Journal of Natural Products
Vol. 58, No. 6, pp. 902-908, June 1995

MURICATOCINS A AND B, TWO NEW BIOACTIVE MONOTETRAHYDROFURAN ANNONACEOUS ACETOGENINS FROM THE LEAVES OF *ANNONA MURICATA*

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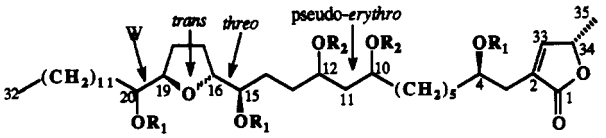
ABSTRACT.—The leaves of *Annona muricata* have yielded the novel monotetrahydrofuran Annonaceous acetogenins, muricatocins A [**1**] and B [**2**]. Each compound possesses five hydroxyl groups, with two hydroxyl groups at the C-10 and C-12 positions. The absolute configurations of **1** and **2** (except for positions C-10 and C-12) were determined by Mosher ester methodology. The C-10, C-12 acetonides (**1c**, **2c**) suggested relative stereochemistry and significantly enhanced cytotoxicity against the A-549 human lung tumor cell line. Three known monotetrahydrofuran acetogenins, annonacin A, (2,4-*trans*)-isoannonacin, and (2,4-*cis*)-isoannonacin, were also found.

Annona muricata L. (Annonaceae) is a small tropical fruit tree named "guanabana" or "sour sop." The seeds and bark have previously yielded a number of cytotoxic and pesticidal monotetrahydrofuran (mono-THF) acetogenins as well as their precursors or metabolites (1–9). In our previous work, eight mono-THF acetogenins have been reported from the leaves of *Annona muricata* (10). In the present investigation, the leaves have yielded two new mono-THF acetogenins, named muricatocins A [**1**] and B [**2**]; the known mono-THF acetogenins, annonacin A, (2,4-*trans*)-isoannonacin, and (2,4-*cis*)-isoannonacin, were also isolated from the leaves, with the latter two compounds having been previously isolated as the cis/trans-mixture from the seeds of this species (5).

As reported previously, powdered leaves of *A. muricata* were extracted with 95% EtOH, and the residue of the extract (F001) was partitioned through a standard extraction scheme (10). A test for lethality to brine shrimp larvae (BST) (11,12) determined the most active partition fraction (F005, BST, LC_{50} value of 0.17 mg/ml), and flash chromatography over Si gel gave an active fraction (No. 129) which was subjected to repeated flash chromatography and hplc to yield compounds **1** and **2**. The known compounds were isolated from other active fractions (Nos. 86–127) using similar methods.

Muricatocins A [**1**] and B [**2**] were obtained as colorless amorphous powders. The ms and nmr spectra indicated that **1** and **2** are mono-THF ring acetogenins (1–4, 6–9) (Figure 1). The hrfabms gave $[M+H]^+$ ions at *m/z* 613.4685 [**1**] and 613.4661 [**2**] (calcd 613.4679) consistent with the same molecular formula of $C_{35}H_{64}O_8$. Both **1** and **2** showed a broad OH stretching absorption in the ir spectrum at 3250–3550 cm^{-1}. Five successive losses of H_2O (*m/z* 18) from the $[M+H]^+$ from **1** and **2** in the cims (*m/z* 595, 577, 559, 541, and 523) showed the existence of five OH groups, and these were confirmed by the formation of pentaacetates (**1a** and **2a**) and penta-trimethylsilyl (TMSi) ethers (**1b** and **2b**). Compounds **1a** and **2a** gave five singlet proton peaks at δ 2.02–



Compound	W	R_1	R_2
1	threo	H	H
1a	threo	Ac	Ac
1b	threo	TMSi	TMSi
1c	threo	H	Acetonide
1s	threo	(*S*)-MTPA	(*S*)-MTPA
1r	threo	(*R*)-MTPA	(*R*)-MTPA
2	erythro	H	H
2a	erythro	Ac	Ac
2b	erythro	TMSi	TMSi
2c	erythro	H	Acetonide
2s	erythro	(*S*)-MTPA	(*S*)-MTPA
2r	erythro	(*R*)-MTPA	(*R*)-MTPA

FIGURE 1. Structures of muricatocins A [**1**], B [**2**], and their derivatives (**1a–c**, **1s**, **1r**, **2a–c**, **2s**, **2r**).

