The 6th International Seminar on Science and Technology (ISST) 2020
July 25th 2020, Institut Teknologi Sepuluh Nopember, Surabaya, Indonesia

Synthesis 1,2-bis ((3-methylbut-2-en-1-yl)oxy) -4-(((3methylbut-2-en-1-yl)oxy)methyl)benzene

Ahmad Rizqi Alima Fabri and Mardi Santoso
Department of Chemistry, Institut Teknologi Sepuluh Nopember, Surabaya
e-mail: tsv09@chem.its.ac.id

***Abstrak*—Kojic acid and arbutin are materials that are used to inhibit melanogenesis, but in their development, these two compounds have an adverse effect on the skin. 3,4-dihydroxybenzaldehyde is a simple phenol compound whose derivatives are used as flavorers and fragrance. The research carried out aims to obtain 3,4-dihydroxybenzaldehyde derivatives in the form of 1,2-bis((3-methylbut-2-en-1-yl)oxy) 4-(((3-methylbut-2-en-1-yl)oxy)methyl)benzene which is estimated based on its structure is able to inhibit melanogenesis, and has a similar structure to the commercial fragrance of methyl diantilis. The synthesis of the target compound is carried out in three step. The first step involves the alkylation of 3,4-dihydroxybenzaldehyde with 3,3-dimethylalyl bromide and sodium hydride in the dimethylformamide solvent at room temperature to obtain 3,4-bis ((3-methylbut-2-en-1-il) benzaldehyde. Reduction of formyl 3,4-bis((3-methylbut-2-en-1-il) benzaldehyde which is carried out in the second stage with sodium borohydride in ethanol obtained 3,4-bis((3-methylbut-2-en-1-yl)oxy)phenyl)methanol. Etherification 3,4-bis ((3-methylbut-2-en-1-il)oxy)phenyl)methanol with 3,3-dimethylalyl bromide and sodium hydride in the solvent dimethylformamide at room temperature is obtained target compound 1,2-bis((3-methylbut-2-en-1-il)oxy)-4-(((3-methylbut-2-en-1 il)oxy)methyl)benzene whose structure is determined by NMR, mass, and IR spectroscopy.**

***Kata Kunci*—Synthesis, 3,4-Dihydroxybenzaldehyde Derivatives, Melanogenesis.**

I. INTRODUCTION

HAVING healthy skin is what everyone wants, especially women. Cosmetics is one way of skincare, which among others plays a role in preventing the occurrence of hyperpigmentation [1]. Kojic acid (**1**) and arbutin (**2**) are used to inhibit hyperpigmentation, but in its development, these two compounds have an impact on the skin. Arbutin (**2**) can cause allergies, and long-term use will worsen hyperpigmentation, whereas kojic acid (**1**) can cause skin irritation [1], [2]. Arung et al (2007) [3] succeeded in separating several compounds (**3**) from jackfruit plants (*Artocapus heterophyllus*) which have activity as melanogenesis inhibitors. The three compounds can be seen in Figure 1. The compounds (**3**) separated from the plant were tested for their bioactivity against melanoma B16 cells with kojic acid (**1**) and arbutin (**2**) as positive controls. The results can be seen in Table 1. Table 1 shows that in general compounds (**3a-f**) have better melanogenesis inhibiting activities than kojic acid (**1**) and arbutin (**2**) against melanoma B16 cells. The data shows that the presence of 3-methyl-2-butenyl groups plays a role in inhibiting melanogenesis as can be seen in the IC_{50} value, the more 3-methyl-2-butenyl groups can increase their activity in inhibiting melanogenesis.

3,4-Dihydroxybenzaldehyde is a simple phenol compound. Derivatives of 3,4-dihydroxybenzaldehyde are used as flavorings and deodorizers, for example, 4-hydroxy-3-methoxybenzaldehyde, 3,4-dimethoxybenzaldehyde and 1,3-benzaldioxol-5-carboxaldehyde [4] Methyl dianthilis (**4**), which was first introduced by the leading company, perfume and flavor Givaudan from Switzerland, has a spicy, carnation, sweet, vanilla aroma. Methyl methylated (**4**) is used as a substitute for isoeugenol (**5**) (see Figure 2) in the use of shampoo and perfume [5].

