

## SYNTHESIS OF PULEGOL FROM PULEGYL ACETATE

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### ABSTRACT

Synthesis of pulegol from pulegyl acetate has been carried out started from citronellal as precursor that achieved by vacuum distillation of citronella oil, and then refluxed it with anhydride of acetic acid catalyzed by Lewis acid followed by hydrolysis of the product in alcoholic KOH. Structure elucidation of the products was determined by GC-FID, GC-MS, FTIR, and <sup>1</sup>H-NMR evidences. Isomers identification was determined by computational simulation. All experimental results were compared to the available literature. Cyclization of citronellal with anhydride of acetic acid catalyzed by Lewis acid FeCl<sub>3</sub> yielded 60% mixture of (-)-isopulegyl acetate, (+)-neoisopulegyl acetate, (+)-isoisopulegyl acetate with ratio of 16:6:1 while 63% mixture of (-)-isopulegyl acetate, (+)-neoisopulegyl acetate, (+)-isoisopulegyl acetate with ratio of 122:43:1 was obtained over Lewis acid ZnCl<sub>2</sub>. Hydrolysis of pulegyl acetate (catalyzed by FeCl<sub>3</sub>) refluxed in KOH/alcohol gave 38% mixture of (-)-isopulegol, (+)-neoisopulegol, (+)-isoisopulegol with ratio of 62:17:2, and 59.5% with ratio of 15:2:3 due to pulegyl acetate (catalyzed by ZnCl<sub>2</sub>) hydrolysis products.

Key words: citronella oil, citronellal, isopulegol, isopulegyl acetate, hydrolysis

### INTRODUCTION

Indonesia had exported 173.294 tons of citronella oil in 2002 to Europe, America, Japan, India, Taiwan, Singapore, and The middle East which total commodities was US\$ 1.150.393. The highest exporting volume was reached in 1975-1980 by 57% of citronella oil in the world (4000 tons/year) [1].

Sastrohamidjojo has stated that Indonesia has no ability yet to process crude essential oil became more valuable product for flavor, fragrance, and cosmetics industry [2]. As the consequences, Indonesia became an imported of essential oil manufacturing product country which more expensive in price then crude essential oil. *Java citronella oil* has nine major components identified by gas chromatography-mass, infrared

spectrophotometer, and  $^1\text{H-NMR}$ :  $\alpha$ -pinena, limonene, linalool, citronellal, citronelol, geraniol, citronelil acetate,  $\beta$ -cariophilena, and elamol [3].

Citronellal and geraniol derivative compounds likes hydroxy citronellal, synthetic menthol, geraniol ester and citronelol ester have been used in perfumery, flavor, fragrance, drugs, and repellent manufacturing for long time. Meanwhile crude citronella oil was used directly as Top/middle Note in home and personal care due to relaxation effect, antiseptic, repellent, limbering up muscle and the odor which can awake enthusiasm [4].

High demands of citronellal and geraniol derivative compounds have encouraged scientist to develop simple and stereoselective synthesis method. This research conducted to converse citronella to pulegol by (1) citronellal isolation from citronella oil, (2) cyclization of citronellal to pulegyl acetate, (3) hydrolysis of pulegyl acetate to pulegol.

Intramolecular cyclization could be initiated by mixing citronellal with HCl,  $\text{H}_2\text{SO}_4$ , anhydride acetic acid, activated acid  $\text{Al}_2\text{O}_3$ , zeolite, bentonit, and even with activated clays. The product was isopulegol as precursor of menthol through Raney-Ni catalytic hydrogenation [3, 5].

Based on Chuah *et al.* [6] investigation, Zirconium hydroxide and zirconium phosphate catalyst have good activity and selectivity toward citronellal cyclization to isopulegol. Lewis and Bronstead acid sites catalyst was very essential for this reaction.

Ifitah has synthesized isopulegol from citronellal catalyzed by Zn/ $\gamma$ -Alumina in methanol. The yield was 95,48% which stereoselectivities 63,87% to (-)-isopulegol [7].

Maki-Arvela, *et al.* [8] has found that zeolit and mesoporous materials behaved good catalytic activity for citronellal cyclization toward isopulegol in cyclohexane under nitrogen atmosphere. Each isopulegol isomer stereoselectivity was controlled by stability of isopulegol protonated intermediate, and meanwhile the concentration of Lewis and Bronstead acid, and the surface of catalyst had only minor effect.