2.08 (Table 1). The positions of the OH groups in **1** and **2** were assigned at C-4, C-10, C-12, C-15, and C-20 by careful analysis of the fragments in the eims spectra of the TMSi derivatives (**1b** and **2b**) at *m/z* 701, 631, 503, 573, 385, 341, 271, and 213 (Figure 2). The placement of the mono-THF ring in each compound was determined to be at C-16, C-19 by the diagnostic fragments at *m/z* 701, 631, 631, 341, and 271 (TMSi-eims).

The mono-THF ring, with the usual flanking OH groups on each side, was indicated in **1** and **2** by ^{1}H-nmr chemical shifts (Table 1) at δ 3.45 (H-15), 3.85 (H-16), 3.87 (H-19), and 3.46 (H-20) for **1**, and at δ 3.45 (H-15), 3.85 (H-16), 3.80 (H-19), and 3.89 (H-20) for **2**: the ^{13}C-nmr signals (Table 1) at δ 74.39 (C-15), 82.69 (C-16), 82.45 (C-19), and 74.03 (C-20) for **1**, and at δ 74.61 (C-15), 82.96 (C-16), 82.21 (C-19), 71.52 (C-20) for **2**, likewise suggested this functionality. However, the configurations of the hydroxyls at C-10, C-12 were the same in **1** and **2**. For **1** and **2**, the carbinol protons at C-10, C-12 resonated at δ 3.94 and 3.86, and the corresponding ^{13}C-nmr signals were at δ 72.82 (C-10) and 72.60 (C-12) for **1**, and at δ 72.87 (C-10) and 72.63 (C-12) for **2**. The chemical shifts of H-4 and C-4 in **1** and **2** were identically located at δ 3.81 and δ 69.90, respectively.

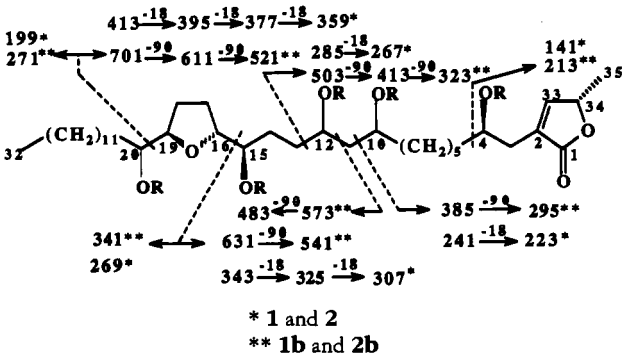


FIGURE 2. Diagnostic eims fragment ions (*m/z*) of **1** and **2** (R=H) and their penta-TMSi derivatives, **1b** and **2b** (R=MeSi).

TABLE 1. ^{1}H-Nmr Spectral Data for **1**, **2**, **1a**, **2a**, **1c**, and **2c**, and ^{13}C-Nmr Data for **1** and **2** ($CDCl_3$, δ).

