Two Unusual Acetogenins from the Roots of *Annona salzmanii*

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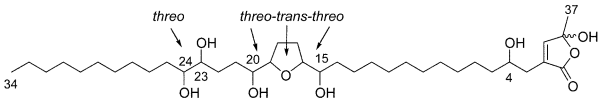
Two new acetogenins, parisin (**1**) and salzmanolin (**2**), were isolated from a MeOH extract of the roots of *Annona salzmanii*. The structures of **1** and **2** were elucidated by spectroscopic methods including LSI-MS/MS, on both the natural compounds and their acetonide derivatives (**1a** and **2a**). Compounds **1** and **2** showed significant activity against the KB and Vero cell lines.

Acetogenins are encountered only in a few genera of the family Annonaceae. These polyketide-derived natural products have received much interest in lately, due to their significant antitumor, cytotoxic, antiparasitic, immunosuppressive, and insecticidal activities.[1,2] In our previous studies of the roots of *Annona salzmanii* D. C. (Annonaceae),[3] we have described five acetogenins.[4] Alkaloidal components have been reported previously from this plant.[5] The present study has led to the isolation and structural elucidation of parisin (**1**) and salzmanolin (**2**), two acetogenins bearing hydroxy groups in unusual positions.

Results and Discussion

The molecular weight of **1**, established by LSIMS as 656 from the $[M + Li]^+$ ion observed at *m/z* 663, is in agreement with the molecular formula $C_{37}H_{68}O_9$. A strong UV absorption at 208.0 nm and another one at 1749 cm^{-1} in the IR spectrum indicated the presence of an α,β-unsaturated γ-lactone moiety, characteristic for acetogenins of subtype 1.[1,2] The ^1H and ^{13}C NMR spectra (Table 1) indicated the presence of a OH group at C-4,[1,2] but several spectral characteristics in the γ-lactone moiety clearly distinguished **1** from other acetogenins previously isolated from the genus *Annona*.



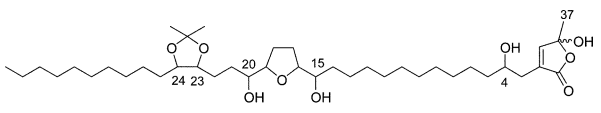
parisin (**1**)

In the ^1H NMR spectrum, the signal of H-36 (ca. δ 5.0) was no longer observed and the protons of the methyl group at C-37 appeared as a singlet at δ 1.70 instead of the usual doublet at ca. δ 1.4, indicating the presence of an additional substituent at C-36. This substitution was confirmed by the unusual chemical shift of H-35 at δ 6.75 instead of δ 6.98. In the ^{13}C NMR spectrum, a signal at δ 104.1, characteristic of an acetal, replaced the signal of the oxymethine carbon usually observed at ca. δ 77. These NMR data indicated the presence of a hydroxy group at C-36. Such γ-hydroxy-γ-methyl-γ-lactones were observed previously only in acetogenins isolated from *Goniothalamus donnaiensis*.[6,7]

The presence of a mono-THF system in the aliphatic chain was deduced from the ^1H NMR signals at δ 3.82 (2H) for **1**, assigned to two oxymethine protons, in agreement with their ^{13}C NMR signals at δ 82.9 (2C).[1,2] Two hydroxymethine groups flanking the THF system were observed at δ 3.40 in the $^1H-^1H$ COSY spectrum and at δ 74.5 in the ^{13}C NMR spectrum. Two further oxymethine protons appeared at δ 3.40 in the ^1H NMR spectrum, and their corresponding ^{13}C NMR resonances at δ 74.3 were indicative of a vicinal diol in the aliphatic region.[8,9]

The establishment of the relative stereochemistry around the THF ring of **1** was carried out by comparison of the ^1H and ^{13}C NMR data with those of several acetogenins having *threo* or *erythro* configurations between the THF ring and the vicinal hydroxymethine groups, according to the observations of Fujimoto et al.[10] and the synthetic models of Harmange et al.[11] These NMR data indicated that the relative stereochemistry around the THF ring was *threo-trans-threo* in **1**.

