



Triterpenoids from the Bark of *Aglaia glabrata* and their *In vitro* Effects on P-388 Murine Leukemia Cells

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ABSTRACT

Four dammarane-type triterpenoids, dammardienon (**1**), aglaiabbreviatin E (**2**), dammar-20, 25-dien-3 β ,24-diol (**3**) and dammar-24-en-3 β ,20-diol (**4**) were isolated from methanolic extract of the bark of *Aglaia glabrata*. The structures of all triterpenoids were elucidated by 1D-, 2D-NMR, and comparison with previously reported data. All triterpenoids were applied into *in vitro* bioassay against P-388 murine leukemia cell. Dammar-24-en-3 β ,20-diol (**4**) has cytotoxic activity with IC₅₀ value of 9.45 μ M towards P-388 murine leukemia cell lines.

Keywords: Meliaceae, *Aglaia glabrata*, dammarane-type triterpenoid, P-388 murine leukemia cell.

INTRODUCTION

Meliaceae family is a woody plant that grows in the tropics consisting of 51 genera and approximately 550 species. Meliaceae plant has been reported to contain many interesting biologically

active compounds related to agriculture and health, such as insecticidal, antifeedant, plant growth regulator, mosquito repellent, larvicidal, antimalarial, antiviral, antioxidant, anticancer, antibacterial, antifungal and inflammatory¹⁻³. The largest genera in the Meliaceae family is *Aglaia*, which is about 130



species. *Aglaia* is a tropical plant that distributed throughout Western Pacific, Indonesia, Malaysia and India^{4,5}. The *Aglaia* species are commonly found in tropical rainforests in Southeast Asia (Malaysia and Indonesia) with a dozen or more different species living together⁴. Phytochemical investigation of plants belonging to *Aglaia* genus have indicated the presence of sesquiterpenoid^{6,7}, diterpenoid^{8,9}, rocaglate derivative^{1,10,11}, lignan^{12,13}, dammarane-type triterpenoids¹⁴⁻¹⁸, protolimonoid¹⁹ and cycloartane-type triterpenoids^{16,20-22}. One of the *Aglaia* plants that only grown in Indonesia is *A. glabrata* which indigenous to East Kalimantan Province, Indonesia. Presently, isolation, structure determination and cytotoxic activity of triterpenoids **1-4** from *A. glabrata* are reported.

MATERIALS AND METHODS

General Experimental Procedure

The melting point values of triterpenoids were obtained using a electrothermal apparatus with uncorrected measurement. A Perkin-Elmer 1760X spectrophotometer was used to obtained infrared spectra of compounds in pellets of potassium bromide. HRTOFMS spectra were recorded on Water, Qtof HR-MS XEVOtm mass spectrometer. All NMR spectra are measured on JEOL NMR A-500 MHz with an internal standard of tetramethylsilane. All chromatography techniques, including vacuum liquid chromatography (VLC) and column chromatography (CC), were undertaken on silica gel (SiO₂, Merck, Darmstadt, Germany). TLC analysis was done on Kieselgel 60 F₂₅₄ (Merck) plates; visualization was performed with UV light and plates were sprayed with 10% H₂SO₄ solution in ethanol and heated.

Plant material

Dried bark of *A. glabrata* were obtained in August 2016 from Bogor Botanical Garden, Bogor, West Java, Indonesia. A voucher specimen

was deposited at the Bogoriense Herbarium (code Bo-1288718).

Cytotoxic Activity

Determination of cytotoxic activities was undertaken based on the MTT assay explained in the previous reports^{18,19}. The P-388 murine leukemia cells were seeded into 96-well plates at an initial cell density of approximately 3 x 10⁴ cells cm⁻³. After 24 h of incubation for cell attachment and growth, varying concentrations of samples were added. The compounds were first dissolved in DMSO (dimethyl sulfoxide) at the required concentration. Six concentrations were prepared using PBS (phosphoric buffer solution, pH = 7.30 - 7.65). Control wells received only DMSO. The assay was terminated after 48 h incubation period by adding MTT reagent [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide] and the incubation was continued for another 4 h in which the MTT-stop solution containing SDS (sodium dodecyl sulphate) was added and another 24 h incubation was conducted. An optical density was read by using a micro plate reader at 550 nm. IC₅₀ values were taken from the plotted graph of percentage live cells compared to control (%), receiving only PBS and DMSO, versus the tested concentration of compounds (µg/mL). The IC₅₀ value is the concentration required for 50% growth inhibition. Each assay and analysis was run in triplicate and averaged.

