Notes

Artoindonesianin C, a New Xanthone Derivative from *Artocarpus teysmanii*

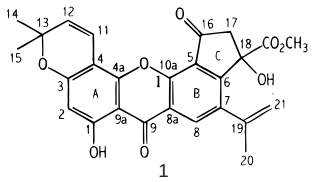
Lukman Makmur,[†] Syamsurizal,[†] Tukiran,[†] Sjamsul A. Achmad,*[,†] Norio Aimi,[‡] Euis H. Hakim,[†] Mariko Kitajima,[‡] and Hiromitsu Takayama[‡]

Department of Chemistry, Institut Teknologi Bandung, Jalan Ganeca 10, Bandung 40132, Indonesia, and Faculty of Pharmaceutical Sciences, Chiba University, 1-33, Yayoi-cho, Inage-ku, Chiba 263-8522, Japan

Received May 10, 1999

A new xanthone derivative, artoindonesianin C (**1**), was isolated from *Artocarpus teysmanii,* together with two known prenylated flavonoids, cycloartobiloxanthone and artonin J. The structure of artoindonesianin C (**1**) was determined on the basis of MS and NMR evidence and by comparison with known related compounds.

Artoindonesianins A and B, which show cytotoxic activity, have been isolated from *Artocarpus champeden*.[1] In this study, a new xanthone derivative, artoindonesianin C (**1**), and two known compounds, cycloartobiloxanthone[2] and artonin J,[3] were isolated from *Artocarpus teysmanii* Miq. (Moraceae), one of the endemic species of the genus *Artocarpus*. In this paper, we report the isolation and structure elucidation of compound **1** on the basis of spectroscopic evidence.



1

The HREIMS of **1** gave an $[M]^+$ ion at *m*/*z* 462.1313 consistent with a molecular formula of $C_{26}H_{22}O_8$. The IR spectrum showed absorptions typical of hydroxyl, cyclic ketone, ester carbonyl, conjugated carbonyl, and benzene ring functionalities, and the UV spectrum was typical of a xanthone derivative. Analysis of its NMR data, including HMQC and HMBC spectra, allowed unambiguous assignment of all proton and carbon signals. The ^{1}H NMR data indicated the presence of two methyl groups and two olefinic protons attributed to a 2,2-dimethylchromene ring. The ^{1}H NMR also showed a methyl group and terminal methylene protons attributed to an isopropenyl group. Sharp singlets at δ 6.30 and 8.15 indicated two aromatic protons, and a singlet at δ 12.58 indicated a chelated hydroxyl group. The ^{1}H NMR also contained signals of a hydroxyl group at δ 6.78, an isolated methylene group at δ 2.92 and 3.28, and a methoxyl group at δ 3.60. The ^{13}C NMR indicated 26 carbons, including three methyl groups, a terminal methylene group, three carbonyl groups (δ 198.0, 178.9, and 172.6), a methoxyl group (δ 52.4), and two oxygenated aliphatic carbons (δ 78.9 and 76.3). These signals from the ^{1}H and ^{13}C NMR suggested that **1** contained fused xanthone, a chromene ring, and cyclic ketone moieties, similar to the arrangement found for the related compounds, artonins Q and R.[4] HMBC measurements allowed the quaternary carbons at δ 162.1 and 141.0 to be assigned to C-1 and C-7, while those at δ 124.3, 158.6, 198.0, 76.3, and 172.6 were assigned to C-5, C-6, C-16, C-18, and the carbonyl carbon of the ester group, respectively. Supporting evidence for structure **1** came from comparison of the ^{13}C NMR spectrum, assigned with the aid of HMQC and HMBC measurements, to those reported for artonins Q and R.[4] Compound **1** has a chiral center; however, the observed $[\alpha]_D$ value was 0°.