Position	^{1}H Nmr (coupling in Hz)						^{13}C Nmr	
	1	**2**	**1a**	**2a**	**1c**	**2c**	**1**	**2**
1	—	—					174.62	174.65
2	—	—					131.15	131.15
3a	2.40 m	2.41 m	2.52 m	2.52 m	2.40 m	2.41 m	33.37	33.37
3b	2.50 m	2.51 m	2.55 m	2.55 m	2.50 m	2.51 m		
4	3.81 m	3.81 m	5.09 m	5.09 m	3.81 m	3.81 m	69.90	69.90
5–9	1.25–1.61 m	1.25–1.61 m	1.25–1.61 m	1.25–1.61 m	1.25–1.61 m	1.25–1.61 m	22–34	22–34
10	3.94 m	3.94 m	5.02 m[a]	5.02 m[b]	3.96 m[c]	3.96 m[d]	72.82	72.87
11	2.00 m	2.01 m	1.96 m	1.98 m	2.02 m	2.03 m	42.94	42.95
12	3.86 m	3.86 m	5.08 m[a]	5.08 m[b]	3.99 m[c]	3.99 m[d]	72.60	72.63
13–14	1.25–1.61 m	1.25–1.61 m	1.25–1.61 m	1.25–1.61 m	1.25–1.61 m	1.25–1.61 m	22–34	22–34
15	3.45 m	3.45 m	4.85 m	4.85 m	3.41 m	3.41 m	74.39[e]	74.61[h]
16	3.85 m	3.85 m	3.95 m	3.95 m	3.86 m	3.88 m	82.69[f]	82.96[i]
17–18	1.57–2.00 m	1.57–2.00 m	1.57–2.00 m	1.57–2.00 m	1.57–2.00 m	1.57–2.00 m	22–34	22–34
19	3.87 m	3.80 m	3.95 m	3.95 m	3.88 m	3.80 m	82.45[f]	82.21[i]
20	3.46 m	3.89 m	3.94 m	4.92 m	3.48 m	3.90 m	74.03[e]	71.52[h]
21–31	1.25–1.61 m	1.25–1.61 m	1.25–1.61 m	1.25–1.61 m	1.25–1.61 m	1.25–1.61 m	22–34	22–34
32	0.88 t (7.0)	0.88 t (7.0)	0.88 t (7.0)	0.88 t (7.0)	0.88 t (7.0)	0.88 t (7.0)	14.10	14.11
33	7.19 d (1.5)	7.19 d (1.5)	7.09 d (1.5)	7.09 d (1.5)	7.19 d (1.5)	7.19 d (1.5)	151.83	151.89
34	5.07 dq (1.5,7.0)	5.07 dq (1.5,7.0)	5.01 dq (1.5,7.0)	5.01 dq (1.5,7.0)	5.06 dq (1.5,7.0)	5.06 dq (1.5,7.0)	78.00	78.01
35	1.43 d (7.0)	1.43 d (7.0)	1.39 d (7.0)	1.39 d (7.0)	1.43 d (7.0)	1.43 d (7.0)	19.10	19.10
4-OAc			2.03 s	2.03 s				
10-OAc			2.04 s	2.05 s				
12-OAc			2.04 s	2.04 s				
15-OAc			2.08 s	2.08 s				
20-OAc			2.07 s	2.04 s				
Me[j]					1.38 s	1.38 s		
Me[j]					1.42 s	1.42 s		

[a–d]Assignments are interchangeable.
[j]Acetonide methyls.

These structural units were further confirmed by COSY and single-relayed COSY nm data in which the proton coupling correlations from (H-3)↔(H-4) and (H-10 and H-12)↔(H-8, H-9, H-11, and H-13), and (H-15 and H-20)↔(H-13, H-14, H-16, H-17, H-18, H-19, H-21, and H-22) (Table 1) could be clearly seen. The assignments of the relative stereochemistries around the mono-THF rings of **1** and **2** were determined using the methodology of Hoye and co-workers (13,14) and Born *et al.* (15), as well as by comparison with several acetogenins having the erythro configuration at C-19 to C-20, including annomuricins A and B (10), annonacin A (16), (2,4-*cis* and *trans*)-annonacin-A-one (17), and jetein (18) (Table 2). In **1** and **2**, the OH-substituted CH centers, at C-15 and C-20, flanking the ring region (C-16 to C-19), gave very similar chemical shifts in the ^{1}H- and ^{13}C-nmr spectra as with the above models (Table 1); the stereochemistries of C-15, C-16 and C-19, C-20 were concluded to be threo and threo for **1**, and threo and erythro for **2**, respectively, and the stereochemistry is trans for the THF ring in each compound (13,14). The relative stereochemistries

TABLE 2. ^{1}H-Nmr Chemical Shifts for the Determination of the Absolute Configuration at C-4 of the Penta (*S*)- and (*R*)-MTPA Esters of **1** and **2**.

