

PREPARATION AND CYTOTOXIC EVALUATION OF VOUACAPANE OXIDATION PRODUCTS

Armando Talavera-Alemán,^a Mario A. Gómez-Hurtado,^a Gabriela Rodríguez-García,^a Alejandra Ochoa-Zarzosa,^b Christine Thomassigny,^c Carlos M. Cerda-García-Rojas,^{d*} Pedro Joseph-Nathan,^d and Rosa E. del Río^{a*}

^aInstituto de Investigaciones Químico-Biológicas, Universidad Michoacana de San Nicolás de Hidalgo, Ciudad Universitaria, Morelia, Michoacán 58030, Mexico;

^bCentro Multidisciplinario de Estudios en Biotecnología, Facultad de Medicina Veterinaria y Zootecnia, Universidad Michoacana de San Nicolás de Hidalgo, Morelia, Michoacán 58893, Mexico;

^cUniversité de Versailles Saint-Quentin-en-Yvelines, ILV, UMR CNRS 8180, 45, Avenue des États-Unis, 78035 Versailles, France;

^dDepartamento de Química, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Apartado 14-740, Mexico City 07000, Mexico. E-mail: ccerda@cinvestav.mx; ndelrio@umich.mx

Abstract – Treatment of (–)-(5*S*,6*R*,8*S*,9*S*,10*R*,14*R*)-6-acetoxylvouacapane (**1**) with DDQ, *m*CPBA, or Cr(VI) reagents afforded diterpenoids with various degrees of oxidation at the furan and C rings. Oxidation of **1** using DDQ provided the known benzofuran **2**, together with the new derivatives dimer **3**, lactone **4**, and aldehyde **5**, while *m*CPBA oxidation gave **2**, spirocassenolide **6**, and cassenolides **7** and **8a**. Oxidation of **1** with CrO₃ gave **4**, **6**, **8a**, and spirocassenolide **9**, while the use of K₂Cr₂O₇ yielded **4**, **9**, and spirocassenolide **10**. The structures of the new compounds followed from HRMS, NMR measurements, and by single-crystal X-ray diffraction of **3**, **4**, **8b**, and **10**. Compounds **1**, **2**, and **6** were evaluated for their cytotoxic activity against the MCF-7 and HL-60 cancer cells, showing moderate cytotoxic activity.

INTRODUCTION

Heterocyclic molecules are involved in many pharmacological, chemical, and catalytic applications due to their peculiar electronic and stereoelectronic properties, entailing strategic molecular modifications.

Among them, furan is highlighted as the most reactive five membered heterocycle and as an efficient precursor in chemical synthesis due to its transformations using mild reagents. Its oxidation reactions are recurrent strategic procedures to synthesize bioactive molecules¹ related to their particular sensitivity for oxidations, thus providing 1,4-dicarbonyls, cyclopentanones, and ring opening products like succinaldehyde and carboxylic acid derivatives.² Such strategies are applied in natural furan compounds,³ highlighting γ -lactonization of furan as a common oxidation modification without ring cleavage.⁴

Efforts for incorporating the lactone moiety into bioactive natural products like taxanes,⁵ progestanes,⁶ and phenylpropanoids⁷ to improve their biological properties have been reported. Intramolecular esterification providing such motif has been generally involved, which is favored by entropic reasons.⁸ Despite their applicative potential, formation of spiro lactones from disubstituted furans is rare. Based on these facts, the preparation of new lactones, including spiro lactones, from natural products seems a pertinent task to be achieved.

As a study model to achieve such investigations, vouacapanes seem to be a suitable natural furanoid option since they contain the perhydrophenanthrene system present in numerous natural products of chemical and biological interest.^{9,10} Vouacapanes also are known as cassane-type furan diterpenoids, isolated principally from plants of the Fabaceae family,^{11,12} which exhibit a variety of biological activities like cytotoxic,^{13,14} antioxidant,¹⁵ antimalarial,^{16,17} anti-inflammatory,¹⁸ or antiviral properties.¹⁹⁻²¹

Compound **1**, which is available in good yields from *Caesalpinia platyloba*,²² was used as a model for photooxidation studies due to its chemical stability and easy management, evidencing the photooxidation susceptibility for lactonization of the furan ring, thereby providing epimeric epoxy lactones.²³ In continuation with our investigations on the reactive versatility of the furan moiety from natural compounds, in the present work, vouacapane **1** was subjected to oxidation reactions using oxidant reagents with different oxidative strength to yield from slighter to higher oxidation products. Thus, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and *meta*-chloroperbenzoic acid (*m*CPBA), as mild oxidants of furan derivatives,²⁴ and CrO₃ and K₂Cr₂O₇ as Cr(VI) sources for stronger oxidation reaction conditions²⁵ were employed. Treatment of **1** with DDQ gave the known (–)-(5*S*,6*R*,10*S*)-6-acetoxylvouacapa- $\Delta^{8(14),9(11)}$ -diene (**2**) and a mixture of the new compounds (–)-16,16'-di-[(5*S*,6*R*,10*S*,5'*S*,6'*R*,10'*S*)-6-acetoxylvouacapa- $\Delta^{8(14),9(11)}$ -dienyl] (**3**), (–)-(5*S*,6*R*,8*S*,9*R*,10*R*,14*R*)-6-acetoxycassa- $\Delta^{11,13(15)}$ -dien-12,16-olide (**4**), and (–)-(5*S*,6*R*,8*S*,9*S*,10*R*,14*R*)-6-acetoxycass- $\Delta^{13(15)}$ -en-16-al-12-one (**5**). In turn, *m*CPBA oxidation of **1** gave the aromatic derivative **2**, lactones (–)-(5*S*,6*R*,8*S*,9*S*,10*R*,11*S*,13*R*,14*R*)-6-acetoxyl-11-hydroxy-13-spirocass- Δ^{15} -en-12,16-olide (**6**), (–)-(5*S*,6*R*,10*S*)-6-acetoxycassa- $\Delta^{8(14),9(11),12}$ -trien-12,16-olide (**7**), and (–)-(5*S*,6*R*,8*S*,9*S*,10*R*,12*R*,14*R*)-6-acetoxyl-12-hydroxycass- $\Delta^{13(15)}$ -en-12,16-olide (**8a**), whose structure was confirmed by acetylation to yield (–)-(5*S*,6*R*,8*S*,9*S*,10*R*,12*R*,14*R*)-6,12-diacetoxycass- $\Delta^{13(15)}$ -en-12,16-olide (**8b**). By increasing the oxidation power using Cr(VI), compound **1**

gave **4**, **6**, **8a**, (-)-(5*S*,6*R*,8*S*,9*S*,10*S*,13*S*,14*R*)-6-acetoxy-13-spirocass- Δ^{15} -en-11-oxo-12,16-olide (**9**), and (+)-(5*S*,6*R*,8*S*, 9*S*,10*S*,13*R*,14*R*)-6-acetoxy-13-spirocass- Δ^{15} -en-11-oxo-12,16-olide (**10**). Spectroscopic characterization of compounds **3**, **4**, **8b**, and **10** was confirmed by single-crystal X-ray diffraction measurements. In addition, the adequate solubility and stability of compounds **1**, **2**, and **6** for *in vitro* cytotoxic assays allowed their evaluation against the MCF-7 breast cancer cell line and HL-60 human promyelocytic leukemia cells using the MTT protocol.

RESULTS AND DISCUSSION

Natural occurring vouacapane **1** was available from a previous study.²² Its structural characteristics provided the opportunity to explore the oxidative performance of the furan ring. Thus, mild oxidation with DDQ yielded compounds **2**, **3**, and **4** (Table 1, entry 1) which were easily separated by column chromatography. Compound **2** was already isolated, although in very low yields, from *Caesalpinia bonduc*, together with other four cytotoxic cassane derivatives.²⁶ The current isolation of **2** in 15% yield can facilitate its biological evaluation as was done for the other cassanes of *C. bonduc*.²⁶

Dimer **3** was also obtained in 15% yield. The NMR data (Tables 2 and 3) were similar with those of **2**, although only one furan singlet at δ 7.10 was visible in the ¹H NMR spectrum. Its HRESIMS showed the [M + H]⁺ ion at *m/z* 679.3981 (calcd for C₄₄H₅₄O₆ + H⁺ 679.3998). These data, together with the single-crystal X-ray analysis (Figure 2, Table 4) confirmed structure **3**.