Isopulegyl acetate was an ester which can be hydrolyzed by acid or base toward isopulegol  $\text{C}_{10}\text{H}_{18}\text{O}$  (relative mass 154) as major product. Isopulegol had refractive index 1,471 (20 °C), density 0,912 g/mL (25 °C), and boiling point 212 °C. Three chiral C atom of isopulegol exposed 8 stereoisomers products if the isopulegol was racemate mixture. Along with the research of Maki-Arvela, *et al.* [8] the major products of

(*R*)-citronellal catalyzed by Lewis acid were (-)-isopulegol (I), (+)-neo-isopulegol (II), (+)-iso-isopulegol (III), (+)-neoiso-isopulegol (IV) (Figure 1).

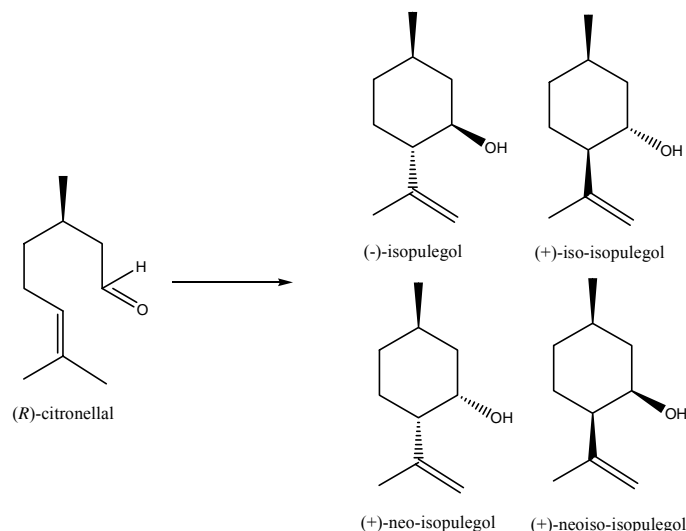


Figure 1 Stereoisomer structures of pulegol from *R*-citronellal

Pulegyl acetate and pulegol compounds classified as simple six member ring organic compound. Physical constant of these compounds can be calculated practically by semiempiric method. PM3 semiempiric method was designed to generate formation energy and geometric structures of mostly organic molecules. The absolute error of PM3 method was more acceptance then AM1 and MNDO method.

## METHOD

### Materials

The materials of this research were citronella oil (Toko Sari Warna Jogjakarta), Iron(III)chloride ( $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ ), anhydride acetic acid ( $(\text{CH}_3\text{CO})_2\text{O}$ ), *n*-hexane, sodium sulphate anhydrate ( $\text{Na}_2\text{SO}_4$ ), potassium hydroxide (KOH), redistilled ethanol 96%, technical sodium chloride (NaCl), redistilled methanol, nitrogen gas, silicon vaselin, pH universal indicator.

### Apparatus

The apparatus of this research were distillation under reduced pressure, reflux, chromatography gas-FID (*Hewlett Packard 5890 Series II*), chromatography gas-mass spectrometer (*Shimadzu QP 2010*), infrared spectrophotometer (*Shimadzu FTIR 8201 PC*),  $^1\text{H}$ NMR spectrometer (*JNM PMX 50 NMR*), XRD spectrometer (*Shimadzu XRD*

6000), polarimeter (*E-Hartnack Ritter Germany*), refractometer (*AB-Refractometer Nar-1T*), hot plate magnetic stirrer (*Cimarec 2 Termolyne*), heating mantle, glass laboratory apparatus and computer with computational software.

## **Procedures**

### **Isolation of citronellal from citronella oil**

Citronella oil was analyzed by GC-MS to determine its composition. Citronellal as the major component isolated by fractional distillation under reduced pressure from 250 mL citronella oil. All fraction were separated each other according to *liquid-vapor* equilibrium temperature and analyzed by GC-FID. The crude of citronellal purified by redistillation and the product identified by GC-MS, FTIR dan  $^1\text{H-NMR}$ .

