PERGAMON

Phytochemistry 50 (1999) 823–828

PHYTOCHEMISTRY

Purpuracenin: a new cytotoxic adjacent bis-tetrahydrofuran annonaceous acetogenin from the seeds of *Annona purpurea*☆,☆☆

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Received 8 April 1998; revised 6 July 1998

Abstract

Purpuracenin, a novel cytotoxic acetogenin and annoglaucin, a known compound, were isolated from the seeds of *Annona purpurea*. Their structures were elucidated by a combination of chemical and spectral methods including MS and NMR spectral measurements. The absolute configurations of both compounds are presented. The new compound and annoglaucin exhibited potent cytotoxic activity in vitro against six human solid tumor cell lines. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: *Annona purpurea*; Annonaceae; Annonaceous acetogenins; Purpuracenin; Annoglaucin

1. Introduction

Annona purpurea Moc. and Sessé ex Dunal (Annonaceae) is a small tree up to 7 m high. The fruit of this plant, commonly known as 'ilama' in Mexico, is edible. The fruit is also used in folk medicine as a remedy for fever and cold. Our previous studies with the seeds of this species yielded the new bioactive bis-tetrahydrofuran (THF) acetogenins, purpurediolin and purpurenin and the known bis-THF acetogenins, annoglaucin, bullatacin, squamocin (annonin I) and motrilin (squamocin C) and the known mono-THF acetogenins, xylomatenin and annonacin A (Chávez & Mata, 1998). In this paper we describe the isolation, structure elucidation, absolute stereochemistry and cytotoxic activity of an additional novel compound, namely purpuracenin (**1**). In addition, the absolute stereochemistry for the known acetogenin annoglaucin (**2**) (Etcheverry, Sahpaz, Fall, Laurens, & Cavé, 1995) is presented.

2. Results and discussion

As previously reported (Chávez & Mata, 1998), the seeds of *A. purpurea* obtained from Veracruz, Mexico, were extracted with $CHCl_3$–MeOH (1:1) and the extract residue was subjected to solvent partition with hexane and 10% H_2O in MeOH. The aqueous MeOH residue exhibited a potent activity in the brine shrimp lethality test (Meyer, Ferrigni, Putnam, Jacobsen, Nichols, & McLaughlin, 1982). This fraction was further fractionated by open column chromatography using Si gel with increasing solvent polarity to yield eleven secondary fractions (F_1–F_{11}) (Chávez & Mata, 1998). Repeated HPLC separation of the active fraction F_7 (brine shrimp lethality test $LC_{50} = 1.47 \times 10^{-2}$ μg/mL) yielded the compound **1** and the known acetogenin **2**.

Purpuracenin (**1**) was obtained as a yellow wax. Its molecular formula was established as $C_{37}H_{66}O_8$ by HRFABMS. The IR spectrum contained absorptions for hydroxyl (3432 cm^{-1}) and α,β-unsaturated lactone (1755 cm^{-1}) functionalities. Sequential losses of four molecules of H_2O from the MH^+ in the FABMS spectral analysis as well as the formation of the tetra-TMSi derivative **1a** confirmed the presence of four hydroxyl groups.

☆ Part 36 in the series 'Chemical Studies on Mexican Plants Used in Traditional Medicine'. For part 35 see (Chávez & Mata, 1998).

☆☆ Taken in part from the Ph.D. thesis of Daniel Chávez.

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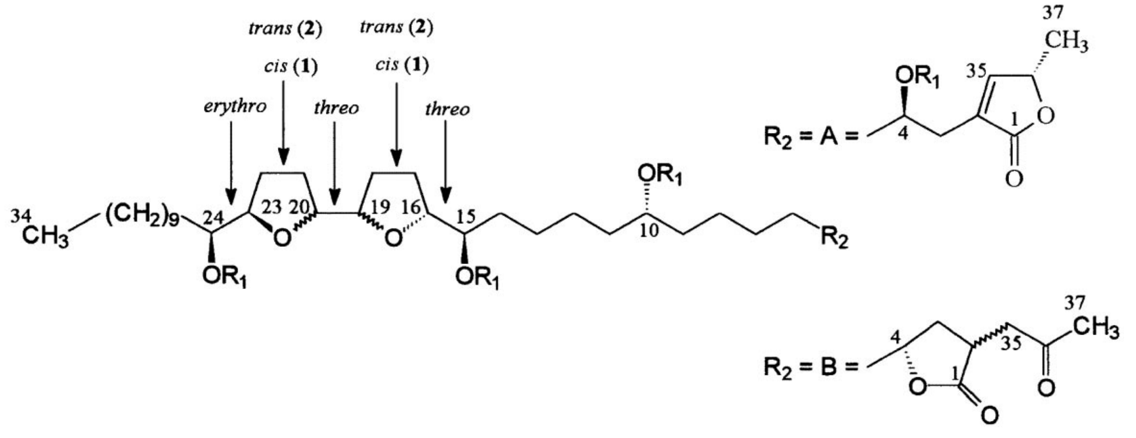
PII: S0031-9422(98)00553-6



