Eremophilane Sesquiterpenes from *Ligularia macrophylla*

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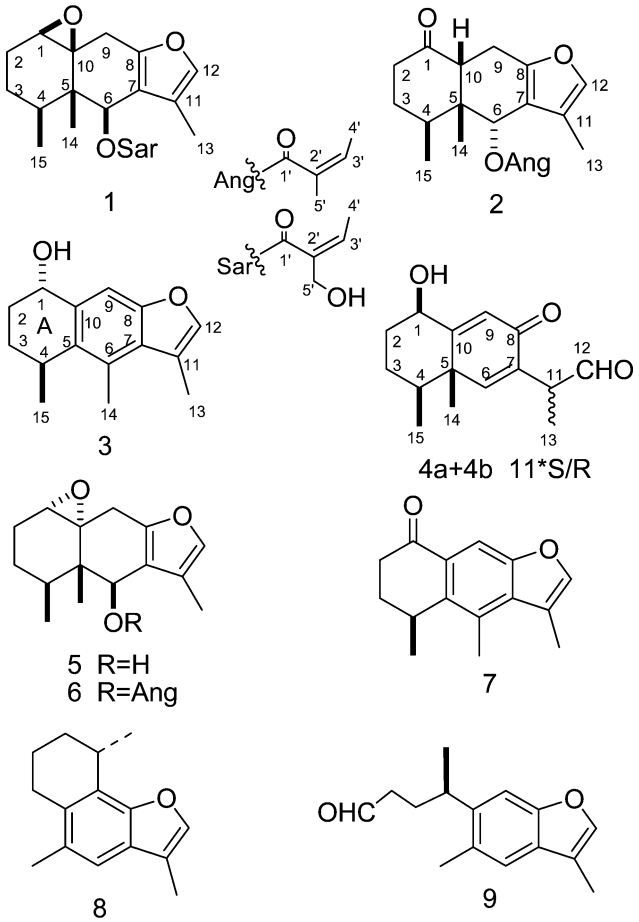
New eremophilane sesquiterpenes, 6β-sarracinoyloxy-1β,10β-epoxy-furanoeremophilane (**1**), 6α-angeloyloxy-10β*H*-furanoeremophil-1-one (**2**), 1α-hydroxy-9-deoxycacalol (**3**), and 1β-hydroxy-11(*R*,*S*)-8-oxoeremophil-6,9-dien-12-al (**4a**+**4b**), together with five known sesquiterpenes (**5**−**9**) were isolated from the roots and rhizomes of *Ligularia macrophylla*. The structures were elucidated by spectroscopic methods including 2D NMR techniques, and the structure of **1** was confirmed by a single-crystal X-ray diffraction experiment. The compounds were also evaluated for cytotoxic activity against human lung carcinoma (A-549) and human breast adenocarcinoma (MCF-7) and were found to show only very weak cytotoxicity.

The roots and rhizomes of *Ligularia macrophylla* (Ledeb.) DC. (Asteraceae) are used as a Chinese folk medicine for the treatment of tracheitis, phthisis, hemoptysis, cough, and asthma.[1] In prior reports, fatty acids, polyenes, pyrrolizidine alkaloids, and eremophilane sesquiterpenes were isolated from this plant, and some of the eremophilane sesquiterpenes showed antibacterial activity against *Pasteurella multocida*.[2−4] As part of our program to discover anticancer agents from Chinese herbs, a phytochemical investigation of the roots and rhizomes of this plant, which is widely distributed in the Tianshan Mountains of China, led to the isolation and characterization the new eremophilane sesquiterpenes, **1**, **2**, **3**, **4a**, and **4b**, along with five known sesquiterpenes, 1,10-epoxy-6-hydroxyeuryopsin (**5**),[5] 6-angeloyloxy-1,10-epoxyeuryopsin (**6**),[6] 1-oxo-9-desoxycacalol (**7**),[7] farfugin A (**8**),[8] and γ,3,5-trimethyl-6-benzofuranbutanal (**9**).[9] The present paper reports the isolation and structural elucidation of the new compounds, as well as *in vitro* cytotoxicity evaluation of all isolates against human lung carcinoma (A-549) and human breast adenocarcinoma (MCF-7) cell lines.

