

TWO NEW NATURAL DIELS-ALDER-TYPE ADDUCTS FROM THE ROOT BARK OF *ARTOCARPUS HETEROPHYLLUS*¹

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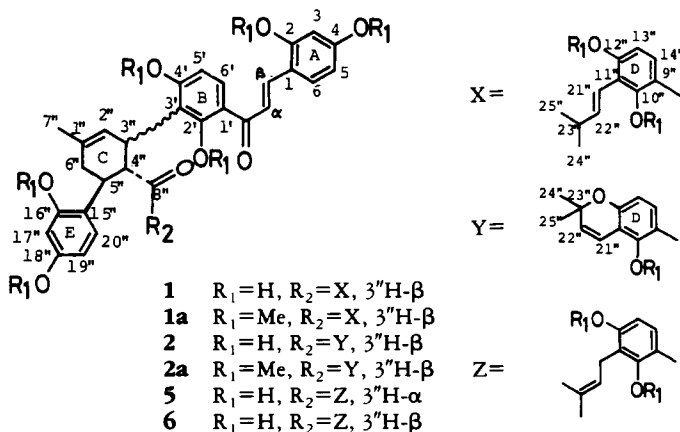
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ABSTRACT.—Two new Diels-Alder-type adducts, artonins C and D, were isolated from the Me₂CO extract of the root bark of *Artocarpus heterophyllus*. The structures of artonins C and D were shown to be **1** and **2**, respectively, on the basis of spectroscopic evidence. Artonins C and D are regarded biogenetically as Diels-Alder type adducts of a dehydroprenylchalcone derivative and chalcone derivatives. These two compounds are the first examples of natural Diels-Alder type adducts found in the plants of *Artocarpus* species.

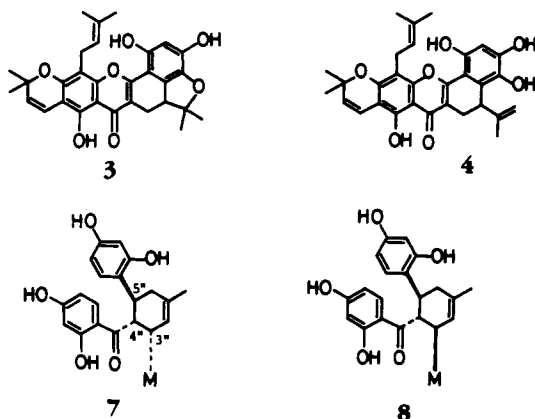
Previously we reported a series of isoprenoid-substituted phenolic compounds isolated from the mulberry tree and related plants (Moraceae) (1). Some of these compounds are regarded biogenetically as natural Diels-Alder type adducts of dehydroprenylphenols and chalcone derivatives (1). On the other hand, *Artocarpus heterophyllus* Lamk. (Moraceae) is a large evergreen tree cultivated for its fruits, and its root and leaves have been used as a traditional medicine in Southeast Asia (2-4). On the constituents of the plant, Venkataraman (2,5) reported a series of isoprenoid-substituted flavones. In continuation of our studies, we examined the phenolic constituents of the root bark of *A. heterophyllus* and reported the characterization of the new flavones artonins A [3] and B [4] (6). Further extensive fractionation of the extract of the root bark has now led to the isolation of two new Diels-Alder type adducts named artonins C [1] and D [2].

The dried root bark of *A. heterophyllus*, collected in Indonesia, was extracted successively with *n*-hexane, C₆H₆, and Me₂CO. Artonins C [1] and D [2] were isolated from the Me₂CO extract.

Artonin C [1] is a yellow crystalline powder, mp 169-171° (dec), [α]_D²² + 20°, and gave a brown color with FeCl₃. The fast atom bombardment mass spectrum (fabms) of **1** showed a protonated molecular ion [M + H]⁺ at *m/z* 679, and the ¹³C-nmr spectrum indicated the presence of forty carbons (Table 2). Treatment of **1** with dimethyl



¹Part 4 in the series: "Constituents of the Moraceae Plants." For Part 3, see Y. Hano, T. Nomura, and S. Ueda, *Heterocycles*, **29**, 2035 (1989).



sulfate gave the octamethyl ether **1a**, the molecular formula of which was determined by hrms to be $C_{48}H_{54}O_{10}$ ($[M]^+$ 790.3731, calcd 790.3717). These results revealed the molecular formula of **1** to be $C_{40}H_{38}O_{10}$.

