Cytotoxic Triterpenoids from *Maytenus retusa*

Sandra M. Oramas-Royo,[†,‡] Haydee Chávez,[§] Patricia Martín-Rodríguez,[⊥,‡] Leandro Fernández-Pérez,[⊥,‡] Ángel G. Ravelo,*,[†,‡] and Ana Estévez-Braun*,[†,‡]

Instituto Universitario de Bio-Orgánica "Antonio González", Avenida Astrofísico Francisco Sánchez 2, 38206, La Laguna, Tenerife, Spain, Instituto Canario de Investigación del Cáncer (ICIC), Facultad de Farmacia, Universidad de San Luis Gonzaga de Ica, Perú, and Departamento de Ciencias Clínicas, Facultad de Ciencias de la Salud, Universidad de Las Palmas de Gran Canaria, Spain

Seven new triterpenoids (**1**−**7**) and 36 known compounds were isolated from the root bark of *Maytenus retusa*. Their structures were determined by 1D and 2D spectroscopic studies. Several compounds were evaluated for their cytotoxicity against the human tumor cell lines HL-60 and MCF-7. Some of them were cytotoxic, with IC$_{50}$ values ranging between 0.2 and 4.7 μM.

The Celastraceae family, a group of dicotyledonous species consisting of about 1300 species in 106 genera, is widely distributed through the warm temperature regions of the world.[1] Celastraceae species have been used for centuries throughout South America and mainland China as insect repellents and insecticides and for the treatment of ailments ranging from stomach complaints to fever, rheumatoid arthritis, and cancer.[2]

Some examples are the peruvian species *Maytenus macrocarpa* and *Maytenus amazonica*,[3] which are used in the treatment for rheumatism, influenza, gastrointestinal diseases, and skin cancer, and *Maytenus ilicifolia*,[4] which is used as an analgesic, antiulcerogenic, antiseptic, and antitumor agent.

Maytenus species constitute a rich source of terpenoids such as friedelane-type triterpenes (quinonemethide, enequinone-methide, and phenolic types),[5−7] lupanes,[8] oleananes,[9,10] dimeric triterpenes,[11−13] diterpenes such as kaurane and abietane,[14−16] sesquiterpenes,[17] and sesquiterpene-triterpene hetero-Diels−Alder adducts.[18]

The aromatic and quinoid triterpenes are of interest due to their antibiotic and cytotoxic activities.[19] Given that metabolites present in *Maytenus* species possess interesting biological activities and the absence of any previous phytochemical studies on *Maytenus retusa* (Poiret) Briq (Celastraceae), we examined this species. In this paper we describe the isolation and structural elucidation of seven new terpenes (**1**−**7**) and 36 known terpenoids. The structures of the isolated compounds were determined by spectroscopic studies (¹H NMR and ¹³C NMR), including bidimensional homonuclear (COSY and ROESY) and heteronuclear (HSQC and HMBC) correlation experiments. Some of the compounds showed cytotoxic activity against the human tumor cell lines HL-60 and MCF-7.

Results and Discussion

Repeated chromatography of a CHCl$_3$ extract of the root bark of *M. retusa* on silica gel and Sephadex LH-20 yielded seven new compounds (**1**−**7**) and 36 known terpenes: α-cyperotundone (**8**),[20] mayteine (**9**),[21] lupeol (**10**),[22] nepeticin (**11**),[23] calenduladiol (**12**),[24] resinone (**13**),[25] 3-oxo-friedel-1-ene (**14**),[26] 3β-hydroxyolean-9(11): 12-diene (**15**),[27] 3β-hydroxyurs-9(11):12-diene (**16**),[26] 3β,29-dihydroxyglut-5-ene (**17**),[28] cangoronine (**18**),[29] tingenone (**19**),[30] 20α-hydroxytingenone (**20**),[31] 20β-hydroxytingenone (**21**),[32] 22β-hydroxytingenone (**22**),[33] pristimerine (**23**),[34] dispermoquinone (**24**),[35] amazoquinone (**25**),[36] 6-oxotingenol (**26**),[37] 3-O-methyl-6-
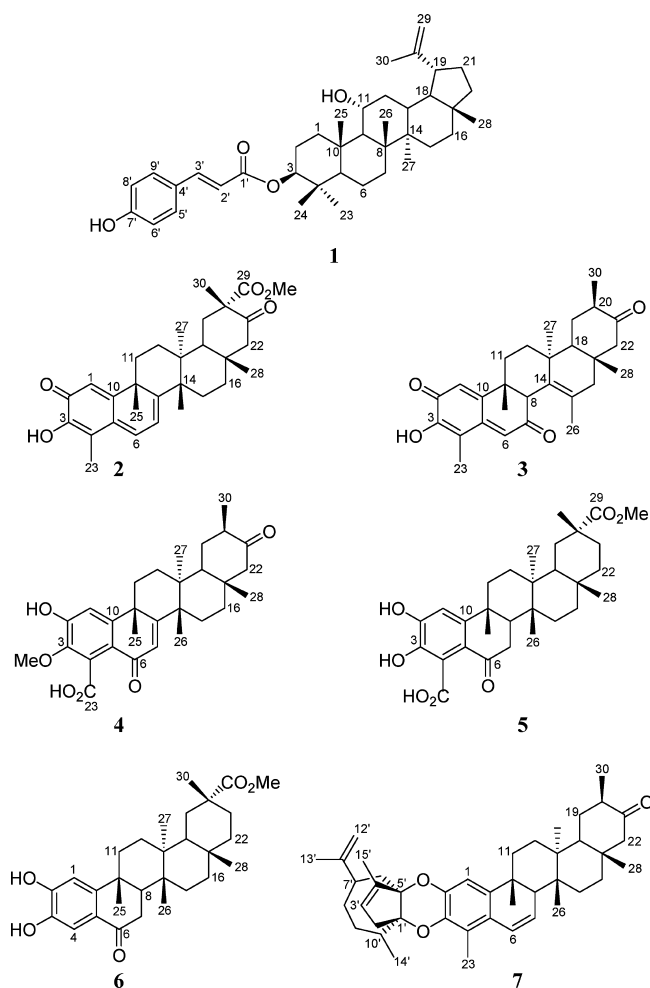
oxotingenol (**27**),[37] 3-O-methyl-23-hydroxy-6-oxotingenol (**28**),[38] 22β-hydroxy-6-oxotingenol (**29**),[39] 6-oxopristimerol (**30**),[37] 7-hydroxy-6-oxopristimerol (**31**),[40] 7,8-dihydro-6-oxoingenol (**32**),[36] 22β-hydroxy-7,8-dihydro-6-oxotingenol (**33**),[39] macrocarpin A (**34**),[41] blepharodol (**35**),[5] 7-oxo-blepharodol (**36**),[42] cheilocline A (**37**),[18] cheilocline B (**38**),[18] cheilocline C (**39**),[18] cheilocline D (**40**),[18] cheilocline F (**41**),[18] cheilocline I (**42**),[18] and milicifoline B (**43**)[43] (for structures of compounds **8**−**43**, see Figure S1 in the Supporting Information).