### **Citronellal cyclization toward pulegyl acetate**

Lewis acid  $\text{FeCl}_3$  1,72 gram (10 mmol) and 7,2 mL (120 mmol) anhydride acetic acid were stirred at room temperature in three neck round bottom flask equiped by condensor, and then 7,0 mL (60 mmol) of citronellal was dropped continuously under nitrogen atmosphere. Mol ratio of citronellal, anhydride acetic acid and  $\text{FeCl}_3$  were 6:12:1.

The crude product partitioned by 10 mL  $\text{H}_2\text{O}$  and 10 mL *n*-hexane after 3 hours reaction. The organic layer was separated from aqueous phase, netralized by  $\text{H}_2\text{O}$  and finally dried by pottasium sulphate anhydrate. Cyclization product was identified by GC-FID, GC-MS, FTIR, and  $^1\text{H-NMR}$ .

In addition some experiments over  $\text{ZnCl}_2$  were carried out under the same method, which amount of  $\text{ZnCl}_2$ , anhydride acetic acid, and citronellal were 1,36 g, 11 mL and 11 mL respectively. The reaction conducted at 80 °C and the Cyclization product was elucidate by GC-FID, GC-MS, FTIR, and  $^1\text{H-NMR}$ .

### **Pulegyl acetate hydrolysis**

Pulegyl acetate produced previously as much as 4 g were hydrolized by 25 mL KOH 0,5 N in ethanol. The mixed reaction refluxed for 3 hours at 80 °C, and then partitioned in separatory funnel with 10 mL of diethyl eter and 10 mL of  $\text{H}_2\text{O}$ . The Organic layer was separated from aqueous phase, netralized by  $\text{H}_2\text{O}$  and finally dried by pottasium sulphate anhydrate. Cyclization product was identified by GC-FID, GC-MS, FTIR, and  $^1\text{H-NMR}$ .

### Isolation of hydrolysis product

The crude of hydrolysis product as much as 20 mL was separated by fractional distillation under reduced pressure, and purified pulegol was obtained according to *liquid-vapor* equilibrium temperature and identified by GC-MS, FTIR and  $^1\text{H-NMR}$ .

### Computational chemistry for determining reaction stereoisomer

Molecular geometry optimization was calculated by semiempiric PM3 method. The most stable structure determination was conducted through *systematical searching* which means conformation considering based on torsion angle. The torsion angle of  $\text{C}_{22}\text{-C}_{15}\text{-C}_5\text{-C}_6$  bond was turned around every  $10^\circ$  for 36 times (Figure 2). Each constructed conformation optimized in order to find the most stable conformation with the lowest energy.

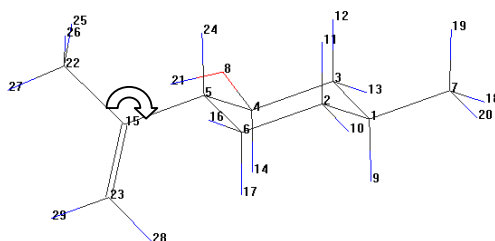


Figure 2 Rotation direction of angle torsion in finding of conformation which the nearest to minimum global energy.

## RESULTS AND DISCUSSION

### Isolation of Citronellal from Citronella Oil

Fractional distillation under reduced pressure of 250 mL citronella oil at  $110\text{-}115^\circ\text{C}/2,5\text{ cmHg}$  yielded 45% citronellal in second fraction ( $\pm 112,5\text{ mL}$ ). Citronellal was obtained up to 89,82% after being redistilled under the same condition. The physic properties of isolated citronellal were  $[\alpha]_D^{27} +8,35^\circ$ ,  $[\rho_{27}] 0,8570\text{ g/mL}$ , and  $[\eta^{20}] 1,4478$ , meanwhile standard citronellal (*E.Merck*) had physic properties  $[\alpha]_D^{27} +3,80^\circ$ ,  $[\rho_{27}] 0,8469\text{ g/mL}$ , and  $[\eta^{20}] 1,4373$ . A direct comparison between two data of those physical properties lead toward conclusion that the isolated citronellal was not racemate mixture. If derivative synthesis was carried out to isolated citronellal, it would produced diastereomer compounds.