RESULTS

Extraction and Isolation

Dried powder of *A. glabrata* (2.5 kg) were extracted by maceration with 80% aqueous methanol. The extract was partitioned with respective *n*-hexane and EtOAc. Fraction C of *n*-hexane extract was VLC-chromatographed twice to yield dammardienon (**1**, 13.6 mg)²³. The second fraction (fraction G) was VLC-chromatographed two times,

Table 1: Characterization data for compounds 1-4.

Compound	Physical state	Melting point (°C)	<i>m/z</i> [M+H] ⁺	IR in KBr λ _{max} (cm ⁻¹)
1	Colorless needle crystals	141-143	425.3698 (calcd. for C ₃₀ H ₄₈ O, <i>m/z</i> 424.3695)	3082, 2949, 1705, 1641, 1460
2	Whiteness amorphous powder	-	441.3872 (calcd. for C ₃₀ H ₄₉ O ₂ , <i>m/z</i> 441.3878)	3431, 2943, 2870, 1725, 1642, 1380, 1245
3	Colorless needle crystals	167-169	443.3811 (calcd. for C ₃₀ H ₄₈ O, <i>m/z</i> 442.3818)	3430, 2949, 1460, 1380, 1050
4	White solid	-	445.3970 (calcd. for C ₃₀ H ₅₂ O ₂ , <i>m/z</i> 444.3977)	3369, 2939, 1639, 1458, 1109

