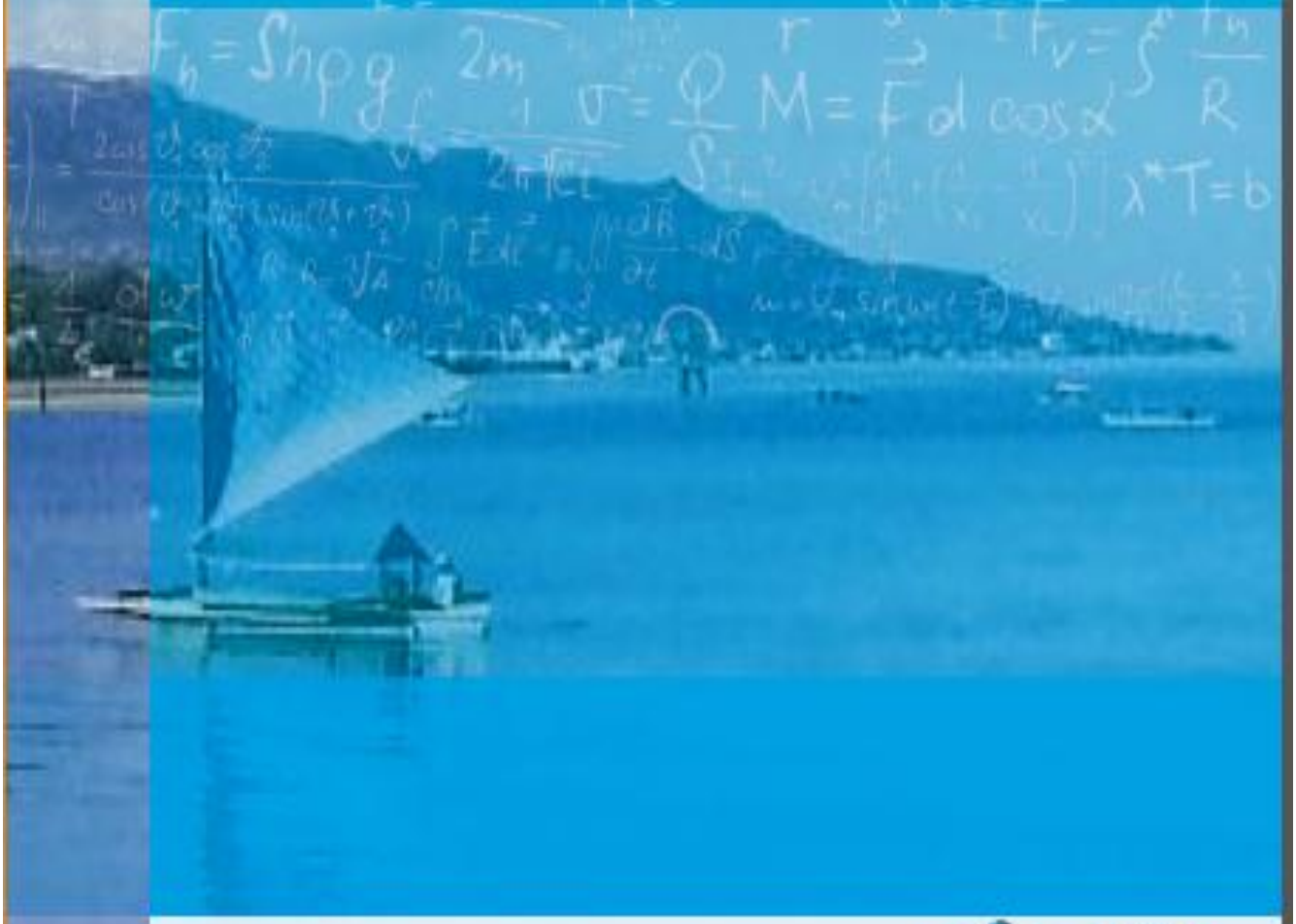
Basic Science
for Sustainable Marine Development

PROCEEDING
INTERNATIONAL SEMINAR 2015

Ambon, 3-4 June 2015



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PROCEEDINGS

1st International Seminar of Basic Science, FMIPA Unpatti - Ambon
June, 3rd – 4th 2015

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Mathematic and Natural Science Faculty
Pattimura University
Ir. M. Putuhena St.
Kampus Poka-Ambon
Pos Code 97233
Email:fmipa_unpatti@gmail.com

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Welcoming Address by The Organizing Committee

The honorable, the rector of Pattimura University

The honorable, the vice rector of academic affair, Pattimura University

The honorable, the vice rector of administration and financial affair, Pattimura University

The honorable, the vice rector of planning, cooperation and information affair, Pattimura University

The honorable, all the deans in Pattimura University

The honorable, the key note speakers and other guests.

