Diterpenoids and Triterpenoids from *Euphorbia retusa*

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Six new *ent*-abietane lactones (**1**−**6**), three new esterified tetracyclic triterpenes (**7**−**9**), and seven known diterpenoids and triterpenoids were isolated from the roots of *Euphorbia retusa*. Their structures were elucidated by means of spectroscopic studies including 1D and 2D NMR, mass spectrometry, chemical transformation, and comparison with literature data.

Euphorbia retusa Forsk. (Euphorbiaceae) is distributed throughout the Mediterranean region.[1,2] *Euphorbia* is the largest Euphorbiaceae genus with over 1000 species,[2] and many of them have been investigated chemically and pharmacologically due to carcinogenic and irritant properties of their latex.[3−5] Diterpenes from *Euphorbia* plants have been found to possess a number of interesting biological activities.[6−8] *E. retusa* is a perennial blue-green desert herb that grows to about 40 cm in height, with long alternate leaves,[1] and it contains a toxic and skin-irritant milky latex. This herb has been used in folk medicine for treatment of warts, trichiasis, and venomous bites.[9] Previously, it was reported that the aerial parts of *E. retusa* contained a number of common flavonol glycosides,[10] triterpenoids,[11,12] and fatty acids.[12]

Our present work describes the isolation and structure elucidation of six new compounds with abietane lactone skeletons, 3,4,18β-cyclopropa-8β-hydroxy-14-oxo-*ent*-abiet-13,15-en-16,12-olide (**1**), 3,4,18β-cyclopropa-14-oxo-*ent*-abieta-8,9,13,15-dien-16,12-olide (**2**), 3,4,18β-cyclopropa-14-oxo-*ent*-abieta-7,13,15-dien-16,12-olide (**3**), 3,4,18β-cyclopropa-7β-hydroxy-14-oxo-*ent*-abieta-8,9,13,15-dien-16,12-olide (**4**), 3,4,18β-cyclopropa-14-oxo-*ent*-abiet-7-en-16,12-olide (**5**), and 3,4,18β-cyclopropa-12β-hydroxy-*ent*-abiet-7-en-16,14-olide (**6**), and three new esterified tetracyclic triterpenes, 24-methylenecycloartanyl formate (**7**), 24-methylenecycloartanyl 2′*E*,4′*E*-decadienoate (**8**), and tirucalla-7,24-dien-3β-yl 2′*E*,4′*E*-decadienoate (**9**) from a dichloromethane extract of the roots of *E. retusa*.

Results and Discussion

Purification of a dichloromethane extract of roots of *E. retusa* by repetitive chromatographic separation provided nine new compounds (**1**−**9**), and the known compounds were identified as jolkinolide E,[13] helioscopinolide E,[14] 24-methylenecycloartanol,[15,16] 24-methylenecycloartanone,[17] cycloart-25-ene-3β,24-diol,[18] cycloeucalenol,[12] and obtusifoliol.[15] Physical and spectroscopic data of the known compounds were identical with those published in the literature.

Compound **1** was obtained as a colorless oil. The HREIMS of **1** indicated a molecular ion peak at *m*/*z* 330.1819, which corresponded to the molecular formula $C_{20}H_{26}O_4$. The IR spectrum showed absorption bands at 3451 cm^{-1} for OH, 1765 cm^{-1} indicating an α,β-unsaturated γ-lactone,[8] and 1685 cm^{-1} also indicating an α,β-unsaturated ketone.[19] The ^{13}C NMR spectrum of compound **1** in $CDCl_3$ was consistent with an abietane skeleton, with signals corresponding to three methyl, six methylene, four methine, and seven quaternary carbons (Table 1). Among these were lactone and ketone carbonyls (δ_C 172.9 and 196.0), a vinylic methyl (δ_C 9.4),[20,21] two methyl groups (δ_C 23.9 and 16.9), and one tertiary OH-bearing carbon (δ_C 76.1). The ^{1}H NMR spectrum in $CDCl_3$ (Table 1) exhibited three signals at high field [δ_H 0.12 (1H, dd, J = 5.7, 4.5 Hz, H-18 *endo*), 0.55 (1H, dd, J = 9.3, 4.5 Hz, H-18 *exo*), and 0.71 (1H, dt, J = 9.3, 5.7 Hz, H-3)] typical of a cyclopropane ring as in spectra of abietane-type diterpenes, suregadolides, isolated from *Suregada multiflora*.[20,21] The ^{1}H−^{1}H COSY spectrum of **1** revealed three proton-correlated fragments, H-3/H-18 *endo* and *exo*, H-3/one of H-2 (α-oriented), H_2-2/H_2-1 for ring A, H-5/H_2-6 and H_2-6/H_2-7 for ring B, and H-9/one of H-11 (β-oriented), H_2-11/H-12, H-12/H_3-17 (homoallylic coupling) for rings C and D. Detailed analysis of ^{1}H NMR, ^{13}C NMR, and HSQC spectra of **1** allowed assignment of carbon and proton signals of these fragments. HMBC correlations observed from the quaternary carbons C-4, C-10, and C-8 to H-3/H-5, H_2-1/H-9, and H_2-7/H-9, respectively, allowed connection of these fragments and established the partial structure of **1**. The HMBC spectrum displayed correlations characteristic of an abietane lactone between H_3-17/C-12, H_3-17/C-13, and H_3-17/C-16 (δ_C 172.9). The second carbonyl (δ_C 196.0) was located at C-14, as indicated by its correlations with H_2-7, H-9, and H_3-17. Correlations observed from C-8 (δ_C 76.1) to H-9, H_2-6, and H-11α placed the tertiary OH group at C-8. Finally, the Me-19 protons were found to be correlated with C-3, C-4, and C-18, while H-3 showed correlations with C-1, C-5, and C-18. The relative configuration of **1** was determined from the NOESY spectrum and the values of the coupling constants. The orientations of H-12 and H-9 were established as axial and equatorial, respectively, in ring C from the coupling constants and multiplicities of H-9β (δ_H 1.82, d, J = 6.3 Hz), H-11α (δ_H 2.66, dd, J = 12.0, 7.7 Hz), H-11β (δ_H 2.14, td, J = 12.0, 6.3 Hz), and H-12α (δ_H 5.39, br, ddq, J = 12.0, 7.7, 2.0 Hz), which were similar to those of reported abietane lactones having H-12α.[14,20−24] NOE correlations (Figure 1) observed between H-12α/Me-20, Me-20/Me-19, and Me-19/H-3 indicated α-orientation of all these protons and consequently β-orientation of the cyclopropane ring. The NOE of H-5 with H-18 *endo* and with H-9β indicated that H-5 was β-oriented and the A/B ring junction was *trans*. Considering the constituents isolated so far from *Euphorbia* species, compound **1** was presumed to be an *ent*-abietane diterpene.[13,14,24] The assigned orientations of H-5, H-9, and Me-20 confirmed this to be a compound belonging to the *ent* series.[20−26] The orientation of the OH group attached to C-8 was determined from the NOESY spectrum recorded in DMSO-d_6. Thus, the hydroxylic proton displayed NOE effects with H-9β and H-7β and was therefore axial (β-oriented). Compound **1** was thus identified as 3,4,18β-cyclopropa-8β-hydroxy-14-oxo-*ent*-abiet-13,15-en-16,12-olide and was named retusolide A.

