Antineoplastic Agents. 558. *Ampelocissus* sp. Cancer Cell Growth Inhibitory Constituents[1]

George R. Pettit,*[,†] Venugopal J. R. V. Mukku,[†] Gordon Cragg,[‡] Delbert L. Herald,[†] John C. Knight,[†] Cherry L. Herald,[†] and Jean-Charles Chapuis[†]

Cancer Research Institute and Department of Chemistry and Biochemistry, Arizona State University, Tempe, Arizona 85287-2404, and Natural Products Branch, Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Frederick Cancer Research and Development Center, P.O. Box B, Frederick, Maryland 21702

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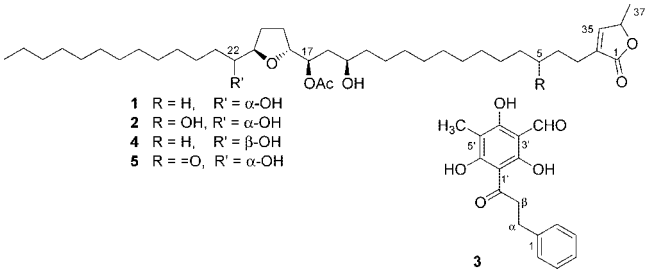
An investigation of the Phillippine *Ampelocissus* sp. roots for cancer cell growth inhibitory components led to the isolation of a new acetogenin characterized as 22-epicalamistrin (**1**) employing primarily 2D NMR and high-resolution mass spectral analysis. Two other antineoplastic constituents proved to be the known acetogenin uvaribonin (**2**) and chalcone **3**. Constituents **1**–**3** were all found to show significant cancer cell growth inhibitory activity against a panel of human cancer cell lines.

The extraordinary contribution of terrestrial natural products to advances in medicine and a variety of scientific disciplines continues to increase. Illustrative are a series of recent cancer cell growth inhibitory constituents that include steroidal lactones,[2a,b] steroidal saponins,[2c] triterpenoid saponins,[2d] terpenes,[2e,f] benzofurans,[2g] quassinoids,[2h] and cyclic peptides.[2i,j] Presently a large majority of terrestrial plants remain to be evaluated for the presence of antineoplastic constituents. The plant family Vitaceae, with 14 genera,[3] is illustrative of many such opportunities. Previous studies have been concerned with flavanols and other phenolic-type constituents in species from seven of these genera.[4] Three species in the genus *Ampelocissus* have been investigated and found to contain ellagic acid, kaempferol, myrcetin, and quercitin.

In collaboration with the U.S. National Cancer Institute (DTP, DCTD) we have undertaken an investigation of the small (~3 m) tree *Ampelocissus* sp. collected in the Phillippines for the purpose of characterizing cancer cell growth inhibitors. Subsequently, we found that the roots of the tree contained three principal antineoplastic constituents, namely, a new acetogenin designated 22-epicalamistrin B (**1**), the previously known acetogenin uvaribonin (**2**), and chalcone **3**. To our knowledge this is the first report of acetogenins occurring in the Vitaceae.[5] As one result of this, the voucher specimens of this plant will be further studied. Generally the acetogenins represent an active class of antineoplastic substances that are becoming of increasing interest owing to their inhibition of mitochondrial complex I.[5g]



By employing our usual modification (see Experimental Section) of a solvent partitioning sequence, the crude extract of the roots of *Ampelocissus* sp. was separated. Bioassay results against a six-cancer-cell-line panel localized the inhibitory activity in the CH_2Cl_2 fraction, which was next subjected to gel permeation (Sephadex LH-20) chromatography using methanol as the mobile phase. Two distinct, active fractions emerged from this partitioning. Separation of the first active fraction was continued by a series of chromatographic steps, once again on Sephadex LH-20, starting with CH_2Cl_2–CH_3OH (3:2), followed by hexane−toluene−CH_3OH (3:1:1), and last hexane−2-propanol−CH_3OH (8:1:1). The resulting active fractions were further purified by reversed-phase HPLC to provide the new compound 22-epicalamistrin B (**1**) and the previously reported uvaribonin[6] (**2**). Both were obtained as colorless oils.

