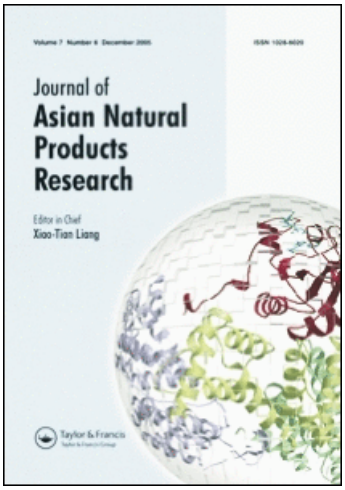

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ORIGINAL ARTICLE

Three polyoxygenated cyclohexenes from *Uvaria calamistrata*

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Three new polyoxygenated cyclohexenes, named uvacanols F, G, H (**1**–**3**), were isolated from the roots of *Uvaria calamistrata* (Annonaceae). Their structures were determined to be 2-acetoxyl-5-chlorine-benzoyloxymethylcyclohex-1 (6)-ene-4-ol-3-benzoate (**1**), benzoyloxy-methylcyclohex-1 (6)-ene-2,3,4-triols-5-benzoate (**2**), 3-acetoxyl-benzoyloxymethylcyclohex-1 (6)-ene-4,5-diols-2-benzoate (**3**) by spectroscopic methods and chemical derivatization.

Keywords: Annonaceae; *Uvaria calamistrata*; polyoxygenated cyclohexenes; uvacanols F, G, H

1. Introduction

Polyoxygenated cyclohexenes (PCs) are a type of constituent with the basic skeleton of hydroxymethyl-cyclohexene. These compounds usually have one double bond and four chiral carbons in the ring, and one oxygen-containing group attached at each stereocenter. Due to the variation of the location of the double bond and the number and position of the attached groups including ethoxyl, methoxyl, hydroxyl, acetoxyl, and benzoate, PCs exhibited a variety of structures. A few of them exhibited *in vitro* antitumor activities [1] and others showed biological activities. The plants from the genus *Uvaria* were claimed to be the plentiful resource for PCs. So far, about 40 PC-type compounds were discovered in plants from the genus *Uvaria* [2–14]. A few PCs were also found in the plants of Piperaceae, Euphorbiaceae, and Zingiberaceae [15–18].

The annonaceous plant *Uvaria calamistrata* is distributed in the Hainan Island of China [19]. In our search for natural antitumor products from the plant in southern China, we found that the ethanolic extract of this plant exhibited significant inhibitory activity on some tumor cell lines. Our earlier papers had reported the isolation of a series of annonaceous acetogenins from the extract [20,21]. We also found that the ethanolic extract was rich in PCs. Several PCs were also isolated from this plant (Figure 1) [22]. This paper reports the results of our further investigation on PCs from this plant.

2. Results and discussion

Compound **1** was obtained as a colorless gum. The molecular formula of **1** was determined to be $C_{23}H_{21}O_7Cl$ by HR-ESI-MS at *m/z* 445.1030. The presence of

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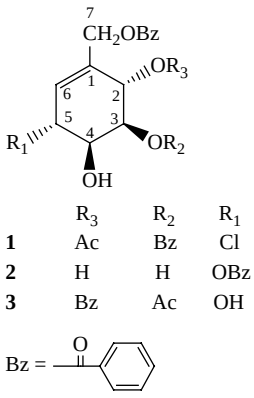

	R_3	R_2	R_1
1	Ac	Bz	Cl
2	H	H	OBz
3	Bz	Ac	OH

Figure 1. Structures of compounds **1**–**3**.