Table 2: ¹H (CDCl₃, 600 MHz) and ¹³C NMR (CDCl₃, 150 MHz) data for Compounds 1-4

Position	¹ H NMR				¹³ C NMR			
	δ _c (mult.)	δ _H , mult., (J Hz)	δ _c (mult.)	δ _H , mult., (J Hz)	δ _c (mult.)	δ _H , mult., (J Hz)	δ _c (mult.)	δ _H , mult., (J Hz)
1a	40.5 (t)	1.44, dd (2.8, 7.2)	40.1 (t)	1.44, dd (1.7, 9.4)	37.9 (t)	1.40, dd (1.9, 7.5)	37.2 (t)	1.37, ddd (1.6, 2.8, 8.6)
1b		1.93, ddd (2.4, 6.2, 7.2)		1.90, ddd (1.4, 4.8, 9.4)		1.44, ddd (2.1, 4.7, 7.5)		1.54, ddd (1.2, 4.5, 8.6)
2a	35.1 (t)	1.92, dd (3.1, 8.2)	35.2 (t)	2.45, dd (3.6, 14.0)	33.6 (t)	2.01, dd (2.1, 8.4)	34.2 (t)	1.63, ddd (1.6, 4.5, 9.8)
2b		2.40, ddd (2.7, 5.6, 8.2)		2.70, dt (14.0, 5.2)		1.86, ddd (1.7, 6.4, 8.4)		1.65, ddd (1.2, 4.5, 9.8)
3	217.6 (s)		217.8 (s)		76.5 (d)	3.39, t (2.6)	77.6 (d)	3.37, dd (1.6, 4.5)
4	46.8 (s)		46.9 (s)		49.7 (s)		48.1 (s)	
5	54.7 (d)	1.39, dd (2.9, 4.5)	55.2 (d)	1.36, dd (2.3, 7.6)	55.2 (d)	1.26, dd (2.6, 4.8)	54.9 (s)	1.43, t (7.2)
6a	20.1 (t)	1.46, dd (4.5, 7.4)	19.4 (t)	1.45, ddd (2.3, 7.6, 10.6)	18.6 (t)	1.41, ddd (2.6, 6.4, 9.5)	18.3 (t)	1.58, dd (7.2, 9.8)
6b	35.2 (t)	1.70, ddd (2.9, 5.1, 7.4)	34.8 (t)	1.54, ddd (1.9, 7.6, 10.6)	35.3 (t)	1.61, ddd (1.9, 5.7, 9.5)	35.2 (t)	1.48, ddd (2.1, 7.2, 9.8)
7a		1.33, dd (5.1, 8.4)		1.68 dd (1.8, 9.8)		1.29, ddd (1.9, 5.7, 10.4)		1.44, ddd (2.1, 7.2, 11.2)
7b		1.58, ddd (2.8, 4.5, 8.4)		1.89, ddd (1.5, 2.5, 9.8)		1.54, ddd (1.8, 6.8, 10.4)		1.75, ddd (2.1, 5.4, 11.2)
8	30.9 (s)		30.4 (s)		30.6 (s)		30.7 (s)	
9	40.6 (d)	1.41, t (5.3)	40.3 (d)	1.40, dd (2.3, 5.7)	38.9 (d)	1.45, t (6.8)	40.3 (d)	1.72, t (6.4)
10	50.5 (s)		50.3 (s)		50.6 (s)		50.4 (s)	
11a	21.9 (t)	1.54, dd (5.3, 8.2)	21.8 (t)	1.40, dd (5.7, 11.6)	22.3 (t)	1.54, ddd (1.8, 6.8, 8.6)	21.4 (t)	1.82, dd (6.4, 8.8)
11b		1.83, ddd (2.1, 5.3, 8.2)		1.50, ddd (2.3, 5.7, 11.6)		1.62, ddd (1.6, 4.7, 8.6)		1.96, ddd (1.7, 6.4, 8.8)
12a	28.8 (t)	1.45, dd (3.6, 7.8)	28.8 (t)	1.07, dd (2.3, 9.8)	27.7 (t)	1.15, ddd (1.8, 4.7, 10.8)	27.4 (t)	1.83, ddd (1.7, 6.4, 12.2)
12b		1.91, ddd (2.1, 3.6, 7.8)		1.58, ddd (2.3, 6.2, 9.8)		1.20, ddd (1.6, 4.7, 10.8)		2.01, ddd (1.4, 5.6, 12.2)
13	46.1 (d)	1.69, dd (7.8, 8.1)	47.5 (d)	2.24, dd (1.8, 8.4)	42.8 (d)	1.61, t (7.2)	42.3 (d)	1.78, t (4.6)
14	50.2 (s)		49.8 (s)		49.7 (s)		50.4 (s)	
15a	30.9 (t)	1.61, dd (1.8, 8.5)	31.1 (t)	1.58, dd (1.8, 9.5)	28.5 (t)	1.45, ddd (1.5, 3.4, 9.6)	31.2 (t)	2.04, dd (7.2, 11.4)
15b		2.01, ddd (1.8, 5.6, 7.8)		1.60, ddd (1.8, 4.8, 9.5)		1.06, ddd (1.8, 3.4, 9.6)		2.45, ddd (2.4, 7.2, 11.4)
16a	26.0 (t)	1.51, ddd (1.9, 2.7, 7.8)	25.9 (t)	1.40, dd (1.6, 10.4)	22.7 (t)	1.88, ddd (3.4, 6.5, 11.2)	22.6 (t)	2.77, ddd (2.4, 7.2, 10.8)
16b		1.98, ddd (2.7, 7.8, 8.1)		1.90, ddd (1.6, 2.5, 10.4)		1.92, ddd (1.8, 3.4, 11.2)		2.32, ddd (2.4, 4.2, 10.8)
17	48.1 (d)	2.20, ddd (2.7, 4.5, 7.8)	46.6 (d)	1.68, dd (3.2, 10.4)	49.9 (d)	1.47, dd (1.8, 3.4)	49.8 (d)	2.29, dd (2.4, 7.2)
18	16.0 (q)	1.00, s	15.7 (q)	1.01, s	16.1 (q)	0.96, s	16.6 (q)	0.93, s
19	17.1 (q)	0.95, s	16.8 (q)	1.08, s	16.7 (q)	0.95, s	16.1 (q)	0.90, s
C-20 (s)			151.3 (s)		124.7 (s)		75.5 (s)	
21a	106.9 (t)		109.0 (t)		140.1 (t)		25.5 (q)	
21b		4.71, d (7.8)		4.88, s		4.85, d (5.6)		1.03, s
22a	35.1 (t)	2.04, dd (2.4, 6.7)	37.2 (t)	2.66, d (4.2)	35.7 (t)	2.66, d (3.8)	40.6 (t)	1.34, dd (2.1, 8.4)
22b		2.32, dd (1.8, 6.7)		2.70, d (4.2)		2.70, d (3.8)		1.72, ddd (2.1, 3.6, 8.4)
23a	28.0 (t)	1.96, dd (1.5, 5.8)	125.6 (d)	5.64, dd (6.5, 8.2)	25.9 (t)	2.80, m	22.6 (t)	1.85, dd (2.1, 9.7)
23b						2.98, dd (2.1, 4.6)		2.01, ddd (1.7, 5.4, 9.7)
24	125.1 (d)	5.11, dd (2.2, 5.8)	139.0 (d)	5.70, dd (6.5, 8.2)	70.5 (d)	4.20, dd (2.1, 4.6)	125.2 (d)	5.10, dd (1.7, 5.4)
25	132.0 (s)		70.7 (s)		141.6 (s)		132.1 (s)	
26	25.9 (q)	1.68, s	28.4 (q)	1.32, s	124.2 (t)	5.10, d (4.6)	25.9 (q)	1.86, s
27	17.9 (q)	1.61, s	28.4 (q)	1.32, s	17.6 (q)	5.20, d (4.6)	17.8 (q)	1.78, s
28	20.9 (q)	1.05, s	25.7 (q)	0.94, s	22.1 (q)	1.70, s	28.4 (q)	0.94, s
29	27.1 (q)	1.08, s	21.5 (q)	1.04, s	26.0 (q)	1.05, s	23.1 (q)	0.88, s
30	15.9 (q)	0.87, s	16.0 (q)	0.87, s	16.1 (q)	1.02, s	17.2 (q)	0.96, s