MTPA ester of	H_2C-5	HC-4	H_2C-3		HC-33	HC-34	H_3C-35	Configuration
1s δ (*S*)	1.59	5.28	2.57	2.52	6.73	4.86	1.27	4*R*
1r δ (*R*)	1.58	5.34	2.65	2.56	6.95	4.90	1.29	
Δδ	+0.01	−0.06	−0.08	−0.04	−0.24	−0.04	−0.02	
2s δ (*S*)	1.57	5.28	2.57	2.52	6.72	4.85	1.27	4*R*
2r δ (*R*)	1.56	5.35	2.65	2.56	6.95	4.89	1.29	
Δδ	+0.02	−0.07	−0.08	−0.04	−0.23	−0.04	−0.02	

around the mono-THF ring were confirmed by comparing the ^{1}H-nmr spectra of the acetates (**1a** and **2a**, Table 1) with those of model compounds of known relative stereochemistry (13,15). The proton signals, for H-15 at δ 3.45 and H-20 at δ 3.46 in **1**, and for H-15 at δ 3.45 and H-20 at δ 3.80 in **2**, were shifted downfield in **1a** to δ 4.85 for H-15 and δ 3.94 for H-20 and in **2a** to δ 4.85 for H-15 and δ 4.92 for H-20.

To determine the configurations at C-10 and C-12, the acetonide (dioxolane) derivatives, **1c** and **2c**, of **1** and **2** were prepared. The ^{1}H-nmr signals for H-10 and H-11 of threo and erythro vicinal diols have been reported previously in other Annonaceous acetogenins (10, 19–21). When the configuration of such a vicinal diol is erythro, the methyls in the resulting acetonide show two separate ^{1}H-nmr singlets (10,21). Thus, a cis configuration of the acetonide, for example, at C-10, C-11, could only be derived from a vicinal diol with an erythro configuration, and the configuration of C-10 and C-11 can be deduced as either being *S* and *R* or *R* and *S* (10). Although the acetonides **1c** and **2c** possess six carbons in their dioxolane rings, they are, nevertheless, analogous with the C-10, C-11 acetonides that bear five carbons in their dioxolane rings. The ^{1}H-nmr signals for H-10 and H-12 in **1c** and **2c**, at δ 3.96 and 3.99, and for their acetonyl methyls, at δ 1.42 and 1.38 (Table 1), showed two separate singlet peaks, respectively, and consequently, a cis configuration was suggested for the dioxolane ring in **1c** and **2c**. The configurations of the hydroxyls at C-10 and C-12 were concluded to be pseudo-erythro and, thus, either *S*, *R* or *R*,*S*. Application of ^{13}C-nmr methods, using a ^{13}C-acetonide across the 1,3-diol, would perhaps have been more conclusive than using the chemical shifts of the acetonyl methyl protons (22).

Our group has reported the determination of the absolute configuration of stereogenic carbinol centers in several Annonaceous acetogenins using Mosher ester methodology (6,23). Thus, the (*S*)- and (*R*)-methoxytrifluoromethyl phenylacetic acid (MTPA) esters (Mosher esters) of **1** and **2** were prepared and numbered **1s**, **1r** and **2s**, **2r**. ^{1}H-Nmr COSY analyses of these derivatives were then performed. The ^{1}H-nmr chemical shift data of **1s**, **1r**, **2s**, and **2r** showed that the absolute configuration at C-4 of **1** and **2** is *R* (Table 2). This result is identical to all acetogenins examined so far that possess an OH at C-4.

Similarly, the Mosher ester data (Table 3) allowed the absolute stereochemical assignments of the carbinol centers adjacent to the mono-THF ring as C-15*R* in **1** and **2** and as C-20*R* in **1** and C-20*S* in **2**. The assignment of the absolute stereochemistry of the asymmetric carbinol centers at C-10, C-12 of **1** and **2** could not be achieved by direct application of the Mosher ester method because of their close proximities.

