Two New Mono-Tetrahydrofuran Ring Acetogenins, Annomuricin E and Muricapentocin, from the Leaves of *Annona muricata*

Geum-soog Kim,[†,§] Lu Zeng,[†] Feras Alali,[†] Lingling L. Rogers,[†] Feng-E. Wu,[†] Jerry L. McLaughlin,*[,†] and Soelaksono Sastrodihardjo[‡]

Department of Medicinal Chemistry and Molecular Pharmacology, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana 47907, and Department of Education and Culture, Center of Interuniversities, Biology Division, Bandung Institute of Technology, 10 Yanesba St., Bandung 40132, Indonesia

Received November 26, 1997

Bioactivity-directed fractionation of the leaf extract of *Annona muricata* L. (Annonaceae) has resulted in the isolation of two new Annonaceous acetogenins, annomuricine (**1**) and muricapentocin (**2**). Compounds **1** and **2** are monotetrahydrofuran ring acetogenins bearing two flanking hydroxyl groups; however, each has three additional hydroxyl groups. Compound **1** has an *erythro* 1,2-diol, and **2** has a 1,5,9-triol moiety. Both **1** and **2** showed significant cytotoxicities against six types of human tumors, with selectivities to the pancreatic carcinoma (PACA-2) and colon adenocarcinoma (HT-29) cell lines.

The Annonaceous acetogenins are a relatively new class of natural products; they constitute a series of C-35/C-37 fatty acid derivatives and are only found in the Annonaceae. More than 250 annonaceous acetogenins have been isolated from some 30 species investigated so far, and most of them exhibit a broad range of potent biological activities, such as in vivo antitumor, cytotoxic, pesticidal, antibacterial, antiparasitic, and immunosuppressive effects.[1−5] Their potent bioactivities have been demonstrated to be due to their depletion of ATP production through inhibition of NADH: ubiquinone oxidoreductase (complex I) in the mitochondrial electron transport system (ETS)[6,7] and the ubiquinone-linked NADH oxidase in the plasma membranes of tumor cells.[8] They are selectively inhibitory to tumor cells,[5] especially those that are multidrug resistant due to an ATP-dependent efflux.[4]

Annona muricata L. (Annonaceae) is grown commercially as a fruit crop and is called "guanabana" or "sour sop" throughout the tropical regions of the world. It has previously yielded a number of monotetrahydrofuran (mono-THF) acetogenins from the bark, seeds, and leaves.[9−21] Our previous studies on the leaves led to 17 new cytotoxic acetogenins.[10−16] Their chromatographic separations (Si gel) are dependent on their degree of hydroxylation. Three of these (annohexocin and murihexocins A and B) are hexahydroxylated mono-THF ring acetogenins,[14,15] and nine (annomuricins A, B, and C,[10,12] muricatocins A, B, and C,[11,12] and annopentocins A, B, and C[16]) are pentahydroxylated mono-THF acetogenins. Annomutacin and *cis*- and *trans*-annomuricin-D-ones are tetrahydroxylated mono-THF acetogenins,[13,16] and *cis*- and *trans*-10-*R*-annonacin-A-ones are trihydroxylated mono-THF compounds.[13]

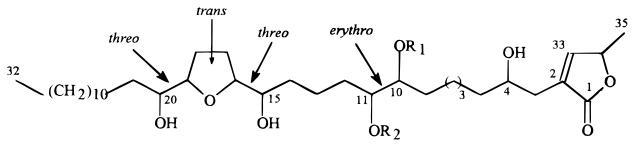

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Figure 1. Structure of annomuricin E (**1**) (R_1=R_2=H) and its acetonide derivative (**1a**) [R1−R2=C(CH_3)$_2$]

In this paper, the isolation and structure elucidation of two new cytotoxic acetogenins, annomuricin E (**1**) and muricapentocin (**2**), having five hydroxyl groups, are reported. Both are mono-THF acetogenins bearing two flanking OH groups. In comparison with annomuricin C,[12] annomuricin E (**1**) has a different relative stereochemistry at the 1,2-vicinal diol, that is, it is *erythro* at C-10/C-11. Muricapentocin has three additional OH groups, in a 1,5,9 sequence at C-4, C-8, and C-12, on the lactone side of the THF ring.