Literature studies that have been carried out provide inspiration to synthesize compound (**6**) which is designed to have activity as an inhibitor of melanogenesis and has a similar structure to methyl dianthilis. The synthesis of the target compound (**6**) was suggested by a retrosynthetic analysis approach as can be seen in Figure 3.

The research carried out aims to obtain 1,2-bis((3-methylbut-2-en-1-il)oxy)-4-((3-methylbut-2-en-1-il)oxy)methyl)benzene (**6**) with the basic ingredients of 3,4-dihydroxy benzaldehyde, using a retrosynthetic analysis approach. It also found three derivatives 3,4-dihydroxybenzaldehyde in the form of 1,2-bis((3-methylbut-2-en-1-il)oxy)-4-((3-methylbut-2-en-1-il)oxy)methyl)benzene (**6**), 3,4-bis((3-methylbut-2-en-1-il-oxy)phenyl)methanol (**7**), 3,4-bis((3-methylbut-2-en-1-il)benzaldehyde (**8**) (see Figure 3).

II. METHOD

A. Tools and Materials

The experiment was carried out using laboratory equipment as follows: goblet, Erlenmeyer, separating funnel, watch glass, weighing bottle, measuring cup, double neck flask, drop pipette, volume pipette, propipet, Socorex Swiss micropipette, magnetic stirrer hotplate, thin layer chromatography (TLC) plat aluminum silica 60 F254 (Merck 1.05554), Sartorius CP224S analytical balance, capillary pipelines, separating funnels, TLC vessels, UV lamps (λ 254 and 366 nm), Shimadzu FTIR 8400S analytical balance, HP 6890 and KP2010 Ultra gas mass spectrometers Jeol ECS NMR spectrometers (400 Mhz).

The materials used in the research included 3,4-dihydroxy benzaldehyde (Merck 8.20475), 3.3-dimethylalyl bromide (Fluka 38925), amberlyst 15 (Sigma Aldrich 216380), sodium hydride (Merck 8.14552), sodium borohydride (Merck 38925), amberlyst 15 15 (Sigma Aldrich 216380), sodium hydride (Merck 8.14552), sodium borohydride (Merck 38925), amberlyst 15 (Sigma Aldrich 216380), sodium hydride (Merck 8.14552), sodium borohydride