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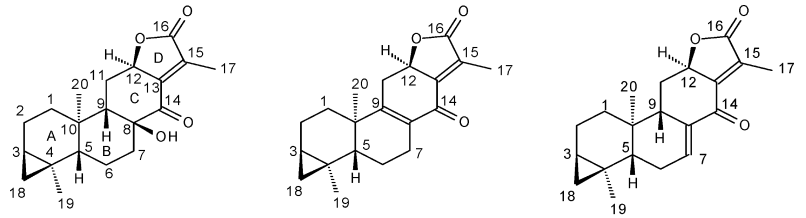
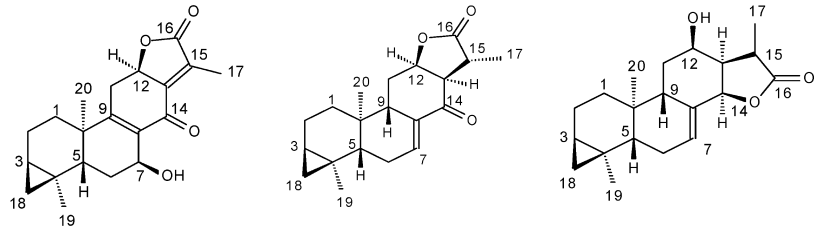
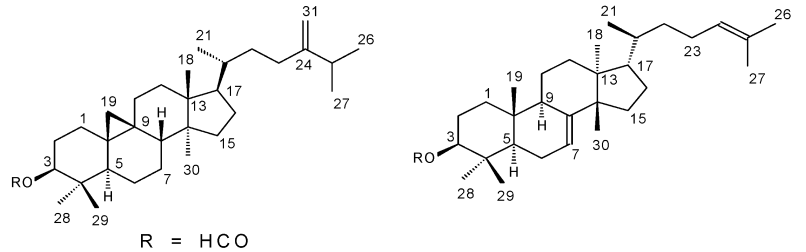


1 **2** **3**



4 **5** **6**



R = HCO
1'

7

R = CH_3-$(CH_2)_4$-CH=CH-CH=CH-CO
10' 6'-9' 5' 3' 1'

8 **9**

Table 1. ^{1}H and ^{13}C NMR Data for **1**

	1[a]		**1**[b]	
atom	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C
H-1α	1.76, dd (12.7, 5.9)	33.6	1.72, m	33.2
H-1*β*	0.83, td (13.4, 6.0)		0.70, m	
H-2α	1.97, m	18.8	1.88, m	19.03
H-2*β*	1.85, m		1.70, td (13.9, 6.9)	
H-3α	0.71, dt (9.3, 5.7)	19.1	0.60, m	19.0
4		15.7		15.8
H-5*β*	1.28, dd (11.0, 2.7)	51.1	1.22, dd (14.3, 5.3)	50.5
H-6α	1.41, m	22.7	1.23, dm (14.3)	22.8
H-6*β*	1.95, m		1.77, m	
H-7α	2.68, dd (12.7, 4.4)	33.5	2.45, dd (13.3, 3.9)	33.1
H-7*β*	1.43, m		1.27, m	
*β*8-OH	not observed	76.1	5.89, br, s	75.8
H-9*β*	1.82, d (6.3)	52.6	1.65, d (6.3)	52.8
10		36.6		36.3
H-11α	2.66, dd (12.0, 7.7)	27.0	2.51, m	26.9
H-11*β*	2.14, td (12.0, 6.3)		1.93, td (11.9, 6.3)	
H-12α	5.39, br, ddq (12.0, 7.7, 2.0)	79.5	5.44, br, ddq (11.9, 7.3, 2.0)	79.9
13		153.3		155.2
14		196.0		197.2
15		131.8		129.6
16		172.9		172.7
H-17	2.05, d (2.0)	9.4	1.84, d (2.0)	9.4
H-18 *endo*	0.12, dd (5.7, 4.5)	21.5	0.07, dd (5.6, 4.1)	21.4
H-18 *exo*	0.55, dd (9.3, 4.5)		0.43, dd (9.2, 4.1)	
H-19	1.00, s	23.9	0.91, s	24.1
H-20	0.85, s	16.9	0.71, s	16.3

[a] Spectra were recorded in $CDCl_3$. [b] Spectra were recorded in DMSO-d_6.

