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ISOLATION AND STRUCTURE OF THREE NEW BIS-TETRAHYDROFURAN ACETOGENINS FROM THE ROOTS OF *ANNONA CHERIMOLIA*[1]

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ABSTRACT.—Three new Annonaceous isoacetogenins have been isolated from a MeOH extract of *Annona cherimolia* roots, isocherimolin-1 [**1**], isomolvizarin-1 [**2**], and isomolvizarin-2 [**3**], in addition to the known compounds, bullatacinone (=isorolliniastatin-2), squamocin, and almunequin. Their structures were established on the basis of nmr spectroscopic techniques.

Used in traditional medicine as insecticide and parasiticide, *Annona cherimolia* Mill. (Annonaceae) is a tropical tree native to Peru, now cultivated for its edible fruits in the South of Spain. Previous work on the leaves and the seeds led to the isolation of aporphine alkaloids (2); in addition, eleven Annonaceous acetogenins (3) have been obtained from the seeds. Some of these compounds exhibit potent antimicrobial and antiparasitic activities (3). As part of our continuing investigation of this plant, we have isolated six acetogenins from a MeOH extract of the *A. cherimolia* roots. According to our recently published classification (4), we report in this paper the structure elucidation of three new subtype-2 acetogenins (isoacetogenins): isocherimolin-1 [**1**] (type C_2), isomolvizarin-1 [**2**] (type B_2), and isomolvizarin-2 [**3**] (type B_2), with the other three being the known compounds bullatacinone (=isorolliniastatin-2) (type B_2), squamocin (type B_1), and almunequin (type C_1) (5).

RESULTS AND DISCUSSION

Compound **1** was isolated as a yellow amorphous solid by successive Si gel column and hplc separations. The mol wt of **1** was suggested as 638 by cims (isobutane) peaks at *m/z* 639 $(MH)^+$ and by Li-fabms (*m*-NBA) at *m/z* 645 $(M+Li)^+$ (6), corresponding to the molecular formula $C_{37}H_{66}O_8$. Spectral characteristics of **1** including ^{1}H-nmr, ^{13}C-nmr (*J*-modulated spin echo) and ms data, suggested that it belongs to the class of non-adjacent bis-THF acetogenins (7).

Sequential losses of three molecules of H_2O from the MH^+ in the cims and Li-fabms spectral analysis indicated the presence of three hydroxyl groups in **1**, which was supported by a broad hydroxyl absorption at 3425 cm^{-1} in the ir spectrum. A negative reaction with Kedde's reagent, a uv (MeOH) λ max at 207.8 nm (log ϵ=3.34), an ir carbonyl absorption at 1755 cm^{-1}, and associated ^{1}H-nmr signals for **1** (Table 1) at δ 2.20 (H-37), 2.61/2.67 (H-35a), 3.03/3.09 (H-35b), and 4.36/4.53 (H-4), specifically indicated the presence of a saturated α-acetonyl γ-lactone fragment. Signals at δ 178.81 (C-1), 78.90/79.28 (C-4), 34.43/36.70 (C-2), 43.80/44.25 (C-35), 205.53 (C-36) and 29.94 (C-37) in the ^{13}C-nmr spectrum supported these assignments. These characteristic shifts revealed that **1** is a mixture of cis and trans C-2/C-4 diastereoisomers according to Hoye and Hanson (8).

The type C (two non-adjacent THF rings) structural profile of **1** was deduced from

[1]Part 31 in the series "Acetogenins from Annonaceae." For Part 30, see Vu-Thi-Tam *et al.* (1).