The second active fraction was purified by subjecting it to a second LH-20 partitioning step using a CH_2Cl_2–CH_3OH (3:2) solvent mixture, followed by a reversed-phase HPLC sequence. The resulting active fractions yielded 3′-formyl-2′,4′,6′-trihydroxy-5′-methyldihydrochalcone (**3**), a constituent that had been previously isolated from *Psidium acutangulum*.[7]

The molecular formula of **1** was determined to be $C_{39}H_{70}O_7$ by APCIMS, indicating five degrees of unsaturation. A ^{13}C NMR spectrum showed signals attributable to two carbonyl groups (δ 173.9, 171.5), six oxygen-bonded carbon atoms (δ 82.9, 82.2, 77.4, 74.0, 71.6, 70.0), two olefinic carbon atoms (δ 148.8, 134.3), and a number of carbon signals between δ 34.9 and 22.6. The latter signals indicated a long hydrocarbon chain. An HMQC spectrum showed that only one olefinic carbon (δ 148.8) had a proton (δ 6.95) attached, implying a trisubstituted double bond. The IR spectrum showed a signal at 1755 cm^{-1} (α,β-unsaturated-γ-lactone), thus revealing one of the carbonyl carbons and the trisubstituted double bond. An ^1H NMR spectrum showed signals corresponding to a secondary methyl (δ 1.37, d, J = 6.4 Hz), a terminal methyl (0.85, t, J = 6.8 Hz), an acetoxy group (δ 2.04, s), and six hydroxymethines apart from the olefinic proton (δ 6.95). The H,H COSY spectrum revealed the olefinic proton (δ 6.95) coupled to a methine (δ 4.92, dq), in turn coupled to the secondary methyl (δ 1.37), indicating the latter group to be part of the α,β-unsaturated-γ-lactone.

Loss of two H_2O molecules from the EIMS spectrum of **1** indicated that two of the seven hydrogens were present in hydroxyl groups. The lactone and acetoxy groups accounted for four more oxygens. The remaining oxygen atom was then assumed to be included in a ring, which would also account for the remaining degree of unsaturation, and suggested the tetrahydrofuran **1** might be an acetogenin-type structure. The latter assumption was supported by signals in the ^1H and ^{13}C NMR specta characteristic of monotetrahydrofuran-type acetogenins.[8] The trans configuration of the tetrahydrofuran ring became transparent from the small $\Delta\delta$ of 0.7 between C-18 and C-21.[9] A literature search confined to the molecular formula and the available data led to calamistrin B (**4**),

* To whom correspondence should be addressed. Tel: 480 965-3351. E-mail: bpettit@asu.edu.
† Arizona State University.
‡ National Cancer Institute.

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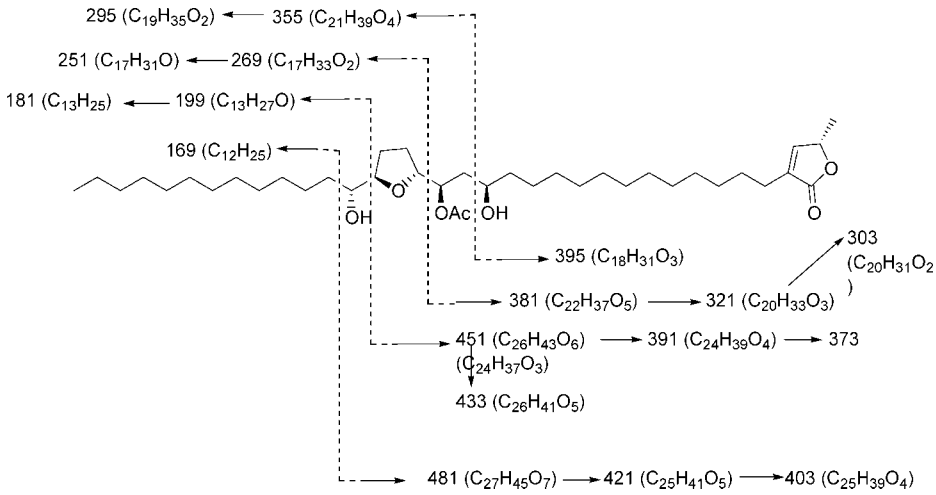

Figure 1. Mass spectral analysis of 22-epicalamistrin B (**1**).

an acetogenin, previously isolated from *Uvaria calamistrata*.[10] In turn that supported the acetogenin assumption of a tetrahydrofuran ring unit.