Compound **4** was obtained as the main reaction product (28%). It showed the HRESIMS ion at *m/z* 358.4712 consistent with the C₂₂H₃₀O₄ elemental composition. Its IR carbonyl group band at 1753 cm⁻¹, the UV absorption at 277 nm, together with resonances at δ 5.85 (H-11) and 5.78 (H-15) observed in the ¹H NMR spectrum (Table 2), and ¹³C NMR signals (Table 3) for a carbonyl group at δ 170.4 and four sp² hybridized carbons at δ 161.2 (C-13), 150.2 (C-12), 111.0 (C-11), and 110.2 (C-15) suggested the presence of an unsaturated enol γ -lactone generated by oxidation of the furan and C-rings. Single-crystal X-ray analysis of **4** confirmed the lactonization of the furan moiety (Figure 2, Table 4). Several molecules structurally related to cassane **4** were reported from Asian folk medicinal plants *Caesalpinia bonduc* (antimalaric and febrifuge),²⁷ *C. magnifoliolata* (antirheumatic),²⁸ and *C. pulcherrima* (antifungal and febrifuge).²⁹

Since the oxidation power of DDQ increases³⁰ by adding HCl, the treatment of **1** under this reaction condition (Table 1, entry 2) was modulated to give only **2** in 75% yield. The oxidative potential of DDQ was changed again when THF/H₂O, as a protic neutral reaction medium (entry 3, Table 1) gave **5**. This white powder gave the HRESIMS molecular ion at *m/z* 361.2386 [M + H]⁺ (calcd for C₂₂H₃₂O₄ + H⁺, 361.2379). Its ¹H NMR spectrum (Table 2) exhibited a doublet at δ 9.64 (*J* = 7.8 Hz) assigned to an

aldehyde proton (H-16) coupled with the H-15 vinyl proton at δ 5.84 (d, $J = 7.8$ Hz) and two protons alpha to a carbonyl group, at δ 2.61 (dd, $J = 15.1, 5.2$ Hz) and δ 2.48 (dd, $J = 15.1, 12.0$ Hz), which were assigned to H-11a and H-11b. The ^{13}C NMR spectrum (Table 3) revealed three carbonyl carbons at δ 204.4 (C-12), 192.0 (C-16), and 169.4 (OAc), a double bond at C-13/C-15 (δ 164.7 and 127.0, respectively) conjugated with the ketone and aldehyde carbonyls as revealed by 2D NMR experiments, thereby confirming the structure of **5**. Aldehyde **5** is unstable and its DDQ oxidation in DCM-HCl provided **2**, thus evidencing the geometry of the double bond. An aldehyde analog to **5** was obtained by oxidizing caesaldekarin b with *m*CPBA.³¹

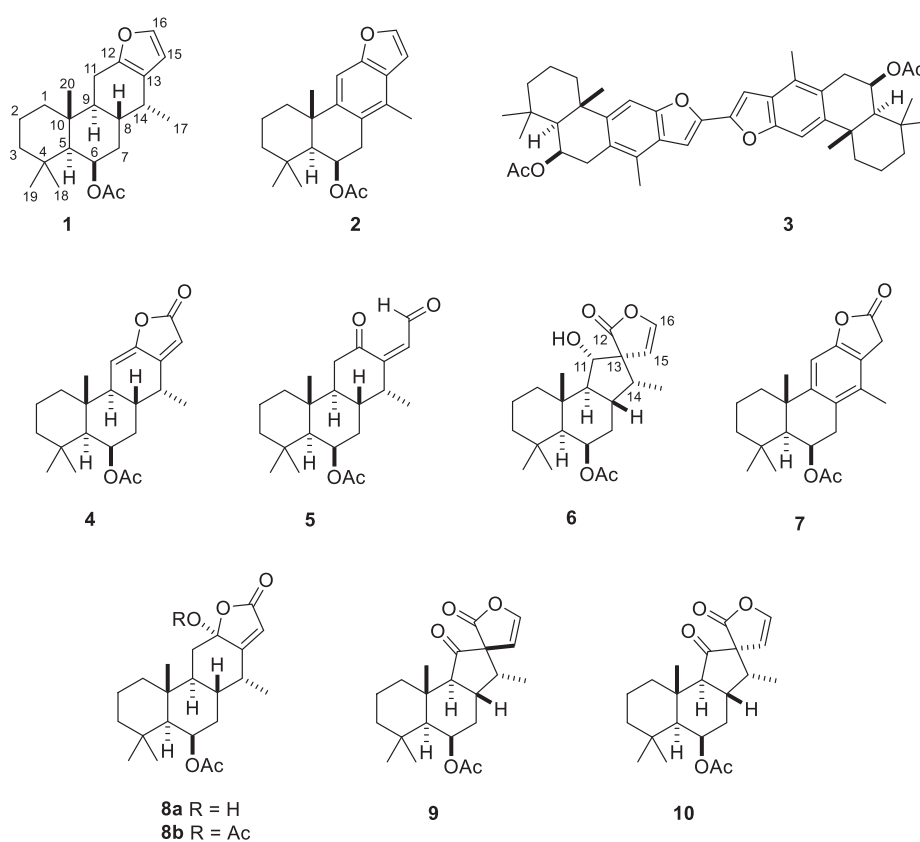


Figure 1. Formulas of diterpenoids **1-10**

Although dimerization of benzofuran with DDQ is known,³⁰ attempts to dimerize **2** to provide **3** were unsuccessful in our hands. However, treatment of **1** under aprotic oxidation conditions in MeCN (Table 1, entry 4) gave **2** (30%) and **3** (23%), while the use of MeCN/H₂O (10:1) as the solvent (Table 1, entry 5) yielded **4** (20%) and **5** (20%). On the basis of these experimental results, we were able to hypothesize the reaction mechanisms to yield **4**, and those to yield **2** and dimer **3**, via the stable intermediate aldehyde **5** as follows: Due to the employed reaction conditions,³² furan radical activation by DDQ **I**³³ allows addition of water (Scheme 1) to yield the hemiacetal type intermediate **II**,³⁴ whose ring opening provided the

1,4-dicarbonylalkene cassane **5**. Consequently a DDQ^{•-} radical might favor the activation of ring-C by H-11 radical abstraction to promote a cyclization as in **III**,³³ from where aprotic **IIIa** or protic (**IIIb**) pathways may be considered. The aprotic pathway could undergo lactonization with loss of H-16 to yield **4**, while the protic pathway could lead to a peroxy radical promoting radical- π conjugation **IV** with the consequent aromatization to give **2**. Alternatively, radical intermediate **IV** can be stabilized by dimerization (**V**) and C-ring aromatization to dimer **3**.

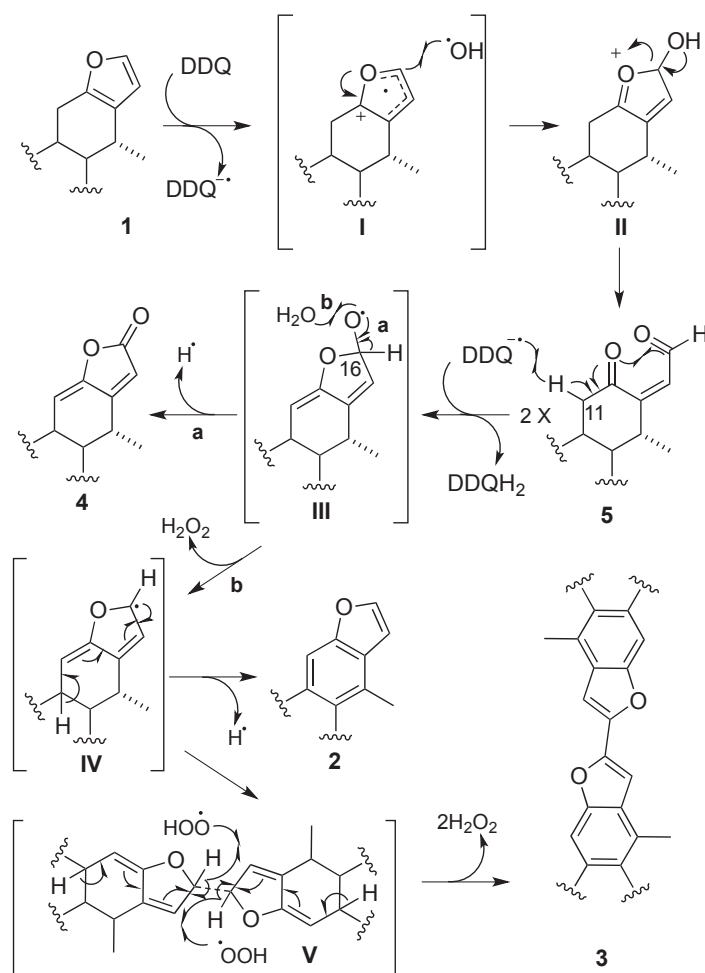
Table 1. Reaction conditions for the oxidation of vouacapane **1**