followed by crystallization to result in aglaiabbreviatin E (**2**, 12.4 mg)¹⁷.

Two fractions of EtOAc extract (Fraction J and N) were chromatographed using successive VLC techniques and were followed recrystallization, yielding respective dammar-20,25-dien-3 β ,24-diol (**3**, 23.4 mg)²⁴ and dammar-24-en-3 β ,20-diol (**4**, 12.4 mg)^{25,26}. The structural determination of all compounds was undertaken on the basis of spectroscopic methods (UV, IR, MS, 1D and 2D NMR) and comparison with those reported in the literature. All of these data can be seen in Table 1 and 2.

DISCUSSION

The barks of *A. glabrata* were macerated with aqueous MeOH at room temperature and the macerated residue was fractionated with respective *n*-hexane, EtOAc and *n*-BuOH. Repetitive SiO₂ CC of the *n*-hexane and EtOAc fractions afforded four dammarane-type triterpenoids **1-4** (Figure 1).

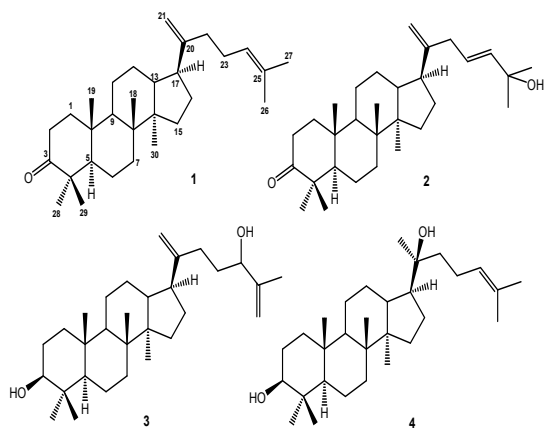


Fig. 1. The structures of compound 1-4

MS data of compound **1** showed that there was a hydrogen deficiency index of seven. The infrared spectra displayed absorbance bands for an aliphatic moiety (3082 and 2949 cm⁻¹), a ketonic carbonyl (1705 cm⁻¹) and an olefin (1645 cm⁻¹). The proton NMR analysis displayed seven methyl protons at δ_{H} 0.87, 0.95, 1.00, 1.05, 1.08, 1.61 and 1.68, which corresponding to tertiary Me-18, Me-19, Me-26, Me-27, Me-28, Me-29, respectively. There are signals of a sp² methine proton at chemical shift of δ_{H} 5.11 and sp² methylene protons at chemical shifts of δ_{H} 4.71 and 4.75, found in the spectrum. Thirty carbon signals were read in the