The ir spectrum of **1** disclosed absorption bands due to hydroxyl, conjugated carbonyl, and benzene ring moieties, and the uv spectrum exhibited maxima at 206, 258, 309, and 391 nm and was similar to those of kuwanons I [**5**] (**7**) and J [**6**] (**8**). Moreover, the uv spectrum of **1** showed no red shift upon addition of $AlCl_3$. It was reported that no $AlCl_3$ -induced shift is observed in uv spectra when a prenyl group is located ortho to a chelated hydroxyl group (**9**). The 1H -nmr spectrum of **1** showed signals assignable to two hydrogen bonded hydroxyl groups at δ 13.39 and 14.40. These data led us to presume that each of the ortho positions of the two hydrogen-bonded hydroxyl groups is substituted by an isoprenoid moiety. The eims of **1a** showed the fragment ions at m/z 557, 394, and 233, and these fragment ions are similar to those of kuwanon J octamethyl ether (**8**).

From the above results, artonin C [**1**] is assumed to be a Diels-Alder-type adduct and an isomer of **5** and **6**. This assumption was substantiated by comparing the 1H -nmr spectrum of **1** with that of **6** (Table 1). In the 1H -nmr spectrum of **1** the chemical shift and coupling constants of all the proton signals except those of the isoprenoid moiety resembled those of the relevant protons of **6** (Table 1). Furthermore, the chemical shift values of carbon atoms, except those of the isoprenoid moiety, were in good agreement with those of the relevant carbon atoms of **6** (Table 2). The presence of the 3-methyl-1-butenyl moiety in the structure was confirmed by the 1H -nmr spectrum. The ^{13}C -nmr spectrum indicated the signals due to the moiety as follows: δ 23.1 (Me- \times 2), 33.9 (H>C<), 117.4, 142.7 (-CH=CH-) (**10**). These results suggested that the structure of artonin C is represented by the formula **1** including the relative configuration (cis-trans in relative configuration of three substituents on the methylcyclohexene ring).

Artonin D [**2**] is a yellow crystalline powder, mp 140–143° (dec), $[\alpha]^{19}_D + 77^\circ$, and gave a brown color with $FeCl_3$. The fabms of **2** showed a protonated molecular ion $[M + H]^+$ at m/z 677, and the ^{13}C -nmr spectrum indicated the presence of 40 carbons (Table 2). Treatment of **2** with dimethyl sulfate gave the heptamethyl ether **2a**, the molecular formula of which was determined by hrms to be $C_{47}H_{36}O_{10}$ ($[M]^+$ 774.3394, calcd 774.3405). These results revealed the molecular formula of **2** to be $C_{40}H_{36}O_{10}$. The ir spectrum of **2** disclosed absorption bands due to hydroxyl, conjugated carbonyl, and benzene ring moieties, and the uv spectrum exhibited maxima at 205, 267, 316, and 390 nm and was similar to those of **1**, **5** (**7**), and **6** (**8**). Moreover, the uv spectrum of **2** showed no red shift upon addition of $AlCl_3$ (**9**). The eims of **2a** showed the fragment ions at m/z 557, 394, 365, and 217 (**8**).

TABLE 1. ¹H-nmr Spectral Data of Artonin C [1], Artonin D [2], and Kuwanon J [6].^a