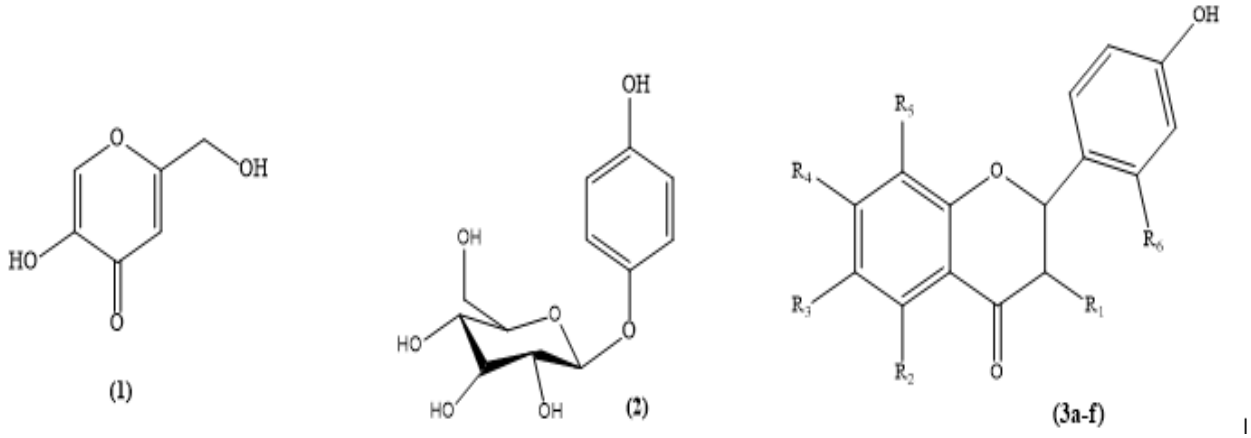

Figure 1. Melanogenesis inhibiting compounds: (**1**) kojic acid, (**2**) arbutin, and (**3**) compounds from *Artocapus heterophyllus.*

Table 1.
Activities of compounds (**3a-f**) as inhibitors of hyperpigmentation

Compound	R_1	R_2	R_3	R_4	R_5	R_6	IC_{50} (µM)
(3a)	3-methyl-2-butenyl	OH	3-methyl-2-butenyl	OMe	H	OH	7.3
(3b)	3-methyl-2-butenyl	OH	3-methyl-2-butenyl	OH	H	OH	3.8
(3c)	H	OH	3-methyl-2-butenyl	OH	H	H	6.6
(3d)	3-methyl-2-butenyl	OH	H	OH	3-methyl-2-butenyl	OH	4.9
(3e)	3-methyl-2-butenyl	OH	H	H	H	OH	40.1
(3f)	H	OH	H	OH	H	H	32.9
(1)							> 3521
(2)							111

(Merck No. 1,00137,2500), methanol (Fulltime-6501), ethanol (Smart Lab A-1035), ethyl acetate (ACS 6801-04), n-hexane (Meck 1.04367), NN-dimethylformamide (DMF) (Merck 1.03053), dichloromethane (Merck 1.06050), Silica GF 60 gel (Merck 1.07734.1000), distilled water, magnesium sulfate heptahydrate (Merck 1.005886).

B. Experiment Procedures

1) Synthesis 3,4-bis((3-methylbut-2-en-1-il)benzaldehyde (8)

Synthesis of 3,4-bis ((3-methylbut-2-en-1-il)benzaldehyde (**8**) was carried out by adapting the 5,6-methylenedioxyaindole methylation procedure [6]. 3,4-dihydroxybenzaldehyde solution (0.156 gram; 1.128 mmol) in anhydrous DMF (15 mL), plus sodium hydride (0.372 grams; 15.506 mmol) and stirred at room temperature. The mixture was then placed in an ice bath and added 3.3-dimethylalyl bromide (0.800 mL; 6.8911 mmol) dropwise while stirring at room temperature. The mixture was stirred further at room temperature, and the reaction is monitored by TLC. The organic phase obtained was combined, and washed with distilled water (3x15 mL), dried with anhydrous magnesium sulfate, and evaporated at low pressure. The synthesized product was then purified by gravity column chromatography with silica gel GF 60 and mobile phase *n*-Hexana: ethyl acetate (9:1), purity test was carried out by 3-dimensional TLC and two-dimensional TLC. The pure synthesis results were weighed and identified by NMR spectrophotometer.

2) Synthesis 3,4-bis((3-methylbut-2-en-1-il)oxy)phenyl)methanol (7)

Synthesis of 3,4-bis ((3-methylbut-2-en-1-il) oxy) phenyl) methanol (**7**) was carried out by adapting the reduction procedure 4,6-dimethoxy-1-methylindol-3-carbaldehyde [6]. 3,4-bis((3-methylbut-2-en-1-il)benzaldehyde (**8**) solution (0.054 gram; 0.196 mmol) in ethanol (10 mL) plus sodium borohydride (0.034 gram; 0.898 mmol), then stirred it at room temperature and the reaction was monitored by TLC, the reaction results were then added with a solution of sodium hydroxide 10% (10 mL) after the reaction was complete, and extracted with dichloromethane (3x10 mL) . The organic phase obtained was combined, washed with distilled water (30 mL)), dried with magnesium sulfate anhydrous, and evaporated at low pressure. The results of the synthesis were tested for purity by TLC and two-dimensional TLC. The pure synthesis results were weighed and identified by NMR spectrophotometer.

