Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 5, No. 11, pp. 1135-1140, 1995

0960-894X/95 $9.50+0.00

0960-894X(95)00182-4

16,19-CIS-MURISOLIN AND MURISOLIN A, TWO NOVEL BIOACTIVE MONO-TETRAHYDROFURAN ANNONACEOUS ACETOGENINS FROM *ASIMINA TRILOBA* SEEDS

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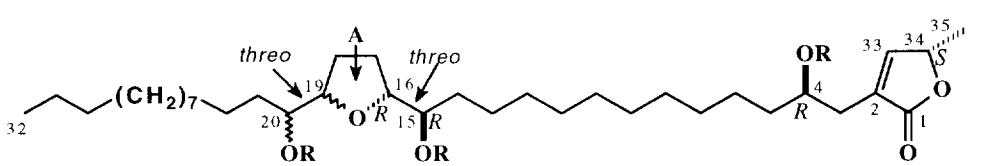
Abstract: Two novel bioactive mono-tetrahydrofuran (THF) γ-lactone acetogenins, 16,19-*cis*-murisolin (**1**) and murisolin A (**2**), were isolated from the seeds of *Asimina triloba* (Annonaceae) by directing the fractionation with brine shrimp lethality. **1** has a 16,19-*cis* mono-THF ring with two flanking hydroxyl groups and represents a new type among the natural Annonaceous acetogenins. Murisolin (**3**), which is new in this species, was also obtained. **1-3** showed potent and selective cytotoxicities among six human tumor cell lines.

Asimina triloba (L.) Dunal (paw paw) is one of several species of the genus *Asimina* (Annonaceae) which are distributed in the eastern regions of the United States. Aside from its delicious fruits, its medicinal values were first recognized by the report of asiminine, purportedly an emetic alkaloid from its seeds, and another alkaloid, anaboline, which is contained in the bark and was once used in medicine.[1] The discovery in the bark and seeds of the acetogenin, asimicin,[2] and its significant cytotoxic and pesticidal properties renewed interest in the bioactive compounds of this species. Subsequent investigation of the bark by Zhao *et al.* led to the isolation and structural elucidation of an additional eleven novel bioactive acetogenins [trilobacin,[3] *cis*- and *trans*-annonacin-A-one, *cis*- and *trans*-gigantetrocin-A-one, *cis*-isoannonacin,[4] asimin, asiminacin, asiminecin,[5] bullatin and bullanin],[6] as well as eleven known compounds [asimicin, bullatacin, *cis*- and *trans*-bullatacinone, N-p-coumaroyltyramine, N-*trans*-feruloyltyramine, (+)-syringaresinol,[3] *trans*-isoannonacin, squamolone,[4] squamocin and



Compounds	1	1a	1b	1r	1s	3
R	H	Ac	TMSi	(*r*)-MTPA	(*s*)-MTPA	H
A	*cis*	*cis*	*cis*	*cis*	*cis*	*trans*

motrilin].[6] Further efforts, using brine shrimp lethality (BST) to direct fractionation of the ethanol extract of the seeds,[7] have now resulted in the isolation of three mono-THF acetogenins, 16,19-*cis*-murisolin (**1**), murisolin A (**2**), and murisolin (**3**). **1** and **2** are novel and are diastereomers of **3**, which is new in this species. The structures were determined by ^{1}H- and ^{13}C-NMR, COSY, MS, and chemical derivations. **1** is the first natural acetogenin to be reported which has the *cis* configuration in a mono-THF subunit bearing two flanking hydroxyl groups.

Compound **1** (8 mg), mp 67-68 °C, $[\alpha]_D$ +11.0° (CH_2Cl_2, c=0.1), UV λ_{max} CH_2Cl_2 (nm) (log ε =3.57), was obtained in an amorphous state. Its molecular weight of 580 was determined by HRCIMS [MH^+ at *m/z* 581.4762 (calcd 581.4781), corresponding to the molecular formula $C_{35}H_{64}O_6$] and was confirmed by MS of its acetate derivative. The presence of three OH groups in **1** was suggested by the formation of its triacetate (**1a**) which gave the expected molecular ion, M^+ at *m/z* 706 in the EIMS, and exhibited three singlet proton peaks at δ 2.03 (3H), 2.08 (3H) and 2.08 (3H). This was supported in the IR spectrum of **1** by a prominent OH absorption at 3443 cm^{-1}, and the carbonyl absorption at 1740 cm^{-1} suggested an α,β–unsaturated γ–lactone, which was confirmed by a positive response to Kedde's reagent.[2,8] The ^{1}H- and ^{13}C-NMR spectra of **1** (Table 1) were similiar to those of the mono-THF acetogenins.[9] The placements of the mono-THF ring system and the three OH groups of **1** along the aliphatic chain were determined based on the MS fragmentation pattern of the tri-TMSi derivative (Figure 1). The assignment of the ^{1}H-NMR spectrum of **1** was based on the ^{1}H-^{1}H COSY.