Compound **1** had the molecular formula C$_{39}$H$_{56}$O$_4$ as determined by HREIMS. The IR spectrum showed absorption bands for OH (3394 cm⁻¹) and carbonyl (1684 cm⁻¹) groups. Preliminary

* To whom correspondence should be addressed. Tel: +34 922318576. Fax: +34 922318571. E-mail: aestebra@ull.es; agravelo@ull.es.

† Instituto Universitario de Bio-Orgánica "Antonio González".
‡ Instituto Canario de Investigacion del Cancer.
§ Facultad de Farmacia, Universidad de San Luis Gonzaga de Ica.
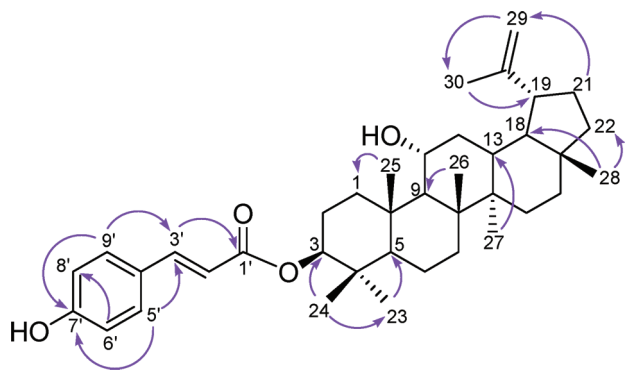⊥ Universidad de Las Palmas de Gran Canaria.

Figure 1. Selected HMBC correlations for compound **1**.

spectroscopic data indicated that **1** was a lupane triterpene related to nepeticin ($3\beta,11\alpha$-dihydroxylup-20(29)-ene, **11**).[23,44] The ^{1}H NMR spectrum had six singlet methyl signals (δ 1.09, 1.05, 0.97, 0.94, 0.90, and 0.78) and a signal for a methyl on a double bond at δ 1.69. The ^{1}H NMR spectrum also displayed two broad singlets (δ 4.72 and 4.59) attributable to two vinylic protons, two protons geminal to an oxygenated function [δ 4.63 (1H, t, $J = 5.7$ Hz), and 2.64 (1H, dt, $J = 13.5, 3.4$ Hz)], an oxymethine proton (δ 3.94), and the typical lupane H_β-19 proton signal at δ 2.38 (1H, td, $J = 11.0, 5.7$ Hz). ^{1}H NMR signals characteristic of a (E)-p-coumaroyl moiety were also detected. The ^{13}C NMR spectrum showed the presence of a carboxylic carbon (δ 167.2) and signals for six aromatic carbons, two olefinic carbons at δ 143.7 (d) and 116.5 (d), two oxymethine carbons (δ 80.5 and 70.5), and two sp^2 carbons [δ 150.2 (s) and 109.9 (t)], characteristic of the $\Delta^{20,29}$ functionality of a lupane skeleton. The data indicated that **1** was a lupane triterpene with an OH group and a p-coumarate moiety, which by comparison with the NMR data of nepetecin must be located at C-3 and at C-11. The position of the p-coumaroyl moiety at C-3 was confirmed by correlations detected in the HMBC spectrum (Figure 1).

The orientation of the oxymethine proton at C-3 was established as α by the value of the coupling constants and the NOE effect detected between H-3 and Me-23.[45] Similarly, the orientation of the OH at C-11 was established as α due to the NOE effects between H-11 and Me-25 and Me-26.[23] Thus, compound **1** was 3β-(E)-p-coumaroylnepeticin.

Compound **2** ($C_{30}H_{38}O_5$) had IR bands for carbonyl (1731 cm^{-1}) and OH (3363 cm^{-1}) groups. The ^{1}H NMR (Table 1) exhibited signals characteristic of *nor*-tritepenequinones belonging to the pristimerine series:[34,46] a methyl ester at δ 3.59 (3H, s), two doublets at δ 3.24 (1H, $J = 14.4$ Hz) and 2.82 (1H, $J = 16.1$ Hz), five methyls (δ 1.51, 1.34, 1.33, 1.00, and 0.73), one methyl at δ 2.21 characteristic of the Me-23, a doublet at δ 6.54 (1H, $J = 1.2$ Hz, H-1), and two protons at δ 7.03 (1H, dd, $J = 7.1, 1.2$ Hz) and 6.34 (1H, d, $J = 7.1$ Hz) attributable to H-6 and H-7, respectively. The ^{13}C NMR spectra (Table 2) indicated carbons characteristic of the A and B rings of triterpene methylenquinones [δ 133.5 (C-6), 119.8 (C-1), 118.2 (C-7), 168.6 (C-8), 164.7 (C-10), 146.0 (C-3), 127.7 (C-5), 117.1 (C-4), and 42.7 (C-9)], two carbonyl groups [δ 209.4 (s) and 178.4 (s)], a methyl ester [δ 175.0 (s) and 52.5 (q)], and six methyl groups (δ 38.7, 32.6, 25.0, 21.9, 17.8, and 10.3). These data agreed with a *nor*-triterpenemethylenequinone of the pristimerine series, with an additional carbonyl group. The location of this carbonyl function at C-21 was established by the following HMBC correlations: H-22a/C-21, H-22b/C-21, H-19a/C-21, H-30/C-21 (Figure 2).

