

## New Constituents from Stems of *Artabotrys uncinatus*

Yu-Hsuan LAN,<sup>a</sup> Hsin-Yu WANG,<sup>a</sup> Chin-Chung WU,<sup>a</sup> Shu-Li CHEN,<sup>a</sup> Chao-Lin CHANG,<sup>a</sup> Fang-Rong CHANG,<sup>\*,a</sup> and Yang-Chang WU<sup>\*,a,b</sup>

<sup>a</sup> Graduate Institute of Natural Products, College of Pharmacy, Kaohsiung Medical University; Kaohsiung, 807 Taiwan; and <sup>b</sup> National SunYat-Sen University-Kaohsiung Medical University Joint Research Center; 807 Taiwan.

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**Two new compounds, 4,5-dioxoartacinatine (1) and 24-methylenelanosta-7,9(11)-diene-3-one (2), together with thirty known compounds were isolated and characterized from the stems of *Artabotrys uncinatus*. Structures of the new compounds were determined by spectral analysis.**

**Key words** *Artabotrys uncinatus*; 4,5-dioxoartacinatine; biological assay; 24-methylenelanosta-7,9(11)-diene-3-one; antioxidant activity

There are more than 100 species of the genus *Artabotrys* throughout tropical Africa and East Asia.<sup>1)</sup> *Artabotrys uncinatus* (LAM.) MERR. (Annonaceae) is widely distributed throughout southern Taiwan, and the roots and fruits are used for the treatment of malaria and scrofula.<sup>2)</sup> Previous literature has shown this genus to contain alkaloids, triterpenoids, lignans, flavonoids, and steroids.<sup>2–6)</sup> Among them, yingzhaosu analogues showed notable antimalarial activities *in vitro*<sup>3)</sup>; alkaloids showed cytotoxic and antithrombotic activities.<sup>5)</sup> In this study, we investigated the stem parts of *A. uncinatus*, and two new compounds, 4,5-dioxoartacinatine (**1**) and 24-methylene lanosta-7,9(11)-diene-3-one (**2**), along with thirty known compounds: cloven-2 $\beta$ ,9 $\alpha$ -diol (**3**),<sup>7)</sup> caryolane-1,9 $\beta$ -diol (**4**),<sup>7)</sup> 1-methoxy-9-caryolanol (**5**),<sup>8)</sup> spathulenol (**6**),<sup>9)</sup> (–)-*ent*-4 $\beta$ -hydroxy-10 $\alpha$ -methoxyaromadendrane (**7**),<sup>10)</sup> 4 $\beta$ -hydroxy-10 $\alpha$ -methoxyaromadendrane (**8**),<sup>10)</sup>  $\beta$ -caryophyllene-8*R*,9*R*-oxide (**9**),<sup>7)</sup> artabotryside A (**10**),<sup>11)</sup> artabotryside B (**11**),<sup>11)</sup> apigenin (**12**),<sup>12)</sup> luteolin (**13**),<sup>13)</sup> 5-hydroxy-7,4'-dimethoxyflavone (**14**),<sup>14)</sup> (+)-catechin (**15**),<sup>15)</sup> lirioidenine (**16**),<sup>2)</sup> atherospermidine (**17**),<sup>16)</sup> artacinatine (**18**),<sup>5)</sup> (–)-asimilobine (**19**),<sup>2)</sup> (–)-artavenustine (**20**),<sup>17)</sup> *N-P*-coumaroyltyramine (**21**),<sup>18)</sup> (+)-syringaresinol (**22**),<sup>19)</sup> (2*R*,3*R*)-3-hydroxy-2-methylbutyrolactone (**23**),<sup>20)</sup> tetrahydrofuran-4-methylidene-3-ol (**24**),<sup>21)</sup> phytol (**25**),<sup>22)</sup> 24-methylenelanosta-7,9(11)-dien-3 $\beta$ -ol (**26**),<sup>23)</sup> (24*R*)-stigmasta-5-en-3 $\beta$ ,7 $\alpha$ -diol (**27**),<sup>24)</sup> (22*E*,24*S*)-stigmasta-5,22-dien-3 $\beta$ ,7 $\alpha$ -diol (**28**),<sup>24)</sup>  $\beta$ -sitosterol (**29**) and stigmasterol (**30**),  $\beta$ -sitosteryl-3-*O*- $\beta$ -D-glucoside (**31**), and stigmasteryl-3-*O*- $\beta$ -D-glucoside (**32**) were isolated. Compounds **13**, **16**, **17**, and **22** were evaluated for their cytotoxicity against several cancer cell lines. Compounds **10**, **11**, **12**, **13**, and **15** were tested for their antioxidant activity.

