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Stilbenoids from the stem of *Diospyros collinsae*, the first evidence for the production of stilbene derivatives in Ebenaceous plants

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ABSTRACT

Two stilbenoids, diptoindonesin D (**1**) and diptoindonesin G (**2**), were isolated from the stem of *Diospyros collinsae* Craib (Ebenaceae), together with four triterpenoids, namely friedelin, lupeol, betulin, and betulinic acid. Their structures were determined by spectroscopic analysis. Diptoindonesin G (**2**) exhibited cytotoxic activity against NCI-H187 cells and antimalarial activity against *Plasmodium falciparum*. The isolation of **1** and **2** provided the first evidence for the production of stilbene derivatives in plants of the family Ebenaceae.

INTRODUCTION

Plants of the genus *Diospyros*, the largest of the family Ebenaceae, have long been known for their medicinal properties, and many of them have been employed for the treatment of various symptoms and diseases in several parts of the world. A number of *Diospyros* species have been phytochemically investigated, revealing a wide variety of isolated chemical compounds, e.g., naphthoquinones and naphthalene derivatives, triterpenoids, steroids, flavonoids, coumarins, and tannins. Of these, naphthoquinones and triterpenoids are considered as major constituents of *Diospyros* plants. Several isolated compounds from these plants have been found to exert interesting bioactivities [1].

Diospyros collinsae Craib is an evergreen tree native to Thailand, known in Thai vernacular name as “Phlab yot

dam.” It is one of *Diospyros* species with no previous report on phytochemical study. In this work, two stilbenoids and four triterpenoids were isolated from the stem of the plant. The isolation of the stilbenoids gave an interesting point in chemotaxonomic aspect. Comparative discussion on the identification of the two stilbenoids is given to illustrate the relationships of their structures. One of the stilbenoids was pharmacologically investigated and found to exhibit certain interesting bioactivities.

MATERIALS AND METHODS

General

An optical rotation was measured on a Perkin Elmer 341 polarimeter. UV spectra were obtained with a Shimadzu UV-160A spectrophotometer. IR spectra (KBr disc and thin

film) were recorded on a Perkin Elmer Fourier transform infrared 1760X spectrometer. ESI-MS spectra were carried out on a Micromass LCT mass spectrometer. Nuclear magnetic resonance (NMR) spectra in dimethyl sulfoxide- d_6 and acetone- d_6 were recorded on a JEOL JNM-A500, Varian Unity INOVA 500 MHz NMR spectrometer (^1H : 500 MHz, ^{13}C : 125 MHz), with TMS as internal standard. Silica gel 60 (No. 9385, E. Merck, 230-400 mesh) was used for column chromatography. TLC was performed with precoated silica gel 60 F254 plates (0.25 mm), and detection was performed by spraying with 10% sulfuric acid in EtOH or anisaldehyde-sulfuric acid reagent and heating at 110°C.

Plant Material

The stem of *D. collinsae* was collected from Suan Luang Rama IX Public Park, Bangkok, Thailand, in June 2009. The plant was identified by Dr. Chirayupin Chandraprasong, the senior botanist of Suan Luang Rama IX Public Park. The voucher specimen (No. DE12947) has been deposited at the herbarium of the Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok, Thailand.

Extraction and Isolation

The dried, powdered stem of *D. collinsae* (1.4 kg) was extracted with 95% EtOH ($\times 5$) at room temperature to yield 154 g of dried crude extract. The crude EtOH extract (150 g) was then suspended in aq. MeOH and partitioned successively with *n*-hexane, CH_2Cl_2 and EtOAc to give 6.24 g of hexane extract, 14 g of CH_2Cl_2 extract, and 16.7 g of EtOAc extract.

A portion of the EtOAc extract (10.0 g) was separated on a silica gel column, eluted with a gradient mixture of CH_2Cl_2 -MeOH (95:5 \rightarrow 70:30), into six fractions (A-F). Betulinic acid (1.3 g) was obtained from fraction A by recrystallization. Fraction B was further fractionated on a silica gel column, eluted with CH_2Cl_2 -MeOH (95:5), to afford four subfractions (B1-B4). Subfraction B2, after removal of the eluent, yielded diptoindonesin G **2** (14.4 mg). Fraction D was rechromatographed on a silica gel column, eluted with CH_2Cl_2 -MeOH (92:8), to give five subfractions (D1-D5). Further separation of subfraction D2 on a silica gel column, using CH_2Cl_2 -MeOH (9:1) as the eluent, afforded diptoindonesin D **1** (8.3 mg).