Compound **3** showed the base peak at m/z 434, corresponding to the molecular formula $C_{28}H_{34}O_4$. Its ^{1}H NMR spectrum (Table 1) showed two doublets (δ 6.43 and 6.38), with a coupling constant of 1.3 Hz, characteristic of H-1 and H-6 in 7-oxo-quinonemethide triterpenoids.[35,36] Six methyls, one of them characteristic of the

rearranged methyl Me-26 at C-15, in 14(15)-ene-quinone-methide-type triterpenoids,[47] were also detected. In this type of quinone-methide triterpene, Me-26 is shifted to lower fields due to the carbonyl group at C-7. The ^{13}C NMR (Table 2), COSY, ROESY, HMBC, and HSQC data for compound **3** agreed with the structure shown. The absolute configuration at C-8 was assumed to be 8S by biogenetic considerations, since the other two quinones of this type (dispermoquinone (**24**) and amazoquinone (**25**)) isolated in this study present the configuration 8S, as determined by analysis of the corresponding CD spectra.[36,48]

Compound **4** had the molecular formula $C_{29}H_{36}O_6$. The IR spectrum indicated OH (3392 cm^{-1}) and carbonyl groups (1710, 1709 cm^{-1}) and a double bond conjugated to a carbonyl group (1460 cm^{-1}). Compound **4** showed spectroscopic data characteristic of a 6-oxo-triterpene phenol related to macrocarpin C,[41] which presents the Me-23 oxidized to CO_2H. Thus, the ^{1}H NMR spectrum exhibited signals for four angular methyl groups [δ 1.65 (Me-25), 1.43 (Me-26), 0.99 (Me-27), 1.04 (Me-28)], a doublet methyl at δ 1.02 ($J = 6.7$ Hz, Me-30), an aromatic hydrogen at δ 7.35 (s, H-1), an olefinic proton at δ 6.52 (s, H-7), and a methoxy group (δ 3.62, 3H). The ^{13}C NMR, DEPT, and HMBC spectra of **4** indicated two carbonyl carbons (δ 213.2 and 187.9), a carboxylic acid (δ 173.7), two olefinic carbons characteristic of an α,β-unsaturated carbonyl system [δ 178.6 (s) and 124.4 (d)], and six aromatic carbons (δ 155.6, 153.5, 153.1, 119.5, 113.7, and 111.4). The main difference of **4**, with respect to macrocarpin C, was the absence of a doublet at δ 4.52 ($J = 3.2$ Hz) characteristic of the 22β-hydroxy moiety in a tingenone skeleton. Since the methoxy group did not show an NOE effect with H-1, its location at C-3 was proposed in agreement with triterpene phenols isolated previously.[43] Thus, compound **4** is 3-methoxy-6-oxotingenol-23-oic acid.

Compound **5** had the molecular formula $C_{30}H_{40}O_7$ by HREIMS. The ^{1}H NMR data were similar to those of macrocarpin A (**34**),[41] a 6-oxo-7,8-dihydrotriterpene phenol having an aldehyde group at C-4. The main differences were the shift of H-1 (in macrocarpin A H-1 appeared at δ 7.14 and in compound **5** it appeared at 7.04) and the absence of a signal corresponding to the aldehyde. The shift of H-1 was similar to that in macrocarpin C,[41] which has a carboxylic acid at C-4. We could not obtain the ^{13}C NMR spectrum of this compound since it decomposed rapidly. Thus, the proposed structure for compound **5** is 6-oxo-7,8-dihydropristimerol-23-oic acid.

Compound **6** showed the base peak at m/z 468, corresponding to the molecular formula $C_{29}H_{40}O_5$. Its ^{1}H NMR (Table 1) had signals for five singlet methyls (δ 1.19, 1.16, 1.08, 0.99, and 0.77), a methyl ester [δ 3.62 s (3H)], and two aromatic protons [δ 7.67 (s) and 6.82 (s)]. These signals were similar to those of blepharodol (**35**).[5] The main difference was the absence of Me-23. The HMBC correlations spectrum (Figure 3) together with the ^{13}C NMR and DEPT data (Table 2) agreed with **6** being 23-*nor*-blepharodol.

