

## A Cytotoxic Rocaglate Compound from The Stembark of *Aglaia argentea* (Meliaceae)

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### ABSTRACT

The *Aglaia* genus belong to Meliceae family is unique plant species because the presence of rocaglate and rocaglamide which is so far isolated only from *Aglaia* genus, indicate that type of this compound as a chemical marker for the genus of *Aglaia*. This type of compound known to have strong activity, such as insecticide and cytotoxic. This study describe the isolation, structure elucidation, and cytotoxic activity of an isolated rocaglate compound. Dried stembark of *A. argentea* extracted with methanol and partition between *n*-hexane, ethyl acetate, and *n*-butanol, respectively The extracts were tested against P-388 murine leukemia cells and the ethyl acetat showed strongest activity with IC<sub>50</sub> value of 15.5 µg/mL. The ethyl acetate then was separated and purified with chromatography technique to obtain isolated compound **1**. The chemical structure of isolated compounds were elucidated by spectroscopic methods including one and two-dimensional NMR as well as high-resolution mass spectrometric analysis and identified as a methyl rocaglate. Compound **1** showed strong cytotoxic activity with an IC<sub>50</sub> value of < 0.1 µg/mL.

**Keywords:** *Aglaia*, *Aglaia argentea*, cytotoxic activity, methyl rocaglate, , P-388 murine leukemia cells.

### INTRODUCTION

*Aglaia* is the largest genus belong to Meliaceae family contain more than 150 species (Su et al., 2006; Awang et al., 2012) and about 65 species grown in Indonesia (Wood, Silverstain & Nakajima, 1970). This genus is an important component of the tropical rain forest in the Indomalesiana area (Muellner et al., 2010) and mainly distributed in tropical countries including India, Indonesia, Malaysia and parts of the Western Pacific (Pannell, 1992; Inada et al., 2001). On the basis of literature study, phytochemical studies on *Aglaia* species have led to the identification and isolation of main compounds such as sesquiterpenoids (Joycharat, Plodpai, Panthong, Yingyongna-rongkul & Voravuthikunchai, 2010; Liu, et al., 2014), diterpenoids (Cai, Wang, Zhao, Li & Luo, 2010; Yodsaoe et al., 2012), rocaglate derivatives (Ishibashi, Satastook, Isman & Towers, 1993; Wu et al., 1997; Nugroho et al., 1999), lignans (Wang et al., 2004; Sianturi et al., 2016), dammarane-type triterpenoids (Roux et al., 1998; Khalit et al., 1999; Xie, Yang, Chen, & Yue, 2007; Zhang, wang, Gu, & Kong, 2010; Harneti et al., 2012, Farabi et al., 2017) and cycloartane-type triterpenoids (Khalit et al., 1999; Awang et al., 2012).

Members of the *Aglaia* genus have recently received considerable attention due to the presence of a structurally unique group of cyclopentabenzofurans, the so-called rocaglamide derivatives, which occur exclusively in this genus (Ishibashi et al., 1993; Wu et al., 1997; Nugroho et al., 1999). The parent compound rocaglamide and many of its congeners are potent natural insecticides comparable in activity to azadirachtin (Nugroho et al., 1999; Chaidir et al., 1999; 2001) In addition to their insecticidal activity, the rocaglamides exhibit pronounced antiproliferative activity against human cancer cells *in vitro*, comparable to that of vinblastine sulfate (Chaidir et al., 2001; Bohnenstengel et al., 1999), thus making these compounds an even more fascinating group of potentially bioactive plant secondary metabolites.

During the course of our continuing search for anticancer candidate compounds from Indonesia *Aglaia* plants, we isolated and described cytotoxic triterpenoids from the bark of *A. smithii* and *A. eximia* (Harneti et al., 2012; 2014) as well as a lignan and bisamides from the bark of *A. eximia* (Sianturi et al., 2015; 2016). In the further screening for cytotoxic compounds from Indonesia *Aglaia*

species, we found that ethyl acetate extracts of the bark of *A. argentea* exhibited a significant cytotoxic activity against P-388 murine leukemia cells with  $IC_{50}$  value of  $15.48 \pm 0.03$   $\mu\text{g/mL}$ . *A. argentea*, also known as *langsap hutan* in Indonesia is a higher plant traditionally used to moisturizing the lungs, reducing fever and for treating contused wound, coughs and skin diseases (Mabberley, Pannel, & Sing., 1995; Muellner et al., 2010).

