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A 2H-tetrahydropyran derivative and bioactive constituents from the bark of *Goniothalamus elegants* Ast

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ABSTRACT

A new 2H-tetrahydropyran derivative, 6-*epi*-goniothalesdiol A (**1**), together with nine known styryllactones (**2**–**10**) and five known aristolactams (**11**–**15**) were isolated from the bark of *Goniothalamus elegants* Ast. The structures were elucidated by spectroscopic methods. The isolated compounds were evaluated for their cytotoxicity toward the KB, MCF7 and NCI-H187 cell lines as well as antimalarial and antimycobacterial activities. Compounds **4** and **10** showed strong activity against all three human cancer cell lines with IC_{50} values in the range of 0.538 to 4.25 μg/ml, while compounds **2**, **4**, **10** and **14** showed potent cytotoxicity against NCI-H187 with IC_{50} values in the range of 0.072 to 2.17 μg/ml. In addition, compounds **4**, **6**, **7**, **9**, **10** and **13** showed strong anti-plasmodial activity with IC_{50} in the range of 2.28 to 5.89 μg/ml.

1. Introduction

The genus *Goniothalamus* (Annonaceae) consists of 160 species distributed throughout the tropical forests of Southeast Asia, some of which are used widely in the folk medicine of several countries [1]. In Thailand, 25 species of the genus have been found [2]. Phytochemical studies on *Goniothalamus* species have led to the identification of a variety of compounds: styryllactones, acetogenins, phenanthrene lactams, naphthoquinones, azaanthraquinones, terpenoids, flavonoids and steroids [3–10]. Several styryllactones have had their cytotoxic activity against human cancer cell lines reported in the literature [11–14]. This study was initiated by the results of a medicinal plant survey in Phu Dong Ee-Pia Forest, Ubonratana District, Khon Kaen Province, Thailand. *Goniothalamus elegants* is called "Kao Nang Nee" and a water decoction has been used as a treatment for heart disease and bloody diarrhea [15]. However, the chemical constituents of *G. elegants* and their biological activities have not been reported. A preliminary biological screen revealed that the crude EtOAc and MeOH extracts from the bark of *G. elegants* showed cytotoxic activity against the KB oral cavity cancer cell line with % inhibition of 98.09 and 69.12, respectively. In the present work, we report the bioactive constituents, a new 6-*epi*-goniothalesdiol A (**1**), nine known styryllactones (**2–10**) and five known aristolactams (**11–15**) isolated from the EtOAc and MeOH extracts of the bark of *G. elegants*. The isolation and structure elucidation as well as bioactivity evaluation of the isolated compounds are discussed. Moreover, a plausible biogenesis pathway of **1** and the isolated styryllactone derivatives (**2–10**) have been proposed.

2. Experimental

2.1. General experimental procedures

Optical rotations were measured on a JASCO DIP-1000 digital polarimeter and UV spectra were recorded using a

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Shimadzu 2450 UV–visible spectrophotometer. IR spectra were obtained using a Perkin-Elmer spectrum 100. NMR spectra were recorded in $CDCl_3$, CD_3OD and acetone-d_6 as solvents on a Varian Mercury Plus 400 spectrometer; the internal standards were referenced from the residue of those solvents. HRESIMS was recorded on a Bruker Micromass Q-TOF-2™ spectrometer. Chromatography was carried out on MERCK silica gel 60 (230–400 mesh) and Sephadex LH-20 (40–70 μm; GE Health care). TLC was performed with precoated MERCK silica gel 60 PF_{254} and aluminum sheets, and the spots were visualized at 254 and 366 nm, sprayed with anisaldehyde reagent and then heated until charred by a heat gun. Commercial grade solvents were distilled at their boiling point ranges prior to use for extraction and chromatographic separations (CC and TLC), whereas AR grade solvents were used for crystallization.

2.2. Plant material

Bark of *G. elegants* was collected from Phu Dong Ee-Pia forest, Ubonratana district, Khon Kaen, Thailand in June 2012. The plant was identified by Professor James F. Maxwell, Chiang Mai University. A voucher specimen (SRITUBTIM 18) was deposited at Udon Thani Rajabhat Universtiy Herbarium, Udon Thani, Thailand.