### Citronellal Cyclization toward Pulegyl Acetate

Citronellal cyclization was conducted over two Lewis acid catalysts at different reaction temperature. First cyclization was carried out between isolated *R*-citronellal 89%, anhydride acetic acid, and FeCl<sub>3</sub> at room temperature under nitrogen atmosphere during 3 hours, and the second cyclization was observed over ZnCl<sub>2</sub> at temperature 80 °C under same condition. The ratio of stereoisomer pulegyl acetate product due to FeCl<sub>3</sub> was 16:6:1, meanwhile for ZnCl<sub>2</sub> was 122:43:1 (Figure 3). Differences of the ratio could be comprehended by their own physical properties and reactivities. Lewis acid FeCl<sub>3</sub> more reactive than ZnCl<sub>2</sub>.

Hammond postulate stated that reactive reagent (exothermic) would generate *reactant like* intermediate while selective reagent (endothermic) would generate *product like* intermediate. These intermediate compounds were the determining rate step. According to this postulate, the determining rate step of citronellal cyclization to pulegyl acetate (FeCl<sub>3</sub> catalyst) would be *reactant like* and for ZnCl<sub>2</sub> catalyst would be *product like*. Cyclization mechanism presented in figure 4 and 5.

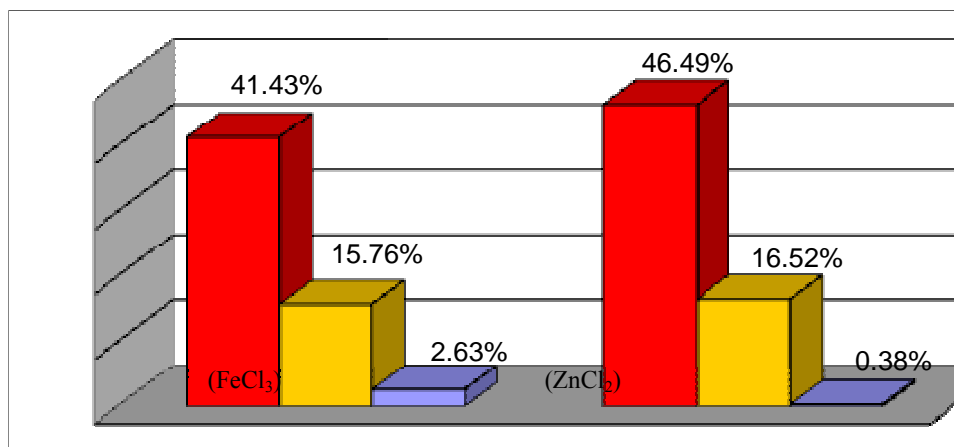


Figure 3 Percentage of pulegyl acetate stereoisomer cyclization product over catalyst FeCl<sub>3</sub> (T room) and ZnCl<sub>2</sub> (T 80 °C)

### Pulegyl Acetate Hydrolysis

Ester of pulegyl acetate was hydrolyzed to pulegol and acetic acid. The reaction mechanism were predicted as described in Figure 6. According to peak sequences of (-)-isopulegol, (-)-neo-isopulegol and (-)-iso-isopulegol the stereoisomer ratio of hydrolysis products was presented in Figure 7.

Hydrolysis of pulegyl acetate (catalyzed by  $\text{FeCl}_3$ ) refluxed in  $\text{KOH}$ /alcohol gave 38% mixture of (-)-isopulegol, (+)-neoisopulegol, (+)-isopulegol with ratio of 62:17:2, and 59.5% with ratio of 15:2:3 due to pulegyl acetate (catalyzed by  $\text{ZnCl}_2$ ) hydrolysis products. The first product ratio was more stereoselective to (-)-isopulegol than the second ones, although it had lower yield than the first one.

The facts that (-)-isopulegol product more abundance than (+)-neo-isopulegol and (+)-iso-isopulegol was being able to be comprehended by total energy of pulegol stereoisomer formation simulated by computational method over Hatree-Fock (HF) basis 6-31 +G approach with software Gaussian 98 [8].

