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Asitrilobins C and D: Two New Cytotoxic Mono-Tetrahydrofuran Annonaceous Acetogenins from *Asimina triloba* Seeds

Mi-Hee Woo,* Soon-Ok Chung and Dal-Hwan Kim

Department of Pharmacy, College of Pharmacy, Catholic University of Taegu-Hyosung, Kyongsan, 712-702, South Korea

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Abstract—Two new bioactive mono-tetrahydrofuran (THF) γ-lactone acetogenins, asitrilobins C (**1**) and D (**2**), were isolated from the seeds of *Asimina triloba* (Annonaceae) by directing the fractionation with brine shrimp lethality. Compounds **1** and **2** have a relative stereochemical relationship of *threo*/*trans*/*threo* across the mono-THF ring with its two flanking hydroxyls. Their structures were established on the basis of chemical and spectral evidence. Compounds **1** and **2** showed selective cytotoxicity comparable with adriamycin for the breast carcinoma (MCF-7) and the colon adenocarcinoma (HT-29) cell lines.

Introduction

Asimicin was the first acetogenin isolated from the seeds and stem bark of the North American paw paw tree, *Asimina triloba* (L.) Dunal (Annonaceae).[1] Its highly potent antitumor and pesticidal activities suggested promising future medicinal and agricultural applications for this group of compounds. Bioactivity-directed isolation using the BST[2,3] has led to the discovery of approximately 54 bioactive acetogenins from the seeds and stem bark of the paw paw.[4–16] As part of our continuing efforts to find new antitumor agents, we have isolated two new acetogenins from the seeds; these are named asitrilobins C (**1**) and D (**2**), and they have a relative stereochemical relationship of *threo*/*trans*/*threo* across the mono-THF ring moiety with its two flanking hydroxyl groups. The structures were determined by ^{1}H and ^{13}C NMR, COSY, MS and chemical derivations.

Results and Discussion

Compound **1** (10 mg), $[\alpha]_D^{20}$ −8° (*c* 0.005, CH_2Cl_2), was obtained as a colorless powder. Its molecular weight of 624 was determined by HRFABMS ($[M+Na]^+$ ions at *m*/*z* 647.4876 (calcd 647.4863), corresponding to the formula $C_{37}H_{68}O_7Na$) and was confirmed by MS of its acetate and TMSi derivatives. The existence of an α,β-unsaturated γ-lactone in **1** was suggested by an IR carbonyl absorption at 1736 cm^{-1}, a UV λ_{max} at 226 nm (log ε 3.7). Six resonances at δ 7.18 (H-35), 5.05 (H-36), 2.53 (H-3a), 2.40 (H-3b), 3.83 (H-4) and 1.42 (H-37) in the ^{1}H NMR are characteristic spectral features for the α,β-unsaturated γ-lactone fragment with a 4-OH group in the Annonaceous acetogenin.[17]

The existence of four OH groups in **1** was evidenced by an IR absorption at 3448 cm^{-1} and resonances due to oxygen-bearing carbons at δ 68.72, 70.01, 71.59 and 74.01, correlated with proton signals at δ 3.41 (1H), 3.74 (1H), 3.83 (1H) and 3.90 (1H). These were further confirmed by preparation of a tetraacetyl derivative (**1a**). The ^{1}H NMR spectrum of **1a** showed four proton singlets at δ 2.02, 2.03, 2.05 and 2.07 and multiplet proton resonances at δ 4.87 (2H), 5.01 (1H) and 5.10 (1H) corresponding to downfield shifts on four secondary OH-bearing carbons as compared with **1**. By comparison of ^{1}H and ^{13}C NMR data of oxygen-bearing protons and carbons with the NMR signals of known acetogenins, we deduced that **1** had two flanking hydroxyl groups adjacent to a THF ring and one isolated hydroxyl group on the carbon chain in addition to 4-OH.

The placements of the THF ring and hydroxyl groups were determined by careful analysis of the EI mass fragments of **1** and its acetyl and TMSi derivatives (Fig. 1). The EI mass spectrum of the TMSi derivative

Keywords: *Asimina triloba*; annonaceae; mono-THF acetogenins; asitrilobins C and D.

*Corresponding author.