chlorine was determined from the $[M + 2]^+$ isotopic peak at *m/z* 447 with about 1/3 relative abundance of M^+. The fragment ions at *m/z* 105 and 77 in EI-MS and IR absorption bands at 1705 and 1272.9 cm^{-1} indicated the presence of a benzoate. Twelve aromatic carbon signals and two carboxyl signals at δ 164.4 and 164.2 in the ^{13}C NMR spectrum and 10 aromatic protons (in the ratio of 2:1:2 in three groups) between δ 8.06 and 7.24 in the ^1H NMR spectrum confirmed that **1** was a bis-benzoate. Carbons at δ 169.5 and 19.2 and protons at δ 2.06 suggested the presence of an acetoxyl group. The proton signals of an olefinic methine, four oxygenated methines, and one methylene between δ 4.0 and 6.5 in the ^1H NMR spectrum and the corresponding carbons in the ^{13}C NMR spectrum suggested the basic skeleton of hydroxymethyl-cyclohexene-1 (6)-ene of **1**, similar to the PCs reported earlier. The relative configuration of the molecule was also identical to uvacanol A or conduritol A due to the similar *J* values from H-2 to H-6 [22]. The successive correlations of protons at δ 5.93, 5.60, 4.40, 4.67, and 6.17 in the ^1H–^1H COSY spectrum and the *J* values between them confirmed the relative configuration. Two benzoates were located at C-3 and C-7 by the comparison of chemical shifts of the protons with those of uvacanol A [22]. The acetoxyl group was attached at C-2 due to the HMBC correlation between the proton at δ 5.93 and the carbon at δ 169.5. A chlorine atom was attached at C-5 due to the lack of esterification shift of H-5 and the obvious downfield shift of H-4 after the acetyl derivation of **1** with Ac_2O/pyridine. The C_1–C_6 double bond of **1** was hydrogenated with hydrogen gas (H_2) and platinum–charcoal (Pt/C) in the pressured methanol solution to afford **1a**. The absolute stereochemistry of C-4 was elucidated to be *R* from the analysis of ^1H NMR spectra of 4*s*- and 4*r*-α-methoxyl-α-(trifluoromethyl)phenylacetic acid (MTPA) ester derivatives. The positive $\Delta\delta$ $(s - r)$ value for H-5 and H-6 and the negative $\Delta\delta$ $(s - r)$ value for H-2 and H-3 determined the absolute configuration of C-4 to be *R*. So, C-2, C-3, and C-5 were elucidated as 2*R*, 3*S*, and 5*S* from its relative configuration, respectively, identical to those in uvacanol A. Thus, the structure of **1** was determined as 2*R*,3*S*,4*R*,5*S*-2-acetoxyl-5-chlorine-benzoyloxymethylcyclohex-1 (6)-ene-4-ol-3-benzoate, named uvacanol F.

Compound **2** has the molecular formula $C_{21}H_{20}O_7$ due to the quasi-molecular ion at *m/z* 385.1270 in HR-ESI-MS. The IR, ^1H and ^{13}C NMR spectra of **2** were similar to those of **1**, except the absence of acetoxyl group and the replacement of the Cl atom by the OH group. So, **2** was also a PC-type compound. The ^1H NMR spectrum of **2** revealed the presence of two benzoxyl groups. The successive correlations of protons at δ 4.52 (d, $J = 7.4$ Hz), 3.90 (d, $J = 7.4$ Hz), 4.51 (s), 5.76 (s), and 5.85 (s) and their *J* values of the acetylation derivative of **2** indicated that it had the same relative configuration as **1**. The two benzoxyl groups were elucidated to be at C-5 and C-7 on the basis of the chemical shift of H-5 (δ 5.76) and H-7. The ^{13}C NMR spectrum (see Table 2) of **2** further substantiated the structural elucidation. Based on the consideration of the same biogeneric route of **2** with **1**, compound **2**

was assumed to have the same absolute configurations at C-2, C-3, C-4, and C-5. The *cis*-diols at C-3 and C-4 in **2** were acetonated with 2,2-dimethoxyl propane to give ketal derivative **2a**, further confirming the relative configuration. Thus, the structure of compound **2** was confirmed as 2*R*,3*S*,4*R*,5*S*-benzoyloxymethylcyclohex-1 (6)-ene-2,3,4-triols-5-benzoate, named uvacanol G.