Previous phytochemical studies of *A. argentea* has revealed the presence of a compounds with cytotoxic activity against KB cells, including cycloartane-type triterpenoids (Omobuwajo et al., 1995) and 3,4-secoapo tirucallane-type triterpenoids (Mohamad et al., 1999). Although secondary metabolites of other *Aglaia* species have been investigated previously, the rocaglamide derivatives of *A. argentea* is yet to be reported. We report herein the isolation and structure identification of rocaglate compound along with its cytotoxic activity against P-388 murine leukemia cells that not yet investigated previously.

## EXPERIMENTAL SECTION

### Plant Material

The stem bark of *A. argentea* were collected in Bogor Botanical Garden, Bogor, West Java Province, Indonesia in June 2015. The plant was identified by the staff of the Bogoriense Herbarium, Research Center for Biology, Indonesian Institute of Science, Bogor, Indonesia and a voucher specimen (No. Bo-1288718) has been deposited at the herbarium.

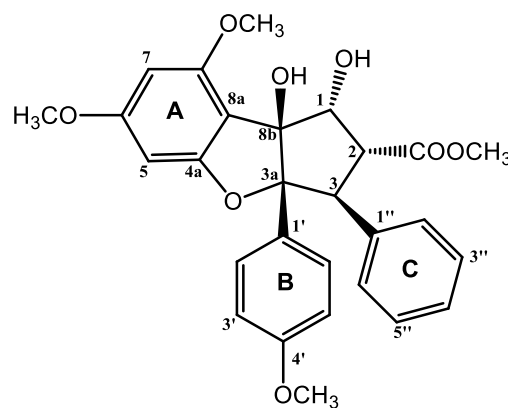
### General Experimental Procedure

The IR spectra were recorded on a Perkin-Elmer spectrum-100 FT-IR (Waltham, MA, USA) in KBr. Mass spectra were obtained with a Synapt G2 mass spectrometer instrument (Waters, Milford, MA, USA).  $^1\text{H}$ ,  $^{13}\text{C}$ , DEPT NMR spectral data and  $^1\text{H}$ - $^1\text{H}$  COSY, HMQC and HMBC experiments were performed on a JEOL ECZ-600 spectrometer at 600 MHz (Tokyo, Japan) with  $\text{CDCl}_3$  as a solvent, chemical shifts are given on a  $\delta$  (ppm) scale and tetramethylsilane (TMS) as an internal standard. Column chromatography was conducted on silica gel 60 (Kanto Chemical Co., Inc., Japan) and (Merck, Darmstadt, Germany). Preparative MPLC using a Buchi Pump Controller C-610, Buchi Pump Modules C-605 with FLH-R10030B

SiliCycle column- ISO04 Siliasep<sup>TM</sup> (Buchi, Switzerland). TLC plates were pre-coated with silica gel GF<sub>254</sub> (Merck, 0.25 mm) and detection was achieved by spraying with 10%  $\text{H}_2\text{SO}_4$  in EtOH, followed by heating and under ultra-violet light at wavenumber 254 and 367 nm.

### Extraction and Isolation

The crushed and dried bark (2.5 kg) of *A. argentea* was extracted with methanol (12 L) at room temperature for 5 days. The methanol extract was evaporated under reduce pressure to give concentrated of MeOH extract (133.5 g). The concentrated MeOH extract was first suspended in  $\text{H}_2\text{O}$  and then partitioned successively with *n*-hexane (4 L), EtOAc (4 L) and *n*-butanol (4 L). The EtOAc layer was subsequently dried over anhydrous sodium sulfate, filtered, and evaporated to dryness. The EtOAc soluble fraction (12.1 g) was fractionated by column chromatography on silica gel using a gradient *n*-hexane-EtOAc to give eight fractions (A–H). Fraction D (1.12 g) was chromatographed on a Medium Pressure Liquid Chromatography (MPLC) column of silica gel, eluted with  $\text{CHCl}_3$ -EtOAc (50:1), to give eight subfractions (D01–D08). Subfraction D05 was separated on preparative TLC silica gel GF<sub>254</sub>, eluted with *n*-hexane: $\text{Me}_2\text{CO}$  (7:3), to give **1** (10 mg).