Chromatographic separation of the hexane and CH_2Cl_2 extracts was also carried out, yielding friedelin and lupeol from the hexane extract, betulin from the CH_2Cl_2 extract, and betulinic acid from both of the extracts. Details of the isolation of the compounds from these extracts are not given here.

Diptoindonesin D (1), orange powder

$[\alpha]_D^{20} = -130^\circ$ (c 0.015, MeOH); UV λ_{max} (MeOH) nm: 207, 224, 245, 273, 375; IR ν_{max} cm^{-1} (KBr): 3434, 2922, 1608, 1514; HRESIMS m/z 377.0662 $[\text{M}-\text{H}]^+$; ^1H and ^{13}C NMR: (Table 1), heteronuclear multiple bond coherence (HMBC) ($\text{H} \rightarrow \text{C}$), H-12a: C-10a, C-11a, C-13a, C-14a; H-14a: C-8a, C-10a, C-12a, C-13a; H-2b/6b: C-2b/6b, C-4b, C-7b; H-3b/5b: C-1b, C-3b/5b; H-7b: C-9a, C-10a, C-11a, C-1b, C-2b/6b, C-8b, C-9b; H-12b: C-10b, C-13b, C-14b; H-14b: C-8b, C-10b, C-12b; 11b-OH: C-10b, C-11b, C-12b.

Table 1: ^1H and ^{13}C NMR data of diptoindonesin D (**1**) (500 and 125 MHz, acetone- d_6) and diptoindonesin G (**2**) (500 and 125 MHz, DMSO- d_6)

| Position | 1 | | 2 | |
|----------|-----------------------------|---------------------|-----------------------------|---------------------|
| | δ_{H} | δ_{C} | δ_{H} | δ_{C} |
| 8a | - | 197.3 | - | 186.8 |
| 9a | - | 142.8 | - | 124.8 |
| 10a | - | 111.2 | - | 124.1 |
| 11a | - | 156.9 | - | 153.2 |
| 12a | 6.80 (<i>d</i> , $J=2.5$) | 107.5 | 7.34 (<i>d</i> , $J=1.7$) | 104.9 |
| 13a | - | 158.8 | - | 157.9 |
| 14a | 6.90 (<i>d</i> , $J=2.5$) | 110.2 | 7.37 (<i>d</i> , $J=1.7$) | 107.9 |
| 1b | - | 130.5 | - | 121.0 |
| 2b/6b | 6.68 (<i>d</i> , $J=8.9$) | 128.9 | 7.73 (<i>d</i> , $J=8.7$) | 131.2 |
| 3b/5b | 6.63 (<i>d</i> , $J=8.9$) | 116.2 | 7.00 (<i>d</i> , $J=8.7$) | 116.8 |
| 4b | - | 157.0 | - | 160.2 |
| 7b | 5.89 (<i>s</i>) | 55.2 | - | 157.1 |
| 8b | - | 196.8 | - | 108.2 |
| 9b | - | 139.6 | - | 134.8 |
| 10b | - | 111.6 | - | 111.0 |
| 11b | - | 167.4 | - | 167.2 |
| 12b | 6.38 (<i>d</i> , $J=2.5$) | 107.1 | 6.27 (<i>d</i> , $J=2.2$) | 102.9 |
| 13b | - | 165.4 | - | 164.9 |
| 14b | 6.92 (<i>d</i> , $J=2.5$) | 113.2 | 7.08 (<i>d</i> , $J=2.2$) | 103.6 |
| 11b-OH | 13.70 (<i>s</i>) | - | 14.13 (<i>s</i>) | - |

DMSO: Dimethyl sulfoxide

Diptoindonesin G (2), brown amorphous solid

UV λ_{max} (MeOH) nm: 210, 248, 285, 360; IR λ_{max} cm^{-1} (KBr): 3391, 1614, 1585, 1466; HRESIMS m/z 359.0563 $[\text{M}-\text{H}]^+$; ^1H and ^{13}C NMR: (Table 1), HMBC ($\text{H} \rightarrow \text{C}$), H-12a: C-10a, C-11a, C-13a, C-14a; H-14a: C-8a, C-10a, C-12a, C-13a; H-2b/6b: C-2b/6b, C-4b, C-7b; H-3b/5b: C-1b, C-3b/5b, C-4b; H-12b: C-10b, C-11b, C-13b, C-14b; H-14b: C-8b, C-10b, C-12b, C-13b; 11b-OH: C-8a, C-10b, C-11b, C-12b, C-13b.

