Cacalol Derivatives from *Roldana angulifolia*

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Four new modified eremophilanes, angulifolide (**1**) and angulifolins A−C (**2**−**4**), and two new triacetylglucosides (**7** and **8**) were isolated from *Roldana angulifolia*, together with several known compounds. The structures of the new compounds were elucidated by spectroscopic analysis and chemical reactions. The absolute configuration of compounds **2** and **3** was established by Mosher ester methodology. Cytotoxicity against selected human cancer cell lines was determined for the more abundant isolated metabolites.

The genus *Roldana* (Asteraceae, Senecioneae), distributed from southern Arizona to Panama, contains 48 species separated mainly from the genera *Senecio* and *Cacalia*.[1,2] Previous reports have shown that sesquiterpenes with eremophilane or oplopane skeletons are the most common secondary metabolites among the six species of *Roldana* chemically studied so far.[3−9] *Roldana angulifolia* (D.C.) H. Rob. and Brettell has been examined for the first time in the present investigation. In this paper, we report the isolation of four new modified furanoeremophilanes, angulifolide (**1**) and angulifolins A−C (**2**−**4**), and the known 13-acetoxy-14-oxocacalohastin (**5**),[7] 13-hydroxy-14-oxocacalohastin (**6**),[7] and maturin acetate.[10] The 3′,4′,6′-triacetylglucoside derivative of (4*S*)-α-terpineol (**7**) and that of 11-hydroxy-4(15)-eremophilene (**8**) are also new metabolites. Structures of the new compounds were determined by spectroscopic methods and chemical transformations. The known compounds senecrassidiol,[11] rutin,[12] phaeophytin *a*,[13] 13-hydroxyphaeophytin *a*,[13] sucrose, and *β*-sitosterol glucoside were also isolated. The cytotoxicity of compounds **1**, **5**, and **6** against selected cancer cell lines was determined.

Angulifolide (**1**), a new modified furaneremophilane, showed the molecular formula $C_{18}H_{16}O_6$ by HRFABMS and exhibited evidence from the IR spectrum of aliphatic ester and conjugated *δ*-lactone groups at 1734 and 1715 cm^{-1}, respectively. In the ^1H NMR spectrum (Table 1), a proton signal of a furan ring (H-12) appeared at *δ* 7.72 (br t, $J = 1.0$), coupled allylically to the C-13 methylene hydrogens (*δ* 5.61 dd, $J = 13.5$, 1.0 Hz and 5.55 dd $J = 13.5$, 1.0 Hz). The absence of C-14 and C-15 methyl groups, characteristic of a cacalol-type skeleton, was in agreement with the inclusion of these carbon atoms in a *δ*-lactone function. This was confirmed by the HMBC spectrum, which showed interaction between the C-14 carbonyl group (*δ* 163.5) and H-15α (*δ* 4.56, dd, $J = 11.0$, 5.0 Hz) and H-15*β* (*δ* 4.26, dd, $J = 12.5$, 11.0 Hz). Signals at *δ* 6.90 (dd, $J = 9.5$, 3.0 Hz) and 6.08 (ddd, $J = 9.5$, 6.5, 3.0 Hz) were assigned to the vinylic hydrogens at C-1 and C-2, according to the correlations observed in the COSY experiment. A methoxyl group (*δ* 4.29) was attached to C-9 in agreement with the cross-peaks between C-9 and CH_3O in the HMBC spectrum. The same experiment allowed placement of the acetoxy group (^1H NMR: *δ* 2.10, ^{13}C NMR: *δ* 170.7 s and 21.0 q) at C-13, since an interaction between its carbonyl group and H-13 was observed. A *β*-orientation was assigned to the C-15 methylene group on biogenetic grounds.[14]