2.3. Extraction and isolation

The air-dried and powdered bark of *G. elegants* (2.2 kg) was extracted with EtOAc (3 × 5 l) and MeOH (3 × 5 l) at room temperature (3 days each time) to provide the EtOAc extract (104 g) and MeOH extract (118 g) after evaporation of the solvents under reduced pressure. The EtOAc extract was subjected to flash column chromatography (FCC) over silica gel (column: 10 × 10 cm) eluted with a gradient system of hexane–EtOAc and EtOAc–MeOH to afford 7 fractions (E1–E7) on the basis of TLC. Fraction E3 (30.5 g) was chromatographed on silica gel column chromatography (CC) (column: 5 × 20 cm) eluted with hexane–EtOAc (80:20) to give **15** as colorless crystals (54.0 mg) and the residue was further purified by Sephadex LH-20 (column: 2.5 × 50 cm) using MeOH as solvent to obtain a pale yellow oil of **10** (280.2 mg) and an additional amount of **15** (70.5 mg). Fraction E4 (38.5 g) was separated by FCC (column: 5 × 20 cm) over silica gel using a hexane–EtOAc gradient to provide 4 subfractions (E4.1–E4.4). Subfraction E4.1 was purified by Sephadex LH-20 column using MeOH as an eluent to give **7** as a yellowish oil (30.0 mg) and a white solid of **14** (25.4 mg). Subfraction E4.2 (1.4 g) was chromatographed on silica gel column (column: 2 × 20 cm) eluted with CH_2Cl_2–EtOAc (50:50) to give **12** as a white solid (28.1 mg) and the remaining mixture was further purified by Sephadex LH-20 column using MeOH as solvent to yield a white solid of **11** (21.4 mg). Subfraction E4.3 (16.5 g) was purified by Sephadex LH-20 column using CH_2Cl_2–MeOH (30:70) as an eluent to give **5** as a white powder (57.5 mg) and subfraction E4.4 (21.3 g) was further purified by Sephadex LH-20 column using MeOH as an eluent to yield **4** as a pale yellow oil (46.0 mg) and a yellow solid **13** (54.0 mg). Fraction E5 (56.5 g) was separated by silica gel CC (column: 5 × 20 cm), eluted with a gradient of CH_2Cl_2–EtOAc to give 4 subfractions (E5.1–E5.4). Subfraction E5.1 (1.3 g) was further purified by Sephadex LH-20 column using MeOH for elution to afford colorless needles of **6** (48.0 mg). Subfraction E5.2 (198.0 mg) was purified by CC (column: 2.5 ×30 cm) over silica gel, eluted with CH_2Cl_2–EtOAc (70:30) and then recrystallized from EtOAc to give **3** as a white solid (43.0 mg). Fraction E6 (148.5 mg) was separated by silica gel CC (column: 2.5 × 40 cm), eluted with CH_2Cl_2–MeOH (95:5) to give **8** as a white solid (36.1 mg). Fraction E7 (120.0 mg) was subjected to Sephadex LH-20 column using MeOH as solvent and followed by silica gel CC (column: 2.5 × 30 cm), eluted with CH_2Cl_2–MeOH (100:0 to 80:20) to give a white solid of **2** (40.5 mg).

The MeOH extract was fractionated by silica gel CC (column: 10 × 10 cm) eluted with a gradient of CH_2Cl_2–MeOH to give 6 fractions (M1–M6). Separation of M2 (270.5 mg) by Sephadex LH-20 column using MeOH as solvent and further purification by silica gel CC (column: 2.5 × 30 cm) eluted with an isocratic system of CH_2Cl_2–EtOAc (70:30) gave an additional amount of **10** (76.0 mg). Fraction M3 (108.7 mg) was chromatographed by silica gel CC (column: 2.5 × 30 cm), eluted with EtOAc–hexane (60:40 to 100:0) and repeatedly purified on Sephadex LH-20 column using MeOH as solvent to give additional amount of **4** (55.6 mg) and **13** (30.4 mg). Fraction M4 (152.4 mg) was separated by silica gel CC (column: 2.5 × 30 cm), eluted with CH_2Cl_2–EtOAc (50:50) and recrystallized from EtOAc to give an additional amount of **5** (34.0 mg). Fraction M5 (160.4 mg) was purified by Sephadex LH-20 column eluted with MeOH to afford an additional amount of **6** (50.3 mg) and then eluted with CH_2Cl_2–MeOH (30:70, 50:50 and 70:30) to give **9** as a white solid (40.7 mg) and an additional amount of **8** (25.1 mg). Fraction M6 (258.0 mg) was subjected to Sephadex LH-20 column using MeOH as solvent and further purified on silica gel CC (column: 2.5 × 30 cm) by elution with a gradient system of CH_2Cl_2–EtOAc and EtOAc–MeOH to give **1** as a white solid (25.4 mg) and an additional amount of **2** (40.0 mg).