The position of the substituents in the aliphatic chain of **1** was further determined by MS.[1,2] The high-energy collision-induced dissociation (CID) spectrum of the $[M + Li]^+$ ion displayed the typical fragmentation pattern of lithiated acetogenins.[12] Two pairs of fragment ion peaks at *m/z* 293 and 361 were assigned to fragmentations across the THF ring (ions Y_1 and B_1, respectively, according to Laprévote and Das[12]). The *m/z* values of these fragments accounted for the presence of the THF ring between C-16 and C-19, with two hydroxy groups between the THF and the terminal lactone, and three others on the methyl-terminal side chain, their locations being deduced from careful scrutiny of the CID mass spectrum. Two series of fragment ion peaks were observed (Figure 1), originating from charge-remote fragmentations of the alkyl chain from the $[M + Li]^+$ precursor ion at *m/z* 663. Among them, the diagnostic fragment ions at *m/z* 521, 491, and 461 were indicative of a C-23/C-24 position of the vicinal diol. The position at C-15 and C-20 of the two hydroxy groups flanking the THF ring was determined in a similar way, as well as the remaining OH group at C-4.



23,24 acetonide of parisin (**1a**)

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Table 1. NMR Data ($CDCl_3$) of **1** and **2** and Their Acetonide Derivatives **1a** and **2a**

	^{1}H NMR (400 MHz)				^{13}C NMR (50 MHz)	
position	**1**	**1a**	**2**	**2a**	**1**	**2**
2					133.9	134.0
3	2.35−2.46 m	2.35−2.46 m	2.26 t, *J*=6.5 Hz	2.26 t, *J*=6.5 Hz	33.3[c]	25.2
4	3.82 m	3.82 m	1.56 m	1.56 m	69.5	27.3
5	1.42 m	1.42 m	1.20−1.30 m	1.20−1.30 m	37.5	26.1−29.7[b]
6−13	1.20−1.30 m	1.20−1.30 m	1.20−1.30 m	1.20−1.30 m	25.2−29.9[a]	26.1−29.7[b]
14	1.42 m	1.42 m	1.44 m	1.44 m	33.1[c]	33.1[c]
15	3.40 m	3.40 m	3.40 m	3.40 m	74.5	74.3
16	3.82 m	3.82 m	3.89 m	3.89 m	82.9	83.0
17	1.52−1.90 m	1.52−1.90 m	3.45 m	3.45 m	25.2−29.9[a]	74.4
18	1.52−1.90 m	1.52−1.90 m	1.95−2.00 m	1.95−2.00 m	25.2−29.9[a]	38.0
19	3.82 m	3.82 m	3.84 m	3.86 m	82.9	82.7
20	3.40 m	3.40 m	3.84 m	3.86 m	74.5	82.1
21	1.42 m	1.42 m	1.57−1.87 m	1.57−1.87 m	31.2[c]	26.1−29.7[b]
22	1.42 m	1.40−1.60 m	1.57−1.87 m	1.57−1.87 m	31.5[c]	26.1−29.7[b]
23	3.40 m	4.04 m	3.89 m	3.89 m	74.3	81.9
24	3.40 m	4.04 m	3.84 m	3.85 m	74.3	71.5
25	1.42 m	1.40−1.60 m	1.44 m	1.44 m	32.5[c]	32.4[c]
26	1.20−1.30 m	1.20−1.30 m	1.20−1.30 m	1.20−1.30 m	25.2−29.9[a]	25.4
27	1.20−1.30 m	1.20−1.30 m	1.44 m	1.40−1.60 m	25.2−29.9[a]	32.3[c]
28	1.20−1.30 m	1.20−1.30 m	3.59 m	4.04 m	25.2−29.9[a]	74.5
29	1.20−1.30 m	1.20−1.30 m	3.59 m	4.04 m	25.2−29.9[a]	74.5
30	1.20−1.30 m	1.20−1.30 m	1.44 m	1.40−1.60 m	25.2−29.9[a]	33.6[c]
31	1.20−1.30 m	1.20−1.30 m	1.20−1.30 m	1.20−1.30 m	25.2−29.9[a]	26.1−29.7[b]
32	1.20−1.30 m	1.20−1.30 m	1.20−1.30 m	1.20−1.30 m	31.5[c]	31.3
33	1.20−1.30 m	1.20−1.30 m	1.20−1.30 m	1.20−1.30 m	22.7	22.5
34	0.87 t, *J*=6.5 Hz	0.87 t, *J*=6.5 Hz	0.87 t, *J*=6.5 Hz	0.87 t, *J*=6.5 Hz	13.9	13.9
35	6.75 s	6.75 s	6.97 d, *J*=1.5 Hz	6.98 d, *J*=1.5 Hz	150.5	148.8
36			4.97 m	4.97 m	104.1	76.3
37	1.70 s	1.70 s	1.43 d, *J* = 6.7 Hz	1.43 d, *J*=6.7 Hz	24.2	19.0
$C(CH_3)_2$		1.33 s		1.35 s, 1.40, s		