Entry	Conditions	Products (yield) ^a
1	DDQ, CH ₂ Cl ₂ , rt, 20 min	2 (15%), 3 (15%), 4 (28%)
2	DDQ, CH ₂ Cl ₂ -HCl (10:1), rt, 20 min	2 (75%)
3	DDQ, THF-H ₂ O (10:1), rt, 20 min	5 (60%)
4	DDQ, MeCN, rt, 15 min	2 (30%), 3 (23%)
5	DDQ, MeCN-H ₂ O (10:1), rt, 30 min	4 (20%), 5 (20%)
6	<i>m</i> CPBA, CHCl ₃ -HCl (10:1), 40 °C, 30 min	2 (40%), 6 (25%), 7 (15%)
7	<i>m</i> CPBA, CHCl ₃ -HCl (10:1), rt, 24 h	2 (30%), 6 (13%), 7 (10%)
8	<i>m</i> CPBA, CHCl ₃ -HCl (10:1), 0-4 °C, 24 h	2 (10%), 6 (54%)
9	<i>m</i> CPBA, toluene, rt, 30 min	8a (75%)
10	CrO ₃ , AcOH-H ₂ O (10:1), rt, 1 h	4 (10%), 6 (10%), 8a (22%), 9 (15%)
11	K ₂ Cr ₂ O ₇ , AcOH-H ₂ O (5:1), rt, 1 h	4 (10%), 6 (20%), 9 (25%),
12	K ₂ Cr ₂ O ₇ , AcOH, reflux, 30 min	9+10 (60%, 1:1) ^b

Reaction conditions: acetoxyvouacapane (**1**), oxidant agent: DDQ (2.5 eq), *m*CPBA (2.5 eq), or Cr(VI) (2.0 eq), and solvent (5 mL). ^aYields after Silica-gel chromatographic purification. ^bProducts ratio determined by NMR of the isolated mixture.

The use of *m*CPBA as a versatile oxidant has been highlighted recently,³⁵ as being capable to generate lactones and spiro-cyclization products from furan derivatives, despite the substitution position at the furan.³⁶ Thus, *m*CPBA/CHCl₃-HCl (10:1) at 40 °C for 30 min (Table 1, entry 6) treatment of **1** yielded **2** (40%), **6** (25%), and **7** (15%). Compound **6** showed the molecular ion at *m/z* 377.2327 [M + H]⁺ (calcd for C₂₂H₃₂O₅ + H⁺, 377.2328) in the HRESIMS method. Its IR spectrum showed a hydroxy group absorption at 3592 cm⁻¹, while its ¹H NMR (Table 2) displayed two vinyl doublets at δ 6.85 and 5.61 (*J* = 3.6 Hz) assigned to H-16 and H-15, respectively, and a third doublet at δ 4.26 (*J* = 8.6 Hz) which was assigned to H-11 since it is geminal to a hydroxy group. The ¹³C NMR spectrum (Table 3) showed a

carbonyl signal at δ 182.7, in addition to that of the acetate at δ 170.6, revealing the oxidation of the furan to a lactone. In addition, a quaternary carbon at δ 60.6 was observed, whose HMBC correlations showed its neighborhood to H-11, H-15, and H-16. The NOESY data showed correlations of H-15 and CH₃-17 (δ 0.92), and of H-11 and CH₃-20 (δ 1.30), from where the 11*S*,13*R* configuration followed.



Scheme 1. Putative mechanism for the oxidation of vouacapanone **1** with DDQ

Compound **7**, isolated in 15% yield, showed a molecular ion at m/z 374.2326 [$M + NH_4$]⁺ (calcd for C₂₂H₂₈O₄ + NH₄⁺ 374.2331) in the HRESIMS. A new carbonyl band was observed in the IR at 1802 cm⁻¹, attributed to a β,γ -unsaturated- γ -lactone chromophore, as those prepared from the benzofuran cacalol.³⁷ Its ¹H and ¹³C NMR spectra (Tables 2 and 3, respectively) were similar with those of aromatic vouacapanone **2**, highlighting the ¹H signal at δ 3.62 (CH₂-15) and the ¹³C signals at δ 174.6 (C-16) and 32.4 (C-15), thus confirming the presence of a rare vouacapanone lactone only precedent by taepenin F, isolated from *Caesalpinia crista*,³⁸ whose synthesis was completed recently.³⁹

Table 2. ¹H NMR spectroscopic data of compounds **3-10** (CDCl₃, δ in ppm, *J* in Hz)

H	3	4	5 ^a	6	7	9	10
1a	2.32 (br d, 12.9)	1.89 (br d, 11.3)	1.64 (m)	1.79 (ddd, 13.4, 4.6, 3.0)	2.19 (br d, 13.0)	2.38 (br d, 12.9)	2.42 (br d, 13.2)
1b	1.50 (m)	1.10 (m)	1.05 (m)	1.70 (dt, 13.4, 3.1)	1.37 (dt, 13.0, 3.6)	1.15 (m)	1.10 (td, 13.2, 3.4)
2a	1.90 (m)	1.65 (m)	1.65 (m)	1.45 (m)	1.87 (dt, 14.3, 3.6)	1.63 (m)	1.68 (qt, 13.5, 3.4)
2b	1.67 (m)	1.54 (m)	1.41 (m)	-	1.65 (dt, 14.3, 3.6)	1.40 (m)	1.47 (m)
3a	1.47 (m)	1.43 (br d, 13.3)	1.48 (m)	1.18 (m)	1.48 (m)	1.46 (m)	1.41 (br d, 13.2)
3b	1.27 (td, 13.3, 6.7)	1.22 (m)	1.19 (m)	-	1.23 (dt, 13.3, 3.6)	1.23 (m)	1.22 (td, 13.2, 3.4)
5	1.57 (br s)	1.12 (d, 2.5)	1.15 (br d, 1.5)	1.00 (d, 1.8)	1.48 (s)	1.01 (d, 2.0)	0.98 (s)
6	5.85 (d, 5.1)	5.53 (dd, 5.2, 2.5)	5.48 (br d, 2.5)	5.51 (br s)	5.80 (dt, 5.5, 1.4)	5.57 (m)	5.55 (q, 2.9)
7a	3.07 (dd, 18.1, 5.1)	1.73 (m)	1.75 (m)	1.87 (dt, 13.6, 3.6)	2.93 (dd, 18.5, 5.5)	2.02 (m)	2.07 (m)
7b	2.99 (d, 18.1)	1.59 (m)	1.54 (m)	1.41 (br d, 13.6)	2.83 (d, 18.5)	1.52 (m)	1.53 (m)
8	-	2.18 (m)	2.32 (tt, 12.4, 4.0)	2.55 (m)	-	2.49 (m)	3.17 (dddd, 14.6, 12.8, 6.5, 3.6)
9	-	2.03 (br d, 11.4)	1.75 (m)	1.47 (dd, 13.1, 8.6)	-	1.97 (d, 14.1)	1.78 (d, 14.6)
11a	7.42 (s)	5.85 (t, 2.1)	2.61 (dd, 15.1, 5.2)	4.26 (d, 8.6)	6.99 (s)	-	-
11b	-	-	2.48 (dd, 15.1, 12.0)	-	-	-	-
14	-	2.84 (qd, 7.2, 4.5)	2.74 (m)	2.31 (quint, 7.8)	-	2.52 (m)	2.64 (quint, 7.5)
15	7.10 (s)	5.78 (s)	5.84 (d, 7.8)	5.61 (d, 3.6)	3.62 (s)	5.56 (d, 3.5)	5.43 (d, 3.8)
16	-	-	9.64 (d, 7.8)	6.85 (d, 3.6)	-	6.96 (d, 3.5)	6.98 (d, 3.8)
17	2.38 (s)	1.06 (d, 7.2)	0.97 (d, 7.2)	0.92 (d, 7.8)	2.11 (s)	1.12 (d, 7.0)	0.98 (d, 7.5)
18	1.08 (s)	0.98 (s)	0.97 (s)	0.96 (s)	1.06 (s)	0.97 (s)	0.96 (s)
19	1.11 (s)	1.00 (s)	1.04 (s)	1.02 (s)	1.08 (s)	0.99 (s)	1.01 (s)
20	1.63 (s)	1.17 (s)	1.23 (s)	1.30 (s)	1.58 (s)	1.22 (s)	1.27 (s)
OAc	2.03 (s)	2.05 (s)	2.03 (s)	2.07 (s)	2.02 (s)	2.09 (s)	2.10 (s)