Results and Discussion

An EtOH extract of roots and rhizomes of *L. macrophylla* was suspended in H_2O and partitioned successively with petroleum ether, EtOAc, and *n*-BuOH. Repeated column chromatography of the EtOAc portion on silica gel and on RP_{18} gel, followed by preparative TLC, yielded new eremophilane sesquiterpenes (**1**−**3**, **4a**+**4b**) and five known sesquiterpenes (**5**−**9**).

Compound **1**, colorless needles (acetone), had the molecular formula $C_{20}H_{26}O_5$ on the basis of HREIMS data (*m*/*z* 346.1764). Its ^{1}H NMR spectrum showed an α proton of a furan at δ_H 7.06 (H-12), two methyl singlets at δ_H 1.81 and 1.23 (CH_3-13 and CH_3-14), and a methyl doublet at δ_H 1.07 (CH_3-15), which are characteristic signals of furansesquiterpenes.[10] Detailed NMR analysis of **1** (Tables 1 and 2) indicated the presence of epoxy [δ_H 3.11 (d, 1H); δ_C 62.9 (CH), 63.2 (C)] and sarracinoyloxy [δ_H 6.47 (tq , 1H), 4.27 (br s, 2H), 2.33 (br s, 1H, −OH), 2.10 (d, 3H); δ_C 166.9 (C), 142.3 (CH), 131.2 (C), 65.2 (CH_2), 15.8 (CH_3)] groups. Its IR spectrum also supported the presence of these two groups with absorption bands for OH (3470 cm^{-1}) and ester carbonyl (1700 cm^{-1}) groups and a furan ring (1565 cm^{-1}). Comparison of the NMR data of **1** and 6-angeloyloxy-1,10-epoxyeuryopsin (**6**)[6] showed that these two compounds differed only by the presence of a sarracinoyloxy group in **1** rather than the angeloyloxy group in **6**.



The location of the OH group at C-5′ was confirmed by HMBC correlations of the methylene protons at δ_H 4.27 (2H, br s) with the carbons at δ_C 166.9 (C-1′), 131.2 (C-2′), and 142.3 (C-3′). The sarracinoyloxy group at C-6 was confirmed by HMBC correlations of the proton at δ_H 6.51 (1H, s) with the carbons at δ_C 166.9 (C-1′), 32.0 (C-4), and 148.4 (C-8). The HMBC spectrum showed that the proton at δ_H 3.11 correlated with the carbons at δ_C 19.8 (C-2), 23.5 (C-3), and 30.5 (C-9), indicating that the δ_H 3.11 resonance could be assigned as H-1 and the epoxy group should be assigned at C-1 and C-10 (Figure 1).

In the ROESY (Figure 1) spectrum of **1**, the correlations between H-1/H-4 and H-6/H-4 suggested that both H-1 and H-6 have an α-orientation. A β-orientation was assigned to the C-15 methyl group on the basis of biogenetic precedents.[11] The structure and

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Table 1. ^{1}H NMR (400 MHz) Data of Compounds **1**−**3** and **4a**+**4b** ($CDCl_3$, δ ppm, J in Hz)[a]