We have to thank The Almighty God for the blessings that allow this International seminar can be held today. This is the first seminar about MIPA Science in which the Faculty of MIPA Pattimura University becomes the host. The seminar under the title Basic Science for Sustainable Marine Development will be carried out on 3 June 2015 at Rectorate Building, the second floor. There are 250 participants from lecturers, research institute, students, and also there are 34 papers will be presented.

This International seminar is supported by the amazing people who always give financial as well as moral supports. My special thanks refer to the rector of Pattimura University, Prof. Dr. Thomas Pentury, M.Si, and the Dean of MIPA Faculty, Prof. Dr. Pieter Kakissina, M. Si. I also would like to express my deepest gratitude to Dr. Kotaro Ichikawa, the director of CSEAS Kyoto University, Prof. Bohari M. Yamin, University of Kebangsaan Malaysia, Prof. Dr. Budi Nurani Ruchjana (Prisident of Indonesian Mathematical Society/Indo-MS), Dr. Ir. A. Syailatua, M.Sc (Director of LIPI Ambon), and Hendry Ishak Elim, PhD as the key note speakers. We expect that this international seminar can give valuable information and contribution especially in developing basic science for sustainable marine development in the future.

Last but not least, we realize that as human we have weaknesses in holding this seminar, but personally I believe that there are pearls behind this seminar. Thank you very much.

Chairman

Dr. Netty Siahaya, M.Si.

Opening Remarks
By Dean of Mathematic and Natural Science Faculty

I express my deepest gratitude to The Almighty God for every single blessing He provides us especially in the process of holding the seminar until publishing the proceeding of International Seminar in celebrating the 17th anniversary of MIPA Faculty, Pattimura University. The theme of the anniversary is under the title Basic Science for Sustainable Marine Development. The reason of choosing this theme is that Maluku is one of five areas in Techno Park Marine in Indonesia. Furthermore, it is expected that this development can be means where the process of innovation, it is the conversion of science and technology into economic value can be worthwhile for public welfare especially coastal communities.

Having the second big variety of biological resources in the world, Indonesia is rich of its marine flora and fauna. These potential resources can be treated as high value products that demand by international market. Basic science of MIPA plays important role in developing the management of sustainable marine biological resources.

The scientific articles in this proceeding are the results of research and they are analyzed scientifically. It is expected that this proceeding can be valuable information in terms of developing science and technology for public welfare, especially people in Maluku.

My special thanks refer to all researchers and reviewers for your brilliant ideas in completing and publishing this proceeding. I also would like to express my gratefulness to the dies committee-anniversary of MIPA Faculty for your creativity and hard working in finishing this proceeding, God Bless you all.

Dean of Mathematic and Natural Science Faculty

Prof. Dr. Pieter Kakisina, M.Si.

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Synthesis 3-benzo[1,3]dioxol-5-yl-propenal as a Precursor Asymmetric Curcumin Analogues from Kulit Lawang Oils

Imanuel Berly D. Kapelle[1,2], Tun Tedja Irawadi[3], Meika Syahbana Rusli[2], Djumali Mangunwidjaja[2], Zainal Alim Mas'ud[3]

[1]Chemistry Department, Mathematic and Natural Science Faculty, Pattimura University, Indonesia
[2]Agricultural Industry Technology Department, Agriculture Technology Faculty, Bogor Agricultural Institute, Indonesia
[3]Chemistry Department, Mathematic and Natural Science Faculty, Bogor Agricultural Institute, Indonesia