Angulifolins A (**2**) and B (**3**) showed the same molecular formula, $C_{18}H_{18}O_7$, established from their HRFABMS. The presence of hydroxyl, aliphatic ester, and aromatic aldehyde groups was observed in the IR spectra of both compounds. Their ^1H and ^{13}C NMR data were very similar (Table 1) and showed evidence of a furan group, an acetoxy attached to C-13, a methoxyl at C-9, and an aldehyde group at C-6 (*δ* 10.55). From COSY, HMBC, and FLOCK NMR experiments, the presence of a hydroxyl at C-1 and an epoxy group between C-2 and C-3 was deduced for **2** and **3**. The signals at *δ* 3.75 (ddd, $J = 4.5$, 2.5, 1.0 Hz) and 3.54 (dd, $J = 4.5$, 2.5 Hz) in the spectrum of **2** and at *δ* 3.59 (ddd, $J = 3.9$, 3.0, 0.9 Hz) and 3.47 (ddd, $J = 3.9$, 3.0, 1.2 Hz) in that of **3** were assigned to the hydrogen atoms geminal to the epoxide functions; the respective carbon signals appeared at *δ* 53.5 and 55.8 for **2** and *δ* 51.8 and 55.0 for **3**.

The absolute stereochemistry of C-1 in angulifolins A and B was determined by treatment of **2** and **3** with (*S*)- and (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride [(*S*)- and (*R*)-MTPA-Cl] to produce their respective esters. Compound **2** afforded **2r** and **2s** derivatives with negative $\Delta\delta = [\delta(S) - \delta(R)]$ values for

1

2 R = H, R_1 = OH
2r R = H, R_1 = O-(*R*)-MTPA
2s R = H, R_1= O-(*S*)-MTPA
3 R = OH, R_1 = H
3r R = O-(*R*)-MTPA, R_1 = H
3s R = O-(*S*)-MTPA, R_1= H
9 R, R_1 = O

4 R = OH, R_1 = Ac
5 R = H, R_1 = Ac
6 R = R_1 = H

7 R = Ac
10 R = H

8

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Table 1. ^{1}H NMR Spectroscopic Data of Compounds **1**−**4**, **7**, and **8** (500 MHz, $CDCl_3$)[a]

position	1	2	3[b]	4	7[b,c]	8[c]
1a	6.90, dd, (9.5, 3.0)	5.40 d (2.5)	5.76 br d (2.4)	7.14 d (10.0)		1.50 dq (9.0, 5.5)
1b						1.24 m
2	6.08 ddd (9.5, 6.5, 3.0)	3.75 ddd (4.5, 2.5, 1.0)	3.59 ddd (3.9, 3.0, 0.9)	6.23 ddd (10.0, 6.0, 1.0)	5.36 m	1.62 m
3a	2.38 ddd (16.5, 7.0, 6.5)	3.54 dd (4.5, 2.5)	3.47 ddd (3.9, 3.0, 1.2)	4.16 dd (6.0, 1.5)	2.03 m	2.29 br d (12.5)
3b	1.96 dddd (16.5, 16.5, 3.0, 3.0)				2.03 m	1.98 ddd (14.0, 12.5, 0.5)
4	3.42 dddd (16.5, 12.5, 7.0, 5.0)	4.56 qd (7.5, 2.5)	4.48 qd (6.9, 3.0)	4.19 qt (7.0, 1.5)	1.60 dddd (11.4, 11.4, 4.2, 2.1)	
5a					2.00 m	
5b					1.23 m	
6a					1.99 m	1.43 br d (12.5)
6b						1.24 m
7					1.64 s	1.52 m
8						1.59 m
9a					1.23 s	1.76 ddd (12.5, 5.0, 2.5)
9b						1.16 q (12.5)
10					1.18 s	1.74 br d (12.0)
12	7.72 br t (1.0)	7.78 br t (1.0)	7.79 br t (0.9)	7.77 br t (1.0)		1.24 s[d]
13a	5.61 dd (13.5, 1.0)	5.39 dd (13.5, 1.0)	5.39 dd (13.2, 0.9)	5.43 dd (13.5, 1.0)		1.22 s[d]
13b	5.55 dd (13.5, 1.0)	5.28 dd (13.5, 1.0)	5.29 dd (13.2, 0.9)	5.35 dd (13.5, 1.0)		
14		10.55 s	10.55 s	10.59 s		0.69 s
15a	4.56 dd (11.0, 5.0)	1.22 d (7.5)	1.45 d (7.0)	1.16 d (7.0)		4.41 d (2.6)
15b	4.26 dd (11.0, 12.5)					4.69 d (2.6)
OCH_3	4.29 s	4.41 s	4.39 s	4.33 s		
Ac	2.10 s	2.08 s	2.08 s	2.09 s		