	1	2	3	4[b]
1	3.11 (1H, d, 4.6)		4.83 (1H, dd, 9.8, 6.3)	4.55 (1H, t, 2.7)
2	1.89 (1H, m)	2.42 (1H, m)	1.82 (1H, m)	1.67 (1H, dddd, 13.3, 13.3, 3.5, 2.7)
	2.05 (1H, m)	2.45 (1H, m)	2.15 (1H, m)	2.07 (1H, dq, 13.3, 3.5)
3	1.39 (1H, m)	1.66 (1H, m)	1.92 (1H, m)	1.55 (1H, m)
	1.61 (1H, m)	2.25 (1H, m)	1.96 (1H, m)	1.95 (1H, dq, 13.3, 3.5)
4	1.94 (1H, m)	1.94 (1H, m)	3.25 (1H, m)	1.50 (1H, m)
5				
6	6.51 (1H, s)	5.80 (1H, s)		6.80/6.81 (1H, s)
7				
8				
9	2.19 (1H, brd, 16.8)	2.70 (1H, dd, 17.6, 5.8)	7.55 (1H, br s)	6.20 (1H, s)
	3.22 (1H, brd, 16.8)	2.86 (1H, dd, 17.6, 11.4)		
10		2.98 (1H, dd, 11.4, 5.8)		
11				3.67 (1H, dq, 1.9, 5.5)
12	7.06 (1H, s)	7.02 (1H, s)	7.30 (1H, q, 1.5)	9.65 (1H, s)
13	1.81 (3H, s)	1.55 (3H, s)	2.39 (3H, s)	1.25/1.26 (3H, d, 7.4)
14	1.23 (3H, s)	0.67 (3H, s)	2.60 (3H, s)	1.35 (3H, s)
15	1.07 (3H, d, 7.3)	0.99 (3H, d, 7.1)	1.25 (3H, d, 6.6)	1.10 (3H, d, 6.2)
1′				
2′				
3′	6.47 (1H, tq, 1.1, 7.3)	6.02 (1H, qq, 5.8, 1.5)		
4′	2.10 (3H, d, 7.3)	1.96 (3H, dq, 5.8, 1.5)		
5′	4.27 (2H, br s)	1.89 (3H, dq, 1.5, 1.5)		
OH	2.33 (1H)			

[a] Values in parentheses are coupling constants in Hz. [b]Isolated as an epimeric mixture.

Table 2. ^{13}C NMR (100 MHz) Data of Compounds **1**−**3** and **4a**+**4b** ($CDCl_3$, δ ppm)

	1	2	3	4[a]
1	62.9d	210.7s	70.6d	73.7d
2	19.8t	35.1t	28.7t	34.3/34.4t
3	23.5t	30.7t	28.3t	24.9t
4	32.0d	41.3d	28.9d	41.4d
5	40.8s	45.6s	134.4s	44.0s
6	69.6d	68.8d	129.2s	154.2d
7	116.8s	116.3s	126.9s	134.9/135.0s
8	148.4s	152.4s	154.3s	185.4s
9	30.5t	20.7t	107.6d	125.5d
10	63.2s	49.7d	136.3s	165.9s
11	119.6s	119.6s	116.3s	45.4/45.5d
12	139.1d	138.3d	141.9d	201.1d
13	8.5q	8.6q	11.4q	12.9/13.0q
14	16.6q	11.2q	14.7q	18.9/19.0q
15	15.2q	14.7q	21.7q	16.1/16.2q
1′	166.9s	166.9s		
2′	131.2s	128.0s		
3′	142.3d	137.5d		
4′	15.8q	15.7q		
5′	65.2t	20.6q		

[a] Isolated as an epimeric mixture.

relative stereochemistry of **1** were confirmed by X-ray crystallography (Figure 2). Therefore, **1** was determined as 6β-sarracinoyloxy-1β,10β-epoxyfuranoeremophilane.

Compound **2**, colorless gum, had the molecular formula $C_{20}H_{26}O_4$, as determined by HREIMS (*m*/*z* 330.1846). Analysis of the NMR data of **2** (Tables 1 and 2) indicated that it has the typical furansesquiterpene carbon skeleton. Its IR spectrum showed absorption bands for a carbonyl (1712 cm^{-1}) and conjugated ester (1667 cm^{-1}), and in addition, the NMR data indicated the presence of a carbonyl carbon (δ_C 210.6) and an angeloyoxy group [δ_H 6.02, 1H, qq, J = 5.8, 1.5 Hz; δ_H 1.89, 1.96, each 3H, dq, J = 1.5, 5.8 Hz, δ_C 166.9 (C), 128.0 (C), 137.5 (CH), 15.7 (CH_3), 20.6 (CH_3)]. These data suggested that **2** had the same planar structure as 6-angeloyloxysenberginone.[12] Careful comparison of their ^{1}H NMR data revealed that the H-6 signal of **2** was shifted upfield to δ_H 5.80 from δ_H 6.09 and the H-14 and H-15 signals of **2** were shifted upfield to δ_H 0.67 and 0.99 from δ_H 0.99 and 1.06, respectively. These differences suggested that the H-6 in **2** should have a β-orientation.[13] This assignment was confirmed by the ROESY correlations between H-6/H-14 and H-6/H-15; Me-14 and Me-15 have a biogenetic β-orientation.[11] Thus, the structure of **2** was determined to be 6α-angeloyloxy-10β*H*-furanoeremophil-1-one.