ABSTRACT

Asymmetric curcumin analogues as potential anticancer compounds. The purpose of this study was to synthesize intermediate product 3-benzo[1,3]dioxol-5-yl-propenal. Product 3-benzo[1,3]dioxol-5-yl-propenal as a precursor can be synthesized from the kulit lawang oil with several stages, among others; isolation safrole, isomerization, oxidation and condensation reactions. Isolation of safrole from kulit lawang oils performed using NaOH solution and purified using distillation fractionation pressure reduction produces 19.30% safrole are tested for purity by GCMS and for the identification of the structure is done by using FTIR and ^{1}H-NMR. The safrole isomerization performed using KOH without solvent at a temperature of 120^{o}C for 8 hours resulted isosafrol (91.53%) which consists of cis-isosafrol and trans-isosafrol. Oxidation isosafrol performed using $KMnO_4$ in acidic conditions using a phase transfer catalyst tween 80 at a temperature of < 30^{o}C and separation by silica gel resulted in 65.63% piperonal were tested with the GC and identification using FTIR and ^{1}H-NMR. Product intermediates 3-Benzo[1,3]dioxol-5-yl-propenal obtained from the condensation reaction of piperonal with acetaldehyde under alkaline conditions has a 70.28% yield.

Keywords : kulit lawang oils, synthesis, asymmetric curcumin analogues

INTRODUCTION

Indonesia is state of being eminent with tufted herbs volatile oil producer but its use not much used to process it into finished products like medicine. The volatile oil are mostly exported to then processed into finished products and entering Indonesia for the cost of what are two-fold. One of the volatile oil which is really potential and produced in eastern Indonesia especially the Moluccas and Papua is the kulit lawang oil. A plant kulit lawang included in family Lauraceae and lawang of cinnamon, with a slimy; leaves white and brittle timber tree and lawang growing wild forest. Kulit lawang oils obtained by the distillation of the bark lawang (*Cinanomum cullilawan,* Blume) with yield 1,49 to 3,80 % (Ketaren 1985).

The process of separating a kulit lawang oil producing two products that eugenol (69,0%) and safrol (21,0 %) (Sastrohamidjojo 2014). And have a difference of eugenol safrol

structure, where having a ring epoxide safrole that were highly active so that can be used as precursor synthetic drugs. Safrole at room temperature is a colorless oil, but can be turns yellow if exposed to the sun, however at low temperatures safrol colorless crystalline is white, have sassafras smell and a spicy taste (Guenter 1990; Villegas et al.2011).

Natural materials have a cluster of the same epoxide safrole with activity as well as having as anticancer is piperine (Soliman 2005). Piperine an alkaloid constituting a compound that has been tested as antitumor activity with a method in vivo could hinder 56,8 % (Bezerral et al.2006), the effects of antioxidant and hepatoprotektif (Mehta et al.2012 and can increase bioavailabilitas (Jin et al.2013). Of a cluster of epoxide reactivity owned by safrole can be used by way of convertible into products anticancer medicine that is a derivative of compounds analogous curcumin. Of compounds analogous (homologous) curcumin is a compound which likely pharmacological of the nature of the same or even better compared to the parent compound. A compound it self is curcumin cancer drugs natural of material that has been reported to have activity as anticancer from curcuma (Moorthi et al.2013; Xiang et al.2012). Curcumin and Curcumin analogous to have biological activity as antiinflammatory, antioxidant, antitumor, and anticancer (digestion, breast, ovary, lungs, a nerve) (Hahm et al.2004; Anand et al.2008b; Anand et al.2011; Labbozzetta et al.2009; Shang et al.2010).

Any compound of activity affected by a difference in a cluster of the functions and structure that affect the nature of physic-chemical and the effects of pleiotropic (Anand et al.2008a). Some analog curcumin with differences in test substituents in activity in vitro and in vivo pharmacokinetic shows that stability analogous mono-carbonyl be improved and profile pharmacokinetic also rose significantly (Liang et al.2009). Based on screening data, structure activity quantitative relations, shows that substituents having the nature of towing of electrons in a benzene ring deeply affect the nature of anti-inflammatory Zhao et al.(2010). Substituents on carbon atoms no-4 in a cluster of phenol is the active compounds analogous curcumin (Zhang et al.2011), in a cluster of the same also synthesized by substituent different and tested secar activity in vitro on tumor cells (Zhang et al.2008) .Side of the active from analog curcumin that gives the result was phenolic and a double bond conjugated protein (Devasena et al.2002).