Compound **2** was isolated as a white, amorphous powder and exhibited a molecular ion peak at *m/z* 312.1723 ($C_{20}H_{24}O_3$) in its HREIMS, H_2O less than that of **1**. The IR spectrum had no OH band, but showed a band at 1618 cm^{-1} (double bond). The ^{1}H and ^{13}C NMR signals of **2** were similar to those of **1** (Tables 2 and 3). The only differences were the lack of signal at δ 76.1 (for C-8 in **1**) and the appearance in the *J*-modulated ^{13}C spectrum of two signals attributed to olefinic carbons of a tetrasubstituted double

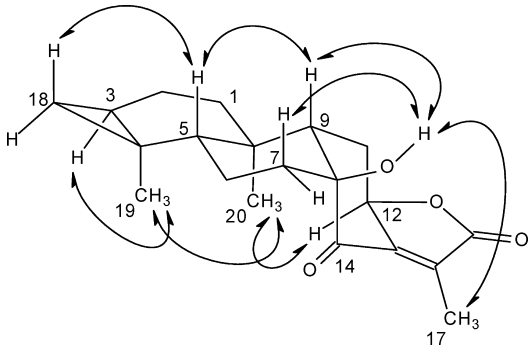


Figure 1. NOESY correlations of **1**.

bond at δ 134.6 and 160.5. In the HMBC spectrum of **2**, H_2-1, H_3-20, and H-6β exhibited ^3J interactions with C-9 and C-8, respectively, while H_2-7 and H_2-11 displayed ^2J and ^3J correlations with the two olefinic carbons. These correlations led to the placement of the double bond in the B/C ring junction (δ_C 134.6, C-8 and 160.5, C-9). The relative configuration of **2** was deduced from analysis of NOE correlations and was the same as **1**. Thus, compound **2**, named retusolide B, was elucidated as 3,4,18β-cyclopropa-14-oxo-*ent*-abieta-8,9,13,15-dien-16,12-olide.

Compound **3**, a white, amorphous powder, showed a molecular ion peak at *m*/*z* 312.1716 corresponding to the same molecular formula ($C_{20}H_{24}O_3$) as **2**. The EIMS, IR, UV, and NMR spectra of **3** were similar to those of **2**, suggesting that **2** and **3** were regioisomers. The ^{13}C NMR spectrum (Table 3) revealed the presence of one olefinic methine (δ 140.4) correlated in the HSQC spectrum with the proton at δ 6.97 (dt, J = 5.3, 2.4 Hz, H-7). This proton coupled in the COSY spectrum with two geminal protons H_2-6 (δ 2.55, ddd, J = 11.2, 5.6, 2.4 Hz and δ 2.36, m), which were correlated with one methine proton (H-5, δ 1.65, dd, J = 11.3, 5.6 Hz). In the HMBC spectrum, the olefinic proton (H-7) showed correlations with the C-14 carbonyl (δ 187.5) and with the C-9 (δ 41.6) and C-5 (δ 44.8) methines. Compound **3** showed the same relative configuration as **1** and **2**, with a characteristic NOE between H-5 and H-9. Consequently, compound **3** was assigned as 3,4,18β-cyclopropa-14-oxo-*ent*-abieta-7,13,15-dien-16,12-olide and was named retusolide C.

Compound **4**, a colorless oil, had the molecular formula $C_{20}H_{24}O_4$, as determined by HREIMS ([M]$^+$, *m*/*z* 328.1682), 16 mass units more than that of **2**. IR absorptions revealed the presence of OH (3438 cm^{-1}), α,β-unsaturated γ-lactone, and ketone (1767 and 1675 cm^{-1}) groups.[8,19] The ^{1}H and ^{13}C NMR spectra of **4** (Tables 2 and 3) showed high similarity to those of **2** and indicated that the difference was mainly the presence of signals for a hydroxymethine group (δ_H 4.72, br, s and δ_C 62.5). This supplementary proton showed correlation with C-14 (δ 187.0) in the HMBC spectrum and was attributed to H-7. Analyses of COSY, HSQC, and HMBC experiments allowed assignments of all protons and carbons. The NOESY correlations indicated that compound **4** possessed the same relative configuration as the compounds described previously. The shape of the H-7 signal (broad singlet) and the small values of its coupling constant with H-6 indicated that H-7 was equatorial (α-oriented). The absence of NOE correlation between β-oriented H-5 and H-7 confirmed this relative configuration. Thus, compound **4** was identified as 3,4,18β-cyclopropa-7β-hydroxy-14-oxo-*ent*-abieta-8,9,13,15-dien-16,12-olide and was named retusolide D.

Compound **5** possessed a molecular ion peak at *m*/*z* 314.1889 ($C_{20}H_{26}O_3$) in the HREIMS, two mass units more than that of **3**. The IR spectrum contained bands at 1777 cm^{-1} (lactone) and 1665 cm^{-1} (α,β-unsaturated ketone).[19] The ^{1}H and ^{13}C NMR spectra of **5** (Tables 2 and 3) were similar to those of **3**. The main difference was that **5** possessed a methyl group (H_3-17, δ_H 1.43, d, J = 7.3 Hz and δ_C 16.2) attached to an sp^3 carbon methine (δ_H 2.98, dd, J = 8.4, 7.3 Hz and δ_C 52.9, CH-13) instead of a vinylic methyl group as in compounds **1**−**4**. Scalar ^{1}H−^{1}H connectivities obtained by COSY experiment allowed us to identify an expanded spin system for rings C and D from H-9 (δ_H 2.23) to H_3-17 (δ_H 1.43) through H_2-11 (δ_H 1.41 and 2.37)/H-12 (δ_H 5.10)/H-13 (δ_H 2.98)/H-15 (δ_H 2.82). Association of all protons with the corresponding carbons by HSQC experiment and analysis of the long-range correlations in the HMBC spectrum led to the abietane lactone structure of **5**. Correlations observed in the NOESY spectrum between H_3-20, H-12, and H-13 indicated α-orientation of H-12 and H-13. The NOE correlation observed from H-12 to H_3-17 suggested that H-15 and H_3-17 were β- and α-oriented, respectively. From these data, compound **5** was elucidated as 3,4,18β-cyclopropa-14-oxo-*ent*-abiet-7-en-16,12-olide and was named retusolide E.