Compound **7** had the molecular formula $C_{43}H_{58}O_3$. The ^{1}H NMR, ^{13}C NMR, and DEPT spectra revealed that **7** was a sesquiterpene-triterpene adduct.[18,43] Its ^{1}H NMR spectrum presented signals characteristic of a triterpenic unit related to the isotingenol series:[49] five methyl groups, one doublet methyl (δ 1.00, $J = 5.9$ Hz), two vinylic protons at δ 6.67 (1H, dd, $J = 9.8, 2.8$ Hz, H-6) and 5.89 (1H, dd, $J = 9.8, 2.5$ Hz, H-7), and an aromatic proton at δ 6.56 (H-1). With respect to the sesquiterpene unit derived from guaia-1(5),3(4),11(3)-triene[18,43] the following characteristic signals were detected: a vinylic proton (δ 5.40, 1H, bs), two singlets [(δ 4.78, 1H, s, H-12'a) and (δ 4.72, 1H, s, H-12'b)], a secondary methyl at δ 1.15 ($J = 6.9$ Hz, Me-14'), and two methyl groups on a double bond [δ 1.78 (Me-13') and 1.47 (Me-15')]. Its ^{13}C NMR confirmed the presence of 43 carbon atoms. Unequivocal assignments of all ^{13}C NMR resonances were made by analysis of the HSQC and HMBC correlations. The linkage between the sesquiterpene and triterpene units and the β-disposition of the cyclopentene

Table 1. ^{1}H NMR (CDCl$_3$)^a Data of Compounds **2**, **3**, **4**, **5**, and **6**

H	2	3	4	5	6
1	6.54, d (1.2)	6.38, d (1.3)	7.35, s	7.04, s	6.82, s
4					7.67, s
6	7.03, dd (7.1, 1.2)	6.43, d (1.3)			
7	6.34, d (7.1)		6.52, s		2.52, m
8		3.01, s			2.25, dd (11.0, 5.8)
11a	2.22, m		2.42, m		1.86, m
11b			2.14, m		
12a	1.86, m		2.35, m		1.62, bs
12b	1.25, m		1.62, m		1.44, m
15a	1.82, m		1.88, m		1.25, bs
15b	1.67, m		1.70, m		
16a	1.93, m		1.51, m		1.69, m
16b	1.52, m				1.37, m
18	1.77, m		1.72, m		1.59, bs
19a	2.82, d (16.1)		2.21, m		2.37, dd (12.5, 6.3)
19b	1.99, d (16.1)		1.80, m		1.60, m
20		2.55, m	2.50, m		
22a	3.24, d (14.4)	2.91, d (14.5)	2.90, d (14.6)		2.01, td (13.9, 3.3)
22b	1.95, d (14.4)		1.83, m		0.86, m
23	2.21, s	2.10, s		10.27, s	
25	1.51, s	1.32, s	1.65, s	1.20, s	1.16, s
26	1.33, s	1.78, s	1.43, s	1.02, s	0.99, s
27	0.73, s	1.05, s	0.99, s	0.99, s	0.77, s
28	1.00, s	0.97, s	1.04, s	1.04, s	1.08, s
30	1.34, s	0.90, d (6.1)	1.02, d (6.7)	1.25, s	1.19, s
−OMe	3.59, s		3.62, s	3.89, s	3.62, s

^{a} Spectra recorded at 400 MHz, except for **4** (300 MHz). *J* values (in Hz) in parentheses.

Table 2. ^{13}C NMR (CDCl$_3$)^a Data of Compounds **2**, **3**, **4**, and **6**

C	2	3	4	6
1	119.8, CH	119.4, CH	113.7, CH	109.5, CH
2	178.4, C	181.3, C	153.5, C	150.8, C
3	146.0, C	146.4, C	153.1, C	141.9, C
4	117.1, C	117.3, C	111.4, C	113.2, CH
5	127.7, C	141.1, C	119.5, C	123.5, C
6	133.5, CH	131.5, CH	187.9, C	200.3, C
7	118.2, CH	200.0, C	124.4, CH	35.4, CH$_2$
8	168.6, C	57.3, CH	178.6, C	43.9, CH
9	42.7, C	41.5, C	42.7, C	36.8, C
10	164.7, C	161.8, C	155.6, C	152.8, C
11	33.5, CH$_2$	31.4, CH$_2$	34.6, CH$_2$	32.4, CH$_2$
12	29.7, CH$_2$	36.1, CH$_2$	30.1, CH$_2$	29.5, CH$_2$
13	39.6, C	39.8, C	40.8, C	39.1, C
14	44.6, C	142.6, C	45.1, C	38.6, C
15	28.7, CH$_2$	130.0, C	28.4, CH$_2$	28.2, CH$_2$
16	35.6, CH$_2$	37.9, CH$_2$	35.3, CH$_2$	35.7, CH$_2$
17	37.1, C	38.1, C	38.1, C	29.9, C
18	43.8, CH	55.5, CH	43.4, CH	44.3, CH
19	34.3, CH$_2$	34.1, CH$_2$	31.9, CH$_2$	30.3, CH$_2$
20	53.6, C	42.0, CH	41.9, CH	40.4, C
21	209.4, C	213.8, C	213.2, C	29.6, CH$_2$
22	51.9, CH$_2$	53.3, CH$_2$	52.5, CH$_2$	36.0, CH$_2$
23	10.3, CH$_3$	10.2, CH$_3$	173.7, C	
25	38.7, CH$_3$	29.7, CH$_3$	37.8, CH$_3$	25.3, CH$_3$
26	21.9, CH$_3$	31.5, CH$_3$	20.1, CH$_3$	15.2, CH$_3$
27	17.8, CH$_3$	18.5, CH$_3$	19.6, CH$_3$	16.7, CH$_3$
28	32.6, CH$_3$	32.4, CH$_3$	32.2, CH$_3$	31.5, CH$_3$
29	175.0, C			179.4, C
30	25.0, CH$_3$	18.0, CH$_3$	15.1, CH$_3$	32.0, CH$_3$
OMe	52.5, CH$_3$		51.6, CH$_3$	51.5, CH$_3$

^{a} Spectra recorded at 100 MHz for **2** and **4** and at 75 MHz for **3** and **6**. Data based on DEPT, HSQC, and HMBC experiments.

ring were established by the NOEs observed in the ROESY spectrum (Figure 4).

The NMR signals attributable to the sesquiterpene unit were similar to those of cheilocline C.[18] This fact, together with the observed NOEs from Me-23 to Me-14′, from Me-25 to Me-15′, and from H-1 to Me-15′, was consistent with the β-disposition of the cyclopentene ring and with substitution similar to that of cheilocline C (**39**).[18] All data mentioned above agreed with the structure assigned to **7**, which we named retusonine.