Compound **1**: white amorphous solid, R_f 0.50 (CH_2Cl_2–acetone, 7:3); $[\alpha]^{23}_D$ - 15.8 (*c* 0.3, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 208.4 nm (3.91); IR (film) ν_{max} 3276, 2952, 2843, 1730, 1443, 1314, 1250, 1152, 1092, 999 cm^{-1}; ^1H NMR and ^{13}C NMR spectral data in acetone-d_6 see Table 1; ^1H NMR ($CDCl_3$, 400 MHz) 7.39–7.37 (m, 5ArH), 4.98 (d, 4.8 Hz, H-2), 4.17–4.14 (m, H-3 and H-6), 3.99 (br dt, 7.6, 3.0 Hz, H-4), 3.69 (s, CH_3O-8), 2.90 (dd, 15.0, 8.6 Hz, H-7a), 2.63 (dd, 15.0, 5.2 Hz, H-7b), 1.88–1.79 (m, H_2-5); ^{13}C NMR spectral data in $CDCl_3$ see Table 1; positive HRESIMS *m/z* 289.1157 $(M + Na)^+$ (calcd for $C_{14}H_{18}O_5Na$, 289.1154).

2.4. Antimalarial assay

Antimalarial activity was evaluated against the parasite *Plasmodium falciparum* (K1, multidrug-resistant strain) [16]. Quantitative assessment of activity in vitro was determined by means of the microculture radioisotope technique [17]. The inhibitory concentration (IC_{50}) represents the concentration that causes 50% reduction in parasite growth as indicated by the in vitro uptake of [^{3}H]-hypoxanthine by *P. falciparum*. The standard compound was mefloquine.

2.5. Cytotoxicity assays

Cytoxicity assays against human epidermoid carcinoma (KB), human breast adenocarcinoma (MCF7), human small cell lung cancer (NCI-H187) and vero cells were performed employing

Table 1
^{1}H and ^{13}C NMR spectroscopic data of goniothalesdiol A [31] and **1**.

Goniothalesdiol A			Compound **1**		
Position	δ_H (*J* in Hz)[a]	δ_C[b]	δ_H (*J* in Hz)[a]	δ_C[a]	δ_C[b]
2	4.87 d (8.0)	73.4	4.86 d (5.2)	75.3 d	75.7 d
3	3.68 dd (8.0, 3.6)	85.7	4.04 dd (5.2, 3.2)	70.2 d	70.3 d
4	4.47 ddd (5.6, 3.6, 2.4)	72.8	3.89 br dt (7.2, 3.6)	66.4 d	66.2 d
5	1.77 ddd (13.6, 4.8, 2.4) 2.35 ddd (13.6, 8.4, 5.6)	39.8	1.90–1.82 m	34.1 t	34.2 t
6	4.38 dddd (8.4, 7.2, 6.4, 4.8)	74.4	4.16 br dq (9.2, 5.0)	67.7 d	67.4 d
7a	2.75 dd (15.2, 7.2)	40.3	2.90 dd (15.2, 9.2)	39.6 t	39.8 t
7b	2.61 dd (15.2, 6.4)		2.62 dd (15.2, 4.8)		
8		172.3		171.8 s	171.8 s
CH_3O-8		51.8	3.62 s	50.7 t	51.7 t
1′		147.7		139.6 s	137.5 s
2′, 6′	7.40 m	126.2	7.45 d (7.6)	127.0 d	127.0 d
3′, 5′	7.31 m	128.4	7.34 t (7.6)	128.1 d	128.7 d
4′	7.28 m	127.8	7.26 t (7.6)	127.1 d	128.0 d

[a] in acetone-d_6.
[b] in $CDCl_3$.

the colorimetric method [18]. The reference substances were ellipticine and tamoxifen.