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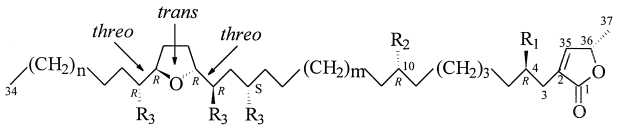


	R_1	R_2	R_3	m	n
1	OH	H	OH	1	9
1a	OAc	H	OAc	1	9
1b	OTMSi	H	OTMSi	1	9
1r	(*R*)-OMTPA	H	(*R*)-OMTPA	1	9
1s	(*S*)-OMTPA	H	(*S*)-OMTPA	1	9
2	H	OH	OH	3	7
2a	H	OAc	OAc	3	7
2b	H	OTMSi	OTMSi	3	7
2r	H	(*R*)-OMTPA	(*R*)-OMTPA	3	7
2s	H	(*S*)-OMTPA	(*S*)-OMTPA	3	7

Figure 1. Structures of **1** and **2** and their derivatives.

(**1b**) of **1** produced intense ions at *m*/*z* 271, 341, 571 and 641 and corresponding signals in the EI mass spectrum of the acetate derivative (**1a**) of **1** at *m*/*z* 311 and 551, which clearly placed the THF ring at C-18 along the hydrocarbon chain and allowed the assignment of the hydroxyl groups at C-17 and C-22 relative to the THF ring. The position of the remaining isolated hydroxyl group at C-15 was illustrated by a fragment in the EIMS spectra of **1a** at *m*/*z* 397 and **1b** at *m*/*z* 455 and 457. These fragments showed losses of acetic acid and TMSi hydroxide, respectively, to give *m*/*z* 277. In the HMBC spectrum of **1**, the hetero correlations observed (δ 71.59→1.60 (m) (C-17→H-16), 68.72→1.60 (m) (C-15→H-16), 37.62→3.90 (m) (C-16→H-15) and 37.62→3.74 (m) (C-16→H-17)) confirmed the placement of the free hydroxyl at C-15.

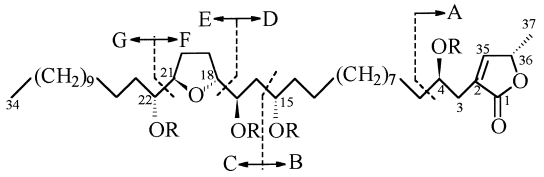
A thorough comparison with the diagnostic NMR chemical shifts of a pair of model mono-THF compounds with adjacent hydroxyl groups in the *threo* and *erythro* configuration[17,18] enabled us to interpret the ^{1}H and ^{13}C NMR spectra of **1** and led us to the assignment of the relative stereochemistry in the mono-THF part. The relative stereochemistry between C-21 and C-22 of **1** was determined as *threo* by comparing the ^{13}C NMR signal of **1** for C-22 (δ 74.01) and the ^{1}H NMR resonances of **1** for H-21 (δ 3.83) and H-22 (δ 3.41) with those of model compounds of known relative stereochemistry.[19] By the technique of Born et al.[19] the ^{13}C NMR chemical shift of **1** for C-17 at δ 71.59 suggested the *erythro* relationship between C-17 and C-18. However, considering the γ-*gauche* effect[20] due to the presence of a hydroxyl group substituted at C-15, the ^{13}C NMR chemical shift of C-17 should be shifted upfield. Therefore, the *threo*-relationship between C-17/C-18 was assigned. In addition the ^{13}C NMR shift of **1** for C-15 upfield shifted to δ 68.72 also supported the presence of a γ-gauche effect due to a hydroxyl group at the β-position; as the carbons having a single isolated hydroxyl group are typically displayed at δ 70–72 in other acetogenins.[17,18] The ^{1}H NMR signals at δ 1.96 and 1.63, corresponding to H-19a/H-20a and H-19b/H-20b, are typical methylene proton signals of a *trans*-THF ring configuration, whereas these are δ 1.93 and 1.74 for the *cis*-THF ring configuration.[21] Thus the relative configuration for these four chiral centers in **1** was assigned as *threo*/*trans*/*threo*. Thus **1** was named asitrilobin C and is a new natural Annonaceous acetogenin.

Compound **2** (10 mg), $[\alpha]_D^{20}$ −4.0° (*c* 0.005, CH_2Cl_2), was also obtained as a colorless powder. A molecular ion peak at *m*/*z* 625 in the FABMS of **2** (Fig. 2) once again indicated a molecular weight of 624. The HRFABMS spectrum showed an exact mass peak of $[M+H]^+$ at *m*/*z* 625.5062, which matched the molecular formula $C_{37}H_{69}O_7$ (calcd 625.5043).