Next it became necessary to ascertain the locations of the two hydroxyl groups, the acetate, and the tetrahydrofuran unit on the hydrocarbon chain. The presence of a proton NMR triplet at δ 2.27 (2H) and its corresponding carbon signal (δ 25.2) precluded the location of either a hydroxyl or acetoxyl group at C-4 and C-5.[11] An in-depth examination of the EIMS spectrum of diol **1** led to the location of the functional groups and is presented in Figure 1. Because of the fragments at *m/z* 381 ($C_{22}H_{37}O_5$) and *m/z* 451 ($C_{26}H_{43}O_6$), the tetrahydrofuran ring was placed between C-18 and C-21. A study of the remaining mass spectrum fragments allowed the placement of the acetate group at C-17 and the two hydroxyl groups at C-15 and C-22. These relative positions for the functional groups proved to be identical with those reported for calamistrin B (**4**).

A comparison of the diol **1** ^{1}H and ^{13}C NMR data with those reported for calamistrin B indicated that it might be a C-22 epimer of calamistrin B. That conclusion was based on the fact that since the C-22 carbon in calamistrin B has been reported to resonate at δ 71.7 whereas in diol **1** C-22 was observed at δ 74, an epimeric relationship was readily assumed. Comparison of the diol **1** NMR data with that shown by uvaribonin (**2**) at C-22, where the stereochemistry was already assigned, provided further evidence for the conclusion. Sootepensin B[12] (**5**) provided another example of an acetogenin with an α-hydroxyl at C-22 that exhibits a carbon signal at about δ 74. Furthermore the structures and stereochemistry of uvaribonin (**2**), calamistrin B (**4**), and sootepensin B (**5**) are identical except for the C-22 β-hydroxyl group in calamistrin B, and hence the structure and stereochemistry (including *S* at C-36[12]) of diol **1** was assigned as 22-epicalamistrin B (**1**).

The remaining two (**2**, **3**) cancer cell growth inhibitory constituents isolated were determined to be uvaribonin and 3′-formyl-2′,4′,6′-trihydroxy-5′-methyldihydrochalcone, respectively, by comparing the ^{1}H and ^{13}C NMR data with those reported in the literature. However, the previous ^{13}C NMR data recorded for chalcone **3** were incomplete. Our new assignments (Table 2) were supported by HMBC data, and the HMBC correlations of most importance in assigning the carbon chemical shifts are shown in Figure 2 and in Table 2.

The overall structure was verified by our X-ray crystal structure determination, as well. An earlier crystal structure analysis had been reported,[7a] but the results between the previous experiment and ours were not identical. The crystal habit of the previously reported crystal structure was classified as orthorhombic ($P2_12_12_1$), whereas the X-ray structure reported herein was on a molecule crystallizing from CH_3OH in the monoclinic space group ($P2_1/c$). An obvious difference between the crystal habits for the two experiments was attributed to the contents of each unit cell. In the latter ($P2_1/c$ experiment), a molecule of solvent CH_3OH was found coassociated with each chalcone molecule, whereas only the parent molecule was present in the orthorhombic experiment. The difference was

Table 1. ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) Data of Compound **1**