Results and Discussion

Annomuricin E (**1**) was obtained as a white solid. The HRFABMS gave a [M + Li]$^+$ ion at *m*/*z* 619.4734 (calcd 619.4761) consistent with a molecular formula of $C_{35}H_{64}O_8$. In the NMR spectrum, the ^{13}C signals at δ 174.8 (C-1), 152.0 (C-33), 131.1 (C-2), 78.1 (C-34), and 19.0 (C-35); ^{1}H signals at δ 7.20 (H-33), 5.06 (H-34), and 1.44 (H-35); and UV absorption [MeOH λ_{max} (ϵ) 218 nm (log ϵ 3.76)], all indicated that **1** has the usual methylated α,β-unsaturated γ-lactone fragment (Figure 1). The ^{13}C signal at δ 69.8, as well as the ^{1}H signal at δ 3.84, indicated the existence of an OH group at C-4, and this was further confirmed by the fragment ion at *m*/*z* 141 in the EIMS (Figure 2).

The ^{13}C NMR spectral signals at δ 82.6 and 82.8, corresponding to two ^{1}H NMR signals at δ 3.79 in **1**, indicated the presence of the mono-THF ring with two flanking OH groups. Additional ^{13}C signals at δ 69.8, 74.5, 73.9, 74.3, and 74.2, corresponding to five ^{1}H signals between δ 3.43 and 3.84, suggested that **1**

* To whom correspondence should be addressed. Tel.: (765) 494-1455. Fax: (765) 494-1414.
† Purdue University.
‡ Bandung Institute of Technology.
§ Visiting Scientist from the Department of Field Crops, Medicinal Crops Division, Yeongnam Agricultural Experiment Station, Rural Development Administration, Milyang, 617-130, Republic of Korea.

S0163-3864(97)00534-X CCC: $15.00
Published on Web 03/11/1998

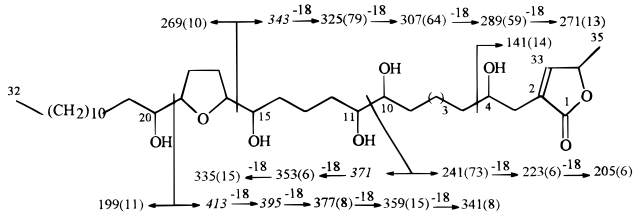

Figure 2. Diagnostic EIMS fragment ions (*m*/*z*) of annomuricin E (**1**); rel int in parentheses; ions not observed are in italics; losses of H_2O indicated by (−18 amu)..

Table 1. ^{13}C NMR (125 MHz, $CDCl_3$) and ^1H NMR (500 MHz, $CDCl_3$) Spectral Data for **1** and **1a**

	1		**1a**
carbon	$\delta^{13}C$	δ^1H (*J* in Hz)	δ^1H (*J* in Hz)
1	174.8		
2	131.1		
3a,3b	33.3	2.40 m, 2.51 m	2.40 m, 2.53 m
4	69.8	3.84 m	3.84 m
5	37.1	1.40−1.48 m	1.40−1.48 m
6−8	25.3−31.1	1.25−1.64 m	1.25−1.64 m
9	25.3−31.1	1.40−1.48 m	1.40−1.48 m
10	74.2[a]	3.60 m	4.02 m[a]
11	74.3[a]	3.60 m	4.03 m[a]
12	25.3−31.1	1.40−1.64 m	1.40−1.64 m
13	21.8	1.25−1.64 m	1.25−1.64 m
14	25.3−31.1	1.36−1.48 m	1.36−1.48 m
15	74.5[a]	3.45 m[a]	3.43 m[b]
16	82.8[b]	3.79 m	3.81 m
17	28.8	1.64 m, 1.98 m	1.64 m, 1.98 m
18	28.8	1.64 m, 1.98 m	1.64 m, 1.98 m
19	82.6[b]	3.79 m	3.79 m
20	73.9[a]	3.43 m[a]	3.41 m[b]
21	33.3	1.36−1.48 m	1.36−1.48 m
22−29	25.3−31.1	1.25−1.64 m	1.25−1.64 m
30	31.9	1.25−1.64 m	1.25−1.64 m
31	22.7	1.25−1.64 m	1.25−1.64 m
32	14.1	0.88 t (7.0)	0.88 t (7.0)
33	152.0	7.20 s	7.20 s
34	78.1	5.06 dq (1.0, 6.5)	5.06 dq (1.0, 6.5)
35	19.0	1.44 d (6.5)	1.44 d (6.5)
acetonyl methyl			1.43 s (3H), 1.33 s (3H)

[a,b] Assignments are interchangeable within the same column.

possessed five OH groups along with the mono-THF ring. The presence of five OH groups was further confirmed by five successive losses of H_2O (18 u) from the [MH^+] in the CIMS (*m*/*z* 613 → 595 → 577 → 559 → 541 → 523).

