cis-Monotetrahydrofuran Acetogenins from the Roots of *Annona muricata*[1]

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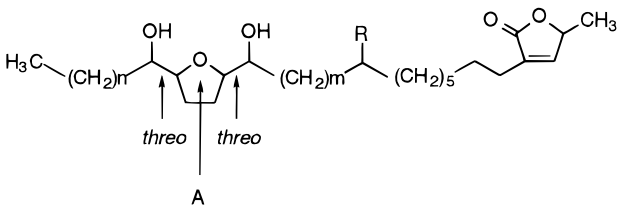
Phytochemical investigation of roots of *Annona muricata* led to the identification of seven mono-tetrahydrofuran (mono-THF) acetogenins. Six new acetogenins having the unusual *cis*-configuration of the THF ring, *cis*-solamin (**1**), *cis*-panatellin (**2**), *cis*-uvariamicin IV (**3**), *cis*-uvariamicin I (**4**), *cis*-reticulatacin (**5**), and *cis*-reticulatacin-10-one (**6**) were identified, in addition to a known compound, solamin.

Acetogenins of the Annonaceae possess a broad biological spectrum, including cytotoxic, antiparasitic, insecticide, and immunosuppressive activities.[2] Intensive chemical investigation of the seeds and leaves of *Annona muricata* L., a well-known tropical fruit tree named " sour sop " or " guanabana ",[3] has led to the identification of more than 45 acetogenins.[2] In the course of our search of bioactive acetogenins in the roots of this species, several biogenetic precursors have been isolated and identified, namely, montecristin,[4] cohibins A and B,[5] and muridienins 1 and 2.[6] Further investigation of the roots has led to the identification of seven mono-tetrahydrofuran (mono-THF) acetogenins. One corresponded to the well-known solamin, a C_{35} mono-THF acetogenin previously isolated from the seeds of *Annona muricata*;[7] the other six are new, having the unusual cis configuration of THF ring acetogenins.[8,9] By considering their relative configuration, these new compounds has been named *cis*-solamin (**1**), *cis*-panatellin (**2**), *cis*-uvariamicin IV (**3**), *cis*-uvariamicin I (**4**), *cis*-reticulatacin (**5**), and *cis*-reticulatacin-10-one (**6**), respectively.



	m	n	R	A
Solamin	4	11	H	*trans*
cis-Solamin (**1**)	4	11	H	*cis*
cis-Panatellin (**2**)	2	13	H	*cis*
cis-Uvariamicin IV (**3**)	2	15	H	*cis*
cis-Uvariamicin I (**4**)	4	13	H	*cis*
cis-Reticulatacin (**5**)	6	11	H	*cis*
cis-Reticulatacin-10-one (**6**)	6	11	O	*cis*

Results and Discussion

The dried and powdered roots of *A. muricata* were extracted with MeOH. The MeOH extract, after concentration under vacuum, was partitioned between H_2O and CH_2Cl_2. The organic layer was dried and submitted to successive fractionations by column chromatography. Final semipreparative HPLC led to the isolation of **1**, **2**, **3**, and **6** as pure compounds and to **4** and **5** as an unresolvable mixture. Study of the spectroscopic data (UV, IR, MS, and NMR) of **1**−**6** suggested that all these compounds belong to the A1a group, characterized by one THF ring and an α,β-unsaturated γ-methyl-γ-lactone.[2]

Table 1. NMR Assignments for Compounds **1** and **2**

	1			**2**	
position	$^1H^a$	^{13}C	position	$^1H^b$	^{13}C
1		173.8	1		173.9
2		134.3	2		134.2
3	2.25 t	25.1	3	2.25 t	25.1
4	1.55 m	27.4	4	1.55 m	27.4
5−13	1.24−1.40	25.7−29.7	5−11	1.25−1.39	25.7−29.8
14	1.46 m	34.0	12	1.46 m	34.1
15	3.41 m	74.3	13	3.41 m	74.3
16	3.81 m	82.8	14	3.81 m	82.7
17a, 18a	1.74m	28.1	15a, 16a	1.74m	28.1
17b, 18b	1.92m	28.1	15b, 16b	1.92m	28.1
19	3.81 m	82.8	17	3.81 m	82.7
20	3.41 m	74.3	18	3.41 m	74.3
21	1.46 m	34.0	19	1.46 m	34.1
22−29	1.24−1.40	25.7−29.7	20−29	1.24−1.40	25.7−29.8
30	1.26 m	31.9	30	1.26 m	31.9
31	1.26m	22.7	31	1.26m	22.7
32	0.88 t	14.1	32	0.88 t	14.1
33	6.98 d	148.8	33	6.98 d	148.8
34	4.99 dq	77.5	34	4.99 dq	77.5
35	1.41 d	19.2	35	1.41 d	19.2