^a NMR measurement using CD₃CN as the solvent

Table 3. ^{13}C NMR spectroscopic data of compounds **3-10** (CDCl_3 , δ in ppm)

Position	3	4	5^a	6	7	9	10
1	43.0	40.6	40.7	42.4	42.5	40.1	40.4
2	19.7	18.6	18.1	18.6	19.5	18.3	18.4
3	43.0	43.8	43.1	44.2	42.9	44.0	44.2
4	34.1	34.0	33.1	33.7	34.0	33.8	33.9
5	51.5	55.1	53.9	56.2	51.4	56.4	56.7
6	67.6	69.1	68.7	69.7	67.1	69.3	69.2
7	35.2	35.2	34.6	33.8	34.9	34.3	34.6
8	124.4	33.1	33.9	33.0	125.3	33.3	32.2
9	147.0	69.1	47.4	62.0	149.7	61.8	62.0
10	38.6	38.2	37.5	37.9	38.4	38.4	38.6
11	105.0	111.0	42.0	78.6	104.8	208.2	207.2
12	153.9	150.2	204.4	182.7	153.1	173.7	174.7
13	126.8	161.2	164.7	60.6	120.1	66.6	66.8
14	128.7	33.0	43.8	42.7	133.0	39.7	39.5
15	101.8	110.2	127.0	110.1	32.4	110.8	109.1
16	147.4	170.2	192.0	142.1	174.6	143.7	144.8
17	16.0	14.6	12.4	13.2	16.5	10.2	11.9
18	33.5	33.1	32.5	33.7	33.4	33.4	33.6
19	23.1	23.0	22.4	23.2	23.0	22.9	23.0
20	27.4	17.6	15.6	16.6	26.8	17.1	17.2
OAc	171.0	170.4	169.4	170.6	170.9	170.1	170.5
	21.8	21.8	20.6	21.9	21.7	21.7	21.8

^a In CD_3CN as the solvent

When the *m*CBPA/ CHCl_3 -HCl (10:1) oxidation of **1** was performed at room temperature for 24 h (Table 1, entry 7) there was no big change since it yielded **2** (30%), **6** (13%), and **7** (10%). However, when performing the reaction at 0-4 °C for 24 h (Table 1, entry 8), compound **6** (54%) was preferred over **2** (10%), and **7** was undetected. These results suggest a chemical interrelation between **2** and **7** which was confirmed by oxidation of **2** using *m*CBPA at room temperature, thus providing **7** in 15% yield. It therefore follows that **2** is an intermediate in the formation of lactone **7**, while **6** seems to be formed through an independent route.

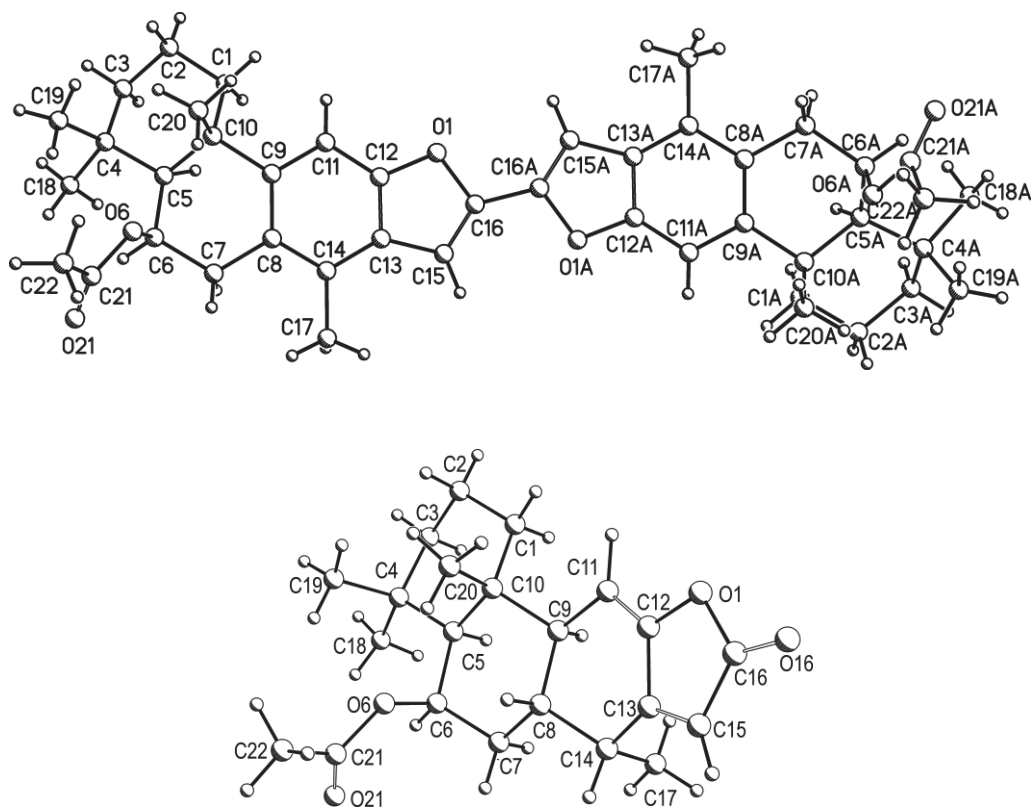


Figure 2. PLUTO drawings of the single-crystal X-ray structures of **3** (top) and **4** (bottom)

When the oxidation was performed in an aprotic medium (Table 1, entry 9), lactonization also occurs, but yielding the known cassane **8a** reported from *Caesalpinia bonduc*,²⁹ whose hydroxy group was confirmed by acetylation to yield **8b**.⁴⁰ A single-crystal X-ray diffraction analysis of **8b** (Figure 3, Table 4) confirmed the described structure and stereochemistry.

It follows that the vouacapane oxidation performance using *m*CPBA is modulable according to temperature and solvent conditions, since the possibility for the obtention of **2**, **6**, or **8a** as the main reaction outcome is possible. Furthermore, the preparation of **7** (see Table 1) complements the oxidation picture of 6 α -acetoxyvouacapane,³⁸ since compounds analogous to **6** and **8a** were generated.