	R1	R2		R1	R2
1	H	A	**2**	H	A
1a	TMSi	A	**2a**	TMSi	A
1b	H	B	**2b**	H	B
1c	(*S*)-MTPA	A	**2c**	(*S*)-MTPA	A
1d	(*R*)-MTPA	A	**2d**	(*R*)-MTPA	A
1e	(*S*)-MTPA	B	**2e**	(*S*)-MTPA	B
1f	(*R*)-MTPA	B	**2f**	(*R*)-MTPA	B

The NMR spectral data of compound **1** (Tables 1 and 2) clearly indicated that it had the rolliniastatin 1 type of adjacent bis-THF structure (Pettit, Cragg, Polonski, Herald, Goswami, Smith et al., 1987; Zengh, Ye, Oberlies, Shi, Gu, He et al., 1996). The resonances for the 4-hydroxy-α,β-unsaturated methyl-γ-lactone were observed at δ 7.18 (H-35), 5.06 (H-36), 3.85 (H-4), 2.53 (H-3a) 2.40 (H-3b) and 1.43 (H-37) in the ^{1}H NMR spectrum (Table 1); and at δ 174.6 (C-1), 151.8 (C-35), 131.2 (C-2), 78.0 (C-36), 70.0 (C-4), 33.4 (C-3) and 19.1 (C-37) in the ^{13}C NMR spectrum (Table 2). The resonances for the adjacent bis-THF α,α′-dihydroxylated portion appeared at δ 73.9 (C-15), 82.9 (C-16), 81.1 (C-19), 80.9 (C-20), 83.1 (C-23) and 71.9 (C-24) in the ^{13}C NMR spectrum and at δ 3.42 (H-15), 3.85 (H-16), 3.90 (H-19), 3.86 (H-20), 3.92 (H-23) and 3.87 (H-24) in the ^{1}H NMR spectrum.

The fourth hydroxyl group appeared in the ^{1}H NMR spectrum at δ 3.59 and in the ^{13}C NMR at δ 71.7. The position of this hydroxyl group, as well as the bis-THF unit with flanking hydroxyls, were located along the aliphatic chain by the analysis of the fragmentation pattern displayed by the tetra-TMSi derivative **1a** (Fig. 1). The hydroxyl group was located at C-10 by the presence of fragment ions at *m*/*z* 643 (cleavage between C-9/10) and 385 (cleavage between C-10/11). The disposition of the adjacent bis-THF rings with two flanking hydroxyls groups was placed at C-15 to C-24 according to the fragment ion peak at *m*/*z* 543, consistent with a cleavage at C-15/16 and the fragments ions at *m*/*z* 683 and 243 (cleavages at C-23/24).

The *threo*/*cis*/*threo*/*cis*/*erythro* relative stereochemistry from C-15 to C-24 was assigned on the basis of the chemical shift values observed for these nuclei in the NMR spectra (Tables 1 and 2), which were very similar to those previously described for rolliniastatin 1 and related compounds (Pettit et al., 1987; Saez, Sahpaz, Villaescusa, Hocquemiller, Cavé, & Cortez, 1993; Abreo & Sneden, 1989). The absolute configuration of the stereogenic carbinol centers was established using the Mosher ester methodology (Rieser, Hui, Rupprecht, Kozlowski, Wood, McLaughlin et al., 1992). The analysis of the $\Delta\delta_H$ (*S*–*R*) data (Table 3) of the per-(*S*)- and per-(*R*)-MTPA Mosher ester derivatives, **1c** and **1d**, showed that the absolute stereochemistry of the chiral centers at C-4, C-15 and C-24, were *R*, *R* and *S*, respectively. Thus, the absolute stereo-

