New Isoprenylated 2-Arylbenzofurans and Pancreatic Lipase Inhibitory Constituents from *Artocarpus nitidus*

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Two new isoprenylated 2-arylbenzofurans, artonitidin A (=(2′*R*)-2′,3′-dihydro-2′-(1-hydroxy-1-methylethyl)-5′,7-bis(3-methylbut-2-en-1-yl)-2,4′-bi-1-benzofuran-6,6′-diol; **1**) and artonitidin B (=5-[6-hydroxy-7-(3-methylbut-2-en-1-yl)-1-benzofuran-2-yl]-4-(3-methylbut-2-en-1-yl)benzene-1,3-diol; **2**), together with 14 known compounds, **3**–**16**, were isolated from the stems of *Artocarpus nitidus* Trec. The structures were elucidated by spectroscopic methods. Norartocarpin (**3**), cudraflavone C (**5**), brosimone I (**8**), artotonkin (**11**), albanin A (**13**), and artopetelin M (**14**) showed inhibitory effects on pancreatic lipase with IC_{50} values ranging from 1.8 ± 0.1 to 63.8 ± 3.6 μM.

Introduction. – The genus *Artocarpus* (Moraceae) consists of *ca.* 50 species, mainly distributed over tropical regions of Asia. There are *ca.* 15 species growing in southern China. Some *Artocarpus* members are known for their medicinal value [1]. *A. altilis* has a long history of being used to treat cirrhosis and hypertension in Taiwan [1a]. In Indonesia, many *Artocarpus* plants are used as traditional folk medicine against inflammation, malarial fever, dysentery, and tuberculosis [1b]. *A. heterophyllus* is used to control blood sugar levels in diabetic patients in Sri Lanka [1c]. Previous studies on this genus provided various isoprenylated flavonoids, 2-arylbenzofurans, and stilbenoids, which showed biological activities such as cytotoxicity, anti-inflammation, cyclooxygenase-inhibitory activity, and antimycobacterial effects [2]. In recent years, our group reported a series of isoprenylated flavones, stilbenes, their novel biogenetic derivatives, and 2-arylbenzofurans from *A. chama* [3] and *A. petelotii* [4]. As part of our continuing research on *Artocarpus* plants, we investigated the chemical constituents of *Artocarpus nitidus* Trec., which has so far not been studied phytochemically and pharmacologically.

Interestingly, the $CHCl_3$-soluble fraction from an EtOH extract of the stems of *A. nitidus* showed inhibitory effect on pancreatic lipase (PL) with an IC_{50} value of 10.7 ± 0.1 μg/ml. PL is the most important enzyme for dietary lipid absorption, and inhibition of PL is generally regarded as an effective approach for the treatment of obesity [5]. Thus, the $CHCl_3$ fraction was subjected to further isolation, which afforded two new isoprenylated 2-arylbenzofurans, artonitidins A and B (**1** and **2**, resp.), and 14 known compounds, *i.e.*, norartocarpin (**3**) [6], cudraflavones A and C (**4** and **5**, resp.) [7][8], cycloartocarpin A (**6**) [3b], artocarpin (**7**) [3b], brosimone I (**8**) [9], morusin (**9**) [10],

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cycloartocarpesin (**10**) [11], artotonkin (**11**) [12], chaplashin (**12**) [13], albanin A (**13**) [9], artopetelin M (**14**) [4c], artoindonesianin X (**15**) [14], and 2,4,2′,4′-tetrahydroxy-3′-(3-methylbut-2-en-1-yl)chalcone (**16**) [15] (*Fig. 1*). To our knowledge, compound **1** is the first 2-arylbenzofuran with a 2-(1-hydroxy-1-methylethyl)dihydrofuran ring from