Compound **3** has the molecular formula $C_{23}H_{22}O_8$ due to the quasi-molecular ion at *m/z* 427.1365 in HR-ESI-MS. The IR, ^{1}H, and ^{13}C NMR spectra of **3** were also similar to those of **1**. So, **3** also belonged to a PC-type compound. The ^{1}H NMR spectrum revealed that **3** contained two benzoxyl groups and one acetoxyl group. The successive correlations of protons at δ 5.70 (d, $J = 4.2$ Hz), 5.49 (dd, $J = 4.2, 2.4$ Hz), 4.13 (d, $J = 7.2$, 2.4 Hz), 4.46 (d, $J = 7.2$ Hz), and 6.15 (s) and their *J* values indicated the similar relative configuration of **3** to **1**. The two benzoxyl groups and one acetoxyl group were elucidated to be at C-2, C-7, and C-3, respectively, due to the HMBC correlation between the proton at δ 5.70 and the carbon at δ 169.9. Based on the consideration of the same biogeneric route as **1** and **2**, compound **3** was assumed to have the same absolute configurations at C-2, C-3, C-4, and C-5. Thus, the structure of **3** was elucidated as 2*R*,3*S*,4*R*,5*S*-3-acetoxyl-benzoyloxymethylcyclohex-1 (6)-ene-4,5-diols-2-benzoate, named uvacanol H.

The cytotoxic assay by the MTT method against four human cancer cell lines, human epidermoid cancer cells (KB), human ileocecal carcinoma cells (HCT-8), human epithelial tumor cells (A2780), and human mammary adenocarcinoma cells (MCF-7), was performed following the procedure in [2]. Although these new compounds were isolated from the ethanolic extract of the title plant with antitumor activity, the result revealed that all the compounds were inactive at the test concentration (100 μg/ml) for these cell lines.

3. Experimental

3.1 General experimental procedures

Melting points were measured on a micromelting point apparatus and are uncorrected. The optical rotations were measured on a Perkin-Elmer 241 polarimeter. IR spectra were recorded on a Perkin-Elmer 683 spectrometer. ^{1}H and ^{13}C NMR spectra were measured on a Bruker AM-500 spectrometer at 500 and 125 MHz, respectively, in $CDCl_3$ with the residual solvent $CHCl_3$ as the internal standard. EI-MS were performed on a VGZAB-2F spectrometer. ESI-MS were performed on a Finnigan LCQ Advantage MAX spectrometer. HR-ESI-MS were recorded on a Micromass Q-TOF mass spectrometer.

3.2 Plant material

Plant material was collected from the Jian-Feng mount on the Hainan Island and authenticated as *U. calamistrata*. A voucher specimen has been deposited at the Department of Botany, Institute of Materia Medica.

3.3 Extraction and isolation

The dried and pulverized roots (10 kg) of *U. calamistrata* were exhaustively extracted with 30 liters (× 3) of methanol under reflux. The extract solution was concentrated *in vacuo* to yield a 1980 g residue (F001), which was partitioned between H_2O and $CHCl_3$ (1:1), giving the $CHCl_3$-soluble extract (575 g) (F002), and the insoluble fraction (120 g) and water-soluble fraction (1100 g). The $CHCl_3$ extract was partitioned between 90% aqueous methanol and petroleum ether (1:1). The methanol layer yielded a 350 g residue, which was chromatographed on a silica gel (16–200 mesh, 3.5 kg) column eluting with the gradient petroleum ether–acetone solvent system. The eluted fractions with dark spots on a GF_{254} Si thin layer plate under UV light

Table 1. ^{1}H NMR spectral data of compounds **1**–**3** (500 MHz, $CDCl_3$, *J* in Hz).