The molecular formula of compound **6**, colorless oil, was determined as $C_{20}H_{28}O_3$ (*m*/*z* 316.2015, HREIMS). Its IR spectrum displayed absorption bands at 3450 cm^{-1} (OH), 1757 cm^{-1} (lactone), and 1650 cm^{-1} (double bond). The ^{1}H and ^{13}C NMR data of **6** (Tables 2 and 3) presented similarities with those of **3** and **5** with identical A and B rings of the *ent*-abietane skeleton. Two secondary hydroxymethines were observed at δ_C 63.8 and 83.3 and one carbonyl at δ_C 181.7. These chemical shifts suggested the presence of a lactone ring and an OH group. In the HMBC spectrum, the hydroxymethines showed correlations with H-9 that allowed placement of them at positions 12 and 14. The cross-peak of the ethylenic proton H-7 (δ 5.99, m, $W_{1/2}$ = 11.0 Hz) with the hydroxymethine at δ_C 83.3 (C-14) indicated that the D lactone ring was fused on C-13 and C-14 to form a rearranged abietane lactone. Consequently, C-12 was attached to a free OH group. The relative configuration of **6** was determined from the NOESY spectrum and by comparison with related *ent*-diterpenes.[20−27] Correlations observed between H_3-20/H_3-19/H-3/H-18 *exo* and H-9/H-5/H-18 *endo* proved that the relative configuration at C-3, C-4, C-5, C-9, and C-10 was the same as that of the other compounds (**1**−**5**). The NOE correlations of H-9 with H-5 and one of H-11 protons at δ 1.94 indicated that these three protons were β-oriented. The values of the coupling constant of the two H-11 signals with H-12 (3.9 and 1.4 Hz) indicated that H-12 was α-equatorial on ring C in a chair conformation. NOE effects observed between H-11α/H-12/H-13/H-14 indicated that these protons were α-oriented. The correlations from H_3-17 to H-11β and H-9β suggested that H_3-17 were β-oriented. The small value of the coupling constant between H-13 and H-14 (J = 4.4 Hz) implied a *cis* C/D ring junction.[28] The structure of compound **6** was thus determined to be 3,4,18β-cyclopropa-12β-hydroxy-*ent*-abiet-7-en-16,14-olide, and it was named retusolide F.

Compound **7** was obtained as a white, amorphous solid and displayed a molecular ion at *m*/*z* 468.3970 in the HREIMS, consistent with the molecular formula $C_{32}H_{52}O_2$. The ^{1}H NMR spectrum of **7** (Table 4) showed signals corresponding to seven methyl groups, one oxygenated methine attributed to H-3, two broad singlets assignable to an exocyclic methylene group, and an aldehydic deshielded signal. The ^{13}C NMR spectrum (Table 4) exhibited 32 signals, for seven methyl, 11 methylene including one ethylenic carbon (=CH_2), seven methine (among them one oxymethine), and six quaternary carbons (among them two sp^2). These structural features confirmed the triterpene nature of **7** and were closely similar to those of tetracyclic cycloartane-type triterpenes such as 24-methylenecycloartanol isolated in this study and identified previously from several *Euphorbia* species.[15,16] The ^{1}H NMR spectrum of **7** included a low-field singlet (δ 8.18, H-1′) that correlated with a carbon that resonated at δ 161.2 (C-1′) in the HSQC experiment and with an oxymethine carbon signal at δ 80.8 (C-3) in the HMBC spectrum. These data indicated a formate group (HCOO) at C-3 in compound **7**.[29] The chemical shift of H-3 (δ 4.75, dd, J = 11.5, 4.7 Hz) confirmed the linkage of the formate group at C-3. COSY, HSQC, and HMBC experiments allowed

Table 2. ^{1}H NMR Data for **2**−**5**[a] and **6**[c]

	δ_H (J in Hz)				
atom	**2**	**3**	**4**	**5**	**6**
H-1α	1.71, dd (12.5, 6.2)	1.64, ddd (13.3, 5.1, 1.6)	1.70, m	1.59, m	1.51, ddm (13.4, 3.2)
H-1*β*	0.90, ddd (12.5, 9.0, 6.4)	0.83, td (13.3, 5.2)	0.95, m	0.88, ddd (16.6, 11.0, 3.5)	0.70, td (13.4, 5.1)
H-2α	2.15, dd (13.7, 9.0)	2.01, tt (13.3, 5.1)	2.15, tt (13.8, 6.0)	1.96, tt (11.0, 5.7)	1.87, tt (13.4, 5.4)
H-2*β*	1.90, dd (13.7, 6.4)	1.83, ddd (13.3, 5.2, 1.6)	1.95, dd (13.8, 6.2)	1.80, m	1.69, dd (13.4, 3.2)
H-3α	0.74, dt (9.3, 6.0)	0.79, dd (8.9, 5.1)	0.76, dt (9.2, 6.0)	0.77, dt (9.2, 5.7)	0.66, m
H-5*β*	1.33, dd (12.7, 2.7)	1.65, dd (11.3, 5.6)	1.76, br, d (13.9)	1.59, dd (11.8, 4.7)	1.64, dd (12.6, 5.1)
H-6α	1.59, dddd (19.1, 12.7, 11.8, 5.7)	2.36, m	1.79, td (13.8, 4.4)	2.28, m	2.08, tm (12.6)
H-6*β*	2.12, m	2.55, ddd (11.2, 5.6, 2.4)	2.25, m	2.55, dm (17.6)	2.28, dm (12.6)
7	2.59, dddd (18.2, 5.7, 3.6, 1.6) H-7α 2.30, m H-7*β*	6.97, dt (5.3, 2.4)	4.72, br, s H-7α	7.19, m	5.99, m ($W_{1/2}$ = 11.0)
H-9*β*		2.40, dd (7.5, 2.7)		2.23, br, s	2.28, dd (13.1, 3.9)
H-11α	3.21, ddd (15.8, 6.5, 1.6)	2.58, ddd (10.7, 7.1, 2.7)	3.27, dd (11.4, 6.4)	1.41, dd (14.6, 3.7)	1.09, td (13.1, 1.4)
H-11*β*	2.21, m	1.67, m	2.29, m	2.37, dm (14.6)	1.94, dt (13.1, 3.9)
H-12α	5.11, ddq (10.4, 6.5, 2.3)	4.98, ddq (11.3, 7.1, 2.2)	5.11, br, ddq (10.1, 6.4, 2.3)	5.10, ddd (8.4, 3.7, 2.3)	4.13 overlapped
H-13α				2.98, dd (8.4, 7.3)	2.23, dt (6.6, 4.3)
H-14α					4.65, d (4.3)
15				2.82, quint (7.3) H-15*β*	2.72, quint (6.6) H-15α
H-17	2.22, d (2.3)	2.24, d (2.2)	2.25, d (2.3)	1.43, d (7.3)	1.35, d (6.6)
H-18 *endo*	0.08, dd (6.0, 4.4)	0.16, dd (5.1, 4.6)	0.19, dd (6.0, 4.9)	0.17, dd (5.7, 4.5)	0.08, dd (5.4, 4.5)
H-18 *exo*	0.59, dd (9.3, 4.4)	0.51, dd (8.9, 4.6)	0.61, dd (9.2, 4.9)	0.50, dd (9.2, 4.5)	0.38, dd (9.1, 4.5)
H-19	1.10, s	1.06, s	1.11, s	1.06, s	0.98, s
H-20	1.20, s	0.91, s	1.20, s	0.75, s	0.67, s