Compound **1** was isolated as yellow needles, positive to

Dragendorff's test. Its molecular formula was determined as C<sub>19</sub>H<sub>17</sub>O<sub>6</sub>N on the basis of its HR-EI-MS spectrum (*m/z* 355.1058 [M]<sup>+</sup>, Calcd 355.1055). The UV spectrum showed absorption at  $\lambda_{\max}$  230, 252, and 282 nm. The IR spectrum showed absorption bands at 1664, 1734, and 3421 indicating carbonyl and hydroxyl groups, respectively. The <sup>1</sup>H-NMR spectra revealed signals for two methoxy groups ( $\delta_{\text{H}}$  4.08, 4.14), two aromatic protons ( $\delta_{\text{H}}$  6.97, 8.25), and an *N*-methyl group ( $\delta_{\text{H}}$  3.75), which appeared at low field, reflecting an unusual dehydroaporphine moiety.<sup>5,25)</sup> The proton signals at  $\delta_{\text{H}}$  2.18, 2.73, 3.15, and 3.29 were ascribed to methylene protons at the 8,9-positions of the D-ring dehydroaporphine moiety (Fig. 3).<sup>5)</sup> The <sup>13</sup>C-NMR spectrum exhibited the presence of three methyl, two methylene, three methine, and eleven quaternary carbons. In comparison with the literature data,<sup>25)</sup> the di-ketone groups in 4,5-dioxoaporphines usually resonate at  $\delta_{\text{C}}$  178 and 157 ppm, respectively. Compound **1** showed the signals at  $\delta_{\text{C}}$  175.0 and 152.4 ppm, which are coincident with the assignments of 4,5-di-ketone groups. H-3 appeared at  $\delta_{\text{H}}$  8.25 indicating the existence of a carbonyl group at the peri-position. The HMBC spectra gave further support for the structure determination of **1**, the correlations between 1-OCH<sub>3</sub> and C-1, and 2-OCH<sub>3</sub> and C-2 confirmed the methoxy groups at C-1 and C-2. The correlations between H-3 and C-2/C-11c/C-4, and between N-CH<sub>3</sub> and C-5/C-6a indicated the ketone groups at C-4 and C-5. The significant NOESY correlation between H-7 and H-8 together with the aforementioned assignments also proved the carbonyl group was located at C-11. The above evidence and comparison with the spectral data reported for artacinatine (**18**), cepharadione-A, and aristolodione indicated the structure of **1** was 4,5-dioxoartacinatine.<sup>25)</sup> In our previous study, artacinatine (**18**) isolated from this plant with the same D-ring moiety had been evidenced by X-ray crystalline analysis. Compound **18** possesses a 10 $\alpha$ -hydroxyl function. Com-

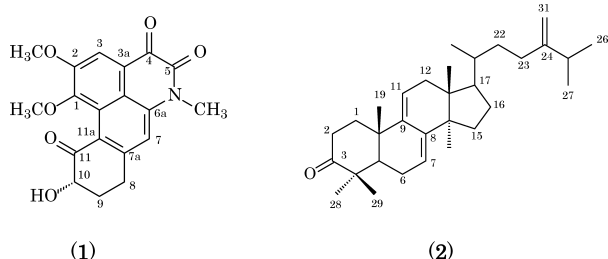


Fig. 1. Structure of 4,5-Dioxoartacinatine (**1**) and 24-Methylenelanosta-7,9(11)-diene-3-one (**2**)