	1		**3** (calamistrin B)	
position	δ_C	δ_H (multiplicity, *J* in Hz)	δ_C	δ_H
1	173.9		173.8	
2	134.3		134.4	
3	25.1	2.23 (t, 8)	25.2	2.27 (t, 6.8)
4–14	22.6–34.9	1.18–1.76 (m)	22.6–38.7	1.10–1.60 (m)
15	70.0	3.38 (m)	70.4	3.38 (m)
16	38.7	1.55 (m)	25.2	1.54 (m)
17	71.6	5.08 (m)	71.5	5.10 (m)
18	82.2	3.78 (m)	82.5	3.84 (m)
19–20	28.6	1.93, 1.63 (m)	22.6–38.7	1.90, 1.62 (m)
21	82.9	3.78 (m)	82.8	3.81 (m)
22	74.0	3.34 (m)	71.7	3.90 (m)
23–33	22.6–34.9	1.18–1.76 (m)	22.6–38.7	1.10–1.60 (m)
34	14.1	0.85 (t, 6.8)	14.1	0.87 (t, 6.8)
35	148.8	6.95 (d, 1.6)	146.8	6.95 (d, 1.5)
36	77.4	4.92 (dq, 7.2, 2)	77.3	4.99 (dq, 6.8,1.5)
37	19.2	1.37 (d, 6.4)	19.2	1.40 (d, 6.8)
Ac	171.5, 21.2	2.04 (s)	171.6, 21.2	2.07 (s)

Table 2. ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) Data of Chalcone **3**

position	δ_C	δ_H	HMBC
1	141.2		
2	128.5	7.26 (m)	C-4
3	128.5	7.31 (m)	C-1, C-2
4	126.1	7.19 (m)	C-3
5	128.5	7.31 (m)	C-1, C-2
6	128.5	7.26 (m)	C-4
α	30.3	3.01 (t)	−C═O, C-β, C-1, C-2
β	45.7	3.44 (t)	−C═O, C-α, C-1
1′	101.0		
2′	167.8		
3′	104.1		
4′	161.7[a]		
5′	103.4		
6′	171.5[a]		
CH_3	6.4	2.01 (s)	C-4′, C-5′, C-6′
−C═O	205.5		
−CHO	191.9	10.12 (s)	C-2′, C-3′

[a] These signals may be interchanged.

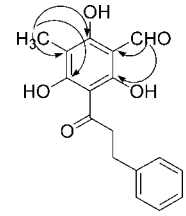

Figure 2. HMBC connectivities in chalcone (**3**).

Table 3. Murine P388 Lymphocytic Leukemia Cell Line and Human Cancer Cell Line Inhibitory Values (GI_{50} in μg/mL) for Constituents **1**−**3**

	cancer cell lines[a]						
structure	P388	BXPC3	MCF7	SF268	NCIH460	KM20L2	DU145
1		7.3	0.12	11.9	1.2	0.034	0.0065
1retest	0.014	7.4	1.7	33.0	0.20	1.4	0.058
2		1.3	0.011	1.4	1.0	0.0013	1.1
2retest		1.4	0.0022	1.6	1.4	0.0051	0.0093
3		0.3	0.3	0.55	0.52	0.36	0.33

[a] Cancer cell type: P388 (murine lymphocytic leukemia); BXPC3 (pancreatic adenocarcinoma); MCF7 (breast adenocarcinoma); SF268 (CNS glioblastoma); NCI-H460 (lung large cell); KM20L2 (colon adenocarcinoma); DU145 (prostate carcinoma).

clearly the result of our growing the chalcone **3** crystal from methanol, and the parent molecule was found to be chalcone **3**, i.e., 2,4,6-trihydroxy-3-methyl-5-(3-phenylpropionyl)benzaldehyde.

Chalcone **3** was previously shown to exhibit antibacterial, antifungal, and antifeedant activities.[7] The cancer cell line inhibitory data obtained for *Ampelocissus* sp. components **1** to **3** are shown in Table 3. Chalcone **3** exhibited the most uniform cancer cell line inhibitory activity, providing GI_{50} values between 0.3 and 0.5 μg/mL across the total six-cell-line panel. However acetogenins **1** and **2** displayed impressive inhibitory activity against the human colon and prostate cancer lines, with GI_{50} values ranging from 10^{-2} to 10^{-3} μg/μL.