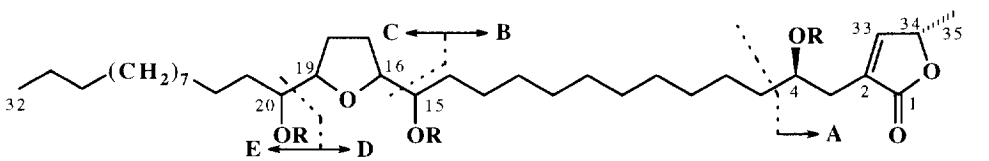
Table 1. ^{1}H-NMR data of **1**, **1a**, **2**, **2a** and **3**, and ^{13}C-NMR data of **1** and **2** ($CDCl_3$, δ)

No. (H & C)	^{1}H-NMR Data (500 MHz)				^{13}C-NMR Data (125 MHz)	
	1	**1a**	**2**	**2a**	**1**	**2**
1	-	-	-	-	174.61	174.60
2	-	-	-	-	131.20	131.17
3a	2.40dd(15.0,8.2)	2.51dd(15.2,8.0)	2.40dd(15.2,8.2)	2.51dd(15.1,8.1)	33.35	33.33
3b	2.53dt(15.0,1.5)	2.56dt(15.5,1.6)	2.53dt(15.0,1.5)	2.56dt(15.4,1.7)	-	-
4	3.82m	5.10m	3.83m	5.10m	69.97	69.97
5	1.47m	1.58m	1.47m	1.60m	37.40	37.39
6-13	1.26brs	1.25brs	1.27brs	1.24brs	25.53-29.66	25.53-29.67
14	1.47m	1.55m	1.37m[a]	1.55m	34.09[i]	33.20
15	3.42m	4.88m	3.40m[b]	4.85m[f]	74.36	74.33
16	3.82m	3.96m	3.82m[c]	3.97m	82.65	83.21
17a	1.75m	1.63m	1.64m[d]	1.63m[g]	28.11	28.58
17b	1.94m	1.90m	2.00m[e]	1.75m[h]	-	-
18a	1.75m	1.63m	1.85m[d]	1.95m[g]	28.11	25.21
18b	1.94m	1.90m	1.90m[e]	1.95m[h]	-	-
19	3.82m	3.96m	3.88m[c]	3.97m	82.65	82.12
20	3.42m	4.88m	3.82m[b]	4.91m[f]	74.36	71.51
21	1.47m	1.55m	1.48m[a]	1.55m	34.08[i]	32.53
22-30	1.26brs	1.25brs	1.27brs	1.24brs	25.64-31.92	25.96-31.89
31	1.28m	1.27m	1.29m	1.28m	22.68	22.66
32	0.88t(7.1)	0.88t(7.1)	0.88t(7.1)	0.88t(7.1)	14.11	14.10
33	7.19q(1.0)	7.08q(1.5)	7.19q(1.0)	7.08q(1.5)	151.78	151.77
34	5.06qq(7.0,1.5)	5.01qq(6.5,1.5)	5.06qq(7.0,1.5)	5.01qq(6.5,1.5)	77.97	77.95
35	1.43d(6.5)	1.40d(6.5)	1.43d(7.0)	1.40d(6.5)	19.11	19.09
4-OAc		2.03s		2.03s		
15-OAc		2.08s		2.08s		
20-OAc		2.08s		2.05s		

[a-i]The assignments may be interchangeable.

The ^{1}H-NMR spectrum of **1** showed resonances at δ 7.19 (q, 1H), δ 5.06(qq, 1H) and δ 1.43 (d, 3H) attributed to H-33, H-34 and H-35 of an α,β–unsaturated γ–lactone; five protons on carbons bearing oxygens at δ 3.82 (m, 3H) and 3.42 (m, 2H); and three protons at δ 3.82, 2.53 and 2.40, characteristic of the presence of an OH group at C-4 as in other acetogenins.[9] The position of this OH group was confirmed by the presence of allylic coupling between H-33 (δ 7.19) and H-3a, 3b (δ 2.53 and 2.40). A long chain was indicated by a triplet signal at δ 0.88 for the terminal methyl coupled with a broad intense signal at δ 1.26 which itself was also coupled with multiplet signals at δ 1.28–1.47. Finally, two multiplet resonances at δ 1.75 and 1.94 (H-17a and H-17b) were coupled with the multiplet at δ 3.82 (H-16), and, similiarly, H-18a and H-18b were coupled with H-19.

