HETEROCYCLES, Vol. 71, No. 5, 2007, pp. 1147 - 1154. © The Japan Institute of Heterocyclic Chemistry
Received, 5th February, 2007, Accepted, 23rd March, 2007, Published online, 27th March, 2007. COM-07-11019

FOUR NEW PRENYLATED 2-ARYLBENZOFURANS FROM THE ROOT BARK OF *ARTOCARPUS PETELOTII*

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Abstract – Four new prenylated 2-arylbenzofurans, artopetelins H–K (**1–4**), were isolated from the root bark of *Artocarpus petelotii* Gagnep. Their structures were elucidated by extensive 1D-, 2D-NMR, and MS spectral analysis.

INTRODUCTION

Artocarpus species (Moraceae) are evergreen plants distributed over tropical regions of Asia, such as Indonesia, Thailand, and Sri Lanka. Primarily known for their large edible fruits, some members have important medicinal value. Especially in Indonesia, many *Artocarpus* plants are used as traditional folk medicine called "Jamu" against inflammation, malaria, fever, dysentery, and tuberculosis.[1] Previous research work on this genus provided a variety of prenylated flavonoids and some stilbenes and 2-arylbenzofurans with chemical and biological diversity.[2–4] In a program searching for bioactive prenylated phenols from Chinese *Artocarpus* plants,[5–8] we have investigated the chemical constituents of *Artocarpus chama* Buch.-Ham. and *Artocarpus petelotii* Gagnep, both plants being cultivated in Xishuangbanna, Yunnan province, China. It is interesting that their phenolic constituents found so far are different. The roots and stems of *A. chama* are rich in prenylated flavones with cytotoxicity, prenylated stilbenes and their biogenetic derivatives being minor constituents.[5,6] On the other hand, a series of prenylated 2-arylbenzofurans, artopetelins A–G, were isolated from the root bark of *A. petelotii*.[7,8] The limited distribution of 2-arylbenzofurans in *Artocarpus* genus and their interesting bioactivities, such as antibacterial,[9] antiviral,[10] cancer-chemopreventive, and cyclooxygenase-inhibitory effects,[4] have attracted our attention. Therefore, a re-examination of the EtOH extract from the root bark of *A. petelotii* yielded four new prenylated 2-arylbenzofurans, artopetelins H–K (**1**–**4**). This paper describes the isolation and

structure elucidation of these compounds.

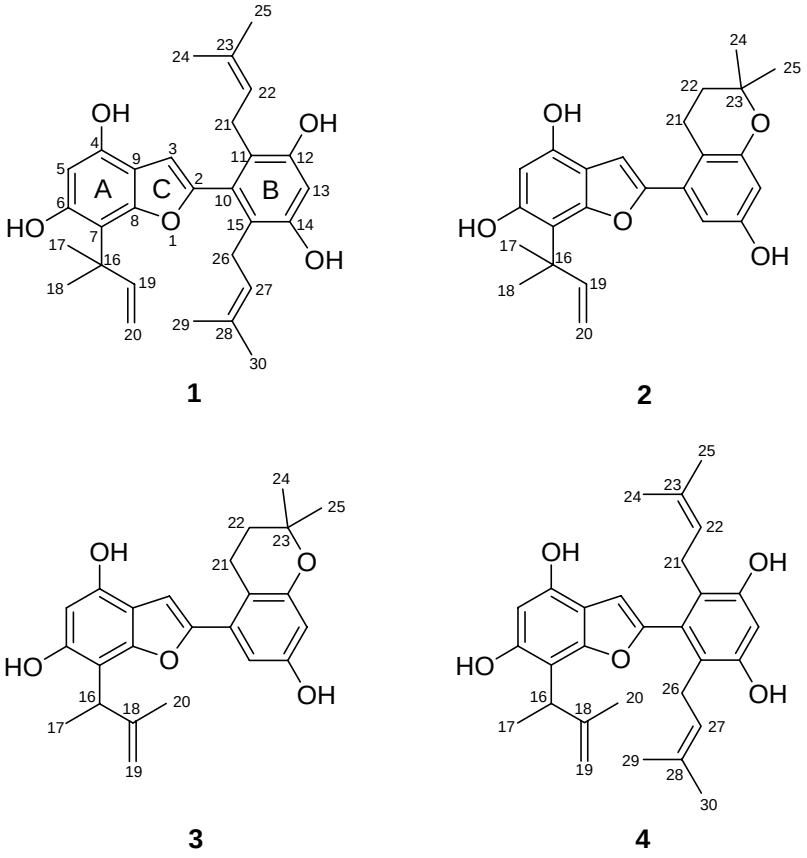

Figure 1. Structures of Compounds (**1**–**4**)