Finally, the oxidative performance of vouacapane **1** was evaluated against Cr(VI) reagents, whose oxidative power can be easily modulated according to the chromium source and the acidity selected for the reaction medium.^{41,42} The use of CrO₃ in aqueous acetic acid (10:1) (Table 1, entry 10) gave **4** (10%), **6** (10%), **8a** (22%), and **9** (15%), which is a levogyre solid showing $[\alpha]_{589} -230.6$. The HRESIMS of **9** exhibited the molecular ion at m/z 397.1992 $[M + Na]^+$ (calcd as 397.1991 for C₂₂H₃₀O₅ + Na). Its ¹H and ¹³C NMR spectra (Tables 2 and 3, respectively) showed two doublets at δ 6.96 and 5.56 ($J = 3.5$ Hz), assigned to the vinyl atoms H-16 and H-15, respectively, a ketone carbonyl signal at δ 208.2, and a quaternary carbon at δ 66.6, suggesting the presence of an 11-oxospirolactone. The NOESY experiment

of **9** revealed a correlation between H-14 (δ 2.52) and H-15 (δ 5.56) suggesting the stereochemistry at C-13 as (*S*). In addition, oxidation of **6** with pyridinium chlorochromate (PCC) gave **10** in 86% yield as dextrogyre crystals ($[\alpha]_{589} +27.5$) whose NOESY experiment showed a correlation between H-15 (δ 5.43) and H-17 (δ 0.98), suggesting the C-13 stereogenic center is (*R*). The elemental composition of **10** followed from the HRESIMS $[M + Na]^+$ ion at m/z 397.1995, congruent with $C_{22}H_{30}O_5 + Na$ (calcd as 397.1991) which is the same as that of **9**. The NMR data of **10** showed several chemical shift differences in comparison with those of **9** (see Table 1). Among others, in **10** H-15 appears at δ 5.43 (*d*, 3.8 Hz) and the ketone carbonyl appears at δ 207.2, while these signals are visible at δ 5.56 (*d*, 3.5 Hz) and δ 208.2 in **9**. A single-crystal X-ray diffraction study of **10** confirmed the stereochemistry of the molecule, as shown in Figure 3, and consequently suggested that compounds **9** and **10** are C-13 epimers. The relevant crystal data are summarized in Table 4.

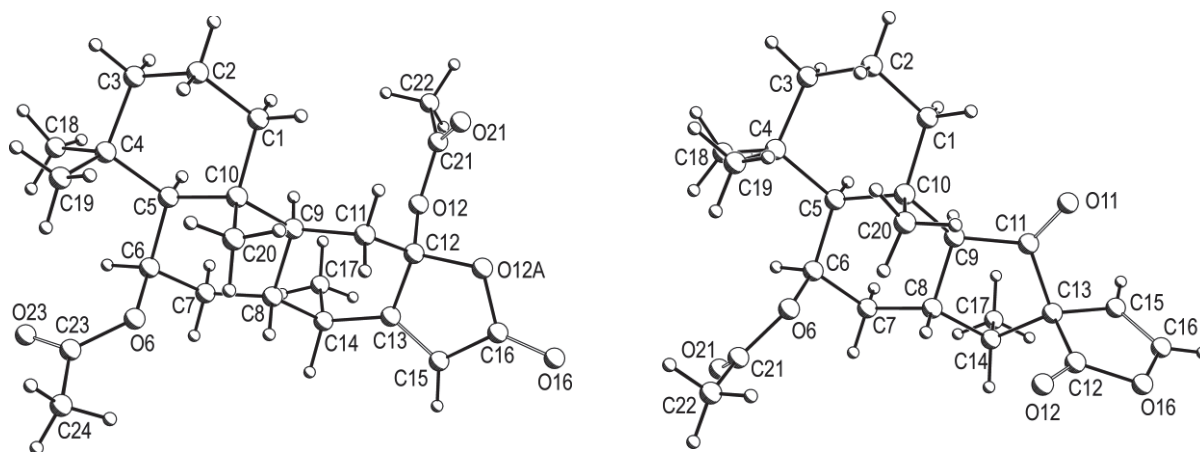


Figure 3. PLUTO drawings of the single-crystal X-ray structures of **8b** (left) and **10** (right)

The use of $K_2Cr_2O_7$ in AcOH-H₂O (5:1) at room temperature (Table 1, entry 11) allowed the preparation of **4** (10%), **6** (20%), and **9** (25%), while the reaction under reflux (Table 1, entry 12) provided an equimolar mixture of spiro lactones **9** and **10** in 60% yield, losing the chiral preferences at C-13, probably attributed to the presence of AcOH.⁴³ These results provide a methodology to control thermodynamic and stereochemistry factors for the preparation of lactones and 11-oxospirolactones from vouacapane **1**, since if the stereochemistry of spiro lactone **9** is required, the oxidation can be done using CrO_3 , while for the spiro lactone **10** stereochemistry the reagents of choice are *m*CPBA followed by PCC.

Regarding the biological potential of the diterpenoids herein described, MTT cytotoxic assays were done against human breast cancer cell lines MCF-7 and human promyelocytic leukemia HL-60 using compounds **1**, **2**, and **6** since they had adequate solubility and stability. The three tested compounds were active against both cancer cell lines, being **1** the most active diterpenoid, followed by **2**, and then by **6**

(Figure 4). In all cases cell viability is concentration dependent, while data profiles suggested non-selectivity between the assayed cell lines.

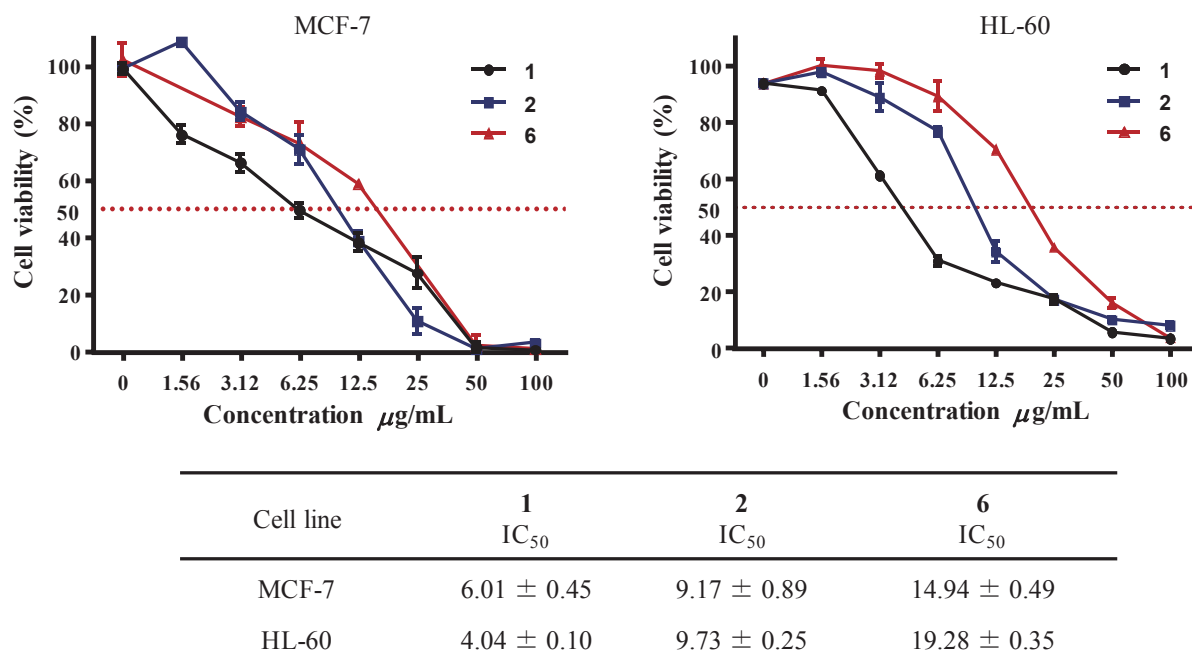


Figure 4. Cytotoxic effect of compounds **1**, **2** and **6** against MCF-7 and HL-60 cell lines after 24 h treatment at 37 °C. Cell viability percentage of breast cancer cell line MCF-7 (top left) and human promyelocytic leukemia HL-60 (top right) are shown. The IC₅₀ data (bottom) are expressed as the mean ± SD in µg/mL (*n* = 3).

It can be concluded from the current study that treatment of (–)-(5*S*,6*R*,8*S*,9*S*,10*R*,14*R*)-6-acetoxy vouacapane (**1**) under several oxidation reaction conditions, using a series of common oxidants, produces different products derived from reactivity at the furan and C-ring of the diterpene and that this group of molecules shows cytotoxic activity.

