

Identification of Side Products From The Hydrogenation Reaction of Bis(substitutedbenzylidene)cyclopentanone/- cyclohexanone by Using Palladium/Carbon Catalyst

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Abstract

Synthesis of some curcumin analogs which are categorised as bis(substitutedbenzylidene)cyclopentanone/cyclohexanone have been published and patented by Faculty of Pharmacy, Universitas Gadjah Mada, Indonesia, few years ago. One of the main identity of the curcumin analogs that discussed is the use of cyclopentanone and cyclohexanone on its synthesis instead of 1,3-diketone as on curcumin's. The tetrahydrocurcumin as metabolite of curcumin also has been successfully synthesised through the hydrogenation reaction of curcumin. This research was aimed to synthesise the tetrahydroform of bis(substituted-dibenzylidene)cyclopentanone/cyclohexanone (analog curcumins). Hydrogenation reaction was applied in this synthesis which carried out by using palladium on carbon as catalyst and hydrogen gas as source of hydrogen at room temperature for 2 – 3.5 hours and this reaction is an auto-indicator type reaction. The reaction gave not only the hydrogenation products which were found in moderate yield but also gave other three side products. All their structures have been characterised by spectroscopic method and the side products are in alkane and alcohol form of the cyclopentane ring.

Keywords: hydrogenation, bis(substitutedbenzylidene)cyclopentanone/cyclohexanone, bis-(substitutedbenzyl)cyclopentanone/cyclohexanone, side product

1. Introduction

Faculty of Pharmacy, Gadjah Mada University has published and patented some of curcumin analogs which have good biological activities. Sardjiman has been successfully synthesised the PGV-0 and investigated its biological activity especially as antioxidant, antibacterial, antifungi agents and their activity as lipid peroxide inhibition (LPO). (Sardjiman et al., 2000; Sardjiman et al., 2004; Sardjiman et al., 2003; Sardjiman et al., 1998; Sardjiman et al., 1997) While the tetrahydroform of PGV-0 has also been successfully synthesised and named as THPGV-0. (Ritmaleni and Simbara, 2010) The biologically activities of THPGV-0 has also been evaluated and prepared for submitting in another paper. In the previous of our publication, we reported the effect of using $AlCl_3$, $ZnCl_2$ and $FeCl_3$ in the hydrogenation process of Pentagamavunon-0. (Ritmaleni et al., 2013) Hydrogenation by using hydrogen gas and palladium on carbon as catalyst is a wellknown method to reduce the double bond in molecules into single bond. This research was aimed to synthesis the bis(substitutedbenzyl)cyclopentanone and cyclohexanone compounds from bis(substitutedbenzylidene)-cyclopentanone and cyclohexanone by using hydrogenation reaction.

Pentagamavunon-0 (PGV-0) is a famous molecule in Indonesia and was reported as antiinflammatory and anticancer agent. (Meiyanto et al., 2008; Septisetyani et al., 2008) Beside PGV-0, HGV-0 is also famous and synthesised in Indonesia. The different between PGV-0 and HGV-0 is the type of its center ring, where PGV-0 has five membered ring while HGV-0 have six membered ring like figure 1 below.

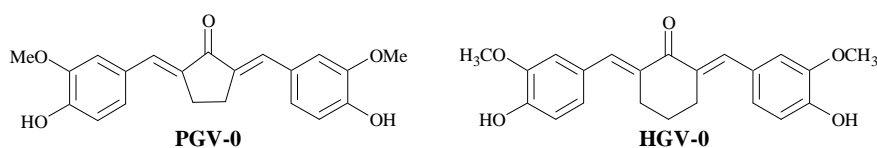


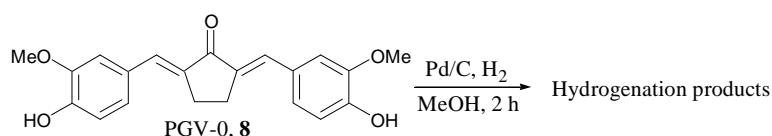
Figure 1. Structure of PGV-0 and HGV-0

The hydrogenation were not done yet on HGV-0 but A4, A6 and A9 have been hydrogentaed. All of these molecules have a six membered ring as the center ring.

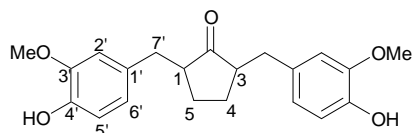
2. Experiment

To round bottom flask, bis(substitutedbenzyl)cyclopentanone or cyclohexanone in suitable solvents was hydrogenated by hydrogen gas in baloon over Pd/C as catalyst at room temperature for 2-3.5 hours. The reaction is autoindicator reaction (change colour form yellow to colourless). The reaction mixture then was filtered and the solvent was evaporated by using rotavapor. The tetrahydroform of bis(substitutedbenzyl)cyclopentanone/cyclohexanone was recrystallised. Structure elucidation was carried out by spectroscopic method (IR, H-NMR, C-NMR, MS). For the reaction set up, please see figure 2.