RESULTS AND DISCUSSION

Artopetelin H **(1)**, a yellow amorphous powder, was assigned a molecular formula of $C_{29}H_{34}O_5$ by HREIMS (*m/z* 462.2414 $[M]^+$). The UV absorption maxima at 207 and 285 nm suggested the presence of a 2-arylbenzofuran skeleton.[7,8,11] The IR spectrum showed absorptions typical of hydroxyl groups (3446 cm^{-1}) and aromatic rings (1614 and 1450 cm^{-1}). The ^{1}H-NMR spectrum showed signals of four hydroxyl groups [δ_H 8.41, 7.53 (each 1H, s) and 7.97 (2H, s)], three downfield singlets [δ_H 6.59, 6.58, and 6.31 (each 1H, s)], two symmetrical 3,3-dimethylallyl (prenyl) side chains [δ_H 5.09 (2H, br t, *J* = 6.7 Hz), 3.17 (4H, br d, *J* = 6.7 Hz), and 1.53, 1.40 (each 6H, br s)], and a 1,1-dimethylallyl group [δ_H 6.43 (1H, dd, *J* = 10.6, 17.5 Hz), 5.03 (1H, br d, *J* = 17.5 Hz), 4.92 (1H, br d, *J* = 10.6 Hz), and 1.65 (6H, s)]. The ^{13}C-NMR and HMQC spectra of **1** revealed the presence of twenty-nine carbon signals, corresponding to a triprenylated and tetrahydroxylated 2-arylbenzofuran with a symmetrical moiety on ring B. On the basis of HMQC and HMBC spectral analysis, we were able to fully assign all ^{1}H- and ^{13}C-NMR signals (Tables 1 and 2) and determine the position of the substituents. The HMBC correlations from 21, 26-H_2

(δ_H 3.17) to C-10 (δ_C 134.0), C-11, 15 (δ_C 121.6), and C-12, 14 (δ_C 154.7), as well as those from 12, 14-OH (δ_H 7.97) to C-11, 15, C-12, 14, and C-13 (δ_C 105.1), indicated that the two prenyl and two hydroxyl groups were located at C-11, 15 and C-12, 14, respectively (Figure 2). The HMBC correlations from 17, 18-H_3 (δ_H 1.65) to C-7 (δ_C 110.3), from 4-OH (δ_H 8.41) to C-4 (δ_C 149.9), C-5 (δ_C 100.4), and C-9 (δ_C 113.6), and from 6-OH (δ_H 7.53) to C-5, C-6 (δ_C 154.6), and C-7, supported the substitution of ring A. Thus, artopetelin H was elucidated as 7-(1,1-dimethylprop-2-enyl)-2-[3,5-dihydroxy-2,6-bis(3-methylbut-2-enyl)phenyl]-1-benzofuran-4,6-diol **(1)**.

Table 1. ^{1}H-NMR Data for Compounds (**1**–**4**) in acetone-d_6 (δ in ppm, J in Hz)