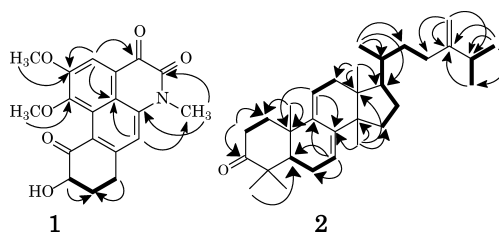


Fig. 2. Key COSY and Key HMBC Correlations for **1** and **2**

\* To whom correspondence should be addressed. e-mail: yachwu@kmu.edu.tw

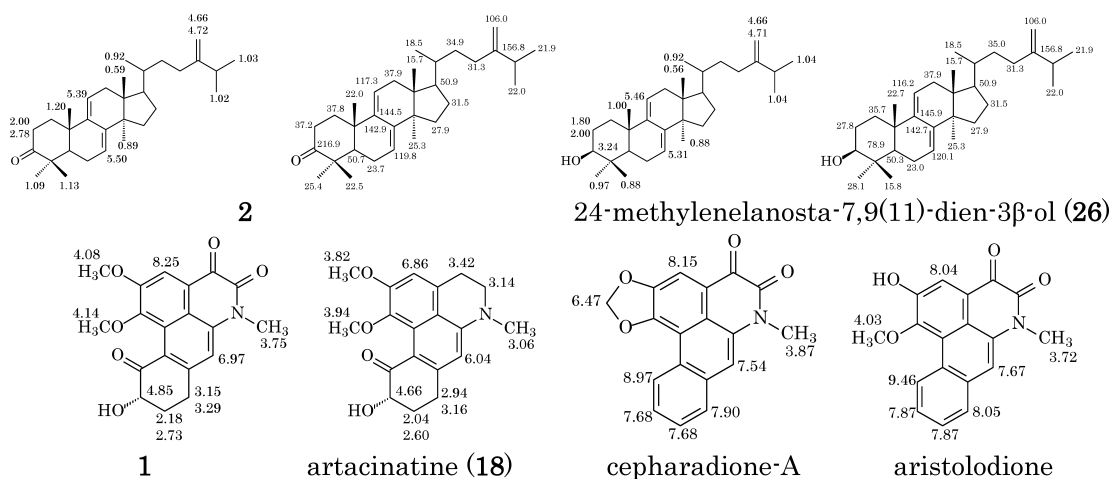


Fig. 3.  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR Spectra Data of **1**, **2**, Artacinatine (**18**), 24-Methylenelanosta-7,9(11)-dien-3 $\beta$ -ol (**26**), Cepharadione-A, and Aristolodione

Table 1.  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR Spectral Data for **1** and **2** in  $\text{CDCl}_3^a$

<b>1</b>			<b>2</b>					
	H	C			H	C	H	C
1		150.0	1	2.00 (2H, m)	37.8	17	1.60 (1H, m)	50.9
2		152.4	2	2.00 (1H, m)	37.2	18	0.59 (3H, s)	15.7
				2.78 (1H, td, $J=14.8, 5.9$ Hz)				
1-OCH <sub>3</sub>	4.14 (3H, s)	61.8	3		216.9	19	1.20 (3H, s)	22.0
2-OCH <sub>3</sub>	4.08 (3H, s)	52.6	4		47.5	20		36.2
3	8.25 (1H, s)	115.9	5	1.50 (1H, m)	50.7	21	0.92 (3H, d, $J=6.4$ Hz)	18.5
3a		125.0	6	2.00 (2H, m)	23.7	22	2.00 (1H, m), 2.30 (1H, m)	34.9
4		175.0	7	5.50 (1H, d, $J=6.4$ Hz)	119.8	23	1.70 (1H, m), 2.30 (1H, m)	31.3
5		156.9	8		142.9	24		156.8
6a		137.0	9		144.5	25	2.00 (1H, m)	33.8
N-CH <sub>3</sub>	3.75 (3H, s)	30.5	10		37.2	26	1.03 (3H, d, $J=2.4$ Hz)	21.9
7	6.97 (1H, s)	112.1	11	5.39 (1H, d, $J=6.0$ Hz)	117.3	27	1.02 (3H, d, $J=2.0$ Hz)	22.0
7a		149.0	12	2.00 (2H, m)	37.9	28	1.09 (3H, s)	25.4
8	3.15 (1H, ddd, $J=17.0, 5.2, 4.0$ Hz)	28.8	13		43.7	29	1.13 (3H, s)	22.5
	3.29 (1H, ddd, $J=17.0, 11.2, 5.2$ Hz)							
9	2.18 (1H, m), 2.73 (1H, m)	35.3	14		50.3	30	0.89 (3H, s)	25.3
10	4.85 (1H, dd, $J=11.2, 6.0$ Hz)	72.8	15	1.30 (1H, m), 2.00 (1H, m)	27.9	31	4.66 (1H, s), 4.72 (1H, s)	106.0
11		200.1	16	1.40 (1H, m), 1.60 (1H, m)	31.5			
11a		146.0						
11b		115.0						
11c		118.0						