Compound **3** was obtained as a colorless gum. The molecular formula $C_{15}H_{18}O_2$ was deduced from the HREIMS (*m*/*z* 230.1315) data. In the ^{1}H NMR spectrum of **3**, one α proton of a furan at δ_H 7.30 (H-12), one aromatic proton at δ_H 7.55 (H-9), two methyl singlets at δ_H 2.39 and 2.60 (CH_3-13 and CH_3-14), and a methyl doublet at δ_H 1.25 (CH_3-15) were characteristic signals of a benzofuran sesquiterpene.[14] Comparison of the NMR data of **3** (Tables 1 and 2) with those of 1-oxo-9-deoxycacalol (**7**)[7] showed that the two compounds differ by the presence of a C-1 hydroxy group (δ_C 70.6, δ_H 4.83) in **3** (further supported by an IR absorption band at 3355 cm^{-1}) rather than the carbonyl group (δ_C 198.7) found in **7**. The location of the hydroxy group at C-1 was confirmed by HMBC correlations of the proton at δ_H 4.83 (1H, dd) with the carbon at δ_C 136.3 (C-10) and of the protons at δ_H 7.55 (1H, br s), 2.15 (1H, m), and 1.92−1.96 (2H, m) with the carbon at δ_C 70.6 (C-1). The α-configuration of the C-1 hydroxyl was deduced from the splitting patterns of H-1 (δ_H 4.83, dd, J = 9.8, 6.3 Hz). The coupling constants (~10 and ~6 Hz) suggested that the dihedral angle between H-1 and H-2a is almost 180° and that between H-1 and H-2b is nearly 35°.[15] This geometry would be consistent with both the OH and CH_3-15 group having equatorial orientation and ring A in **3** adopting a twist-chair conformation. On the other hand, if the C-1 OH group was β-oriented, the observed NMR data of H-1 would require ring A to adopt a boat conformation with greater torsion. Thus, the OH was assigned to an α-orientation, and **3** was determined to be 1α-hydroxy-9-deoxycacalol.

Compound **4** was obtained as an epimeric mixture of **4a**+**4b** (ca. 1:1 by ^{1}H and ^{13}C NMR). The molecular formula of $C_{15}H_{20}O_3$ was predicted from HREIMS (*m*/*z* 248.1407) data. The IR spectrum of **4** revealed absorption bands for a OH (3418 cm^{-1}), an $\alpha,\beta,\alpha',\beta'$-unsaturated skeleton (1693, 1624 cm^{-1}), and an aldehyde group (1724 cm^{-1}). Fifteen carbon signals and three methyl signals (δ_H 1.25, 3H, d, J = 7.4 Hz; δ_H 1.35, 3H, s; δ_H 1.10, 3H, d, J = 6.2 Hz) were found in the ^{13}C and ^{1}H NMR spectra, respectively, suggesting that **4** is an eremophilane sesquiterpene. Furthermore, two olefinic proton singlets at δ_H 6.20 (H-9) and 6.80 (H-6) in conjunction with ^{13}C NMR resonances at δ_C 154.2 (CH), 134.9 (C), 185.4 (C), 125.5 (CH), and 165.9 (C), strongly suggested the presence of a 6(7),9(10)-dien-8-oxo moiety.[16] In addition, the ^{1}H NMR signal at δ_H 9.65 (1H, s) and ^{13}C NMR signal at δ_C 201.1

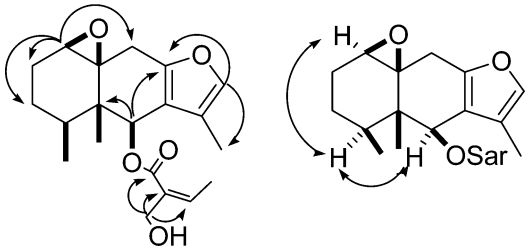

Figure 1. Key HMBC and ROESY correlations of compound **1**.