No.	1	2	3
2	5.93 (d, $J = 5.6$)	4.52 (d, $J = 7.4$)	5.70 (d, $J = 4.2$)
3	5.60 (d, $J = 5.6, 2.2$)	3.90 (d, $J = 7.4$)	5.49 (dd, $J = 4.2, 2.4$)
4	4.40 (dd, $J = 5.9, 2.2$)	4.51 (s)	4.13 (dd, $J = 7.2, 2.4$)
5	4.67 (dd, $J = 5.9, 3.1$)	5.76 (s)	4.46 (d, $J = 7.2$)
6	6.17 (d, $J = 3.1$)	5.85 (s)	6.15 (s)
7	4.87 (s)	5.25 (d, $J = 13.0$), 4.79 (d, $J = 13.0$)	4.81 (s)
Ar	8.10–7.40 (m)	8.07–7.45 (m)	8.10–7.30 (m)
Ac	2.06 (s)		2.03 (s)

after development were repeatedly chromatographed to afford compounds **1** (200 mg), **2** (50 mg), and **3** (35 mg).

3.3.1 *Uvacanol F (**1**)*

Colorless gum, mp 57–58°C; $[\alpha]_D^{25} + 9.8$ ($c = 0.40$, MeOH); IR ν_{max} (KBr) cm^{-1}: 3452, 2925, 1721, 1697, 1603, 1315, 1273, 1070, 712; ^{1}H and ^{13}C NMR spectral data, see Tables 1 and 2; ESI-MS (positive) *m/z*: 467 $[M + Na]^+$; HR-ESI-MS (positive) *m/z*: 445.1030 $[M + H]^+$ (calcd for $C_{23}H_{22}O_7Cl$, 445.1055).

*3.3.1.1 (R)- and (S)-MTPA derivatives (**1r** and **1s**).* (*R*)- or (*S*)-MTPA, *N*,*N*-dicyclohexylcarbodiimide, and **1** in the molar ratio of 5:7:1 were added into 2 ml of anhydrous CH_2Cl_2 with a few crystals of 4-(dimethylamino)-pyridine. The mixture was stirred at room temperature for 10 h. Comparative TLC with **1** was used to check the end of the reaction. The reacted solution was used for the purification of MTPA esters. The purified (*R*)- and (*S*)-MTPA derivative esters (**1r** and **1s**) of **1** were obtained by preparative TLC.

*3.3.1.2 **1s**.* ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.9 (2H, dd, $J = 8.1$, 2.5 Hz, Ar-H-2′,6′), 7.82 (2H, dd, $J = 8.1$, 2.5 Hz, Ar-H-2″,6″), 7.57 (2H, dt, $J = 8.1$, 2.4 Hz, Ar-H-4′,4″), 7.43 (5H, m, H-3′,3″,5′,5″, mtpa-H-4‴), 7.29 (4H, m, mtpa-H), 6.19 (1H, d, $J = 3.3$ Hz, H-6), 5.88 (1H, d, $J = 4.2$ Hz, H-2), 5.74 (1H, dd, $J = 4.2$, 2.4 Hz, H-3), 5.72 (1H, dd, $J = 5.7$, 2.4 Hz, H-4), 4.89 (1H, s, H-7), 4.83 (1H, d, $J = 5.7$, 3.3 Hz, H-5), 3.52 (3H, s, mtpa-OMe), 2.09 (3H, s, OAc).

Table 2. ^{13}C NMR spectral data of compounds **1**–**3** (125 MHz, $CDCl_3$).

No.	1	2	3
1	133.0	137.5	131.0
2	67.5	68.7	68.2
3	72.5	73.8	73.2
4	56.7	70.1	71.7
5	72.1	71.7	69.1
6	129.8	121.5	131.7
7	64.4	64.0	64.4
1′	129.5, 129.4	129.8, 129.7	131.7
2′, 6′	129.2, 129.0	129.3, 129.0	129.6, 129.8
3′, 5′	128.6, 128.3	128.4, 128.2	128.4, 128.5
4′	132.2	132.9	133.2, 133.5
7′	164.2, 164.4	165.2	166.0, 166.3
Ac	169.5, 19.2		169.9, 20.7