*a)* Chemical shift values are given in ppm, and  $J$  values in parentheses are given in Hz. Assignments were confirmed by  $^1\text{H}$ - $^1\text{H}$  COSY, HMQC, and HMBC experiment.

pound **1** shows the exact pattern as **18** in NMR assignment, thus, we predicted that **1** also has a 10 $\alpha$ -hydroxyl function.

Compound **2** was obtained as a colorless solid. The UV spectrum showed characteristic absorptions at  $\lambda_{\text{max}}$  242, 235 nm. The IR spectrum of **2** contained absorption for the carbonyl group at  $1707\text{ cm}^{-1}$ . The EI-MS spectrum showed a molecular ion peak at  $m/z$  436 and HR-EI-MS spectrum gave  $m/z$  436.3708 for the  $[\text{M}]^+$  ion (Calcd 436.3705) corresponding to the molecular formula  $\text{C}_{31}\text{H}_{48}\text{O}$ . The  $^1\text{H}$ -NMR spectrum of **2** indicated three secondary methyl groups ( $\delta_{\text{H}}$  0.92, 1.02, 1.03), five tertiary methyl groups ( $\delta_{\text{H}}$  0.59, 0.89, 1.09, 1.13, 1.20), two olefinic protons ( $\delta_{\text{H}}$  5.39, 5.50), and geminal protons for one terminal double bond ( $\delta_{\text{H}}$  4.66, 4.72). The  $^{13}\text{C}$ -NMR spectrum of **2** showed signals due to a 7,9(11)-conjugated diene at  $\delta_{\text{C}}$  119.8, 142.9, 144.5, and 117.3, eight methyls at  $\delta_{\text{C}}$  25.4, 25.3, 22.5, 22.0, 22.0, 21.9, 18.5, and

15.7, and a ketone at  $\delta_{\text{C}}$  216.9. Further evidence from COSY, HMQC, and HMBC spectra also confirmed the planar structure of **2**. The HMBC cross peaks between H-2 and C-3, and  $\text{CH}_3$ -28 and C-3 indicated the carbonyl group was located at C-3, the COSY correlations from H-15 to H-23 and HMBC cross peaks between  $\text{CH}_3$ -21 and C-17/C-20/C-22,  $\text{CH}_2$ -31 and C-23/C-24/C-25, and  $\text{CH}_3$ -26 and C-24/C-25/C-27 revealed the side chain was situated at C-17. The stereochemistry of **2** was deduced by NOESY experiments, the NOE correlation between H-5 and H-28 indicated that H-5 was assigned to be in a  $\alpha$  orientation. According to the aforementioned evidence, analyses of 1D and 2D NMR spectra and comparison with data of 24-methylenelanosta-7,9(11)-dien-3 $\beta$ -ol (**26**) (Fig. 3),<sup>23</sup> confirmed that the structure of **2** was 24-methylenelanosta-7,9(11)-diene-3-one.

According to the previous literature, caryolane-1,9 $\beta$ -diol

(4), liriodenine (16), atherospermidine (17), (+)-syringaresinol (22), and 24-methylenelanosta-7,9(11)-dien-3 $\beta$ -ol (26) had significant cytotoxicity, anti-HIV activity, and anti-inflammatory activity.<sup>26,27)</sup>

In biological assay, atherospermidine (17) and (+)-syringaresinol (22) show significant inhibition against several cancer cell lines,<sup>28)</sup> including Hep G2 (human hepatocellular carcinoma) cell line with IC<sub>50</sub> values of 0.97 and 0.35  $\mu$ g/ml, respectively.