Proton	**1** [a])	**2** [a])	**3** [b])	**4** [a])
3	6.59 (s)	6.98 (s)	6.98 (s)	6.56 (s)
5	6.31 (s)	6.35 (s)	6.38 (s)	6.34 (s)
13	6.58 (s)	6.28 (d, J = 2.5)	6.28 (d, J = 2.5)	6.57 (s)
15		6.97 (d, J = 2.5)	6.95 (d, J = 2.5)	
16			4.07 (q, J = 7.2)	4.00 (q, J = 7.4)
17	1.65 (s)	1.72 (s)	1.58 (d, J = 7.2)	1.50 (d, J = 7.4)
18	1.65 (s)	1.72 (s)		
19a			4.99 (br s)	4.82 (br s)
19b			4.84 (br s)	4.73 (br s)
19	6.43 (dd, J = 10.6, 17.5)	6.48 (dd, J = 10.6, 17.5)		
20a	5.03 (br d, J = 17.5)	5.06 (dd, J = 1.4, 17.5)		
20b	4.92 (br d, J = 10.6)	4.96 (dd, J = 1.4, 10.6)		
20			1.69 (br s)	1.65 (br s)
21	3.17 (br d, J = 6.7)	2.89 (t, J = 6.8)	2.88–2.92 (m)	3.13 (br d, J = 6.5)
22	5.09 (br t, J = 6.7)	1.85 (t, J = 6.8)	1.84 (t, J = 6.7)	5.05 (br t, J = 6.5)
24	1.40 (br s)	1.34 (s)	1.33 (s)	1.36 (br s)
25	1.53 (br s)	1.34 (s)	1.33 (s)	1.51 (br s)
26	3.17 (br d, J = 6.7)			3.13 (br d, J = 6.5)
27	5.09 (br t, J = 6.7)			5.05 (br t, J = 6.5)
29	1.40 (br s)			1.36 (br s)
30	1.53 (br s)			1.51 (br s)
4-OH	8.41 (s)			8.93 (s)
6-OH	7.53 (s)			8.35 (s)
12-OH	7.97 (s)			8.49 (s)
14-OH	7.97 (s)			8.49 (s)

[a]) At 400 MHz. [b]) At 500 MHz.

Artopetelin I **(2)**, a yellow amorphous powder, was assigned a molecular formula of $C_{24}H_{26}O_5$ by HREIMS (*m/z* 394.1796 $[M]^+$). The UV and IR data resembled those of 2-arylbenzofuran derivatives. The ^{1}H-NMR spectrum showed signals of a 1,1-dimethylallyl group [δ_H 6.48 (1H, dd, J = 10.6, 17.5 Hz), 5.06 (1H, dd, J = 1.4, 17.5 Hz), 4.96 (1H, dd, J = 1.4, 10.6 Hz), and 1.72 (6H, s)], two *meta*-coupled aromatic protons [δ_H 6.97 and 6.28 (each 1H, d, J = 2.5 Hz)], two downfield singlets [δ_H 6.98 and 6.35

(each 1H, s)], and a 3,4-dihydro-2,2-dimethylpyran ring [δ_H 2.89, 1.85 (each 2H, t, J = 6.8 Hz) and 1.34 (6H, s)]. Comparison of the NMR spectroscopic data of **2** and **1** (Tables 1 and 2) indicated that they should have the same moiety of rings A and C. However, **2** contained a 3,4-dihydro-2,2-dimethylpyran ring attached at ring B rather than two symmetrical prenyl groups in **1**. This pyranoid moiety was fused at C-11 and C-12, as established by the HMBC correlations from 21-H_2 (δ_H 2.89) to C-10 (δ_C 132.5), C-11 (δ_C 110.6), and C-12 (δ_C 156.5) and from 22-H_2 (δ_H 1.85) to C-11. The two *meta*-coupled aromatic protons (δ_H 6.97 and 6.28) were assigned to C-15 and C-13, respectively, supported by the HMBC correlations shown in Figure 2. Thus, the structure of artopetelin I was elucidated as 7-(1,1-dimethylprop-2-enyl)-2-(3,4-dihydro-7-hydroxy-2,2-dimethyl-2*H*-1-benzopyran-5-yl)-1-benzofuran-4,6-diol **(2)**.

Table 2. ^{13}C-NMR Data for Compounds (**1**–**4**) in acetone-d_6 (δ in ppm)

