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Structure Elucidation of 20*S*,24*S*-epoxydammarane-type Triterpenoids from the bark of *Aglaia cucullata* (Meliaceae)

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ABSTRACT

Triterpenoids are the major class of terpenoid group that is widely found in the Meliaceae family. The *Aglaia* genus is one of the genera that is known to contain a few secondary metabolite compounds with a variety of interesting structures and biological activities, especially triterpenoids. *Aglaia cucullata*, as a mangrove plant can be found in Indonesia, which its exploration of dammarane-type existence remains very limited. Therefore, this study aims to isolate the dammarane compounds and focus on the elucidation of their distinctive moiety. Two 20*S*,24*S*-epoxydammarane-triterpenoids have been successfully obtained from the stem bark of *A. cucullata* using several chromatographic techniques in normal and reversed stationary phases. The elucidation structure was established based on spectroscopic methods, including MS, FT-IR, 1D- and 2D-NMR. Compound **1** was established as 20*S*,24*S*-epoxy-3α,25-dihidroxydammarane or known as 3-*epi*-ocotillol II, while **2** was eichlerianic acid. The cytotoxic activity against human breast cancer MCF-7 cells showed that the two isolated compounds were inactive by their IC_{50} values >100 μM.

Keywords: *Aglaia cucullata*, cytotoxic activity, 20*S*,24*S*-epoxydammarane-type, MCF-7, Triterpenoids.

INTRODUCTION

Triterpenoids belong to the terpenoid group which consists of six isoprene units and are formed via the mevalonate pathway. In addition, roughly 20.000 triterpenoids have been discovered with 200 distinctive frameworks, leading to the most diverse chemical structures in the terpenoid group [1]. This compound and its derivatives have demonstrated extraordinary biological activities, including antiviral [2], antifungal [3], antibacterial [4], antioxidant [5], anti-inflammatory [6], antidiabetic [7], and cytotoxic [8,9].

The *Aglaia* genus is popularly known for its ability to yield different dammarane-type triterpenoids, with around 31 new compounds being reported [10,11]. Furthermore, Zhang et al. obtained six new compounds that showed intriguing cytotoxic activity against several cancer cells [12]. In previous studies, dammarane-type triterpenoids from *A. smithii* and *A. eximia* were found to exhibit cytotoxic activity against P388 murine leukemia cells [13]. Triterpenoids from *A. elaeagnoidea* have effects on human prostate cancer (DU145) and cervical cancer (HeLa) cells [14] and from *A. elliptica* [10] show cytotoxic effects on breast cancer (MCF-7) and melanoma cells (B16-F10).

Aglaia cucullata, commonly called "Pacific maple", is the sole plant found in South Asia's coastal forests, growing most abundantly in mangrove areas [15]. This plant can be found across the Indonesian islands, such as Sumatra, Kalimantan, Sulawesi, Maluku, and Papua. Historically employed as firewood, building materials for homes, and boat materials [16]. This herb is used in some tribes to cure heart issues,

rheumatism, diarrhea, dysentery, and skin infections [17]. These previous findings motivated us to isolate the dammarane-type triterpenoids from the stem bark of *A. cucullata* together with exploring their potential on cytotoxic against breast cancer MCF-7 cells. Hence, we present the isolation, and elucidation structure of two 20*S*,24*S*-epoxydammaranes as well as their activity on the viability of MCF-7 cells. The isolation was carried out using several chromatography techniques, while the elucidation structure was determined through an extensive spectroscopic method, including MS, IR, ^{1}H and ^{13}C-DEPT, HMQC, HMBC, COSY, and NOESY. Additionally, the cytotoxic assay was conducted based on the presence of resazurin as a reagent to detect the viable cells.