Flavonoids were reported to possess antioxidant and free radical scavenging activities.<sup>29)</sup> Compounds 10, 11, 12, 13, and 15 were tested for their antioxidant activity.<sup>30)</sup> Among them, artabotryside A (10), luteolin (13), and (+)-catechin (15) were found to be powerful scavengers of DPPH free radicals with IC<sub>50</sub> values of 14.09, 15.32, and 5.55  $\mu$ g/ml, respectively. Artabotryside A (10) showed a significant effect (IC<sub>50</sub> 10.19  $\mu$ g/ml) on scavenging hydroxyl radical and luteolin (13) showed good SOD-like activity (IC<sub>50</sub> 24.52  $\mu$ g/ml).

### Experimental

Melting points were measured on a Yanagimoto micro-melting point apparatus and were uncorrected. The UV spectra were obtained on a Jasco V-530 UV/VIS spectrophotometer. The IR spectra were recorded on a Mattson Genesis II spectrophotometer. <sup>1</sup>H-NMR (400 MHz) and <sup>13</sup>C-NMR (100 MHz) spectra were recorded with Varian NMR spectrometers. LR-EI-MS were collected on a Finnigan POLARISQ mass spectrometer. HR-EI-MS were collected on a Bruker DALTONICS Apex II mass spectrometer. TLC analysis was carried out on Si gel GF<sub>254</sub> pre-coated plates with detection using 50% H<sub>2</sub>SO<sub>4</sub> followed by heating on a hot plate.

**Plant Material** Fresh stems of *A. uncinatus* were collected in Kaohsiung, Taiwan in February, 2004. The voucher specimen is deposited in the Graduate Institute of Natural Products, Kaohsiung Medical University, Kaohsiung, Taiwan.

**Extraction and Isolation** Air-dried stems (4.5 kg) of *A. uncinatus* were extracted with methanol at room temperature, the concentrated methanolic extract was partitioned with CH<sub>3</sub>OH (H<sub>2</sub>O : CH<sub>3</sub>OH = 7 : 3) and *n*-hexane, the CH<sub>3</sub>OH layer was partitioned with CH<sub>3</sub>OH (H<sub>2</sub>O : CH<sub>3</sub>OH = 1 : 1) and EtOAc. The *n*-hexane residue was subjected to Sephadex LH-20 (42 $\times$ 4 cm) column chromatography, eluting with *n*-hexane : EtOAc = 1 : 1, and the collected fractions were combined on the basis of their TLC characteristics to give 4 fractions. Fraction 1 was separated by CC over silica gel and eluted with gradient mixtures of CHCl<sub>3</sub>/EtOAc/CH<sub>3</sub>OH to give 20 fractions. Fraction 1-2 was further chromatographed on silica gel column chromatography and high performance liquid chromatography (HPLC), and three compounds were obtained: 24-methylenelanosta-7,9(11)-diene-3-one (2) (4.0 mg), spathulenol (6) (8.5 mg), and  $\beta$ -caryophyllene-8*R*,9*R*-oxide (9) (2.2 mg). Fractions 1-3—1-5 were purified by recrystallization from CH<sub>3</sub>OH to afford 24-methylenelanosta-7,9(11)-dien-3 $\beta$ -ol (26) (60.0 mg) and a mixture of  $\beta$ -sitosterol and stigmasterol (29, 30) (407.0 mg), and subfraction 1-3-11 was further chromatographed on high performance liquid chromatography (HPLC) to afford phytol (25) (28.0 mg). Fraction 1-8 was chromatographed on Sephadex LH-20 column chromatography and high performance liquid chromatography (HPLC) to afford a mixture of (2*R*)-stigmasta-5-en-3 $\beta$ ,7 $\alpha$ -diol and (2*E*,2*S*)-stigmasta-5,22-dien-3 $\beta$ ,7 $\alpha$ -diol (27, 28) (2.2 mg). Fraction 1-11 was chromatographed on silica gel column chromatography to afford atherospermidine (17) (9.2 mg). Fr. 1-18 was purified by recrystallization from EtOAc to afford a mixture of  $\beta$ -sitosteryl-3-*O*- $\beta$ -D-glucoside and stigmasteryl-3-*O*- $\beta$ -D-glucoside (31, 32) (450.0 mg).