Table 1
^{1}H NMR spectral data of purpuracenin (**1**) and annoglaucin (**2**)[a]

Position	Compound **1**	Compound **2**
3a	2.53 dddd (15.5, 3.5, 1.5, 1.5)	2.51 dddd (15.5, 3.5, 1.5, 1.5)
3b	2.40 dddd (15.5, 8.5, 1.5, 1.5)	2.40 dddd (15.5, 8.5, 1.5, 1.5)
4	3.85 m	3.84 m
5	1.49 m	1.48 m
6–8	1.20–1.65 m	1.20–1.63 m
9, 11	1.40 m	1. 41 m
10	3.59 m	3.58 m
12–13	1.20–1.65 m	1.20–1.63 m
14	1.46 m	1.40 m
15	3.42 m	3.40 m
16	3.85 m	3.85 m
17	1.82 m, 1.94 m	1.62 m, 1.97 m
18	1.78 m, 1.93 m	1.62 m, 1.97 m
19	3.90 m	3.93 m
20	3.86 m	3.85 m
21	1.83 m, 1.94 m	1.60 m, 1.97m
22	1.76 m, 1.98 m	1.80 m, 1.90m
23	3.92 m	3.94 m
24	3.87 m	3.86 m
25	1.41 m	1.41 m
26–33	1.20–1.65 m	1.20–1.63 m
34	0.88 t (7.0)	0.88 t (7.0)
35	7.18 ddd (1. 5, 1.5, 1.5)	7.20 cidd (1.5, 1.5, 1.5)
36	5.06 qq (7.0, 1.5)	5.06 qq (7.0, 1.5)
37	1.43 d (7.0)	1.43 d (7.0)

[a] $CDCl_3$, 500 MHz. (*J* in Hz).

Table 2
^{13}C NMR spectral data of purpuracenin (**1**) and annoglaucin (**2**)[a]

Position	Compound **1**	Compound **2**
1	174.6	174.5
2	131.2	131.2
3	33.4	33.3
4	69.9	69.9
5	37.3	37.3
6–8	25.5–29.7	25.3–29.6
9	37.3	37.2
10	71.7	71.7
11	37.3	37.2
12–13	25.5–29.7	25.3–29.6
14	34.2	33.3
15	73.9	74.0
16	82.9	83.2
17	28.7	28.9
18	27.9	28.9
19	81.1	82.2
20	80.9	82.4
21	28.4	28.3
22	23.7	24.5
23	83.1	82.8
24	71.9	71.4
25	32.8	32.4
26–31	25.5–29.7	25.3–29.6
32	31.9	31.8
33	22.7	22.6
34	14.1	14.0
35	151.8	151.8
36	78.0	77.9
37	19.1	19.0

[a] $CDCl_3$, 125 MHz.

chemistry for C-16, C-19, C-20 and C-23 was deduced as *R*, *S*, *S* and *R*, respectively. The absolute stereochemistry at C-10 was not solvable by spectral analysis of the (*S*)- and (*R*)-per-Mosher ester derivatives (**1c**, **1d**) of compound **1**. Therefore, a translactonization reaction was necessary (He, Shi, Zhao, Zeng, Ye, Schwedler et al., 1996). Treatment of **1** with a weak base (diethylamine) (Duret, Laurens, Hocquemiller, Cortez, & Cavé, 1994) afforded the mixture of the C-2/C-4 *cis* and *trans* translactonized isomers **1b**. The tri-Mosher esters of the translactonized mixture (**1e** and **1f**) indicated the *R* configuration at C-10, because the difference values for H-4 were positive (Table 3).

