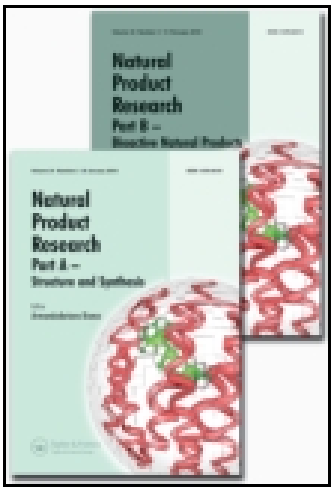

Natural Product Research: Formerly Natural Product Letters
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gnpl20

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Published online: 31 Jan 2007.

To cite this article: U.L.B. Jayasinghe , S. Puvanendran , N. Hara & Y. Fujimoto (2004) Stilbene derivatives with antifungal and radical scavenging properties from the Stem Bark of artocarpus nobilis , Natural Product Research: Formerly Natural Product Letters, 18:6, 571-574, DOI: 10.1080/14786410310001643867

To link to this article: http://dx.doi.org/10.1080/14786410310001643867

Natural Product Research, Vol. 18, No. 6, December 2004, pp. 571–574

STILBENE DERIVATIVES WITH ANTIFUNGAL AND RADICAL SCAVENGING PROPERTIES FROM THE STEM BARK OF *ARTOCARPUS NOBILIS*

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(In final form 20 November 2003)

Antifungal activity-guided fractionation of the *n*-butanol extract from the methanol extract of the stem bark of *Artocarpus nobilis* furnished two stilbene derivatives (*E*)-4-isopentenyl-3,5,2′,4′-tetrahydroxystilbene and (*E*)-4-(3-methyl-*E*-but-1-enyl)-3,5,2′,4′-tetrahydroxystilbene. Both compounds showed strong antifungal activity against *Cladosporium cladosporioides* and high radical scavenging activity towards the DPPH radical in TLC bio-autography method.

Keywords: *Artocarpus nobilis*; Moraceae; Stilbene derivatives; Antifungal; *Cladosporium cladosporioides*; Radical scavenging; DPPH

INTRODUCTION

In a continuation of our research work on the search for biologically active compounds from Sri Lankan plants, the present investigation was carried out on the stem bark of *Artocarpus nobilis* Thw. *A. nobilis* is an endemic tree of the family Moraceae growing in mid country regions of Sri Lanka. This is the only endemic species of the genus *Artocarpus* abundant in Sri Lanka. Several pyranodihydrobenzoxanthones, chromenoflavonoids, triterpenes have been reported from the bark of the plant [1–4]. In this article, we report the isolation of two stilbene derivatives with antifungal activity against *Cladosporium cladosporioides* and radical scavenging properties towards 2,2′-diphenyl-1-picrylhydrazyl radical (DPPH) from the stem bark of *A. nobilis*.

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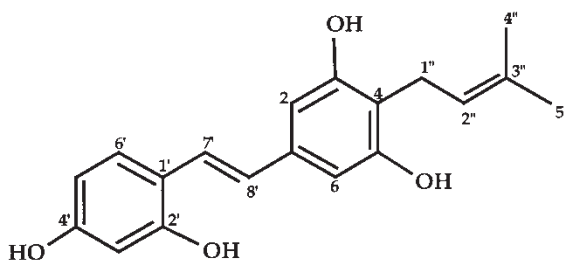
Natural Product Research
ISSN 1478-6419 print: ISSN 1029-2349 online © 2004 Taylor & Francis Ltd
http://www.tandf.co.uk/journals
DOI: 10.1080/14786410310001643867

RESULTS AND DISCUSSION

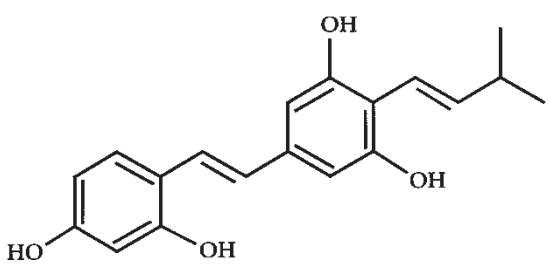
The preliminary investigation of the methanol extract and the *n*-butanol extract from the methanol extract of the stem bark of *A. nobilis* showed positive response in antifungal bioassay against *C. cladosporioides*. Antifungal activity-guided fractionation of the *n*-butanol extract from the methanol extract of the stem bark of *A. nobilis* with a combination of chromatography with silica gel, RP-18 silica gel, sephadex LH-20 and reversed phase HPLC furnished two stilbene derivatives, (*E*)-4-isopentenyl-3,5,2′,4′-tetrahydroxystilbene (**1**) and (*E*)-4-(3-methyl-*E*-but-1-enyl)-3,5,2′,4′-tetrahydroxystilbene (**2**). Structure elucidation of these compounds was based on the detailed analysis of UV, ^{1}H- and ^{13}C-NMR, and MS spectral data.

Both compounds showed strong antifungal activity at 10 μg/spot against *C. cladosporioides* on TLC bio-autography method, wherein spore germinates as black zones and antifungal compounds appear as white zones [5]. Benlate was used as the positive control.