TABLE 1. ^{1}H-Nmr (J in Hz) and ^{13}C-Nmr Data for Isocherimolin-1 [**1**] and Isomolvizarin-1 [**2**].[a]

Position	Compound			
	^{1}H nmr		^{13}C nmr[b,c]	
	1	**2**	**1**	**2**
1	—	—	178.81 (C)	178.81 (C)
2	2.99 m	3.00 m	34.43/36.70 (CH)	34.43/36.69 (CH)
3a/3b	1.98/2.26 m	1.99/2.24 m	25.19–35.57 (CH_2)	24.47–35.43 (CH_2)
4 cis	4.36 m	4.38 m	79.28 (CH)	79.36 (CH)
trans	4.53 m	4.54 m	78.90 (CH)	78.90 (CH)
5–11	1.20–1.65	1.20–1.68	25.19–35.57 (CH_2)	24.47–35.43 (CH_2)
12	3.80 m	1.20–1.68	79.28 (CH)	24.47–35.43 (CH_2)
13	1.20–1.98	3.38 m	25.19–35.57 (CH_2)	74.07 (CH)
14	1.20–1.98	3.85 m	25.19–35.57 (CH_2)	83.13 (CH)
15	3.75	1.75–2.00	81.99 (CH)	24.47–35.43 (CH_2)
16	3.35 m	1.75–2.00	74.54 (CH)	24.47–35.43 (CH_2)
17	1.20–1.98	3.85 m	25.19–35.57 (CH_2)	82.48 (CH)
18	1.20–1.98	3.85 m	25.19–35.57 (CH_2)	82.80 (CH)
19	3.35 m	1.75–2.00	74.46 (CH)	24.47–35.43 (CH_2)
20	3.79 m	1.75–2.00	83.30 (CH)	24.47–35.43 (CH_2)
21	1.68–1.98	3.85 m	25.19–35.57 (CH_2)	82.22 (CH)
22	1.68–1.98	3.85 m	25.19–35.57 (CH_2)	71.27 (CH)
23	3.82 m	1.20–1.68	82.16 (CH)	24.47–35.43 (CH_2)
24	3.75 m	1.20–1.68	71.51 (CH)	24.47–35.43 (CH_2)
25–31	1.20–1.65	1.20–1.68	25.19–35.57 (CH_2)	22.65–35.43 (CH_2)
32	1.20–1.65	0.86 t (6.8)	31.89 (CH_2)	14.06 (CH_3)
33 cis	1.20–1.65	33a 2.61 dd (18.8,8.0) 33b 3.07 dd (13.5,3.4)	22.67 (CH_2)	43.80 (CH_2)
trans		33a 2.68 dd (18.8,8.1) 33b 3.14 dd (11.3,3.4)		44.23 (CH_2)
34	0.86 t (7.0)	—	14.11 (CH_3)	205.50 (C)
35 cis	35a 2.61 dd (18.3,8.9) 35b 3.03 dd (14.5,3.3)	2.20 s	43.80 (CH_2)	29.92 (CH_3)
trans	35a 2.67 dd (18.3,9.3) 35b 3.09 dd (11.3,3.3)		44.25 (CH_2)	
36	—	—	205.53 (C)	—
37	2.20 s	—	29.94 (CH_3)	—

[a]The assignments were confirmed by comparison with spectral data of (2,4-*cis*- and *trans*)-isoannonacin (11) and (2,4-*cis* and *trans*)-bullatacinone (19).

[b]Multiplicities were determined by spin-echo correlated spectroscopy.

[c]Chemical shifts (^{13}C nmr) within a difference $\Delta\delta<1$ ppm, may be inverted.

proton resonances at δ 3.80 (H-12), 3.75 (H-15), 3.79 (H-20), and 3.82 (H-23), and carbon resonances at δ 79.28 (C-12), 81.99 (C-15), 83.30 (C-20), and 82.16 (C-23). Three additional signals in the ^{13}C-nmr spectrum of **1** due to hydroxyl-bearing carbons adjacent to THF rings occurred at δ 74.54 (C-16), 74.46 (C-19), and 71.51 (C-24), with corresponding ^{1}H-nmr resonances, respectively, at δ 3.35, 3.35, and 3.75. The signal at δ 79.28 suggested that there was no hydroxyl group adjacent to one side of one of the THF rings (9). The protons of **1** were assigned by analysis of data from a 2D homo-decoupling experiment (COSY 45). The 2D ^{1}H-^{13}C heteronuclear correlation was carried out to determine the relationship between the carbon atoms and their respective protons. In the ^{13}C-nmr spectrum of **1**, the multiplicities of the carbon atoms were determined by spin-echo correlated spectroscopy. Hence the signals at δ 43.80/44.25 were attributed to the secondary carbon atom C-35 as in rollinone (10), isoannonacin (11), isoannoreticuin (12) and squamone (13), but not to the tertiary carbon atom C-2 as in erroneous ^{13}C-nmr assignments of bullatacinone (14), bullatalicinone (15), bullatanocinone (9), and hydroxybullatacinones (16).