2.6. Antimycobacterial assay

Antimycobacterial activity was assessed against *Mycobacterium tuberculosis* $H_{37}Ra$ using the Microplate Alamar Blue Assay (MABA) [19]. The standard drug was ethambutol.

3. Results and discussion

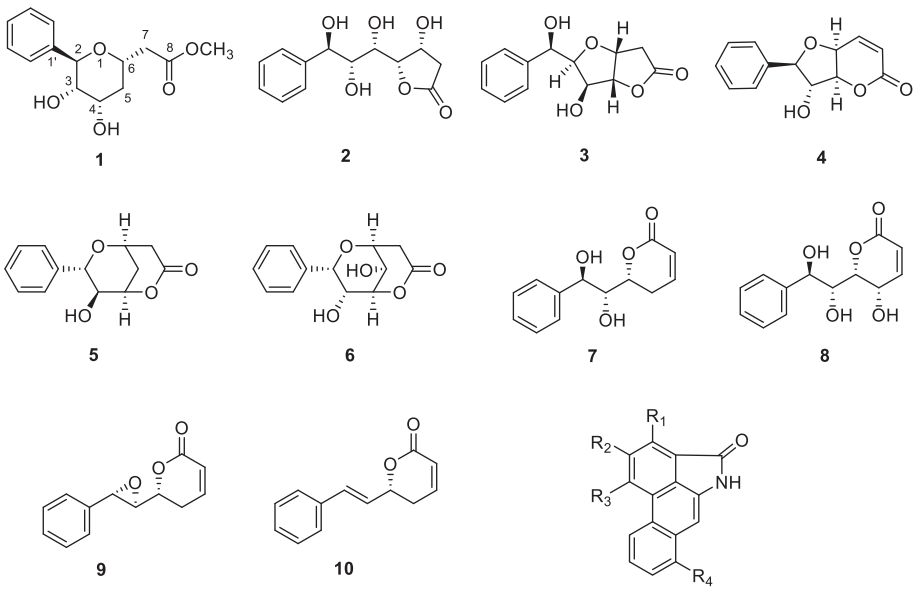
Chromatographic separation of the crude EtOAc and MeOH extracts from the bark of *G. elegants* yielded a new 6-*epi*-goniothalesdiol A (**1**) and 14 known compounds (**2–15**). These compounds were identified on the basis of spectroscopic methods and comparison of the data with literature values as (+)-cardiobutanolide (**2**) [20], (+)-goniofufurone (**3**) [21], (+)-altholactone (**4**) [22], (−)-8-*epi*-9-deoxygoniopypyrone (**5**) [23], (+)-goniopypyrone (**6**) [21,22], (+)-goniodiol (**7**) [21,24], (+)-goniotriol (**8**) [22,25], (+)-goniothalamin oxide (**9**) [26], (+)-goniothalamin (**10**) [27], piperolactam B (**11**) [28], goniopedaline (**12**) [29], velutinam (**13**) [29], aristolactam BII (**14**) [30] and piperolactam C (**15**) [30].

Compound **1** was obtained as a white amorphous solid. Its molecular formula was designated as $C14H_{18}O_5$ based on the $[M + Na]^+$ ion peak at *m/z* 289.1157 (calcd 289.1154) in the HRESIMS, indicating six indices of hydrogen deficiency. The UV spectrum displayed an absorption maximum at 208 nm due to an aromatic ring. The IR spectrum revealed the presence of hydroxy (3276 cm^{-1}) and ester carbonyl (1730 cm^{-1}) groups. The ^{1}H NMR data (Table 1) showed typical signals for a monosubstituted benzene ring with resonances at δ 7.45 (d, $J = 7.6$ Hz, H-2′ and H-6′), 7.34 (t, $J = 7.6$ Hz, H-3′ and H-5′) and 7.26 (t, $J = 7.6$ Hz, H-4′). The ^{1}H and ^{13}C NMR spectra showed signals at $\delta_{H/C}$ 4.86/75.3 (C-2), 4.04/70.2 (C-3), 4.16/67.7 (C-6), 3.89/66.4 (C-4), indicating four oxymethine units. The ^{1}H NMR spectrum also showed a multiplet signal of methylene protons at δ_H 1.82–1.90 (H_2-5), two doublet of doublets of methylene protons at δ 2.90 (dd, $J = 15.2$, 9.2 Hz, H-7a) and 2.62 (dd, $J = 15.2$, 4.8 Hz, H-7b) and a singlet of methyl ester at δ 3.62 (CH_3O-8). The COSY data exhibited the coupling correlations through the sequence of H-2 to H-6 (Fig. 2) and the HMBC spectrum showed correlations from H-2 to C-3/C-4/C-6 and H-5 to C-3/C-4/C-6/C-7, supporting that **1** was consistent with a tetrahydropyran ring. The COSY correlation of H-6 with H-7 as well as HMBC correlations from H-7 to C-5/C-6/C-8; H-2 to C-1′/C-2′; and methoxy protons to a carbonyl carbon (δ_C 171.4, C-8) supported the location of the acetyl on a methylene carbon (C-7), as well as, methylene and aromatic groups on C-6 and C-2 of the tetrahydropyran moiety, respectively. (See Fig. 1.)