One of the ways to increase the added value of the kulit lawang oil is to synthesize the compound Curcumin analogues as anticancer drugs. The process of product technology an anticancer drug analogous curcumin through several phases among others isolation safrol from kulit lawang oil, isomerization safrol, oxidation and condensation. Safrol can be isolated from oil by using chemical and physical methods. A method of chemical by using NaOH (Kapelle et al.2010; Sastrohamidjojo 2014) while the physical a method based on boiling points differences components. The principle of making isosafrol is a isomerization reaction, where safrol will undergo a change the structure because of the influence of a alkali so that going to happen the displacement the double bond of a chain straight toward the approaching ring benzene conjugated in position. Mechanism isomerization reaction through a substance between (intermediate) namely the establishment of carbocation that is a determining the rate of reaction, the results of isomerization produce isosafrol with isomeric cis and trans (Kapelle et al.2010). Isomerization safrol reaction mainly use excess a catalyst a alkali with the temperature of the process of 120oc for six hours (Kapelle et al.2010) to the reaction without a solvent.

The process of oxidation isosafrol produce piperonal is reaction is an oxidation alkenes, where a product produced depends on the condition of reactions and alkenes structure used. Reaction is an oxidation undertaken by using KMnO4 oxidizing as in a system of two in

phase namely water and organic the phase, hence to increase reaction a catalyst is added transfer phases (Sastrohamidjojo, 2004). A catalyst transfer reaction in phase took place on two stages, in the first transfer one of the phase a reactant normal to the second phase. The second stage is the reaction between a reactant transferred to a reactant in the second phase and will travel continuously to be no longer a reactant to be transferred (Shabestary et al.1998). Oxidation of the double bond in dilute alkene KmnO4 will produce diol and both groups in compound diol situated upon it the same. Diol formed to be oxidized further to the ketones, aldehydes or carboxylic acid (Allinger et al.1976). In a very strong reaction (75 ºC, 0.2 M KOH) KMnO4 able to decide on the double bond alkene (Smith 1994).

This reaction allegedly passing through the formation of an intermediate glycol (1,2-diol) being oxidized further by the termination of a bond carbon (Salomons 1990). Synthesis analogous curcumin asymmetrical products are a condensation reaction between two compounds different carbonyl which is called by condensation an aldol cross. Condensation an aldol cross reaction involving alkyl compounds aromatic aldehyde compounds and a ketone or aril a ketone Claisen-Schmdt as a reaction known as the reactants. The reaction from the condensation an aldol divided over two stages in the stage an addition and dehydration (Carey et al.1990). Piperonal is a compound aromatic aldehyde that can be reacted with the compounds of carbonyl the other so as produce analog curcumin asymmetrical. Analogous curcumin products made by using a condensation reaction phase, and the first stage of a compound produce intermediate 3-benzo[1,3]dioxol-5-yl-propenal. The purpose to be achieved from the study is to produce an intermediate 3-benzo[1,3]dioxol-5-yl-propenal from kulit lawang oil.

MATERIAL AND METHODS

Material

Kulit lawang oils from Maluku-Indonesia, NaOH, KOH, $KMnO_4$, CH_3COOH, Na_2SO_4, H_2SO_4, Diethyl ether, petroleum ether, Dichloromethane, Methanol, Acetaldehyde and all other chemicals were purchased from Sigma Chemical Co.(USA), Polisorbat (Tween 80) (Brataco).

Isolation safrole

137.42 g kulit lawang oil was added 40 g of NaOH in 300 mL of Aquades. The mixture was stirred to form two layers, and then the upper layer was separated. The bottom layer was extracted twice with 100 mL of petroleum ether and added to the top layer, then washed with distilled water until neutral and dried with Na_2SO_4 anhydrous. Petroleum ether was separated using evaporator and conducted distillation at reduced pressure. Products tested by gas chromatography, ^{1}H-NMR and FTIR.

Isomerization of safrole

Into a three-neck flask 500 mL size that has been equipped with a magnetic stirrer, thermometer, cooling tube, and blue silica gel. Added 71.56 g (0.44 mol) safrole and 50 g (0.89 mol) KOH. The mixture was refluxed at a temperature of 120ºC for 6 hours, and cooled then added 250 mL of aquades and then extracted with diethyl ether. Results dried with Na_2SO_4 and diethyl ether separated using evaporator. Purification was performed using

distilled under reduced pressure and purity was tested by GC, the structure was determined by FTIR and ^{1}H-NMR.