Carbon	**1** [a])	**2** [a])	**3** [b])	**4** [a])
2	152.2	152.6	152.9	152.2
3	103.9	103.9	103.6	104.0
4	149.9	150.2	149.9	149.3
5	100.4	100.4	98.7	98.8
6	154.6	155.61 [c])	154.3	153.5
7	110.3	110.0	107.1	107.3
8	156.5	155.64 [c])	155.8	156.5
9	113.6	113.7	112.7	112.4
10	134.0	132.5	132.3	133.5
11	121.6	110.6	110.4	121.2
12	154.7	156.5	156.2	154.4
13	105.1	104.8	104.5	104.6
14	154.7	157.6	157.2	154.4
15	121.6	108.0	107.6	121.2
16	41.6	41.5	36.4	36.7
17	29.6	29.4	18.0	17.9
18	29.6	29.4	149.4	149.5
19	150.5	150.5	109.2	109.4
20	110.1	109.7	22.48 [d])	22.4
21	27.4	22.9	22.54 [d])	27.0
22	125.8	34.0	33.6	125.4
23	130.2	74.4	74.1	129.9
24	18.2	27.2	26.8 [e])	17.8
25	26.2	27.2	26.9 [e])	25.8
26	27.4			27.0
27	125.8			125.4
28	130.2			129.9
29	18.2			17.8
30	26.2			25.8

[a]) At 100 MHz. [b]) At 125 MHz. [c]), [d]), [e]) Signals may be exchangeable.

Artopetelin J **(3)**, a yellow amorphous powder, was assigned a molecular formula of $C_{24}H_{26}O_5$ by HREIMS (*m/z* 394.1770 $[M]^+$). The NMR data of **3** resembled those of **2** (Tables 1 and 2), except for signals due to a 1,2-dimethylallyl group: δ_H 4.99 and 4.84 (each 1H, br s, 19-H_2), 4.07 (1H, q, J = 7.2 Hz, 16-H), 1.69 (3H, br s, 20-H_3), and 1.58 (3H, d, J = 7.2 Hz, 17-H_3); δ_C 36.4 (C-16), 18.0 (C-17), 149.4 (C-18), 109.2 (C-19), and 22.48 (C-20). The HMBC correlations from 16-H to C-6 (δ_C 154.3), C-7 (δ_C 107.1), and C-8 (δ_C 155.8) and from 17-H_3 to C-7 showed that the 1,2-dimethylallyl group was located at C-7 (Figure 2). Thus, the planar structure of artopetelin J was elucidated as 7-(1,2-dimethylprop-2-enyl)-2-(3,4-dihydro-7-hydroxy-2,2-dimethyl-2*H*-1-benzopyran-5-yl)-1-benzofuran-4,6-diol **(3)**. Similarly to artopetelins D and E,[8] the configuration at C-16 remains to be determined.