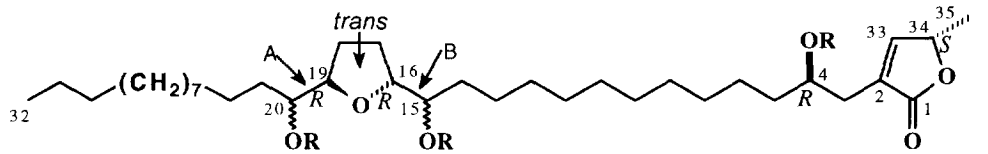
Comparative analysis of the spectral data between **1** and **3**[10] showed the same molecular weight and fragmentation patterns in the MS (Figure 1) and close similarities of resonances of protons and carbons in the NMR spectra (Table 1), except for H-17ab (δ 1.75 and 1.94) and H-18ab (δ 1.75 and 1.94), clearly suggesting that **1** was a diastereomer of **3** [mp 72-73 °C; $[\alpha]_D$ +16.0° ($CHCl_3$, c=0.1), UV λ max MeOH (nm) 228 (log ε =2.97)]. In the ^{1}H-NMR of **3**, two methylene signals for the mono-THF ring were observed at δ 1.66 and 1.98 for the *trans* ring configuration, whereas these are at δ 1.74 and 1.93 for the *cis* ring configuration.[11] On the basis of spectroscopic (MS, ^{1}H- and ^{13}C-NMR) evidence, **3** was identified as murisolin[10] which has the usual *threo/trans/threo* relative stereochemical relationships between the chiral centers of C-15/C-16, C-16/C-19 and C-19/C-20.[9] For a ^{13}C-NMR study, Fujimoto *et al.* synthesized several stereochemically defined model mono-THF compounds.[11] These were *threo/trans-*, *threo/cis-*, *erythro/trans-* and *erythro/cis-* isomers of 2-heptyl-5-(1-hydroxyheptyl) tetrahydrofurans, and *threo/trans/threo-*, *threo/cis/threo-*, *erythro/trans/threo-* and *erythro/cis/threo-* isomers of 2,5-di-(1-hydroxyheptyl) tetrahydrofuran. ^{1}H- and ^{13}C-NMR chemical shifts (Table 1) of the mono-THF ring moiety in **1** had good agreement with those of the *threo/cis/threo* model. Thus, the relative stereochemistry of **1** was concluded to be *threo/cis/threo* between C-15/C-16, C-16/C-19 and C-19/C-20. To



R	Compound	$MH^+/M(Ac)_3$ $+/M(TMSi)_3^+$	A	B	C	D	E
H (cims)	**1**	581,563(a), 545(a),527(a)		311,293(a), 275(a)	269,251(a)	381,363(a), 345(a)	
H (cims)	**2**	581,563(a), 545(a),527(a)	141,123(a)	311,293(a), 275(a)	269,251(a)*	381,363(a), 345(a)	199
Ac (eims)	**1a**	706,646(b), 586(b),526(b)	183	395*,335(b)*, 275(b)*	311,251(b)	465,405(b), 345(b)	241,181(b)
Ac (eims)	**2a**	706,646(b), 586(b),526(b)	183*	395*,335(b)*, 275(b)*	311,251(b)	465,405(b), 345(b)	241*,181(b)*
TMSi (cims)	**1b**	796,706(c), 616(c),526(c)	231,123(c)	455,365(c), 275(c)	341,251(c)	525,435(c), 345(c)	271,181(c)
TMSi (eims)	**2b**	616(c),526(c), 796,706(c))	231,123(c)	455,365(c), 275(c)	341,251(c)	525,435(c), 345(c)	271,181(c)

Figure 1. Diagnostic cims and eims fragment ions of **1** and **2** and their triacetates (**1a**, **2a**) and tri-TMSi derivatives (**1b**, **2b**). (a): loss of H_2O(*m/z* 18) ; (b): loss of HAc(*m/z* 60) ; (c): loss of TMSi-OH(*m/z* 90)). Ions indicated with an asterisk(*) were not observed.