Synthesis of piperonal

Into a 250 mL three-neck flask included 2,97 g (0.02 mol) isosafrol, 100 mL aquades, 2 mL CH_3COOH, 15 ml H_2SO_4 50%, 100 mg twin 80 and 100 mL dichloromethane. Further 9.79 g (0.062 mol) $KMnO_4$ was added about 500 mg every minute, the temperature is < 30°C by placing in an ice bath. After $KMnO_4$ added, the flask is heated slowly at 40°C until the purple color disappeared (15 minutes). The solution is cooled for a few minutes and precipitate MnO_2 filtered using silica gel. Separation of the resulting solution is then poured into a separating funnel and the layers separated. Water layer (upper layer) was extracted with dichloromethane (2 x 30 mL). All organic layers are combined, and then washed with 2 x 30 mL aquades. The organic layer was dried with Na_2SO_4, filtered and evaporated at the evaporator. The residue was added 20% NaOH solution and the mixture was stirred for 30 minutes. Furthermore, the mixture was extracted with dichloromethane, washed with aquades, dried with Na_2SO_4 anhydrous and evaporated back. Recrystallization performed using methanol, the results obtained were analyzed by GC, FTIR, ^{1}H-NMR.

Synthesis of 3-Benzo[1,3]dioxol-5-yl-propenal

An intermediate product done by mixing 16 g (0.4 mol) NaOH, 100 ml aquades and 150 ml methanol. Stirred the mixture, next 8.8 g (0.2 mol) acetaldehyde a mixture is poured into. As many as 30 g (0.2 mol) piperonal poured into mix and stirred for 3 hours (modification Tran et al.2012). The result then cooled and included in refrigerator for 12 hours. Solids results filtered with filters Buchner and washed with aquades until neutral. Crystals that form in a recrystallization and analyzed, product formed then analyzed using GCMS.

RESULTS AND DISCUSSION

Isolation safrole

Safrole can be separated from kulit lawang oils by using NaOH. Eugenol and other phenolic components will react with NaOH to form water-soluble salts and formed two layers that can be separated, safrole layer which is not soluble in water are at the top of the mixture. Safrole were then purified using fractionation distillation at pressure reduction. In Fraction 2 at temperatures 90-123 °C / 1 mmHg obtained safrole with yield 19.30%. The properties of the resulting safrole is a clear liquid form, fragrant, insoluble in water but soluble in ethanol, chloroform and ether. Safrole analysis using gas chromatography obtained with a purity of 89.186% safrole. Infrared spectrum of safrole shows absorption bands in the region 3000-2800 cm^{-1} which is the absorption C_{sp3}-H, this was confirmed by the appearance of absorption at 1442.7 cm^{-1} for -CH_2- (methylene). Uptake range of C=C aromatic absorptions appeared at 1608.5 cm^{-1} and is supported by absorption at 3150-3000 cm^{-1} which is the absorption band for =C_{sp2}-H (aromatic). Absorption band at 1247.9 cm^{-1} region and 1041.5 cm^{-1} shows the range of C-O-C (ether) supported by each tape 916.1 cm^{-1} and 808,1cm^{-1}. Analysis and interpretation safrole ^{1}H-NMR spectrum of 60 MHz (δ: ppm) are as follows; δ = 3.2 ppm (d, -CH_2-), δ = 5.0 ppm (d =CH_2), δ = 5.5 to 6.2 ppm (m, = CH-), δ = 5.9 ppm (s, -O-CH_2-O-), δ = 6.8 ppm (m, 3H Ar). Safrole analysis using mass spectrum gives the following description, (m / z): 39, 51, 63, 77, 91, 104, 119, 131, and 162 $[C_{10}H_{10}O_2]^+$ (base peak).

Isomerization of safrole

Isosafrole can be carried on without solvent system using KOH at 120 °C for 8 hours and obtained yield 77.56%. The properties of the resulting isosafrole is light yellow viscous liquid and fragrant. Analysis using gas chromatography obtained *cis*-isosafrole the 3rd peak with a retention time of 3.375 minutes (15.40%) and *trans*-isosafrole the peak-to-5 with a retention time of 3.700 minutes (69.34%).