To determine the location of the two THF rings, mass spectral studies were undertaken. Eims and Li-fabms fragmentations clearly located the THF rings at C-12 and C-20 along the hydrocarbon chain and also supported the placement of the three hydroxyl groups at C-16, C-19, and C-24 (Figure 1). Careful comparison of the ^{13}C-nmr

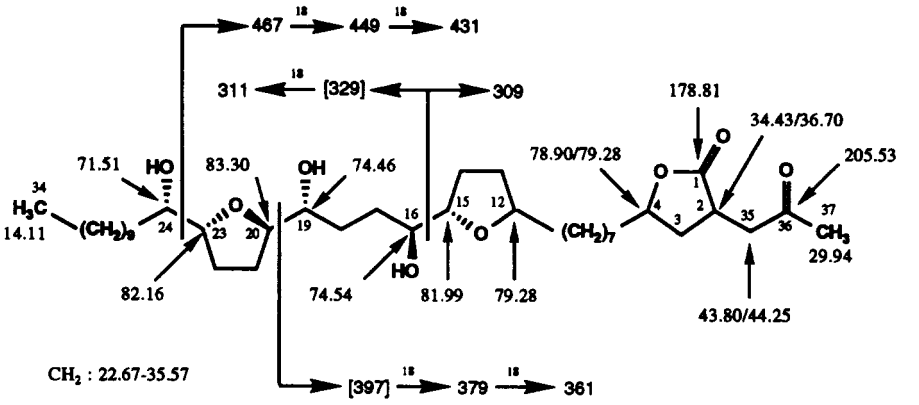

FIGURE 1. ^{13}C-nmr data (50 MHz, $CDCl_3$, δ) of isocherimolin-1 [**1**]; Ms fragment ions of **1** (*m/z*).

signals of **1** for the oxygenated carbons C-15, C-16, C-19, C-20, C-23, and C-24 at δ 81.99, 74.54, 74.46, 83.30, 82.16, and 71.51, respectively, with those of the previously isolated almunequin and cherimolin-1 (5) allowed us to fix the relative configuration within the carbon centers of the bis-THF moiety at C-15/C-16, C-19/C-20, C-20/C-23, and C-23/C-24 of **1**, as threo-threo/trans/erythro (Figure 1). The absolute stereochemistry shown in structure **1** and those depicted in structures **2** and **3** have been chosen arbitrarily and could be inverted. As with most published isoacetogenins (7), **1** was concluded to be a mixture of C-2/C-4 diastereoisomers, and has been named *cis*- and *trans*-isocherimolin-1.

Another chromatographic fraction exhibiting a sole spot on tlc with several different solvent systems was obtained as a white wax after flash cc and prep. tlc. A molecular weight of 594 was established by cims (isobutane) from the $(MH)^+$ at *m/z* 595 corresponding to $C_{35}H_{63}O_7$. The ir spectrum showed a strong absorption at 1720 cm^{-1} for a ketone and 1770 cm^{-1} for a saturated γ-lactone supported by the transparency of the compound under uv light with a λ max at 204.0 nm (log ε=3.56) in MeOH (4). Examination of the ms and ^{1}H-nmr spectra revealed characteristics of adjacent bis-THF acetogenins that have been isolated from Annonaceous species previously. The significant signals in the ^{1}H-nmr spectrum at δ 2.20, 4.38, and 4.54, as well as the ^{13}C-nmr double signals at 78.90/79.36 and 43.80/44.23 suggested the presence of cis and trans diastereoisomers as is typical with all isoacetogenins.