2.1 Hydrogenation of PGV-0

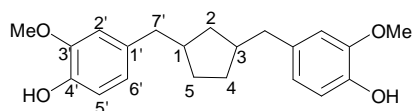


Tetrahydropentagamavunon-0 (THPGV-0), **13**



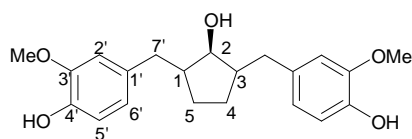
White crystals 40 %, m.p. = 122 – 123 °C (EtOH : H₂O = 2 : 1), R_f = 0.56 (CHCl₃ : EtOAc), ¹H-NMR (500 MHz, ppm, acetone): δ 7.52 (2H, *s*, -OH x 2); δ 6.75 (2H, *d*, J= 1.8 Hz, H2'-Ph x 2); δ 6.70 (2H, *m*, H5'-Ph x 2); δ 6.58 (2H, *m*, H6'-Ph x 2); δ 3.76 and 3.78 (6H, *s*, -OCH₃ x 2); δ 2.97 and 2.85 (2H, *dd*, J= 4.25 and J=13.45 Hz, H7'-a) [lit. (Ritmaleni and Simbara, 2010; δ 2.97 and 2.85 (2H, *dd*, J= 4.25 and J=13.45 Hz, H7'-a) δ 2.97 and 2.85 (2H, *dd*, J= 4.25 and J=13.45 Hz, H7'-a); δ 2.35 and 2,46 (2H, *dd*, J= 9.15 and J=13.45 Hz, H7'-b); δ 2.26 (2H, *dddd*, J= 4.30, J= 7.95, J= 9.15 and J=11.65, H2&5); δ 1.89 and 1.80 (2H, *dddd*, J=3.05, J= 5.50, J= 7.95 and 9.15 Hz, H3&4a); δ 1.39 and 1,55 (2H, *dddd*, J=3.05, J= 5.5, J= 9.15 and J= 11.60 Hz, H3&4b).

2.1.1 Side product 1 of THPGV-0, 1,3-bis-(4'-hydroxy-3'-methoxybenzyl)cyclopentane, **18**



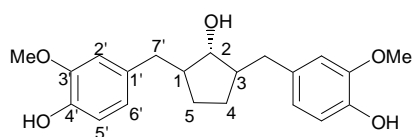
White crystals 3.7 %, m.p. = 106 – 108 °C (EtOH : H₂O = 2 : 1), R_f = 0.75 (CHCl₃ : EtOAc), IR (ν_{max}, cm⁻¹, KBr): 2939.5 and 2850.3 (C-H, *stretching*, aliphatic); 1440.9 (CH₂, *bending*); 798.2 (C-H, *bending*) ¹H-NMR (500 MHz, ppm, CDCl₃): δ 6.81 (2H, *dd* J = 1.95 Hz, J = 8.4 Hz, H6'-Ph x 2); δ 6.65 (2H, *d* J = 1.95 Hz, H5'-Ph x 2); δ 6.64 (2H, *d* J = 8.4 Hz, H2'-Ph x 2); δ 5.45 (2H, *s*, -OH x 2); δ 4.12(1H, *dd* J = 14.24 Hz, J = 7.15 Hz, H7'-a); δ 3.86 (6H, *s*, -OCH₃ x 2); δ 2.51 (1H, *dd*, J= 7.15 Hz, J = 2.6 Hz, H7'-b); δ 2.20 (1H, *dd* J = 14.25 Hz, J = 7.15 Hz, H7'-d); δ 2.09 - 2.06(1H, *m*, H7'-c); δ 1.84 - 1.81(1H, *m*, H5-a), δ 1.79 - 1.77 (1H, *m*, H4-b); δ 1.72 - 1.67 (1H, *m*, H2-a); δ 1.44 - 1.41 (1H, *m*, H3); δ 1.33-1.28 (1H, *m*, H4-a); δ 1.27 - 1.24 (1H, *m*, H1); δ 1.22 - 1.19 (1H, *m*, H5); δ 0.91- 0.83 (1H, *m*, H2), ¹³C-NMR (125 MHz, ppm, CDCl₃): δ 146.39 (*s*); δ 143.71 (*s*); δ 134.34 (*s*); δ 121.50 (*d*); 121.45 (*d*); δ 114.18 (*d*); δ 111.52 and 111.45 (*d*); δ 56.03 (*q*); δ 42.48 (*d*) 42.18 (*d*); δ 40.80 (*t*); 40.35 (*t*); δ 38.16 (*t*); 32.58 (*t*); 31.40 (*t*): MS (EI-MS, m/z) C₂₁H₂₆O₄ : 342 (18), 137 (100), 122 (10), 77 (4)

2.1.2 Side product 2 of THPGV-0, 1,3-bis-(4'-hydroxy-3'-methoxybenzyl)cyclopentanol, **20**



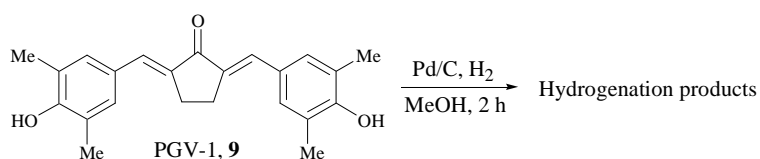
Colourless oil, 10.9 %, Rf = 0.33 (CHCl₃ : EtOAc), IR (ν_{max}, cm⁻¹, KBr): 3422.5 (O-H); 2940.9 (C-H, *stretching*, aliphatic); 1452.0 (CH₂, *bending*), ¹H-NMR (500 MHz, ppm, CDCl₃): δ 6.80 (2H, d, J = 7.75 Hz, H2'-Ph x 2); δ 6.70 (2H, dd, J = 7.75 Hz, J = 1.25, H6'-Ph x2); δ 6.67 (2H, d, J = 1.25 Hz, H5'-Ph x 2); δ 5.55 (2H, s, -OH-Ph x 2); δ 3.84 (6H, s, 2 x -OCH₃); δ 3.79 (1H, m, -OH); δ 2.75 (2H, dd, J = 13.6 Hz, J = 7.15 Hz, H7'-a and H7'-b); δ 2.59 (2H, dd J = 13.6 Hz, J = 7.15 Hz, H7'-c and H7'-d); δ 2.08 - 2.11 (2H, m, H4-a and H4-b); δ 1.73 - 1.77 (2H, m, H2 and H5); δ 1.53 - 1.56 (2H, m, H3-a and H3-b), ¹³C-NMR (125 MHz, ppm, CDCl₃) : δ 146.51 (s); δ 143.77 (s); δ 133.78 (s); δ 121.28 (d); δ 114.36 (d); δ 111.47 (d); δ 75.25 (d); δ 56.01 (q); δ 47.59 (t); δ 35.98 (t); δ 28.28 (t), MS (EI-MS, m/z) C₂₁H₂₆O₅ : 358 (40), 137 (100), 122 (13), 79 (18)