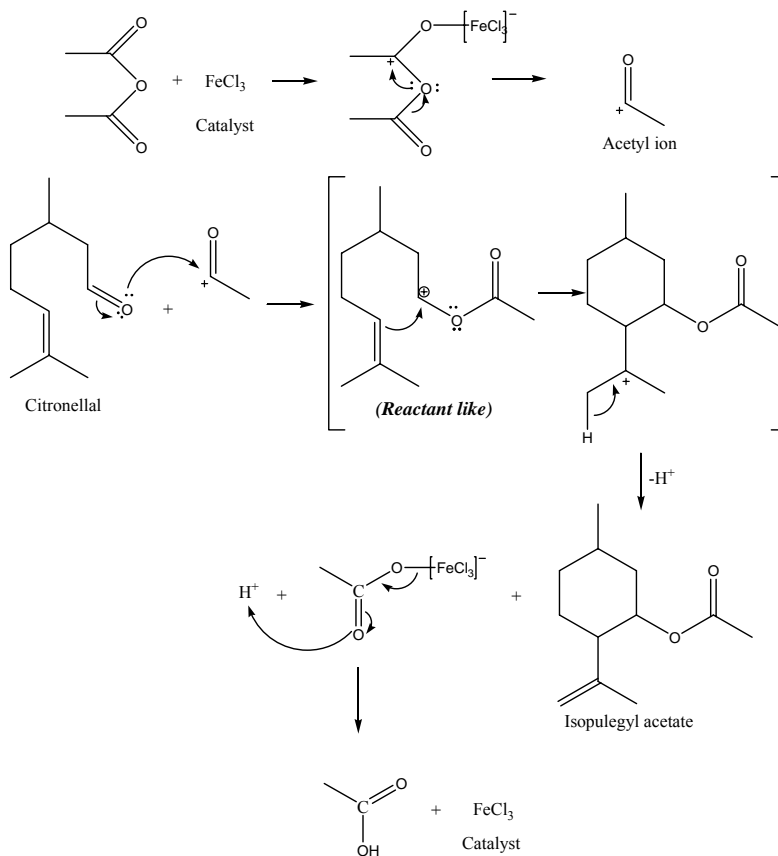


Figure 4 Intramolecular cyclization mechanism of citronellal with anhydride acetic acid over  $\text{FeCl}_3$  catalyst

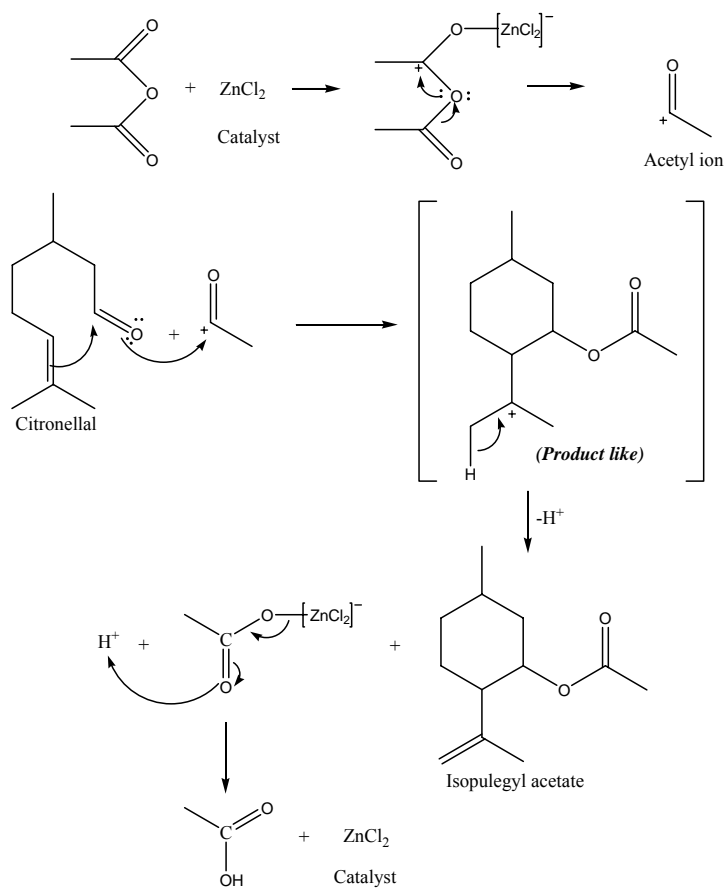


Figure 5 Intramolecular cyclization mechanism of citronellal with anhydride acetic acid over  $\text{ZnCl}_2$  catalyst