The EtOAc layer (101 g) was subjected to silica gel column chromatography and eluted with gradient mixtures of CHCl<sub>3</sub>/CH<sub>3</sub>OH. The collected fractions were combined into 15 fractions on the basis of TLC monitoring. Fraction 2 was further chromatographed on silica gel column chromatography and high performance liquid chromatography (HPLC) to give 1 (0.5 mg), 1-methoxy-9-caryolanol (5) (2.6 mg), (-)-*ent*-4 $\beta$ -hydroxy-10 $\beta$ -methoxyaromadendrane (7) (8.2 mg), 4 $\beta$ -hydroxy-10 $\alpha$ -methoxyaromadendrane (8) (3.0 mg), liriodenine (16) (3.0 mg), artacinatine (18) (26.0 mg), and (+)-syringaresinol (22) (8.0 mg). Fraction 4 was chromatographed on silica gel column chromatography and preparative TLC to afford cloven-2 $\beta$ ,9 $\alpha$ -diol (3) (2.6 mg), caryolan-1,9 $\beta$ -diol (4) (3.0 mg), and (2*R*,3*R*)-3-hydroxyl-2-methylbutyrolactone (23) (12.0 mg). Fraction 5 was chromatographed on

Sephadex LH-20 column chromatography to give apigenin (12) (3.1 mg) and 5-hydroxy-7,4'-dimethoxyflavone (14) (1.0 mg). Fraction 6 was further chromatographed on silica gel column chromatography and high performance liquid chromatography (HPLC) to afford luteolin (13) (8.0 mg) and *N*-*P*-coumaroyltyramine (21) (7.0 mg). Fraction 7 was further chromatographed on silica gel column chromatography and high performance liquid chromatography (HPLC) to give (+)-catechin (15) (5.0 mg), (-)-asimilobine (19) (2.5 mg), and tetrahydrofuran-4-methylidene-3-ol (24) (32.0 mg). Fractions 10 and 12 were chromatographed on silica gel column chromatography to afford artabotryside A, (10) (45.0 mg), artabotryside B (11) (109.0 mg), and (-)-artavenustine (20) (45.0 mg).

4,5-Dioxoartacinatine (1): Yellow needles. mp 167—169 °C. [ $\alpha$ ]<sub>D</sub> +52.2° ( $c$ =0.03, CH<sub>3</sub>OH). <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz) and <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 100 MHz) see Table 1. IR  $\nu_{\max}$  cm<sup>-1</sup>: 3421, 2924, 1734, 1664, 1461, 1142, 1055. UV  $\lambda_{\max}$  nm: 396, 355, 345, 282, 252, 230. FAB-MS  $m/z$  (rel. int. %): 356 ([M+H]<sup>+</sup>). EI-MS (70 eV) (rel. int. %):  $m/z$ =328 (33), 283 (28), 174 (34), 146 (36), 106 (79), 98 (79), 91 (100). HR-EI-MS: Calcd for C<sub>19</sub>H<sub>17</sub>O<sub>6</sub>N  $m/z$  [M]<sup>+</sup> 355.1055, found 355.1058.

24-Methylenelanosta-7,9(11)-diene-3-one (2): Colorless solid. mp 164—166 °C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz) and <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 100 MHz) see Table 1. IR  $\nu_{\max}$  cm<sup>-1</sup>: 2930, 1707, 1378. UV  $\lambda_{\max}$  nm: 242, 235. EI-MS (70 eV) (rel. int. %):  $m/z$ =436 (14), 421 (19), 309 (100), 268 (83), 171 (34). HR-EI-MS: Calcd for C<sub>31</sub>H<sub>48</sub>O  $m/z$  [M]<sup>+</sup> 436.3705, found 436.3708.

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