2.1.3 Side product 3 of THPGV-0, 1,3-bis-(4'-hydroxy-3'-methoxybenzyl)cyclopentanol, 22

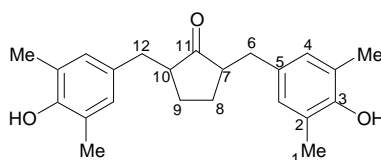


Colourless oil, 29.3 %, Rf = 0.23 (CHCl₃ : EtOAc), IR (ν_{max}, cm⁻¹, KBr): 2938.8 (C-H, *stretching*, aliphatic); 1430.5 (CH₂, *bending*); 795.2 (C-H, *bending*), ¹H-NMR (500 MHz, ppm, CDCl₃): δ 6.81 (2H, d J = 7.8 Hz, 2 x H2'-Ph); δ 6.70 (2H, d J = 1.95 Hz, 2 x H5'-Ph); δ 6.67 (2H, dd J = 7.8, J = 1.95 Hz, 2 x H6'-Ph); δ 5.49 (2H, s, 2 x -OH); δ 4.12 (1H, dd J = 14.25 Hz, J = 7.15 Hz, H7'-b); δ 3.85 (6H, m, 2 x -OCH₃); δ 2.76 - 2.82 (1H, m, H7'-a); δ 2.61 - 2.65 (1H, m, H7'-c); δ 2.43 - 2.56 (2H, m, H2 and H5); δ 2.12-2.18 (1H, m, H7'-d); δ 1.88-1.94 (1H, m, H3-a); δ 1.67 - 1.75 (1H, m, H3-b); δ 1.46 - 1.52 (1,25 (1H, m, H4-b); δ 1.19 - 1.23 (1H, m, H4-a), ¹³C-NMR (125 MHz, ppm, CDCl₃): δ 146.56 (s); δ 143.95 (s); 143.83 (s); δ 133.78 (s); 133.08 (s); δ 121.55 (s); 121.35 (d); δ 114.38 (d); 114.33 (d); δ 111.50 (d); 111.45 (d); δ 60.59 (d); δ 56.06 (q); 56.01 (q); δ 49.86 (d); 48.99 (d); δ 35.07 (t); δ 29.08 (t); 29.22 (t), MS (EI-MS, m/z) C₂₁H₂₆O₅ : 358 (40), 137 (100), 122 (13), 79 (18)

2.2 Hydrogenation of PGV-1



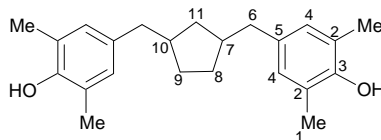
Tetrahydropentagamavunon-1, THPGV-1, 9



PGV-1 (250 mg; 0.718 mmol) in MeOH (3 mL), Pd/C (10 mol %; 76 mg), yield **THPGV-1, 9** as a white crystal product : 18 %, m.p. = 133-135 °C (ethanol: H₂O = 2:1), Rf = 0.40 (CHCl₃:EtOAc = 20:1), IR (ν_{max}, cm⁻¹, KBr): 1723 (C=O), 2915 (C-H), 1442 (C-H), ¹H-NMR (500 MHz, ppm, CDCl₃): δ 6.76 (4H, s, 4 x H4-Ph); 4.60 (2H, s, 2 x -OH); 3.04 (1H, dd J = 3.90 and J = 13.65 Hz, H6a); 2.92 (1H, dd J = 3.90 and J = 13.60 Hz, H12); 2.47 (1H, dd J = 9.10 and J = 14.25 Hz, H6b); 2.52 - 2.41 (1H, m, H7); 2.32 (1H, dd J = 9.70 and J = 13.60 Hz, H12); 2.25 - 2.20 (1H, m, H10); 2.21 (12H, s, 4 x H1); 2.04 - 1.94 (1H, m, H9a); 1.87 (1H, dddd J = 18.03, J = 12.10, J = 8.50, J = 4.50 Hz, H8a); 1.58 (1H, dddd J = 18.03, J = 12.90, J = 8.50, J = 4.50 Hz, H8b); 1.45 - 1.34 (1H, m,

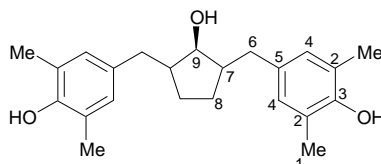
H9b), $^{13}\text{C-NMR}$ (125 MHz, ppm, CDCl_3): δ 220.2 (q), 150.7 (q), 150.69 (q); 131.57 (q) 131.53 (q); 129.24 (q) 129.19 (q); 123.07 (d); 51.92 (d); 50.71 (d); 35.26 (t); 35.11 (t); 27.27 (t); 26.06 (t); 16.10 (q), MS (EI-MS, m/z); 352,2 (40); 217.1 (20); 135,1(100); 161.1 (5); 55.1 (3)

