

## SYNTHESIS OF TETRAHYDROHEXAGAMAVUNON-5 AND TETRAHYDROHEXAGAMAVUNON-7

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### ABSTRACT

Synthesis of Tetrahydrohexagamavunon-5 (THHGV-5) and Tetrahydrohexagamavunone-7 (THHGV-7) were prepared by catalytic hydrogenation reaction on Hexagamavunon-5 (HGV-5) and Hexagamavunone-7 (HGV-7) by using gas H<sub>2</sub> as source of hydrogen gas, Pd/C 10 % as metal catalyst and methanol as solvent at room temperature. According to previous study, Pd/C catalyst is more specific than other metal catalyst to reduce  $\alpha,\beta$ -unsaturated double bond without reduction of its carbonyl functional group. The products were characterized by IR Spectroscopy, Gas Chromatography-Mass Spectroscopy (GCMS), 1D-NMR (<sup>1</sup>H-NMR and <sup>13</sup>C-NMR) and 2D-NMR (<sup>1</sup>H-<sup>13</sup>C HMQC) Spectroscopy to determine the product structure molecules. According to the data of IR, GC-MS, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR and <sup>1</sup>H-<sup>13</sup>C HMQC spectra, the products are THHGV-5 and THHGV-7 as white crystalline powders.

**Key words:** Tetrahydrohexagamavunon-5, Tetrahydrohexagamavunone-7, Hexagamavunon-5, Hexagamavunone-7

### INTRODUCTION

Tetrahydrocurcumin (THC) is a main metabolite of curcumin. THC has a better antioxidant activity than curcumin itself (Sugiyama, *et al.*, 1996) and its mechanism has been described by Yoysungnoen *et al.* (2008). THC also has some biological activities apart from antioxidant such as antidiabetic and antihyperlipidemia on diabetic mouse (Murugan and Pari, 2007), and anticancer with antiangiogenic mechanism (Yoysungneon *et al.*, 2008). THC itself is normally isolated with curcumin from turmeric extracts of curcuminoids. THC is easier absorbed in gastrointestinal than curcumin (Okada *et al.*, 2001) and showed that THC is more stable than curcumin in physiological buffer pH 7.2 and blood plasma.

In our previous publication, there are almost fifty analogs curcumin that successfully been made (Sardjiman *et al.*, 1997; Sardjiman *et al.*, 2003; Sardjiman *et al.*, 2004). These analogs have many different biological activities. Some of the analogs that we focus on are PGV-0, Hexagamavunone-5 (HGV-5) and Hexagamavunone-7 (HGV-7). PGV-0 is a promising anti-inflammatory agent, HGV-5 has a potent antioxidant activity and HGV-7 is

more potent as antibacterial agent against *S. pneumonia* than PGV-0 and curcumin (Sardjiman, 2000).

Some analogs of THC such as Tetrahydropentagamavunone-0 (THPGV-0) and Tetrahydropentagamavunone-1 (THPGV-1) have been also successfully synthesized in Curcumin Research Center, Faculty of Pharmacy, Gadjah Mada University, Yogyakarta, Indonesia (Ritmaleni and Simbara, 2010; Ritmaleni, *et al.*, 2013). Its biological activities also have been investigated (Ritmaleni *et al.*, 2013). THPGV-0 is made from PGV-0 and showed better antioxidant activity compared to PGV-0 and vitamin E. According to this, THHGV-5 and THHGV-7 might have biological activities better than HGV-5 and HGV-7. This research is aimed to synthesized Hexagamavunone-5 (HGV-5) and Hexagamavunone-7 (HGV-7).

### MATERIAL AND METHODS

HGV-5 and HGV-7 (Curcumin Research Center, Faculty of Pharmacy UGM), Pd/C 10% (Aldrich), hydrogen gas (H<sub>2</sub>) (Samator, Yogyakarta), methanol (p.a., Merck), *n*-hexane (p.a., Merck), dichloromethane (p.a., Merck), ethyl acetate (p.a., Merck).