carbon NMR spectra after associated with DEPT analysis, which consisted of seven tertiary methyls, ten methylenes of sp³, four methines of sp³, four quaternary carbons of sp³, one carbonyl (δ_{C} 217.6), one sp² methylene (δ_{C} 106.9) one sp² methines (δ_{C} 125.1) and two sp² quaternary carbons (δ_{C} 132.0 and 151.4). Four remaining of hydrogen deficiency index was corresponding to four ring dammarane-type triterpenoid^{18,19}. The presence of dammarane-type in **1** was also supported by a combined experiment of ¹H-¹H COSY and HMBC (Fig. 2). Correlations of an olefinic proton signals at δ_{H} 5.11 (H-24) to δ_{C} 132.0 (C-25) and δ_{C} 28.0 (C-23) and at δ_{H} 1.68 (Me-26) and δ_{H} 1.61 (Me-27) to δ_{C} 132.0 (C-25) strongly supported that double bond was positioned at C-24/C-25. A double bond at terminal C-20/C-21 was deduced from correlations between two protons at δ_{H} 4.71 and 4.75 and C-20 (δ_{C} 151.4), δ_{C} 35.1 (C-22) and δ_{C} 48.1 (C-17). Correlations of Me-28 (δ_{H} 1.05), 1.92 (H-2a) and 2.40 (H-2b) to carbonyl signal at δ_{C} 217.6, indicated the position of carbonyl ketone at C-3. NMR data of **1** were superimposed with those of dammardienon²³, consequently, compound **1** was determined as a dammardienon.

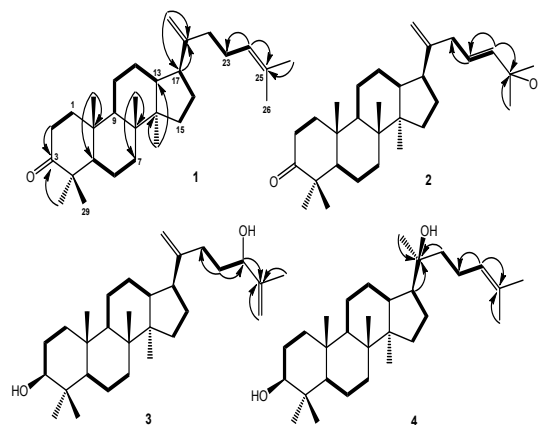


Fig. 2. HMBC and 1H-1H COSY correlations for 1-4

Similar to compound **1**, there was a hydrogen deficiency index of seven in compound **2**, based on the MS data. The infrared spectrum displayed absorbance band for groups of an alcohol (3431 cm⁻¹), an aliphatic (2943 and 2870 cm⁻¹), a ketonic carbonyl (1725 cm⁻¹), olefine (1642 cm⁻¹) and ether moieties (1245 cm⁻¹). The molecular weight of **2** has 17 atomic mass unit higher than **1**, describing an additional OH group in **2**. The NMR spectra of **2** have similarity with spectra of **1**.

The main differences are the presence of newly double bond at δ_H 5.64 and 5.70 and one signal of oxygenated carbon at δ_C 70.7 instead of a proton signal of olefin at δ_H 5.11, δ_C 125.1, showing a double bond in new position and a hydroxyl group in **2**. HMBC correlations of olefinic protons at δ_H 5.64 to δ_C 37.2 (C-22) and δ_C 125.6 (C-23) and δ_H 5.70 to δ_C 125.6 (C-23) and δ_C 70.7 (C-25) were used to determine the newly double bond (23,24). Additionally, correlations from two methyls at Me-26 (δ_C 28.4) and Me-27 (δ_C 28.4) to an oxygenated carbon (δ_C 70.7) were used to determine the newly hydroxyl group at C-25. NMR data of **2** were superimposed with those of aglaiabbreviatin E¹⁷, which strongly recommended that compound **2** was aglaiabbreviatin E.