EXPERIMENTAL

General Experimental Procedures

Solvents (ACS grade reagent) were distilled prior to use. DDQ (D60400), *m*CPBA (273031), CrO₃ (236470), and K₂Cr₂O₇ (207802) were used as purchased from Sigma-Aldrich®. Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Optical rotations were determined on a Perkin Elmer 341 polarimeter. The UV spectra were obtained on Perkin-Elmer Hitachi or Perkin-Elmer Lambda 12 spectrophotometers. The infrared spectra were recorded on Perkin-Elmer 599B or

Perkin-Elmer 16F PC spectrophotometers. 1D and 2D NMR spectra were measured at 300 or 400 MHz for ^1H and at 75.4 or 100 MHz for ^{13}C on Varian Mercury 300 or 400 spectrometers from CDCl_3 or CD_3CN solutions using tetramethylsilane as the internal reference. Chemical shift values are reported in parts per million, and coupling constants (J) are in Hz. High resolution electrospray ionization mass spectra (HRESIMS) were measured on a Waters Synapt G2 spectrometer at the Department of Biochemistry, University of Colorado, Boulder, CO, USA. Column chromatography was carried out on Merck Silica Gel 60 (230-400 mesh). Acetoxycouacapanone (**1**) was available from a previous study²² as colorless crystals and showed mp 114-116 °C.

General procedure for the oxidation of 1 with DDQ

Samples of 100 mg of **1** in 5 mL of the solvent indicated in Table 1 were treated with 2.5 equivalents of DDQ under stirring at room temperature for 15 or 20 min (Table 1). The solvent was evaporated under reduced pressure and the residue was dissolved in CH_2Cl_2 , washed with water, dried over anhydrous Na_2SO_4 , and evaporated to dryness. The residue was column chromatographed on silica gel and hexanes-EtOAc mixtures to provide the purified compounds indicated in Table 1. Compound **5** was treated under the same reaction condition to yield **2** in 90%.

General procedure for the oxidation of 1 with *m*CPBA

Samples of 100 mg of **1** in 5 mL of the solvent indicated in Table 1 were treated with 2.5 equivalents of *m*CPBA using the reaction conditions indicated in Table 1, entries 6-9. After solvent evaporation the residues were dissolved in CH_2Cl_2 , washed with water, aq NaHCO_3 , and water, dried over anhydrous Na_2SO_4 , filtered, and evaporated. Each residue was column chromatographed on silica gel and hexanes-EtOAc mixtures to yield the products indicated in Table 1. The crude reaction outcome from entry 9 (Table 1) was purified by EtOAc washes, affording lactone **6**. Compound **2** was treated under the above reaction conditions, yielding **7** (15%) after column chromatography on silica gel using hexanes-EtOAc (9:1) mixtures.

Oxidation of 1 with CrO_3

A solution of 100 mg of **1** in 5 mL of AcOH- H_2O (10:1) was treated with 2 equivalents of CrO_3 , and stirred at room temperature for 1 h. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with water, aqueous NaHCO_3 , and water, dried over anhydrous Na_2SO_4 , filtered, and evaporated. The residue was column chromatographed using silica gel and mixtures of hexanes-EtOAc yielding the products indicated in Table 1.

General procedure for the oxidation of **1** with $K_2Cr_2O_7$

A solution of 100 mg of **1** in 5 mL of AcOH-H₂O (5:1) or AcOH, was treated with 2 equivalents of $K_2Cr_2O_7$. The reaction mixture was stirred at room temperature for 1 h or refluxed for 30 min, diluted with water and extracted as above to provide, after column chromatography, the products indicated in Table 1.

Oxidation of **6** with PCC

A solution of **6** (20 mg) in CH₂Cl₂ (2 mL) was added to a suspension of freshly prepared PCC (50 mg) dissolved in 1 mL of CH₂Cl₂. The mixture was stirred at room temperature for 2 h and worked up as above to yield **10** (86%).

Acetylation of **8a**

It was done as described⁴⁰ to yield **8b** (80%).

(-)-16,16'-Di-[(5*S*,6*R*,10*S*,5'*S*,6'*R*,10'*S*)-6-acetoxycouacapa- $\Delta^{8(14),9(11)}$ -dienyl] (**3**)

White crystals (CH₂Cl₂), mp 245-248 °C. $[\alpha]_{589} -41.5$, $[\alpha]_{578} -43.3$, $[\alpha]_{546} -49.1$ (*c* 2.14, CHCl₃); UV (dioxane) λ_{max} (log ϵ) nm: 215 (4.48), 248 (4.04), 256 (4.01), 314 (4.16), 323 (4.37), 338 (4.60), 357 (4.59); IR (CHCl₃) ν_{max} 2928, 2863, 1724, 1459, 1382 cm⁻¹; for ¹H NMR (400 MHz, CDCl₃) and ¹³C NMR (100 MHz, CDCl₃) see Tables 2 and 3; HRESIMS⁺ *m/z* 679.3981 [M + H]⁺ (calcd for C₄₄H₅₄O₆ + H⁺, 679.3998).

(-)-(5*S*,6*R*,8*S*,9*R*,10*R*,14*R*)-6-Acetoxycassa- $\Delta^{11,13(15)}$ -dien-12,16-olide (**4**)

Colorless crystals (hexanes- EtOAc), mp 236-239 °C. $[\alpha]_{589} -26.4$, $[\alpha]_{578} -27.6$, $[\alpha]_{546} -30.9$, $[\alpha]_{436} -37.1$ (*c* 0.42, CHCl₃); UV (EtOH) λ_{max} (log ϵ) nm: 218 (3.73), 277 (3.85); IR (CHCl₃) ν_{max} 2935, 2872, 1753, 1729, 1459, 1366 cm⁻¹; for ¹H NMR (400 MHz, CDCl₃) and ¹³C NMR (100 MHz, CDCl₃) see Tables 2 and 3; HRESIMS⁺ *m/z* 358.4712 [M]⁺ (calcd for C₂₂H₃₀O₄⁺, 358.4780).

(-)-(5*S*,6*R*,8*S*,9*S*,10*R*,14*R*)-6-Acetoxycass- $\Delta^{13(15)}$ -en-16-al-12-one (**5**)

White powder, $[\alpha]_{589} -58.2$, $[\alpha]_{578} -60.6$, $[\alpha]_{546} -66.9$, $[\alpha]_{436} -97.0$ (*c* 0.68, CHCl₃); IR (CHCl₃) ν_{max} 2930, 1724, 1428, 1250 cm⁻¹; for ¹H NMR (300 MHz, CD₃CN) and ¹³C NMR (75.4 MHz, CD₃CN) see Tables 2 and 3; HRESIMS⁺ *m/z* 361.2386 [M + H]⁺ (calcd for C₂₂H₃₂O₄ + H⁺, 361.2379).

(-)-(5*S*,6*R*,8*S*,9*S*,10*R*,11*S*,13*R*,14*R*)-6-Acetoxy-11-hydroxy-13-spirocass- Δ^{15} -en-12,16-olide (**6**)

White crystals (EtOAc), mp 109-112 °C. $[\alpha]_{589} -7.5$, $[\alpha]_{578} -7.7$, $[\alpha]_{546} -8.3$, $[\alpha]_{436} -9.9$, $[\alpha]_{365} -6.3$ (*c*

10.2, CHCl₃); IR (CHCl₃) ν_{\max} 3592, 3489, 2933, 2863, 2845, 1783, 1717, 1615 cm⁻¹; for ¹H NMR (400 MHz, CDCl₃) and ¹³C NMR (100 MHz, CDCl₃) see Tables 2 and 3; HRESIMS⁺ m/z 377.2327 [M + H]⁺ (calcd for C₂₂H₃₂O₅ + H⁺, 377.2328).

(-)-(5*S*,6*R*,10*S*)-6-Acetoxyassa- $\Delta^{8(14),9(11),12}$ -trien-12,16-olide (7)

White powder, mp 196-198 °C. [α]₅₈₉ -22.3, [α]₅₇₈ -23.2, [α]₅₄₆ -26.4, [α]₄₃₆ -41.4 (*c* 0.46, CHCl₃); IR (CHCl₃) ν_{\max} 2928, 2864, 1802, 1725, 1618, 1254 cm⁻¹; for ¹H NMR (400 MHz, CDCl₃) and ¹³C NMR (100 MHz, CDCl₃) see Tables 2 and 3; HRESIMS⁺ m/z 374.2326 [M + NH₄]⁺ (calcd for C₂₂H₂₈O₄ + NH₄⁺, 374.2331).