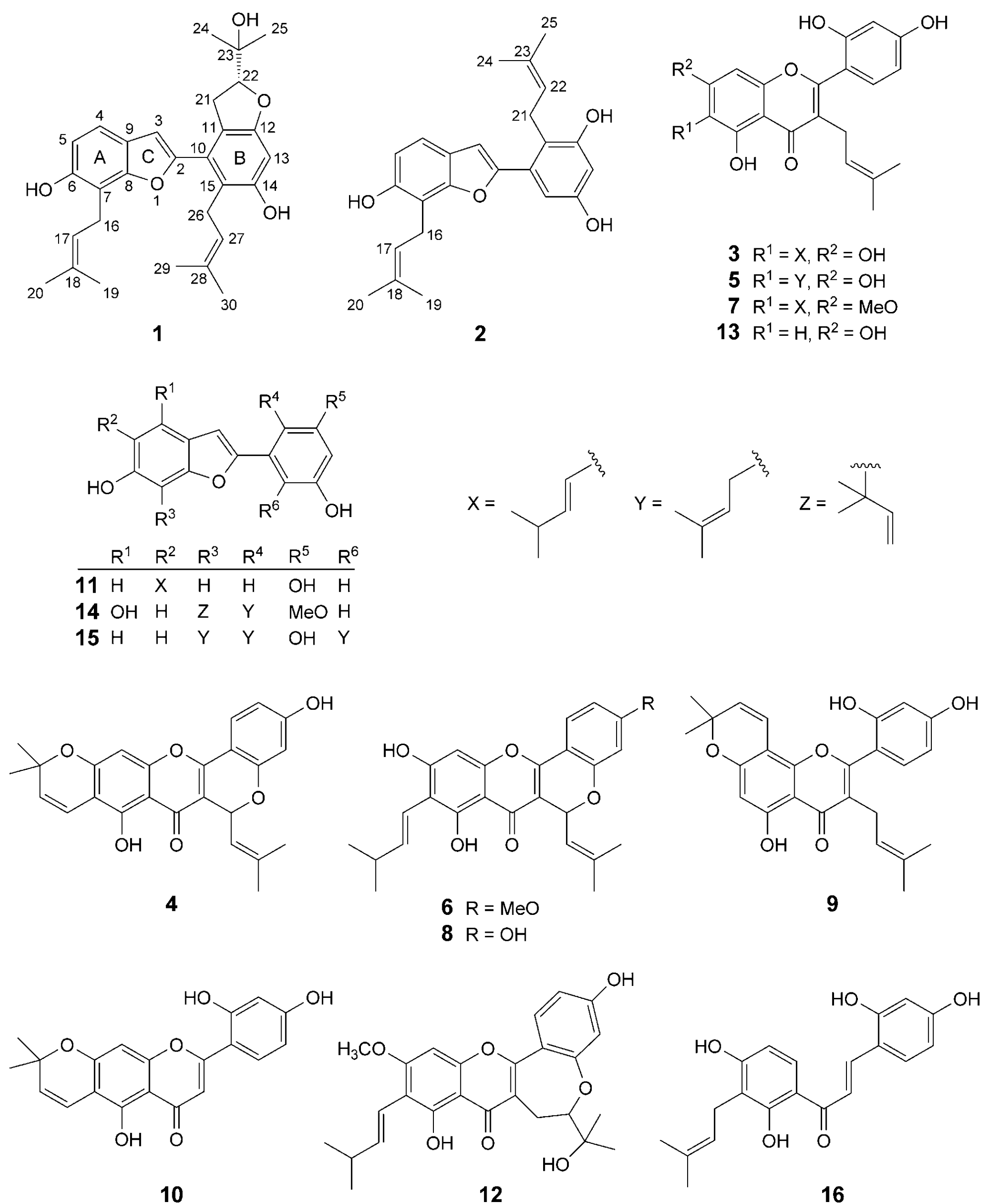

Fig. 1. *Structures of compounds* **1**–**16**

Artocarpus species, some examples having been found in *Morus* plants [16]. Some of the isolated compounds were tested for PL-inhibitory activity. Here, we describe the structure elucidation of compounds **1** and **2**, and the biological evaluation.

Results and Discussion. – Artonitidin A (**1**), an optically active compound ($[\alpha]_D^{20} = -25.7$), was isolated as a yellow amorphous powder. Its molecular formula was deduced as $C_{29}H_{34}O_5$ by HR-EI-MS at *m/z* 462.2401 (M^+; calc. 462.2406). The IR absorptions of **1** implied the presence of OH (3419 cm^{-1}) and aromatic ring (1651 and 1457 cm^{-1}) moieties. The UV absorption maxima at 206 and 306 nm suggested the presence of a 2-arylbenzofuran skeleton [4]. The ^{1}H-NMR spectrum (*Table 1*) displayed signals of two OH groups at δ(H) 8.29 and 8.27 (2*s*, 1 H each), two *ortho*-

Table 1. *^{1}H- and ^{13}C-NMR Data of* **1** and **2**. At 500 and 125 MHz, respectively, in (D_6)acetone; δ in ppm, *J* in Hz (C-atom numbering as indicated in *Fig. 1*).