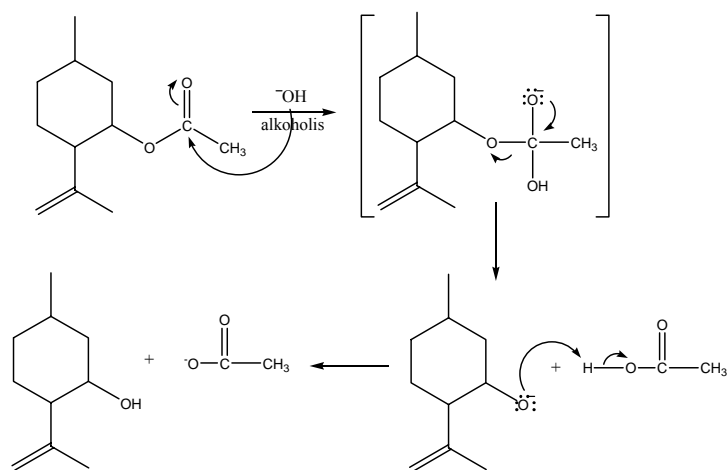


Figure 6 Pulegyl acetate hydrolysis mechanism over basic catalyst



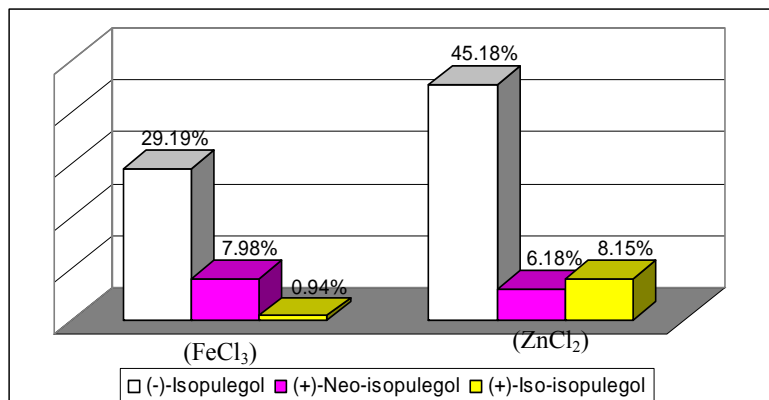


Figure 7 Pulegol stereoisomer ratio as pulegyl acetate hydrolysis product (FeCl<sub>3</sub> and ZnCl<sub>2</sub> catalyst)

### Isolation of Hydrolysis Product

Pure pulegol was isolated from 20 mL of pulegyl acetate hydrolysis product by fractional distillation under reduced pressure at 80-90 °C/2,5 cmHg. The purified pulegol was found in second fraction. Chromatography gas showed that the isolated pulegol content was 76,86% with isomer ratio (-)-isopulegol: (+)-neo-isopulegol: (+)-iso-isopulegol due to 31,7:1:8,8.

Computational simulation over semiempiric PM3 method (Table 1) showed that total energy of (-)-isopulegol formation was the lowest among two other pulegol isomers. As the consequences (-)-isopulegol was the most stable and abundance among other isomers.

Table 1 Total energy of Formation and dipole moment of three pulegol isomers simulated by semiempiric PM3 method

Pulegol	Energy (ccal/mol)	Dipole Moment (Debyes)
(-)-Isopulegol	-40523,065	1,506
(+)-Neo-isopulegol	-40522,119	1,614
(+)-Iso-isopulegol	-40521,916	1,500

## CONCLUSIONS

1. Cyclization of citronellal with anhydride of acetic acid catalyzed by Lewis acid  $\text{FeCl}_3$  yielded 60% mixture of (-)-isopulegyl acetate, (+)-neoisopulegyl acetate, (+)-isoisopulegyl acetate with ratio of 16:6:1 while 63% mixture of (-)-isopulegyl acetate, (+)-neoisopulegyl acetate, (+)-isoisopulegyl acetate with ratio of 122:43:1 was obtained over Lewis acid  $\text{ZnCl}_2$ .
2. Hydrolysis of pulegyl acetate (catalyzed by  $\text{FeCl}_3$ ) refluxed in KOH/alcohol gave 38% mixture of (-)-isopulegol, (+)-neoisopulegol, (+)-isoisopulegol with ratio of 62:17:2, and 59.5% with ratio of 15:2:3 due to pulegyl acetate (catalyzed by  $\text{ZnCl}_2$ ) hydrolysis products.

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