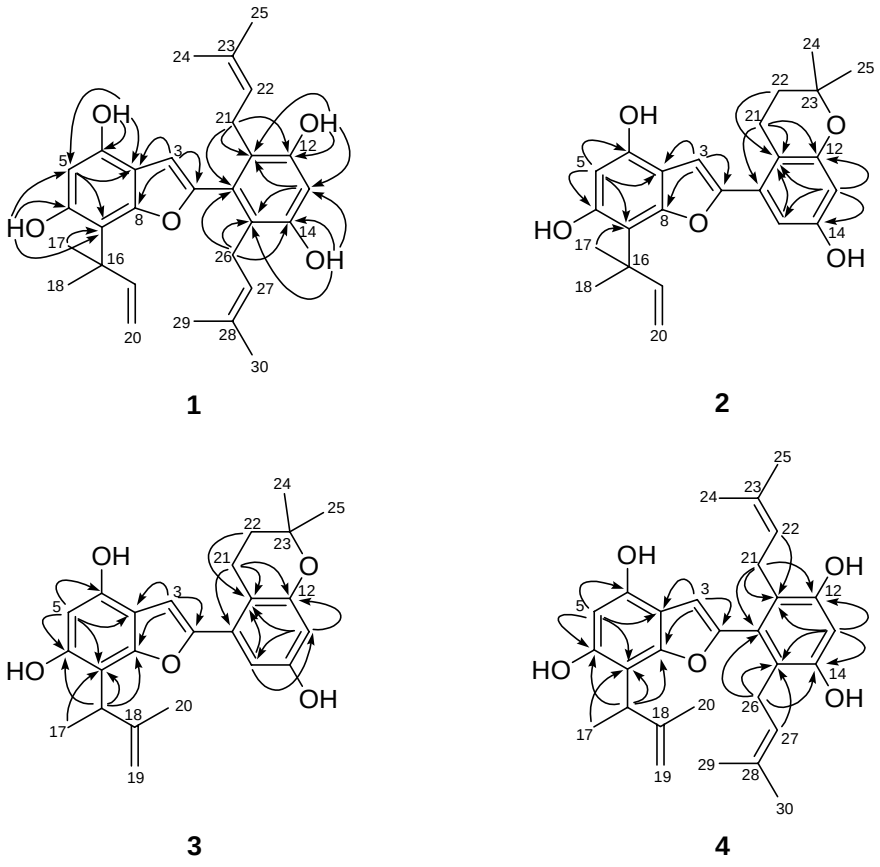

Figure. 2 Key HMBC (H → C) correlations of Compounds (**1**–**4**)

Artopetelin K **(4)**, a yellow amorphous powder, was assigned a molecular formula of $C_{29}H_{34}O_5$ by HREIMS (*m/z* 462.2416 $[M]^+$). The NMR characteristics of **4** (Tables 1 and 2) showed that it was a 2-arylbenzofuran with the same symmetrical substituents on ring B as **1** and the same moiety of ring A as **3**. This result was corroborated by the HMBC correlations shown in Figure 2. Thus, the planar structure of artopetelin K was elucidated as 7-(1,2-dimethylprop-2-enyl)-2-[3,5-dihydroxy-2,6-bis(3-methylbut-2-enyl)phenyl]-1-benzofuran-4,6-diol **(4)**. The configuration at C-16 remains to be determined.

EXPERIMENTAL

General Experimental Procedures. Melting points were measured with an XT-4 micro-melting point apparatus and are uncorrected. Optical rotations were measured with a JASCO P1030 polarimeter. UV spectra were obtained with a Shimadzu UV-2401PC spectrophotometer. IR spectroscopic data were recorded with a Nicolet Avatar 360 spectrometer with KBr pellets. EIMS and HREIMS data were recorded with a Finnigan MAT-95 mass spectrometer. NMR spectra were obtained with a Bruker DRX-400 and -500 instruments. Chemical shifts are reported with respect to acetone-d_6 (δ_H = 2.04, δ_C = 206.0 ppm). Column chromatography was performed on silica gel H (10–40 μm and 200–300 mesh; Yantai Institute of Chemical Technology, China), Chromatorex PR-18 gel (20–45 μm; Fuji Silysia Chemical, Ltd., Kasugai, Japan), MCI gel CHP-20P (75–150 μm; Mitsubishi Chemical Corporation, Japan), Toyopearl HW-40C (Tosoh Corporation, Japan), and Sephadex LH-20 (Amersham Biosciences, GE Health Care). Preparative and analytical TLC was run on precoated silica gel GF_{254} plates (10–40 μm; Yantai Institute of Chemical Technology, China).

Plant Material. The root bark of *A. petelotii* Gagnep was collected in Xishuangbanna, Yunnan, P. R. China, in July 1998, and air-dried. The plant was identified by Prof. Han-Dong Sun, Kunming Institute of Botany, and a voucher specimen (TCM 98-07-02 Hou) was deposited in the Herbarium of the Department of Pharmacognosy, School of Pharmacy, Fudan University.

Extraction and Isolation. The air-dried and powdered root bark (6.4 kg) of *A. petelotii* was percolated with 95% EtOH (60 L) at rt. The filtrate was concentrated to give a residue (800 g), which was suspended in H_2O (2 L) and partitioned successively with petroleum ether (4×800 mL) and EtOAc (4×800 mL). The EtOAc extract (110 g) was subjected to column chromatograph (CC) on silica gel [petroleum ether-Me_2CO (8 : 2 →2 : 8)] to yield fractions A–I. Fraction F (9.5 g) was chromatographed over silica gel [$CHCl_3$-EtOAc (30 : 1 → 1 : 2)] to give fractions F1–F6. Fraction F3 was separated by CC on silica gel [$CHCl_3$-Me_2CO (40 : 1)] to provide fractions F3.1–F3.6. Fraction F3.5 was subjected to CC on RP-18 [MeOH-H_2O (6.5 : 3.5)] and MCI gel CHP-20P [MeOH-H_2O (6.5 : 3.5)], followed by Sephadex LH-20 [$CHCl_3$-MeOH (1:1)] to yield **4** (15 mg). Fraction F3.6 was separated by CC on RP-18 [MeOH-H_2O (5.5 : 4.5)] and MCI gel CHP-20P [MeOH-H_2O (6.5 : 3.5)] to give fractions F3.6.1–F3.6.4. Fraction F3.6.2 was further purified by preparative TLC [$CHCl_3$-2-propanol (30 : 1)] to give **1** (3 mg). Fraction F3.6.3 was separated by preparative TLC [$CHCl_3$-2-propanol (20 : 1)] to afford **2** (5 mg). Fraction F4 was isolated by CC on RP-18 [MeOH-H_2O (6.5 : 3.5)] and Toyopearl HW-40C [MeOH-H_2O (7.5 : 2.5)], followed by Sephadex LH-20 [$CHCl_3$-MeOH (1 : 1)] to yield **3** (30 mg).