3) Synthesis 1,2-bis((3-methylbut-2-en-1-il)oxy)-4-((3-methylbut-2-en-1-il)oxy)methyl)-benzene (6)

Synthesis of 1,2-bis((3-methylbut-2-en-1-il)oxy)-4-((3-methylbut-2-en-1-il)oxy)methyl)benzene (**6**) was done by adapting 3,4-methylenedioxybenzyl methyl ether synthesis procedure [2]. 3,4-bis solution((3-methylbut-2-en-1-il)oxy)phenyl)methanol (**7**) (0.041 gram; 0.148 mmol) in DMF (15 mL) plus sodium hydride (0.022 gram; 0.917 mmol) then stirred at room temperature. The mixture was then placed in an ice bath and added 3.3-dimethylalyl bromide

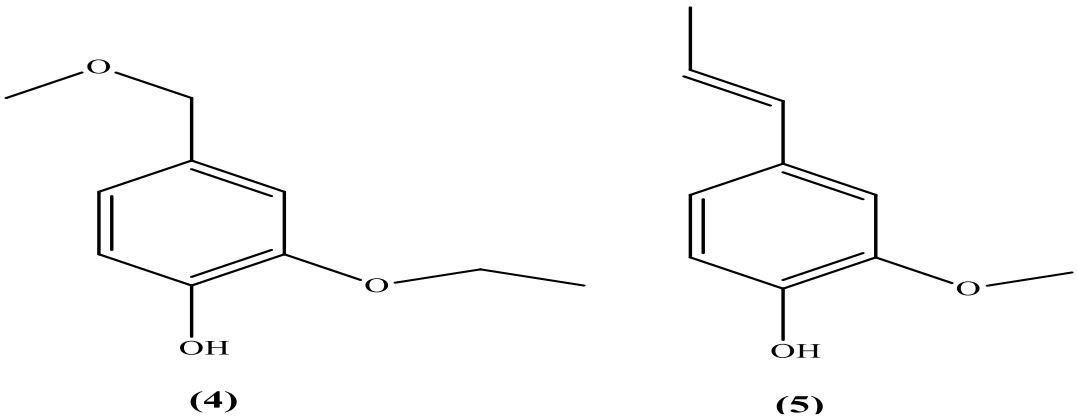

Figure 2. Compounds of methyl dianthilis (4) and isoeugenol (5).