The existence of four OH groups in **2** was confirmed by IR, oxygen-bearing protons and carbons (Table 1) in its ^{1}H and ^{13}C NMR spectra, and EIMS spectra of its tetraacetate (**2a**) and tetra-TMSi (**2b**) derivatives (Fig. 2) as in **1**. The positions of the OH groups in **2** were assigned at C-10, C-17, C-19 and C-24 by careful analysis of the fragments in the EIMS spectrum at *m*/*z* 267, 423, 509 and 579 in its tetraacetate (**2a**), and at *m*/*z* 297, 483, 599 and 669 in its tetra-TMSi derivative (**2b**). The relative stereochemistry of the mono-THF ring with two flanking hydroxyl groups in **2** is *threo*/*trans*/*threo* such as in **1**. Thus **2** was named asitrilobin D and is also a new natural compound.

To determine the absolute stereochemistry of the carbinol centers at C-4, C-15, C-17 and C-22 in **1**, and at C-10, C-17, C-19 and C-24 in **2**, their tetra-(*R*)- and tetra-(*S*)-methoxytrifluoromethyl phenylacetic acid (MTPA) esters (Mosher esters) (**1r**, **1s**, **2r** and **2s**) were prepared.[22–24] ^{1}H–^{1}H COSY analysis of these Mosher ester derivatives was then performed. **1s** and **1r** provided about the absolute stereochemistries across the THF ring from which C-15 and C-22 could be concluded to have the *S* and *R* configurations, respectively; therefore, **1** has C-21*R*, C-18*R* and C-17*R* configurations. Hoye et al. synthesized (+)-*SS* (like) and (±)-*RS* (unlike) model butenolides[25] and permitted the assignments of the relative configurations between C-4 and C-36 in acetogenins by using the magnitudes of the Δδ values for the ^{1}H and ^{19}F nuclei in their Mosher esters.[26] The $\Delta\delta_H$ values for H-35 and H-36 in **1r** and **1s** at 0.23 and 0.04 suggested that **1** has the 4*R*, 36*S* configurations, as is usual. The ^{1}H NMR chemical shift data of **2r** and **2s** showed that the absolute configurations at both C-10 and C-24 are *R* and that at C-17 is *S* (Table 2); therefore **2** has C-23*R*, C-20*R* and C-19*R* configurations.

Bioactivity data obtained with **1** and **2** are summarized in Table 3. Compounds **1** and **2** were toxic to the brine shrimp larvae and showed cytotoxicity comparable with adriamycin for the breast carcinoma (MCF-7) and the colon adenocarcinoma (HT-29) cell lines. The acetogenins exert their effects through inhibition of mitochondrial electron transport (complex I) and the inhibition of the plasma membrane NADH oxidase of cancer cells.[27,28]



R	$MH^+/M(Ac)_4^+$ /$M(TMSi)_4^+$	A	B	C	D	E	F	G
H	625, 607(a), 589(a),	141,	311, 293(a),	313, 295(a),	355, 337(a),	269,	425, 407(a),	199,
(FABMS)	571(a), 553(a)	123(a)	275(a)	277(a)	319(a), 301(a)	251(a)	389(a), 371(a)	181(a)
Ac	792, 732(b), 672(b),	183*,	395*, 335(b)	397, 337(b),	481*, 421(b)*,	311,	551, 491(b),	241*,
(EIMS)	612(b), 552(b)	123(b)	275(b)*	277(b)	361(b), 301(b)*	251(b)	431(b), 371(b)	181(b)
TMSi	912, 822(c),732(c),	213,	455, 365(c)*,	457, 337(c),	571, 481(c),	341,	641, 551(c),	271,
(EIMS)	642(c), 552(c)	123(c)	275(c)	277(c)	391(c)*, 301(c)	251(c)	461(c), 371(c)	181(c)

Figure 2. Diagnostic FABMS and EIMS fragment ions of **1** and its tetraacetate (**1a**) and tetra-TMSi (**1b**) derivatives. (a): loss of H_2O (m/z 18); (b): loss of HOAc (m/z 60); (c): loss of TMSiOH (m/z 90). Ions indicated with an asterisk (*) were not observed.