**Figure 1.** Chemical structure of compound **1**.

### Determination of Cytotoxic Activity

The cytotoxicity assay was conducted according to the method described by Sahidin et al., 2005 and Alley et al., 1998. P-388 cells were seeded into 96-well plates at an initial cell density of approximately  $3 \times 10^4$  cells  $\text{cm}^{-3}$ . After 24 h of incubation for cell attachment and growth, varying concentrations of samples were added. The compounds added were first dissolved in DMSO at the required

concentration. Subsequent six desirable concentrations were prepared using PBS (phosphoric buffer solution, pH = 7.30 - 7.65). Control wells received only DMSO. The assay was terminated after a 48 h incubation period by adding MTT reagent [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide; also named as thiazol blue] 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. Optical density was read by using a micro plate reader at 550 nm. IC<sub>50</sub> 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 ( $\mu\text{g/mL}$ ). The IC<sub>50</sub> value is the concentration required for 50% growth inhibition. Each assay and analysis was run in triplicate and averaged.

## RESULT AND DISCUSSION

The dried bark of *A. eximia* were grounded and successively extracted with *n*-hexane, ethyl acetate and methanol. All of the extracts were evaluated cytotoxic activity against P-388 murine leukemia cells and the ethyl acetate showed strongest cytotoxic activity. Subsequent phytochemical analysis was therefore focused on the ethyl acetate extract. By using the cytotoxic activity to follow the separations, the ethyl acetate extract was chromatographed over a vacuum-liquid chromatographed (VLC) column packed with silica gel 60 by gradient elution. The VLC fractions were repeatedly subjected to normal-phase column chromatography, medium pressure liquid chromatography and preparative thin layer chromatography (PTLC) on silica gel GF<sub>254</sub> to afford a cytotoxic compounds **1** (Figure 1).

Compound **1** was obtained as a white amorphous powder. The High Resolution Time of Flight Mass spectroscopy (HRTOFMS) spectrum showed  $[\text{M}+\text{H}]^+ m/z$  493.1870 (calcd.  $m/z$  492.1874), which corresponded to the molecular formula of C<sub>28</sub>H<sub>28</sub>O<sub>8</sub> thus requiring fifteen degrees of unsaturation. The IR spectra showed absorption peaks at 3430 cm<sup>-1</sup> (OH), 2985 (C-H aliphatics), 1675 cm<sup>-1</sup> (conjugated carbonyl), 1560 (C=C aromatics), 1478 cm<sup>-1</sup> (C=C olefinic), 1168 cm<sup>-1</sup> (asymmetric C-O-C stretch) and 825 cm<sup>-1</sup> (substituted benzene). The <sup>1</sup>H-NMR spectrum of compound **1** showed

a characteristic AA'BB' pattern of B ring at  $\delta_{\text{H}}$  7.10 (2H, dd,  $J = 1.8, 6.6$  Hz) and  $\delta_{\text{H}}$  6.66 (2H, dd,  $J = 1.8, 6.6$  Hz), corresponding to H-2'/H-6' and H-3'/H-5' in benzene ring. The resonances of two *meta*-coupling protons of ring A were observed at  $\delta_{\text{H}}$  6.27 (1H, d,  $J = 1.8$  Hz, H-5) and  $\delta_{\text{H}}$  6.11 (1H, d,  $J = 1.8$  Hz, H-7). The addition of olefinic signal at  $\delta_{\text{H}}$  7.04 (2H, m) and 6.85 (2H, m), indicate the presence of C ring as a monosubstituted benzene ring. Resonance of signals at  $\delta_{\text{H}}$  3.63, 3.69, 3.82, and 3.86 (each 3H, s) were assigned that compound **1** have four methoxy groups. The oxymethine protons at  $\delta_{\text{H}}$  5.01 (1H, d,  $J = 6$  Hz, H-1), 3.89 (1H, dd,  $J = 6.6, 14.4$  Hz, H-2), and 4.28 (1H, d,  $J = 13.8$  Hz, H-3), which very similar with characteristic of core skeleton in cyclopenta[*b*]benzofuran-type rocaglate (Othman et al., 2016). The <sup>13</sup>C-NMR spectrum showed twenty eight carbon resonances, which were classified by their chemical shifts and DEPT (Distortionless Enhancement by Polarization Transfer) spectra as four methoxy, fourteen methines, and ten quaternary carbons, include eighteen *sp*<sup>2</sup> carbons (eleven methines and seven quaternary carbons). This functionalities accounted for ten out of the total fifteen degrees of unsaturation. The remaining of five degree of unsaturation were consistent with cyclopenta[*b*]benzofuran-type rocaglate skeleton to form three benzene ring and an ester group at C-2, which resonating at  $\delta_{\text{C}}$  170.7 ppm. To determine the connectivity of the partial structure due to the presence of methoxy, hydroxy and ester groups, <sup>1</sup>H-<sup>1</sup>H COSY (correlated spectroscopy) and HMBC (Heteronuclear multiplicity bond connectivity) experiments were carried out, and the results are shown in Figure 2. The <sup>1</sup>H-<sup>1</sup>H COSY spectra confirm for neighboring protons at H-1/H-2/H-3 in core skeleton, H-2'/H-3' and H-5'/H-6' in B ring, H-2''/H-3''/H-4''/H-5''/H-6'' in C ring. All these data showed in line to the <sup>1</sup>H NMR spectrum. In the HMBC spectrum, two *meta*-coupling protons of A ring, H-5 at  $\delta_{\text{H}}$  6.27 (1H, d,  $J = 1.8$  Hz) and H-7 at  $\delta_{\text{H}}$  6.11 (1H, d,  $J = 1.8$  Hz) exhibited correlations to C-6 ( $\delta_{\text{C}}$  164.2) and C-8 ( $\delta_{\text{C}}$  157.2), indicate that two methoxy groups attach to C-6 and C-8, respectively. The other methoxy group was determined by correlation of methoxy signal at  $\delta_{\text{H}}$  3.69 (3H, s) to C-4' ( $\delta_{\text{C}}$  158.8), indicated that another methoxy group was attached to C-4.