Due to the previously reported cytotoxic activity for related *nor*-triterpenequinone and *nor*-triterpenephenols,[3a,4,41,50] compounds **2**−**4** and the known triterpenoids cangoronine (**18**), tingenone (**19**), 20α-hydroxytingenone (**20**), 20β-hydroxytingenone (**21**), 22β-hydroxytingenone (**22**), pristimerine (**23**), dispermoquinone (**24**), amazoquinone (**25**), 6-oxotingenol (**26**), macrocarpin A (**34**), and blepharodol (**35**) were tested for cytotoxicity against the tumor cell lines HL60 and MCF7 (see Supporting Information). The IC$_{50}$ values of the most active compounds were also calculated (Table
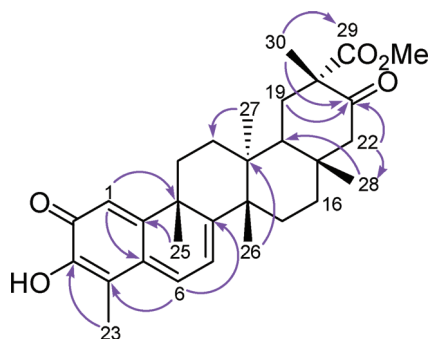
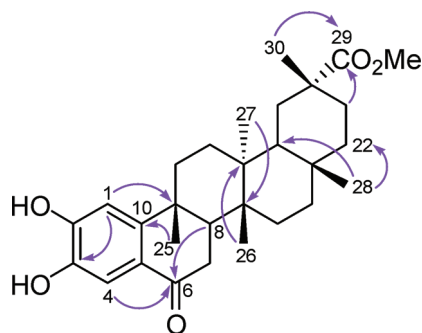**Figure 2.** Selected HMBC correlations for compound **2**.

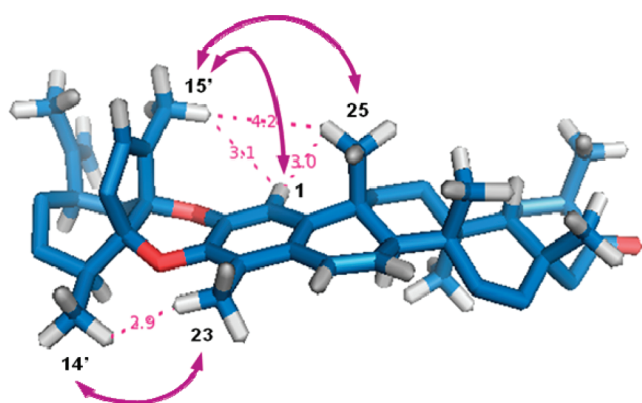**Figure 3.** Selected HMBC correlations for compound **6**.

Figure 4. Selected ROESY correlations for compound **7**.

Table 3. Cytotoxicity against Cultured Cell Lines (IC$_{50}$ μM)^a

compound	HL60	MCF7
2	1.4 ± 0.36	10 ± 0.00
19	0.5 ± 0.15	3 ± 0.38
20	0.4 ± 0.15	4.7 ± 0.62
21	0.2 ± 0.00	1.4 ± 0.26
22	0.7 ± 0.15	4.4 ± 0.91
23	0.2 ± 0.06	0.4 ± 0.12
24	1.7 ± 0.20	>30
34	1.7 ± 0.73	>30
adriamicine	0.1 ± 0.01	>10

^{a} HL60: human promyelocytic leukemia cell line; MCF7: Michigan Cancer Foundation 7, human breast adenocarcinoma cell line.

3). The results shown in Table 3 indicate that, for these two tumor cell lines, quinone-methide triterpenes are more cytotoxic than phenolic-methide triterpenes. Among quinones, the functionalities present in ring E seem to modulate the activity. The best cytotoxicities were achieved with compounds having an ester at C-30 (i.e., **2**, **23**, and **24**) and with an OH at C-20 and a carbonyl group at C-21 (i.e., **20** and **21**). Of the phenolic triterpenes tested (**4**, **6**, **26**, **34**, and **35**), only **34** was cytotoxic, which indicates the

importance of an aldehyde group at C-4 for activity (compare **34** vs **6**, and **34** vs **35**).

In conclusion, *M. retusa* is a rich source of triterpenes, *nor*-triterpene quinones, and *nor*-triterpene phenols, including the new compounds **1−7**. Some of the isolated triterpenes were cytotoxic against the tumor cell lines HL60 and MCF7.

Experimental Section

General Experimental Procedures. Optical rotations were measured with a Perkin-Elmer 241 automatic polarimeter. UV spectra were collected in absolute EtOH on a JASCO V-560 spectrophotometer. IR spectra were obtained using a Bruker IFS28/55 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in CDCl$_3$ at 400 and 100 or at 300 and 75 MHz, respectively, with TMS as the internal reference. 2D NMR experiments were conducted on a Bruker WP-400 SY NMR spectrometer at 400 MHz and on a Bruker Avance 500 spectrometer at 500 MHz. High- and low-resolution mass spectra were obtained on a VG Autospec spectrometer. Analtech silica gel GF preparative layer with UV254 was used for TLC. Silica gel (0.2−0.63 mm) and Sephadex LH-20 (Biosigma) were used for column chromatography. Silica gel 60 (Merck) was used on a Harrison Research 7924T Chromatotron.

Plant Material. *Maytenus retusa* was collected in the department of San Martín, Perú, in Dececember 2003, and it was identified by the botanist J. Ruiz. A voucher specimen is on file (No. 5659) at the Herbarium of the Departamento de Botánica, Universidad Nacional de la Amazonía (Iquitos, Perú).