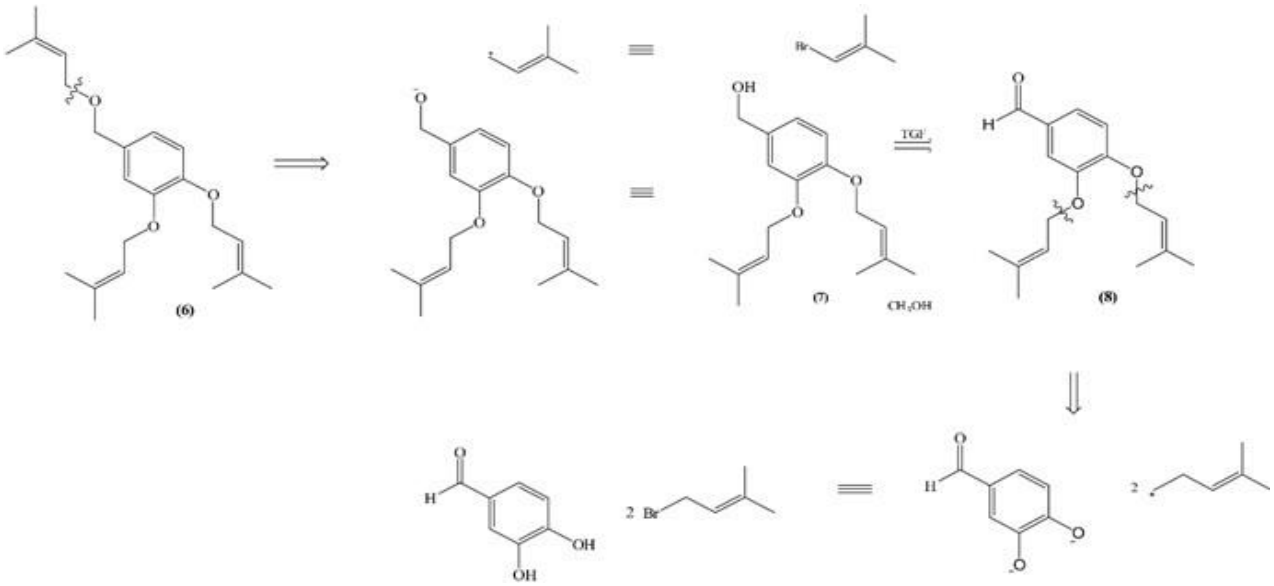

Figure 3. Retrosynthetic Analysis of Target Compounds.

(0.030 mL; 0.255 mmol) dropwise while stirring at room temperature. The mixture was stirred further at room temperature, and the ongoing reaction was monitored by TLC. The reaction mixture was added with cold distilled water (20 ml) after the reaction was complete, and extracted with dichloromethane (3x10 mL). The obtained organic phase was combined, and washed with distilled water (15 mL), dried with anhydrous magnesium sulfate, and evaporated at low pressure. The synthesized product was then purified by gravity column chromatography with silica gel GF 60 stationary phase and *n*-hexane: ethyl acetate (10:1) mobile phase, purity test was carried out by 3-dimensional TLC and two-dimensional TLC. The pure synthesis results were weighed and identified by IR and NMR spectrometers, and KG-SM.

III. RESULTS AND DISCUSSION

A. Synthesis 3,4-bis((3-methylbut-2-en-1-il)benzaldehyde (8)

Synthesis of 3,4-bis((3-methylbut-2-en-1-il)benzaldehyde (**8**) was carried out in two stages. The first step involved the reaction of 3,4-dihydroxybenzaldehyde with sodium hydride in DMF solvent at room temperature for 15 minutes; in the second stage the reaction results in the first stage were further reacted with 3,3-dimethylalyl bromide and the ongoing reaction was monitored by TLC, the reaction results were then added with cold distilled water (30 mL), and extracted with dichloromethane (3x10 mL). The obtained organic phase was combined, washed with distilled water (15 mL), dried with anhydrous magnesium sulfate, and evaporated at low pressure to obtain a clear liquid of 0.22 grams. The subsequent synthesis was purified using gravity column chromatography with silica gel GF 60 and the mobile phase of *n*-hexane: ethyl acetate (9:1) The chromatography column gravity results obtained 27 fractions, fractions 14-25 which showed a single stain then combined, evaporated at low pressure, and tested for purity by TLC.

Identification of the structure of the pure synthesized compound with an NMR spectrometer given a ^{1}H NMR spectrum. The ^{1}H NMR spectrum showed six signals from upfield to downfield with an integration ratio of 6:6:4:2:1:2:1. The prenyl group gave four signals as follows: two singlet signals with a 6: 6 integration in the chemical shift (δ) 1.73 and 1.76 ppm were signals from the protons of the two methyl groups; doublet signal doublet with integration 4 at 64 4.64 (J

= 17.4; 6.2 Hz) ppm is the signal of the protons of the two methylene groups, and the multiplex signal with integration 2 at δ 5.47-5.49 ppm is a signal from two protons of a metin group. A doublet signal with integration 1 at δ 6.94 (d, J = 8 Hz) ppm is a signal from one aromatic proton, a multiplex signal with integration 2 at δ 7.38-7.41 ppm was a signal of two aromatic protons, and singlet signals with integration 1 at δ 9.80 ppm were signals from protons of formal groups.