[a] ^1H data ($CDCl_3$, δ) of **1**: $J_{3-4} = 7.1$ Hz; $J_{31-32} = 6.8$ Hz; $J_{33-34} = 1.5$ Hz; $J_{34-35} = 6.8$ Hz. [b] ^1H and data ($CDCl_3$, δ) of **2**: $J_{3-4} = 7.1$ Hz; $J_{31-32} = 6.7$ Hz; $J_{33-34} = 1.6$ Hz; $J_{34-35} = 6.8$ Hz.

The molecular weight of **1** was established as 564 by HRCIMS (methane) at *m/z* 565 (565.4828, calcd 565.4832 for $C_{35}H_{65}O_5$ $[MH]^+$), corresponding to the molecular formula $C_{35}H_{64}O_5$. The existence of two hydroxyl groups was indicated by two successive losses of H_2O from the molecular ion and by an IR absorption band centered at 3420 cm^{-1}. A weak UV λ_{max} at 217.2 nm for **1**, a strong IR absorption band at 1759 cm^{-1}, and resonances at δ 6.98 (H-33), 4.99 (H-34), 2.25 (H-3), 1.55 (H-4), and 1.41 (H-35) in the ^1H NMR spectrum, which correlated with resonances (HMQC, HMBC) at δ 173.8 (C-1), 148.8 (C-33), 134.3 (C-2), 77.5 (C-34), 27.4 (C-4), 25.1 (C-3), and 19.2 (C-35) in the ^{13}C NMR spectrum (Table 1), revealed the presence of an α,β-unsaturated γ-methyl-

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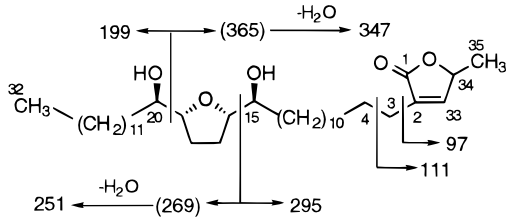

Figure 1. CIMS fragmentations of **1**. Values in brackets were not observed. Absolute configurations may be inverted.

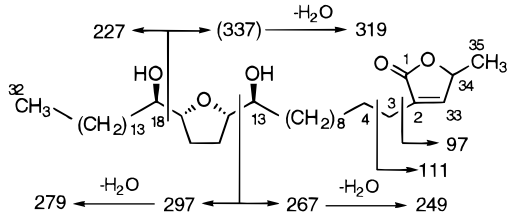

Figure 2. CIMS fragmentations of **2**. Value in brackets was not observed. Absolute configurations may be inverted.

γ-lactone.[2] The absence of a characteristic ABX system between the H-3 and H-4 protons suggested the lack of a hydroxyl group at C-4.[2] The presence of a mono-THF ring flanked by two OH groups was suggested by ^{1}H NMR and ^{13}C NMR resonances at δ 3.41 (H-15, H-20), 3.81 (H-16, H-19) and 74.3 (C-15, C-20), 82.8 (C-16, C-19), respectively, for **1**.