Position	1		2	
	δ(C)	δ(H)	δ(*C*)	δ(H)
2	153.9		155.7	
3	106.9	6.74 (*s*)	105.8	6.77 (*s*)
4	118.8	7.25 (*d*, *J* = 8.3)	118.8	7.24 (*d*, *J* = 8.3)
5	112.9	6.85 (*d*, *J* = 8.3)	112.9	6.84 (*d*, *J* = 8.3)
6	153.3		153.3	
7	112.1		112.1	
8	155.3		155.3	
9	122.2		122.5	
10	129.1		132.9	
11	119.2		118.6	
12	159.7		157.5	
13	98.2	6.38 (*s*)	103.8	6.50 (*d*, *J* = 2.4)
14	156.4		156.9	
15	119.4		107.8	6.77 (*d*, *J* = 2.4)
16	23.4	3.58 (br. *d*, *J* = 7.0)	23.4	3.62 (br. *d*, *J* = 7.3)
17	123.4	5.41 (br. *t*, *J* = 7.0)	123.3	5.43 (br. *t*, *J* = 7.3)
18	131.8		131.9	
19	18.0	1.79 (br. *s*)	18.0	1.83 (br. *s*)
20	25.8	1.64 (br. *s*)	25.8	1.66 (br. *s*)
21	31.8	3.25 (*dd*, *J* = 8.5, 15.8), 3.18 (*dd*, *J* = 9.4, 15.8)	26.3	3.53 (br. *d*, *J* = 6.5)
22	90.5	4.58 (*dd*, *J* = 8.5, 9.4)	125.5	5.22 (br. *t*, *J* = 6.5)
23	71.5		130.9	
24	25.5[a])	1.23 (*s*)[b])	18.0	1.66 (br. *s*)
25	25.9[a])	1.19 (*s*)[b])	25.8	1.64 (br. *s*)
26	26.8	3.44 (br. *d*, *J* = 6.6)		
27	125.7	5.20 (br. *t*, *J* = 6.6)		
28	130.5			
29	17.9	1.55 (br. *s*)		
30	25.8	1.61 (br. *s*)		
6-OH		8.27 (*s*)		
14-OH		8.29 (*s*)		

[a]) and [b]) Signals may be interchangeable.

coupled aromatic H-atoms at δ(H) 7.25 and 6.85 (2*d*, J=8.3, 1 H each), two downfield *singlet*s at δ(H) 6.74 and 6.38 (2*s*, 1 H each), and two γ,γ-dimethylallyl (prenyl) side chains, one at δ(H) 5.41 (br. *t*, J=7.0, 1 H), 3.58 (br. *d*, J = 7.0, 2 H), and 1.79 and 1.64 (2 br. *s*, 3 H each), the other at δ(H) 5.20 (br. *t*, J=6.6, 1 H), 3.44 (br. *d*, J=6.6, 2 H), and 1.61 and 1.55 (2 br. *s*, 3 H each). Furthermore, a 2-(1-hydroxy-1-methylethyl)dihydrofuran moiety was inferred from the following ^{1}H- and ^{13}C-NMR data: δ(H) 4.58 (*dd*, J=8.5, 9.4, 1 H), 3.25 (*dd*, J=8.5, 15.8, 1 H), 3.18 (*dd*, J=9.4, 15.8, 1 H), and 1.23, 1.19 (2*s*, 3 H each), as well as δ(C) 31.8 (C(21)), 90.5 (C(22)), 71.5 (C(23)), 25.5 (C(24)), and 25.9 (C(25)). These data suggest that **1** is a triply isoprenylated and dihydroxylated 2-arylbenzofuran. Analysis of the HMBC data revealed the position of the substituents (*Fig. 2*). The two prenyl groups were located at C(7) and C(15), respectively, as established by HMBC from CH_2(16) (δ(H) 3.58) to C(6) (δ(C) 153.3), C(7) (δ(C) 112.1), and C(8) (δ(C) 155.3), and from CH_2(26) (δ(H) 3.44) to C(10) (δ(C) 129.1), C(14) (δ(C) 156.4), and C(15) (δ(C) 119.4). The 2-(1-hydroxy-1-methylethyl)dihydrofuran ring was at C(11) and C(12) according to HMBC from CH_2(21) (δ(H) 3.25 and 3.18) to C(11) (δ(C) 119.2). The two OH groups were connected to C(6) and C(14), respectively, as supported by HMBC from OH−C(6) (δ(H) 8.27) to C(7), and from OH−C(14) (δ(H) 8.29) to C(15). The absolute configuration at C(22) was preliminarily proposed as (*R*) by comparison of the optical rotation of **1** with those of (+)-(*S*)- and (−)-(*R*)-2,3-dihydro-2-(2-hydroxyisopropyl)-6-methoxybenzofurans [17]. Thus, the structure of **1** was elucidated as (2′*R*)-2′,3′-dihydro-2′-(1-hydroxy-1-methylethyl)-5′,7-bis(3-methylbut-2-en-1-yl)-2,4′-bi-1-benzofuran-6,6′-diol, and **1** was named artonitidin A (*Fig. 1*).