Proton	Compound		
	1	2	6
H-3	6.48 (d, <i>J</i> = 2)	6.49 (d, <i>J</i> = 2)	6.49 (d, <i>J</i> = 2)
H-5	6.43 (dd, <i>J</i> = 2, 8)	6.43 (dd, <i>J</i> = 2, 8)	6.43 (dd, <i>J</i> = 2, 9)
H-6	7.66 (d, <i>J</i> = 8)	7.65 (d, <i>J</i> = 8)	7.63 (d, <i>J</i> = 9)
H-α	7.72 (d, <i>J</i> = 15)	7.72 (d, <i>J</i> = 15)	7.71 (d, <i>J</i> = 15)
H-β	8.15 (d, <i>J</i> = 15)	8.15 (d, <i>J</i> = 15)	8.14 (d, <i>J</i> = 15)
H-5'	6.35 (d, <i>J</i> = 9)	6.35 (d, <i>J</i> = 9)	6.37 (d, <i>J</i> = 9)
H-6'	7.84 (d, <i>J</i> = 9)	7.85 (d, <i>J</i> = 9)	7.84 (d, <i>J</i> = 9)
1"-Me	1.94 (3H, br s)	1.93 (3H, br s)	1.92 (3H, br s)
H-2"	5.68 (br s)	5.67 (br s)	5.68 (br s)
H-3"	4.18 (br)	4.20 (br)	4.18 (br)
H-4"	4.68 (dd, <i>J</i> = 4, 5)	4.67 (dd, <i>J</i> = 4, 5)	4.67 (dd, <i>J</i> = 4, 5)
H-5"	3.81 (m)	3.82 (m)	3.80 (m)
H-6"	2.25 (br d, <i>J</i> = 17)	2.27 (br d, <i>J</i> = 17)	2.24 (br d, <i>J</i> = 18)
	2.52 (br d, <i>J</i> = 17)	2.52 (br d, <i>J</i> = 17)	2.51 (br d, <i>J</i> = 18)
H-13"	6.45 (d, <i>J</i> = 9)	6.26 (d, <i>J</i> = 9)	6.45 (d, <i>J</i> = 9)
H-14"	8.34 (d, <i>J</i> = 9)	8.37 (d, <i>J</i> = 9)	8.36 (d, <i>J</i> = 9)
H-17"	6.53 (d, <i>J</i> = 2)	6.51 (d, <i>J</i> = 2)	6.52 (d, <i>J</i> = 2)
H-19"	6.30 (dd, <i>J</i> = 2, 8)	6.30 (dd, <i>J</i> = 2, 8)	6.31 (dd, <i>J</i> = 2, 8)
H-20"	6.96 (d, <i>J</i> = 8)	6.96 (d, <i>J</i> = 8)	6.98 (d, <i>J</i> = 8)
H-21"	6.55 (d, <i>J</i> = 16)	6.58 (d, <i>J</i> = 10)	3.27 (2H, br d, <i>J</i> = 7)
H-22"	6.64 (dd, <i>J</i> = 7, 16)	5.65 (d, <i>J</i> = 10)	5.17 (m)
H-23"	2.38 (m)	—	—
23"-Me	1.03 (6H, d, <i>J</i> = 7)	1.38, 1.41 (3H, s)	1.58, 1.70 (3H, s)
2'-OH	14.40 (s)	14.35 (s)	14.28 (s)
10"-OH	13.39 (s)	12.89 (s)	12.86 (s)

^aMeasured at 400 MHz in Me₂CO-*d*₆.

These results suggest that **2** is a Diels-Alder-type adduct and a dehydro-compound of **1**. This suggestion was substantiated by examination of the ¹H-nmr and ¹³C-nmr spectra of **2**. In the ¹H-nmr spectrum of **2** the chemical shifts and the coupling constants of the protons, except those of the protons at the C-13" position and of the isoprenoid moiety, resembled those of the relevant protons of **1** (Table 1). The chemical shift values of all the carbon atoms, except those of the carbon atoms of the D ring and of the isoprenoid moiety, were in good agreement with those of the relevant carbon atoms of **1** (Table 2). The presence of a 2,2-dimethylpyran ring was confirmed by the ¹H-nmr spectrum as follows: δ 1.38, 1.41 (each 3H, s), 5.65 (1H, d, *J* = 10 Hz), 6.58 (1H, d, *J* = 10 Hz). This confirmation was further supported by the ¹³C-nmr spectrum of **2** (Table 2). From the above results, formula **2** was confirmed as the structure of artonin D including the relative configuration (cis-trans in relative configuration on the methylcyclohexene ring).

On the other hand, our previous work established the cis-trans adduct **7** as 3"*S*, 4"*R*, 5"*S* with positive optical rotations as found with **1** and **2**, while the all-trans adduct **8** as 3"*R*, 4"*R*, 5"*S* displayed a negative rotation (1, 11, 12). Therefore, **1** and **2** were assigned the 3"*S*, 4"*R*, 5"*S* conformation.

Although a series of natural Diels-Alder-type adducts has been isolated from the mulberry tree (1) and recently from the root of *Brosimopsis oblongifolia* (Moraceae) (13, 14), artonins C [**1**] and D [**2**] were isolated as the first examples of optically active Diels-Alder-type adducts from the plants of *Artocarpus* species.