[a] 25.2, 25.6, 28.3, 28.6, 29.1, 29.3, 29.5, 29.6, 29.9. [b] 26.1, 26.5, 28.3, 29.1, 29.4, 29.5, 29.7. [c] Signals may be interchanged.

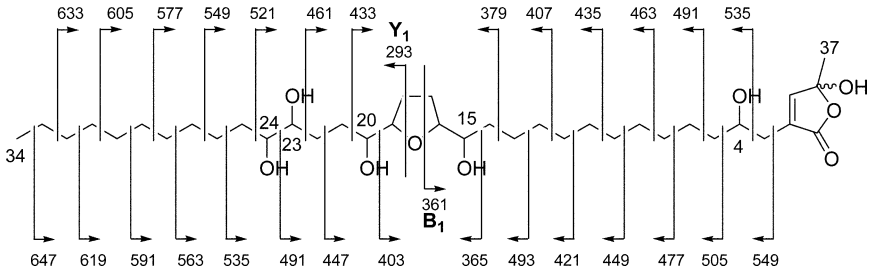
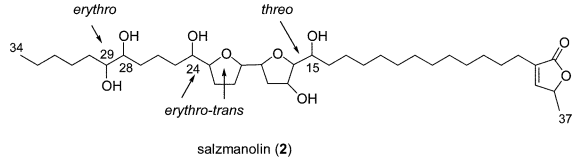


Figure 1. CID fragmentations (*m*/*z* values) of the $[M + Li]^+$ ion (*m*/*z* 663) generated by LSI-MS from parisin (**1**).

The relative configuration of the 1,2-diol at C-23/C-24 was deduced from the configuration of the dioxolane ring of the acetonide derivative **1a** prepared from **1**. The *threo* or *erythro* configurations of vicinal diols in the Annonaceous acetogenins have been previously determined from the observation of the ^{1}H NMR data of their acetonides.[13,14] If the configuration of the vicinal diol is *threo*, the two methyl signals of the acetonide appear together as a six-proton singlet in the ^{1}H NMR spectrum; for an *erythro* configuration, the methyl groups appear as two isolated three-proton singlets.[15] The methyl protons of the acetonide group in **1a** were observed as one six-proton singlet at δ 1.33 (Table 1), demonstrating the *threo* configuration of the vicinal diol at C-23/C-24 in **1**.



salzmanolin (**2**)

The molecular weight of **2**, established by LSIMS as 654 from the $[M + Na]^+$ ion observed at *m*/*z* 677.3, is in agreement with the molecular formula $C_{37}H_{66}O_9$. Strong absorptions at 209 nm and 1750 cm^{-1} in the UV and IR spectra, respectively, indicated the presence of an α,β-unsaturated γ-lactone moiety, characteristic for acetogenins of subtype 1.[1,2] This structural feature was confirmed by typical resonances in the ^{1}H and ^{13}C NMR spectra (Table 1), also indicating the absence of an OH group at C-4.[1,2] The presence of an adjacent bis-THF system was deduced from the ^{13}C NMR signals at δ 83.0 (1C), 82.7 (1C), 82.1 (1C), and 81.9 (1C), which correlated with four oxymethine protons at δ 3.84 (2H) and 3.89 (2H) in the ^{1}H NMR spectrum.[16] Five hydroxymethine groups were also observed between δ 71.5 and 74.5 in the ^{13}C NMR spectrum. Two of the latter carbons were attributed to hydroxymethine groups flanking the bis-THF system, as indicated by correlations at δ 74.3/3.40 and 71.5/3.84 in the HMQC spectrum. Two others appeared at δ 3.59 in the ^{1}H NMR spectrum, and their ^{13}C NMR resonances at δ 74.5 were indicative of a vicinal diol in the aliphatic chain.[8,9] The last hydroxymethine group was detected by signals at δ 74.4 and 3.45 in the ^{13}C and ^{1}H NMR spectrum, respectively. Homonuclear correlations in the DQF-COSY spectrum with one oxymethine group at δ 3.89 and the two methylene protons at δ 1.95−2.00 indicated that the last hydroxyl