Extraction and Isolation. Root bark of *M. Retusa* (1.361 kg) was extracted with CHCl$_3$ in a Soxhlet apparatus. Evaporation of the solvent under reduced pressure provided 74 g of a dark orange extract. This CHCl$_3$ extract was chromatographed on Sephadex LH-20 using mixtures of *n*-hexane−CH$_2$Cl$_2$−MeOH (2:1:1), yielding seven fractions, A−G. These fractions were repeatedly chromatographed on silica gel, preparative TLC, or a chromatotron, using mixtures of *n*-hexane−EtOAc or toluene−EtOH as eluents, affording 44 terpenes. Compounds **1−7** were new to the literature. Fraction A yielded **37**[18] (208.8 mg), **40**[18] (824.8 mg), **41**[18] (57.1 mg), and **43**[43] (169.3 mg). Compounds **7** (48.2 mg), **38**[18] (156.3 mg), **39**[18] (207.9 mg), **40**[18] (570.3 mg), **41**[18] (99.8 mg), **42**[18] (87.8 mg), and **43**[43] (67.5 mg) were isolated from fraction B. Compounds **1** (5.1 mg), **2** (4.1 mg), **7** (2.5 mg), **8**[20] (3.6 mg), **9**[21] (34.5 mg), **10**[22] (1.0 mg), **11**[23] (12.6 mg), **14**[26] (2.7 mg), **15**[27] (1.6 mg), **16**[26] (4.7 mg), **17**[28] (1.9 mg), **19**[30] (700.8 mg), **20**[31] (6.0 mg), **21**[32] (17.2 mg), **22**[33] (7.4 mg), **23**[34] (140.1 mg), **34**[41] (58.0 mg), **27**[37] (8.1 mg), **28**[38] (41.4 mg), **37**[18] (1.0 mg), **39**[18] (20.3 mg), **40**[18] (20.6 mg), **41**[18] (15.0 mg), and **43**[43] (11.4 mg) were isolated from fraction C. Fraction D yielded **12**[24] (2.5 mg), **13**[25] (1.2 mg), **19**[30] (146.1 mg), **34**[41] (245.0 mg), **29**[39] (2.6 mg), **33**[39] (2.0 mg), **27**[37] (6.9 mg), **30**[37] (25.2 mg), **4** (4.3 mg), and **5** (10.0 mg). Compounds **18**[29] (7.3 mg), **24**[35] (14.0 mg), **25**[36] (3.6 mg), **19**[30] (10.5 mg), **20**[31] (3.5 mg), **21**[32] (11.0 mg), **22**[33] (21.0 mg), **32**[36] (10.3 mg), **30**[37] (12.1 mg), **35**[5] (62.4 mg), and **6** (26.4 mg) were isolated from faction E. Fraction F yielded **24**[35] (16.8 mg), **25**[36] (16.7 mg), **26** (110.0 mg), **31**[40] (2.1 mg), and **36**[42] (1.8 mg). Compound **4** (10.5 mg) was isolated from fraction G.

3β-(E)-p-Coumaroylnepeticin (1): amorphous, white solid; [α]^{20}$_D$ +25.0 (c 0.1, CHCl$_3$); UV (EtOH) λ$_{max}$ (log ε) 341 (2.85), 244 (5.28) nm; IR (neat) ν$_{max}$ 3394, 2927, 2857, 1684, 1632, 1604, 1541, 1514, 1456, 1379, 1277, 1168, 1103, 986, 884, 832 cm$^{−1}$; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.60 (1H, d, J = 16.0 Hz, H-3′), 7.43 (2H, d, J = 8.5 Hz, H-5′ + H-9′), 6.83 (2H, d, J = 8.5 Hz, H-6′ + H-8′), 6.30 (1H, d, J = 16.0 Hz, H-2′), 5.35 (1H, bs, −OH), 4.72 (1H, bs, H-29a), 4.63 (1H, t, J = 5.7 Hz, H-3α), 4.59 (1H, bs, H-29b), 3.94 (1H, m, H-11), 2.64 (1H, dt, J = 13.5, 3.4 Hz, H-1α), 2.38 (1H, dt, J = 11.0, 5.7 Hz, H-19), 2.05 (1H, m, H-12a), 2.00 (2H, m, H-2), 1.87 (1H, m, H-21a), 1.79 (1H, td, J = 13.2, 3.7 Hz, H-13), 1.69 (3H, s, H-30), 1.69 (1H, m, H-15a), 1.61 (1H, m, H-12b), 1.51 (2H, m, H-16 + H-7), 1.43 (1H, m, H-18), 1.39 (2H, m, H-6), 1.37 (2H, m, H-22), 1.34 (1H, m, H-9), 1.09 (3H, s, H-25), 1.05 (3H, s, H-26), 0.97 (3H, s, H-27), 0.94 (3H, s, H-24), 0.90 (3H, s, H-23), 0.84 (1H, m, H-5), 0.78 (3H, s, H-28); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 167.2 (C, C-1′), 157.4 (C, C-7′), 150.2 (C, C-20), 143.7 (CH, C-3′), 129.8 (CH, C-9′ + C-5′), 127.5 (C, C-4′), 116.5 (CH, C-2′), 115.8 (CH, C-8′ + C-6′), 109.9 (CH$_2$, C-29), 80.5 (CH, C-3), 70.5 (CH, C-11), 55.7 (CH, C-9), 55.7 (CH, C-5), 47.7 (CH, C-19), 47.7 (CH, C-18), 43.0 (C, C-17), 42.6 (C, C-14), 42.6 (C, C-8), 40.7 (CH$_2$, C-1), 39.8 (CH$_2$, C-22), 38.9 (C, C-10), 38.5 (C, C-4), 37.6 (CH$_2$, C-2), 37.1 (CH, C-13), 35.4 (CH$_2$, C-16), 35.2 (CH$_2$, C-7),