Table 1. ^1H NMR data of **1**, **1a**, **2**, **2a** and ^{13}C NMR data of **1** and **2** ($CDCl_3$, δ)

Position	^1H NMR data (500 MHz)			^{13}C NMR data (125 MHz)		
	1	**1a**	**2**	**2a**	**1**	**2**
1	—	—	—	—	174.60	173.93
2	—	—	—	—	131.09	134.31
3a	2.40 dd (15.0, 8.2)	2.51 m	1.26 brs	1.18–1.62 m	33.42	33.52
3b	2.53 dt (15.0, 1.5)	2.56 m	1.26 brs	1.18–1.62 m	—	—
4	3.83 m	5.10 m	1.26 brs	1.18–1.62 m	70.01	25.17–31.92
5–9	1.26 brs	1.21–1.60 m	1.26 brs	1.18–1.62 m	37.47	25.17–31.92
10	1.26 brs	1.21–1.60 m	3.58 m	4.87 m	25.62–31.99	71.61
11–14	1.26 brs	1.21–1.60 m	1.26 brs	1.18–1.62 m	25.62–31.99	25.17–31.92
15	3.90 m	5.01 m	1.26 brs	1.18–1.62 m	68.72	25.17–31.92
16	1.60 m	1.54 m	1.26 brs	1.18–1.62 m	37.62	25.17–31.92
17	3.74 m	4.87 m	3.91 m	5.00 m	71.59	68.67
18	3.83 m	3.97 m	1.60 m	1.55 m	82.55	37.47
19	1.63 m,1.96 m	1.60 m, 1.95 m	3.75 m	4.87 m	25.62–31.99	71.95
20	1.63 m, 1.96 m	1.60 m, 1.95 m	3.87 m	3.97 m	25.62–31.99	82.57
21	3.83 m	3.97 m	1.63 m, 1.96 m	1.59 m, 1.94 m	82.67	25.17–31.92
22	3.41 m	4.87 m	1.63 m, 1.96 m	1.59 m, 1.94 m	74.01	25.17–31.92
23	1.40 m	1.21–1.60 m	3.82 m	3.97 m	25.62–31.99	82.72
24	1.26 brs	1.21–1.60 m	3.41 m	4.87 m	25.62–31.99	74.08
25	1.26 brs	1.21–1.60 m	1.26 brs	1.18–1.62 m	25.62–31.99	25.17–31.92
26–32	1.26 brs	1.21–1.60 m	1.26 brs	1.18–1.62 m	25.62–31.99	25.17–31.92
33	1.29 m	1.21–1.60 m	1.29 brs	1.18–1.62 m	22.78	22.70
34	0.88 t (7.0)	0.88 t (6.9)	0.88 t (7.0)	0.88 t (6.9)	14.24	14.13
35	7.18 q (1.0)	7.08 q (1.5)	7.05 q (1.0)	6.98 q (1.5)	151.67	148.91
36	5.05 qq (7.0, 1.5)	5.01 qq (7.01, 1.5)	4.99 qq (6.9, 1.5)	5.00 qq (6.8, 1.5)	77.98	78.06
37	1.42 d (7.0)	1.39 d (6.9)	1.41 d (7.5)	1.41 d (6.9)	19.22	19.23
4-OAc		2.03 s				
10-OAc				2.04 s		
15-OAc		2.02 s				
17-OAc		2.05 s		2.02 s		
19-OAc				2.05 s		
22-OAc		2.07 s				
24-OAc				2.07 s		

Experimental

General experimental procedures

Mps were determined on a Yanaco micro melting point apparatus and were uncorrected. Optical rotations were taken on a Jasco DIP-370 digital polarimeter. IR spectra were measured on a Jasco FT/IR 300E spectrophotometer. UV spectra were obtained on a Shimadzu UV-1601PC spectrophotometer. ^1H, ^{13}C and COSY NMR spectra were taken on a Brucker AM-300 or AM-500 spectrophotometer in $CDCl_3$ using TMS as an internal standard. Low- and high-resolution FABMS data were collected on a JEOL JMS-HX110 spectrometer. EIMS spectra were recorded on a Quattro spectrometer. For TLC, silica gel 60 F-254 (EM 5717) glass plates (0.25 mm) were used and visualized by spraying with 5% phosphomolybdic acid in MeOH and heating. HPLC was carried out with a Waters 600E HPLC instrument using the Autochrowin software system (Young Su Scientific Co., Korea) and a C_{18} column equipped with a Waters 486 detector set at 230 nm.