3.3.1.3 ***1r***. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.97 (2H, dd, $J = 8.1$, 2.4 Hz, Ar-H-2′,6′), 7.93 (2H, dd, $J = 8.1$, 2.5 Hz, Ar-H-2″,6″), 7.61 (2H, dt, $J = 8.1$, 2.4 Hz, Ar-H-4′), 7.58 (1H, dt, $J = 8.1$, 2.4 Hz, H-4″), 7.53 (1H, t, $J = 8.1$ Hz, mtpa-Ar-H4), 7.40 (4H, m, H-3′,3″,5′,5″), 7.28 (4H, m, mtpa-Ar-H), 6.13 (1H, d, $J = 3.0$ Hz, H-6), 6.02 (1H, d, $J = 6.6$ Hz, H-2), 5.84 (1H, dd, $J = 6.6$, 2.4 Hz, H-3), 5.80 (1H, dd, $J = 5.4$, 2.4 Hz, H-4), 4.83 (2H, d, $J = 13.4$ Hz, H-7), 4.70 (1H, d, $J = 5.4$, 3.0 Hz, H-5), 3.49 (3H, s, mtpa-OMe), 2.07 (3H, s, OAc).

*3.3.1.4 Hydrogenated derivative (**1h**).* An excess of activated Pt/C was added to a solution of **1** in EtOH (10 ml). The reaction mixture was filled with hydrogen gas under 5 air pressures at room temperature in a hydrogenation reactor and shaken for 24 h. The solvent was filtered, and the reacted product (**1h**) in the solution was purified by flash column chromatography with the petroleum ether–acetone eluant system. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.03 (4H, m, H-2′,2″,6′,6″), 7.57 (2H, m, Ar-H-4′,4″), 7.52 (4H, m, Ar-H-3′,5′,3″,5″), 6.09 (1H, m, H-3), 6.00 (1H, d, $J = 5.7$ Hz, H-2), 5.36 (1H, dd, $J = 6.0$, 2.4 Hz, H-4), 4.77 (2H, s, H-7), 4.38 (1H, dt, $J = 6.0$, 3.3 Hz, H-5), 2.64 (1H, d, $J = 18.3$ Hz, H-6a), 2.45 (1H, dd, $J = 18.3$, 3.3 Hz, H-6b), 2.16 (1H, br s, H-1).

*3.3.1.5 Acetyl derivative (**1a**).* A small amount (10 mg) of **1** was treated with Ac_2O/pyridine at room temperature for 12 h. Preparative TLC of the reacted solution yielded the purified mono acetyl derivative **1a** (gum, 8 mg): colorless crystal, mp 75–76°C; $[\alpha]_D^{22} + 21.4$ ($c = 0.11$, MeOH); IR ν_{max} (film) cm^{-1}: 3063, 2953, 1724, 1601, 1450, 1271, 1113, 1026, 712; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.99 (4H, t, $J = 8.1$ Hz, Ar-H-2′,6′,2″,6″), 7.57 (2H, m, Ar-H-4′,4″), 7.39 (4H, t, $J = 8.1$ Hz, Ar-H-3′,5′,3″,5″), 6.17 (1H, d, $J = 2.7$ Hz, H-6), 5.93 (1H, d, $J = 5.7$ Hz, H-2), 5.70 (1H, dd, $J = 5.7$, 2.4 Hz, H-3), 5.53 (1H, dd, $J = 5.7$, 2.4 Hz, H-4), 4.88 (2H, s, H-7), 4.72 (1H, dd, $J = 5.7$, 2.7 Hz, H-5), 2.11 (3H, s, Ac), 2.09 (3H, s, Ac); ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 8.03 (2H, d, $J = 8.1$ Hz, Ar-H), 7.98 (2H, d, $J = 8.1$ Hz, Ar-H), 7.65 (2H, dq, $J = 8.1$ Hz, Ar-H), 7.51 (4H, q, $J = 8.1$ Hz, Ar-H), 5.63 (1H, s, H-6), 5.50 (1H, s, H-5), 4.93 (1H, d, $J = 13.3$ Hz, H-7a), 4.82 (1H, d, $J = 13.3$ Hz, H-7b), 4.24 (1H, d, $J = 7.4$ Hz, H-2), 4.14 (1H, d, $J = 1.7$ Hz, H-4), 3.57 (1H, dd, $J = 7.4$, 1.7 Hz, H-3); CI-MS *m/z*: 469 (0.5), 467 (1), 451 (20), 427 (35), 393 (3), 365 (4), 331 (2), 305 (1), 271 (2), 262 (1), 245 (4), 227 (5), 211 (5), 207 (1), 183 (1), 165 (3), 149 (4), 123 (25), 105 (100), 91 (12), 77 (8), 69 (4); EI-MS *m/z* (rel. int.): 451 (30) ($[M + H - H_2O]^+$), 427 $[M + H - Ac]^+$, 365 (1), 331 (1), 269 (4), 262 (2), 244 (1), 227 (7), 207 (2), 165 (3), 123 (3), 105 (100), 94 (1), 77 (22), 51 (12), 43 (15).