2.2.1 Side Product of THPGV-1, 1,3-bis-(4'-hydroxy-3',5'-dimethylbenzyl)cyclopentane, **19**



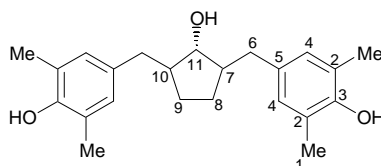
Side Product of THPGV-1 as a white crystal product : 30 %; $R_f = 0.49$ (CHCl_3 :EtOAc = 20:1); m.p. = 146 – 148 °C (ethanol: $\text{H}_2\text{O} = 2:1$), IR (vmaks, cm^{-1} , KBr): 2917 and 1383 (C-H), $^1\text{H-NMR}$ (500 MHz, ppm, CDCl_3): δ 6.76 (4H, s, 2 x H4-Ph); 4.43 (2H, s, 2 x -OH); 2.48 (2H, dd, $J=13.3$ Hz; 7.4 Hz, 2 x H-6a); 2.44 (2H, dd, $J= 13.3$ Hz, 9.7 Hz; 2 x H-6b); 2.21 (12H, s, 2x H1a-Ph); 2.00 – 2.13 (1H, m, H7); 1.81 – 1.88 (1H, m, H10); 1.73 – 1.81 (1H, m, H9a); 1.64 – 1.73 (1H, m, H8a); 1.43 – 1.40 (1H, m, H11); 1.24 – 1.34 (1H, m, H8b); 1.14 - 1.25 (1H, m, H9b); 0.79 – 0.91 (1H, m, H11b), $^{13}\text{C-NMR}$ (125 MHz, ppm, CDCl_3): δ 150.22 (s); 134.08 (s);134.04 (s); 129.07 (d); 128.99 (d); 122.72 (d); 42.51 (d); 41.95 (t); 41.8 (t); 40.72 (d); 38.29 (t); 32.59 (t); 31.45 (t); 16.12(q), MS (EI-MS, m/z) $\text{C}_{23}\text{H}_{30}\text{O}_2$; 338 (18); 203 (6); 135 (100); 121 (6); 105 (6)

2.2.2 Side Product of THPGV-1, 2,5-bis-(4'-hydroxy-3',5'-dimethyl)benzyl)cyclopentanol, **21**



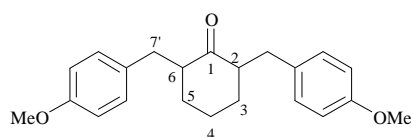
Side Product of THPGV-1 as a white crystal product : 7 %, m.p. = 159 – 160 °C (ethanol: $\text{H}_2\text{O} = 2:1$), $R_f = 0.24$ (CHCl_3 :EtOAc = 20:1), IR (vmaks, cm^{-1} , KBr): 2944 and 1382 (C-H); $^1\text{H-NMR}$ (500 MHz, ppm, acetone- d_6): δ 6.92 (2H, s, 2 x H3-Ph); 6.78 (4H, s, 2 x H4-Ph); 3.72 – 3.74 (1H, m, H9a); 3.31-3.30 (2H, d $J= 5.2$, 2 x -OH); 2.46 - 2.42 (2H, dd $J=13.6$, 7.4, 2 x H6c,d); 2.74 - 2.69 (2H, dd $J= 13.6$, 7.8, 2 x H6a,b); 2.15 (12H, s, 2 x H1-Ph); 2.02-1.99 (2H, m, H7); 1.50 – 1.49 (2H, dddd $J= 1.95$, 6.45, 10.35, 2 x H8a,b); 1.62 (2H, dddd $J= 1.95$, 5.85, 7.8, 13.6, 2 x H8c,d), $^{13}\text{C-NMR}$ (125 MHz, ppm, CDCl_3): δ 151.95 (s); 133.99 (s); 129.53 (s); 124.25 (d); 74.87 (d); 48.95 (d); 36.14 (t); 28.92 (t); 16.70 (t), MS (EI-MS, m/z) $\text{C}_{23}\text{H}_{29}\text{O}_3$; 354 (28); 336 (6); 201 (34); 185 (6); 135 (100); 121 (6); 105 (6)

2.2.3 Side Product of THPGV-1, 2,5-bis-(4'-hydroxy-3',5'-dimetil)benzyl)cyclopentanol, **23**



Side Product of THPGV-1 as a white crystal product : 15 %, m.p. = 152 – 154 °C (ethanol: $\text{H}_2\text{O} = 2:1$), $R_f = 0.18$ (CHCl_3 :EtOAc = 20:1), IR (vmaks, cm^{-1} , KBr): 2917 and 1382 (C-H); $^1\text{H-NMR}$ (500 MHz, ppm, acetone- d_6): δ 6.98 (2H, s, 2 x H3-Ph); 6.78 (4H, s, 2 x H4a-Ph); 6.73 (4H, s, 2 x H4b-Ph); 3.79 – 3.73 (2H, d $J= 8.45$, 2 x H11); 3.42 - 3.41 (2H, d $J= 6.45$; 2 x -OH); 2.81 - 2.77 (2H, dd $J=13.6$, 6.45, 2 x H8a); 2.60 - 2.56 (2H, dd $J=12.95$, 6.5, 2 x H6a); 2.40 - 2.35 (2H, dd $J=13.6$, 9.5, 2 x H8b); 2.32 - 2.20 (4H, m, 2 x H6b); 2.18 - 2.17 (4H, s, 2 x H1); 2.12 – 2.15 (4H, m, 2 x H10); 2.13 - 2.08 (4H, m, 2 x H7); 1.86 - 1.77 (2H, m, 2 x H9b); 1.18 - 1.15 (2H, m, 2 x H9a), $^{13}\text{C-NMR}$ (125 MHz, ppm, CDCl_3): δ 152.12 (s); 151.96 (s); 134.10 (s); 133.18 (s); 129.67 (s); 129.62 (s); 124.35 (d) 124.29 (d); 78.55 (d); 50.37 (d); 46.68 (d) ; 40.74 (t) 35.21 (t); 29.30 (t); 29.38 (t); 16.73 (s); 16.70 (s), MS (EI-MS, m/z) $\text{C}_{23}\text{H}_{29}\text{O}_3$; 354 (18); 336 (4); 200 (22); 135 (100); 121 (22); 105 (7)