Biological Assays

The isolated compound **2** was subjected to biological evaluation for cytotoxic and antimalarial activities. Assays for both of the activities were performed at the National Center for Genetic Engineering and Biotechnology (BIOTEC), Pathum Thani, Thailand.

In vitro cytotoxicity assay

Cytotoxicity against NCI-H187, KB, and MCF-7 cell lines
The cytotoxic activity against human small cell lung carcinoma (NCI-H187, ATCC CRL-5804), epidermoid carcinoma of oral cavity (KB, ATCC CCL-17), and breast adenocarcinoma (MCF-7, ATCC HTB-22) cell lines was determined by resazurin microplate assay using the method described by O'Brien *et al.* [2]. Ellipticine and doxorubicin were used as positive controls in the tests for cytotoxic activities against NCI-H187 and KB cell lines, and

doxorubicin and tamoxifen for cytotoxic activity against MCF-7 cell line.

Cytotoxicity against Vero cell lines

The cytotoxic activity against African green monkey kidney cell line (Vero, ATCC CCL-81) was determined by green fluorescent protein-based assay using the method described by Hunt *et al.* [3]. Ellipticine was used as a positive control.

In vitro antimalarial assay

Plasmodium falciparum (K1, multidrug resistant strain) parasites were cultured continuously *in vitro* according to the method of Trager and Jensen [4]. The antimalarial activity was quantitatively assessed using the microculture radioisotope technique based on the method described by Desjardins *et al.* [5]. Dihydroartemisinin and mefloquine were used as positive controls.

RESULTS AND DISCUSSION

Compounds **1** and **2** were found to be stilbenoids, identified as diptoindonesin D [6,7] and diptoindonesin G [8], respectively. The HRESIMS pseudomolecular ion $[M-H]^+$ of **1** at m/z 377.0662 corresponded to the molecular formula of $C_{21}H_{14}O_7$, and that of **2** at m/z 359.0563 to the molecular formula of $C_{21}H_{12}O_6$. The 1H NMR and COSY spectra of **1** and **2** were similar in displaying two pairs of doublets representing two pairs of reciprocally *meta*-coupled protons (**1**: δ_H 6.80, H-12a – δ_H 6.90, H-14a and δ_H 6.38, H-12b – δ_H 6.92, H-14b; **2**: δ_H 7.34, H-12a – δ_H 7.37, H-14a, and δ_H 6.27, H-12b – δ_H 7.08, H-14b) and one pair of doublets (2H each) representing a pair of reciprocally *ortho*-coupled protons (**1**: δ_H 6.63, H-3b/5b – δ_H 6.68, H-2b/6b; **2**: δ_H 7.00, H-3b/5b with – δ_H 7.73, H-2b/6b), which indicated the presence of two 1,2,3,5-tetrasubstituted and one *p*-substituted phenyl rings, respectively. In addition, the downfield singlets at δ_H 13.70 in the spectra of **1** and at δ_H 14.13 in those of **2**, each of which implied the presence of a chelated hydroxyl group (11b-OH), were observed. The spectra of **1** also displayed a relatively downfield singlet of a methine proton (δ_H 5.89, H-7b) while there was no such signal in the spectra of **2**. In the ^{13}C NMR and DEPT spectra of **1**, two signals of conjugated carbonyl carbons were discernible at δ_C 196.8 (C-8b) and 197.3 (C-8a), and a signal of an aliphatic methine carbon (C-7b) at δ_C 55.2. In the spectra of **2**, the lack of one carbonyl signal as well as a signal of an aliphatic methine carbon and the addition of two signals of olefinic carbons (δ_C 108.2, C-7b, and δ_C 157.1, C-8b), as compared with the spectra of **1**, were observed. Data obtained from the HMBC experiments (2.3.1 and 2.3.2) fully supported the structures of diptoindonesin D and diptoindonesin G for **1** and **2**, respectively. Diptoindonesin D possesses two stereoisomeric forms due to its chiral carbon (C-7b). Compound **1** was assigned to be (-) form according to its specific rotation ($[\alpha]_D^{20} = -130^\circ$). The chemical structures of the two isolated stilbenoids and importance heteronuclear multiple bond coherence correlations in the compounds are shown in Figures 1 and 2, respectively.