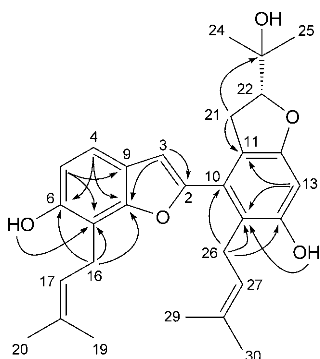

Fig. 2. *Selected HMBC* (H→C) *data of compound* **1**

Artonitidin B (**2**), a yellow amorphous powder, was assigned a molecular formula of $C_{24}H_{26}O_4$ by HR-EI-MS at *m*/*z* 378.1833 (M^+; calc. 378.1831). The IR absorptions of **2** indicated the presence of OH (3416 cm^{-1}) and aromatic ring (1616 and 1450 cm^{-1}) moieties. The UV data resembled those of 2-arylbenzofuran derivatives [4]. The ^{1}H-NMR spectrum showed signals of two *ortho*-coupled H-atoms at δ(H) 7.24 and 6.84 (2*d*, J = 8.3, 1 H each), two *meta*-coupled H-atoms at δ(H) 6.77 and 6.50 (2*d*, J=2.4, 1 H each), an olefinic *singlet* at δ(H) 6.77 (*s*, 1 H), and two prenyl groups at δ(H) 5.43 (br. *t*, J=7.3, 1 H), 3.62 (br. *d*, J=7.3, 2 H), and 1.83, 1.66 (2 br. *s*, 3 H each), 5.22 (br. *t*,

$J = 6.5$, 1 H), 3.53 (br. *d*, $J = 6.5$, 2 H), and 1.66, 1.64 (3 br. *s*, 3 H each). Comparison of the ^{1}H- and ^{13}C-NMR data of **1** and **2** (*Table 1*) indicated that they should have the same rings *A* and *C*, which was confirmed by the HMBC data shown in *Fig. 3*. The substitution pattern of ring *B* was deduced by HMBC cross-peaks from CH_2(21) (δ(H) 3.53) to C(10) (δ(C) 132.9), C(11) (δ(C) 118.6), and C(12) (δ(C) 157.5), from H−C(13) (δ(H) 6.50) to C(11) and C(15) (δ(C) 107.8), and from H−C(15) (δ(H) 6.77) to C(11) and C(13) (δ(C) 103.8) (*Fig. 3*). Thus, the structure of **2** was elucidated as 5-[6-hydroxy-7-(3-methylbut-2-en-1-yl)-1-benzofuran-2-yl]-4-(3-methylbut-2-en-1-yl)benzene-1,3-diol, and **2** was named artonitidin B (*Fig. 1*).

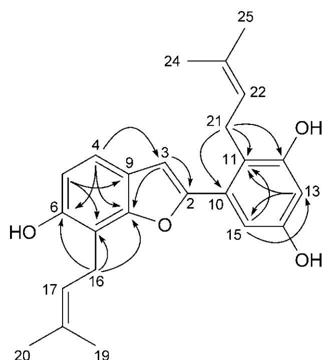

Fig. 3. *Selected HMBC* (H→C) *data of compound* **2**

It is interesting that the isoprenylated constituents from three *Artocarpus* plants investigated by our group are very different. The roots and stems of *A. chama* are rich in isoprenylated flavones and prenylated stilbenes, their biogenetic derivatives being minor constituents [3]. However, only isoprenylated 2-arylbenzofurans have been found in the roots of *A. petelotii* so far [4]. The present study revealed that *A. nitidus* contained both isoprenylated flavones and 2-arylbenzofurans.