determine the absolute stereochemistry of C-4, C-15 and C-20 in **1**, its tri-(*R*)- and -(*S*)- methoxytrifluoromethyl phenyl acetic acid (MTPA) esters (Mosher esters) (**1r** and **1s**) were prepared. Rieser *et al.* have reported the determination of the absolute configuration of stereogenic carbinol centers in several Annonaceous acetogenins using advanced Mosher ester methodology.[12] ^{1}H-^{1}H COSY analyses of these Mosher ester derivatives were then performed. The ^{1}H-NMR chemical shift data of **1r** and **1s** showed that the absolute configuration at both C-4 and C-15 is *R* and that at C-20 is *S* (Table 2). Therefore, compound **1** was assigned as 16,19-*cis*-murisolin having the absolute configuration of C-15*R* and C-20*S*. Hoye *et al.* synthesized (+)-*SS* (like) and (±)-*RS* (unlike) model butenolides[13] and assigned the relative configuration between C-4 and C-34 in these models by observing the magnitudes of the Δδ values for the ^{1}H and ^{19}F nuclei in their Mosher esters.[14] The $\Delta\delta_H$ values for H-33 and H-34 in **1r** and **1s**, 0.25 and 0.05, suggested that **1** has the 4*R*, 34*S* configuration, as is usual. The absolute configuration of **1** is C-20*S*, C-19*S*, C-16*R*, C-15*R*, C-4*R* and C-34*S*.



2	2a	2b	2r	2s	A	B
H	Ac	TMSi	(*r*)-MTPA	(*s*)-MTPA	*erythro* or *threo*	*threo* or *erythro*

Compound **2** (80 mg), mp 83-84 °C, $[\alpha]_D$ +17.0° ($CHCl_3$, c=0.1), UV λmax MeOH (nm) 226 (log ε =3.02), was isolated as a colorless powder. A molecular ion peak at *m/z* 581 in the CIMS (isobutane) spectrum of **2** (Figure 2) once again indicated a molecular weight of 580. The HRCIMS (isobutane) spectrum showed an exact mass peak at *m/z* 581.4775, which matched the molecular formula $C_{35}H_{64}O_6$ (calcd 581.4781). The IR, UV and MS spectra of **2** and its triacetate and TMSi-derivatives (Figure 1) were quite similiar to those of **1** and **3**, suggesting that **2** was another diastereomer of **1** and **3**. The relative configuration of the mono-THF ring moiety was defined as having the *erythro/trans/threo* pattern by the analysis of the usual diagnostic ^{1}H- and ^{13}C-NMR chemical shifts in the spectra of **2** (Table 1).[11,15] In an attempt to determine the absolute configuration of the carbinol centers in **2**, its tri-(*R*)- and -(*S*)-MTPA esters, **2r** and **2s**, were prepared, and ^{1}H-^{1}H COSY analyses

Table 2. ^{1}H-NMR Chemical Shifts for the Determination of the Absolute Configuration at C-4,C-15 and C-20 of the Tri (*R*)- and (*S*)- MTPA Esters (**1r**, **1s**, **2r** and **2s**) of **1** and **2**

MTPA ester	5-Hab	4-H	3-Hab	33-H	34-H	35-H	14-Hab	15-H	16-H	17-Hab	18-Hab	19-H	20-H	21-Hab
1r	1.56	5.38	2.60	6.97	4.91	1.31	1.30	5.08	3.88	1.44	1.32	4.10	4.91	1.68
	1.64		2.68				1.35			1.54	1.82			1.72
1s	1.63	5.31	2.58	6.72	4.86	1.28	1.33	5.08	3.87	1.34	1.36	4.11	4.92	1.66
	1.69		2.58				1.40			1.46	1.82			1.70
δ1s-1r	+0.07	*R*[a]	-0.02	-0.25	-0.05	-0.03	+0.03	*R*[a]	-0.01	-0.10	+0.04	+0.01	*S*[a]	-0.02
	+0.05		-0.10				+0.05			-0.08	0.00			-0.02
2r	1.56	5.38	2.59	6.97	4.91	1.31	1.35[b]	4.97[c]	3.75[d]	1.50[e]	1.69[e]	3.99[d]	5.27[c]	1.60[b]
	1.65		2.68				1.40			1.86	1.85			1.57
2s	1.63	5.32	2.58	6.72	4.86	1.28	1.60[f]	5.02[g]	3.93[h]	1.52[i]	1.70[i]	3.94[h]	5.22[g]	1.52[f]
	1.69		2.58				1.62			1.89	1.74			1.47
δ2s-2r	+0.07	*R*[a]	-0.01	-0.25	-0.05	-0.03	+0.25	*R*[a]	+0.17	+0.02	0.00	-0.05	*S*[a]	-0.08
	+0.04		-0.10				+0.22			+0.03	-0.11			-0.10