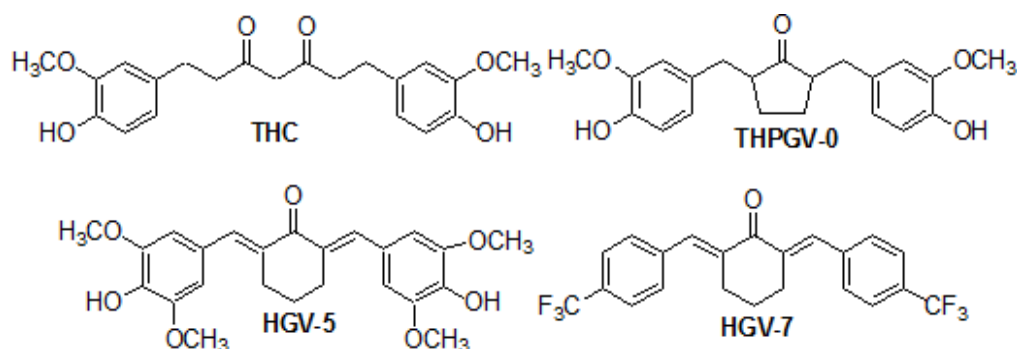


Figure 1. Chemical Structure of THC, THPGV-0, HGV-5 and HGV-7

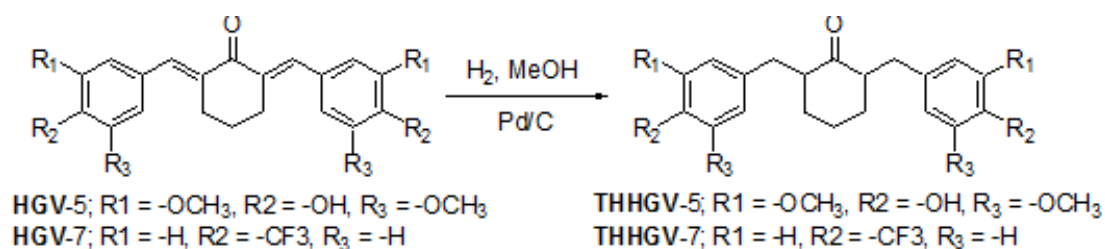


Figure 2. Hydrogenation Reaction of HGV-5 and HGV-7 to be THHGV-5 and THHGV-7

### General procedure

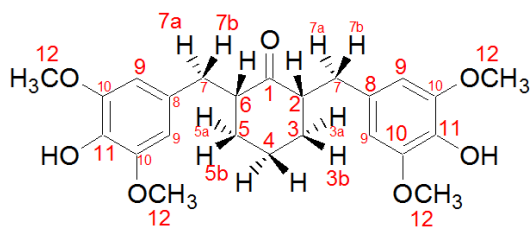
This synthesis was done based on the published method (Ritmaleni and Simbara, 2010). In round bottom flask, HGV-5 or HGV-7 in 5.0mL methanol *p.a* was added Palladium/Carbon (Pd/C) 10% (10 mole %). Hydrogen gas (H<sub>2</sub>) in balloon was blown for three hours into the reaction mixture. The reaction was an auto indicator reaction; the color of reaction mixture is changing from yellow to colourless. Then, the mixture was filtered and the solvent was evaporated by using rotavapor. The products were isolated by Flash Column Chromatography and purified by recrystallization method. The structure elucidation of the targeted product was carried out by using Spectroscopy method (IR, GC-MS, 1D-NMR (<sup>1</sup>H-NMR and <sup>13</sup>C-NMR) and 2D-NMR (<sup>1</sup>H-<sup>13</sup>C HMQC)).