(-)-(5*S*,6*R*,8*S*,9*S*,10*S*,13*S*,14*R*)-6-Acetoxy-13-spirocass- Δ^{15} -en-11-oxo-12,16-olide (9)

White solid, mp 218-220 °C. [α]₅₈₉ -230.6, [α]₅₇₈ -243.5, [α]₅₄₆ -285.0, [α]₄₃₆ -588.8 (*c* 0.88, CHCl₃); IR (CHCl₃) ν_{\max} 2972, 2924, 2844, 1978, 1734, 1462, 1392 cm⁻¹; for ¹H NMR (300 MHz, CDCl₃) and ¹³C NMR (75.4 MHz, CDCl₃) see Tables 2 and 3; HRESIMS m/z 397.1992 [M + Na]⁺ (calcd for C₂₂H₃₀O₅ + Na⁺, 397.1991).

(+)-(5*S*,6*R*,8*S*,9*S*,10*S*,13*R*,14*R*)-6-Acetoxy-13-spirocass- Δ^{15} -en-11-oxo-12,16-olide (10)

Colorless crystals (acetone) mp 186-188 °C. [α]₅₈₉ +27.5, [α]₅₇₈ +29.0, [α]₅₄₆ +33.5, [α]₄₃₆ +61.0, [α]₃₆₅ +34.6 (*c* 0.48, CHCl₃); IR (CHCl₃) ν_{\max} 2923, 2845, 2723, 1789, 1735, 1613, 1507, 1462 cm⁻¹; for ¹H NMR (300 MHz, CDCl₃) and ¹³C NMR (75.4 MHz, CDCl₃) see Tables 2 and 3; HRESIMS m/z 397.1995 [M + Na]⁺ (calcd for C₂₂H₃₀O₅ + Na⁺, 397.1991).

Single-Crystal X-Ray Diffraction Analysis of 3, 4, 8b, and 10

Data of **3** were collected on an Enraf-Nonius CAD4 diffractometer with graphite monochromated Cu *K* α radiation ($\lambda = 1.54184$ Å) in the ω -2 θ scan mode. Crystal data of **4** and **8b** were collected on a Bruker Smart 6000 CCD with graphite monochromated Mo *K* α radiation ($\lambda = 0.71073$ Å), while those of **10** were collected on a Bruker D8 Venture diffractometer also with Cu *K* α radiation. All data were collected at 293(2) K. The structures of **4** and **8b** were solved by direct methods using the SHELXS-97 software and those of **3** and **10** were solved also by direct methods with the Sir2004 software. All structure refinements were done by full-matrix least squares on F^2 , the non-hydrogen atoms were treated anisotropically, and the hydrogen atoms, included in the structure factor calculation, were refined isotropically. A molecule of acetone co-crystallized with **10** which is not drawn in Figure 3. A very disordered dichloromethane molecule was squeezed to allow proper refinement of **3** and therefore the density given in Table 4 is low. Relevant crystal data for all molecules are summarized in Table 4. The data were deposited with the

Cambridge Crystallographic Data Centre from where copies can be obtained, free of charge, via <http://www.ccdc.cam.ac.uk/conts/retrieving.html>. The deposition numbers for **3**, **4**, **8b**, and **10** are 1976648, 1976649, 1976650, and 1976651, respectively.

Table 4. Crystal data, structure solution, and refinement parameters for compounds **3**, **4**, **8b** and **10**

Compound	3	4	8b	10
Formula	C ₄₄ H ₅₄ O ₆	C ₂₂ H ₃₀ O ₄	C ₂₄ H ₃₄ O ₆	2(C ₂₂ H ₃₀ O ₅).C ₃ H ₆ O
MW	678.87	358.46	418.51	807.00
Size (mm)	0.20 × 0.16 × 0.11	0.34 × 0.26 × 0.28	0.30 × 0.28 × 0.28	0.20 × 0.18 × 0.14
System	Monoclinic	Orthorhombic	Triclinic	Triclinic
Group	<i>C</i> 2	<i>P</i> 2 ₁ 2 ₁ 2 ₁	<i>P</i> 1	<i>P</i> 1
<i>a</i> (Å)	20.395(4)	7.9791(4)	7.88(2)	7.6047(3)
<i>b</i> (Å)	9.026(2)	13.4264(8)	8.32(2)	7.6166(3)
<i>c</i> (Å)	12.758(3)	18.2780(9)	10.03(3)	20.6169(8)
α (°)	90	90	71.9(2)	83.335(2)
β (°)	104.28(3)	90	86.7(1)	88.593(2)
γ (°)	90	90	62.7(1)	68.802(2)
<i>V</i> (Å ³)	2276.2(8)	1958.1(2)	553.0(3)	1105.65(8)
<i>D</i> _{calcd} g cm ⁻³	0.991	1.216	1.258	1.125
<i>Z</i>	2	4	1	1
μ (mm ⁻¹)	0.261	0.082	0.089	0.636
<i>F</i> ₀₀₀	732	776	226	404
θ _{range} (°)	3.58 to 59.97	2.97 to 27.51	2.91 to 26.65	4.32 to 59.35
Refl. Total	3627	12945	20422	47845
Refl. Uniq	3601	4368	4170	6184
<i>R</i> _{int}	0.0084	0.0507	0.0645	0.0645
Refl. Observ.	2272	2132	3436	4753
Parameters	237	270	303	536
<i>R</i> (%)	4.9	4.7	5.7	4.9
<i>R</i> _w (%)	15.0	8.7	12.0	11.9
<i>e</i> _{max} (eÅ ⁻³)	0.145	0.118	0.240	0.233

Cytotoxic assays

MCF-7 and HL-60 cells were obtained from ATCC (Manassas, VA, USA) and fetal bovine serum (FBS) was obtained from Gibco. Cytotoxicity assays were performed as described.⁴⁴ MCF-7 cells were cultured

in F-12 Ham (Sigma) medium supplemented with 10% (v/v) FBS and 100 U/mL penicillin and streptomycin (Gibco) and grown in a 5% CO₂ atmosphere at 37 °C. Typically, 10 × 10³ cells per well were seeded in 96-well plates, and incubated for 24 h. Then the medium was replaced with 100 μL of freshly medium without serum and incubated for 24 h. Afterwards, the medium was replaced again for 100 μL of new medium containing the respective concentrations of compounds **1**, **2**, or **6** (100 to 1.56 μg mL⁻¹), and cells were incubated for 24 h. HL-60 cells were cultured in RPMI (Sigma) medium supplemented with 10% (v/v) fetal bovine serum (corning) and 100 U/mL penicillin and streptomycin (Gibco) and grown in a 5% CO₂ atmosphere at 37 °C. HL-60 cells were synchronized in RPMI medium supplemented with 2% of serum (24 h). Thereafter, 2 × 10⁴ cells per well were seeded in 96-well plates, different concentrations of **1**, **2**, or **6** (100 to 1.56 μg mL⁻¹) were added, and cells were incubated for 24 h. Cell viability was determined in both cases using the MTT assay; for which a 10 μL of MTT solution (5 mg mL⁻¹, Sigma) in phosphate buffer saline (PBS) was added to each well and the plates were incubated for 4 h at 37 °C. Formazan crystals were dissolved by adding 100 μL of isopropanol-HCl (1 N) (19:1) (100 μL) and absorbance (595 nm) was recorded on a Bio-Rad 680 microplate reader. Negative control: cells incubated with medium (*n* = 3). Positive control: actinomycin D (1 μM).

ACKNOWLEDGEMENTS

We thank to CIC-UMSNH for financial support and to CONACYT-Mexico for grant 284194, ATA is grateful to CONACYT-Mexico for scholarship 398462.