Muricatocins A and B [**1** and **2**] were significantly bioactive in the BST and were also cytotoxic (seven-day MTT assays) to human solid tumor cell lines in culture (Table 4). In comparison with annonacin (5), **1** and **2** have one addi-

TABLE 3. ^{1}H-Nmr Chemical Shifts for the Determination of the Absolute Configurations at C-15 and C-20 of the Penta (*S*)- and (*R*)-MTPA Esters of **1** and **2**.

MTPA ester of	H_2C-14	HC-15	HC-16	H_2C-17/18	HC-19	HC-20	H_2C-21	Configuration
1s δ (*S*)	1.53	5.18	3.88	1.85	3.88	4.83	1.51	15*R*
	1.46			1.65			1.43	20*R*
1r δ (*R*)	1.48	5.26	3.98	1.82	3.94	4.93	1.54	
	1.42			1.56			1.47	
Δδ	+0.05	−0.08	−0.10	+0.03	−0.06	−0.10	−0.03	
	+0.04			+0.09			−0.04	
2s δ (*S*)	1.53	5.18	3.89	1.86	3.89	5.01	1.51	15*R*
	1.46			1.65			1.43	20*S*
2r δ (*R*)	1.48	5.25	3.96	1.83	3.69	4.90	1.54	
	1.42			1.57			1.47	
Δδ	+0.05	−0.07	−0.07	+0.03	+0.20	+0.11	−0.03	
	+0.04			+0.08			−0.04	

TABLE 4. Bioactivity of **1** and **2** and Their Acetonide Derivatives (**1c** and **2c**).

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)
1[e]	6.99×10^{-1}	7.55×10^{-2}	1.23×10^{-1}	1.56
2[e]	5.57×10^{-1}	3.34×10^{-1}	1.03×10^{-1}	1.66
1c[f]	2.06×10^{-1}	3.67×10^{-3}	1.65×10^{-1}	5.08×10^{-1}
2c[f]	2.66×10^{-1}	7.18×10^{-3}	8.78×10^{-1}	>1.0
Adriamycin[e,g]	—	3.56×10^{-3}	1.42×10^{-1}	3.01×10^{-2}

[a]Brine shrimp lethality test (11,12).
[b]Human lung carcinoma (26).
[c]Human breast carcinoma (27).
[d]Human colon adenocarcinoma (28).
[e,f]Same cytotoxicity runs; values in different runs were within one order of magnitude of each other.
[g]Positive control standard.

tional OH group, but their cytotoxic effects to these tumor cell lines are notably reduced (5,19). However, if a second ring were to be formed, using the 1,3-diol groups in **1** and **2**, the cytotoxicities of the resultant bis-ring products would likely increase because the bis-THF compounds almost always are more bioactive than the mono-THF acetogenins (19,20,24,25). This trend was substantiated by the acetonides (**1c** and **2c**), which were onefold to threefold more cytotoxic against the lung cell line (A-549) and three times more toxic in the BST than were **1** and **2** (Table 4). The presence of the second ring seems to account for the increased bioactivities. The similar susceptibilities of the cell lines to **1**, **2** and **1c**, **2c**, respectively, (Table 4) suggests that the stereochemistry at C-20 does not play a significant role in controlling selectivity toward specific cell lines and tumor types. All of the Annonaceous acetoginins act, at least in part, as potent inhibitors of complex I in mitochondria (24,25).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—As described previously (10).

PLANT MATERIAL.—As described previously (10).

EXTRACTION AND ISOLATION.—Steps for extraction and chromatographic fractionation were identical to those reported previously (10). The EtOH extract of the leaves (20 kg) gave a bioactive aqueous MeOH fraction (F005) which was separated, by gradient elution over a large Si gel column, to afford fraction Nos. 1–154 (10). The BST active fraction No. 129 (BST, LC_{50}=1.80 μg/ml) was further subjected to repeated flash chro-

matography to yield crude compounds **1** and **2**; each was then purified with hplc over Si gel, eluted by hexane-MeOH (90:1, flow rate 10 ml/min), to afford the two colorless, amorphous powders **1** and **2**. Three additional mono-THF acetogenins were isolated from other fractions (Nos. 86–127) using similar methods and were identified as annonacin A, (2,4-*trans*)-isoannonacin, and (2,4-*cis*)-isoannonacin (19,20).