### Synthesis of THHGV-5 [TRIVIAL]; 2,6-bis-(4'-Hydroxy-3',5'-dimethoxybenzil)-cyclohexanon [IUPAC]

HGV-5 (250mg; 0.46mmol) in MeOH (5mL), Pd/C 10% (49.72mg; 0.46mmol), isolated by flash column chromatography

(Chloroform : Ethyl acetate (5:1), recrystallized from ethanol : water (EtOH : H<sub>2</sub>O = 2:1 v/v), THHGV-5 as white crystalline powder; yielded 23% of THHGV-5; *R<sub>f</sub>* = 0.60 (kloroform : etil asetat (5:1 v/v)); mp = 139.1 – 139.8°C (EtOH : H<sub>2</sub>O = 2:1 v/v); IR(*v<sub>maks</sub>*, cm<sup>-1</sup>, KBr), 3410.63 (OH, *bonded*); 2935.25 (C-H, *stretching*, aliphatis); 1704.33, (C=O, *stretching*); 1611.02 (C=C, *stretching*, aromatic); 1459.51 (C-H, *bending*, aromatis); 1114.87 (C-O, *stretching*, aromatic), Gas Chromatography (GC): *capillary column* with constantly flow gas; temperature of injection = 300°C; *split injection mode*; *column flow* 0.5 mL/minute; *gas pressure* 8.19 *psi*; time of retention (*t<sub>R</sub>*) 37.338min; MS (EI-MS, m/z): 430.2 [M<sup>+</sup>] (35%), 281 (15%), 207 (34%), 167 (100%), 122.9 (6%), 96 (6%), 73 (9%), dan 44 (8%). H-NMR (500 MHz, *ppm*, CDCl<sub>3</sub>) : δ 6.37 (4H, *s*, H<sub>9</sub>-Ph x 4), δ 5.36 (2H, *s*, -OH x 2), δ 3.85 (4H, *s*, -OCH<sub>3</sub> x 4), δ 3.16 (2H, *dd*, H<sub>7a</sub>, J = 5.2; J = 14.3), δ 2.53 (2H, *dddd*, H<sub>2</sub> and H<sub>6</sub>, J = 5.2; J = 5.85; J = 13; J = 13 Hz), δ 2.33 (2H, *dd*, H<sub>7b</sub>, J = 5.85; J = 14.3 Hz) δ 2.10 (2H, *dddd*, H<sub>3a</sub> dan H<sub>5a</sub>, J = 2.6; J = 10.35; J = 13; J = 13.6 Hz), δ 1.81 (2H, *ddd*, H<sub>4</sub>, J = 2.6; J = 5.85; J =

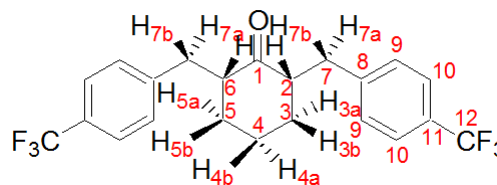
13.6 Hz),  $\delta$  1.35 (2H, *dddd*, H<sub>3b</sub> and H<sub>5b</sub>, J = 5.85; J = 13; J = 13; J = 13.6 Hz). C-NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  213.18 (C=O),  $\delta$  146.96 (C-10),  $\delta$  133.02 (C-8),  $\delta$  131.90 (C-11),  $\delta$  105.87 (C-9),  $\delta$  56.44 (C-12),  $\delta$  53.63 (C-2 and C-6),  $\delta$  35.90 (C-7),  $\delta$  35.44 (C-3 and C-5), and  $\delta$  25.59 (C-4).