The proton assignments for **1** (Table 1) and the determination of the relative stereochemistry of the α,α' dihydroxylated THF moiety were made by detailed analysis of the ^{1}H$-^1$H and ^{1}H$-^{13}$C correlated 2D spectra (COSY, HMQC, HMBC) and by comparison with those of model compounds of known relative configuration.[10,11] These spectral data for the relative configuration between the vicinal hydroxylated carbons of the THF system indicated that **1** was threo. A close examination of the NMR spectra showed the proton resonances for the two methylene groups of the mono-THF ring, which were observed at δ 1.74 and 1.92 (H-17a, H-18a, and H-17b, H-18b), corresponding to the cis configuration, whereas signals at δ 1.66 and 1.98 indicated the trans configuration, according to Fujimoto et al.[11] Thus, the relative configuration of **1** was determined as threo/cis/threo. These stereochemical relationships were substantiated by the ^{13}C NMR signals for the oxygenated carbons of the THF subunit at δ 74.3 (C-15, C-20) and 82.8 (C-16, C-19) for **1**. Moreover, in the same fraction, we have isolated a compound that showed ^{1}H NMR, ^{13}C NMR, and MS spectra identical to those of an authentic sample of solamin isolated from the seeds of *A. muricata* in our laboratory.[7] Consequently, a close analysis of the spectral data of **1** and solamin showed the same molecular weight and fragmentation patterns in the MS (Figure 2) and identical resonances in the NMR spectra, except for H-17a, H-18a and H-17b, H-18b, thereby clearly suggesting that **1** is a diastereoisomer of solamin. This new acetogenin, named *cis*-solamin, exhibits unusual[8,9] threo/cis/threo relative stereochemical relationships among the chiral centers C-15/C-16, C-16/C-19, and C-19/C-20. It might be identical with the synthetic 15,16-di-*epi*-solamin, the spectral data of which were not precisely compiled.[12] Comparative analysis of the spectral data of **1** and **2** showed the same molecular weight and similar ^{1}H NMR and ^{13}C NMR spectra (Table 1),

Table 2. NMR Assignments for Compounds **3** and **4**

	3			**4**	
position	^{1}H[a]	^{13}C	position	^{1}H[b]	^{13}C
1		173.9	1		173.8
2		134.2	2		134.4
3	2.25 t	25.1	3	2.26 t	25.0
4	1.55 m	27.3	4	1.55 m	27.3
5−11	1.22−1.40	25.7−29.8	5−13	1.24−1.40	25.7−29.6
12	1.47 m	34.0	14	1.46 m	34.1
13	3.41 m	74.3	15	3.41 m	74.3
14	3.82 m	82.7	16	3.81 m	82.7
15a, 16a	1.75 m	28.1	17a, 18a	1.74 m	28.1
15b, 16b	1.92 m	28.1	17b, 18b	1.94 m	28.1
17	3.82 m	82.7	19	3.81 m	82.7
18	3.41 m	74.3	20	3.41 m	74.3
19	1.47 m	34.0	21	1.46 m	34.1
20−31	1.22−1.40	25.7−29.8	22−31	1.24−1.40	25.7−29.6
32	1.26 m	31.8	32	1.26 m	31.9
33	1.26m	22.6	33	1.26m	22.7
34	0.87 t	14.0	34	0.88 t	14.1
35	7.00 d	148.8	35	6.98 d	148.8
36	4.99 dq	77.3	36	4.99 dq	77.3
37	1.41 d	19.2	37	1.41 d	19.1

[a] ^{1}H data ($CDCl_3$, δ) of **3**: $J_{3-4} = 7.1$ Hz; $J_{33-34} = 6.7$ Hz; $J_{35-36} = 1.6$ Hz; $J_{36-37} = 6.8$ Hz. [b] ^{1}H data ($CDCl_3$, δ) of **4**: $J_{3-4} = 7.1$ Hz; $J_{33-34} = 6.9$ Hz; $J_{35-36} = 1.6$ Hz; $J_{36-37} = 6.8$ Hz.

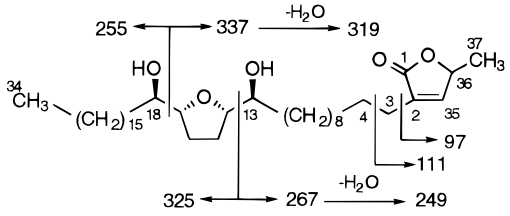

Figure 3. CIMS fragmentations of **3**. Absolute configurations may be inverted.

but differences in fragmentation patterns in the MS (Figure 2) permitted the location of the THF ring to be determined between C-13 and C-18 for **2**. These data suggested clearly that **2** is a regioisomer of **1**, which has been named *cis*-panatellin (*trans*-panatellin has not yet been isolated).