The absolute configuration of C-36 was determined according to the Hoye's method (Hoye, Hanson, Hasenwinkel, Ramirez, & Zhuang, 1994). The $\Delta\delta_{S-R}$ values for H-35 and H-36 were –0.12 and –0.03 ppm, respectively (Table 3), suggesting an unlike relative configuration for C-4/C-36. Since C-4 has the *R* configuration, C-36 must possess the *S* configuration. Compound **1** showed a negative Cotton effect at 237.5 nm in the CD spectrum, which provided further evi-

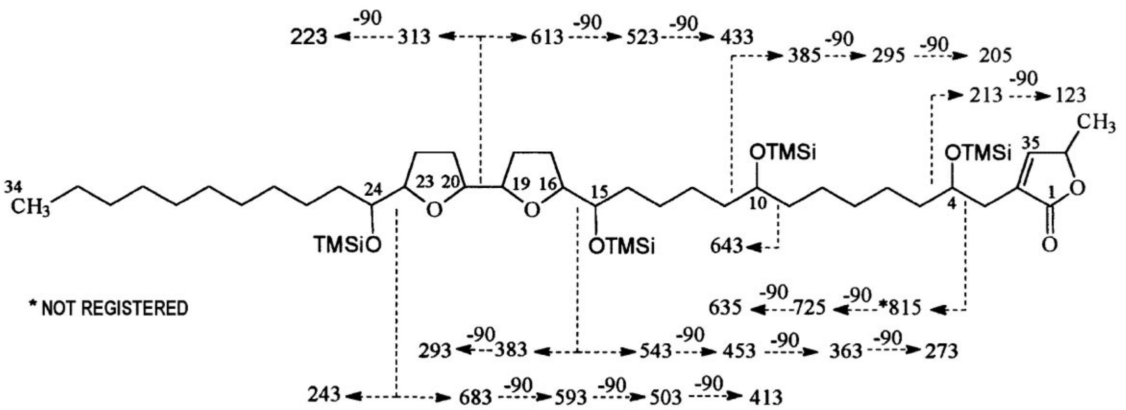


Fig. 1. Diagnostic EIMS fragment ions of **1a** and **2a** (shown as *m*/*z* values).

Table 3
Partial ^{1}H NMR spectral data of the Mosher esters of **1c**, **1d**, **1e**, **1f**, **2c**, **2d**, **2e** and **2f**[a]

	Compound **1**				Compound **2**			
Protons	(*S*)-MTPA	(*R*)-MTPA	$\Delta\delta_{S-R}$	Absolute configuration	(*S*)-MTPA	(*R*)-MTPA	$\Delta\delta_{S-R}$	Absolute configuration
4	4.54	4.52	+ 0.02	10*R*	4.55	4.53	+ 0.02	10*R*
(**e** and **f**)	4.37	4.35	+ 0.02		4.39	4.37	+ 0.02	
14	1.67	1.50	+ 0.17		1.60	1.49	+ 0.11	
15	5.06	5.09	–	15*R*	5.03	5.02	–	15*R*
16	4.02	3.99	+ 0.03		4.03	3.99	+ 0.04	
17a	1.86	1.89	−0.03		1.90	2.00	−0.10	
17b	1.71	1.78	−0.07		1.47	1.58	−0.11	
18a	1.76	1.73	−0.03		1.84	1.88	−0.04	
18b	1.67	1.76	−0.09		1.67	1.69	−0.02	
19	3.65	3.67	−0.02		3.80	3.83	−0.03	
20	3.69	3.67	+ 0.02		3.80	3.65	+ 0.15	
21a	1.76	1.73	+ 0.03		1.86	1.84	+ 0.02	
21b	1.68	1.73	+ 0.05		1.67	1.62	+ 0.05	
22a	1.88	1.78	+ 0.10		1.84	1.79	+ 0.05	
22b	1.79	1.67	+ 0.12		1.72	1.62	+ 0.10	
23	3.99	3.90	+ 0.09		3.99	3.94	+ 0.05	
24	5.22	5.22	–	24*S*	5.27	5.27	–	24*S*
25	1.67	1.69	−0.02		1.53	1.58	−0.05	
5	1.63	1.60	+ 0.03		1.65	1.59	+ 0.06	
4	5.35	5.39	–	4*R*	5.33	5.37	–	4*R*
3a	2.55	2.59	−0.04		2.54	2.59	−0.05	
3b	2.61	2.67	−0.06		2.61	2.67	−0.06	
35	6.78	7.00	−0.12		6.75	6.98	−0.13	
36	4.87	4.90	−0.03		4.87	4.91	−0.04	
37	1.24	1.27	−0.03		1.27	1.29	−0.02	

[a] $CDCl_3$, 500 MHz.

dence for the 36 *S* configuration (Zhao, Gu, Zeng, Chao, Kozlowski, Wood et al., 1995).