[a] Spectra were recorded in $CDCl_3$. [c] Spectrum was recorded in $CDCl_3$ + CD_3OD.

Table 3. ^{13}C NMR Data (δ) for **2**−**5**[a] and **6**[b]

atom	**2**	**3**	**4**	**5**	**6**
1	30.4	31.0	29.8	31.4	30.9
2	19.3	19.1	19.2	19.2	18.9
3	18.5	19.9	18.4	19.9	19.9
4	16.4	14.7	16.6	14.8	14.7
5	47.6	44.8	41.6	44.1	44.4
6	20.6	27.5	28.9	27.6	26.7
7	24.4	140.4	62.5	139.9	133.0
8	134.6	136.8	135.7	134.8	131.3
9	160.5	41.6	164.9	40.6	37.4
10	38.9	34.3	39.8	35.2	32.2
11	34.2	27.2	33.9	27.7	30.6
12	78.8	77.9	78.4	76.7	63.8
13	150.6	151.1	149.9	52.9	44.4
14	185.7	187.5	187.0	196.2	83.3
15	131.1	132.5	132.8	40.0	39.7
16	172.8	173.5	173.3	178.2	181.7
17	9.8	10.0	9.9	16.2	8.8
18	22.3	20.5	22.2	20.4	20.1
19	23.2	24.5	23.2	24.7	24.3
20	16.8	11.5	15.7	12.4	12.8

[a] Spectra were recorded in $CDCl_3$. [b] Spectrum was recorded in $CDCl_3$ + CD_3OD.

complete assignment of all protons and carbons. The relative configuration of **7** was deduced from the NOESY spectrum and conformed to that reported for 24-methylenecycloartanol. Alkaline hydrolysis of **7** yielded 24-methylenecycloartanol, which was determined by the ^{1}H NMR spectrum and the value of $[\alpha]_D$.[15] Thus, the structure of **7** was established as 24-methylenecycloartanyl formate.

Compound **8**, a colorless gum, exhibited a quasi-molecular ion $[M + Na]^+$ at *m*/*z* 613 4971 in the HRESIMS, consistent with the molecular formula $C_{41}H_{66}O_2$. The ^{1}H and ^{13}C NMR shifts of **8** were close to those of **7** (Table 4), suggesting that **8** was also a derivative of 24-methylenecycloartanol. Alkaline hydrolysis of **8** gave 24-methylenecycloartanol.[15] The residue was a $C_{10}H_{15}O$ unit. The ^{1}H and ^{13}C NMR spectra of **8** displayed signals of an acyl ester moiety including four olefinic methines at δ_H 5.86 (d, J = 15.3 Hz, H-2′) and δ_C 119.8 (C-2′), δ_H 7.29 (dd, J = 15.3, 10.1 Hz, H-3′) and δ_C 144.7 (C-3′), δ_H 6.21 (dd, J = 15.3, 10.1 Hz, H-4′) and δ_C 128.3 (C-4′), and δ_H 6.19 (dd, J = 15.3, 7.0 Hz, H-5′) and δ_C 144.5 (C-5′). These signals formed a conjugated 1,3-diene system, as indicated by HMBC correlations of H-2′ and H-3′ with carbonyl C-1′. NOE interactions H-2′/H-4′ and H-3′/H-5′ indicated a *trans* configuration of the double bonds. COSY and HSQC experiments allowed assignments of protons and carbons to a 2′*E*,4′*E*-decadienoyl ester. In the HMBC spectrum, H-3 (δ_H 4.70, dd, J = 10.9, 4.7 Hz) correlated with the carbonyl group C-1′ (δ 167.2), implying that the ester moiety was connected to C-3 of 24-methylenecycloartanol. Therefore, the structure of **8** was determined to be 24-methylenecycloartanyl 2′*E*,4′*E*-decadienoate.

Compound **9** had a quasi-molecular ion $[M + Na]^+$ at *m*/*z* 599.4792 (HRESIMS), which corresponded to the molecular formula $C_{40}H_{64}O_2$. Comparison of ^{1}H and ^{13}C NMR spectra (Table 4) suggested that **9** had the same ester moiety as **8**. The ^{1}H NMR spectrum displayed signals due to two olefinic protons, a terminal isopropylidene group, a secondary methyl, five tertiary methyl groups, and an oxymethine. The ^{13}C NMR exhibited resonances typical of a tetracyclic skeleton possessing double bonds $\Delta^{7(8),24(25)}$ at δ 117.6 (C-7), 145.6 (C-8), 125.2 (C-24), and 130.9 (C-25).[15] The COSY, HSQC, and HMBC experiments indicated that **9** was a euphane- or tirucallane-type triterpenoid differing in configuration at C-20 (20*R*/euphane[30] and 20*S*/tirucallane[31]). Characteristic NOESY interactions were detected between H_3-30 (14*β*-Me) and H-17*β* and between H_3-21 (20-Me) and H-12α. These correlations were consistent with those of tirucallane-type triterpenes.[19,32] Absence of an NOE effect between H_3-21/H-16 typical of euphane compounds[33] and the chemical shift of protons H_3-21 at δ 0.94 confirmed that **9** belonged to the tirucallane rather than the euphane series.[19,32] Alkaline hydrolysis of **9** afforded tirucalla-7,24-dien-3*β*-ol.[34] These data led to characterization of **9** as tirucalla-7,24-dien-3*β*-yl 2′*E*,4′*E*-decadienoate.