29.6 (CH$_2$, C-21), 28.3 (CH$_3$, C-23), 27.4 (CH$_2$, C-12), 24.0 (CH$_2$, C-15), 19.3 (CH$_3$, C-30), 18.0 (CH$_3$, C-28), 18.0 (CH$_2$, C-6), 17.2 (CH$_2$, C-26), 16.8 (CH$_3$, C-24), 16.4 (CH$_3$, C-25), 14.5 (CH$_3$, C-27); EIMS *m/z* 588 [M]$^+$ (11), 570 (81), 406 (16), 391 (17), 255 (16), 216 (12), 189 (21), 187 (11), 159 (12), 149 (12), 147 (100), 145 (15), 135 (17), 134 (15), 133 (23), 131 (11), 123 (15), 109 (25), 107 (22), 105 (18), 95 (33), 69 (28); HREIMS *m/z* 588.4155 (calcd for C$_{39}$H$_{56}$O$_4$, 588.4179).

21-Oxopristimerine (2): amorphous, orange solid; [α]^{20}$_D$ +40.0 (*c* 0.1, CHCl$_3$); UV (EtOH) λ$_{max}$ (log ε) 239 (3.42), 230 (2.71), 214 (3.38) nm; IR (neat) ν$_{max}$ 3363, 2932, 2871, 1731, 1720, 1597, 1551, 1514, 1442, 1378, 1287, 1231, 1187, 1091, 868 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 6.96 (1H, bs, OH), for the rest of the signals see Table 1; ^{13}C NMR (CDCl$_3$, 100 MHz) see Table 2; EIMS *m/z* 478 [M]$^+$ (29), 466 (19), 422 (19), 420 (11), 253 (14), 241 (30), 227 (15), 204 (26), 203 (40), 202 (51), 201 (72), 200 (10), 189 (55), 188 (100), 187 (53), 159 (11), 135 (10), 133 (11), 121 (15), 109 (15), 95 (23), 91 (15); HREIMS *m/z* 478.2630 (calcd for C$_{30}$H$_{38}$O$_5$, 478.2719).

7-Oxo-7,8-dihydroscutione (3): amorphous, orange solid; [α]^{20}$_D$ −38.3 (*c* 0.1, CHCl$_3$); UV (EtOH) λ$_{max}$ (log ε) 341 (3.03), 329 (3.13), 262 (3.14), 244 (3.16) nm; IR (neat) ν$_{max}$ 3375, 2928, 2869, 1775, 1707, 1630, 1517, 1457, 1419, 1383, 1295, 1197, 1168, 1065, 880 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 6.97 (1H, bs, OH), for the rest of the signals see Table 1; ^{13}C NMR (CDCl$_3$, 75 MHz) see Table 2; EIMS *m/z* 434 [M]$^+$ (16), 423 (11), 286 (13), 257 (11), 236 (22), 235 (37), 231 (13), 230 (12), 217 (100), 216 (88), 215 (14), 205 (30), 202 (15), 188 (18), 179 (12), 178 (11), 165 (13), 140 (14), 137 (49), 136 (13), 105 (33), 93 (36), 91 (36); HREIMS *m/z* 434.2429 (calcd for C$_{28}$H$_{34}$O$_4$, 434.2457).

3-Methoxy-6-oxotingenol-23-oic Acid (4): amorphous, yellow solid; [α]^{20}$_D$ −38.6 (*c* 0.1, CHCl$_3$); UV (EtOH) λ$_{max}$ (log ε) 341 (3.09), 276 (3.11), 247 (3.13) nm; IR (neat) ν$_{max}$ 3392, 2926, 2858, 1710, 1709, 1596, 1460, 1380, 1300, 1068, 886, 742 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.18 (1H, s, OH), for the rest of the signals see Table 1; ^{13}C NMR (CDCl$_3$, 100 MHz) see Table 2; EIMS *m/z* 480 [M]$^+$ (4), 423 (26), 422 (60), 421 (28), 408 (14), 407 (44), 245 (13), 229 (15), 217 (39), 216 (15), 204 (100), 203 (64), 202 (18), 191 (11), 130 (19), 121 (26), 109 (29), 107 (24), 105 (12); HREIMS *m/z* 480.2300 (calcd for C$_{29}$H$_{36}$O$_6$, 480.2512).

6,23-Dioxo-7,8-dihydropristimerol-23-oic Acid (5): amorphous, yellow solid; ^{1}H NMR (CDCl$_3$, 400 MHz) see Table 1; EIMS *m/z* 468 [M − CO$_2$]$^+$ (6), 466 (100), 464 (11), 438 (11), 423 (15), 245 (21), 230 (13), 218 (11), 217 (35), 204 (12), 109 (11); HREIMS *m/z* 468.2855 (calcd for C$_{29}$H$_{40}$O$_5$, [M − CO$_2$]$^+$, 468.2876).

23-*nor*-Blepharodol (6): amorphous, yellow solid; [α]^{20}$_D$ −15.3 (*c* 0.2, CHCl$_3$); UV (EtOH) λ$_{max}$ (log ε) 339 8 (3.00), 258 (3.01), 245 (3.16) nm; IR (neat) ν$_{max}$ 3364, 2936, 2871, 1727, 1661, 1590, 1513, 1455, 1380, 1298, 1202, 1060, 887 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.05, (1H, s, −OH), 3.88 (1H, s, OH), 2.16 (1H, bd, H-21a), 1.29 (1H, m, H-21b), for the rest of the signals see Table 1; ^{13}C NMR (CDCl$_3$, 75 MHz) see Table 2; EIMS *m/z* 468 [M]$^+$ (100), 466 (12), 257 (10), 245 (17), 231 (17), 217 (17), 190 (50), 189 (65), 151 (10), 123 (15), 109 (46), 107 (16), 93 (11); HREIMS *m/z* 468.2884 (calcd for C$_{29}$H$_{40}$O$_5$, 468.2876).