### Synthesis of THHGV-7 [TRIVIAL]; 2,6-bis-(4'-trofluoromethylbenzil)-cyclohexanon [IUPAC]

HGV-7 (250 mg; 0.6098mmol) in MeOH (5mL), Pd/C 10% (64.883mg; 0.06098mmol), isolated by flash column chromatography (*n*-hexane:dichloromethane (C<sub>6</sub>H<sub>14</sub>: CH<sub>2</sub>Cl<sub>2</sub> = 5:3 v/v)), recrystallized from ethanol : water (EtOH : H<sub>2</sub>O = 2:1 v/v), THHGV-7 as white crystalline powder; yielded 19 % of THHGV-7; R<sub>f</sub> = 0.72 (*n*-C<sub>6</sub>H<sub>14</sub>: CH<sub>2</sub>Cl<sub>2</sub> = 5:3 v/v); mp = 161.3-162.1°C (EtOH : H<sub>2</sub>O = 2:1 v/v); IR ( $\nu_{\max}$ , cm<sup>-1</sup>, KBr): 3045.81 (C-H, *stretching*, aromatic); 2930.39 (C-H, *stretching*, aliphatic); 1695.53 (C=O, *stretching*); 1617.88 (C=C, *stretching*, aromatic); and 1326.19 (C-F); Gas Chromatography (GC): *capillary column* with constantly flow gas; temperature of injection = 300°C; *split injection mode*; *column flow* 0.5mL/min; *gas pressure* 8.19 *psi*; time of retention (*t<sub>R</sub>*) 23.004 minutes; MS (EI-MS, *m/z*): 414 [M<sup>+</sup>] (42%); 395.1 (25%); 255.1 (68%); 237.0 (38%); 185.0 (20%); 159.0 (100%); and 109.0 (22%). <sup>1</sup>H-NMR (500 MHz, *ppm*, CD<sub>3</sub>OD):  $\delta$  7.53 (4H, *d*, J = 7.8 Hz; H<sub>10</sub>-Ph x 4);  $\delta$  7.36 (4H, *d*, J = 7.8 Hz; H<sub>9</sub>-Ph x 4);  $\delta$  3.19 (2H, *dd*, J = 5.85 Hz and 14.25 Hz; H<sub>7a</sub>);  $\delta$  2.79 (2H, *ddd*, J = 5.85 Hz; J = 12.3 Hz and J = 18.15 Hz; H<sub>2</sub> and H<sub>6</sub>);  $\delta$  2.51 (2H, *dd*, J = 7.75 Hz and J = 14.25 Hz; H<sub>7b</sub>);  $\delta$  2.04 (2H, *m*, H<sub>3a</sub> and H<sub>5a</sub>);  $\delta$  1.81 – 1.78 (1H, *m*, H<sub>4a</sub>);  $\delta$  1.68 (1H, *dddd*, J = 3.85 Hz; J = 7.8 Hz; 12.95 Hz and 16.85 Hz; H<sub>4b</sub>);  $\delta$  1.35-1.39 (2H, *m*, H<sub>3b</sub> and H<sub>5b</sub>). <sup>13</sup>C-NMR (125 MHz, *ppm*, CD<sub>3</sub>OD):  $\delta$  213.96 (C=O);  $\delta$  146.82 (*s*, C-11);  $\delta$  130.92 (*s*, C-9);  $\delta$  129.7; 129.45; 129.19 and 128.9 (*q*, J<sub>C,F</sub> = 31.25 Hz and J<sub>C,F</sub> = 62.5 Hz, -

CF<sub>3</sub>);  $\delta$  126.13 (*d*, C-10);  $\delta$  126.10 (*d*, C-8);  $\delta$  53.62 (*s*, C-2 and C-6);  $\delta$  36.45 (*s*, C-7);  $\delta$  36.34 (*s*, C-3 and C-5);  $\delta$  26.30 (*s*, C-4).



### RESULT AND DISCUSSION

Tetrahydrohexagamavunone-5 (THHGV-5) and Tetrahydrohexagamavunone-7 (THHGV-7) were synthesized by using catalytic hydrogenation reaction on Hexagamavunone-5 (HGV-5) and Hexagamavunone-7 (HGV-7) subsequently. Both reactions were catalyzed by Palladium/Carbon (Pd/C) 10% as metal catalyst. Palladium/Carbon (Pd/C) 10% is usually used in this kind of reaction because this catalyst could make the hydrogenation be done at room temperature and certainly accelerate the rate of reaction. According to previous study, Pd/C catalyst is more specific than other metal catalyst to reduce  $\alpha,\beta$ -unsaturated double bond without reduction of its carbonyl functional group (Solomons, 1990).