TABLE 2. ^{13}C -nmr Spectral Data of Artonin C [1], Artonin D [2], and Kuwanon J [6].^a

Carbon	Compound			Carbon	Compound		
	1	2	6		1	2	6
C-1	115.2	115.3	115.4	C-6''	32.8	33.0	32.5
C-2	160.0	159.9	159.9	C-7''	23.9	23.8	23.8
C-3	103.7	103.7	103.7	C-8''	209.7	209.7	209.6
C-4	162.4	162.3	162.3	C-9''	113.5	114.1	113.5
C-5	109.1	109.2	109.2	C-10''	164.8	160.8	164.6
C-6	131.8	131.8	131.8	C-11''	113.0	109.7	116.0
C- α	117.4	117.5	117.6	C-12''	163.1	160.8	163.3
C- β	141.0	141.0	141.0	C-13''	108.5	108.9	108.2
C=O	193.4	193.4	193.4	C-14''	132.2	133.8	132.1
C-1'	114.0	114.3	114.1	C-15''	121.8	121.9	121.9
C-2'	163.6	163.6	163.6	C-16''	156.5	156.5	156.5
C-3'	116.1	116.0	116.3	C-17''	103.6	103.7	103.7
C-4'	165.8	165.8	165.7	C-18''	158.0	158.0	158.0
C-5'	110.0	110.0	110.1	C-19''	107.5	107.6	107.7
C-6'	130.7	130.8	130.7	C-20''	128.8	128.9	128.8
C-1''	135.0	135.1	134.9	C-21''	117.4	116.1	22.2
C-2''	123.3	123.3	123.5	C-22''	142.6	129.1	123.2
C-3''	32.7	32.9	32.7	C-23''	33.9	78.6	131.5
C-4''	47.5	47.7	47.5	C-24''	23.1	28.6	17.9
C-5''	36.3	36.2	36.4	C-25''	23.1	28.5	25.8

^aMeasured at 100.4 MHz in $\text{Me}_2\text{CO}-d_6$.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points were measured with a Yazawa Micro-Melting Point Apparatus (hot-stage type). Uv spectra were measured with a Shimadzu UV-265 Spectrophotometer and the ir spectra with a Hitachi 260-30 IR Spectrophotometer. ^1H -nmr and ^{13}C -nmr spectra were recorded with a JEOL GX-400 FTNMR Spectrometer. TMS was used as an internal standard, and chemical shifts are reported on the δ (ppm) scale. Optical rotations were measured with a JASCO DIP-4 Digital Polarimeter. Eims, fabms, and hrms were obtained with JEOL JMS D-300 and DX-303 instruments. Hplc analyses were carried out with an SSC (Senshu Scientific, Tokyo, Japan) High Pressure Liquid Chromatograph with an uv detector. Wakogel C-200 (Si gel, Wako Pure Chemical Industries, Osaka, Japan) was used for cc. Analytical tlc was performed on Wakogel B-5FM (Si gel, Wako), and the spots were visualized under uv light. Preparative tlc was run on Wakogel B-5F (Si gel, Wako).

PLANT MATERIAL.—Root bark of *A. heterophyllus* was collected in the Botanical Garden of Bogor, Indonesia, in February 1988, and was identified by the members of Botanical Garden of Bogor. A voucher specimen has been deposited in the Herbarium of Toho University.

ISOLATION OF ARTONINS C [1] AND D [2].—The dried root bark of *A. heterophyllus* (1 kg) was extracted successively with *n*-hexane (8 liters \times 3), C_6H_6 (8 liters \times 4), Me_2CO (8 liters \times 3), and MeOH (8 liters \times 3). Evaporation of the *n*-hexane, C_6H_6 , Me_2CO , and MeOH solutions to dryness yielded 15 g, 30 g, 20 g, and 40 g of residues, respectively. The Me_2CO extract (20 g) was chromatographed on Si gel (200 g) using *n*-hexane– Me_2CO (1:0 \rightarrow 1:1) and then Me_2CO as an eluent, each fraction monitored by tlc. The fractions eluted with *n*-hexane– Me_2CO (1:1) were evaporated to give the residue (0.7 g). From the residue, artonin C [1] (9 mg) was obtained sequentially by preparative tlc [solvent system CHCl_3 –MeOH (5:1), C_6H_6 – Me_2CO (2:1)] and by preparative hplc [column Shiseido Capcell Pak C18, solvent system MeCN– H_2O (4:1); column Senshu Pak SSC–Silica 425 1–N, solvent system Et_2O only]. The fractions eluted with *n*-hexane– Me_2CO (6:4) were evaporated to give the residue (0.6 g). From the residue, artonin D [2] (9 mg) was obtained sequentially by preparative tlc [CHCl_3 –MeOH (6:1), C_6H_6 – Me_2CO (3:1)] and by preparative hplc [Shiseido Capcell Pak C18, MeCN– H_2O (4:1)].