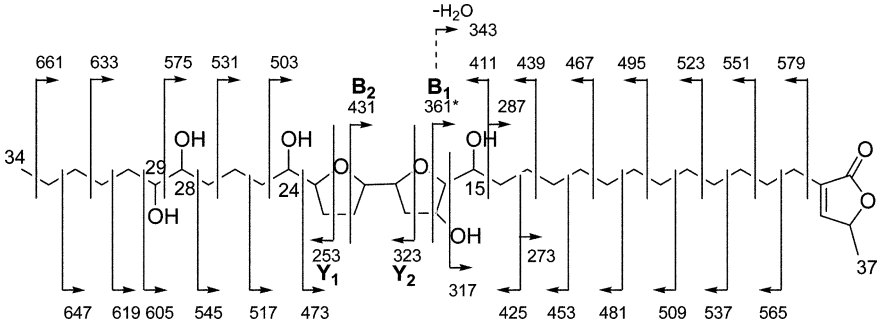


Figure 2. CID fragmentations (*m*/*z* values) of the $[M + Na]^+$ ion (*m*/*z* 677) generated by LSI-MS from salzmanolin (**2**). *Nondetected ion.

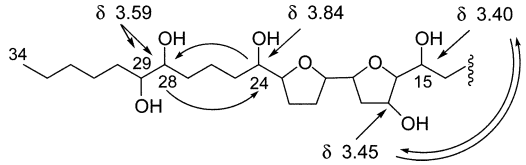


Figure 3. $^1H-^1H$ magnetization transfers in the HOHAHA NMR spectrum of **2**.

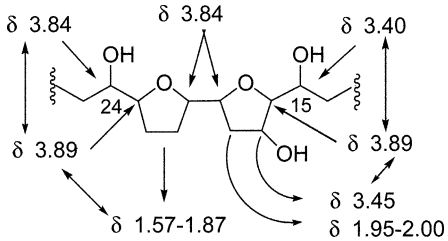
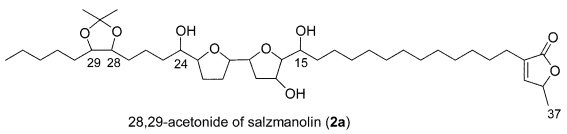


Figure 4. Correlations in the $^1H-^1H$ COSY NMR spectrum of **2**.

group of salzmanolin (**2**) was unusually substituted at one of the THF rings.[17]

The relative stereochemistry around the bis-THF system was then determined by comparing the ^1H and ^{13}C NMR data of **2** (Table 1), with those of synthetic compounds of known relative stereochemistry.[18,19] The comparison suggested that the relative configurations at C-15/C-16 and C-23/C-24 were different, as deduced from the chemical shifts observed for H-15 and H-24. In the HOHAHA spectrum of **2**, magnetization transfers were observed from H-28 (δ 3.59) to H-24 (δ 3.84), with the latter chemical shift being indicative of an *erythro* configuration at C-23/C-24. The methine signal at δ 3.40 (δ 74.3) was therefore located at C-15, indicating a *threo* configuration at C-15/C-16 (Figure 3).

With the relative configurations at C-15/C-16 and C-23/C-24 already in hand, the determination of the complete stereochemistry of **2** between C-15 and C-24 was achieved with the help of the homonuclear correlations observed in the DQF COSY spectrum (Figure 4). From their correlations with H-24 (δ 3.84) and H-23 (δ 3.89), the protons at C-21 and C-22 were assigned to signals at δ 1.57−1.87, indicating a *trans* stereochemistry for the C-20/C-23 THF ring.[15] In the same way, the methylene protons at C-18 were assigned to signals at δ 1.95−2.00, and their HMQC correlations were observed with both C-16 and C-17. Unfortunately, the data available did not allow a complete assignment of the relative configurations between C-16/C-19, C-19/C-20, and C-16/C-17.