The 1H and ^{13}C NMR data of **1** and **2** are shown in Table 1. The 1H NMR assignment of **1** was found to be slightly different from the first report for diptoindonesin D [6], concerning reverse chemical shifts assignment for H-2b/6b (**1**, δ_H 6.68; reported value, δ_H 6.63) and H-3b/5b (**1**, δ_H 6.63; previous

reported value, δ_H 6.68). However, the assignments for C-2b/6b (**1**, δ_C 128.9; previous reported value, δ_C 128.5) and C-3b/5b (**1**, δ_C 116.2; reported value, δ_C 115.8) were found to be in agreement. The signal assignments for H-2b/6b and H-3b/5b of **1** were based on the evidence obtained from the HSQC spectrum which showed the correlations of the proton signals at δ_H 6.68 and δ_H 6.63 with the carbon signals at δ_C 128.9 and δ_C 116.2, respectively, and from the HMBC spectrum, analysis of which was able to differentiate between the two protons.

Comparison of the NMR data of **2** with those previously reported [8] also revealed some differences, which were the different chemical shift assignments for C-11a, C-13a, C-9a, and C-9b. In the case of C-11a and C-13a, their chemical shifts were reversely assigned (**2**: δ_{C-11a} 153.2, δ_{C-13a} 157.9; previous reported values, δ_{C-11a} 158.3, δ_{C-13a} 154.0). The assignments for these two carbons of **2** were based on analysis of the HMBC spectrum where the correlation of H-12a with both C-11a and C-13a, as well as the correlation of H-14a with C-13a, was clearly observed. In the previous report, the correlation of H-12a with two carbons, supposed to be C-11a and C-13a, was reported, but the correlation of H-14a with one of these carbons, which could differentiate C-13a from C-11a, was not documented. The assignment for C-9a and C-9b, which could not be accomplished through HMBC analysis, were based on the ^{13}C NMR data of hopeachinol A [9], a stilbenoid structurally related to diptoindonesin G. C-9a (**2**: δ 124.8; previous reported value, δ 135.6) and C-9b (**2**: δ 134.8; previous reported value, δ 139.3) were assigned according to the chemical shift assignments for their corresponding carbons (δ 126.3 and 135.6, respectively).

In addition to **1** and **2**, four triterpenoids were isolated from the plant material including friedelin, lupeol, betulin, and betulinic acid. These compounds are pentacyclic triterpenoids commonly found in *Diospyros* plants. All of them have been reported of their biological activities [1,10]; the most important is betulinic acid which has been found to exert a variety of interesting biological activities and is considered to be promising in cancer drug development due to its remarkable anticancer effects [11-13]. It is noted here that *D. collinsae* is an interesting natural source for betulinic acid (more than 0.1% yield of dried plants).

Triterpenoids are found widespread in *Diospyros* plants and regarded as a major group of compounds of the genus. On the contrary, there are no previous reports on the occurrence of stilbenoids in any member of *Diospyros*, of which more than 130 species have been phytochemically investigated [1]. Stilbenoids are not widely distributed in the plant kingdom. Among the higher plants, including gymnosperms and angiosperms, these compounds have been so far found in about 39 families [14,15], the important ones being Dipterocarpaceae, Fabaceae, and Vitaceae. To the best of our knowledge, the isolated compounds diptoindonesin D (**1**) and diptoindonesin G (**2**) represented the first evidence for the production of stilbenoids not only in the genus *Diospyros* but also the family Ebenaceae.

In biogenetic point of view, the biogenesis of diptoindonesin G has been proposed by Juliawaty *et al.* [8] as involving a condensation between resveratrol (3,5,4'-trihydroxystilbene) and a 3,5-dihydroxybenzoyl ester, not that between a

2-arylbenzofuran, derived from 2,4,4'-trihydroxystilbene, and a 2,4-dihydroxybenzoyl ester. Since no other stilbenoids have been reported as chemical constituents of *Diospyros* plants, the stilbene precursor of **1** and **2**, evident from previously isolated compounds of the genus, could not be deduced. However, the cooccurrence of these two compounds in *D. collinsae* might be considered as supporting the proposed biogenesis of Juliawaty *et al.* The only possible stilbene precursor of diptoindonesin D

(**1**) is 3,5,4'-trihydroxystilbene, and compounds **1** and **2** could be regarded as originating from the same benzoyl and stilbene precursors (i.e., 3,5-dihydroxybenzoyl ester and 3,5,4'-trihydroxystilbene) joining at different sites. It can be postulated that **1** is derived from the initial product of condensation which contains 7b, 8b double bond via the 8b-OH intermediate. The cooccurrence of diptoindonesin D and its 8b-OH analog, parviflorol, in *Hopea dryobalanoides* has also been reported [6].