In spite of a single molecular peak in the cims, the ^{13}C-nmr spectrum showed six signals due to the THF oxygen-bearing carbons at δ 83.21, 83.13, 82.80, 82.48, 82.22, and 81.73. Two hypotheses were considered to explain this multiplicity: (a) the presence of a tris-THF system (a careful ms analysis did not confirm this hypothesis) or (b) a mixture of two compounds, in which the relative configurations in the THF ring moiety would be threo/trans/threo/trans/threo and threo/trans/threo/trans/erythro. The latter might explain the unequal intensities of ^{13}C-nmr signals at δ 74.07 and 71.27 (Figures 2 and 3). An hplc study of the substance was undertaken to confirm this assumption. The chromatograms revealed two peaks which were in agreement with suggestion (b): 70% of compound **2** with a relative configuration threo/trans/threo/trans/erythro of the bis-THF α,α′-dihydroxylated system as in molvizarin (17) (Figure 2), and 30% of compound **3** with a relative configuration threo/trans/threo/trans/threo as in asimicin (5) (Figure 3).

These compounds were separated to a great extent on reversed-phase hplc eluted with MeCN-H_2O-THF (70:30:2) and detected by refractometry. Thus, purified com-

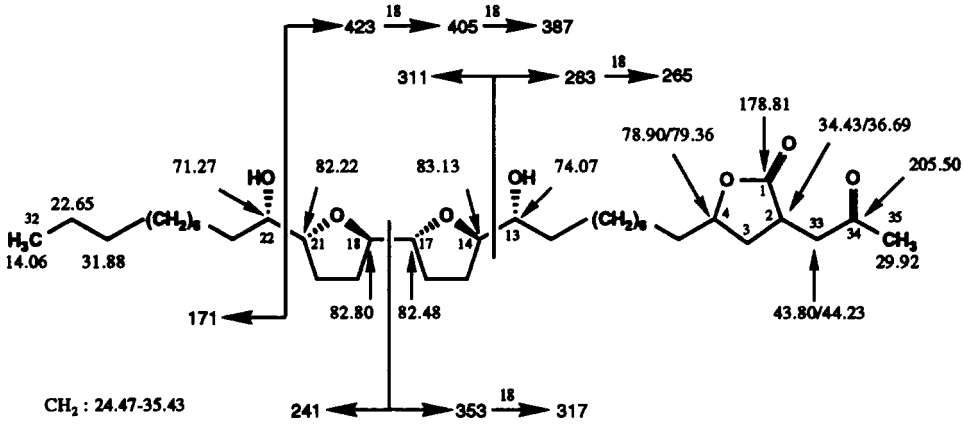

FIGURE 2. ^{13}C-Nmr data (50 MHz, $CDCl_3$, δ) of isomolvizarin-1 [**2**]; Ms fragment ions of **2** (*m/z*).

pound **2** was obtained and its ^{13}C-nmr spectrum (Table 1) confirmed the fact that it was a mixture: signals at δ 83.13, 82.80, 82.48, and 82.22 belonged to the major isomer **2**, and the absence of resonances at δ 83.21 and 81.73 of the isomer **3**, were observed (Figures 2 and 3).

Although insufficient quantities of pure **3** were available to obtain spectral data, its structure could be implied from the mixture of **2** and **3** by comparison with the data of **2** obtained from the purified sample (Table 1). The lower intensity group of carbon signals in the ^{13}C-nmr spectrum of the mixture at δ 83.21 and 81.73 belong to the compound with the threo/trans/threo/trans/threo configuration which was assigned as **3** (Figure 3), while the higher intensity group of carbon signals at δ 83.13, 82.80, 82.48, and 82.22 belong to the compound with the threo/trans/threo/trans/erythro configuration which was assigned as **2** (Figure 2). The structures of compounds **2** and **3** were concluded to be as illustrated from the above data, and were named, respectively, isomolvizarin-1 and isomolvizarin-2, with both being a mixture of C-2/C-4 cis and trans diastereoisomers.