[a] Assignments are based on COSY, HSQC, and HMBC experiments. [b]300 MHz, assignments are based on COSY, HETCOR, and FLOCK experiments. [c]Glucose signals of **7**: δ 4.55 (1H, d, J = 7.5 Hz, H-1′), 3.53 (1H, brt, J = 9.0 Hz, H-2′), 5.15 (1H, t, J = 9.6 Hz, H-3′), 4.98 (1H, t, J = 9.6 Hz, H-4′), 3.66 (1H, ddd, J = 2.7, 6.3, 9.9 Hz, H-5′), 4.20 (1H, dd, J = 12.0, 6.3 Hz, H-6′a), 4.08 (1H, dd, J = 12.0, 2.7 Hz, H6′b), 2.07 s, 2.05 s, 2.03 s (3H each, Ac). Glucose signals of **8**: δ 4.54 (1H, d, J = 7.5 Hz, H-1′), 3.54 (1H, dd, J = 9.0, 7.5 Hz, H-2′), 5.15 (1H, t, J = 9.0 Hz, H-3′), 4,98 (1H, t, J = 9.0 Hz, H-4′), 3,65 (1H, ddd, J = 2.5, 6.0, 9.0 Hz, H-5′), 4.19 (1H, dd, J = 12.0, 6.0 Hz, H-6′a), 4.07 (1H, dd, J = 12.0, 2.5 Hz, H6′b), 2.07 s, 2.06 s, 2.03 s (3H each, Ac). [d]Exchangeable signals.

H-2, H-3, and H-4 and positive differences for OCH_3, CHO, H-12, and H-13, indicating *R* absolute stereochemistry of C-1. The **3r** and **3s** derivatives obtained from compound **3** showed positive $\Delta\delta = [\delta(S) - \delta(R)]$ values for H-2, H-3, and H-4 and negative differences for OCH_3, CHO, H-12, and H-13, supporting the *S* absolute stereochemistry of C-1. Oxidation of **2** and **3** produced the same keto derivative (**9**), indicating that they are epimers at C-1. Compound **3** exhibited a low-field shift of H-1 ($\Delta\delta$ 0.36) relative to that in compound **2** (Table 1), which could be explained by the deshielding effect of the epoxide function. Furthermore, the CD curve of **9** showed a negative Cotton effect, similar to that observed for Δ^1,3-ketosteroids with an α-oriented 4,5-oxirane ring.[15] Consequently, the epoxide function should have an α-orientation in both compounds. Therefore, the absolute stereochemistry of compound **2** is 1*R*, 2*R*, 3*S*, 4*R*, and that of compound **3** is 1*S*, 2*R*, 3*S*, 4*R*.

The ^{1}H and ^{13}C NMR spectra of angulifolin C (**4**), $C_{18}H_{18}O_7$, presented the same pattern as those of compounds **2** and **3**, with differences in the signals assigned to ring A. Signals at δ 7.14 (d, J = 10.0 Hz) and 6.23 (ddd, J = 10.0, 6.0, 1.0 Hz) were assigned to the C-1 double bond, and the alcohol function was placed at C-3 since the H-3 signal appeared at δ 4.16 (dd, J = 6.0, 1.5 Hz) coupled to H-2 and to H-4. Since the NOESY experiment did not conclusively establish the stereochemistry of C-3, **4** was treated with Mosher's reagents, but only a dehydration product[10] was obtained.