Annoglaucin (**2**) was previously isolated by Cave's research group from the roots of *Annona glauca*, but the absolute stereochemistry and biological evaluations were not reported. The NMR properties (Tables 1 and 2) of the compound that we isolated were very close with those described for annoglaucin (Etcheverry et al., 1995). The analysis of the EIMS of the tetra-TMSi derivative **2a** (Fig. 1) confirmed the presence of the bis-THF with two flanking hydroxyls from C-15 to C-24 and the remaining hydroxyls at C-4 and C-10. The relative configuration of the adjacent bis-THF α,α′-dihydroxylated portion from C-15 to C-24 was

Table 4
Brine shrimp lethality and cytotoxicity data for compounds **1** and **2** from*A. purpurea*

	BST[a] (μg/mL)	Tumor cell line [ED_{50} (μg/mL)]					
Compound		A-549[b]	MCF-7[c]	HT-29[d]	A-498[e]	PC-3[f]	PACA-2[g]
1	3.0	4.8×10^{-2}	>10	>10	$<10^{-3}$	$<10^{-3}$	>10
2[*]	2.2×10^{-2}	1.08	1.56	$<10^{-7}$	1.01	3.56×10^{-1}	1.45
Adriamycin	–	8.89×10^{-3}	3.69×10^{-1}	3.71×10^{-2}	8.35×10^{-2}	5.68×10^{-2}	1.13×10^{-2}
Adriamycin[*]	–	3.67×10^{-3}	2.12×10^{-1}	9.66×10^{-3}	1.98×10^{-3}	2.27×10^{-2}	1.45×10^{-3}

[*] Samples tested in the same cytotoxicity runs. Taken from Chávez and Mata, 1998.
[a] Brine shrimp lethality test.
[b] Human lung carcinoma.
[c] Human breast carcinoma.
[d] Human colon adenocarcinoma.
[e] Human kidney carcinoma.
[f] Human prostate adenocarcinoma.
[g] Human pancreatic carcinoma.

deduced as *threo*/*trans*/*threo*/*trans*/*erythro* considering the similarity of the ^{1}H and ^{13}C data of **2** (Tables 1 and 2) with those of the bullatacin-type of acetogenins (Gu, Zeng, Schwedler, Wood, & McLaughlin, 1995; Zeng et al., 1996).

The absolute configuration of the carbinol centers was also determined by the analysis of the ^{1}H NMR data of the (*S*)- and (*R*)-per-Mosher ester derivatives **2c** and **2d**. The $\Delta\delta_{S-R}$ values (Table 3) around the bis-THF rings were very similar to those of the related protons of bullatacin (Rieser et al., 1992). Thus, the absolute stereochemistries for C-15 and C-24 were *R* and *S*, respectively. The positive difference for H-5 and the negative difference values for H-3, H-35, H-36 and H-37 indicated the *R* stereochemistry for C-4. As in the case of compound **1**, the absolute configuration at C-10 was determined on basis of the analysis of the tri-Mosher ester derivatives of the mixture C-2/C-4 *trans* and *cis* translactonized isomers (**2e** and **2f**). The $\Delta\delta_{S-R}$ showed positive differences (0.02 and 0.02 ppm) for H-4; this result is according to an *R* configuration at C-10 (He et al., 1996). Finally, the configuration at C-36 was determined to be *S* by the Hoye's Mosher ester method (Hoye et al., 1994) and by CD measurements (Zhao et al., 1995).

Purpuracenin (**1**) represents the first annonaceous acetogenin with four hydroxyl groups possessing the stereochemistry of rolliniastatin 1 (*threo*/*cis*/*threo*/*cis*/*erythro*) around the adjacent bis-THF unit with two flanking hydroxyls. The acetogenins **1** and **2** were significantly bioactive in the brine shrimp lethality test and were also cytotoxic to six human solid tumor cell lines in a 7-day MTT test using adriamycin as the positive control (Table 4). The stereochemistry around the adjacent bis-THF makes a notable difference in the cytotoxic activity of compounds **1** and **2**. Purpuracenin (**1**) with a *threo*/*cis*/*threo*/*cis*/*erythro* configuration showed selectivity against A-549, A-498 and PC-3. On the other hand, annoglaucin (**2**) with *threo*/*trans*/*threo*/*trans*/*erythro* configuration displayed selectivity against HT-29.