Bullatacinone was obtained as a white wax by flash chromatography eluting with toluene-EtOAc (40:60). Cims (NH_3) and Li-fabms (*m*-NBA) spectra gave peaks at *m/z* 640 $(MNH_4)^+$ and 629 $(M+Li)^+$ which indicated a mol wt of 622. The structure of a similar bis-THF isoacetogenin with the cis and trans diastereoisomeric system was clearly established by uv, ir, ^{1}H- and ^{13}C-nmr spectral analysis, as well as comparisons with data of compounds **2** and **3**. The ^{1}H- and ^{13}C-nmr shifts of the bis-THF α,α′-dihydroxylated system of bullatacinone were very similar to those of **2**, squamocin and rolliniastatin-2 (18) [=bullatacin (14), the relative configuration of which was recently

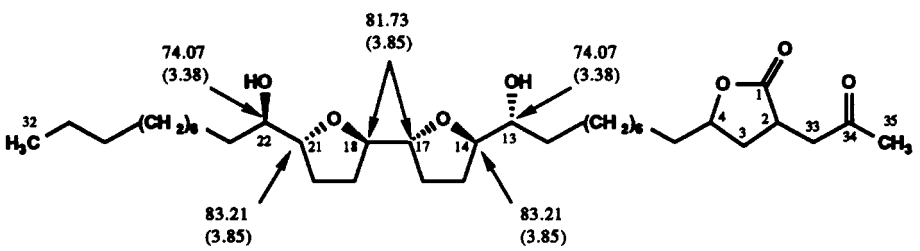

FIGURE 3. ^{1}H- and ^{13}C-nmr data (δ) of the dis-THF α,α′-dihydroxylated system of isomolvizarin-2 [**3**]. ^{1}H-Nmr signals of the saturated α-acetonyl γ-lactone fragment and the alkyl chain of **3**, as well as its ms fragment ions are identical with those of **2** (Table 1).

revised (19)]; all of these structures showed a threo/trans/threo/trans/erythro relative configuration. Thus, taking into account not only the previous articles on rolliniastatin-2 (18) and bullatacin (14) but also on the structural revision of the latter (19), these results led us to propose a mixture of C-2/C-4-*cis* and *trans*-bullatacinone (20) (=isorolliniastatin-2).

Indeed, isocherimolin-1 [**1**], isomolvizarin-1 [**2**], isomolvizarin-2 [**3**], and isorolliniastatin-2, as well as all described isoacetogenins obtained as mixtures of C-2/C-4 cis and trans diastereoisomers must not be considered as natural products but, according to our previously expressed assumption (4) and a recent proof, as artifacts of purification (20). Thereby, the use of prefix "iso-" (4) asserts itself.

Squamocin and almunequin showed identical ^{1}H-nmr, ^{13}C-nmr, and ms spectra to those of reference compounds previously isolated from *A. cherimolia* seeds (3).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Optical rotations were determined on a Schmidt-Haensch Polartronic I polarimeter. Uv spectra were obtained on a Philips PU 8720 spectrometer. Ir spectra were measured on a Perkin-Elmer 257 spectrometer. The ^{1}H- and ^{13}C-nmr spectra (in $CDCl_3$) were obtained with a Bruker AC-200 instrument at 200 and 50 MHz, respectively. Eims and cims (isobutane and NH_3) were performed on a Nermag-Sidar spectrometer; Li-fabms (*m*-NBA) were obtained with Kratos MS80RF mass spectrometer. Hplc was carried out with a Millipore-Waters (Milford, MA) system equipped with a differential refractometer.

PLANT MATERIAL.—The roots of *A. cherimolia* were collected in December 1989, at Almunecar in "Cherimoya-Vale," near Granada, Spain. A voucher specimen is deposited in the herbarium of the Department of Botany, University of Valencia, Spain, under the reference number VF 10463.

EXTRACTION AND ISOLATION.—The pulverized roots of *A. cherimolia* (1.5 kg) were macerated with MeOH. The MeOH extract was partitioned between hexane/95% aqueous MeOH. The hydroalcoholic fraction was partially evaporated and extracted with CH_2Cl_2. The CH_2Cl_2-soluble extract (10 g), fractionated by Si gel chromatography [eluted with CH_2Cl_2-MeOH (97:3)], afforded six bis-THF γ-lactone acetogenins: isocherimolin-1 (12 mg), isomolvizarin-1 and isomolvizarin-2 as a mixture (17 mg), isorolliniastatin-2 (18 mg), squamocin (55 mg), and almunequin (8 mg). Hplc employing a Si gel μPorasil cartridge [10 μm, 25×100 mm, elution with CH_2Cl_2-MeOH (97:3) at flow rate of 9 ml/min] and a μBondapak C_{18} prepacked column [10 μm, 8×100 mm, elution with MeCN-H_2O-THF (70:30:2) at flow rate of 6 ml/min] was used respectively to purify isocherimolin-1 [**1**], and to separate isomolvizarin-1 [**2**] (8 mg) from isomolvizarin-2 [**3**].