The placement of the mono-THF ring was established to be at C-16/C-19 by the EIMS fragment ions at *m*/*z* 325, 269, 377, and 199 (Figure 2). The relative stereochemistry associated with the mono-THF ring from C-15 to C-20 in **1** was concluded to be *threo*/*trans*/*threo*. ^{13}C signals were observed at δ 28.8 (C-17, C-18), corresponding to ^1H signals at δ 1.98 and 1.64 (H-17a, H-17b, H-18a, H-18b) (Table 1), and the correlation cross-peak appeared between δ 3.79 (H-16, H-19) and 3.43 or 3.45 (H-15, H-20), corresponding to ^{13}C spectral signals at δ 82.8, 82.6, 73.9, and 74.5, in the $^1H-^1H$ COSY. This moiety matched well with the annonacin type (*threo*/*trans*/*threo*) of acetogenins[21−28] and the model suggested by Fujimoto et al.[29]

The ^{13}C NMR signals at δ 74.3 and 74.2, as well as the ^1H signal at δ 3.60 (2H) in **1**, directly showed the presence of a 1,2-vicinal diol, bearing an *erythro* configuration, based on comparisons with other known and model compounds.[10−12,16,20,26,30,31] The relative configuration was further confirmed by the chemical shift of the acetonide derivative (**1a**) of **1** (Table 1).[10,11] The acetonyl methyl ^1H signals in **1a** appeared as two separated three-proton singlets at δ 1.33 and 1.43, respectively, and demonstrated the presence of the 1,2-diol as *erythro*. If the configuration of the 1,2-vicinal diol were *threo*, two acetonyl methyl ^1H signals would have been observed together as a six-proton singlet at ca. δ 1.37.[12]

The placement of the 1,2-vicinal diol along the hydrocarbon chain in **1** was determined by careful analyses of the fragment ions in the EIMS. The diagnostic fragment ions at *m*/*z* 241, 353, and 271 placed the diol at C-10/C-11. Particularly, the prominently high intensity in the EIMS of the fragment ion at *m*/*z* 241, due to cleavage between the carbon linkage of the diol, is a common characteristic.[10,12] Compared to normal ^{13}C chemical shifts at ca. δ 29.0 for methylene groups, a ^{13}C signal was observed shifted upfield to δ 21.8 (C-13); this was attributed to a double β-effect resulting from the two oxygenated carbons at C-15 and C-11.[14,16,24] Thus, the presence of the 1,2- diol at C-10/C-11 gave a double β-effect to the carbon at C-13, and the placement of OH groups in **1** was confidently determined to be at C-4, C-10, C-11, C-15, and C-20**.**

Compound **1** differs from the previously known and similar compound, annomuricin C, only in the stereochemistry of the 1,2-diol. While annomuricin C has a 1,2-vicinal diol at C-10/C-11 with a *threo* configuration,[12] **1** has the *erythro* configuration at the same position. *cis*- and *trans*-Annomuricin-D-ones, previously reported from the leaves of *A. muricata*, have the same relative configurations *threo*/*trans*/*threo* around the mono-THF ring and an *erythro* vicinal diol at C-10/C-11, but these acetogenins have four OH groups.[16] Thus, **1** was named annomuricin E and is a new compound in this series.