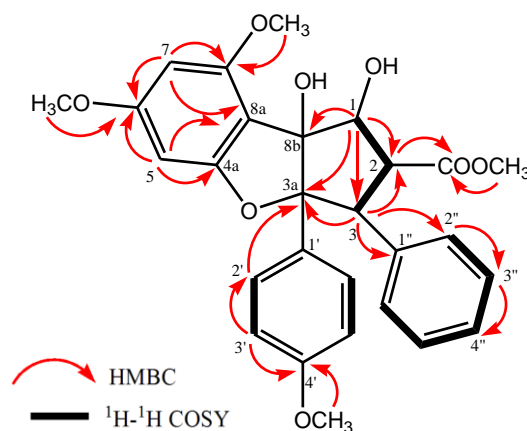
**Table 1.** NMR data for **1** (600 MHz for  $^1\text{H}$  and 150 MHz for  $^{13}\text{C}$ , in  $\text{CDCl}_3$ ) and methyl rocaglate (An et al., 2016)

No.	<b>1</b>		methyl rocaglate	
	$^{13}\text{C}$ NMR $\delta_{\text{C}}$ (mult.)	$^1\text{H}$ NMR $\delta_{\text{H}}$ (Integral, mult., $J=\text{Hz}$ )	$^{13}\text{C}$ NMR $\delta_{\text{C}}$ (mult.)	$^1\text{H}$ NMR $\delta_{\text{H}}$ (Integral, mult., $J=\text{Hz}$ )
1	79.6 (d)	5.01 (1H, d, 6)	79.8 (d)	5.02 (1H, dd, 1.6, 6.8)
2	50.5 (d)	3.89 (1H, dd, 6.6, 14.4)	50.5 (d)	3.91 (1H, dd, 6.8, 14.4)
3	55.0 (d)	4.28 (1H, d, 13.8)	55.0 (d)	4.32 (1H, d, 13.4)
3a	101.9 (s)	-	102.2 (s)	-
4a	160.9 (s)	-	160.7 (s)	-
5	89.5 (d)	6.27 (1H, d, 1.8)	93.4 (d)	6.29 (1H, d, 2.4)
6	164.2 (s)	-	167.7 (s)	-
7	92.7 (d)	6.11 (1H, d, 1.8)	93.6 (d)	6.13 (1H, d, 2.4)
8	157.0 (s)	-	157.2 (s)	-
8a	107.8 (s)	-	110.0 (s)	-
8b	93.8 (s)	-	93.5 (s)	-
6-OMe	55.8 (q)	3.82 (3H, s)	55.7 (q)	3.88 (3H, s)
8-OMe	55.9 (q)	3.86 (3H, s)	56.0 (q)	3.84 (3H, s)
1'	126.4 (s)	-	126.4 (s)	-
2',6'	129.1 (d)	7.10 (2H, dd, 1.8, 6.6)	129.1 (d)	7.11 (1H, d, 8.8)
3',5'	112.8 (d)	6.66 (2H, dd, 1.8, 6.6)	112.7 (d)	6.68 (1H, d, 8.8)
4'	158.8 (s)	-	158.8 (s)	-
4'-OMe	55.2 (q)	3.69 (3H, s)	55.1 (q)	3.71 (3H, s)
1''	135.9 (s)	-	136.9 (s)	-
2'',6''	127.8 (d)	7.04 (2H, m)	127.9 (d)	6.88 (2H, m)
3'',5''	127.9 (d)	6.85 (2H, m)	127.7 (d)	7.07 (2H, m)
4''	126.7 (d)	7.04 (1H, m)	126.6 (d)	6.88 (2H, m)
2-CO <sub>2</sub> CH <sub>3</sub>	170.7 (s)	-	170.4 (s)	-
2-CO <sub>2</sub> CH <sub>3</sub>	52.1 (q)	3.63 (3H, s)	51.9 (q)	3.65 (3H, s)