EXPERIMENTAL SECTION

Material and Instrumental

SHIMADZU IR Prestige-21 was used to record the IR spectra in KBr, while the mass spectra were measured on a Waters Q-TOF Xevo mass spectrometer. Employing tetramethyl silane (TMS) as an internal standard, NMR spectra were acquired at 500 MHz for ^{1}H and 125 MHz for ^{13}C on a Bruker Topspin spectrometer. Column chromatography utilizing silica gel G_{60} (Merck) with a mesh size of 70–230 is used for crude separation and 200–400 mesh for purification. Silica gel GF_{254} (Merck, 0.25 mm) was used as a precoat for Thin Layer Chromatography (TLC) plates. To detect the sample, ethanol was sprayed with 10% H_2SO_4, heated, and exposed to UV light at wavelengths of 254 and 365 nm.

Plant Material

A. cucullata's stem bark was collected from the Manggar River, Balikpapan, East Kalimantan, Indonesia. The identification was conducted by the Wanariset staff, Herbarium Balikpapan, in December 2020 with specimen number FF7.20.

Isolation Process

The dried sample (3.5 kg) was macerated with ethanol (EtOH) (5 x 3 L, for each) at 25 ºC. The EtOH crude extract (523.0 g) was afforded through evaporation under low pressure, which was then partitioned in gradual polarity to produce *n*-hexane, ethyl acetate (EtOAc), and *n*-butanol fractions. A total of 64 g *n*-hexane extract was further separated using various chromatography techniques. The separation of crude *n*-hexane was performed by using vacuum liquid chromatography (VLC) on silica gel 60 with gradient elution of *n*-hexane: EtOAc: MeOH (10: 0: 0- 0: 0: 10, stepwise 10%, v/v) to obtain eight fractions (A-H). Subfraction B (21 g) was subjected to silica gel (70-230 mesh) with *n*-hexane: EtOAc (10: 0- 1: 1, 2.5% gradient) as the eluent system to produce six subfractions (B1-B6). Compound **1** (5 mg) was obtained from subfraction B1e (146 mg) by separating on silica gel (230-400 mesh) using *n*-hexane: EtOAc, 50: 1, which was then purified on reverse ODS using methanol (MeOH): Water (H_2O), 20: 1. Furthermore, subfraction B2 (1.48 g) was separated on silica gel (230-400 mesh) using of *n*-hexane: EtOAc (10: 0- 9:1, 0.5% gradient) to yield 11 subfractions (B2a-B2k). Subfraction B2c (248 mg) was subjected to ODS (MeOH: H_2O, 8: 2) to obtain compound **2** (73.3 mg).

Spectroscopic Data

Compound **1**, white solid, IR (KBr) ν_{max} 3457, 2940, 1650, 1449, 1380, dan 1055 cm^{-1}. HR-ESI-TOFMS at *m/z* 461.3993 (calcd. for $C_{30}H_{53}O_3^+$, *m/z* 461.3995, $[M+H]^+$). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ_H 1.43 (2H, m, H-1), 1.62 (2H, m, H-2), 3.39 (1H, t, *J*= 3.0 Hz, H-3), 1.25 (1H, m, H-5), 1.38 (2H, m, H-6), 1.65 (2H, m, H-7), 1.46 (1H, m, H-9), 1.55 (2H, m, H-11), 1.77 (2H, m, H-12), 1.64 (1H, m, H-13), 1.05 (2H, m, H-15), 1.52 (2H, m, H-16), 1.45 (1H, m, H-17), 0.85 (3H, s, CH_3-18), 0.96 (3H, s, CH_3-19), 1.14 (3H, s, CH_3-21), 1.23 (2H, m, H-22), 1.86 (1H, m, H-23), 3.64 (1H, dd, *J*= 4.9 Hz, 10.4 Hz, H-24), 1.20 (3H, s, CH_3-26), 1.12 (3H, s, CH_3-27), 0.95 (3H, s, CH_3-28), 0.83 (3H, s, CH_3-29), 0.89 (3H, s, CH_3-30). ^{13}C-NMR ($CDCl_3$, 125 MHz), see Table 1.