Muricapentocin (**2**) was also obtained as a white solid. The molecular formula of **2** was suggested to be $C_{35}H_{64}O_8$ from a peak at *m*/*z* 613 [MH^+] in the CIMS, and this was confirmed by a peak at *m*/*z* 619.4754 (calcd 619.4761) for the $[M + Li]^+$ in the HRFABMS. NMR spectral signals indicated that **2** has a typical methylated α,β-unsaturated γ-lactone fragment with a 4-OH (Table 2). In the ^{13}C NMR spectrum of **2**, five ^{13}C signals appeared between δ 69.3 and 74.3, which suggested the presence of five OH groups (Figure 3). Five successive losses of H_2O (18 u) from the [MH^+] in the CIMS clearly confirmed the existence of the five hydroxyls. Two of the five OH groups were indicated to be flanking a mono-THF ring by comparison of the NMR spectral data with those of other known and model compounds.[22−25] The ^{13}C signals at δ 28.8 and 28.9 (C-17, C-18), corresponding to the ^1H signals at δ 1.98 and 1.62, and the correlation between δ 3.79 (2H) and 3.45 and 3.40 (H-15 ↔ H-16, H-19 ↔ H-20), corresponding to the ^{13}C signals δ 82.8, 82.3, 74.3, and 74.2 in the $^1H-^1H$ COSY, further confirmed the presence of the mono-THF ring, with two flanking OH groups, as *threo*/*trans*/*threo*.

When four of the OH groups of **2** were confirmed to be placed on the lactone side of the mono-THF ring (see Figure 4), the placement of the ring was clearly indicated to be at C-16/C-19 by the fragment ions in the EIMS at *m*/*z* 343, 269, 377, and 199 (Figure 4). Particularly, the series of fragment ions from *m*/*z* 343 to

Table 2. ^{13}C NMR (125 MHz, $CDCl_3$) and ^1H NMR (500 MHz, $CDCl_3$) Spectral Data for **2**

	2	
carbon	$\delta^{13}C$	δ^1H (J in Hz)
1	174.7	
2	131.0	
3a,3b	33.3	2.48 m,2.40 m
4	69.3	3.85 m
5	37.1[a]	1.52 m
6	21.6[b]	1.25−1.68 m
7	37.3[a]	1.40−1.52 m
8	71.3	3.61 m[a]
9	36.9[a]	1.40−1.52 m
10	21.6[b]	1.25−1.68 m
11	36.7[a]	1.40−1.52 m
12	71.3	3.66 m[a]
13	29.3−29.7	1.40−1.52 m
14	29.3−29.7	1.37−1.40 m
15	74.3[c]	3.45 m[b]
16	82.8[d]	3.79 m
17	28.8[e]	1.98 m,1.62 m
18	28.9[e]	1.98 m,1.62 m
19	82.3[d]	3.79 m
20	74.2[c]	3.40 m[b]
21	33.3	1.37−1.40 m
22	25.5	1.25−1.68 m
23−29	29.3−29.7	1.25−1.68 m
30	31.9	1.25−1.68 m
31	22.7[b]	1.25−1.68 m
32	14.1	0.88 t (7.5)
33	152.0	7.2 s
34	78.0	5.06 dq (1.5, 7.0)
35	19.1	1.43 d (7.0)

[a−e] Assignments are interchangeable within the same column.

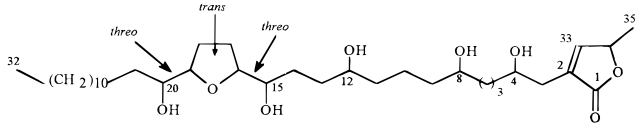

Figure 3. The structure of muricapentocin (**2**).

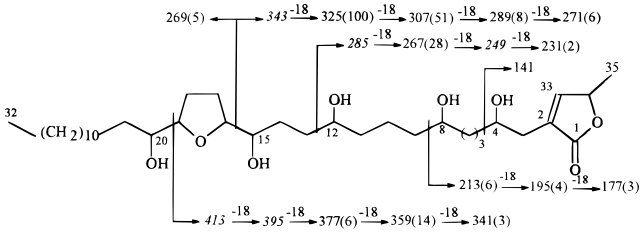

Figure 4. Diagnostic EIMS fragments ions (m/z) of muricapentocin (**2**); rel int in parentheses; ions not observed are in italics; losses of H_2O indicated by (−18 amu).

m/z 271, by their successive losses of H_2O (18 u), exhibited very strong peaks compared with other fragment ions from **2**. The high intensity of the peak, produced by cleavage at C-15/C-16, provided additional evidence for the placement of the mono-THF ring, with flanking OH groups, from C-16 to C-19. Relatively high intensities of fragment ions from m/z 343 to 271 were also observed in the EIMS of **1** due to this placement of the mono-THF ring.