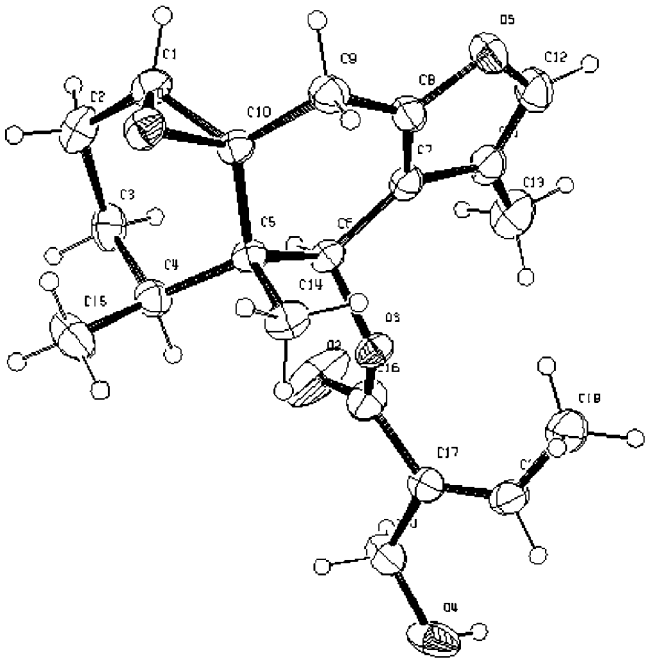

Figure 2. X-ray crystal structure of compound **1**.

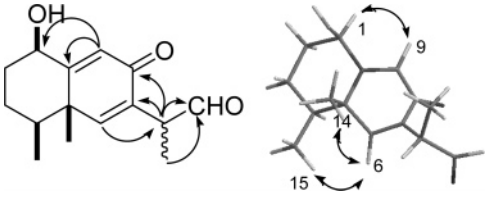

Figure 3. Key HMBC and ROESY correlations of compound **4a**+**4b**.

were consistent with the presence of an aldehyde group. The location of the aldehyde group at C-11 was deduced from the HMBC correlations of the proton at δ_H 9.65 (1H, s) with the carbon at δ_C 45.4 (C-11) and of the protons at δ_H 3.67 (1H, q) and 1.25 (3H, d) with the carbon at δ_C 201.1 (C-12).

The HMBC correlations of the proton at δ_H 4.55 (1H, t) with the carbons at δ_C 24.9 (C-3) and 44.0 (C-5) and of the protons at δ_H 6.20 (1H, s) and 2.07 (1H, dd) with the carbon at δ_C 73.7 (C-1) indicated that the OH group should be located at C-1 (Figure 3). The β-orientation of this OH was deduced from the splitting pattern of H-1 (t, J = 2.7 Hz) and supported by ROESY correlations of the protons at H-1/H-9, H-6/H-14, and H-6/H-15 (Figure 3). On the basis of the aforementioned information, **4** was deduced to have the basic structure of 1β-hydroxy-8-oxoeremophila-6,9-dien-12-al. The small differences in the ^{13}C NMR signals of C-2, C-7, C-11, C-13, C-14, and C-15, as well as the ^{1}H NMR signal of H-6, indicated that **4** is epimeric at C-11, an active center prone to facile enolization, and it was identified as a 1:1 mixture of **4a**+**4b**.

All isolates were screened in an *in vitro* cytotoxicity assay against human lung carcinoma (A-549) and human breast adenocarcinoma (MCF-7) cell lines according to a literature method.[17] Compounds

Table 3. Cytotoxicity Data of Compounds **1**−**9** (EC_{50} μg/mL)

	cell line	
compound	A549	MCF-7
1	>20	17.3
2	>20	>20
3	13.8	15.2
4	18.4	>20
5	>20	>20
6	9.4	>20
7	11.9	15.2
8	10.9	13.6
9	10.0	>20
etoposide	0.8	2.8

2 and **5** showed no cytotoxicity ($EC_{50} \geq 20$ μg/mL), and the remaining compounds showed only very weak cytotoxicity against one or both cancer cell lines (Table 3).