The phytochemical study of *E. retusa* resulted in the isolation and characterization of *ent*-abietane-type diterpenes and tetracyclic triterpenes with cycloartane, lanostane, and tirucallane skeletons. Related *ent*-abietane lactones have been reported previously in this genus.[8,13] However, the six new diterpenoids (**1**−**6**), named retusolide A−F, belong to the rare class of *ent*-abietane-type diterpenes containing a cyclopropane ring bridging C-3 and C-4 of the basic abietane skeleton[20,21] and illustrate the interesting chemodiversity of this species. In this plant, compounds having ketone functions at C-14 were found (**1**−**5**). Compound **6** is the first example of a rearranged *ent*-abietane lactone isolated from the plant kingdom. The three esterified tetracyclic triterpenes (**7**−**9**)

Table 4. ^{1}H and ^{13}C NMR Data for **7**, **8**, and **9** (in $CDCl_3$)

	7		**8**		**9**	
position	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C
1	1.33−1.70, m	31.5	1.31−1.70, m	31.6	1.30−1.74, m	36.8
2	1.75−1.85, m	26.9	1.71−1.86, m	26.9	1.72−1.78, m	24.2
3α	4.75, dd (11.5, 4.7)	80.8	4.70, dd (10.9, 4.7)	80.3	4.65, dd (11.1, 4.1)	80.7
4		39.4		39.6		38.0
5α	1.46, dd (12.2, 4.3)	47.1	1.48, dd (12.5, 5.0)	47.1	1.49, dd (13.0, 6.5)	50.7
6	0.87−1.64, m	20.9	0.86−1.64, m	20.9	2.01−2.19, m	23.7
7	1.13−1.39, m	25.78	1.15−1.38, m	25.8	5.30, br, q (2.7)	117.6
8β	1.57, dd (12.2, 4.8)	47.8	1.57, dd (12.5, 4.3)	47.8		145.6
9α		20.2		20.1	2.29, m $W_{1/2} = 25$	48.8
10		25.79		25.9		34.8
11	1.17, m H-11β	26.4	1.18, m H-11β	26.5	1.56, m	18.1
	2.05, m H-11α		2.05, dt (16.0, 9.0) H-11α			
12	1.69, m	32.8	1.69, br, t (9.0)	32.5	1.67−1.83, m	33.7
13		45.2		45.2		43.5
14		48.8		48.8		51.1
15	1.34, m	35.5	1.37, m	35.5	1.52, m	33.9
16	1.33−1.97, m	28.1	1.33−1.98, m	28.1	1.35−1.98, m	28.2
17	1.66, m H-17α	52.2	1.67, br, t (12.0) H-17α	52.2	1.52, q (10.0) H-17β	52.9
18	1.02, s	17.9	1.03, s	17.9	0.86, s	21.8
19	0.64, br, d (4.1) H-19 *endo*	29.7	0.64, d (3.8) H-19 *endo*	29.8	0.83, s	13.1
	0.41, d (4.1) H-19 *exo*		0.41, d (3.8) H-19 *exo*			
20	1.45, m	36.1	1.46, m	36.1	1.44, m	35.9
21	0.94, d (7.1)	18.3	0.96, d (6.7)	18.2	0.94, d (6.5)	18.3
22	1.22−1.62, m	34.9	1.20−1.64, m	34.9	1.09−1.50, m	36.1
23a	2.18, ddd (15.0, 10.5, 4.5)	31.3	2.17, m	31.2	2.10, m	24.9
23b	1.94, m		1.93, m		1.92, m	
24		156.9		156.9	5.16, t (6.6)	125.2
25	2.29, sept (6.8)	33.7	2.29, sept (6.7)	33.8		130.9
26	1.09, d (6.8)	21.9	1.09, d (6.7)	21.9	1.74, s	25.7
27	1.08, d (6.8)	21.8	1.08, d (6.7)	21.8	1.66, s	17.6
28	0.93, s	25.3	0.92, s	25.4	0.91, s	27.6
29	0.96, s	15.1	0.99, s	13.9	1.01, s	15.9
30	0.95, s	19.3	0.96, s	19.3	1.02, s	27.2
31a	4.76, br, s	105.9	4.77, br, s	105.9		
31b	4.72, br, s		4.72, br, s			
1′	8.18, s	161.2		167.2		167.1
2′			5.86, d (15.3)	119.8	5.86, d (15.2)	119.7
3′			7.29, dd (15.3, 10.1)	144.7	7.29, dd (15.2, 10.0)	144.7
4′			6.21, dd (15.3, 10.1)	128.3	6.21, dd (15.2, 10.0)	128.3
5′			6.19, dd (15.3, 7.0)	144.5	6.19, dd (15.2, 6.9)	144.5
6′			2.22, q (7.0)	32.9	2.21, q (6.9)	32.9
7′			1.49, m	28.4	1.47, m	28.4
8′			1.35, m	31.3	1.33, m	31.3
9′			1.37, m	22.4	1.36, m	22.4
10′			0.93, t (6.6)	14.0	0.95, t (6.5)	14.0

possessing a cycloartane or tirucallane genin are used as chemotaxonomic markers of the genus *Euphorbia*.[35]