3. Experimental

3.1. General

Mp determinations were performed on a Fisher–Johns apparatus and are uncorrected. Optical rotations were taken on a JASCO DIP-360 polarimeter. UV spectra were obtained on a Shimadzu 160 UV spectrometer in MeOH solution. CD spectra were performed on a JASCO 720 spectropolarimeter at 25°C in MeOH solution. IR spectra (film) were measured on a Perkin Elmer 599 spectrometer. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra (all in $CDCl_3$) were obtained on a Varian Unity Plus 500 spectrometer. FABMS data were recorded using a glycerol matrix on a JEOL DX300 mass spectrometer. HRFABMS (NBA) were obtained in a JEOL JX102A mass spectrometer using a NBA matrix. The EIMS for TMSi derivatives was performed on a JEOL JMS-AX505HA mass spectrometer. HPLC was carried out with a Waters HPLC instrument equipped with Waters UV photodiode array detector (900) set at 209–220 nm, using a silica gel column (19 mm ID ×300 mm). Control of the equipment, data acquisition, processing and management of chromatographic information were performed by the millennium 2000 software program (Waters).

3.2. Plant material

The seeds of *A. purpurea* were collected in July, 1994 in Catemaco, Veracruz, Mexico. A voucher specimen of the plant (CA94-1) is preserved in the Herbarium of the Instituto de Ecología (XAL), Xalapa, Veracruz.

3.3. Bioassays

Brine shrimp lethality test of the extract, fraction and isolated compounds was performed as described (Meyer et al., 1982). Cytotoxicity against human solid tumors cells was measured in a 7-day MTT assay at the Purdue Cell Culture Laboratory using adriamycin as a positive control (He et al., 1996).

3.4. Extraction and isolation

The air-dried and ground seeds of *A. purpurea* (4.9 kg) were extracted and treated as previously described to yield 11 secondary chromatographic fractions (F_1–F_{11}) (Chávez & Mata, 1998). HPLC purification of the active fraction F_7 (500 mg, brine shrimp lethality test $LC_{50} = 1.47 \times 10^{-2}$ µg/mL) on a normal phase silica column [8.3 mL/min, hexane–*i*-PrOH–MeOH (85:7.5:7.5)] afforded compounds **1** and **2** (retention times 37.2 and 42.0 min, respectively).

3.5. Purpuracenin (*1*)

Pale yellow wax (10.4 mg); mp 42–44°C; $[\alpha]_D$ +26° (*c* 1.0 mg/mL, MeOH); UV (MeOH) λ_{max} (log ε) 207 (4.32); CD (MeOH) $\Delta\varepsilon$ (nm): -1.06×10^3 (237.5); IR ν_{max} (film) 3100–3650, 3023, 2929, 1755, 1642, 1429, 1215, 1028, 930 cm^{-1}; ^{1}H and ^{13}C NMR (Tables 1 and 2); FABMS (glycerol) *m*/*z* $[MH]^+$ 639; HRFABMS (NBA) *m*/*z* 639.4837 $[MH]^+$, calcd for $C_{37}H_{66}O_8$, 639.4835.

3.6. Annoglaucin (2)

Pale yellow wax (46 mg); mp 58–59°C; $[\alpha]_D$ +31 (*c* 1.0 mg/mL, MeOH); CD (MeOH) $\Delta\varepsilon$ (nm): -2.14×10^3 (238); ^1H and ^{13}C NMR (Tables 1 and 2); FABMS (glycerol) *m/z* $[MH]^+$ 639; HRFABMS (NBA) *m/z* 639.4836 $[MH]^+$, calcd for $C_{37}H_{66}O_8$, 639.4835. For UV and IR data see Etcheverry et al. (1995).