Infrared spectrum of isosafrole showed absorption at area 3000-2800 cm^{-1} which is C_{sp3}-H absorption. Absorption range of C=C aromatic appeared at 1608.5 cm^{-1}. Absorption band C_{sp2}-H (aromatic) appears in the area 3150-3000 cm^{-1}, this CONCLUSIONS is supported by the presence of sharp band with moderate strength at 1490.9 cm^{-1}. Absorption at 1247.9 to 1091.6 cm^{-1} shows the range of the C-O-C. Analysis by ^{1}H-NMR-60 MHz (δ: ppm) are as follows; δ = 1.8 ppm (d, -CH_2), δ = 5.9 ppm (s, -O-CH_2-O-), δ = 6.3 ppm (d, -CH =), δ = 6.7 - 6.9 ppm (d, H Ar).

Synthesis of piperonal

Piperonal properties produced in the form of white crystals and fragrant, insoluble in water but soluble in methanol (mp = 56-57°C). The results obtained by recrystallization using methanol piperonal to yield 65.63%. Infrared spectrum of piperonal obtained their range C=C aromatic appearing on uptake 1604.7 cm^{-1} is supported by absorption above 3000 cm^{-1} as absorption C_{sp2}-H (aromatic). Absorption area between 3000-2800 cm^{-1} which indicates the absorption C_{sp3}-H are reinforced by the presence of absorption 1448.9 cm^{-1} and 1357.8 cm^{-1} for methylene group (-CH_2-). Aldehyde group is shown by the presence of a weak absorption in the area twins 2711.7 cm^{-1} and 2781.2 cm^{-1} which is very typical for aldehyde compound. This was confirmed by uptake 1689.5 cm^{-1} which shows the carbonyl group. Absorption band 1249.8 cm^{-1}, 1099.3 cm^{-1} and 1037.6 cm^{-1} shows the compound ether (C-O-C). Beside the loss of the double bond in isosafrol characterized by loss of absorption area at 962.4 cm^{-1}.

Analysis by ^{1}H-NMR piperonal yield spectrum with the following peaks (δ: ppm); δ = 5.9 ppm (d, -O-CH_2-O-), δ = 6.9 ppm (d, 1H Ar), δ = 7.2 ppm (d, 2H Ar), δ = 9.9 ppm (d, CH = O). Hints of the data ^{1}H-NMR is a powerful clue oxidation of the double bond isosafrol is δ = 9.9 ppm peak which is the aldehyde proton unprotected because the induction effect of the carbonyl oxygen atom which is electronegative.

Synthesis of 3-Benzo[1,3]dioxol-5-yl-propenal

An intermediate product 3-Benzo[1,3]dioxol-5-yl-propenal obtained from condensation piperonal reaction with acetaldehyde having yield 70,28%. Time retention 12,43 minutes to an intermediate product with purity 23.59 % showed compound with the molecular weight of 176 g/mol. The product that has the highest concentration in the retention 9,58 minute is piperonal who had not participated in react. Synthesis of compounds 3-Benzo[1,3]dioxol-5-yl-propenal based on Claisen-Schmidt reaction involving two stages reaction. The first stage is an addition reaction nucleophile stage. At this stage carboanion of acetaldehyde will attack the carbonyl group on piperonal. The results of an addition reaction nucleophile above will experience the transfer of protons from the molecule of water produces β-hidroksiketon. Reaction the second stage is dehydration compound β-hidroksiketon because compound β-hidroksiketon have atoms Hα against the carbonyl group, so that in the course of an alkali atoms Hα easily off. It is speed up dehydration compound β-hidroksiketon produce products

with stable because they have the double bond that conjugated aromatic within the ring. A product produced purity all produce low caused due comparative concentration vested equally among acetaldehyde with piperonal so that in the final outcome there are piperonal that is not be fit react .

CONCLUSIONS

An intermediate product 3-Benzo[1,3]dioxol-5-yl-propenal can be synthesized from kulit lawang oil with several phases among others isolation safrole (19,30 %), isomerization (91,53 %), oxidation of isosafrole (65,63 %) and reaction condensation piperonal with acetaldehyde (70,28 %).

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