REFERENCES

1. R. Banerjee, H. K. S. Kumar, and M. Banerjee, *Int. J. Rev. Life Sci.*, 2012, **2**, 7.
2. L. A. Badovskaya and L. V. Povarova, *Chem. Heterocycl. Compd.*, 2009, **45**, 1023.
3. S. N. Montoya and A. de Klerk, *Appl. Petrochem. Res.*, 2018, **8**, 55.
4. A. Quintavalla, *Curr. Med. Chem.*, 2018, **25**, 917.
5. M. V. Trmcic, R. V. Matovic, G. I. Tovilovic, B. Z. Ristic, V. S. Trajkovic, Z. B. Ferjancic, and R. N. Saicic, *Org. Biomol. Chem.*, 2012, **10**, 4933.
6. W. Elger, S. Beier, K. Pollow, R. Garfield, S. Q. Shi, and A. Hillisch, *Steroids*, 2003, **68**, 891.
7. A. V. Rama Rao, M. K. Gurjar, and P. A. Sharma, *Tetrahedron Lett.*, 1991, **32**, 6613.
8. A. Bartoli, F. Rodier, L. Commeiras, J. L. Parrain, and G. Chouraqui, *Nat. Prod. Rep.*, 2011, **28**, 763.
9. M. C. P. Yeh, M. N. Lin, Y. S. Chou, T. C. Lin, and L. Y. Tseng, *J. Org. Chem.*, 2011, **76**, 4027.
10. M. Y. Chang and Y. T. Hsiao, *J. Org. Chem.*, 2017, **82**, 11594.
11. R. Maurya, M. Ravi, S. Singh, and P. P. Yadav, *Fitoterapia*, 2012, **83**, 272.
12. R. A. Dickson, T. C. Fleischer, and P. J. Houghton, *Phcog. Commn.*, 2011, **1**, 63.

13. J. Deguchi, K. Horiguchi, C. P. Wong, T. Hosoya, A. Iihoshi, T. Kaneda, and H. Morita, *J. Nat. Med.*, 2014, **68**, 723.
14. O. Yodsaoue, S. Cheenpracha, C. Karalai, C. Ponglimanont, S. Chantrapromma, H. K. Fun, and A. Kanjana-Opas, *Phytochemistry*, 2008, **69**, 1242.
15. J. S. Zhang, Y. O. Guo, J. M. Bao, M. H. Jiang, S. L. Lin, Z. Y. Su, G. H. Tang, and S. Yin, *Helv. Chim. Acta*, 2015, **98**, 1387.
16. S. K. Kalauni, S. Awale, Y. Tezuka, A. H. Banskota, T. Z. Linn, P. B. S. Asih, D. Syafruddin, and S. Kadota, *Biol. Pharm. Bull.*, 2006, **29**, 1050.
17. T. Z. Linn, S. Awale, Y. Tezuka, A. H. Banskota, S. K. Kalauni, F. Attamimi, J. Ueda, P. B. S. Asih, D. Syafruddin, K. Tanaka, and S. Kadota, *J. Nat. Prod.*, 2005, **68**, 706.
18. G. Xiang, M. Fan, Y. Ma, M. Wang, J. Gao, J. Chen, X. Li, W. Xue, Y. Wang, H. Gao, Y. Shen, and Q. Xu, *Biochem. Pharmacol.*, 2018, **150**, 150.
19. J. Wu, G. Chen, X. Xu, X. Huo, S. Wu, Z. Wu, and H. Gao, *Fitoterapia*, 2014, **92**, 168.
20. R. G. Jiang, S. C. Ma, Z. D. He, X. S. Huang, P. P. H. But, H. Wang, S. P. Chan, V. E. C. Ooi, H. X. Xu, and T. C. W. Mak, *Bioorg. Med. Chem.*, 2002, **10**, 2161.
21. R. W. Jiang, P. P. H. But, S. C. Ma, W. C. Ye, S. P. Chana, and T. C. W. Mak, *Tetrahedron Lett.*, 2002, **43**, 2415.
22. M. A. Gómez-Hurtado, F. E. Álvarez-Esquivel, G. Rodríguez-García, M. M. Martínez-Pacheco, R. M. Espinoza-Madrigal, T. Pamatz-Bolaños, J. L. Salvador-Hernández, H. A. García-Gutiérrez, C. M. Cerda-García-Rojas, P. Joseph-Nathan, and R. E. del Río, *Phytochemistry*, 2013, **96**, 397.
23. A. Talavera-Alemán, M. A. Gómez-Hurtado, R. E. del Río, J. Marrot, C. Thomassigny, and C. Greck, *Tetrahedron Lett.*, 2017, **58**, 2901.
24. A. S. Makarov, M. G. Uchuskin, and I. V. Trushkov, *Synthesis*, 2018, **50**, 3059.
25. K. H. Theopold, 'Encyclopedia of Inorganic Chemistry: Chromium: Inorganic and Coordination Chemistry', ed. by R. B. King, Wiley & Sons Ltd., United Kingdom, 2006, pp. 1-14.
26. P. P. Yadav, R. Maurya, J. Sarkar, A. Arora, S. Kanojiya, S. Sinha, M. N. Srivastava, and R. Raghubir, *Phytochemistry*, 2009, **70**, 256.
27. T. Kinoshita, *Chem. Pharm. Bull.*, 2000, **48**, 1375.
28. Y. Yin, L. Ma, and L. H. Hu, *Helv. Chim. Acta*, 2008, **91**, 972.
29. W. Pranithanchai, C. Karalai, C. Ponglimanont, S. Subhadhirasakul, and K. Chantrapromma, *Phytochemistry*, 2009, **70**, 300.
30. T. Wirtanen, M. Muuronen, J. Hurmalainen, H. M. Tuononen, M. Niegera, and J. Helaja, *Org. Chem. Front.*, 2016, **3**, 1738.

31. I. Kitagawa, P. Simanjuntak, T. Watano, H. Shibuya, S. Fujii, Y. Yamagata, and M. Kobayashi, *Chem. Pharm. Bull.*, 1994, **42**, 1798.
32. A. Bierbach, I. Barnes, and K. H. Becker, *Atmos. Environ.*, 1995, **29**, 2651.
33. K. H. Kim, C. H. Lim, J. W. Lim, and J. N. Kim, *Adv. Synth. Catal.*, 2014, **356**, 697.
34. Y. Yuan, X. Zhao, S. Wang, and L. Wang, *J. Phys. Chem. A*, 2017, **121**, 9306.
35. H. Hussain, A. Al-Harrasi, I. R. Green, I. Ahmed, G. Abbas, and N. U. Rehman, *RSC Adv.*, 2014, **4**, 12882.
36. P. Merino, 'Organic Reactions', Vol. 87, ed. by S. E. Denmark, Wiley-VCH, Weinheim, 2015, pp. 1-256.
37. P. Joseph-Nathan, J. J. Morales, and J. Romo, *Tetrahedron*, 1966, **22**, 301.
38. S. Cheenpracha, R. Srisuwan, C. Karalai, C. Ponglimanont, S. Chantrapromma, K. Chantrapromma, H. K. Fun, S. Anjumd, and Atta-ur-Rahman, *Tetrahedron*, 2005, **61**, 8656.
39. P. Gutierrez, J. Altarejos, P. J. Linares-Palomino, R. Chahboun, and E. Alvarez-Manzaneda, *Org. Chem. Front.*, 2018, **5**, 2537.
40. J. C. Pardo-Novoa, H. M. Arreaga-González, S. Galván-Gómez, G. Rodríguez-García, R. E. del Río, C. M. Cerda-García-Rojas, P. Joseph-Nathan, and M. A. Gómez-Hurtado, *J. Nat. Prod.*, 2019, **82**, 485.
41. Y. Matsuno, J. Deguchi, Y. Hirasawa, K. Ohyama, H. Toyoda, C. Hirobe, W. Ekasari, A. Widyawaruyanti, N. C. Zaini, and H. Morita, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 3774.
42. G. G. Rao, *Talanta*, 1966, **13**, 1473.
43. J. Tadanier, J. R. Martin, R. S. Egan, A. W. Goldstein, R. S. Stanaszek, E. Hirner, and F. Fischner, *J. Org. Chem.*, 1974, **39**, 2495.
44. L. J. Flores-Álvarez, J. J. Guzmán-Rodríguez, R. López-Gómez, R. Salgado-Garciglia, A. Ochoa-Zarzosa, and J. E. López-Meza, *Int. J. Biochem. Cell. B.*, 2018, **99**, 10.