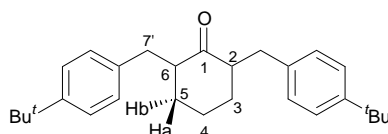
2.3 Hydrogenation of A4, THA4, **15**



The same procedure was done to **A4**

A4 (201 mg; 0.6015 mmol) in CHCl_3 (3 mL), Pd/C (10 mol %; 64 mg), yield **DH-A4** as a white crystal product : 27 %, m.p. = 156 - 157 °C (ethanol), $R_f = 0.68$ (CCl_4 :ethyl acetate = 5:1), IR (ν_{maks} , cm^{-1} , KBr): 1687 (C=O), 2856.7 (C-H), 1510 (aromatic), 832 (C-H), $^1\text{H-NMR}$ (90 MHz, ppm, CDCl_3): δ 7.13 (4H, d $J = 6,7$ Hz, 2 x H2'-Ph and 2 x H6'-Ph); δ 6.79 (4H, d $J = 6,7$ Hz, 2 x H3'-Ph and 2 x H5'-Ph); δ 3.77 (6H, s , 2 x -OCH₃); δ 3.39 - 2.90 (2H, m , H6&2); δ 2.74 - 2.26 (4H, m , 2 x Ph-CH₂(7')-CH); δ 2.26 - 1.87 (2H, m , H3&5a); δ 1.87 - 1.45 (2H, m , H3&5b); δ 1.45 - 0.96 (2H, m , H4), MS (EI-MS, m/z) $\text{C}_{22}\text{H}_{26}\text{O}_3$; 338.2 (18), 267 (2), 121.1 (100), 91.1 (8), 41.1 (2)

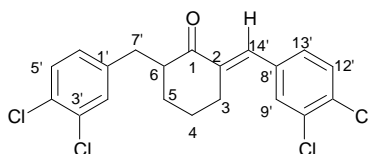
2.4 Hydrogenation of **A6**, **THA6**, **16**



The same procedure was done to **A6**

A6 (133 mg; 0.344 mmol) in ethanol (3 mL), Pd/C (10 mol %; 36,6 mg), yield **TH-A6** as a white crystal product : 24 %, m.p. = 146 - 147 °C (ethanol), $R_f = 0.67$ (CCl_4 :ethyl acetate = 5:1), IR (ν_{maks} , cm^{-1} , KBr): 2933 (C-H), 1688 (C=O), 1511 (aromatic), 832 (=C-H), $^1\text{H-NMR}$ (90 MHz, ppm, CDCl_3): δ 7.29 (4H, d , $J = 6.7$ Hz, 2 x H2'-Ph and 2 x H6'-Ph); δ 7.09 (4H, d , $J = 6.7$ Hz, 2 x H3' and 2 x H5'); δ 3.39 - 3.00 (2H, m , H6&2); δ 2.84 - 2.28 (4H, m , 2 x H7'); δ 2.28 - 1.91 (4H, m , H3&5); δ 1.89 - 1.65 (2H, m , H4); δ 1.65-1.46 (18H, s , 2 x -C₄H₉), MS (EI-MS, m/z) $\text{C}_{28}\text{H}_{28}\text{O}$: 390.3 (58); 243.1 (18); 147.1 (100); 91.1 (36); 57.1 (100); 41.1 (29).

2.5 Hydrogenation of **A9**, **DHA9**, **17**



The same procedure was done to **A9**.

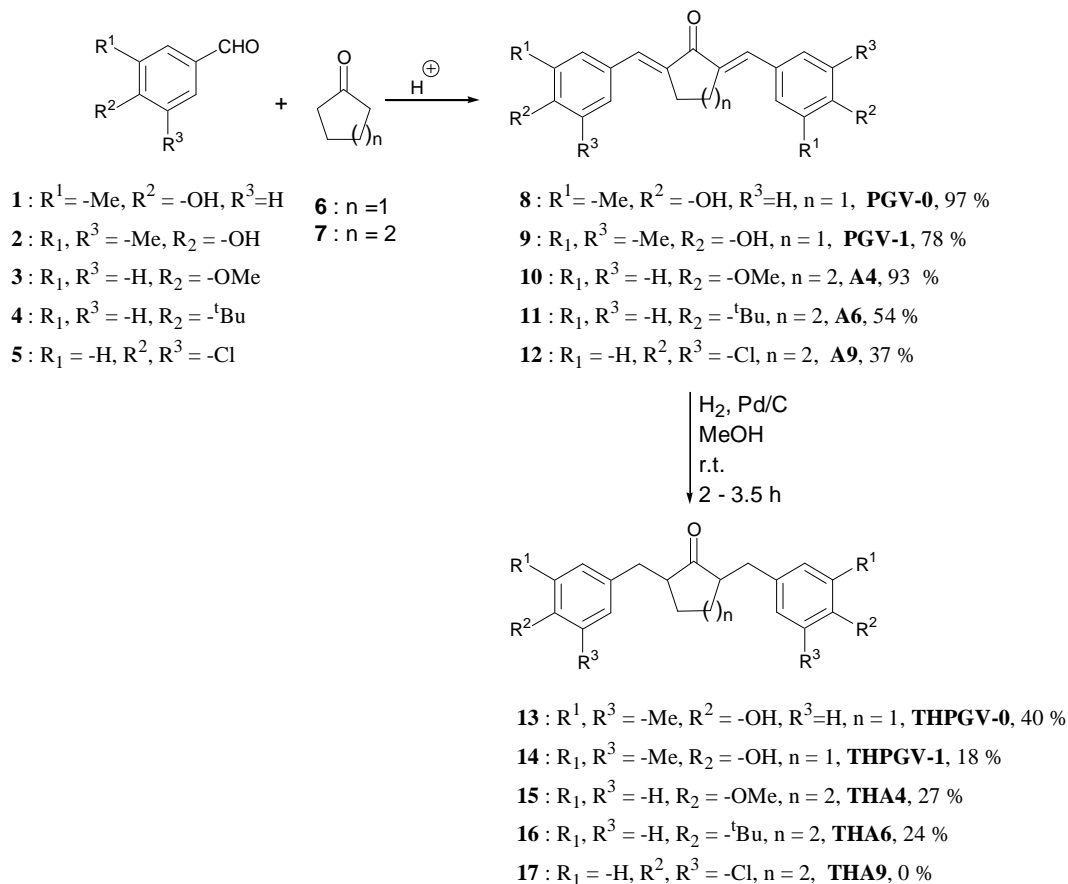
A9 (205 mg; 0.500 mmol) in CHCl_3 (3 mL), Pd/C (10 mol %; 53 mg), yield **DH-A9** as a yellow crystal product : 80 %, m.p. = 146 - 148 °C (ethanol), $R_f = 0.74$ (CCl_4 :ethyl acetate = 5:1), IR (ν_{maks} , cm^{-1} , KBr): 1662 (C=O), 1606 (C=C), 1471 (aromatic), 1166 and 1134 (C-Cl), 822 (C-H); $^1\text{H-NMR}$ (90 MHz, ppm, CDCl_3): δ 7.62 (1H, s , Ph-CH(H14')-CH), δ 7.52 (1H, s , H9'-Ph), δ 7.41 (1H, s , H2'-Ph), δ 7.39-7.28 (2H, m , H5'-Ph and H12'-Ph), δ 7.28 - 7.25 (1H, m , H13'-Ph), δ 7.25 - 7.20 (1H, m , H6'-Ph), δ 3.84 - 3.58 (1H, m , H6), MS (EI-MS, m/z) $\text{C}_{20}\text{H}_{16}\text{OCl}_4$; 414 (50), 159.0 (100), 115.0 (42), 41.1 (51)