Compound **2**, white solid, IR (KBr) ν_{max} 3448, 2924, 1704, 1425, 1370, dan 1011 cm^{-1}. HR-ESI-TOFMS at *m/z* 443.3817 (calcd. for $C_{30}H_{51}O_2^+$, *m/z* 443.3817, $[M+H]^+$). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ_H 1.89 (2H, m, H-1), 2.39 (1H, m, H-2a), 2.45 (1H, m, H-2b), 1.32 (1H, m, H-5), 1.53 (1H, m, H-6a), 1.43 (1H, m, H-6b), 1.48 (1H, m, H-7a), 1.27 (1H, m, H-7b), 1.36 (1H, m, H-9), 1.46 (1H, m, H-11a), 1.27 (1H, m, H-11b), 1.82 (1H, m, H-12a), 1.25 (1H, m, H-12b), 1.65 (1H, m, H-13), 1.40 (1H, m, H-15a), 1.03 (1H, m, H-15b), 1.69 (1H, m, H-16a), 1.45 (1H, m, H-16b), 1.66 (1H, m, H-17), 0.97 (3H, s, CH_3-18), 0.95 (3H, s, CH_3-19),

1.15 (3H, s, CH_3-21), 1.43 (2H, m, H-22), 1.98 (1H, m, H-23), 5.12 (1H, tt, *J*= 1.4, 7.1 Hz, H-24), 1.69 (3H, s, CH_3-26), 1.63 (3H, s, CH_3-27), 1.09 (3H, s, CH_3-28), 1.03 (3H, s, CH_3-29), 0.89 (3H, s, CH_3-30). ^{13}C-NMR ($CDCl_3$, 125 MHz), see Table 1.

RESULTS AND DISCUSSION

The concentrated *n*-hexane (64.0 g) was afforded by partitioning of EtOH extract (523.0 g) from the stem bark of *A. cucullata* with *n*-hexane, ethyl acetate (EtOAc), and *n*-butanol (*n*-BuOH), successively. Two isolated compounds were obtained from *n*-hexane fraction using chromatography on the normal phase (silica gel 60) and reverse phase (C18-ODS). The thin layer chromatography (TLC) using silica gel GF_{254} was used to detect and guide the isolation process.