Table 2. Characteristic ^{1}H NMR data of Mosher esters of **1s**, **1r**, **2s** and **2r** for determinations of stereochemistries

Position	**1s** δ*S*	**1r** δ*R*	δ *S*-*R*	Position	**2s** δ*S*	**2r** δ*R*	δ *S*-*R*
5	1.60	1.57	+0.03	3	2.28	2.27	+0.01
	1.69	1.65	+0.04	4	1.50–1.67	1.46–1.61	Positive
4	5.33	5.36	*R*	10	4.89	4.93	*R*
3	2.56	2.60	−0.04	16	1.47–1.59	1.50–1.62	Negative
	2.58	2.65	−0.07	17	5.08	5.10	*S*
35	6.73	6.96	−0.23	18	1.69–1.92	1.60–1.83	Positive
36	4.85	4.89	−0.04	19	4.98	4.87	*R*
37	1.27	1.30	−0.03	20	4.14	3.84	+0.30
14	1.54–1.64	1.57–1.70	Negative	21	1.32	1.30	+0.02
15	4.96	4.88	*S*		1.60	1.79	−0.19
16	1.78–1.90	1.59–1.77	Positive	22	1.42	1.52	−0.10
17	4.96	4.84	*R*		1.69	1.80	−0.11
18	3.94	3.81	+0.13	23	3.95	3.99	−0.04
19	1.37	1.28	+0.09	24	4.98	5.03	*R*
	1.69	1.76	−0.07	25	1.46–1.63	1.43–1.58	Positive
20	1.30	1.46	−0.16				
	1.64	1.76	−0.12				
21	3.82	3.94	−0.12				
22	4.96	5.00	*R*				
23	1.73–1.84	1.38–1.50	Positive				

Table 3. Brine shrimp lethality and cytotoxicities in human solid tumor cell lines for **1** and **2**

		Human cancer cell line ED_{50} (μg/mL)					
Compound	BST[a] LC_{50} (μg/mL)	A-549[b]	MCF-7[c]	HT-29[d]	A-498[e]	PC-3[f]	MIA PaCa-2[g]
1	3.91×10^{-1}	1.12×10^{-1}	1.85	3.77×10^{-1}	2.24	1.77	1.29×10^{-1}
2	9.12×10^{-2}	1.76×10^{-1}	1.10	2.18×10^{-1}	1.00	3.94	1.02×10^{-1}
Adriamycin[h]	NT[i]	4.30×10^{-3}	1.29×10^{-1}	1.18×10^{-2}	1.56×10^{-2}	4.99×10^{-2}	1.01×10^{-3}

[a]Brine shrimp test.[2,3]
[b]Human lung carcinoma.[28]
[c]Human breast carcinoma.[29]
[d]Human colon adenocarcinoma.[30]
[e]Human kidney carcinoma.[28]
[f]Human prostate adenocarcinoma.[31]
[g]Human pancreatic carcinoma.[32]
[h]Positive control standard.
[i]NT, not tested.

Plant material

The seeds of *Asimina triloba* were collected in the fall of 1993, from a plantation of authenticated paw paw trees grown at the University of Maryland, Western Agricultural Research Station, Keadysville, Maryland, and were provided through the cooperation of R. Neal Peterson and the Paw Paw Foundation, Washington, DC. The identification was confirmed by R. Neal Peterson.

Bioassays

The extracts, fractions, and isolated compounds were routinely evaluated for lethality to brine shrimp larvae (BST).[2,3] Seven-day in vitro MTT cytotoxicity tests against human tumor cell lines were carried out at the cell culture laboratory, Purdue Cancer Center, using standard protocols for A-549 (human lung carcinoma),[29] MCF-7 (human breast carcinoma),[30] HT-29 (human colon adenocarcinoma),[31] A-498 (human kidney carcinoma),[28] PC-3 (human prostate adenocarcinoma),[32] and MIA PaCa-2 (human pancreatic carcinoma)[33] with adriamycin as a positive control.

Extraction, isolation and purification

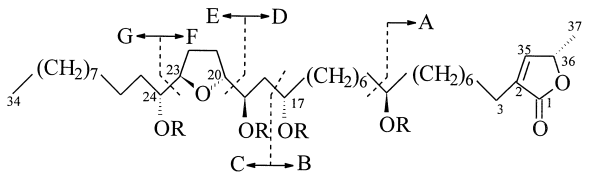
Steps for extraction and chromatographic fractionation were identical to those reported previously.[5] The BST active fractions F (BST, $LC_{50}=1.31\times10^{-1}$ μg/mL) and H (BST, $LC_{50}=4.20\times10^{-3}$ μg/mL) were further subjected to repeated open column chromatography and HPLC to yield pure compounds **1** and **2**.

