C-N stretching, indicating no longer found nitro group in the reduction product. Even an N-H absorption was found around wavelength 3400 cm^{-1}, which is strengthened by vibration at a wavenumber of 1254 cm^{-1}, indicating the presence of a primary amine functional group. It is a potential leading indicator for the formation of AC products from the reduction reaction of NC.

The synthesized products were then analyzed using LCMS at = 330 nm with a retention time of 0.653 minutes had a peak concentration of 13.101%. In positive mode scanning single ion monitoring (SIM), the mass spectra shown in Figure 9, by screening the molecular ion peak of the compound, can be shown the presence of a $[M]^+$ peak of the compound AC with an m/z value of 147. The analysis results support the statement that the compound obtained is an AC compound with a relative index of 98.57% compared to other compounds in the product. The other compounds in the product are assumed to be formed due to the Fe catalyst used, which tends to be non-specific in reaction and can form intermediates. According to Sudarma et al., (2010), the nitro group must generally compete with the unsaturated carbon and aldehyde group to convert it into an amine group.

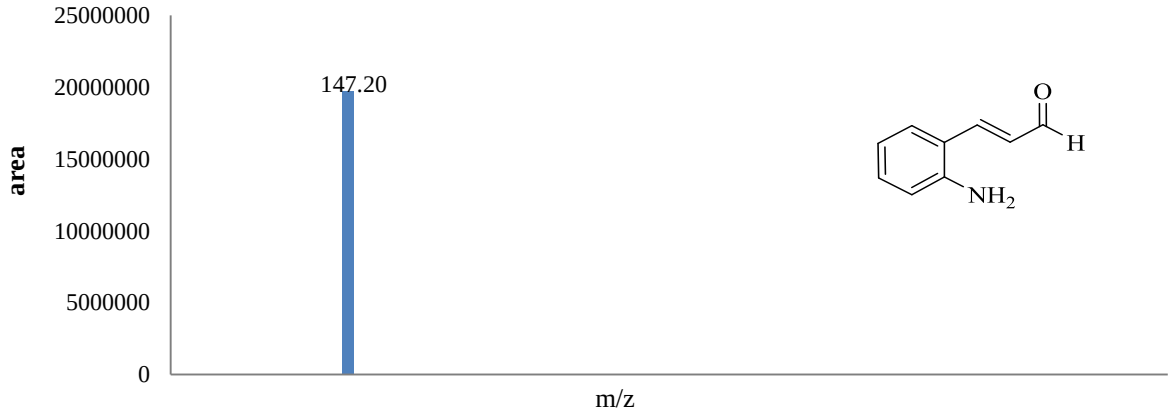
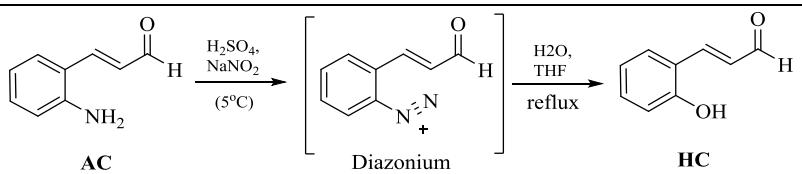


Figure 9. LCMS analysis results of AC

The synthesis of HC

Table 6. Optimization of hydrolysis product



Entry no.	AC (mmol)	$NaNO_2$ (mmol)	Reaction time (min)	Yield* (%)
1	1	1.1	20	74.59
2	1	1.2	20	80.05
3	1	1.3	20	51.07
4	1	1.5	20	31.06
5	1	1.1	10	82.17
6	1	1.1	20	79.53
7	1	1.1	40	40.04

*Average Yield value of crude

The standard method used to produce phenolic compounds is by thermal decomposition of diazonium salts in an acidic medium (Zhang et al., 2011). The hydrolysis reaction of the amino group to the hydroxy group adopts Taniguchi et al., (2009) method, as shown in Figure 6(c-d), through 2 stages: formation of a diazonium salt by reacting a primary amine compound with $NaNO_2$ and acid, then followed by a hydrolysis reaction with two-phase. Thus, the formation of diazonium salt as a compound species with a high reactivity (good leaving group) becomes the primary alternative for the substitution reaction for nucleophilic functional groups attached to the benzene ring.

Solids dissolved in water were also produced to obtain the key intermediate of the diazonium cation. According to a study reported by Taniguchi et al., (2009), which synthesized p-nitrobenzene to p-aminobenzene, there was a side reaction in tar. The strategy of the hydrolysis reaction of CD derivatives using water and THF facilitates the separation of products in the solvent phase and by-products in the water phase. Optimization is done by adjusting the mole variation in the diazotation process and the reaction time during the hydrolysis reaction shown in Table 6.

The amount of reagent $NaNO_2$ in the diazonium formation process contributes to product formation, with the optimum ratio between AC and $NaNO_2$ in this study being 1: 1.1, with a crude yield of 80.05%. However, based on the report by Reynold et al., (2018), there is a solubility problem in water and an increase in the total $NaNO_2$ in the reaction. If the number of moles added exceeds the variation of 1.1 mmol, the resulting product decreases. So, it is assumed that it can interfere with the activity of forming diazonium salts so that the yield produced in the experiment decreases.

An effort to improve the performance of hydrolysis reaction carried out variations in reaction time. The amount of product produced is inversely proportional to the reaction time, with the best time in this study being 10 minutes. Heating in the hydrolysis process aims to speed up the reactions so that hydrolysis can occur extensively. However, it is inversely proportional to the prolonged heating time in organic compounds, especially compounds with many reaction centers, such as CD derivatives that can produce cyclized by-products. It is also influenced by the nature and purity of the reacted products and compounds reported by Mardina et al., (2016), who hydrolyze Furfural compounds, yields will decrease due to the degradation process into other compounds. The degradation process can be observed in the hydrolyzed solution, where a by-product precipitate is formed.