Experimental Section

General Experimental Procedures. Specific rotation data were determined with a Perkin-Elmer 241 polarimeter. IR spectra were recorded with an Avatar 360 FT-IR instrument with the sample prepared as a film in $CHCl_3$. The NMR data were obtained using a Varian Unity Inova 400 spectrometer operating at 400 and 100 MHz for ^{1}H and ^{13}C NMR, respectively. High-resolution APCI mass spectra were measured using a JEOL LCMate instrument, and EI+ mass spectra were obtained using a JEOL JMS GC Mate and a direct inlet probe (70 eV). Reversed-phase HPLC was performed employing either a Zorbax SB C18 column (250 × 4.6 mm, 5 μm) or a Discovery C8 column (250 × 4.6 mm, 5 μm) with a Waters HPLC instrument and detected using a Waters 2487 UV detector.

Plant Source. The plant material used in the following experiments was provided by Dr. Domingo Madulid (Philippine National Museum, Manila) and Dr. Doel Soesarto (University of Illinois at Chicago) and initially identified as an *Ampelocisus* sp. (Vitaceae). The small tree (~3 m) was collected at 122.02° E, 11.02° N (Barangy Li Pata Natana Barotac Biejo, Ilo-ilo, Philippines) as part of a program conducted between the U.S. National Cancer Institute and the University of Illinois at Chicago directed by one of us (G.C.) and Dr. David Newman (NC). Voucher specimens of the leaves and twigs (Q-6601155) and roots (Q6601156) have been deposited in the Smithsonian Institution, Natural History Museum, Washington, DC. The first extracts (N-26935, N-26966, leaves and twigs; N-26719, roots) of the plant were prepared and evaluated in the NCI Frederick Cancer Center, Frederick, MD.

Separation and Isolation. The crude ethanol extract of *Ampelocissus* sp. roots (9.87 g) was partitioned between 9:1 and 3:2 CH_3OH-H_2O with hexane and CH_2Cl_2, respectively, using our modification[13a] of the early Bligh and Dryer procedure.[13b] The fraction obtained from the CH_2Cl_2 partition was subjected to an initial column chromatographic separation on Sephadex LH-20 using CH_3OH as the mobile phase. Two distinct fractions, A and B, emerged from this initial separation. Fraction A was subjected to column chromatographic separations on Sephadex LH-20 using $CH_2Cl_2-CH_3OH$ (3:2), followed by hexane−toluene−CH_3OH (3:1:1) to obtain fractions C and D. Continued Sephadex LH-20 separation of C using hexane−2-propanol−CH_3OH (8:1:1), followed by RP HPLC, resulted in the isolation of 22-epicalamistrin B (**1**, 9 mg). Semipreparative and subsequent RP HPLC of fraction D resulted in the isolation of uvaribonin (**2**, 8 mg). Final purifications of **1** and **2**[6] were accomplished on a Discovery C8 column (250 × 4.6 mm, 5 μm) and monitored by UV (220 nm) with CH_3CN-H_2O (9:1) as eluent. Fraction B was subjected to one more Sephadex LH-20 column separation using $CH_2Cl_2-CH_3OH$ (3:2) and followed by RP HPLC to obtain 3′-formyl-2′,4′,6′-trihydroxy-5′-methyldihydrochalcone (**3**, 10 mg).[7]

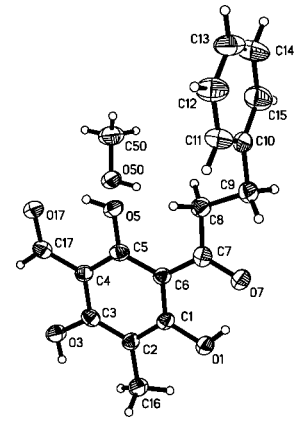

Figure 3. X-ray structure of chalcone **3**, showing the contents of the asymmetric portion of the unit cell. Atoms of the parent molecule and solvent methanol are shown as 50% thermal probability ellipsoids.

22-Epicalamistrin B (1): colorless oil; $[\alpha]^{23}_D$ +27.6 (*c* 0.3, $CHCl_3$); R_f (0.64, hexane−2-propanol, 4:1); IR ($CHCl_3$) ν_{max} 3450, 1755, 1740 cm^{-1}; NMR data, see Table 1; HRMS (APCI positive) *m*/*z* 651.5163 $[M + H]^+$ (calcd for $C_{39}H_{70}O_7$, 651.5200).