28,29-acetonide of salzmanolin (**2a**)

To determine the relative configuration at C-28/C-29, the acetonide derivative **2a** was prepared. The ^1H NMR signals for H-28 and H-29 were observed as expected at δ 4.04 in **2a**, and the acetonide methyl groups, appearing as two singlet peaks at δ 1.35 and 1.40, indicated the *cis* configuration for the dioxolane ring. The configuration of the 1,2-diol was subsequently determined as *erythro* in **2**.[13,14] From all these results, the relative configuration of salmanolin (**2**) was determined as *threo* between C-15 and C-16, *threo*/*trans*/*erythro* from C-19 to C-24, with a *erythro* stereochemistry for the vicinal diol at C-28/C-29.

The position of the substituents in the aliphatic chain was further determined by MS. The high-energy collision-induced dissociation (CID) spectrum of the $[M + Na]^+$ ion displayed typical fragmentations, similar to those observed for the lithiated acetogenins. Two fragment ion peaks at *m*/*z* 253/323 and a single one at *m*/*z* 431 were assigned to fragmentations across two adjacent THF rings (ions Y_1-Y_2 and B_2, respectively, according to Laprévote and Das[12]), indicating the position of the bis-THF system along the alkyl chain (Figure 2). The absence of the expected B_1 fragment ion at *m*/*z* 361 was explained by the unusual substitution of the THF ring by a hydroxy group. This was replaced by a strong ion peak at *m*/*z* 343, resulting from the dehydration of the unstable B_1 ion, in agreement with the hypothesis of a hydroxyl group in the THF ring, on the lactone side of the molecule. Two series of fragment ion peaks were also observed, corresponding to charge-remote fragmentations of the alkyl chain from the $[M + Na]^+$ precursor ion at *m*/*z* 677. Among them, the diagnostic fragment ions at *m*/*z* 605, 575, and 545 were indicative of a vicinal diol at the C-28/C-29 position. Significant fragments at *m*/*z* 287/317 and 473/503 indicated the presence of two other hydroxyl groups at C-15 and C-24, on both sides of the bis-THF system. The *m*/*z* values observed for all fragments, together with the dehydration of the B_1 ion, were in full agreement with the substitution of one THF ring by a further hydroxyl located at C-17.

Because of the small amounts of **1** and **2** available after the chemical transformations, Mosher esters could not be prepared, so the absolute configurations of the carbinolic carbons remain unknown.

The cytotoxic activity of **1** and **2** was investigated.[20] The two acetogenins displayed significant activities for a cancer cell line (KB, $ED_{50} = 1 \times 10^{-4}$ μg/mL for **1** and 1×10^{-3} μg/mL for **2**) when compared with normal cells (Vero, $ED_{50} = 1 \times 10^{-2}$ μg/mL for **1** and $>1 \times 10^{-2}$ μg/mL for **2**). The comparison of salzmanolin (**2**) with spinencin,[21] which differs only by the presence of a hydroxyl group in the THF ring, revealed a strong reduction of the cytotoxic activity. Probably the reduction of the cytotoxic activity observed for compounds **1** and **2** compared with other mono- or bis-THF acetogenins can be related to the greater degrees of

hydroxylation, as previously reported for hexahydroxylated and heptahydroxylated acetogenins.[22,23]

Experimental Section

General Experimental Procedures. Optical rotations were determined using a Schmidt-Haensch Polartronic I polarimeter. UV spectra were recorded on a Philips PU 8700 series UV/vis spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively, on a Bruker AC-200 P spectrometer, and the ^{1}H−^{1}H (COSY-DQF, HOHAHA) and ^{1}H−^{13}C (HMQC and HMBC) correlation spectra at 400 MHz, on a Bruker ARX-400 spectrometer. HPLC was carried out with a Millipore-Waters (Milford, MA) system equipped with a Waters 484 spectrophotometer. CIMS and EIMS were obtained on a Nermag R1010 C spectrometer. LSI-MS/MS were obtained from a Zabspec-T five-sector tandem mass spectrometer (Micromass, VG Organic, Manchester, UK) using the experimental conditions described earlier.[24] HRES-IMS were obtained from a Navigator MAT 955 mass spectrometer (Thermo-Finnigan, France).

Plant Material. Roots of *Annona salzmanii* were collected in September 1996 in João Pessoa, Paraiba, Brazil. Voucher specimens are deposited at the "Prof. Lauro Pires Xavier" herbarium, No. 23.158, and identified by Prof. Carlos Alberto B. de Miranda of the Department of Natural Sciences, University of Paraiba, Brazil.