The IR spectrum of compound **7** showed strong bands at 3593 and 1747 cm^{-1}, characteristic of alcohol and carbonyl groups. The presence of 22 carbon atoms deduced from the ^{13}C NMR spectrum was in agreement with the molecular formula $C_{22}H_{34}O_9$ (HR-FABMS). Five C−H (δ 97.1, 74.5, 72.4, 71.7, and 68.9) and one CH_2 (δ 62.7) signals suggested the presence of a sugar moiety whose anomeric proton signal was observed at δ 4.55 (d, J = 7.5 Hz). The downfield shift of H-3′, H-4′, and H-6′ together with the evidence of three methyl signals at δ 2.07, 2.05, and 2.03, and three carbonyl groups in the ^{13}C NMR spectrum (δ 170.6, 170.6, and 169.7), supported the presence of three acetyl groups at C-3′, C-4′, and C-6′. The remaining 10 carbons were assigned as part of a cyclic monoterpene with three methyl groups and a double bond. The singlet at δ 1.64 was attributed to the vinylic methyl at C-1, in agreement with a FLOCK NMR experiment. The other two methyl groups (δ 1.23 and 1.18) were placed at C-8, which appeared as a singlet (δ 81.0) in the ^{13}C NMR spectrum. The interaction between the anomeric hydrogen and C-8, observed in the FLOCK spectrum, allowed placement of the sugar moiety at this carbon. Compound **7** by partial acid hydrolysis produced compound **10**, whose physical and spectroscopic features were identical to those reported for (4*S*)-α-terpineol glucopyranoside.[16]

The IR spectrum of **8** exhibited bands attributable to ester and alcohol groups, while the ^{1}H NMR spectrum (Table 1) revealed the presence of the triacetylglucopyranose moiety, already described in **7**. The ^{13}C NMR spectrum (Table 2) contained 15 additional signals indicating that the basic skeleton was that of a sesquiterpene. The EIMS showed fragments of triacetylglucopyranose (*m*/*z* 305, $C_{12}H_{17}O_9$) and aglucon moieties (*m*/*z* 205, $C_{15}H_{25}$). Signals at δ 4.41 (d, J = 2.6 Hz) and 4.69 (d, J = 2.6 Hz) were attributed to the exocyclic methylene group of C-15, while the attachment of the triacetylglucopyranose moiety to C-11 was indicated by the interaction in the HMBC spectrum between H-1′ (δ 4.54, d, J = 7.5 Hz) and C-11 (δ 80.9). The NOESY experiment showed cross-peaks of CH_3-14 with CH_3-12, CH_3-13, and H-10, suggesting a *cis*-decalin configuration and β-orientation of the isopropyl portion since on biogenetic grounds CH_3-14 is β-oriented.

Structures of the known compounds 13-acetoxy-14-oxocacalohastin (**5**),[7] maturin acetate,[10] 13-hydroxy-14-oxocacalohastin (**6**),[7] senecrassidiol,[11] rutin,[12] phaeophytin *a*,[13] and 13-hydroxyphaeophytin *a*[13] were determined by comparison of their physical constants and spectroscopic features with those reported in the literature. Sucrose and β-sitosterol glucoside were identified by comparison with authentic samples.

Table 2. ^{13}C NMR Spectroscopic Data of Compounds **1**−**4**, **7**, and **8** (125 MHz, $CDCl_3$)[a]