Complete ^{1}H and ^{13}C NMR assignments of **1** were made by comparison of the NMR values to those reported for a known goniothalesdiol A (Table 1) [31]. The differences between **1** and goniothalesdiol A were the coupling constants of H-2 and H-3 ($J_{2/3} = 5.2$ and 8.0 Hz); H-6 and H_2-5 ($J_{6/5ax} = 5.0$ and 8.4 Hz) and a coupling pattern of methylene protons (H_2-5), providing evidence for **1** to be a stereoisomer of goniothalesdiol A. Goniothalesdiol A has been clearly identified by the coupling constants as a 2,3,4,6-tetrasubstituted tetrahydropyran ring showing a chair conformation with *cis*-1,3-diequatorial bulky groups at C-2 and C-6 [31].

The stereochemistry of **1** was identified by analysis of coupling constants and NOE experiment. The vicinal coupling constants of H-2 and H-3 ($J_{2/3} = 5.2$ Hz) and H-6 and H_2-5 ($J_{6/5a} = J_{6/5b} = 5.0$ Hz) are not clarified by a chair conformation. Instead, these values agree well with those reported for a twist-boat conformation for **1** [32] suggesting the steric effect of the bulky groups. In addition, the NOE correlations between H-3/H-4; H-3/H-6; H-4/H-5; H-4/H-6; and H-5/H-6 (Fig. 2) supported a plausible conformation with the *trans* 1,3-dibulky groups, revealing the relative stereochemistry of C-2 and C-6. Moreover, the resonance signal of H-3 in **1** appears lower field (δ 4.04) than in goniothalesdiol A (δ 3.68). While the signal of H-4 (δ 3.89) shows higher field than goniothalesdiol A (δ 4.47), suggesting an anisotropic effect of a benzene ring at C-2. From the above evidence, the structure of **1** was established as a new 6-*epi*-goniothalesdiol A.

According to the previous literature [14,31,33–35], a plausible biogenetic pathway for the isolated compounds (**1–10**) has been proposed (Fig. 3). Goniomicin A undergoes (a) methylation, oxidation, and Michael cyclization gives a new 6-*epi*-goniothalesdiol A (**1**), alternatively (b) cyclization should give



	R_1	R_2	R_3	R_4
11	OCH_3	OCH_3	OH	H
12	OCH_3	OH	OCH_3	H
13	H	OCH_3	OCH_3	OH
14	H	OCH_3	OCH_3	H
15	OCH_3	OCH_3	OCH_3	H

Fig. 1. Structures of compounds **1**–**15**.

(+)-goniothalamin (**10**) which further give two epoxidized products **9** and isogoniothalamin oxide. *Trans*-ring opening of epoxide **9** yields (+)-goniodiol (**7**), and this is followed by allylic hydroxylation to give (+)-goniotriol (**8**). Rearrangement of pyrone **8** should give butenolide **16** which further goes hydration to **2**. Epimerization of **8** should give 7-*epi*-goniotriol followed by an intramolecular ring closing with inversion at the benzylic carbon to give **4**. Finally, bicyclic lactones **3**, **5** and **6** might be obtained by Michael cyclization.