Retusonine (7): amorphous, pale yellow solid; [α]^{20}$_D$ −33.8 (*c* 0.2, CHCl$_3$); UV (EtOH) λ$_{max}$ (log ε) 316 (2.98), 288 (3.21), 245 (3.23) nm; IR (neat) ν$_{max}$ 2930, 2869, 1710, 1645, 1582, 1456, 1378, 1318, 1253, 1206, 1142, 1110, 1090, 1069, 1046, 1019, 986, 913, 888, 818, 771 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 6.67 (1H, dd, *J* = 9.8, 2.8 Hz, H-6), 6.56 (1H, s, H-1), 5.89 (1H, dd, *J* = 9.8, 2.5 Hz, H-7), 5.40 (1H, bs, H-3′), 4.78 (1H, s, H-12′a), 4.72 (1H, s, H-12′b), 2.96 (1H, d, *J* = 14.3 Hz, H-22α), 2.90 (1H, dd, *J* = 11, 2.4 Hz, H-7′), 2.62 (1H, bs, H-18), 2.59 (1H, bs, H-8), 2.43 (2H, d, *J* = 16.9 Hz, H-2′), 2.23 (1H, m, H-19a), 2.17 (3H, s, H-23), 2.05 (1H, m, H-9′a), 2.05 (1H, m, H-6′a), 2.03 (1H, m, H-10′), 1.91 (1H, m, H-8′a), 1.87 (1H, m, H-11a), 1.87 (1H, m, H-9′b), 1.85 (1H, m, H-16a), 1.84 (1H, d, *J* = 14.3 Hz, H-22β), 1.78 (3H, s, H-13′), 1.75 (1H, dd, *J* = 14.6, 2.4 Hz, H-12a), 1.70 (1H, m, H-6′b), 1.65 (1H, m, H-19b), 1.65 (1H, m, H-20), 1.60 (1H, m, H-12b), 1.47 (3H, s, H-15′), 1.43 (1H, m, H-8′b), 1.32 (3H, s, H-27), 1.30 (1H, m, H-16b), 1.27 (1H, m, H-11b), 1.15 (1H, d, *J* = 6.9 Hz, H-14′), 1.10 (3H, s, H-26), 1.05 (3H, s, H-25), 1.01 (3H, s, H-28), 1.00 (3H, d, *J* = 5.9 Hz, H-30); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 214.3 (C, C-21), 151.4 (C, C-11′), 142.3 (C, C-2*), 142.2 (C, C-10*), 142.1 (C, C-3*), 142.0 (C, C-4′*), 127.9 (CH, C-7), 125.3 (C, C-3′), 125.0 (C, C-5), 124.7 (CH, C-6), 121.0 (C, C-4), 108.9 (CH$_2$, C-12′), 108.4 (CH, C-1), 91.2 (C, C-1′), 90.3 (C, C-5′), 54.0 (CH$_2$, C-22), 45.5 (CH$_2$, C-2′), 45.1 (CH, C-8), 43.9 (CH, C-10′), 43.9 (CH, C-20), 42.2

(CH, C-18), 40.7 (CH, C-7′), 40.2 (C, C-13), 39.0 (C, C-14), 38.4 (C, C-17), 37.3 (C, C-9), 36.9 (CH$_2$, C-6′), 36.6 (CH$_2$, C-8′), 35.4 (CH$_2$, C-16), 32.9 (CH$_3$, C-28), 31.8 (CH$_2$, C-19), 31.1 (CH$_2$, C-11), 30.5 (CH$_2$, C-9′), 30.0 (CH$_2$, C-12), 27.5 (CH$_2$, C-15), 23.0 (CH$_3$, C-25), 20.8 (CH$_3$, C-13′), 18.7 (CH$_3$, C-27), 18.7 (CH$_3$, C-14′), 16.2 (CH$_3$, C-26), 15.2 (CH$_3$, C-30), 11.5 (CH$_3$, C-15′), 10.8 (CH$_3$, C-23), *interchangeable values; EIMS *m/z* 662 [M]$^+$ (79), 422 (23), 189 (26), 159 (85), 147 (10), 145 (77), 133 (18), 121 (17), 109 (15), 107 (21), 105 (29), 93 (16), 91 (19); HREIMS *m/z* 622.4388 (calcd for C$_{43}$H$_{58}$O$_3$, 622.4386).

MTT Proliferation Assay. HL60 and MCF-7 cells were purchased from ATCC and cultured in RPMI and DMEN containing 10% FBS, respectively. For 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium (MTT) (Sigma-Aldrich, St. Louis, MO) analysis, cells were plated in 96-well plates at 10 000 cells/well. Twenty-four hours after plating, vehicle (0.1% DMSO, final concentration) or compound was added to cells at indicated concentrations. Forty-eight hours following compound addition, MTT was added to each well (0.5 mg/mL, final concentration), and plates were incubated for an additional 3 h at 37 °C. Medium was then aspirated, and the formazan product was solubilized in SDS−HCl (20% SDS; HCl 0.02 M). The absorbance of each well was measured at 570 nm using a microplate reader. Nonlinear regresion anaylisis was performed to calculate IC$_{50}$ values using GraphPad software v 5.

Supporting Information Available: NMR spectra of the new compounds, structures of the known compounds, percentage of inhibition of compounds **2−4**, **18−26**, and **34−35**, proposed biogenetic conversion of pristimerine into tingenone through 21-oxopristimerine (**2**), and tables of NMR data of compounds **1**, **7**, **11**, and **39**. This material is available free of charge via the Internet at http://pubs.acs.org.

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