carbon	1	2	3[b]	4	7[b,c]	8[c]
1	121.4 d	65.1 d	62.5 d	122.8 d	134.2 s	41.1 t
2	125.3 d	53.5 d	51.8 t	125.7 d	120.3 d	22.4 t
3	23.9 t	55.8 d	55.0 d	68.1 d	27.0 t	36.8 t
4	31.9 d	30.2 d	30.3 d	36.6 d	43.7 d	151.1 s
5	137.0 s	138.9 s	138.9 s	140.6 s	23.8 t	35.9 s
6	119.1 s	147.9 s	147.7 s	122.4 s	30.8 t	41.8 t
7	127.9 s	122.0 s	121.7 s	129.0 s	23.3 q	48.4 d
8	146.4 s	130.5 s	131.1 s	145.3 s	81.0 s	23.4 t
9	144.3 s	145.1 s	144.6 d	145.2 s	24.8 q	24.8 t
10	111.2 s	121.9 s	121.0 s	118.7 s	22.5 q	49.8 s
11	118.2 s	116.6 s	116.6 s	117.1 s		80.9 s
12	146.9 d	147.2 d	147.4 d	147.6 d		25.6 q[d]
13	59.6 t	58.6 t	58.6 t	58.9 t		23.4 q[d]
14	163.5 s	189.9 d	189.7 d	189.8 d		16.3 q
15	70.9 t	21.4 q[d]	21.1 q[d]	19.6 q		105.3 t
OMe	60.9 q	61.4 q	60.9 q	60.9 s		
Ac	170.7 s	170.6 s	170.6 s	170.6 s		
	21.0 q	20.9 q[d]	20.9 q[d]	20.9 q		

[a] Assignments are based on DEPT, HSQC, and HMBC experiments. [b]75 MHz, assignments are based on DEPT, HETCOR, and FLOCK experiments. [c]Glucose signals of **7**: δ 97.1 (d, C-1′), 72.4 (d, C-2′), 74.5 (d, C-3′), 68.9 (d, C-4′), 71.7 (d, C-5′), 62.7 (t, C-6′), 170.6 s, 170.6 s, 169.7 s, 20.8 q, 20.7 q, 20.6 q (Ac signals). Glucose signals of **8**: δ 97.1 (d, C-1′), 72.4 (d, C-2′), 74.5 (d, C-3′), 68.9 (d, C-4′), 71.6 (d, C-5′), 62.6 (t, C-6′), 170.7 s, 170.6 s, 169.7 s, 20.8 q, 20.7 q, 20.6 q (Ac signals). [d]Exchangeable signals.

Compounds **1**, **5**, and **6** were tested against central nervous system (U-251), prostate (PC-3), leukemia (K562), colon (HCT-15), breast (MCF-7), and lung (SKLU-1) human cancer cells following the protocols established by the National Cancer Institute (Bethesda, MD).[17] However, none of these compounds were active ($IC_{50} > 10$ μM for all cell lines).

Experimental Section

General Experimental Procedures. Melting points were determined on a Fisher-Jones melting point apparatus and are uncorrected. Optical rotations were determined on a Perkin-Elmer 343 polarimeter. UV and IR spectra were recorded on a Shimadzu UV 160U and a Bruker Tensor 27 spectrometer, respectively. 1D and NMR spectra were obtained on an Eclipse JEOL 300 MHz, Bruker Avance 300 MHz, or a Varian-Unity Inova 500 MHz spectrometer with tetramethylsilane (TMS) as internal standard. EIMS data were determined on a Bruker Daltonics Analysis 3.2 mass spectrometer. FABMS were obtained on a JEOL JMS-SX102A mass spectrometer operated with an acceleration voltage of 10 kV, and samples were desorbed from a nitrobenzyl alcohol matrix using 6 kV xenon atoms. HRFABMS were performed at 10 000 resolution using electric field scans and polyethylene glycol ions (Fluka 200 and 300) as the reference material. Column chromatography was carried out under vacuum on silica gel G 60 (Merck, Darmstadt, Germany). TLC was performed on Si gel 60 and preparative TLC on Si gel GF_{254} (Merck), layer thickness 2.0 mm.

Plant Material. *Roldana angulifolia* (D.C.) H. Rob. and Bretell was collected near Nevado de Toluca (Toluca-Sultepec Rd., km 3), México State, México, in November 2002. A voucher specimen (MEXU 1045506) has been deposited at the Herbario del Instituto de Biología, Universidad Nacional Autónoma de México.