Xanthone derivatives have been isolated from Moraceae species; however, artoindonesianin C (**1**) represents the first monoprenylated derivative structurally analogous to artonins Q and R to be isolated from moraceous plants.[4−7] Artoindonesianin C did not inhibit leucine uptake into brush border membrane vesicles from *Bombyx mori* larval midgut and was considered inactive at a concentration of 0.2 mM.[8] Compound **1** was inactive (LC_{50} > 500 μg/mL) in the *Artemia salina* shrimp bioassay.[9]

Experimental Section

General Experimental Procedures. Melting points were determined on a micro-melting point apparatus and are uncorrected. UV and IR spectra were measured with Beckman DU-7000 and Shimadzu FT-IR 8501 spectrophotometers, respectively. ^{1}H and ^{13}C NMR spectra were recorded with a JEOL JNM A500 spectrometer, operating at 500.0 MHz (^{1}H) and 125.65 MHz (^{13}C), using TMS as an internal standard. MS were obtained with JEOL JMS-AM20 or JEOL JMS-HX110 (HR−MS) mass spectrometers, using the EI mode. VLC was carried out using Merck Si gel 60 GF_{254}, flash chromatography with Merck Si gel 60 (230−400 mesh), and TLC on precoated Si gel plates (Merck Kieselgel 60 F_{254}, 0.25 mm).

Plant Material. Samples of the root bark of *A. teysmanii* were collected in July 1996, from the wild trees growing in the village of Boli, the region of Muncang, Enrekang District, South Sulawesi, Indonesia. The plant was identified by the staff at the Herbarium Bogoriense, Bogor Botanical Garden, Bogor, Indonesia, and a voucher specimen has been deposited at the herbarium.

Extraction and Isolation. The milled, dried root bark (4.0 kg) was extracted exhaustively by percolation with methanol. The MeOH extract, on removal of solvent under reduced

* To whom correspondence should be addressed. Tel.: 62-22-250 2103; Fax: 62-22-250 4154. E-mail: <sjamsul@hq.chem.itb.ac.id>.
[†] Institut Teknologi Bandung.
[‡] Chiba University.

10.1021/np990220u CCC: $19.00
Published on Web 01/12/2000

pressure, gave a brown residue (690 g, 17.3%). The residue was solubilized in a mixture of H_2O−Me_2CO (75:25), and the soluble portion was sequentially extracted with hexane, benzene, $CHCl_3$, and finally with EtOAc. The benzene extract (29.9 g) was fractionated by Si gel VLC (250 g, 6.0 × 10.0 cm, hexane, hexane−EtOAc, EtOAc, MeOH) to give 64 fractions. Nine fractions (A−I) were ultimately obtained on combining the eluates on the basis of TLC. Fraction G (6.7 g) was further fractionated by Si gel VLC (70 g, 6.0 × 6.0 cm, hexane, hexane−EtOAc, EtOAc, Me_2CO in order of increasing polarity) to afford six major fractions. The second fraction (fractions 9−15) was subjected to column chromatography over Si gel (14.7 g, 1.5 × 17 cm) using hexane−Me_2CO (9:1) as eluent to afford a yellow crude compound (35 mg), which was crystallized from hexane−Me_2CO to yield **1** (10 mg). A known compound, cycloartobiloxanthone (26 mg),[2] was identified from the fourth fraction (fractions 20−26). Using the same methods, a methanol extract (750 g) obtained from the dried tree bark (6.0 kg) was sequentially partitioned with hexane, benzene, $CHCl_3$, and EtOAc. The benzene extract (17.5 g) was fractionated by Si gel VLC (40 g, 6.0 × 6.0 cm, hexane, hexane−EtOAc, EtOAc, Me_2CO) to afford five major fractions. The second fraction was further subjected to VLC over Si gel (10 g, 1.5 × 17 cm, hexane, $CHCl_3$, MeOH) to afford 17 fractions. From fractions 11−13 a precipitate of artonin J (15 mg) was obtained.[3]