The resulting product was then analyzed by TLC using the eluent ratio n-hexane: ethyl acetate: Dichloromethane= 5:4:1. There were 3 product spots with Rf values produced, respectively 0.19, 0.46, and 0.92, and then each spot was analyzed by FT-IR. TLC results of the first stain had the same Rf value as reagent AS, so it is assumed that there is still a reagent remaining in the hydrolysis product. While purification results by column chromatography on the stains, R_f = 0.19 and R_f = 0.46 have identical FT-IR spectrum results, to the difference in the wavenumber of 808 cm^{-1} where the absorption indicates that the compound is a compound with a substitution of 1.4 (para). So, it is assumed that the stain with R_f 0.46 is an isomer of the compound at R_f 0.19. The functional groups resulting from the FT-IR analysis of nitration, reduction, and diazotation-hydrolysis synthesis product indicate the differences between the three CD-derived compounds, namely NC, AC, and HC, are shown in Figure 3.

Based on the FTIR spectrum in Figure 3, there are differences in the absorption of important functional groups indicating the nitro substituent in NC and amine substituent in AC with vibrational absorption in the hydrolysis product. There is a broad absorption in the area around 3400 cm^{-1}, indicating O-H vibrations from alcohol. In addition, in the fingerprint area, there is absorption of C-O of the phenol group, which is around 1254 cm^{-1} which leads to the assumption of the formation of hydrolysis products in the form of HC. In addition, the absence of absorption at 1269 cm^{-1}, namely the C-N uptake of aromatic amines in the diazotation-hydrolysis product, indicated the change of the amine substituent to alcohol in the diazotation-hydrolysis product. However, the absorption of vibrations from the important synthesized groups was not found on CD, so it can be concluded that the hydrolysis products are derived from compounds synthesized from CD.

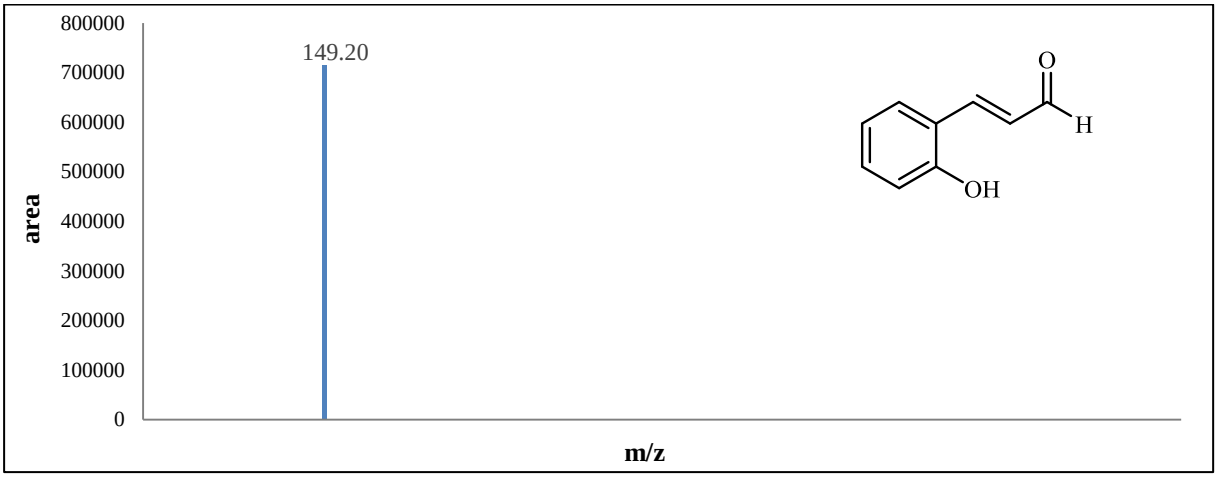


Figure 9. LCMS analysis results of HC

The product analysis results using UV-Vis showed in Figure 6 (HC in blue line). The UV AC (in green line) spectrum has two absorption peaks at wavelengths of 230 nm and 338 nm, while the results of HC synthesis have one absorption peak at a wavelength of 253 nm. The difference in the number of spectra indicates that the two compounds produced are also different. Then the crude product is analyzed by LCMS at a wavelength of 330 nm and a retention time of 0.609. The mass spectra in Figure 9 show the relative intensity of the specific ion-molecule the HC compound, with a peak in the mass spectra with an m/z value of 149.20 indicating the presence of $[M+H]^+$ from the mass of protonated HC molecules with a relative intensity of 9.82% compared to other compounds in the crude HC product. The value of the protonated molecular mass follows the calculation of the relative molecular mass HC in Chemdraw. The other compound in by-products produced in a crude product is assumed to result from cyclization. According to Zhang et al., (2011), the formation of phenolic coupling with diazonium salts causes the formation of tar as a by-product that can inhibit the hydrolysis process.

4. CONCLUSION

In this study, we developed a 3-step strategy for synthesizing cinnamaldehyde derivatives 2-hydroxycinamaldehyde from cinnamaldehyde compounds as a base material through a disconnection approach, nitration reduction, and diazotation-hydrolysis. The basic ingredients of cinnamaldehyde were obtained from isolation using the sodium bisulfite salting method, which produced cinnamaldehyde with a purity of about 100% and the highest average optimization yield of 36.96%. After optimization, each reaction stage produces products with fairly good yields, with an overall average crude yield of HC of about 82.17%.

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