Artopetelin H (1): yellow amorphous powder, mp 138–140 °C; UV (MeOH) λ_{max} (log ε): 285 (3.86), 207 (4.47) nm; IR (KBr) ν_{max}: 3446, 2924, 2853, 1614, 1450, 1145, 1087 cm^{-1}; EIMS *m/z* (*rel. int.* %): 462 (M^+, 100), 445 (11), 419 (26), 407 (12), 391 (12), 363 (24), 351 (17), 253 (15), 213 (12); HREIMS:

m/z 462.2414 $[M]^+$ (calcd for $C_{29}H_{34}O_5$: 462.2406); ^{1}H-NMR and ^{13}C-NMR data: shown in Tables 1 and 2, respectively.

Artopetelin I (2): yellow amorphous powder, mp 146–148 °C; UV (MeOH) λ_{max} (log ε): 316 (4.15), 218 (4.26) nm; IR (KBr)ν_{max}: 3423, 2971, 2925, 1614, 1445, 1421, 1368, 1327, 1279, 1152, 1119, 1055, 1023, 966 cm^{-1}; EIMS *m/z* (*rel*. *int*. %): 394 (M^+, 100), 379 (38), 339 (13), 108 (15), 101 (15), 90 (33); HREIMS: *m/z* 394.1796 $[M]^+$ (calcd for $C_{24}H_{26}O_5$: 394.1780); ^{1}H-NMR and ^{13}C-NMR data: shown in Tables 1 and 2, respectively.

Artopetelin J (3): yellow amorphous powder, mp 158–160 °C; $[\alpha]_D^{20}$ +1.4° (*c* 0.38, acetone); UV (MeOH) λ_{max} (log ε): 314 (4.17), 217 (4.24) nm; IR (KBr) ν_{max}: 3386, 2972, 2925, 1616, 1444, 1372, 1284, 1153, 1120, 1023 cm^{-1}; EIMS *m/z* (*rel*. *int*. %): 394 (M^+, 100), 379 (9), 339 (17), 338 (9), 323 (6); HREIMS: *m/z* 394.1770 $[M]^+$ (calcd for $C_{24}H_{26}O_5$: 394.1780); ^{1}H-NMR and ^{13}C-NMR data: shown in Tables 1 and 2, respectively.

Artopetelin K (4): yellow amorphous powder, mp 119–120 °C; $[\alpha]_D^{20}$ +1.2° (*c* 0.34, acetone); UV (MeOH) λ_{max} (log ε): 288 (3.96), 207 (4.55) nm; IR (KBr) ν_{max}: 3441, 2965, 2924, 1699, 1616, 1435, 1375, 1262, 1160, 1132, 1086, 1032 cm^{-1}; EIMS *m/z* (*rel*. *int*. %): 462 (M^+, 100), 419 (26), 391 (11), 363 (13), 337 (12), 253 (20), 225 (10), 207 (21); HREIMS: *m/z* 462.2416 $[M]^+$ (calcd for $C_{29}H_{34}O_5$: 462.2406); ^{1}H-NMR and ^{13}C-NMR data: shown in Tables 1 and 2, respectively.

ACKNOWLEDGEMENTS

Financial support from the National Natural Science Foundation of China (30572247) is gratefully acknowledged.

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