Extraction and Isolation. Dried and ground roots (680 g) were extracted successively with hexane and acetone at room temperature. The hexane extract (16 g) was separated by column chromatography eluted with a hexane−acetone gradient mixture system. Fractions eluted with hexane afforded 3.7 g of 13-acetoxy-14-oxocacalohastin (**5**)[7] as a yellow pale oil. Fractions eluted with hexane−acetone (19:1, 550 mg) after further column separation eluted with hexane−acetone (19:1) afforded maturine acetate (35 mg, mp 80−82 °C).[10] Fractions eluted with hexane−acetone (4:1, 980 mg), after purification by column chromatography eluted with hexane−acetone (9:1), yielded angulifolide (**1**, 51 mg, mp 223−224 °C) and mixture A (230 mg). Mixture A was separated by preparative TLC (benzene−acetone, 49:1, × 3) to give 55 mg of 13-hydroxy-14-oxocacalohastin (**6**)[7]and 110 mg of **1**.

The acetone extract (16 g) was separated by column chromatography eluting with hexane−acetone mixtures of increasing polarity. From the hexane fractions, 350 mg of **5** was isolated. Fractions eluted with 9:1 and 4:1 mixtures (1.5 g), after a new purification with hexane−acetone (9:1), afforded 250 mg of compound **6** and 180 mg of **1**. Fractions obtained with hexane−acetone (7:3 and 6:4) (800 mg) were further separated over silica gel; elution with hexane−acetone (4:1) furnished fractions A and B. Fraction A (450 mg) was purified by column chromatography with hexane−acetone (4:1) to give 50 fractions. Fractions 30−39 (95 mg) and 40−47 (120 mg) were each submitted to preparative TLC (hexane−acetone, 7:3). Angulifolin B (**3**, yellow oil, 52 mg) was obtained from fractions 30−39. Additionally 32 mg of **3** and 58 mg of angulifolin C (**4**, yellow needles, mp 123−124 °C) were isolated from fractions 40−47. Senecrassidiol[11] (colorless oil, 15 mg) was isolated from fractions 48−50 (preparative TLC, CH_2Cl_2−acetone, 8:2). Fraction B (100 mg) was subjected to preparative TLC (hexane−acetone, 7:3) to yield angulifolin A (**2**, yellow oil, 40 mg).

The dried and ground aerial parts (1.1 kg) were extracted successively with hexane, acetone, and methanol. The hexane extract (11.5 g) was subjected to column chromatography eluted with hexane−acetone gradient mixtures. Fractions eluted with hexane−acetone (4:1, 1.2 g) were purified by column chromatography eluted with hexane−acetone (4:1) followed by passage over a flash column, eluted with hexane−acetone (9:1), to afford compound **7** (colorless needles, mp 90−91 °C, 28 mg) and compound **8** (white needles, mp 148−150 °C, 82 mg).

Fractions of the acetone extract (19 g), eluted with a hexane−acetone (9:1) mixture, were purified by column chromatography eluted with hexane−CH_2Cl_2 (9:1) to produce phaeophytin *a* (dark brown oil, 50 mg)[13] and 13-hydroxyphaeophytin *a* (dark brown oil, 62 mg).[13]

From the methanolic extract (45 g) an insoluble portion (18 g) was separated. The methanol-soluble portion was purified by passage over a column eluted with an EtOAc−MeOH gradient system to afford β-sitosterol glucoside (0.5 g) and sucrose (0.8 g). A sample (2 g) of the methanol-insoluble fraction was purified through a Sephadex column eluted with MeOH−H_2O (1:1) to obtain rutin[12] (78 mg).

Angulifolide (1): white needles (EtOAc); mp 223−224 °C; $[\alpha]_D^{25}$ −216.5 (*c* 0.23, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 262 (3.96), 295 (3.78) nm; IR ($CHCl_3$) ν_{max} 1734, 1717 cm^{-1}; ^1H NMR data, see Table 1; ^{13}C NMR data, see Table 2; EIMS *m*/*z* 328 $[M]^+$ (30), 285 (100), 267 (20); HRFABMS *m*/*z* 329.1020 $[M + H]^+$ ($C_{18}H_{17}O_6$ requires 329.1025).