Two hydroxylated ^{13}C signals in **2** appeared at ca. δ 71.3 (δ 71.30, 71.32), corresponding to the ^1H signals at δ 3.61 and 3.66, which suggested the two hydroxylated carbons were located at least two methylene groups away from other hydroxylated carbons.[17,22,23,27,32,33] Two methylene ^{13}C signals were observed upfield at ca. δ 21.6 (δ 21.60, 21.61), experiencing a double β-effect,[14,16,24] which suggested that three hydroxylated carbons were successively located three methylene units away, inasmuch as four hydroxylated carbons were already assigned on the lactone side by the analyses of the fragment ions in the EIMS of **2** (Figure 4). From the relative placement of three such OH groups, the presence of two possible triols was assumed: a 1,5,9-triol moiety at C-4/C-8/C-12 or a 1,4,8-triol moiety at C-4/C-7/C-11. Both of these triol moieties would show two up-field shifted methylene carbon signals by two double β-effects from C-4 to C-15. Two hydroxylated carbons were clearly indicated be at C-8 and C-12 by the fragment ions at m/z 213 and 267 in the EIMS (Figure 4) due to the cleavages between C-8/C-9 and C-12/C-13, respectively; this observation proved the placement of the 1,5,9-triol moiety from C-4 to C-12 and solved the planar structure of **2** (Figure 3). This new pentahydroxylated mono-THF ring acetogenin was named muricapentocin.

The bioactivities of **1** and **2** are summarized in Table 3. Both **1** and **2** showed significant bioactivities in the brine shrimp lethality test (BST) and among six human solid tumor cell lines; **1** and **2** were particularly selective in their cytotoxicities to the pancreatic carcinoma (PACA-2) and the colon adenocarcinoma (HT-29) cell lines, with ED_{50} values of 2.42×10^{-2} μg/mL and 5.03×10^{-2} μg/mL against PACA-2 and 6.68×10^{-2} μg/mL and 7.10×10^{-2} μg/mL against HT-29, respectively. Usually these pentahydroxylated mono-THF ring acetogenins[10−12] are less cytotoxic than their tetrahydroxylated mono-THF ring counterparts.[9,16,17]

Experimental Section

General Experimental Procedures. HPLC was carried out with Rainin HPLC pumps, a Rainin model UV-1 detector using the Dynamax software system and a C-18 column (250 × 21 mm, 8 μm, 60 Å), UV detection at 220 nm. Optical rotations were determined by using a Perkin-Elmer 241 polarimeter. IR spectra were obtained on a Perkin-Elmer 1600 FT-IR spectrophotometer. UV spectra were made on a Beckman DU 640 spectrophotometer in MeOH. ^1H NMR, $^1H-^1H$ COSY, and ^{13}C NMR spectra were obtained on a Varian VXR-500S spectrometer. LREIMS and CIMS were taken on a Finnigan 4000 spectrometer. HRFABMS were performed on a Micro Mass AutoSpec spectrometer.

Bioassays. The BST (*Artemia salina* Leach) was routinely employed for evaluating the crude extracts, fractions, and isolated compounds from the leaves of *A. muricata*.[34,35] Cytotoxicities to human solid-tumor cell lines were evaluated at the Purdue Cancer Center, Cell Culture Laboratory, using the standard seven-day MTT assays for A-549 (human lung carcinoma),[36] MCF-7 (human breast carcinoma),[37] HT-29 (human colon adenocarcinoma),[38] A-498 (human kidney carcinoma),[36] PC-3 (human prostate adenocarcinoma),[39] and PACA-2 (human pancreatic carcinoma).[40] Adriamycin was used as a positive antitumor control.

Plant Material. The leaves (2.0 kg) of *Annona muricata* L. were obtained from fruit-producing trees growing in the experimental orchard of Bandung Institute of Technology, Bandung, Indonesia, and were dried and pulverized through an 8-mm sieve in an electric mill.

Table 3. Bioactivities of **1** and **2** from *Annona muricata* (ED_{50}: μg/mL)

compounds	BST[a]	A-549[b]	MCF-7[c]	HT-29[d]	A-498[e]	PC-3[f]	PACA-2[g]
1	1.84×10	1.12×10^{-1}	1.45	6.68×10^{-2}	1.41	1.46×10^{-1}	2.42×10^{-2}
2	1.86	1.93×10^{-1}	1.90	7.10×10^{-2}	1.72	4.50×10^{-1}	5.03×10^{-2}
adriamycin[h]		2.94×10^{-3}	1.24×10^{-1}	3.81×10^{-2}	1.58×10^{-2}	3.55×10^{-2}	4.56×10^{-3}

[a] The brine shrimp (*Artemia salina* Leach) test (LD_{50}: μg/mL). [b] Human lung carcinoma. [c] Human breast carcinoma. [d] Human colon adenocarcinoma. [e] Human kidney carcinoma. [f] Human prostate adenocarcinoma. [g] Human pancreatic carcinoma. [h] Positive antitumor control.