Experimental Section

General Experimental Procedures. Melting points were measured on an XT-4 micro-melting point apparatus and are uncorrected. Optical rotations were run on a JASCO P-1020 polarimeter at room temperature. UV spectra were measured on a Shimadzu UV-260 spectrophotometer in absolute MeOH. IR spectra were recorded on a Avatar TM 360 E. S. P TM Fourier transform infrared spectroscopy instrument in CH_2Cl_2. Mass spectra were determined on a HP5989A mass spectrometer for EIMS and a Waters Micromass GCT mass spectrometer for HREIMS. ^{1}H NMR and ^{13}C NMR spectra were taken on a Bruker DRX-400 spectrometer in $CDCl_3$. Analytical and preparative TLC were run on silica gel plates (GF_{254}, Yantai Institute of Chemical Technology, Yantai, China). Spots on the plates were observed under UV light and visualized by spraying with 10% H_2SO_4, followed by heating. Column chromatography was performed on silica gel (200−300 mesh and 300−400 mesh; Qingdao Marine Chemical Factory, Qingdao, China) and Lichroprep RP_{18} gel (40−60 μm, Merck, Darmstadt, Germany). X-ray crystallographic analysis was carried out on a Bruker Smart Apex CCD diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). The structure was solved by direct methods using the program SHELXS. Non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were located by geometry and rode on the related atoms during refinements with a temperature factor 1.5 times that of the latter.[18]

Plant Material. The roots and rhizomes of *Ligularia macrophylla* were collected in August 2005 on the Tianshan Mountains (altitude 2100 m) in Xinjiang, China. The identity of the plant material was verified by Prof. Ping Yan at Shihezi University, and a voucher specimen (WQ-LM-05-1) has been deposited in the Herbarium of Materia Medica, Department of Pharmacognosy, School of Pharmacy, Fudan University, Shanghai, People's Republic of China.

Extraction and Isolation. The dried and powdered materials (5.1 kg) were extracted with 95% EtOH at reflux temperature three times and filtered. The filtrate was evaporated *in vacuo* to give a residue (600 g), a portion of which (550 g) was suspended in H_2O (2 L) and partitioned successively with petroleum ether, EtOAc, and *n*-BuOH. The EtOAc extract (180 g) was chromatographyed on a Si gel (200−300 mesh, 2 kg, 10 × 120 cm) column, eluting successively with petroleum ether−acetone (30:1, 15:1, 9:1, 7:1, 5:1, 3:1, 2:1, 1:1) and acetone to yield fractions 1−6. Fraction 2 (26 g) was subjected to silica gel CC with petroleum ether−acetone (30:1) and with ether−EtOAc (20:1) to give **6** (1.2 g). Fraction 3 (66 g) was applied to silica gel CC with petroleum ether−EtOAc (20:1) to yield two fractions, 3a and 3b. Fraction 3a (21 g) was applied to silica gel CC with petroleum ether−acetone (15:1) to afford **1** (9.5 g), and fraction 3b (12 g) was applied to silica gel CC with petroleum ether−acetone (18:1) to afford **5** (3.6 g). Fraction 4 (39 g) was subjected to silica gel CC with petroleum ether−acetone (10:1) to give two fractions, 4a and 4b. Fracton 4a (32 mg) was applied to preparative TLC with petroleum ether−acetone (6:1) to give **7** (9 mg), and fraction 4b (19 mg) was applied to preparative TLC with petroleum ether−EtOAc (7:1) to give **8** (3 mg). Fraction 5 (18 g) was applied to a silica gel column with petroleum ether−acetone (5:1), followed by column chromatography on RP_{18} gel with MeOH−H_2O (75:25), to give **2** (15 mg) and **9** (11 mg). Fraction

6 (28 g) was applied to a silica gel column with petroleum ether−acetone (6:1) to give two fractions, 6a and 6b. Fraction 6a (52 mg) was applied to preparative TLC with $CHCl_3$−acetone (20:1) to afford **3** (22 mg), and fraction 6b was purified over a silica gel column with ether−EtOAc (5:1) to afford **4a**+**4b** (116 mg).