Preparation of TMSi derivatives

Approximately 10 μg of compounds **1** and **2** was separately treated with 0.2 μL pyridine and 2 μL of *N*, *O*-bis-(trimethylsilyl)acetamide for 5 h to give a **1b** and a **2b**: EIMS *m*/*z* see Figures 2 and 3.

Preparation of per-(*S*) and per-(*R*)-mosher esters

A previously described method was used.[21–23] To 1 mg of **1** or **2** in 0.5 mL of CH_2Cl_2 were added sequentially 0.2 mL pyridine, 0.5 mg 4-(dimethylamino)-pyridine, and 12 mg of (*R*)-(−)-α-methoxy-α-(trifluoromethyl)-phenylacetyl (MTPA) chloride, separately. The mixture



R	$MH^+/M(Ac)_4^+$ /$M(TMSi)_4^+$	A	B	C	D	E	F	G
H	625, 607(a), 589(a),	225,	339, 321(a),	285, 267(a),	383, 365(a),	241,	453, 435(a),	171,
(FABMS)	571(a), 553(a)	207(a)	303(a)	249(a)	347(a), 329(a)	223(a)	417(a), 399(a)	153(a)
Ac	792, 732(b), 672(b),	267*,	423*, 363(b)	369, 309(b),	509*, 449(b)*,	283,	579, 519(b),	213*,
(EIMS)	612(b), 552(b)	207(b)	303(b)*	249(b)	389(b), 329(b)	223(b)	459(b), 399(b)	153(b)
TMSi	912, 822(c),732(c),	297,	483, 393(c),	429*, 339(c)*,	599, 509(c),	313,	669, 579(c),	243,
(EIMS)	642(c), 552(c)	207(c)	303(c)	249(c)*	419(c), 329(c)	223(c)	489(c), 399(c)	153(c)*

Figure 3. Diagnostic FABMS and EIMS fragment ions of **2** and its tetraacetate (**2a**) and tetra-TMSi (**2b**) derivatives (a): loss of H_2O (m/z 18); (b): loss of HOAc (m/z 60); (c): loss of TMSiOH (m/z 90). Ions indicated with an asterisk (*) were not observed.

was left at room temperature overnight and purified over a micro-column (0.6×6 cm) of silica gel (230–400 mesh) eluted with 3–4 mL of hexane:CH_2Cl_2 (1:2); the eluate was dried, CH_2Cl_2 (5 mL) was added, and the CH_2Cl_2 was washed using 1% $NaHCO_3$ (5 mL×3) and H_2O (5 mL×2); the washed eluate was dried in vacuo to give the *S* Mosher esters of **1** and **2**, respectively. Using (*S*)-(+)-α-methoxy-α-(trifluoromethyl)-phenylacetyl (MTPA) chloride afforded the *R* Mosher esters. Their pertinent ^{1}H NMR chemical shifts are given in Table 2.

Preparation of acetylated derivatives

Each treatment of compounds **1** and **2** (2 mg) with anhydrous pyridine and acetic anhydride (at room temperature overnight) and subsequent work up gave a **1a** and a **2a**: EIMS m/z see Figures 2 and 3; ^{1}H NMR (500 MHz, $CDCl_3$) see Table 1.

Asitrilobin C (1). Colorless powder, mp 85.3–86.4 °C; $[\alpha]_D^{20}$ −8° (*c* 0.005, CH_2Cl_2); UV (MeOH) λ_{max} = 226 nm (log ε = 3.7); IR ν_{max} 3448 (OH), 1736 cm^{-1} (C=O, α,β-unsaturated γ-lactone); FABMS m/z see Figure 2; HRFABMS m/z $[M+Na]^+$ 647.4876 for $C_{37}H_{68}O_7Na$ (calcd 647.4863); ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) see Table 1.

Asitrilobin D (2). Colorless powder, mp 87.2–88.1 °C; $[\alpha]_D^{20}$ −4.0° (*c* 0.005, CH_2Cl_2); UV (MeOH) λ_{max} = 226 nm (log ε = 3.7); IR ν_{max} 3448 (OH), 1736 cm^{-1} (C=O, α,β-unsaturated γ-lactone); FABMS m/z see Figure 3; HRFABMS m/z $[M+H]^+$ 625.5062 for $C_{37}H_{69}O_7$ (calcd 625.5043); ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) see Table 1.

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