Extraction and Isolation. The leaves (2.0 kg) were percolated by 95% EtOH to give 386 g of an extract (F001, BST LC_{50} 30.5 ppm). The EtOH extract was partitioned between CH_2Cl_2 and H_2O (1:1). The H_2O-soluble fraction (F002) was freeze-dried to yield a sticky yellow mass (260 g), while the CH_2Cl_2-soluble fraction was concentrated by rotary evaporation to yield a residue of 126 g (F003, BST LC_{50} 19.6 ppm). F003 was then partitioned between 90% aqueous MeOH and hexane (1:1). The two phases were dried by rotary evaporation to yield the hexane-soluble fraction (F006, BST LC_{50} >100 ppm) (11 g) and an aqueous MeOH-soluble fraction (F005, BST LC_{50} 1.6 ppm) (115 g).

Open column chromatography of F005 (55 g) was performed on 250 g of Amberlite XAD-2 resin eluted by hexane, hexane−Me_2CO (1:1), and then Me_2CO. Flash column chromatography of the hexane−Me_2CO (1:1) residue (10.2 g, BST LC_{50} 0.98 ppm) from the Amberlite column, with 0−25% MeOH in CH_2Cl_2, eluted over Baker 40-μm Si gel, separated mixtures of active compounds from inert materials as determined by the BST. Active fractions were pooled by activity and subjected to repeated chromatography, by open columns over Si gel using gradient solvent systems of $CHCl_3$−MeOH or CH_2Cl_2−MeOH. From these active impure fractions, **1** and **2** (annomuricin E, muricapentocin) were isolated by repeated reversed-phase HPLC using gradient solvent systems of 60−90% MeCN in H_2O for 90 min (flow rate: 10 mL/min).

Preparation of Acetonide Derivative (1a). Compound **1**, 0.5 mg, was dissolved in 0.4 mL of reagent (0.04 mL 37% HCl and 20 mL Me_2CO). The mixture was set at room temperature for 3 days and checked with TLC to make sure that the reaction was completed. The mixture was then dried in vacuo to yield the pure derivative, **1a**; ^{1}H NMR data (500 MHz, $CDCl_3$), see Table 1.

Annomuricin E (1): white solid, 4.6 mg, $[\alpha]_D$ +12.5° (*c* 0.04, MeOH), UV (MeOH) λ_{max} (ϵ) 218 nm (logϵ 3.76); IR ν_{max} 3381, 2920, 2851, 1744, 1466 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) data, see Table 1, CIMS data *m/z* 613 (100), 595 (61), 577 (44), 559 (50), 541 (22), 523 (12); HRFABMS *m/z* 619.4734 (calcd 619.4761 for $C_{35}H_{64}O_8{}^7Li^+$); EIMS *m/z* 377 (8), 359 (15), 353 (11), 341 (8), 335 (15), 325 (79), 317 (2), 307 (64), 289 (59), 271 (13), 269 (10), 253 (7), 251 (2), 241 (73), 223 (6), 205 (6), 199 (11), 141 (14), 123 (22).

Muricapentocin (2): white solid, 5.7 mg, $[\alpha]_D$ +8.01° (*c* 0.05, MeOH), UV (MeOH) λ_{max} (ϵ) 220 nm (log ϵ 3.54); IR ν_{max} 3398, 2920, 2851, 1743, 1458 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$), ^{13}C NMR (125 MHz, $CDCl_3$), data, see Table 2; CIMS data *m/z* 613 (100), 595 (41), 577 (23), 559 (13), 541 (2), 523 (1); HRFABMS *m/z* 619.4754 (calcd 619.4761 for $C_{35}H_{64}O_8{}^7Li^+$); EIMS *m/z* 377 (6), 359 (14), 343 (3), 341 (30), 325 (100), 307 (51), 289 (9), 271 (6), 269 (5), 267 (28), 231 (2), 213 (6), 199 (1), 195 (4), 177 (3), 141(7), 123 (7).