Compound **1** was isolated as a white solid ($CHCl_3$). Its molecular formula was determined as $C_{30}H_{52}O_3$ based on the HR-TOFMS spectrum at *m/z* 461.3993 $[M+H]^+$ (calculated for $C_{30}H_{53}O_3$, *m/z* 461.3995), indicating five degrees of unsaturation. The IR spectrum of **1** suggested the presence of hydroxyl (3457 cm^{-1}), C-H sp^3 (2866 cm^{-1}), C=C (1650 cm^{-1}), *gem*-dimethyl (1380 cm^{-1} and 1457 cm^{-1}), and C-O ether (1050 cm^{-1}) groups. As shown in Table 1, the ^{1}H-NMR of **1** presented the signals of eight tertiary methyls (including three deshielded protons) at δ_H 0.84 (3H, s, CH_3-18), 0.87 (3H, s, CH_3-19), 0.92 (3H, s, CH_3-28), 0.82 (3H, s, CH_3-29), 0.95 (3H, s, CH_3-30), and δ_H 1.13 ppm (3H, s, CH_3-21), 1.17 ppm (3H, s, CH_3-26), 1.09 ppm (3H, s, CH_3-27). The three slightly deshielded protons indicated that they were attached by an oxygenated quaternary carbon. The existence of two oxygenated methines at δ_H 3.38 (1H, t, *J*= 2.9 Hz, H-3) and 3.62 (1H, dd, *J*= 4,8, 10,2 Hz, H-24) was also observed. The above data implied that **1** was a triterpenoid compound. Moreover, the ^{13}C-NMR with the aid of DEPT 135° as well as its HSQC spectrum showed the existence of 30 carbons consisting of eight sp^3 methyls at δ_C 16.2 (C-18), 16.6 (C-19), 27.3 (C-21), 27.9 (C-26), 24.1 (C-27), 28.4 (C-28), 22.2 (C-29), and 15.6 (C-30), 10 sp^3 methylenes at δ_C 33.7 (C-1), 25.4 (C-2), 18.3 (C-6), 34.8 (C-7), 21.7 (C-11), 27.1 (C-12), 31.5 (C-15), 25.9 (C-16), 35.3 (C-22), and 26.4 (C-23), six sp^3 methines (including two oxygenated carbons) at δ_C 49.6 (C-5), 50.7 (C-9), 42.8 (C-13), 49.8 (C-17), and 76.4 (C-3), 86.3 (C-24), six sp^3 non protonated carbons (involving two oxygenated carbons) at δ_C 37.3 (C-4), 40.7 (C-8), 37.7 (C-10), 50.2 (C-14), and 86.7 (C-20), 70.2 (C-25). Since compound **1** had no double bond equivalents and the appearance of four sp^3 non-protonated carbons, the five degrees of unsaturation were supposed to be a tetracyclic triterpenoid skeleton with an additional ring system. Furthermore, the formation of tetrahydrofuran by C-20 and C-24 in the side chain was deduced by the HMBC correlations of H_3-21 and H-24 to C-20. The observed correlations of two sets of *gem*-dimethyl between CH_3-28/CH_3-29 to C-3 and CH_3-26/CH_3-27 to C-25 confirmed the attachment of hydroxyls at C-3 and C-25, respectively. Compound **1** was then elucidated as a dammarane-type triterpenoid. This conclusion was drawn by clear HMBC correlations of CH_3-18 to C-13/C-14, and CH_3-30 to C-8/C-9/C-30, confirming the position of methyls at C-8 and C-14. Notably, dammarane and protostane types have the same planar structure, yet the NOESY cross-peaks of H-9 (α-oriented) to CH_3-18 and CH_3-19 (β-oriented) to H_3-30 data of **1** clarified the dammarane-type as the main skeleton. The α orientation of hydroxyl at C-3 was deduced by the clear cross-peak between CH_3-29/CH_3-19 and H-3 (Fig. 2). Consequently, the configurations at C-20 and C-24 were determined through further literacy with related compounds. According to the previous work conducted by Seger et al [18], the *S* isomer of C-20 and C-24 appears in a more deshielded field at δ_C 86.5 ppm, while the *R* isomer shows at 83.2 ppm for both carbons. Thus, the configurations 20*S* (δ_C 86.5) and 24*S* (δ_C 86.2) of epoxy dammarane in **1** were deduced. Compound **1** was identified as 20*S*,24*S*-epoxy-3*α*,25-dihidroxydammarane or known as 3-*epi*-ocotillol II due to its NMR-1D data were identical to those of previously reported data [11] (Table 1).

Compound **2** was obtained as a white solid ($CHCl_3$). Based on its HR-TOFMS data at *m/z* 475.3793 (calculated for $C_{30}H_{51}O_4$, *m/z* 461.3995, $[M+H]^+$), molecular formula of **1** was determined as $C_{30}H_{50}O_4$, requiring six degrees of unsaturation. The IR spectrum of **2** indicated the presence of hydroxyl (3421 cm^{-1}), C-H sp^3 (2968 cm^{-1}), C=O (1704 cm^{-1}), *gem*-dimethyl (1376 cm^{-1} and 1452 cm^{-1}), and C-O ether (1078 cm^{-1}) groups. Furthermore, the ^{1}H-NMR of **2** exhibited the existence of seven tertiary methyls at δ_H 0.89 (CH_3-18), 0.86 (CH_3-19), 1.15 (CH_3-21), 1.12 (CH_3-27), 1.20 (CH_3-26), 1.02 (CH_3-30), and one deshielded proton at δ_H 1.73 (CH_3-29) suggesting that it was adjacent to an sp^2 carbon. Compound **2** also implied the presence of 20,24-epoxydammarane similar to those of **1** by the signals of an oxygenated methine at δ_H 3.64 (1H, dd, *J*=5.5, 9.5 Hz, H-24). This assignment was further confirmed by the ^{13}C-DEPT NMR data (Table 1) which revealed the existence of seven methyls at δ_C 16.3 (C-18), 20.2 (C-19), 27.9 (C-26), 23.2 (C-27), 24.0 (C-29), 27.2 (C-