*3.3.2 Uvacanol G (**2**)*

Colorless crystal, mp 156–157°C; $[\alpha]_D^{22} - 104.2$ ($c = 0.6$, MeOH); ^{1}H and ^{13}C NMR spectral data, see Tables 1 and 2; IR ν_{max} (KBr) cm^{-1}: 3450, 2922, 1720, 1699, 1601, 1315, 1273, 1069, 710; ESI-MS (positive) *m/z*: 407.6 $[M + Na]^+$; CI-MS *m/z* (rel. int.): 385 (0.5) $[M + H]^+$, 384 (1), 367 (30), 351 (1), 263 (30), 245 (5), 247 (3), 229 (4), 227 (3), 163 (2), 141 (12), 123 (100), 105 (82), 95 (13), 91 (4), 79 (11), 71 (7); HR-ESI-MS (positive) *m/z*: 385.1270 $[M + H]^+$ (calcd for $C_{21}H_{21}O_7$, 385.1287).

*3.3.2.1 Acetonide derivative (**2a**).* A 10.0 mg amount of **2**, 0.1 ml of 2,2-dimethoxyl propane, and 1 ml of CH_2Cl_2 were mixed. The mixture was stirred with a magnetic stirrer at room temperature for 8 h, and then subjected to preparative TLC on a silica gel GF_{254} plate to obtain **2a**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.11 (2H, d,

$J = 8.1$ Hz, Ar-H), 8.04 (2H, d, $J = 8.1$ Hz, Ar-H), 7.59 (2H, t, $J = 8.1$ Hz, Ar-H), 7.42 (4H, t, $J = 8.1$ Hz, Ar-H), 6.17 (1H, d, $J = 3.6$ Hz, H-6), 5.88 (1H, dd, $J = 3.0$, 3.6 Hz, H-5), 4.96 (2H, s, H-7), 4.76 (1H, dd, $J = 7.2$, 3.0 Hz, H-4), 4.57 (1H, d, $J = 3.0$ Hz, H-2), 4.53 (1H, dd, $J = 7.2$, 3.0 Hz, H-3), 1.36 (1H, s, Me), 1.35 (3H, s, Me).

3.3.3 *Uvacanol H (**3**)*

Mp 43–45°C; $[\alpha]_D^{22} - 24.9$ ($c = 0.3$, MeOH); IR ν_{max} (KBr) cm^{-1}: 3452, 2924, 1722, 1601, 1452, 1330, 1273, 1223, 1175, 1113, 1075, 1026, 712; ^1H and ^{13}C NMR spectral data, see Tables 1 and 2; CI-MS *m/z* (rel. int.): 409 ($[M + H]^+ - H_2O$) (5), 367 ($[MH]^+$–HOAc) (13), 351, 305 ($[M + H]^+$–HOBz) (8), 287 ($[M + H]^+ - H_2O$–HOBz) (3), 262 ($[M + H]^+$–HOBZ–Bz) (2), 244 (12), 233 (3), 227 (4), 215 (3), 211 (15), 182 (3), 165 (3), 153 (4), 123 (5), 105 (100), 94 (10), 77 (15), 69 (8); ESI-MS (positive) *m/z*: 427 $[M + Na]^+$; HR-ESI-MS (positive) *m/z*: 427.1365 $[M + H]^+$ (calcd for $C_{23}H_{23}O_8$, 427.1393).

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