Acknowledgment. This investigation was supported by RO1 grant no. CA 30909 from the National Cancer Institute, National Institute of Health. G.-S. Kim, gratefully acknowledges the support of the Ministry of Government Administration, Republic of Korea. We are also grateful to the Cell Culture Laboratory, Purdue Cancer Center. Thanks are due to the Nebraska Center for Mass Spectrometry for the HRFABMS measurements.

References and Notes

(1) Zeng, Lu.; Ye, Q.; Oberlies, N. H.; Shi, G.; Gu, Z. M.; He, K.; McLaughlin, J. L. *Nat. Prod. Rep.* **1996**, *13*, 275−306.
(2) McLaughlin, J. L.; Zeng, L.; Oberlies, N. H.; Alfonso, D.; Johnson, H. A.; Cummings, B. A. In *Phytochemicals for Pest Control*; Hedin, P. A., Hollingworth, R. M., Masler, E. P., Miyamoto, J., Thompson, D. G., Eds.; ACS Symposium Series, American Chemical Society: Washington, DC. 1997; pp 117−133
(3) Cavé, A.; Figadère, B.; Laurens, A.; Cortes, D. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Kirby, G. W., Moore, R. E., Steglich, W., Tamm, Ch., Eds.; Springer-Verlag: NewYork, 1997; Vol. 70, pp 81−288.
(4) Oberlies, N. H.; Croy, V. L.; Harrison, M. L.; McLaughlin, J. L. *Cancer Lett*. **1997**, *115*, 73−79.
(5) Oberlies N. H.; Jones, J. L.; Corbett, T. H.; Fotopoulos, S. S.; McLaughlin, J. L. *Cancer Lett*. **1995**, *96*, 55−62.
(6) Lewis, M. A.; Arnason, J. T.; Philogene, B. J. R.; Rupprecht, J. K.; McLaughlin, J. L. *Pestic. Biochem. Physiol*. **1993**, *45*, 15−23.
(7) Londershausen, M.; Leicht, W.; Lieb, F.; Moeschler, H.; Weiss, H. *Pestic. Sci*. **1991**, *33*, 427−438.
(8) Morrè, J. D.; DeCabo, R.; Farley, C.; Oberlies, N. H.; McLaughlin, J. L. *Life Sci*. **1995**, *56*, 343−348.
(9) Rieser, M. J.; Fang, X. P.; Rupprecht, J. K.; Hui, Y. H.; Smith, D. L.; McLaughlin, J. L. *Planta Med*. **1993**, *59*, 91−92.
(10) Wu, F. E.; Gu, Z. M.; Zeng, L.; Zhao, G. X.; Zhang, Y.; McLaughlin, J. L.; Sastrodihardjo, S. *J. Nat. Prod*. **1995,** *58*, 830−836.
(11) Wu, F. E.; Zeng, L.; Gu, Z. M.; Zhao, G. X.; Zang, Y.; Schwedler, J. T.; McLaughlin, J. L.; Sastrodihardjo, S. *J. Nat. Prod*. **1995**, *58*, 902−908.
(12) Wu, F. E.; Zeng, L.; Gu, Z. M.; Zhao, G. X.; Zang, Y.; Schwedler, J. T.; McLaughlin, J. L.; Sastrodihardjo, S. *J. Nat. Prod*. **1995**, *58*, 909−915.
(13) Wu, F. E.; Zhao, G. X.; Zeng, L.; Zhang, Y.; Schwedler, J. T,; McLaughlin, J. L.; Sastrodihardjo, S. *J. Nat. Prod*. **1995**, *58*, 1430−1437.
(14) Zeng, L.; Wu, F. E.; McLaughlin, J. L. *Bioorg. Med. Chem. Lett*. **1995**, *5*, 1865−1868.
(15) Zeng, L.; Wu, F. E.; Gu, Z. M.; McLaughlin, J. L. *Tetrahedron Lett*. **1995**, *36*, 5291−5294.
(16) Zeng, L.; Wu, F. E.; Oberlies, N. H.; McLaughlin, J. L. *J. Nat. Prod*. **1996**, *59*, 1035−1042.
(17) Rieser, M. J.; Gu, Z. M.; Fang, X. P.; Zeng, L.; Wood K. V.; McLaughlin, J. L. *J. Nat. Prod*. **1996**, *59*, 100−108.
(18) Roblot, F.; Laugel, T.; Leboeuf, M.; Cavé, A.; Laprévote, O. *Phytochemistry* **1993**, *34*, 281−285.
(19) Rieser, M. J.; Kozlowski, J. F.; Wood, K. V.; McLaughlin, J. L. *Tetrahedron Lett*. **1991**, *32*, 1137−1140.
(20) Hisham, A.; Sreekala, U.; Pieters, L.; De Bruyne, T. Van den Heuvel, H.; Claeys, M. *Tetrahedron* **1993**, *49*, 6913−6920.
(21) Myint, S. H.; Cortes, D. C.; Laurens, A.; Hocquemiller, R.; Leboeuf, M.; Cavé A.; Cotte, J.; Quéro, A. M. *Phytochemisty* **1991**, *30*, 3335−3338.
(22) Colman-Saizarbitoria, T.; Zambrano, J.; Ferrigni, N. R.; Gu, Z. M.; Ng, J. H.; McLaughlin, J. L. *J. Nat. Prod*. **1994**, *57*, 486−493.
(23) Colman-Saizarbitoria, T.; Gu, Z. M.; McLaughlin, J. L. *J. Nat. Prod*. **1994**, *57*, 1661−1669.