Muricatocin A [**1**].—White powder (9 mg); $[\alpha]^{22}D$ +21.8° (*c*=0.001, EtOH); hrfabms (glycerol) *m/z* $[M+H]^+$ 613.4685 for $C_{35}H_{65}O_8$ (calcd 613.4679); cims (*n*-BuOH) *m/z* 613 (36), 595 (19), 577 (23), 559 (23), 541 (10), 523 (2), 413 (1), 395 (1), 377 (2), 359 (3), 353 (9), 343 (2), 325 (11), 285 (5), 271 (3), 269 (5), 241 (57), 223 (9), 205 (7), 199 (7), and 141 (11); eims *m/z* 325 (15), 307 (15), 269 (2), 241 (26), 223 (3), 213 (3), 199 (3), 141 (6); ^{1}H- ($CDCl_3$, 500 MHz) and ^{13}C-nmr ($CDCl_3$, 125 MHz) data, see Table 1; ir (film) ν max 3433 (br OH), 2920, 2851, 1747, 1466, 1321, 1076 cm^{-1}; uv (MeOH) λ max (ϵ) 216 (8.5×10^3) nm; acetonide [**1c**], ^{1}H-nmr data, Table 1; per-MTPA-esters (**1s** and **1r**), pertinent ^{1}H-nmr data, see Tables 3 and 4.

Muricatocin B [**2**].—White powder (8 mg); $[\alpha]^{22}D$ +62.5° (*c*=0.001); hrfabms (glycerol) *m/z* $[M+H]^+$ 613.4694 for $C_{35}H_{65}O_8$ (calcd 613.4679); cims *m/z* $[M+H]^+$ 613 (11), 595 (9), 577 (20), 559 (29), 541 (11), 523 (3), 413 (1), 395 (1), 377 (3), 359 (3), 343 (2), 325 (7), 285 (4), 271 (3), 269 (6), 267 (18), 253 (3), 241 (63), 223 (6), 205 (6), 199 (4); eims *m/z* 413 (2), 377 (6), 359 (13), 343 (5), 325 (99), 307 (92), 285 (2), 269 (14), 253 (5), 241 (100), 223 (9), 213 (3), 199 (2), 141 (8); ^{1}H-($CDCl_3$, 500 MHz), and ^{13}C-nmr ($CDCl_3$, 125 MHz) data, see Table 1; ir (film) ν max 3416 (br OH), 2920, 2850, 1744, 1467, 1322, 1075 cm^{-1}; uv (MeOH) λ max (ϵ) 214 (9.5×10^3) nm; acetonide [**2c**], ^{1}H-nmr data, see Table 1; per-MTPA-esters (**2s** and **2r**), pertinent ^{1}H-nmr data, see Tables 3 and 4.

TMSi DERIVATIZATIONS.—Samples of 1 mg of **1** or **2** yielded the respective penta-TMSi derivatives (**1b** and **2b**) (10); eims of **1b** *m/z* 701 (1), 631 (4), 611 (4), 573 (1), 541 (11), 521 (2), 503 (1), 483 (2), 413 (2), 385 (40), 341 (9), 323 (1), 295 (6), 271 (23), 213 (10); eims of **2b** *m/z* 701 (2), 631 (5), 611 (5), 573 (1), 541 (10), 521 (5), 503 (1), 483 (3), 413 (2), 385 (68), 341 (16), 323 (1), 295 (8), 271 (42), 213 (14).

ACKNOWLEDGMENTS

This work was supported, in part, by R01 grant No. CA 30909 from the National Cancer Institute, NIH. One of the authors, F.-E. Wu (Chengdu Institute of Biology, the Chinese Academy of Sciences, People's Republic of China), gratefully acknowledges the support of the K.C. Wang Education Foundation, Hong Kong. The plant material was collected with travel support from the Indonesian University Development Projects, which were financed by the World Bank.

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Received 23 August 1994