Uvaribonin (2): colorless oil; $[\alpha]^{23}_D$ +17.8 (*c* 0.196, $CHCl_3$); $[\alpha]^{15}_D$ (lit.)[6] +13 (*c* 0.2, $CHCl_3$); R_f (0.41, hexane−2-propanol, 4:1); IR ($CHCl_3$) ν_{max} 3467, 1757, 1745 cm^{-1}; HRMS (APCI positive) *m*/*z* 667.5108 $[M + H]^+$ (calcd for $C_{39}H_{70}O_8$, 667.5148), 607 $[M + H - AcOH]^+$.

3′-Formyl-2′,4′,6′-trihydroxy-5′-methyldihydrochalcone (3): colorless needles; mp 157–158 °C (lit.[7a,b] mp 157–58 °C); (APCI positive) *m*/*z* 301.1161 $[M + H]^+$ (calcd for $C_{17}H_{17}O_5$, 301.1076).

X-Ray Crystal Structure Determination of 3′-Formyl-2′,4′,6′-trihydroxy-5′-methyldihydrochalcone (3). A thin, colorless, needle-shaped crystal (~0.26 × 0.05 × 0.103 mm), grown from a CH_3OH solution, was mounted on the tip of a glass fiber. Cell parameter measurements and data collection were performed at 123 ± 2 K on a Bruker SMART 6000 diffractometer. Final cell constants were calculated from a set of 1627 reflections from the actual data collection. Frames of data produced by 15 s scans were collected in the θ range of 5.21−69.51° ($-15 \le h \le 14$, $-6 \le k \le 5$, $-26 \le l \le 28$) using 0.396° steps in ω such that a comprehensive coverage of the sphere of reflections was performed. After data collection, an empirical absorption correction was applied with the program SADABS.[14] Subsequent statistical analysis of the complete reflection set using the XPREP[9] program indicated the monoclinic space group $P2_1/c$.

Crystal data: $C_{17}H_{16}O_5 \cdot CH_3OH$, $a = 12.9809(8)$ Å, $b = 5.0615(3)$ Å, $c = 24.6990(19)$ Å, $\beta = 95.792(4)°$, $V = 1614.51(19)$ Å,[3] λ = (Cu Kα) = 1.54178 Å, $\mu = 0.856$ mm^{-1}, $\rho_c = 1.367$ g cm^{-3} for $Z = 4$ and fw = 332.34, $F(000) = 704$. A total of 8912 reflections were collected, of which 2846 were unique ($R_{int} = 0.0877$), and 1532 were considered observed ($I_o > 2\sigma(I_o)$). These were used in the subsequent structure solution and refinement with SHELXTL-V5.1.[15] All non-hydrogen atoms for **3** were located using the default settings of that program. Hydrogen atoms were placed in calculated positions and assigned thermal parameters equal to either 1.2 or 1.5 (depending upon chemical type) of the U_{iso} value of the atom to which they were attached, then both coordinates and thermal values were forced to ride that atom during

final cycles of refinement. All non-hydrogen atoms were refined anisotropically in a full-matrix least-squares refinement process. The final standard residual R_1 value for the model shown in Figure 3, which consists of a molecule of the parent chalcone molecule associated with a molecule of CH_3OH, converged to 0.0472 (for observed data) and 0.0880 (for all data). The corresponding Sheldrick R values were wR_2 of 0.1074 and 0.1221, respectively, and the GOF = 0.841 for all data. The difference Fourier map showed small residual electron density, the largest difference peak and hole being +0.293 and −0.299 e/Å,^{3} respectively. Final bond distances and angles were all within acceptable limits.[16]

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Supporting Information Available: The X-ray structure of chalcone **3** (Figure 1) and tables[16] containing full details of the crystallographic data obtained for structure **3** are available free of charge via the Internet at http://pubs.acs.org.

References and Notes

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(16) Crystallographic data for chalcone **3** has been deposited as a CIF file with the Cambridge Crystallographic Centre. The data can be obtained free of charge on application to the Director, CCDC, 12 Union Road, Cambridge CB 2 1EZ, United Kingdom.

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