Experimental Section

General Experimental Procedures. The optical rotations were measured on a Perkin-Elmer 241 polarimeter. UV spectra were obtained using a Kontron UVS900 lite, Uvikon 941 spectrophotometer. IR spectra were measured on an Avatar 320 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DRX 500 NMR spectrometer in $CDCl_3$, CD_3OD, or DMSO-d_6 (^{1}H at 500 MHz and ^{13}C at 125 MHz). 2D NMR experiments were performed using standard Bruker microprograms (XWIN-NMR version 2.6 software). EIMS and HREIMS were recorded using a GCT Micromass apparatus. ESIMS were obtained using a MSQ Thermofinnigan instrument. HRESIMS experiments were recorded using a Micromass Q-TOF instrument. Column chromatography (CC) was carried out on Kieselgel 60 (70−230 mesh, Merck) or LiChroprep RP-18 (40−63 μm, Merck). HPLC was performed on a Dionex apparatus equipped with an ASI-100 autosampler, a P580 pump, a diode array detector UVD 340S, and Chromeleon software. An Interchim column (UP5ODB.25M, 250 × 10 mm, 5 μm) was used for semipreparative HPLC using isocratic elution (MeCN/H_2O, 4:1) at 25 °C and a flow rate of 5 mL/min; the chromatograms were monitored at 205, 225, 254, and 280 nm. TLC was carried out in silica gel plates (Kieselgel 60 F_{254} Merck).

Plant Material. Roots of *E. retusa* were collected during May 2005 in the vicinity of Biskra (Algeria). The plant was identified by Pr. Bachir Oudjehih, Agronomic Department of the University of Batna. A voucher specimen has been deposited in the herbarium of the Agronomic Department under reference LCCE/373.

Extraction and Isolation. Powdered roots (600 g) of *E. retusa* were extracted with CH_2Cl_2 (2 × 5 L) at room temperature during 3 days to obtain a crude extract (10 g). A portion of the extract (3 g) was subjected to silica gel vacuum liquid chromatography (VLC) (50 × 50 mm; fractions of 100 mL) using a gradient of *n*-hexane/EtOAc (100:0 to 0:100). Fractions having similar TLC profiles were pooled to give nine fractions. Fraction 2 was subjected to silica gel CC using *n*-hexane/EtOAc (100:0 to 0:100) as eluent to afford 17 fractions. Fractions eluted with *n*-hexane/EtOAc (98:2) gave 60 mg of 24-methylenecycloartanol in pure form. Preparative TLC of fractions eluted with *n*-hexane/EtOAc (99.5:0.5), developed with a mixture of cyclohexane/toluene/EtOAc (18:1.5:0.5), allowed isolation of compounds **7** (6.3 mg), **8** (5.1 mg), and **9** (6.8 mg). Fractions eluted with *n*-hexane/EtOAc (99:1) were separated by silica gel CC using a gradient of *n*-hexane/$CHCl_3$ (100:0 to 90:10). Fractions eluted with *n*-hexane/$CHCl_3$ (97:3) provided 24-methylenecycloartanone (7.5 mg). Preparative TLC of fractions eluted with *n*-hexane/EtOAc (97:3), developed with cyclohexane/EtOAc (85:15), afforded a mixture of two compounds, cycloeucalenol and obtusifoliol (10.6 mg). The fraction F-3 was subjected to silica gel CC eluting with cyclohexane/EtOAc (100:0 to 90:10) to afford 12 fractions. Fractions eluted with cyclohexane/EtOAc (99:1) were purified using silica gel CC and elution with *n*-hexane/EtOAc (98:2), which yielded jolkinolide E (13.5 mg). Fractions eluted with cyclohexane/EtOAc (98:

2) were purified by semipreparative HPLC using isocratic elution (MeCN/H_2O, 4:1), yielding 4.5 and 4.3 mg of pure compounds **2** and **3**, respectively. Fractions F-4 and F-5 were mixed and applied to silica gel CC eluting with *n*-heptane/EtOAc (100:0 to 80:20) to give 19 fractions. Fractions eluted with *n*-heptane/EtOAc (95:5) were purified using silica gel CC and elution with CH_2Cl_2/EtOH (99.3:0.7), to provide 6.8 mg of cycloart-25-ene-3β,24-diol. Fractions eluted with *n*-heptane/EtOAc (93:7) were submitted to silica gel CC using a gradient of cyclohexane/EtOAc (100:0 to 80:20) to afford seven fractions. Purification of fractions eluted with cyclohexane/EtOAc (95:5) by semipreparative HPLC eluting with an isocratic system (MeCN/H_2O, 4:1) yielded 7.6 mg of compound **6**. Fractions eluted with *n*-heptane/EtOAc (90:10) were subjected to reversed-phase (RP-18) CC, using a gradient of MeOH/H_2O (60:40 to 100:0) as eluent, to provide compounds **1** (5.4 mg) and **4** (3.3 mg). Original fraction 6 was submitted to silica gel CC eluting with cyclohexane/EtOAc (100:0 to 50:50) to obtain 10 fractions. Fractions eluted with cyclohexane/EtOAc (90:10) were further purified on RP-18 CC, with MeOH/H_2O (60:40 to 100:0), to give compound **5** (3.6 mg). Original fraction 7 was applied to RP-18 CC eluting with MeOH/H_2O (40:60 to 100:0) to afford eight fractions. Fractions eluted with MeOH/H_2O (70:30) were purified by silica gel CC eluting with a gradient of cyclohexane/EtOAc (100:0 to 70:30). Fractions eluted with cyclohexane/EtOAc (90:10) contained 4.2 mg of helioscopinolide E.

Alkaline Hydrolysis. Each esterified triterpene, **7** (6.3 mg), **8** (5.1 mg), and **9** (6.8 mg), dissolved in $CHCl_3$ (15 mL) was hydrolyzed separately with 5% alcoholic KOH for 5 h at room temperature. The reaction mixtures were exhaustively extracted with ethyl acetate (3 × 20 mL). The EtOAc solubles were dried with anhydrous Na_2SO_4, filtered, and evaporated in vacuo to give three fractions. After CC of each fraction on silica gel, eluting with *n*-hexane and EtOAc (9:1), the corresponding free alcohols were obtained.