The reactions of 3,4-dihydroxybenzaldehyde (0.156 grams; 1.128 mmol), 3,3-dimethylalyl bromide (0.800 mL; 6.911 mmol), sodium hydride (0.372 gram; 15.506 mmol) in DMF solvents at room temperature resulting in 3,4-bis(3-methylbut-2-en-1-il)benzaldehyde (**8**) as much as 0.13 grams or with a yield of 45%. The reaction time required for 3,4-bis synthesis((3-methylbut-2-en-1-il)benzaldehyde (**8**) was 75 minutes, which was shorter than reported by Li et al. (2011) [7] which takes 24 hours. Li et al. (2011) [7] used potassium carbonate as the base, and acetone as solvents Hydride ions as a base react with two groups hydroxies of 3,4-dihydroxybenzaldehyde to form anions with better nucleophility, which then react with prenyl bromide through sub-reaction mechanisms nucleophilic substitutes to form 3,4-bis ((3-methylbut-2-en-1-il)benzaldehyde (**8**) with by-products in the form of hydrogen gas and sodium bromide.

B. Synthesis 3,4-bis((3-methylbut-2-en-1-il)oxy)phenyl)methanol (7)

Synthesis of 3,4-bis((3-methylbut-2-en-1-il)oxy)phenyl)methanol (7) was carried out by reducing the formyl group of 3,4-bis((3-methylbut-2-en-1-il)benzaldehyde (**8**) with sodium borohydride carried out in ethanol at room temperature The ongoing reaction was monitored by TLC. The TLC results showed that the reaction has been completed after the reaction has lasted for 15 minutes. The reduction results were then added with a 10% sodium hydroxide solution (10 mL), then extracted with dichloromethane (3x10 mL) The organic phase obtained was combined, washed with distilled water (30 mL), dried with anhydrous magnesium sulfate, and evaporated at low pressure to obtain the synthesis results in the form of yellow liquid as much as 0.041 grams.

The identification of the reduced structure with NMR spectrometers gives ^{1}H NMR spectrum. The ^{1}H NMR spectrum clearly showed that the singlet signal of the formal group at δ 9.81 ppm was not visible, this showed that the reduction was successful. The prenyl group gave four signals as follows: two singlet signals with 6: 6 integration at 1.73 and 1.79 ppm respectively were signals of the protons of two methyl groups; singlet signals with integration 6 at δ 4.95 ppm were signals from protons of two methylene groups (including methylene protons from hydroxymethyl groups), and multiplet signals with integration 2 at δ 5.46-5.48 ppm were signals from two protons of a metin group. Multiplet signal with integration 3 at pada 6,82-6,94 ppm was a signal of three aromatic protons.

Reduction of 3,4-bis((3-methylbut-2-en-1-il) enzaldehyde (**8**) (0.054 gram; 0.196 mmol) with sodium borohydride (0.034 gram; 0.898 mmol) in ethanol (10 mL) at room temperature 3.4-bis((3-methylbut-2-en-1-il)oxy)phenyl)methanol (**7**) of 0.041 grams or with a yield of 77%. The reduction mechanism of 3,4-bis((3-methylbut-2-en-1-il)benzaldehyde (8) was suggested to proceed as the reduction of aldehyde groups in general [8].