Angulifolin A (2): yellow oil; $[\alpha]_D^{25}$ +114.4 (*c* 0.18, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 207 (4.02), 240 (4.06), 304 (3.83) nm; IR ($CHCl_3$) ν_{max} 3423, 1741, 1679 cm^{-1}; ^1H NMR data, see Table 1; ^{13}C NMR data, see Table 2; EIMS *m*/*z* 346 $[M]^+$ (12), 302 (30), 257 (100); HRFABMS *m*/*z* 347.1134 $[M + H]^+$ ($C_{18}H_{19}O_7$ requires 347.1131).

Angulifolin B (3): yellow oil; $[\alpha]_D^{25}$ +61.8 (*c* 0.22, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 208 (4.02), 240 (4.06), 305 (3.85) nm; IR ($CHCl_3$) ν_{max} 3422, 1740, 1678 cm^{-1}; ^1H NMR data, see Table 1; ^{13}C NMR data, see Table 2; EIMS *m*/*z* 346 $[M]^+$ (20), 302 (30), 257 (100); HRFABMS *m*/*z* 347.1125 $[M + H]^+$ ($C_{18}H_{19}O_7$ requires 347.1131).

Angulifolin C (4): yellow pale needles (EtOAc); mp 123−124 °C; $[\alpha]_D^{25}$ −74.0 (*c* 0.25, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 205 (3.95), 275 (4.05), 301 (3.78) nm; IR ($CHCl_3$) ν_{max} 3591, 1741, 1681 cm^{-1}; ^1H NMR data, see Table 1; ^{13}C NMR data, see Table 2; EIMS *m*/*z* 330 $[M]^+$ (35), 312 (45), 269 (55), 253 (100); HRFABMS *m*/*z* 330.1112 $[M]^+$ ($C_{18}H_{18}O_6$ requires 330.1107).

(4*S*)-α-Terpineol 8-*O*-β-D-(3′-*O*,4′-*O*,6′-*O*-triacetyl)glucopyranoside (7): white needles (EtOAc); mp 90−91 °C; $[\alpha]_D^{25}$ −3.0 (*c* 0.20, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3593, 1747 cm^{-1}; ^1H NMR data, see Table 1; ^{13}C NMR data, see Table 2; FABMS *m*/*z* 443 $[M + H]^+$ (10), 399 (40), 289 (100); HRFABMS *m*/*z* 443.2303 $[M + H]^+$ ($C_{22}H_{35}O_9$ requires 443.2281).

11-Hydroxy-7Hα,10Hβ-eremophil-4(15)-ene 11-*O*-β-D-(3′-*O*,4′-*O*,6′-*O*-triacetyl)glucopyranoside (8): white needles (EtOAc); mp 148−150 °C; $[\alpha]_D^{25}$ +20.0 (*c* 0.20, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3465, 1748 cm^{-1}; ^1H NMR data, see Table 1; ^{13}C NMR data, see Table 2; EIMS *m*/z 305 $[C_{12}H_{17}O_9]^+$ (2), 289 $[C_{12}H_{17}O_8]^+$ (40), 229 $[C_{10}H_{13}O_6]^+$ (25), 205 $[C_{15}H_{25}]^+$ (45), 169 $[C_8H_9O_4]^+$ (75), 109 $[C_{10}H_{13}O_6]^+$ (60), 161 $[C_{12}H_{17}]^+$ (20), 204 $[C_{15}H_{24}]^+$ (100).

Esterification of Compound 2. Compound **2** (5 mg) in anhydrous pyridine (100 mg) was treated with (*S*)- or (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride [(*S*) or (*R*)-MTPA-Cl] (10.5 mg each) and stirred at room temperature for 4 h to afford the *O*-(*R*)- or *O*-(*S*)-MTPA ester derivatives: **2r** (3.2 mg) and **2s** (3.5 mg). Selected $\Delta\delta$ values [$\delta(S) - \delta(R)$]: H-2 = −0.143, H-3 = −0.05, H-4 = −0.031,