The correlation between H-2' ( $\delta_{\text{H}}$  7.10 ppm) to C-3a ( $\delta_{\text{C}}$  101.9), showed that tetra substituted benzene (B ring) was attached to C-3a. The presence of mono-substituted benzene ring (C ring) at C-3 was supported by correlation between H-3 ( $\delta_{\text{H}}$  4.28) to C-1'' ( $\delta_{\text{C}}$  135.9) and C-2'' ( $\delta_{\text{C}}$  127.8). The position of ester group in C-2 was determined by correlation of methoxy group ( $\delta_{\text{H}}$  3.63) and H-2 ( $\delta_{\text{H}}$  3.89 ppm) to ester carbonyl at  $\delta_{\text{C}}$  170.7 ppm. An oxygenated methine at  $\delta_{\text{H}}$  5.01 ( $\delta_{\text{C}}$  89.5) were correlated to an oxygenated carbon at C-8b ( $\delta_{\text{C}}$  93.8) and C-2 ( $\delta_{\text{C}}$  50.5), indicated that secondary and tertiary alcohols were located at C-1 and C-8b, respectively.

The stereochemistry of **1** was determined by comparison to those coupling constant in  $^1\text{H}$  NMR spectra ( $^1J$  and  $^2J$ ) and chemical shift of  $^{13}\text{C}$  NMR spectra with previously literature data along with biogenetic point of view the occurrence of cyclopenta[*b*]benzofuran-type rocaglate in *Aglaia* genus (Othman et al., 2016). The full

assignments of compound **1** are shown in **Table 1**. Comparison of the NMR data of **1** with those of methyl rocaglate previously reported (An et al., 2016) showed high similarity, consequently compound **1** was identified as a methyl rocaglate and showed in this plant for the first time.

**Figure 2.** Selected HMBC and  $^1\text{H}$ - $^1\text{H}$  COSY correlations for **1**.

The cytotoxicity effects of the isolated compound **1** against P-388 murine leukemia cells were investigated according to the method described in previous papers (Harneti et al., 2012; Sianturi et al., 2015) and artonin E (IC<sub>50</sub> 0.3 µg/mL) was used as a positive control (Hakim et al., 2007). The cytotoxic activity of isolated compound **1** showed very strong activity with an IC<sub>50</sub> value of < 0.1 µg/mL.

Rocaglate compounds known as cytotoxic agent. Since rocaglate and its derivatives have been found to have anticancer activities in experimental animal models, efforts have been taken to explore the molecular mechanisms of their actions. In several early publications, rocaglate derivatives were reported to function mainly in a cytostatic rather than a directly cytotoxic manner (Bohnenstengel et al., 1999; Lee, Cui, Mehta, Kinghorn & Pezzuto, 1998). It was shown that treatment of the human lung carcinoma cells Lu1 with 40-demethoxy-30,40-methylenedioxy-methyl rocaglate resulted in inhibition of tumor cell proliferation with cell accumulation in the G1/G0 phase of the cell cycle with only marginal cell death. Thereafter, didesmethyl-rocaglamide, agla-roxin D (aglaiastatin), and silvestrol were shown to inhibit cell proliferation of different human malignant cell lines with the cell cycle blocked at the G2/M phase with negligible death. Based on these observations, it was thought that inhibition of translation is the key mode of action by which cyclopenta[*b*]benzofurans exert their antitumor activities. Induction of apoptosis is now known to be also an important mechanism of rocaglamide mediated anticancer activity (Ebada et al., 2011).

## CONCLUSION

A rocaglate-type compound was identified as a methyl rocaglate (**1**) has been isolated from the stem bark of *Aglaia argentea* for first time. This investigation supported the occurrence of rocaglate-type compound in *Aglaia* genus. Methyl rocaglate **1**, was evaluated for its cytotoxic activity against P-388 murine leukemia cells, *in vitro* and showed strong cytotoxic activity with IC<sub>50</sub> value of < 0.1 µg/mL. A rocaglate is a unique compound only isolated from *Aglaia* genus. This type of compound known as a cytotoxic agent to inhibit cell proliferation and cell translation.

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