The molecular weights of **3** and the mixture, of **4** and **5** were established as 592 by HRCIMS (methane) at *m/z* 593 (593.5162 for **3** and 593.5154 for **4**+**5**, calcd. 593.5148 for $C_{37}H_{69}O_5$ $[MH]^+$), corresponding to the molecular formula $C_{37}H_{68}O_5$. NMR spectra (Table 2) of **3** and **4**+**5** were identical to those of **1** and **2**, suggesting that they were acetogenins of type A1a with a threo/cis/threo relative configuration. The fragmentation pattern observed in the CIMS and EIMS of **3** (Figure 3) demonstrated the THF ring location between C-13/C-18 as in uvariamicin IV,[13] a threo/trans/threo diastereoisomer. Therefore, compound **3** corresponds to *cis*-uvariamicin IV.

CIMS and EIMS of the combination **4** and **5** (Figure 4) showed that it was an unresolvable mixture of two regioisomers with the THF ring, respectively, between C-15/C-20 (fragmentations at *m/z* 295 and 297) for **4**, as in the corresponding diastereoisomer threo/trans/threo uvariamicin I,[13] and C-17/C-22 (fragmentations at *m/z* 323 and 269) for **5**, as in the threo/trans/threo reticulatacin.[14] Consequently, these new acetogenins were named *cis*-uvariamicin I and *cis*-reticulatacin, respectively. In the same way as for *cis*-solamin, *cis*-reticulatacin was synthesized as 17, 18-di-*epi*-reticulatacin without any NMR data.[12]

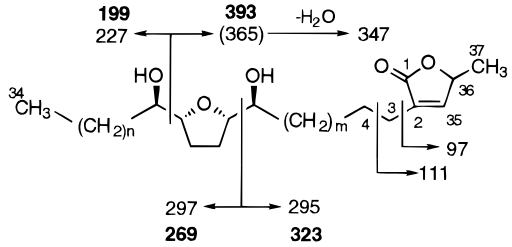

Figure 4. CIMS fragmentations of **4** ($n = 10$, $m = 11$) and **5** ($n = 12$, $m = 9$). Bold type refers to compound **5** only. Value in brackets was not observed. Absolute configurations may be inverted.

Table 3. NMR Assignments for Compound **6**

position	^{1}H[a]	^{13}C
1		173.8
2		134.2
3	2.26 t	25.1
4	1.55 m	27.1
5−7	1.25−1.30	25.1−29.7
8	1.57 m	23.6
9	2.38 m	42.7
10		211.4
11	2.38 m	42.7
12	1.57 m	23.6
13−15	1.25−1.30	25.1−29.7
16	1.49 m	34.0
17	3.42 m	74.3
18	3.81 m	82.7
19a, 20a	1.75 m	28.1
19b, 20b	1.93 m	28.1
21	3.81 m	82.7
22	3.42 m	74.3
23	1.49 m	34.0
24−31	1.25−1.30	25.1−29.7
32	1.26 m	31.7
33	1.26 m	22.6
34	0.88 t	14.0
35	6.99 d	148.8
36	4.99dq	77.4
37	1.41 d	19.2

[a] ^{1}H data ($CDCl_3$, δ) of **6**: $J_{3-4} = 7.1$ Hz; $J_{33-34} = 7.0$ Hz; $J_{35-36} = 1.6$ Hz; $J_{36-37} = 6.8$ Hz.