(24) Jossang, A.; Dubaele, B.; Cavé. A. *Tetrahedron Lett.* **1990**, *31*, 1861−1864.
(25) Chang, F. R.; Wu, Y. C.; Duh, C. Y.; Wang, S. K. *J. Nat. Prod.* **1993**, *56*, 1688−1694.
(26) Zhao, G. X.; Rieser, Y. H.; Miesbauer, L. R.; Smith, D. L.; McLaughlin, J. L. *Phytochemistry* **1993**, *33*, 1065−1073.
(27) Alali, F.; Zeng, L.; Zhang, Y.; Ye, Q.; Hopp, D. C.; Schwedler J. T.; McLaughlin, J. L. *Bioorg. Med. Chem.* **1997**, *5*, 549−555.
(28) Hopp, D. C.; Zeng, L.; Gu, Z. M.; Kozlowski, J. F.; McLaughlin, J. L. *J. Nat. Prod.* **1997**, *60*, 581−586.
(29) Fujimoto, Y.; Murasaki, C.; Shimada, H.; Nishioka, S.; Kakinuma, K.; Singh, S.; Singh, M.; Gupta, Y. K.; Sahai, M. *Chem. Pharm. Bull.* **1994**, *42*, 1175−1184.
(30) Shi, G.; MacDougal, J. M.; McLaughlin, J. L. *Phytochemistry* **1997**, *45*, 719−723.
(31) Silva, E. L. M.; Roblot, F.; Laprévote, O.; Sérani, L.; Cavé, A. *J. Nat. Prod.* **1997**, *60*, 162−167.
(32) Jossang, A.; Dubaele, B.; Cavé, A.; Bartoli, M. H.; Bériel, H. *J. Nat. Prod.* **1991**, *54*, 967−971.
(33) Yu, J. G.; Ho, D. K.; Cassady, J. M.; Xu, L.; Chang, C. J. *J. Org. Chem.* **1992**, *57*, 6198−6202.
(34) McLaughlin, J. L.; In *Methods in Plant Biochemistry*; Hostettmann, K., Ed.; Academic: London, 1991; Vol. 6, pp 1−32.
(35) McLaughlin, J. L.; Rogers, L. L.; Anderson, J. E. *Drug Inform. J.*, in press.
(36) Giard, D. J.; Aronson, S. A.; Todaro, G. J.; Arnstein, P.; Kersey, H. J.; Dosik, H.; Parks, W. P. *J. Natl. Cancer Inst.* **1973**, *51*, 1417−1423.
(37) Soule, H. D.; Vazquez, J.; Long, A.; Albert, S.; Brennam, M. *J. Natl. Cancer Inst.* **1973**, *51*, 1409−1416.
(38) Fogh, J.; Trempe, G. In *Human Tumor Cells*; Fogh, J. Ed.; Plenum: New York, 1975; pp 115−159.
(39) Kaighn, M. E.; Narayan, K. S.; Ohnuki, Y.; Lechner, J. F.; Jones, L. W. *Invest. Urol.* **1979**, *17*, 16−23.
(40) Yunis, A. A.; Arimura, G. K.; Russian, D. *Int. J. Cancer* **1997**, *19*, 128−135.

NP970534M