21), and 15.3 (C-30), 11 methylenes (including one olefinic carbon) at δ_C 34.3 (C-1), 28.2 (C-2), 24.6 (C-6), 33.9 (C-7), 22.3 (C-11), 26.9 (C-12), 31.5 (C-15), 25.8 (C-16), 34.7 (C-22), 26.4 (C-23), and 113,5 (C-28), five methines (consisting of one oxygenated carbon) at δ_C 50.8 (C-5), 41.2 (C-9), 42.9 (C-13), 49.7 (C-17), and 86.4 (C-24), six quaternary carbons (involving two oxygenated and one olefinic carbons) at δ_C 40.0 (C-8), 39.1 (C-10), 50.4 (C-14), and 70.3 (C-25), 86.6 (C-20), 147.5 (C-4), as well as one carbonyl carboxyl at δ_C 179.8 (C-3). On the other hand, triterpenoid intact with a tetracyclic-based skeleton bears eight methyls and four quaternary sp^3 non-oxygenated carbons [10]. Therefore, the above NMR-1D data of **1** strongly indicated the presence of a *seco*-dammarane-type triterpenoid since compound **1** had only seven and three carbons, for each. The demolition of A ring followed by the formation of carboxylic acid at C-3 and methylene sp^2 at C-29 was deducted through a biogenetic perspective of triterpenoid isolated from *Aglaia* genus, which mainly occurred in the A ring of dammarane compounds [19]. The structure of the side chain including the substitution of hydroxyl at C-25 and 20*S*,24*S*-epoxy ring was predicted to be identical to its previous analog, *epi*-ocotillol II (**1**) due to high similarity on their 1D-NMR data (Table 1). Subsequently, a comparison of ^{13}C-NMR shifts between **2** and a known *seco*-epoxydammarane showed that they resembled. Hence, compound **2** was completely identified as eichlerianic acid (Fig. 1).

Table 1. The ^{13}C-NMR data of compounds **1** and **2** ($CDCl_3$, 125 MHz) and their analogs

Carbon Position	Compounds			
	1*	**3-*epi*-ocotillol II****	**2***	**Eichlerianic acid****
	^{13}C-NMR δ_C	^{13}C-NMR δ_C	^{13}C-NMR δ_C	^{13}C-NMR δ_C
1	33.7	33.6	34.3	34.3
2	25.4	25.3	28.2	28.5
3	76.4	76.2	179.3	179.5
4	37.3	37.2	147.5	147.5
5	49.6	49.5	50.8	50.8
6	18.3	18.2	24.6	24.6
7	34.8	34.7	33.9	33.9
8	40.6	40.6	40.0	40.0
9	50.7	50.6	41.2	41.2
10	37.7	37.6	39.1	39.0
11	21.7	21.6	22.3	22.3
12	27.1	27.0	26.9	26.9
13	42.8	42.7	42.9	42.9
14	50.2	50.1	50.4	50.3
15	31.5	31.4	31.5	31.4
16	25.9	25.8	25.8	25.8
17	49.8	49.8	49.7	49.7
18	16.0	16.0	16.3	16.3
19	15.6	15.5	20.2	20.2
20	86.7	86.5	86.6	86.6
21	27.3	27.1	27.2	27.1
22	35.3	35.1	34.7	34.7
23	26.4	26.3	26.4	26.3
24	86.3	86.2	86.4	86.3
25	70.3	70.2	70.3	70.3
26	27.9	27.8	27.9	27.8
27	24.1	24.0	23.2	23.2
28	28.4	28.3	113.5	113.4
29	22.2	22.1	24.0	24.0
30	16.6	16.5	15.3	15.3

*($CDCl_3$; ^{1}H-NMR 500 MHz; ^{13}C-NMR 125 MHz). **($CDCl_3$; ^{1}H-NMR 500 MHz; ^{13}C-NMR 125 MHz)