Table 2: *In vitro* cytotoxic activity of the test compounds

| Compounds | IC ₅₀ values (μM) | | | |
|-------------------------------|------------------------------|------|-------|------------|
| | NCI-H187 | KB | MCF-7 | Vero cells |
| Diptoindonesin G (2) | 5.38 | >100 | >100 | >100 |
| Ellipticine | 2.88 | 4.63 | - | 8.04 |
| Doxorubicin | 0.99 | 0.64 | 16.23 | - |
| Tamoxifen | - | - | 25.49 | - |

IC₅₀: Inhibitory concentration

Table 3: *In vitro* antimalarial activity of the test compounds

| Compounds | IC ₅₀ values (μM) |
|-------------------------------|------------------------------|
| Diptoindonesin G (2) | 19.09 |
| Dihydroartemisinin | 1.25 × 10 ⁻³ |
| Mefloquine | 24.5 × 10 ⁻³ |

IC₅₀: Inhibitory concentration

Compound **2**, diptoindonesin G, was investigated for cytotoxic and antimalarial activities. The results obtained are shown in Tables 2 and 3, respectively. As shown in Table 2, compound **2** exhibited cytotoxic activity against small-cell lung cancer (NCI-H187) cell line but it was relatively inactive against epidermoid carcinoma (KB) and breast adenocarcinoma (MCF-7) cell lines. The compound showed high toxicity toward NCI-H187 cells with inhibitory concentration (IC₅₀) value of 5.38 μM, however, was less active than ellipticine and doxorubicin. Compound **2** appeared to be inactive against Vero cells, suggesting its selective cytotoxicity on the cancerous cells in comparison with the normal mammalian cells. The results shown in Table 3 indicated that compound **2** exhibited antimalarial activity against K1 strain of *P. falciparum* with the IC₅₀ value of 19.09 μM (6.88 μg/ml). Before this study, diptoindonesin G was reported of its strong cytotoxicity against murine leukemia P-388 cells [8] and immunosuppressive activity [9]. Recently, the compound has been demonstrated to reciprocally regulate ER_α and ER_β in breast cancer cells, representing a new class or selective estrogen receptor modulators which could be beneficial for the treatment of human breast cancer [16].

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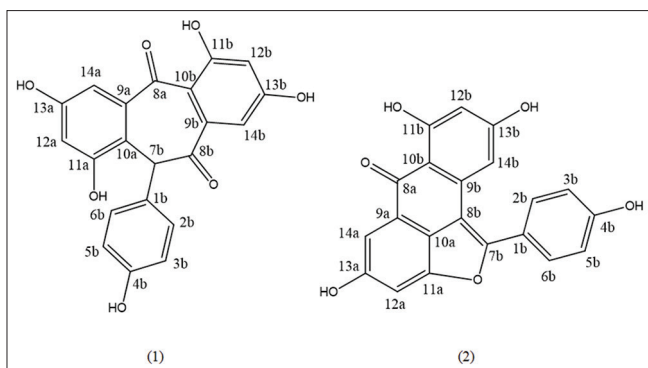


Figure 1: The chemical structure of **1** and **2**

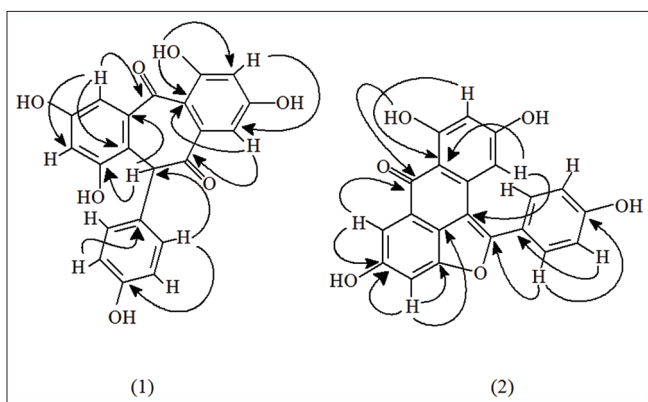


Figure 2: Selected important heteronuclear multiple bond coherence correlations in **1** and **2**

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