The molecular formula of **6** was established as $C_{37}H_{66}O_6$ by HRCIMS at *m/z* 607 (607.4926, calcd 607.4940 for $C_{37}H_{67}O_6$ $[MH]^+$). The NMR spectra of **6** (Table 3) are closely comparable to those for compounds **1**−**5**. Therefore, **6** is also an acetogenin of subtype A1a with the relative configuration threo/cis/threo. In addition, a chemical shift at δ 211.4 was observed in the ^{13}C NMR spectrum corresponding to the carbonyl group of a ketone, confirmed by a band at 1700 cm^{-1} in the IR spectrum. In the ^{1}H NMR spectrum, a system of four protons at δ 2.38 was attributed to protons adjacent to the carbonyl group and were correlated with a carbon signal at δ 42.7 in the HMQC spectrum.[15] EIMS allowed the location of the carbonyl group at C-10 and the THF between C-17 and C-22 (Figure 5). Therefore, **6** was identified as *cis*-reticulatacin-10-one.

In conclusion, besides the well-known solamin, six new *cis*-acetogenins were isolated from roots of *A. muricata*. The simultaneous identification of *cis*- and *trans*-solamin in the same species strongly confirms NMR assignments made by Fujimoto et al.[11]

Experimental Section

General Experimental Procedures. Melting points were determined with a Reichert apparatus and are uncorrected. Optical rotations were measured with a Schmidt−Haensch polartronic E polarimeter at 25 °C. UV spectra were measured in MeOH on a Philips PU 8720 spectrophotometer. IR spectra were recorded on a Perkin−Elmer 257 spectrophotometer. The ^{1}H NMR spectra were obtained with a Brüker ARX-400 (at 400 MHz). The ^{13}C NMR spectra were obtained with a Brüker AC-200 at 50 MHz. EIMS (48 eV) and CIMS (CH_4) were registered with a Nermag R10-10C mass spectrometer. HPLC was performed with a Waters 590 pump, detector UV (Waters 84), and injector (Waters SSV).

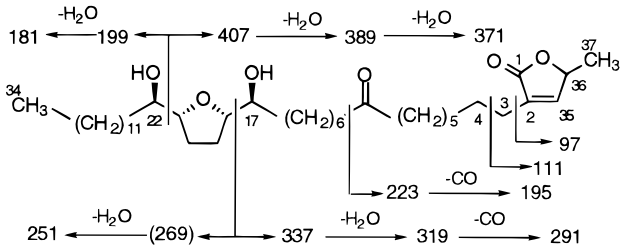

Figure 5. CIMS fragmentations of **6**. Value in brackets was not observed. Absolute configurations may be inverted.

Plant Material. Roots of *A. muricata* (Annonaceae) were collected and authenticated by Professor A. Sylla at Conakry, Guinea, in October 1993. A voucher specimen has been deposited at the Faculty of Medicine and Pharmacy at the University of Conakry.

Extraction and Isolation. The dried and powdered roots (600 g) were extracted with MeOH to give a brown extract (60 g). The MeOH extract was partitioned between H_2O and CH_2Cl_2 to yield 45 g of CH_2Cl_2 extract. This extract was subjected to Si gel column chromatography (Si gel 60 Merck 70−230 mesh) and eluted with hexane containing increasing amounts of EtOAc. The fractions collected were analyzed by TLC (Si gel Merck $60F_{254}$), on which basis they were grouped into 17 pooled fractions.

The solvent from fraction 7 was removed, and the resulting residue (1.5 g) was subjected to two successive column chromatographies over Si gel (60 H Merck) eluted with CH_2Cl_2−EtOAc (100:15) and with $CHCl_3$−iPrOH (100:5). The impure acetogenins (**1**, **2**, **3**, **4**+**5**) were subjected to a semipreparative HPLC procedure using a reversed-phase Waters μBondapak C_{18} 10-μm semipreparative cartridge column (25 × 100 mm), flow rate 9 mL/min, 20 mg/injection, and eluent CH_3OH−H_2O−THF (92:8:5). Altogether, 13 mg of **1** were obtained. A second HPLC purification procedure with eluent CH_3OH−H_2O−THF (90:10:5) was used to separate solamin (3 mg), **2** (13 mg), **3** (3 mg), and a mixture of **4**+**5** (10 mg).

Fraction 11 (175 mg) was fractionated by Si gel column chromatography (Si gel 60 H Merck) eluted with CH_2Cl_2−EtOAc− iPrOH (100:5:3). Compound **6** (5 mg) was obtained after final purification by a semipreparative HPLC procedure using a reversed-phase Waters μBondapak C_{18} 10-μm preparative cartridge column 25 × 100 mm, flow rate 9 mL/min, 20 mg/injection, and eluent CH_3OH−H_2O−THF (87:13:5).