C. Synthesis of 1,2-bis((3-methylbut-2-en-1-il)oxy)-4 -((3-methylbut-2-en-1-il)oxy)methyl)benzene (6)

Synthesis of 1,2-bis((3-methylbut-2-en-1-il)oxy)-4-((3-methylbut-2-en-1-il) oxy)methyl)benzene (**6**) was carried out in two steps. The first step involved the reaction of 3,4-bis((3-methylbut-2-en-1-il)oxy)phenyl)methanol (**7**) with sodium hydride in the DMF solvent at room temperature for 15 minutes. The results of the reaction in the first step were further reacted with 3,3-dimethylalyl bromide (second step). The reactions that take place in the second stage were monitored by TLC. The results of monitoring the reactions that took place at minutes 15, 30, and 60 there were no significant changes; the reaction product was then added with cold distilled water (20 mL) and extracted with dichloromethane (3x10 mL). The organic phase obtained was combined, washed with distilled water (15 mL), dried with anhydrous magnesium sulfate, and evaporated at low pressure so that a clear liquid of 0.043 gram is obtained.

The synthesized product was further purified by gravity column chromatography with silica gel GF stationary phase and *n*-hexane: ethyl acetate (10:1) mobile phase. Fractions 25-31 which showed a single stain were then combined, evaporated at low pressure, and tested for purity by TLC. Analysis of the results of the reaction by gas chromatography mass spectrometers showed a major peak with a retention time of 32.836 minutes. The spectrum showed the peak of the molecular ion at *m/z* 344.2 which corresponds to the relative mass of 1,2-bis((3-methylbut-2-en-1-il)oxy)-4-((3-methylbut-2-en -1-il)oxy)metl)-benzene (6). The compound molecule ion (6) released successive isoprene molecules so that fragments with peaks at *m/z* 276, 208, and 140 are produced. Fragments with peaks at *m/z* 208 then release 3-methyl-2-butenal molecules resulting in fragments with a peak at *m/z* 124 (base peak). Release of hydrogen gas from a fragment with a peak at *m/z* 140 produced fragments with a peak at *m/z* 138. Molecular ion compounds (**6**) also undergo fragmentation to form prenyl cations with peaks at *m/z* 69 which subsequently release etuna and hydrogen to form cations with peaks at *m/z* 43 and 41.

Further identification of the structure of the synthesized compound with an NMR spectrometer gives a ^{1}H NMR spectrum. The ^{1}H NMR spectrum showed ten signals from the upfield to downfield in a ratio of 3:3:3:6:3:2:2:4:1:3. The prenil group gave six signals as follows: five singlet signals with 3:3:3:6:3 integration on chemical shift (δ) 1.65; 1.71; 1.72; 1.75 and 1.76 ppm respectively are signals from the protons of the methyl group; two doublet signals with 2: 4 integration at δ 3.97 (J = 6.8 Hz) and 4.58 (J = 6.8 Hz) ppm respectively were signals of two and four protons from the methylene group coupled with the methane proton ; and two triplet signals with 1:2 integration at δ 5.39 (J = 1.2 Hz) and 5.50 (J = 6.4 Hz) ppm respectively were signals of one and two protons from the proton-coupled metin group -proton

methylene group. The ^{1}H NMR spectrum also showed a singlet signal with integration 2 at 42 4.42 ppm which was a signal of two protons from the methylene benzyl group; and multiplet signals with the integration of 3 δ 6.83-6.91 ppm were signals of three aromatic protons.

This identification was strengthened by the ^{13}C NMR spectrum of 1,2-bis((3-methylbut-2-en-1-il)oxy)-4-((3-methylbut-2-en-1-il)oxy)methyl)benzene (**6**), which showed 21 signals. Signals at δ 18.17; 18.33; 25,90; 25.93 ppm was a signal of carbon-metal metal groups of three prenyl groups. The carbons of the methylene group give signals at 94 65.94; 66.14; 66.34; and 72.11 ppm. Signals at δ 120.33; 120.46; and 120.58 ppm were the signals of three methane carbons from three prenyl groups; and signals at δ 137.11; 137.23, and 137.27 ppm were quaternary carbon signals from three prenyl groups. Aromatic carbons gave signals at δ 113.70; 113.74; 121.21; 131.27; 148.32; and 148.94 ppm.