Compounds **3**–**9**, **11**, and **13**–**15** were evaluated for inhibitory effects on pancreatic lipase (PL). The results are shown in *Table 2*. Compound **3** showed the highest activity against PL with an IC_{50} value of 1.8 ± 0.1 µM, followed by **8** (IC_{50} = 3.4 ± 0.1 µM) and **11** (IC_{50} = 3.7 ± 0.1 µM). Compound **5** exhibited intermediate inhibitory activity (IC_{50} = 17.0 ± 0.7 µM). Compounds **13** and **14** exerted weak inhibitory activities against PL

Table 2. *Pancreatic Lipase Inhibitory Activity* (IC_{50} in [µM]) *of Compounds* **3**–**9**, **11**, *and* **13**–**15**

Compound	IC_{50} [µM]	Compound	IC_{50} [µM]
3	1.8 ± 0.1	**9**	NA
4		**11**	3.7 ± 0.1
5	NA	**13**	63.8 ± 3.6
6	NA	**14**	46.5 ± 2.9
7	NA	**15**	NA
8	3.4 ± 0.1	Orlistat	0.72 ± 0.03

NA: Not active.

(IC_{50} = 63.8 ± 3.6 and 46.5 ± 2.9 μм, resp.). Compounds **4**, **6**, **7**, **9**, and **15** were inactive against PL. In these tests, orlistat was used as positive control.

An analysis of the bioactive results and the structure characteristics of the tested isoprenylated flavones led to a hypothesis of structure–activity relationship: the coexistence of two sets of hydrophobic (isoprenoid groups at C(3) or ring *A*) and hydrophilic groups (OH groups at C(7) or ring *B*) at separated domains is very important for the activity. For example, compounds **3**, **5**, and **8** showed significant activities against PL, with one set of isoprenoid and OH groups at C(6) and C(7), and another set at C(3) and ring *B*. In compound **13**, the absence of a hydrophobic group at ring *A* possibly decreased its activity. In compounds **4** and **9**, the cyclization between the OH group at C(7) and the adjacent isoprenyl side chain led to the loss of activity. In compounds **6** and **7**, the methylation of the OH group at C(7) or ring *B* also deprived the inhibitory effect. However, further studies are necessary to confirm this hypothesis.

Natural products obtained from medicinal plants provide abundant PL inhibitors, such as saponins, polyphenolics, and terpenes. Comparison of the biological data with those reported [5] indicates that norartocarpin (**3**) is a promising candidate as a PL inhibitor.

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Experimental Part

General. Column chromatography (CC): silica gel *H* (SiO_2; 200–300 mesh; *Yantai Institute of Chemical Technology*, P. R. China) and *Bondesil-C_{18}* gel (40 μm; *Varian Inc.*, USA). TLC: precoated SiO_2 *GF_{254}* plates (10–40 μm; *Yantai Institute of Chemical Technology*, P. R. China). HPLC: *Agilent 1200* system (*Agilent Technologies*, USA), *Sepax Amethyst C_{18}* column (10 × 150 mm, 5 μm; *Sepax Techologies, Inc.*, USA. Optical rotations: *Jasco P1030* polarimeter. UV Spectra: *Shimadzu UV-2401PC* spectrophotometer; λ_{max} (log ε) in nm. IR Spectra: *Nicolet Avatar-360* spectrometer; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra: *Bruker DRX-400* and *-500* instruments, at 500 and 125 MHz, resp., in (D_6)acetone; δ in ppm rel. to residual solvent peaks ((D_6)acetone, δ(H) 2.04, δ(C) 206.0) or rel. to Me_4Si, *J* in Hz. EI-MS: *Finnigan MAT 95* mass spectrometers; in *m/z* (rel. %).

Plant Material. The stems of *A. nitidus* Trec. were collected in Hainan Province, P. R. China, in September 2006 and air-dried. The plant was identified by *A.-J. H.*, Fudan University, and a voucher specimen (TCM 2006-09-01 Hou) was deposited with the Herbarium of the Department of Pharmacognosy, School of Pharmacy, Fudan University.