3. Result and Discussion

In a continuation of our previous work on the synthesis of tetrahydropentagamavunon-0 (THPGV-0) we have explored the synthesis of some bis(substitutedbenzyl)cyclopentanone and cyclohexanone. And the identification of their side products resulted from the hydrogenation of pentagamavunon-0 (PGV-0) and pentagamavunon-1 (PGV-1) also have been carried out. This hydrogenation reaction is an autoindicator reaction which means that the colour of reaction mixture is changed and in this case from yellow to colourless. This gave assumption that the hydrogenation caused the disappearance of the double bond on α,β -unsaturated system and shorten the chromophore system of the molecules. The reaction was run in 2 - 3.5 hours. According to the TLC monitoring, the whole starting materials transformed into the hydrogenation products during that time.

3.1 Synthesis of bis(substitutedbenzyl)cyclopentanone/cyclohexanone

The bis(substitutedbenzylidene)cyclopentanone/cyclohexanone (**8 – 12**) were made from aldehydes (**1 – 5**) and cyclopentanone (n = 1) or cyclohexanone (n = 2) through the condensation reaction in basic condition. (Sardjimana, 2000) Afterwards, the hydrogenation was done on these di-benzylidene (**8 – 12**) at room temperature for 2 – 3.5 h reaction (like scheme 1 below). Bis(substitutedbenzyl)cyclopentanone and cyclohexanone is known as tetrahydroform of bis(substitutedbenzylidene)cyclopentanone /cyclohexanone

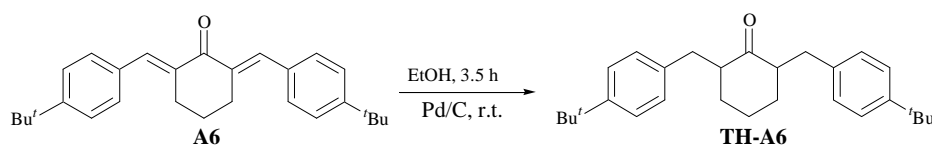


Scheme 1. Synthesis of Tetrahydroform of bis(dibenzylidene)cyclopentanone/cyclohexanone

From the reaction above, synthesis of PGV-0 gave very high yield around 97 % while synthesis of A9 only gave 37 % yield. (Sardjiman, 2000) There are 49 analogs curcumin that have been successfully synthesised at the same time when PGV-0 synthesised. In this publication, only five of them (PGV-0, PGV-1, A4, A6 and A9) that have been hydrogenated while other are still in progress. See table 1 for yield detail.

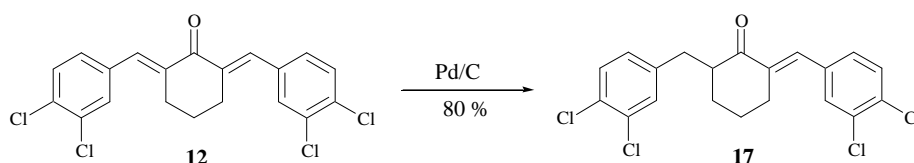
Hydrogenation were started by using starting material of PGV-0 and PGV-1. As mentioned before, both compounds are known as very potential anticancer agents. In order to see if these molecules have higher anticancer activity when they were transformed into their tetrahydroforms like tetrahydrocurcumin. From our results, it showed that the reaction produced four product, one is THPGV-0 or THPGV-1 and three are side products which will explained in the section below.