The reaction of 3,4-bis((3-methylbut-2-en-1-il)oxy)phenyl)methanol (**7**) (0.041 gram; 0.148 mmol), 3.3-dimethylalyl bromide (0.030 mL; 0.255 mmol), and sodium hydride (0.022 gram; 0.917 mmol) obtained 1,2-bis((3-methylbut-2-en-1-il)oxy)-4-((3-methylbut-2-en-1-il)oxy)methyl)-benzene (**6**) 0.013 grams or with a yield of 26%. The hydride ion as a base reacts with a hydroxy group of 3,4-bis ((3-methylbut-2-en-1-il) oxy) phenyl) methanol (**7**) to form anions with better nucleophility, which then reacts with prenyl bromide through the nucleophilic substitution reaction mechanism to form 1,2-bis((3-methylbut-2-en-1-il)oxy)-4((3-methylbut-2-en-1-il)oxy)methyl)-benzene (**6**) with the byproducts in the form of hydrogen gas and sodium bromide.

IV. CONLUSION

The reaction of 3,4-dihydroxybenzaldehyde, 3,3-dimethylalyl bromide, sodium hydride in DMF solvent at room temperature resulted in 3,4-bis((3-methylbut-2-en-1-il)benzaldehyde (8) with a yield of 45% The reduction of 3,4-bis((3-methylbut-2-en-1-il)benzaldehyde (**8**) with sodium borohydride in ethanol at room temperature obtained 3,4-bis((3-methylbut-2-en-1-il)oxy)phenyl)methanol (**7**) with 77% yield 3,4-bis((3-methylbut-2-en-1-il)oxy)phenyl)methanol (**7**), 3,3-dimethylalyl bromide, and sodium hydride obtained 1,2-bis((3-methylbut-2-en-1-yl)oxy)-4-((3-methylbut-2-en-1-yl) oxy)methyl)-benzene (**6**) with a yield of 26%.

V. ACKNOWLEDGMENT

The authors thank to the Laboratory of Natural Product and Synthesis Chemistry, Department of Chemistry, Faculty of Science, Institut Teknologi Sepuluh Nopember.

REFERENCES

[1] P. E. Grimes, "Management of Hyperpigmentation in Darker Racial Ethnic Groups," *Seminars in Cutaneous Medicine and Surgery*, vol. 28, no. 2. Semin Cutan Med Surg, pp. 77–85, Jun-2009.
[2] K. Ishida and E. Tamai, "Melanogenesis inhibitor and skin preparation containing the same," US7576125B2, 12-Feb-2009.
[3] E. T. Arung, K. Shimizu, and R. Kondo, "Structure–Activity Relationship of Prenyl-Substituted Polyphenols fromArtocarpus heterophyllus as Inhibitors of Melanin Biosynthesis in Cultured Melanoma Cells," *Chemistry & Biodiversity*, vol. 4, no. 9, pp. 2166–2171, Sep. 2007.
[4] A. Braga, C. Guerreiro, and I. Belo, "Generation of Flavors and Fragrances Through Biotransformation and De Novo Synthesis," *Food and Bioprocess Technology*, vol. 11, no. 12, pp. 2217–2228, Dec. 2018.
[5] W. H. Miles and K. B. Connell, "Synthesis of Methyl Diantilis, a commercially important fragrance," *Journal of Chemical Education*, vol. 83, no. 2, pp. 285–286, Feb. 2006.
[6] M. Santoso, K. Somphol, N. Kumar, and D. S. C. Black, "Synthesis of indolocyclotriveratrylenes," *Tetrahedron*, vol. 65, no. 31, pp. 5977–5983, Aug. 2009.
[7] J. Li *et al.*, "Studies on synthesis and structure-activity relationship (SAR) of derivatives of a new natural product from marine fungi as inhibitors of influenza virus neuraminidase," *Marine Drugs*, vol. 9, no. 10, pp. 1887–1901, 2011.
[8] F. A. Carey, *Organic Chemistry, 4th Edition,*. Virginia, 2000.