ARTONIN C [1].—Compound 1 was obtained as a yellow crystalline powder: mp 169–171 $^\circ$ (dec); $[\alpha]^{22}\text{D} + 20^\circ$ ($c = 0.090$, MeOH); FeCl_3 test positive (brown); fabms m/z $[\text{M} + \text{H}]^+ 679$; uv λ max (EtOH)

(log ϵ) 206 (4.39), 258 (3.98), 309 (3.87), 391 (4.03); ir ν max (KBr) 3400 (br), 1660 (sh), 1640 (sh), 1615, 1590 (sh), 1580 (sh), 1560.

ARTONIN D [2].—Compound **2** was obtained as a yellow crystalline powder: mp 140–143° (dec); [α]_D¹⁹ +77° (c = 0.172, MeOH); FeCl₃ test positive (brown); fabms m/z [M + H]⁺ 677; uv λ max (EtOH) (log ϵ) 205 (4.56), 267 (4.17), 316 (4.02), 390 (4.22); ir ν max (KBr) 3400 (br), 1660 (sh), 1640 (sh), 1610, 1560.

ARTONIN C OCTAMETHYL ETHER [1a].—A mixture of **1** (40 mg), Me₂SO₄ (0.25 ml), and K₂CO₃ (3 g) in Me₂CO (20 ml) was refluxed for 6 h and treated as usual. The product was purified by preparative tlc [C₆H₆-Et₂O (6:1)] to give artonin C octamethyl ether [1a] (3 mg): hrms m/z [M]⁺ 790.3731 (calcd for C₄₈H₅₄O₁₀, 790.3717); eims (70 eV) m/z (rel. int.) [M]⁺ 790 (45), 557 (98), 394 (20), 365 (23), 363 (26), 233 (100); ¹H nmr (CDCl₃) δ 1.12 (6H, d, J = 7), 1.77 (3H, s), 2.22, 2.32 (each 1H, m), 3.47, 3.51, 3.64 (\times 2), 3.74, 3.76, 3.86 (\times 2) (OMe), 4.28 (1H, m), 4.68 (1H, br), 4.76 (1H, dd, J = 8 and 10), 5.38 (1H, br s), 6.32–6.38 (2H, m), 6.40 (1H, d, J = 16), 6.46 (2H, d, J = 2), 6.52 (2H, m), 6.53 (1H, dd, J = 7 and 16), 6.79 (1H, br), 7.13 (1H, d, J = 8), 7.97 (1H, d, J = 15).

ARTONIN D HEPTAMETHYL ETHER [2a].—A mixture of **2** (20 mg), Me₂SO₄ (0.25 ml), and K₂CO₃ (3 g) in Me₂CO (20 ml) was refluxed for 6 h and treated as usual. The product was purified by preparative tlc [C₆H₆-Et₂O (6:1)] to give artonin D heptamethyl ether [2a] (11 mg): hrms m/z [M]⁺ 774.3394 (calcd for C₄₇H₅₀O₁₀, 774.3405); eims (70 eV) m/z (rel. int.) [M]⁺ 774 (35), 557 (67), 394 (28), 365 (70), 363 (30), 217 (100); ¹H nmr (CDCl₃) δ 1.36, 1.38, 1.77 (3H, s), 2.29, 2.40 (each 1H, m), 3.45, 3.47, 3.49, 3.69, 3.72, 3.85, 3.87 (each 3H, s, OMe), 4.20 (1H, m), 4.58 (1H, br), 4.61 (1H, m), 5.43 (1H, br s), 5.58 (1H, d, J = 10), 6.33 (1H, dd, J = 2 and 8), 6.34 (1H, d, J = 2), 6.40 (1H, d, J = 8), 6.45 (1H, d, J = 9), 6.46 (1H, d, J = 2), 6.51 (1H, dd, J = 2 and 8), 6.51 (1H, d, J = 10), 7.08 (1H, d, J = 8), 7.12 (1H, J = 9), 7.38 (1H, d, J = 8), 7.40 (1H, d, J = 15), 7.61 (1H, d, J = 8), 7.94 (1H, d, J = 15).

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