Hydrogenation of A4 gave THA4 in 27 % yield and A4 also found at the end of the reaction. In the A6 system, the reaction mixture has one product with R_f 0.67 while A6 itself has R_f = 0.77 by CCl₄ : ethyl acetate (5:1) eluent system. While in the A9 system, the product has R_f = 0.74 and A9 has R_f = 0.72. These showed that the hydrogenation product of A6 has a similar polarity with A6, while in A9, the hydrogenation product is more non-polar than A9 itself. Products were recrystallised from EtOH formed an amorphous white crystals and yellow crystals with melting point 146 - 147 °C (A6) dan 146 - 148 °C (A9). The reactions are like below:



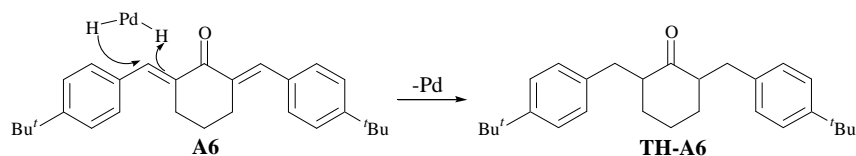
Scheme 2. Hydrogenation reaction on A6

These results indicated that the both double bonds on A6 have been reduced and in A9, only one double bond was reduced as shown by the yellow crystal product formed. Hydrogenation of A9 did not give the same reaction like in A6. The obtained product are called as TH-A6 (tetrahydro-A6) and DH-A9 (tetrahydroA9, $R_f = 0.74$). As proven by MS spectra, only 14 % of A9 transformed to DH-A9 (MW = 414 g/mol) while 86 % still remained as A9 (MW = 412 g/mol) as shown below. And its structure elucidation was confirmed by spectroscopic method.



Scheme 3. Hydrogenation reaction on A9

The reaction mechanism was started by the binding of hydrogen gas to the palladium and followed by A6 or A9 (in this picture, only showed the mechanism of A6). Then, the hydrogen was transferred into the alkene double bond of A6 or A9. The more detail processes are with the presence of palladium catalyst, the H-H bond in H_2 cleaves, and each hydrogen attaches to the palladium surface, forming metal-hydrogen bonds. The palladium absorbed the A6 or A9 onto its surface. A hydrogen atom was then transferred to the A6 or A9, forming a new C-H bond. A second hydrogen atom was transferred forming another C-H bond. At this point, two hydrogens have been added to the carbons across the double bond. Because of the physical arrangement of the A6 or A9 and the hydrogens on a flat palladium surface, the two hydrogens added to the same face of the double bond, displaying syn addition.



Scheme 4. Hydrogenation reaction mechanism on A6

Hydrogenation reaction on A6 gave tetrahydro-A6, it means the both alkene double bonds were hydrogenated but on A9, only one side of alkene double bond was hydrogenated at the same time (3.5 h). This phenomena can be explained as due to the stability of benzene ring on A9. Probably, if the time is applied longer, both alkene double bond could be hydrogenated as proved by TLC that for 3.5 hours reaction only 14 % of A9 converted to DH-A9. Another explanation is because of the effect of two chloride atom on each benzene ring. As chloride atom is electron withdrawing group, the effect of both will deactivate the benzene ring which cause the benzene ring become less negative. Eventually, the electron on alkene double bond will induce to the ring that make it is more positive and not readily available to be hydrogenated. On the other hand, the yield is high around 80% while only 24 % of TH-A6 was obtained.

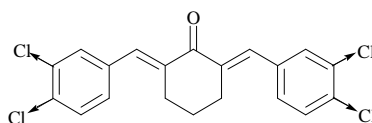
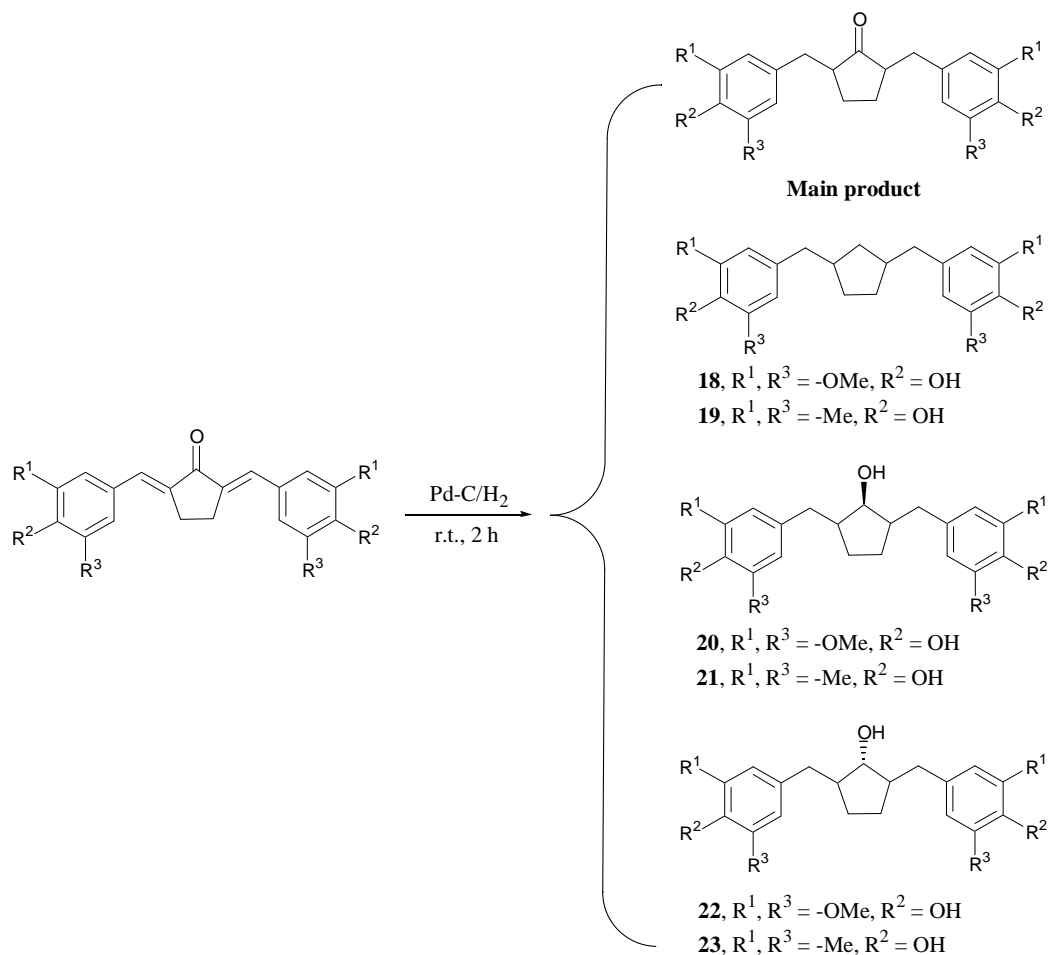


Figure 3. The effect of chloride atom on A9 structure

3.2 Identification of side products.

Generally, hydrogenation of alkenes give the corresponding alkanes in high yield, around 90 %. In this hydrogenation case, the obtained product not only the corresponding alkane but also the reduction products of ketone on the molecule to $-CH_2-$ and alcohols, like scheme below.