3.7. TMSi derivatizations

A small amount (1.0 mg) of compounds **1** and **2** were treated with 100 µL of Sigma-Sil-A (trimethylchlorosilane–hexadimethyl silane–pyridine 1:3:9) and heated at 60°C for 10 min to yield the respective TMSi derivatives **1a** and **2a**. **1a**: EIMS *m/z* (rel. int.): 725 (3), 683, (10), 643 (3), 635 (2), 613 (4), 593 (9), 543 (49), 523 (9), 503 (9), 453 (27), 433 (5), 413 (7), 385 (54), 383 (14), 363 (11), 313 (19), 293 (11), 295 (13), 273 (11), 243 (100), 223 (11), 213 (29), 205 (9), 123 (14). **2a**. EIMS *m/z* (rel. int.): 725 (11), 683, (38), 643 (6), 635 (7), 613 (11), 593 (32), 543 (100), 523 (17), 503 (22), 453 (45), 433 (8), 413 (9), 385 (43), 383 (10), 363 (9), 313 (7), 293 (5), 295 (5), 273 (4), 243 (25), 223 (3), 213 (11), 205 (3), 123 (3).

3.8. Preparation of the translactonized mixtures 1b and 2b

3 mg of **1** was treated with 10% diethylamine (0.3 mL) in MeOH/H_2O (95/5) (2.7 mL) at room temperature for 24 h; the solution was dried under vacuum to give the mixture **1b** (3 mg). ^1H NMR ($CDCl_3$, 500 MHz) δ 4.55 (m, H-4_{trans}) 4.40 (m, H-4_{cis}), 3.91 (2H, m, H-20, H-23), 3.86 (3H, m, H-16, H-20, H-24), 3.60 (m, H-10), 3.42 (m, H-15), 3.02-3.08 (2H, m, H-35_b, H-2), 2.60-2.70 (m H-35_a), 2.20 (3H, s, CH_3-37), 0.88 (3H, t, $J = 7.0$, CH_3-34). Treatment of 5 mg of **2** as described above yielded 5 mg of the mixture **2b**. ^1H NMR ($CDCl_3$, 500 MHz) δ 4.55 (m, H-4_{trans}) 4.40 (m, H-4_{cis}), 3.93 (2H, m, H-19, H-23), 3.86 (3H, m, H-16, H-20, H-24), 3.59 (m, H-10), 3.42 (m, H-15), 3.02–3.08 (2H, m, H-35_b, H-2), 2.58–2.70 (m H-35_a), 2.20 (3H, s, CH_3-37), 0.88 (3H, t, $J = 7.0$, CH_3-34).

3.9. Preparation of per-(S)- and per-(R)-MTPA ester derivatives

To a solution of **1**, **1b**, **2** or **2b** (1.5 mg in 0.5 ml of $CDCl_3$ in a NMR tube) were sequentially added pyridine-d_5, (100 µL), 4-(dimethylamino) pyridine (0.5 mg) and (*R*)-(−)α-methoxy-α-(trifluoromethyl) phenylacetyl chloride (25 mg). The mixture was heated at 50°C for 4 h under nitrogen atmosphere to give the *S*-Mosher esters **1c**, **1e**, **2c** and **2e** (^1H NMR data, Table 3). Treatment of **1**, **1b**, **2** or **2b** (1.5 mg) with (*S*)-(+)α-methoxy-α-(trifluoromethyl)phenylacetyl chloride as described above yielded the *R*-Mosher esters **1d**, **1f**, **2d** and **2f**, respectively (^1H NMR data, Table 3).

Acknowledgements

This work was supported by grants from PADEP (No. 005358, 005379 and 005321), CONACyT (convenio 400313-5-2576 PM) and DGAPA IN205197. We thank M. en C. Isabel Chávez, M. en C. Beatríz Quiroz, I.Q. Luis Velasco-Ibarra, M. en C. Javier Pérez-Flores, M. en C. Héctor Rios-Olivares and QFB Rocío Patiño, (Instituto de Química, UNAM), for recording the NMR, MS, UV, IR and CD spectra. We are also grateful to M. en C. Nuria Esturau-Escofet, QFB Oscar S. Yañez-Muñoz, QFB Graciel Chávez, QFB Marisela Gutiérrez, Q. Georgina Duarte-Lisci and QFB Jose Luis Gallegos-Pérez (Facultad de Química, UNAM), for obtaining the NMR, IR and HRFABMS spectra. The technical support of Laura Acevedo Arteaga is also acknowledged. Special thanks are due to Dr. Jerry McLaughlin, West Lafayette, IN, USA, who kindly arranged for the cytotoxicity evaluations. Daniel Chávez acknowledges a graduate student fellowship awarded by Consejo Nacional de Ciencia y Tecnología (CONACyT).

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