Extraction and Isolation. The dried and powdered roots (4.7 kg) of *A. nitidus* were extracted with 95% EtOH (100 l) at r.t. The filtrate was evaporated *in vacuo* to give a residue (328 g), which was suspended in H_2O and partitioned successively with $CHCl_3$ and AcOEt. The $CHCl_3$ extract showed significant inhibitory effect of pancreatic lipase (PL) *in vitro*. This extract (8.7 g) was subjected to CC (SiO_2; petroleum ether (PE)/acetone 10 : 1, 7 : 1, 4 : 1, and 1 : 1) to afford twelve fractions: *Frs. 1–12*. *Fr. 3* (200 mg) was separated by CC (SiO_2; cyclohexane/AcOEt 10 : 1) and prep. HPLC (MeOH/H_2O 9 : 1, 1.5 ml/min, 210 nm) to yield compound **4** (7 mg; t_R 25min). *Fr. 4* (300 mg) was purified by CC (SiO_2; cyclohexane/AcOEt 8 : 1) to afford compound **6** (7 mg). *Fr. 5* (500 mg) was fractionated by prep. HPLC (MeOH/H_2O 17 : 3, 1.0 ml/min, 254 nm) to afford compounds **7** (80 mg; t_R 30 min), **8** (11 mg; t_R 35 min), and **9** (4 mg; t_R 43 min). *Fr. 7* (800 mg) was isolated by CC (SiO_2; PE/^{i}PrOH) to give 17 fractions: *Frs. 7.1–7.17*. *Fr. 7.5* was purified by CC (SiO_2; $CHCl_3$) to yield compound **15** (6 mg). *Fr. 7.9* (150 mg) was separated by CC (*Bondesil-C_{18}*; MeOH/H_2O 13 : 7), followed by prep. HPLC (MeOH/H_2O 4 : 1, 1.0 ml/min, 210 nm), to afford compounds **10** (2 mg; t_R 25 min), **1** (3 mg; t_R 40 min), **14** (3 mg; t_R 45 min), and **2**

(4 mg; t_R 55 min). *Fr. 7.10* (200 mg) was purified by CC (SiO_2; $CHCl_3$/MeOH 100:1, 50:1, and 30:1), then by prep. HPLC (MeOH/H_2O 4:1, 1.0 ml/min, 210 nm) to yield compounds **5** (5 mg; t_R 28 min) and **3** (5 mg; t_R 36 min). *Fr. 7.11* (60 mg) was separated by CC (*Bondesil-C$_{18}$*; MeOH/H_2O 13:7) and prep. HPLC (MeOH/H_2O 3:1, 1.0 ml/min, 210 nm) to yield compounds **12** (2 mg; t_R 50 min) and **11** (4 mg; t_R 40 min). *Fr. 7.13* was isolated by prep. HPLC (MeOH/H_2O 3:1, 1.0 ml/min, 210 nm) to give compound **13** (5 mg; t_R 30 min). *Fr. 7.14* was purified by CC (SiO_2; PE/acetone 3:1) to provide compound **16** (3 mg).

Artonitidin A (= *(2′*R*)-2′,3′-Dihydro-2′-(1-hydroxy-1-methylethyl)-5′,7-bis(3-methylbut-2-en-1-yl)-2,4′-bi-1-benzofuran-6,6′-diol*; **1**). Yellow amorphous powder. $[\alpha]_D^{20} = -25.7$ ($c = 0.20$, MeOH). UV (MeOH): 206 (4.45), 306 (4.40). IR (KBr): 3419, 2923, 2854, 1651, 1457, 1386, 1249, 1161. ^{1}H- and ^{13}C-NMR: see *Table 1*. EI-MS: 462 (38, M^+), 445 (30), 396 (18), 359 (16), 309 (16), 174 (30), 149 (100), 105 (40), 71 (46), 57 (72). HR-EI-MS: 462.2401 (M^+, $C_{29}H_{34}O_5^+$; calc. 462.2406).

Artonitidin B (= *5-[6-Hydroxy-7-(3-methylbut-2-en-1-yl)-1-benzofuran-2-yl]-4-(3-methylbut-2-en-1-yl)benzene-1,3-diol*; **2**). Yellow amorphous powder. UV (MeOH): 212 (4.45), 310 (4.14). IR (KBr): 3416, 2975, 2925, 1616, 1450, 1424, 1386, 1154, 947. ^{1}H- and ^{13}C-NMR: see *Table 1*. EI-MS: 378 (100, M^+), 361 (20), 322 (32), 307 (16), 279 (24), 267 (16), 188 (16). HR-EI-MS: 378.1833 (M^+, $C_{24}H_{26}O_4^+$; calc. 378.1831).

Assay of Pancreatic Lipase (*PL*) *Activity.* The activity of PL was determined by measuring the release of 4-nitrophenol from 4-nitrophenyl acetate. The assay system was carried out at 25° in 100 μl of phosphate buffer (PBS, pH 7.4), containing 0.25 mg/ml PL and 0.54 mM 4-nitrophenyl acetate. The release of 4-nitrophenol was assayed using *SoftMax Pro 5.2* at an absorption wavelength of 405 nm for 20 min. The inhibitory effect of each tested compound on PL is expressed as the concentration for 50% inhibition (IC_{50}).

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