Antioxidant properties of **1** and **2** were evaluated against the DPPH radical by TLC bio-autography method [6]. In this assay, antioxidants react with the free radical DPPH and produce colorless 2,2′,phenyl-1-picrylhydrazine. α-Tocopherol was used as the positive control. Both compounds **1** and **2** (1 μg/spot) appeared as off-white spots in purple background. This is the first report of the compounds **1** and **2** from *A. nobilis* and their radical scavenging property. Compound **1** has been previously isolated from mulberry shoot xylem tissue infected with *Fusarium* sp. [7], *Artocarpus incisus* [8] and *Artocarpus integer* [9], while compound **2** from *A. integer* [9]. Antifungal,



1



2

enzyme (tyrosinase and steroid-5α-reductase) inhibitory and antimalarial activities of **1** were reported previously [7–9].

EXPERIMENTAL

Melting points were determined by Gallenkamp apparatus and are uncorrected. UV spectra were recorded on a UV-160 A Spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a Brucker DRX500 (500 MHz for ^{1}H and 125 MHz for ^{13}C) spectrometer in $CDCl_3$ solution. Tetramethylsilane was used as an internal standard. EI-MS (70 eV) were obtained on JEOL JMS-AX505HA spectrometer. HPLC analysis were carried out on Shimadzu LC-6A apparatus equipped with UV detector under a reversed phase C_{18} column under isocratic solvent condition.

Plant Material

The stem bark of the *A. nobilis* was collected from the central province of Sri Lanka in August 2002. A voucher specimen is deposited at the Institute of Fundamental Studies.

Extraction and Isolation

Dried, ground stem bark of *A. nobilis* (400 g) was defatted with *n*-hexane and extracted with methanol. Evaporation of methanol gave dark brown methanol extract (21.8 g). A portion of methanol extract (20 g) was partitioned with *n*-butanol and water. The *n*-butanol extract was subjected to antifungal activity test on TLC bio-autography method against *C. cladosporioides*. Inhibition zones on TLC appeared in the range of R_f 0.2–0.4 (TLC aluminium sheets, Merck 1.05554 silica gel 60 F_{254}; eluant – 10% MeOH in $CHCl_3$). A portion of the *n*-butanol extract was chromatographed over a column of silica gel (Merck Art. 7734) eluting with *n*-hexane–EtOAc–MeOH. Each column fraction was tested for antifungal activity. The fractions, which showed antifungal activity, were combined and further chromatographed over silica gel (eluant: *n*-hexane–EtOAc–MeOH); sephadex LH-20 (eluant: MeOH); RP-18 silica gel (eluant: H_2O–MeOH) and HPLC (STR Prep-ODS 20 × 250 mm column, 40% H_2O–MeOH, 5 mL/min; UV detection 254 nm) to give compound **1** (20 mg) and **2** (18 mg).

(*E*)-4-Isopentenyl-3,5,2′,4′-tetrahydroxystilbene (1)

Melting point 197–199°C; UV λ_{max}^{EtOH}: 215, 240, 310, 328 nm; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.65 (3H, s, Me-4″), 1.75 (3H, s, Me-5″), 3.26 (2H, d, $J = 7.8$ Hz, H-1″), 5.23 (1H, t, $J = 7.8$ Hz, H-2″), 6.29 (1H, d, $J = 2.2$ Hz, H-3′), 6.29 (1H, dd, $J = 8.2$, 2.2 Hz, H-5′), 6.45 (2H, s, H-2, H-6), 6.75 (1H, d, $J = 16.4$ Hz, H-8′), 7.21 (1H, d, $J = 16.4$ Hz, H-7′), 7.29 (1H, d, $J = 8.2$ Hz, H-6′); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 17.9 (C-4″), 23.3 (C-1″), 26.0 (C-5″), 103.5 (C-3′), 105.5 (C-2, C-6), 108.3 (C-5′), 115.4 (C-4), 118.0 (C-1), 123.7 (C-7′), 124.7 (C-2″), 126.6 (C-8′), 128.1 (C-6′), 131.0 (C-3″), 138.5 (C-1′), 157.1 (C-2′, C-3, C-5), 159.0 (C-4′); EIMS m/z: 312 $[M]^+$.

(*E*)-4-(3-Methyl-*E*-but-1-enyl)-3,5,2′,4′-tetrahydroxystilbene (2)

Sticky solid; UV λ_{max}^{EtOH}: 217, 243, 311, 346 nm; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.08 (6H, d, $J = 6.7$ Hz, Me-4″, Me-5″), 2.39 (1H, m, H-3″), 6.29 (1H, d, $J = 2.2$ Hz, H-3′), 6.29 (1H, dd, $J = 8.2$, 2.2 Hz, H-5′), 6.45 (2H, s, H-2, H-6), 6.57 (1H, br, H-1″, H-2″), 6.74 (1H, d, $J = 16.4$ Hz, H-8′), 7.24 (1H, d, $J = 16.4$ Hz, H-7′), 7.30 (1H, d, $J = 9$ Hz, H-6′); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 23.4 (C-4″, C-5″), 34.4 (C-3″), 103.5 (C-3′), 105.7 (C-2, C-6), 108.3 (C-5′), 112.6 (C-4), 117.9 (C-1), 119.5 (C-1″), 124.2 (C-7′), 126.2 (C-8′), 128.2 (C-6′), 138.9 (C-1′), 141.2 (C-2″), 157.3 (C-3, C-2′, C-5), 159.2 (C-4′); EIMS m/z: 312 $[M]^+$.

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