Solamin: white powder (3 mg); mp 62−65 °C; $[\alpha]_D$ +23° (*c* 0.15, MeOH); UV (MeOH) λ_{max} (log ϵ) 216.5 (3.55) nm; IR ν_{max} (MeOH) 3420, 2914, 2840, 1761, 1473, 1322, 1114, 1080, 1030, 962, 842, 751, 715 cm^{-1};

exhibited ^{1}H NMR, ^{13}C NMR, and CIMS data similar to literature values.[7]

***cis*-Solamin (1):** white powder (13 mg); mp 63−66 °C; $[\alpha]_D$ +22° (*c* 0.55, MeOH); UV (MeOH) λ_{max} (log ϵ) 217.2 (3.61) nm; IR ν_{max} (MeOH) 3420, 2916, 2840, 1759, 1471, 1321, 1114, 1080, 1033, 962, 845, 751, 717 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) and ^{13}C NMR ($CDCl_3$, 50 MHz), see Table 1; CIMS and EIMS, see Figure 1, HRCIMS (CH_4) *m/z* 565.4828 $[MH]^+$ (calcd for $C_{35}H_{65}O_5$ 565.4832).

***cis*-Panatellin (2):** white powder (13 mg); mp 62−64 °C; $[\alpha]_D$ +20° (*c* 0.60, MeOH); UV (MeOH) λ_{max} (log ϵ) 219.6 (3.65) nm; IR ν_{max} (MeOH) 3420, 2917, 2841, 1760, 1471, 1324, 1120, 1078, 1033, 963, 753 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) and ^{13}C NMR ($CDCl_3$, 50 MHz), see Table 1; CIMS and EIMS, see Figure 2, HRCIMS (CH_4) *m/z* 565.4841 $[MH]^+$ (calcd for $C_{35}H_{65}O_5$ 565.4832).

***cis*-Uvariamicin IV (3):** white powder (3 mg); mp 60−62 °C; $[\alpha]_D$ +20° (*c* 0.15, MeOH); UV (MeOH) λ_{max} (log ϵ) 221.3 (3.58) nm; IR ν_{max} (MeOH) 3422, 2916, 2839, 1762, 1473, 1325, 1124, 1077, 1034, 965, 748 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) and ^{13}C NMR ($CDCl_3$, 50 MHz), see Table 2; CIMS and EIMS, see Figure 3, HRCIMS (CH_4) *m/z* 593.5162 $[MH]^+$ (calcd for $C_{37}H_{69}O_5$ 593.5148).

***cis*-Uvariamicin I and *cis*-Reticulatacin (4 and 5):** white powder (10 mg); mp 60−62 °C; $[\alpha]_D$ +18° (*c* 0.40, MeOH); UV (MeOH) λ_{max} (log ϵ) 220.8 (3.63) nm; IR ν_{max} (MeOH) 3423, 2916, 2840, 1760, 1474, 1325, 1120, 1073, 1032, 968, 742, 717 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) and ^{13}C NMR ($CDCl_3$, 50 MHz), see Table 2; CIMS and EIMS, see Figure 4, HRCIMS (CH_4) *m/z* 593.5154 $[MH]^+$ (calcd for $C_{37}H_{69}O_5$ 593.5148).

***cis*-Reticulatacin-10-one (6):** white powder (5 mg); mp 62−64 °C; $[\alpha]_D$ +23°(*c* 0.18, MeOH); UV (MeOH) λ_{max} (log ϵ) 219.6 (3.59) nm; IR ν_{max} (MeOH) 3416, 2911, 2839, 1753, 1700, 1464, 1410, 1373, 1310, 1068, 1032, 958, 915 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) and ^{13}C NMR ($CDCl_3$, 50 MHz), see Table 3; CIMS and EIMS, see Figure 5, HRCIMS (CH_4) *m/z* 607.4926 $[MH]^+$ (calcd for $C_{37}H_{67}O_6$ 607.4940).

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