*(2,4-*cis *and* trans*)-Isocherimolin-1* [**1**].—Yellowish amorphous solid, $[\alpha]_D$ +27° (*c*=0.15, MeOH); uv (MeOH) λ max 207.8 nm (ε 2169); ir (film) ν max 3425, 2927, 2855, 1755, 1714, 1470, 1313, 1193, 1061, 1004, 961 cm^{-1}; cims (isobutane) *m/z* $[MH]^+$ 639 (100%), $[MH-H_2O]^+$ 621, $[MH-2H_2O]^+$ 603, 515, 449, 395, 379, 361, 325, 309, 246, 241, 214, 141; eims *m/z* $[M]^+$ 638, $[M-H_2O]^+$ 620, $[M-2H_2O]^+$ 602, $[M-3H_2O]^+$ 584, 467, 449, 431, 413, 379 (100%), 361, 348, 335, 309, 293, 291, 267, 241; Li-fabms (*m*-NBA) *m/z* $[M+Li]^+$ 645 (100%), 627, 601, 531, 473, 403, 363, 273, see Figure 1; ^{1}H nmr (200 MHz, $CDCl_3$), see Table 1; ^{13}C nmr (50 MHz, $CDCl_3$), see Figure 1 and Table 1.

*(2,4-*cis *and* trans*)-Isomolvizarin-1* [**2**].—White wax, $[\alpha]_D$ +24° (*c*=0.32, MeOH); uv λ max (MeOH) 206.1 nm (ε 3325); ir (film) ν max 3434, 2922, 2851, 1767, 1715, 1465, 1360, 1313, 1167, 1120, 1075, 1011, 960, 722 cm^{-1}; cims (isobutane) *m/z* $[MH]^+$ 595 (100%), $[MH-H_2O]^+$ 557, $[MH-2H_2O]^+$ 559, 481, 463, 311, 281, 241; eims *m/z* $[M-H_2O]^+$ 576, $[M-2H_2O]^+$ 558, 551, 423, 405, 387, 353, 335, 317, 293, 283 (100%), 265, 241, 141; Li-fabms (*m*-NBA) *m/z* $[M+Li]^+$ 601 (100%), 557, 487, 493, 441, 429, 404, 244, see Figure 2; ^{1}H nmr (200 MHz, $CDCl_3$), see Table 1; ^{13}C nmr (50 MHz, $CDCl_3$), see Figure 2 and Table 1.

*(2,4-*cis *and* trans*)-Isomolvizarin-1* [**2**] *and isomolvizarin-2* [**3**].—Colorless wax, $[\alpha]_D$ +33° (*c*=0.19, MeOH); uv λ max (MeOH) 204.0 nm (ε 3674); ir (film) ν max 3432, 2929, 2856, 1771, 1721, 1570, 1467, 1408, 1372, 1310, 1165, 1063, 722 cm^{-1}; cims (isobutane) *m/z* $[MH]^+$ 595 (100%), $[MH-H_2O]^+$ 557, $[MH-2H_2O]^+$ 559, 481, 463, 311, 281, 241; eims *m/z* $[M-H_2O]^+$ 576, $[M-2H_2O]^+$ 558, 551, 423, 405, 387, 353, 335, 317, 293, 283 (100%), 265, 241, 141; Li-fabms (*m*-NBA) *m/z* $[M+Li]^+$ 601 (100%), 557, 493, 487, 441, 429, 404, 244, see Figure 2; ^{1}H nmr (200 MHz, $CDCl_3$), see Table 1 and Figure 3; ^{13}C nmr (50 MHz, $CDCl_3$) see Table 1, and Figures 2 and 3.

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