[a] Absolute configuration.

were made (Table 2). Protons of the mono-THF ring itself, *i.e.*, at H-16, Hab-17, Hab-18 and H-19, could not be determined stereochemically because these protons had shielding effects of the phenyl groups of both flanking MTPA esters due to the coplanarity of the *erythro/trans/threo* relationship in **2**. The ^{1}H NMR regions of Hab-14 and Hab-21, H-15 and H-20, H-16 and H-19, and Hab-17 and Hab-18 could not be, respectively, differentiated in **2**, **2a**, **2s**, and **2r**. However, the chemical shifts of H-15 and H-20 of the tri-(*R*)-MTPA ester (**2r**) of **2** were in good agreement with those of *erythro,threo,trans*-(2*R*,5*R*)-di-(1-hydroxypentyl)-tetrahydrofuran, rather than *erythro,threo,trans*-(2*S*,5*S*)-di-(1-hydroxypentyl)-tetrahydrofuran, which are model compounds made by Shimada *et al.*[16] Since the mirror image of 15*S* and 20*R* is possible, this ambiguity still remains. The absolute configuration between C-4 and C-34 in **2** was the same as that in **1**. Consequently, the structure of **2** was determined to be the same as murisolin (**3**) except that **2** has the *erythro* configuration between C-19 and C-20 or C-15 and C-16, and **2** was named murisolin A.

Table 3. Brine Shrimp Lethality and Cytotoxicities in Human Solid Tumor Cell Lines for **1-3**.

Compound	BST[a] LC_{50}(μg/ml)	A-549[b] ED_{50}(μg/ml)	MCF-7[c] ED_{50}(μg/ml)	HT-29[d] ED_{50}(μg/ml)	A-498[e] ED_{50}(μg/ml)	PC-3[f] ED_{50}(μg/ml)	MIA PaCa-2[g] ED_{50}(μg/ml)
1	3.46×10^{-1}	3.41×10^{-3}	1.58×10^{-2}	1.27	4.16	1.42	1.53×10^{-2}
2	1.83×10^{-1}	3.16×10^{-6}	5.40	1.06×10^{-8}	6.67×10^{-2}	8.41	5.18×10^{-2}
3	2.07×10^{-1}	5.90×10^{-8}	3.15	6.58×10^{-8}	1.09×10^{-9}	2.36	1.50×10^{-3}
Adriamycin[h]	NT	3.99×10^{-3}	4.20×10^{-1}	2.43×10^{-2}	2.26×10^{-3}	3.49×10^{-2}	1.36×10^{-3}

NT : Not tested. [a]Brine shrimp lethality test.[7] [b]Human lung carcinoma.[17a] [c]Human breast carcinoma.[17b] [d]Human colon adenocarcinoma.[17c] [e]Human kidney carcinoma.[17a] [f]Human prostate adenocarcinoma.[17d] [g]Human pancreatic carcinoma.[17e] [h]Positive control standard.

Bioactivity data obtained with **1-3** are summarized in Table 3. All of these acetogenins were toxic to the brine shrimp larvae and showed potent cytotoxicities against six human solid tumor cell lines in culture. Selectivities in **2** and **3**, with activities sometimes over one-million times that of adriamycin, were exhibited for the lung carcinoma (A-549), colon adenocarcinoma (HT-29), and kidney carcinoma (A-498). **1-3** showed quite similiar activity for the BST, but the *trans* mono-THF configuration appears to be more active and selective than the *cis* one across the human tumor cell lines, *i.e.*, A-549, HT-29 and A-498. 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.[18]

Acknowledgments

This investigation was supported in part by R01 grant no. CA30909 from the National Cancer Institute, National Institute of Health. Mi Hee Woo gratefully acknowledges the support of the Taegu Hyosung Catholic University for the sabbatical leave. Thanks are due to the Cell Culture Laboratory, Purdue Cancer Center, for cytotoxicity testing, and to Neal Peterson of the Paw Paw Foundation for the collection of seeds.

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(*Received in USA* 17 *February* 1995; *accepted* 20 *April* 1995)