Artoindonesianin C (**1**): yellow powder; mp 209−211 °C; $[\alpha]^{24}_D$ 0° (*c* 0.16, $CHCl_3$); IR (KBr) ν_{max} 3600−3300 (br), 1720−1730 (br), 1653, 1593, 1479, 1442 cm^{-1}; UV (MeOH) λ_{max} (log ϵ) 204 (4.13), 228 (3.85), 276 (3.89), 330 (3.26), 394 (2.85) nm; (MeOH + NaOH) 204 (4.25), 230 (3.91), 282 (3.90) nm; ^{1}H NMR (DMSO-d_6, 500.0 MHz) δ 12.58 (1H, s, OH-1), 8.15 (1H, s, H-8), 6.89 (1H, d, J = 10.0 Hz, H-11), 6.78 (1H, s, OH-18), 6.30 (1H, s, H-2), 5.90 (1H, d, J = 10.0 Hz, H-12), 5.25 (1H, s, H-21), 5.04 (1H, s, H-21), 3.60 (3H, s, OCH_3), 3.28 (1H, d, J = 18.3 Hz, H-17), 2.92 (1H, d, J = 18.3 Hz, H-17), 2.10 (3H, s, Me-20), 1.46 (6H, s, Me-14 and Me-15); ^{13}C NMR (DMSO-d_6, 125.65 MHz) δ 198.0 (s, C-16), 178.9 (s, C-9), 172.6 (s, C=O ester), 162.1 (s, C-1), 160.6 (s, C-3), 158.6 (s, C-6), 150.9 (s, C-4a), 150.1 (s, C-10a), 141.0 (s, C-7), 137.6 (s, C-19), 131.3 (d, C-8), 128.4 (d, C-12), 124.3 (s, C-5), 120.7 (s, C-8a), 117.5 (t, C-21), 113.8 (d, C-11), 103.5 (s, C-9a), 101.1 (s, C-4), 99.1 (d, C-2), 78.9 (s, C-13), 76.3 (s, C-18), 52.6 (t, C-17), 52.4 (q, OCH_3), 28.0 (q, Me-14), 28.0 (q, Me-15), 24.5 (q, Me-20); EIMS *m/z* $[M]^+$ 462 (17.7), 449 (26.7), 448 (77.6), 447 (100), 388 (9.9), 387 (14.1); HREIMS *m/z* $[M]^+$ 462.1313 (calcd for $C_{26}H_{22}O_8$, 462.1314).

Bioassay. Artoindonesianin C (**1**) did not inhibit leucine uptake into brush border membrane vesicles from *Bombyx mori* larval midgut at a concentration of 0.2 mM with inhibition rate 20−30%.[8] Compound **1** was inactive, LC_{50} >500 μg/mL when tested against *A. salina* using established protocols.[9]

Acknowledgment. We thank Professor Paolo Parenti, Dipartimento di Fisiologia e Biochimica Generali, Università degli Studi di Milano, Milano, Italy, for assistance with the amino acid transport experiments.

References and Notes

(1) Hakim, E. H.; Fahriyati, A.; Kau, M. S.; Achmad, S. A.; Makmur, L.; Ghisalberti, E. L.; Nomura, T. *J. Nat. Prod*. **1999**, *62*, 613−615.
(2) Sultanbawa, M. U. S.; Surendrakumar, S. *Phytochemistry* **1989**, *28*, 599−605.
(3) Aida, M.; Shinomiya, K.; Hano, Y.; Nomura, T. *Heterocycles* **1993**, *36*, 575−583.
(4) Aida, M.; Shinomiya, K.; Matsuzawa, K.; Nomura, T. *Heterocycles* **1994**, *39*, 847−858.
(5) Nomura, T. *Prog. Chem. Org. Nat. Prod*. **1988**, *53*, 87−201.
(6) Nomura, T.; Hano, Y. *Nat. Prod. Rep*. **1994**, *11*, 205−218.
(7) Nomura, T.; Hano, Y.; Aida, M. *Heterocycles* **1998**, *47*, 1179−1205.
(8) Parenti, P.; Villa, M.; Hanozet, G. M. *J. Biol. Chem*. **1992**, *267*, 15391−15397.
(9) Meyer, N.; Ferrigini, N. R.; Putnam, J. E.; Jacobsen, D. E.; Nochols, D. E.; McLaughlin, J. L. *Planta Med*. **1992**, *45*, 31−34.

NP990220U