Retusolide A (1): colorless oil; $[\alpha]^{25}_D$ +29.5 (*c* 0.35, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 241 (0.64), 204 (0.53) nm; IR ($CHCl_3$) λ_{max} 3451, 2925, 2863, 1765, 1685, 1654, 1615, 1221, 1092, 1020 cm^{-1}; ^1H and ^{13}C NMR ($CDCl_3$ and DMSO-d_6), see Table 1; EIMS *m*/*z* 330 $[M]^+$ (10), 312 (40), 244 (43), 177 (100); HREIMS *m*/*z* 330.1819 (calcd for $C_{20}H_{26}O_4$, 330.1831).

Retusolide B (2): white, amorphous powder; $[\alpha]^{25}_D$ −80.3 (*c* 0.34, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 256 (0.84), 205 (0.78) nm; IR (KBr) λ_{max} 2928, 2860, 1760, 1682, 1650, 1620, 1381, 1230, 1106, 1050 cm^{-1}; ^1H and ^{13}C NMR ($CDCl_3$), see Tables 2 and 3; EIMS *m*/*z* 312 $[M]^+$ (30), 297 (15), 223 (60), 205 (50), 148 (100); HREIMS *m*/*z* 312.1723 (calcd for $C_{20}H_{24}O_3$, 312.1725).

Retusolide C (3): white, amorphous powder; $[\alpha]^{25}_D$ −37.3 (*c* 0.40, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 256 (1.22), 206 (1.04) nm; IR (KBr) λ_{max} 2926, 2858, 1765, 1658, 1618, 1322, 1219, 1096, 1018 cm^{-1}; ^1H and ^{13}C NMR ($CDCl_3$), see Tables 2 and 3; EIMS *m*/*z* 312 $[M]^+$ (30), 297 (20), 257 (30), 223 (25), 205 (20), 148 (100); HREIMS *m*/*z* 312.1716 (calcd for $C_{20}H_{24}O_3$, 312.1725).

Retusolide D (4): colorless oil; $[\alpha]^{25}_D$ −126.6 (*c* 0.16, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 275 (0.38), 206 (1.05) nm; IR ($CHCl_3$) λ_{max} 3438, 2926, 2865, 1767, 1675, 1645, 1384, 1329, 1258, 1158, 1125, 1079, 1013 cm^{-1}; ^1H and ^{13}C NMR ($CDCl_3$), see Tables 2 and 3; EIMS *m*/*z* 328 $[M]^+$ (6), 310 (80), 265 (100), 267 (65), 242 (70), 227 (50), 149 (85); HREIMS *m*/*z* 328.1682 (calcd for $C_{20}H_{24}O_4$, 328.1675).

Retusolide E (5): white, amorphous solid; $[\alpha]^{25}_D$ +9.2 (*c* 0.08, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 248 (0.36), 204 (0.60) nm; IR (KBr) λ_{max} 2923, 2853, 1777, 1665, 1635, 1580, 1449, 1380, 1250, 1080, 1010 cm^{-1}; ^1H and ^{13}C NMR ($CDCl_3$), see Tables 2 and 3; EIMS *m*/*z* 314 $[M]^+$ (20), 299 (10), 279 (50), 167 (25), 149 (100); HREIMS *m*/*z* 314.1889 (calcd for $C_{20}H_{26}O_3$, 314.1882).

Retusolide F (6): colorless oil; $[\alpha]^{25}_D$ −44.8 (*c* 0.24, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 281 (0.14), 241 (0.33), 205 (0.78) nm; IR ($CHCl_3$) λ_{max} 3450, 2926, 2850, 1757, 1625, 1453, 1381, 1184, 1018 cm^{-1}; ^1H and ^{13}C NMR ($CDCl_3$ + CD_3OD), see Tables 2 and 3; EIMS *m*/*z* 316 $[M]^+$ (5), 298 (30), 266 (20), 159 (65), 121 (60), 107 (100); HREIMS *m*/*z* 316.2015, (calcd for $C_{20}H_{28}O_3$, 316.2038).

24-Methylenecycloartanyl formate (7): white, amorphous solid; $[\alpha]^{25}_D$ +33.6 (*c* 0.36, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 203 (0.60) nm; IR (KBr) λ_{max} 2928, 2865, 1727, 1641, 1465, 1376, 1213, 1198, 1175, 1040 cm^{-1}; ^1H and ^{13}C NMR ($CDCl_3$), see Table 4; EIMS *m*/*z* 468 $[M]^+$ (2), 396 (20), 298 (20), 284 (100), 175 (10), 174 (15); HREIMS *m*/*z* 368.3970 (calcd for $C_{32}H_{52}O_2$, 468.3967).

24-Methylenecycloartanyl 2′*E*,4′*E*-decadienoate (8): colorless gum; $[\alpha]^{25}_D$ +32.4 (*c* 0.32, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 280 (0.34), 262 (0.56), 203 (1.20) nm; IR ($CHCl_3$) λ_{max} 2954, 2930, 2864, 1718, 1641, 1615,1460, 1376, 1244, 1145, 984 cm^{-1}; ^1H and ^{13}C NMR ($CDCl_3$), see Table 4; ESIMS *m*/*z* 613 $[M + Na]^+$; HRESIMS *m*/*z* 613.4971 (calcd for $C_{41}H_{66}O_2Na$, 613.4961).

Tirucalla-7,24-dien-3β-yl 2′*E*,4′*E*-decadienoate (9): colorless gum; $[\alpha]^{25}_D$ −9.4 (*c* 0.37, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 281 (0.30), 251 (0.50), 207 (1.24) nm; IR ($CHCl_3$) λ_{max} 2952, 2929, 2862, 1712, 1642, 1617, 1458, 1375, 1247, 1140, 990 cm^{-1}; ^1H and ^{13}C NMR ($CDCl_3$), see Table 4; ESIMS *m*/*z* 599 $[M + Na]^+$, 615 $[M + K]^+$; HRESIMS *m*/*z* 599.4792 (calcd for $C_{40}H_{64}O_2Na$, 599.4804).

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Supporting Information Available: ^1H NMR and ^{13}C NMR spectra of new compounds **1**−**9** and their tables with a full listing of ^1H NMR, COSY, HMBC, and NOESY spectroscopic data are available free of charge via the Internet at http://pubs.acs.org.

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