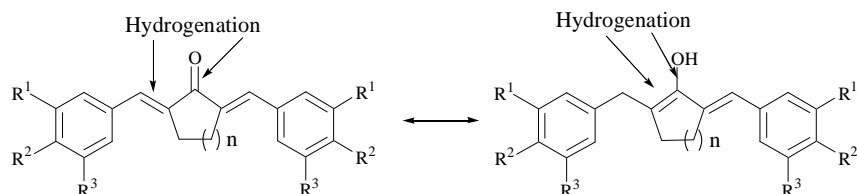
Scheme 5. Side products resulted from hydrogenation of PGV-0 and PGV-1

In this research, only hydrogenation of PGV-0 and PGV-1 that give side products. The side products of THPGV-0 are 1,3-bis-(4'-hydroxy-3'-methoxybenzyl)cyclopentane and 2 compounds of 2,5-bis-(4'-hydroxy-3'-methoxybenzyl)cyclopentanol (**20** and **22**). And side products of THPGV-1 are 1,3-bis-(4'-hydroxy-3'-methylbenzyl)cyclopentane and also 2 compounds of 2,5-bis-(4'-hydroxy-3'-methylbenzyl)cyclopentanol (**21** and **23**). Both 2,5-bis-(4'-hydroxy-3'-methylbenzyl)cyclopentanol are identified as one with hydrogen from the back attack with higher Rf and one with hydrogen from the front attack with lower Rf. Also these compounds are in meso form.

Kolyadina et al. (1996) did the hydrogenation reaction on fulvene in the presence of rhenium heptasulfide as catalyst. The reaction resulted three products : 9-(4-pyridyl-methyl)fluorene, 9-(4-piperidylmethyl)fluorene and fluorene were isolated by flash column chromatography in 33, 16 and 10 % yields, respectively. In addition, Mebi and Frost (2005) have done the hydrogenation reaction on benzylidene acetone by employing rhenium catalyst (CpRu(PTA)2H) yielded 4-phenylbutan-2-one, 4-phenylbutan-2-ol and 4-phenylbut-3-en-2-ol.(Mebi and Frost, 2005)

This research also explored the time of the side products's formation. It was found that since the catalyst added to the reaction mixture, the side products directly formed. The reaction was monitored by TLC. The other reason is because of the nature of molecule. When molecules have benzylidene-ketone part on it, the hydrogenation not only work at alkene double bond but also on the ketone group even on the alcohol group when it forms enol

group. So, it can be concluded that the hydrogenation on bis(dibenzylidene)cyclopentanone/cyclohexanone (on alkene and ketone group) were happened at the same time. It was not consequently hydrogenated from alkene, ketone and alcohol.



Scheme 6. Hydrogenation on α,β -unsaturated ketone and enol form of bis(dibenzylidene)cyclopentanone/cyclohexanone

4. Conclusion

Hydrogenation of bis(disubstitutedbenzylidene)cyclopentanone (PGV-0 and PGV-1) each gave three side products, one product in cyclopentane-form and two products in cyclopentanol-form. Hydrogenation of A4, A6 and A9 gave only one product each.

Acknowledgement

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Attachment

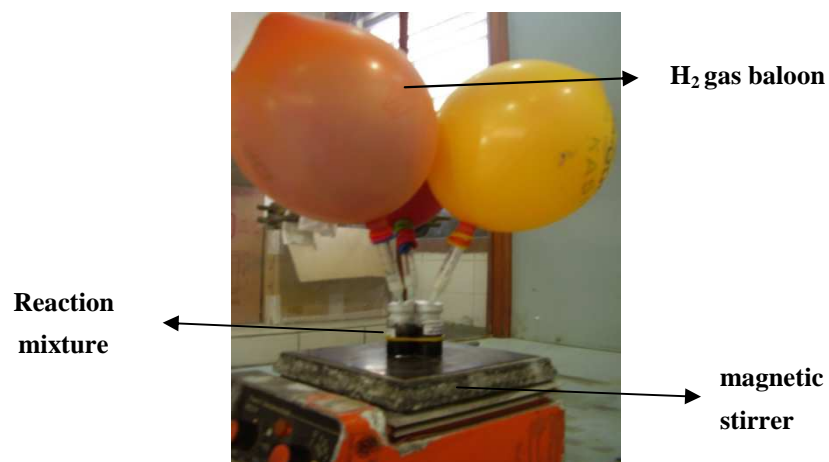


Figure 2. Reaction set up

Table 1. Synthesis of bis-(substitutedbenzylidene)cyclopentanone/cyclohexanone

No	Name	R ¹	R ²	R ³	n	Yield (%)
1	PGV-0, 8	-OMe	-OH	-H	1	98
2	PGV-1, 9	-Me	-OH	-Me	1	78
3	A4, 10	-H	-OMe	-H	2	93
4	A6, 11	-H	- ^t Bu	-H	2	54
5	A9, 12	-H	-Cl	-H	2	37

Table 2. Hydrogenation reaction time of bis-(substitutedbenzylidene)cyclopentanone/cyclohexanone

No	Name	Time (h)	Yield (%)
1	PGV-0, 8	2	40
2	PGV-1, 9	2	18
3	A4, 10	2	27
4	A6, 11	2	24
5	A9, 12	3.5	0

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