All compounds were evaluated for their cytotoxicity against three cancer cell lines, antimalarial and antimycobacterial activities which are summarized in Table 2. Compounds **4**, **6**, **7**, **9**, **10** and **13** exhibited strong in vitro antimalarial activity against *P. falciparum* with IC_{50} values of 2.80, 4.46, 3.28, 2.28, 2.65 and 5.89 μg/ml, respectively. Styryllactones **4** and **10** showed strong cytotoxicity toward all three human cancer cell lines, with IC_{50} in the range of 0.538 to 4.25 μg/ml, and also showed weak antimycobacterial activity against *M. tuberculosis*, which agreed with that previously been reported in literature [36,37]. In addition, compounds **2**, **4**, **10**, and **14** showed potent cytotoxicity against the NCI-H187 cell line with IC_{50} values of 2.17, 1.44, 0.538 and 0.072 μg/ml, respectively. Among the fifteen compounds, it is very interesting to note that aristolactam **14** showed not only non-cytotoxicity to normal cell, but also exhibited significant

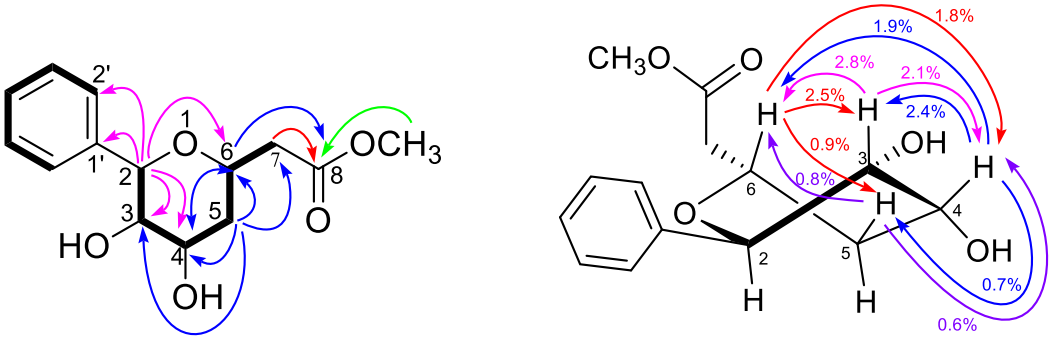


Fig. 2. Selected HMBC (arrow) and COSY (bold) (left) and NOE correlations (right) of **1**.