A molecular formula of compound **3** suggested a hydrogen deficiency index of six, based on its MS data. The IR spectrum showed functional group wavenumbers at 3430 cm^{-1} (hydroxyl), 2949 and 2875 cm^{-1} (aliphatic), 1610 cm^{-1} (olefinic), 1450 and 1354 cm^{-1} (*gem*-dimethyl) and 1050 cm^{-1} (ether). The NMR spectral data of **3** were superimposed with spectral data of dammaradienon (**1**), unless the absence of a ketonic carbonyl (δ_C 218.4) at C-3 and the presence of an oxymethine (δ_C 76.5), which were confirmed by HMBC analysis through correlations of CH_2 -2 (δ_H 1.86 and 2.01) and two methyl signals (δ_H 1.05) to C-3 (δ_C 76.5). Another difference is the presence of an oxygenated sp^3 methines at δ_H 4.20 and δ_C 70.5. A proton signal of oxygenated methine at δ_H 4.20 was correlated to C-23 (δ_C 25.9) and quaternary sp^2 carbon at C-25 (δ_C 141.6), suggesting that a secondary hydroxyl group was located at C-24. Another double bond was assigned to be at position C-25/C-26 based on the correlation of terminal double bond at δ_H 5.10 and 5.20 as well as a methyl at C-27 (δ_H 1.70) to sp^2 quaternary carbon at C-25 (δ_C 141.6). NMR data of **3** were highly overlapped to those of dammar-20, 25-dien-3 β ,24-diol²⁴, eventually, compound **3** was identified as a dammar-20,25-dien-3 β ,24-diol.

A hydrogen deficiency index of five was also found for compound **4** based on the MS data. IR wavenumbers of 3369 cm^{-1} , 2939 cm^{-1} , 1639 cm^{-1} , 1458 and 1230 cm^{-1} , and 1109 cm^{-1} were analyzed for respective hydroxyl, aliphatic, olefinic, *gem*-dimethyl, and ether groups. NMR spectral data of **4** were similar to spectral data of dammar-20,

25-dien-3 β ,24-diol **3**, except the absence of one of two terminal double bonds at δ_H 4.85, 4.90 and one oxygenated methine at δ_H 4.20 and appearance of newly an olefinic double bond at δ_H 5.10 and δ_C 124.8 and 131.7 and a tertiary methyl at δ_H 1.13, δ_C 25.5, suggesting that compound **4** was the lack of one of the olefinic moiety and appearance of a hydroxyl group. In the HMBC spectrum, correlation from tertiary methyl at δ_H 1.13 and sp^3 methine at δ_H 1.69 to sp^3 oxygenated carbon at δ_C 75.5, were used to determine the C-20 position of the tertiary hydroxy group. A remaining olefine was positioned at C-24/C-25 that was determined based on the correlation of an olefinic proton at δ_H 5.10 and tertiary methyl at δ_H 1.66 to sp^2 tertiary carbon at C-25 (δ_C 131.7). The NMR spectra data of **4** were superimposed with those of dammar-24-en-3 β , 20-diol^{25,26}, therefore, compound **4** was characterized as a dammar-24-en-3 β ,20-diol.

Table 3. Cytotoxicity activity of compounds 1–4

Compounds	IC ₅₀ ($\mu\text{g/mL}$)
Dammardienon (1)	40.25 \pm 0.12
Aglaiabbreviatin E (2)	34.25 \pm 0.12
Dammar-20,25-dien-3 β ,24-diol (3)	32.20 \pm 0.10
Dammar-24-en-3 β ,20-diol (4)	9.45 \pm 0.10

The cytotoxic properties of compounds **1-4** were tested towards P-388 murine leukemia cells using a modified method priority described.^{18,20,26} Artonin E was used as a positive control with IC₅₀ 0.68 μM ²⁷. The results of cytotoxic assay of isolated compounds **1-4** (Table 3), showed that dammar-24-en-3 β ,20-diol (**4**), having two hydroxy groups and one double bond, has the strongest activity among all, whereas dammardienon (**1**) has the weakest activity, suggesting that the presence of hydroxyl and double bond moieties are significant structural element for the cytotoxic activity.

CONCLUSION

Four dammarane-type triterpenoids, **1-4**, were isolated from the bark of *A. glabrata*, for the first time in this species. These findings support the presence of dammarane triterpenoid in the *Aglaiia* genus. In dammarane-type triterpenoids, hydroxyl and double bond groups are important requirements for the cytotoxic properties.

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