Extraction and Isolation. The dried and pulverized roots (3 kg) were percolated with MeOH. The concentrated MeOH extract was diluted with water (10%) and extracted with *n*-hexane to yield the hexane extract (40 g). The aqueous MeOH fraction was then extracted with CH_2Cl_2 to yield 30 g of extract, 25 g of which were fractionated by column chromatography (Si gel 60 M, 230−400 mesh), eluting with a CH_2Cl_2−MeOH (99:1 to 60:40) gradient. The two crude acetogenins were purified by HPLC, using a μBondapak C_{18} prepacked column [10 μm, 25 × 100 mm] and UV detection at 214 nm. Elution with MeOH−H_2O (82:18), flow rate 9 mL/min, afforded pure **1** (28.6 mg, t_R = 50 min). A MeOH−H_2O (80:20) eluent at 9 mL/min afforded **2** (12.5 mg, t_R = 15 min).

Parisin (1): transparent oil; $[\alpha]^{20}_D$ +22° (*c* 1.0, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 208 (4.6) nm; IR ν_{max} (film) 3675, 3474, 1749, 1652, 1458 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) and ^{13}C NMR ($CDCl_3$, 50 MHz), see Table 1; LSI-MS/MS of the $[M + Li]^+$ (*m*/*z* 663) ion, see Figure 1; HRESIMS of the $[M + Li]^+$ ion at *m*/*z* 663.5019 (calcd for $C_{37}H_{68}O_9Li$, 663.50229).

23,24 -Acetonide of Parisin (1a). To **1** (10.1 mg) dissolved in C_6H_6 (1 mL) was added 2,2-dimethoxypropane (10 μL) and traces of *p*-toluenesulfonic acid. The mixture was stirred under reflux for 1 h. K_2CO_3 (0.2 mg) was added, and the mixture stirred for 4 h at room temperature, then extracted with CH_2Cl_2 to give **1a** (9.4 mg, 88.6%). ^{1}H NMR ($CDCl_3$, 400 MHz), see Table 1.

Salzmanolin (2): transparent oil; $[\alpha]^{20}_D$ +25° (*c* 1.0, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 209 (4.0) nm; IR ν_{max} (film) 3675, 2992, 2857, 1750 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) and ^{13}C NMR ($CDCl_3$, 50 MHz), see Table 1; LSI-MS/MS of the $[M + Na]^+$ (*m*/*z* 677.3) ion, see Figure 2; LSI-MS/MS of the $[M + Li]^+$ (*m*/*z* 661) ion terminal methyl-containing fragment ions, *m*/*z* 563, 549, 535, 521, 507, 493, 479, 465, 451, 437, 423, 409, 395, 365, 307 (Y_2), 237 (Y_1); lactone-containing fragment ions, *m*/*z* 645, 631, 617, 603, 589, 559, 529, 515, 501, 487, 457, 415 (B_2), 327 (B_1−H_2O), 257; HRESIMS of the $[M + Na]^+$ ion at *m*/*z* 677.4601 (calcd for $C_{37}H_{66}O_9Na$, 677.46044).

28,29-Acetonide of Salzmanolin (2a). To **2** (5.1 mg) dissolved in C_6H_6 (1 mL) were added 2,2-dimethoxypropane (10 μL) and traces of *p*-toluenesulfonic acid. The mixture was stirred under reflux for 1 h. K_2CO_3 (0.2 mg) was added, and the mixture stirred for 4 h at room temperature, then extracted with CH_2Cl_2 to give **2a** (4.3 mg, 80%). ^{1}H NMR ($CDCl_3$, 400 MHz), see Table 2.

Cytotoxicity Evaluation of 1 and 2. Cytotoxic activity (ED_{50}, μg/mL) was determined according to the procedure described by Fleury et al.[20] against human nasopharyngeal carcinoma cells (KB) and monkey epithelioid renal cells (VERO). The compounds with ED_{50} values < 10^{-1} μg/mL are considered active if the factor of selectivity is at least 2 log between KB and VERO cell lines. Vinblastine was used as reference compound (0.1×10^{-4} μg/mL for KB and >1×10^{-1} μg/mL for VERO cell lines).

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