6β-Sarracinoyloxy-1β,10β-epoxyfuranoeremophilane (1): colorless needles (acetone); mp 93−94 °C; $[\alpha]_D^{22}$ −12 (*c* 0.5, MeOH); IR ν_{max} (KBr): 3470, 3145, 2931, 1700, 1648, 1565 cm^{-1}; for ^1H NMR ($CDCl_3$) and ^{13}C NMR ($CDCl_3$) data, see Tables 1 and 2; EIMS *m*/*z* 346 $[M]^+$ (1), 230 (42), 212 (67), 197 (100), 173 (96) ; HREIMS *m*/*z* 346.1764 (calcd for $C_{20}H_{26}O_5$, 346.1780). Crystal data:[19] $C_{20}H_{26}O_5$, M_r = 346.41, orthorhombic, space group $P2_12_12_1$, a = 7.687(2) Å, b = 14.383(4) Å, c = 16.341(5) Å, V = 1806.7(9) $Å^3$, Z = 4, D_{calc} = 1.274 Mg/m^3. The final R values were R1 = 0.0368 and wR2 = 0.0914 for 2768 observed reflections [$I > 2\sigma(I)$].

6α-Angeloyloxy-10βH-furanoeremophil-1-one (2): colorless gum, $[\alpha]_D^{22}$ −20.5 (*c* 0.2, MeOH); IR ν_{max} (CH_2Cl_2): 3055, 2924, 1712, 1667, 1421 cm^{-1}; for ^1H NMR ($CDCl_3$) and ^{13}C NMR ($CDCl_3$) data, see Tables 1 and 2; EIMS *m*/*z* 330 $[M]^+$ (0.4), 230 (66), 215 (21), 188 (41), 173 (46), 83 (100), 55 (54); HREIMS *m*/*z* 330.1846 (calcd for $C_{20}H_{26}O_4$, 330.1831).

1α-Hydroxy-9-deoxycacalol (3): colorless gum, $[\alpha]_D^{22}$ −23 (*c* 0.5, MeOH); IR ν_{max} (KBr) 3355, 2935, 1706, 1618, 1573, 1454, 1230 cm^{-1}; for ^1H NMR ($CDCl_3$) and ^{13}C NMR ($CDCl_3$) data, see Tables 1 and 2; EIMS *m*/*z* 230 $[M]^+$ (36), 215 (66), 215 (12), 197 (59), 188 (34), 169 (18); HREIMS *m*/*z* 230.1315 (calcd for $C_{15}H_{18}O_2$, 230.1307).

1β-Hydroxy-11(*R*,*S*)-8-oxoeremophil-6,9-dien-12-al (4a+4b): colorless gum, $[\alpha]_D^{22}$ −40 (*c* 1.4, MeOH); UV λ_{max} (MeOH) nm (log ϵ) 247 (4.42); IR ν_{max} (CH_2Cl_2) 3418, 2967, 1724, 1693, 1660, 1624, 1463, 1018 cm^{-1}; for ^1H NMR ($CDCl_3$) and ^{13}C NMR ($CDCl_3$) data, see Tables 1 and 2; EIMS *m*/*z* 248 $[M]^+$ (0.8), 230 (7), 202 (15), 187 (8), 173 (8), 135 (100), 115 (16), 91 (38); HREIMS *m*/*z* 248.1407 (calcd for $C_{15}H_{20}O_3$, 248.1412).

Growth Inhibition Assay. Stock solutions were prepared in DMSO and stored at −70 °C. Upon dilution into culture medium, the final DMSO concentration was ≤1% DMSO (v/v), a concentration without effect on cell replication. The human tumor cell line panel consisted of lung carcinoma (A-549) and breast adenocarcinoma (MCF-7). Cell culture and other procedures were the same as those reported previously.[17]

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Supporting Information Available: NMR spectra of the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center. Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

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