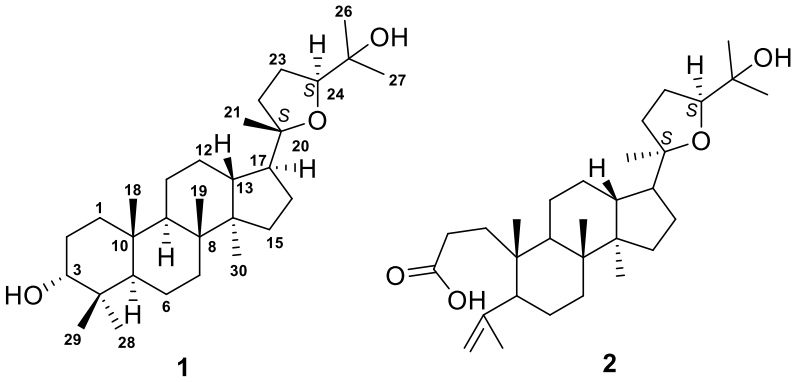

Figure 1. Structure of compounds **1** and **2.**

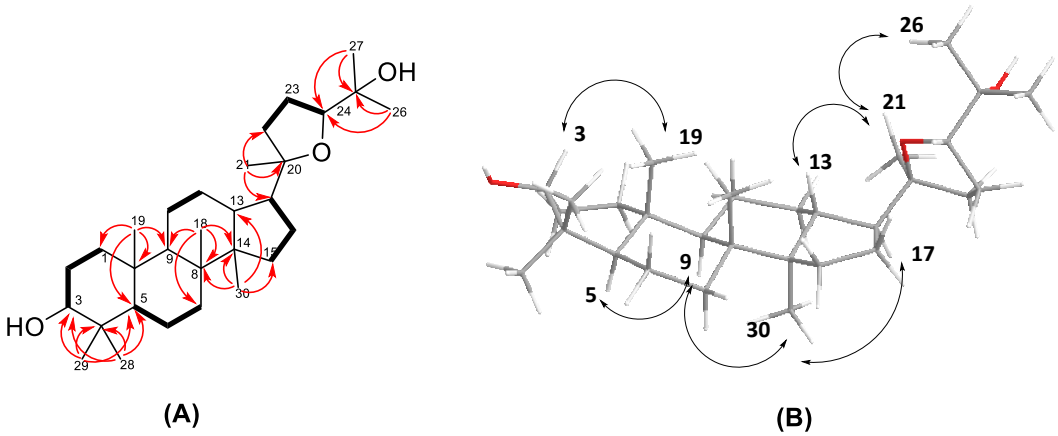

Figure 2. Key HMBC (red arrows) and COSY (black bold) correlations (A) and NOESY interactions (black arrows) (B) of compound **1.**

The biological activity of isolated compounds **1** and **2** was examined against breast cancer MCF-7 cells using resazurin assay according to a method described [20-23]. The results showed that the two compounds were inactive with IC_{50} values of >100 μM, for each, while cisplatin as the positive control was 53.0 μM. These findings were consistent with the previous work, showing that *epi*-ocotillol II (**1**) and eichlerianic acid (**2**) also isolated from *Agalaia* genus had no activity against MCF-7 cells [24].

CONCLUSION

To sum up, we describe the two known 20*S*,24*S*-epoxydammarane-type triterpenoids, identified as *epi*-ocotillol II (**1**) and eichlerianic acid (**2**). Both compounds were found in the *n*-hexane extract of *A. cucullata* stem bark. The elucidation structure of **1** and **2** was deduced based on the ^{1}H and ^{13}C-DEPT NMR together with a comprehensive 2D-NMR and comparison with those of previous NMR data. The determination structure revealed that 20*S*,24*S*-configuration of tetrahydrofuran ring in the side chain had the specific chemical shifts at δ_C 86.5 (20*S*) and 86.2 (24*S*). The biological activity assay of two isolated compounds **1** and **2** exhibited that these two compounds had no activity (IC_{50} >100 μM) against breast cancer MCF-7 cells.

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