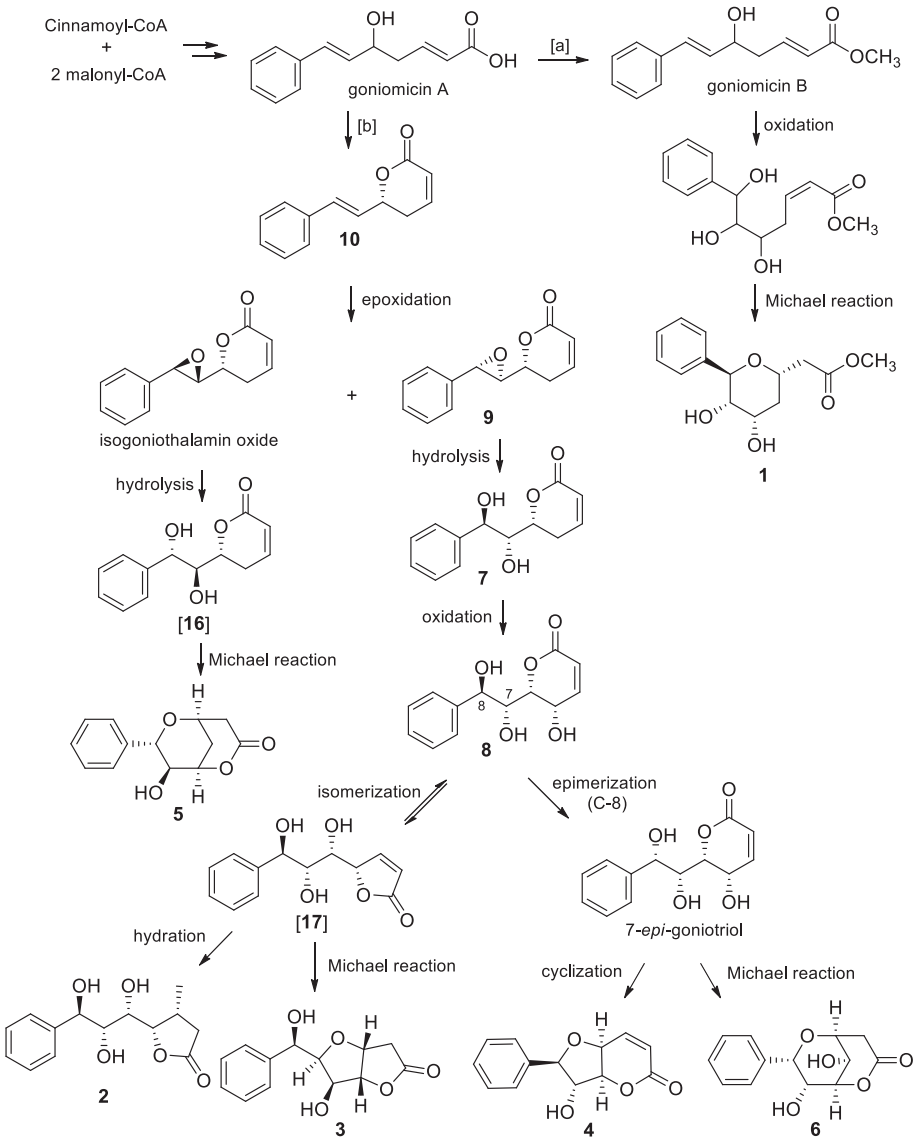


Fig. 3. A plausible biogenesis pathway of **1** and styryllactones (**2**–**10**).

cytotoxicity against the small cell lung cancer with an IC_{50} value of 0.072 μg/ml, that was stronger than the standard drug, ellipticine (IC_{50} = 1.12 μg/ml).

In summary, a new 6-*epi*-goniothalesdiol A (**1**), along with nine styryllactones (**2–10**) and five aristolactams (**11–15**) were isolated from the bark of *G. elegants*. Biological activities of the isolated compounds were evaluated and it was found that most of them exhibited cytotoxicity against one or more cancer cell lines including KB, MFC7 and NCI-H187 cells. The results demonstrate that *G. elegants*, a Thai herbal plant, can be utilized as an excellent source of bioactive compounds.

Conflict of interest

There is no conflict of interest.

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Appendix A. Appendix data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.fitote.2015.04.005.

Table 2
Biological activities of the isolated compounds (**1–15**).

Compound	Antimalarial[a] IC_{50} (μg/ml)	TB[b] MIC (μg/ml)	Cytotoxicity IC_{50} (μg/ml)			
			KB[c]	MCF7[d]	NCI-187[e]	Vero cell
1	Inactive	Inactive	Inactive	Inactive	Inactive	Non-cytotoxic
2	Inactive	Inactive	Inactive	Inactive	2.17	Non-cytotoxic
3	Inactive	Inactive	Inactive	34.06	Inactive	Non-cytotoxic
4	2.80	50.00	0.96	4.25	1.44	6.28
5	Inactive	Inactive	Inactive	Inactive	13.34	Non-cytotoxic
6	4.46	Inactive	Inactive	Inactive	17.41	16.27
7	3.28	Inactive	5.27	29.45	Inactive	Non-cytotoxic
8	Inactive	Inactive	14.57	11.90	6.37	15.48
9	2.28	Inactive	5.63	8.25	7.46	Non-cytotoxic
10	2.65	25.00	0.786	3.61	0.538	0.675
11	Inactive	Inactive	27.33	20.54	Inactive	Non-cytotoxic
12	Inactive	Inactive	9.39	13.90	Inactive	6.14
13	5.89	Inactive	6.43	2.30	7.13	28.17
14	Inactive	Inactive	Inactive	15.4	0.072	Non-cytotoxic
15	Inactive	Inactive	Inactive	Inactive	Inactive	Non-cytotoxic
Tamoxifen[f]				5.78		
Ellipticine[f]			1.15		1.12	1.00
Mefloquine[f]	0.013					
Ethambutol[f]		1.88				

[a] Plasmodium falciparum.
[b] Mycobacterium tuberculosis.
[c] Oral cavity cancer.
[d] Breast cancer.
[e] Small cell lung cancer and,
[f] Standard drug.

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