The hydrogenation on HGV-5 and HGV-7 removed their chromophores (conjugation double bond) which appeared as yellow color and they were transformed into  $\alpha,\beta$ -unsaturated ketone which appeared as white color compounds, THHGV-5 (23%) and THHGV-7 (19%), respectively. Low yields were obtained due to the side products formation. In this kind of reactions, around four side products were present in the reaction mixture. This type of structure make the reduction possible not only on the  $\alpha,\beta$ -unsaturated ketone but also reduce the keton to alcohol and alkane (Ritmaleni *et al.*, 2013).

### Structure elucidation of THHGV-7 [TRIVIAL]; 2,6-bis-(4'-trofluoromethylbenzil)-cyclohexanon [IUPAC]

Hydrogenation means hydrogenation addition. On this reaction the hydrogen was added to the  $\alpha,\beta$ -unsaturated ketone only the double bond that received the hydrogen. According to the IR spectra, no peak indicated the double bond functional group of  $\alpha,\beta$ -

unsaturated ketone, only aliphatic C-H bond at 2935.2cm<sup>-1</sup> can be seen while the C=O bond of carbonyl functional group was still can be seen at 1704.3cm<sup>-1</sup>. On the H-NMR spectra, there is no alkene peak obtained, there are one peak appeared at 3.16ppm and one peak more appeared at 2.33ppm. These both are peaks of proton of alkane on benzyl functional group. Another proton that can indicate that addition of hydrogen has been successfully added to the double bond is the proton that appeared on 2.53 ppm as *doublet of doublet of doublet of doublet* and this is corresponding to proton on alpha position of cyclohexanone. Also no carbon alkene was found on the C-NMR spectra. And the other spectra have strongly recommended that the product is THHGV-5.

**Structure elucidation of THHGV-5 [TRIVIAL]; 2,6-bis-(4'-Hydroxy-3',5'-dimethoxybenzil)-cyclohexanone [IUPAC]**

Based on the data of GC chromatogram and MS spectra, the level of THHGV-7's purity is about 97.02 %. Furthermore, the structure of THHGV-7 was characterized by IR, 1D-NMR (<sup>1</sup>H-NMR, <sup>13</sup>C-NMR), and 2D-NMR (<sup>1</sup>H-<sup>13</sup>C HMQC) Spectroscopy.

THHGV-7 and HGV-7 only differ in  $\alpha,\beta$ -unsaturated carbonyl. IR spectra shown that no double bond of  $\alpha,\beta$ -unsaturated ketone was obtained but the C=O stretching is still there where a peak at 1695.53 was obtained. <sup>1</sup>H-NMR spectra of THHGV-7 showed a peak signal at 2.79 ppm (-CH- $\alpha$ -carbonil; methyne group), whereas it was undetected on HGV-7's. Furthermore, <sup>1</sup>H-NMR spectra of THHGV-7 showed the existence of -CH<sub>2</sub>- $\beta$ -carbonyl (methylene group) at 3.19 ppm (H<sub>7a</sub>); and 2.51 ppm (H<sub>7b</sub>). <sup>13</sup>C-NMR spectra showed chemical shift of -C- $\alpha,\beta$ -carbonyl on THHGV-7 (53.62 and 36.45 ppm). At last, analyzing THHGV-7 by <sup>1</sup>H-<sup>13</sup>C HMBC and HMQC Spectroscopy were carried out. These methods analyze the data correlation between atom H and atom C spectra of the product that coupling each other. According to that there were some data correlation between atom H and atom C, such as cross peak diagonal between atom H<sub>2</sub> at  $\delta$  2.79 ppm and atom C<sub>2</sub> at  $\delta$  53.62 ppm. These data strongly recommend that the product is THHGV-7.

## CONCLUSION

THHGV-5 and THHGV-7 can be synthesized by catalytic hydrogenation reaction on Hexagamavunone-5 (HGV-5) and Hexagamavunone-7 (HGV-7) respectively by using hydrogen gas as hydrogen source, Pd/C 10 % as metal catalyst and methanol as solvent at room temperature with 23 and 19 % yields.

## ACKNOWLEDGEMENT

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