OCH_3 = +0.316, H-12 = +0.054, H-13a = +0.024, H-13b = 0.026, CHO = +0.011. **Compound 2r**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.725 (1H, d, J = 3.3 Hz, H-1), 3.887 (1H, dd, J = 3.3, 4.2 Hz, H-2), 3.585 (1H, dd, J = 2.1,4.2 Hz, H-3), 4.670 (1H, qd, J = 7.2, 2.1 Hz, H-4), 7.746 (1H, s, H-12), 5.363 (1H, d, J = 13.2 Hz, H-13a), 5.259 (1H, d, J = 13.2 Hz, H-13b), 10.509 (1H, s, H-14), 1.225 (3H, s, J = 7.2 Hz, H-15), 3.969 (3H, s, OCH_3), 2.068 (H, s, AcO), 3.660 (3H, OCH_3), 7.40−7.75 (5H, aromatic H). **Compound 2s**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.823 (1H, d, J = 3.3 Hz, H-1), 3.744 (1H, dd, J = 3.3, 4.2 Hz, H-2), 3.535 (1H, dd, J = 2.1, 4.2 Hz, H-3), 4.639 (1H, qd, J = 7.2, 2.1 Hz, H-4), 7.800 (1H, s, H-12), 5.387 (1H, d, J = 13.2 Hz, H-13a), 5.285 (1H, d, J = 13.2 Hz, H-13b), 10.520 (1H, s, H-14), 1.226 (3H, s, J = 7.2 Hz, H-15), 4.275 (3H, s, OCH_3), 2.080 (3H, s, AcO), 3.490 (3H, OCH_3), 7.38−7.67 (5H, aromatic H).

Esterification of Compound 3. *O*-(*R*)- and *O*-(*S*)-MTPA ester derivatives **3r** and **3s** were obtained by the same method as described for compound **2**. Selected $\Delta\delta$ values [$\delta(S) - \delta(R)$]: H-2 = +0.031, H-3 = +0.083, H-4 = +0.06, OCH_3 = −0.088, H-12 = −0.028, H-13a = −0.014, H-13b = −0.007, CHO = +0.002. **Compound 3r**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.040 (1H, d, J = 3.3 Hz, H-1), 3.673 (1H, dd, J = 3.9, 3.3 Hz, H-2), 3.381 (1H, dd, J = 2.4, 3.9 Hz, H-3), 4.463 (1H, qd, J = 7.2, 2.4 Hz, H-4), 7.820 (1H, s, H-12), 5.387 (1H, d, J = 12.9 Hz, H-13a), 5.270 (1H, d, J = 12.9 Hz, H-13b), 10.511 (1H, s, H-14), 1.162 (3H, s, J = 7.2 Hz, H-15), 4.379 (3H, s, OCH_3), 2.077 (3H, s, AcO), 3.555 (3H, OCH_3), 7.33−7.59 (5H, aromatic H). **Compound 3s**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.044 (1H, d, J = 3.0 Hz, H-1), 3.704 (1H, dd, J = 3.0, 4.2 Hz, H-2), 3.464 (1H, dd, J = 3.0, 4.2, Hz, H-3), 4.530 (1H, qd, J = 7.2, 3.0 Hz, H-4), 7.792 (1H, s, H-12), 5.373 (1H, d, J = 13.2 Hz, H-13a), 5.263 (1H, d, J = 13.2 Hz, H-13b), 10.509 (1H, s, H-14), 1.329 (3H, s, J = 7.2 Hz, H-15), 4.291 (3H, s, OCH_3), 2.074 (3H, s, AcO), 3.580 (3H, OCH_3), 7.35−7.63 (5H, aromatic H).

Acid Hydrolysis of Compound 7. Compound **7** (50 mg) was refluxed for 2 h with 10% HCl. The reaction mixture was extracted with EtOAc and purified by column chromatography. Elution with hexane−acetone (19:1) furnished 12 mg of **10**, $[\alpha]_D^{25}$ −42.0 (*c* 0.60, MeOH).[16]

Oxidation of Angulifolins A and B (2 and 3). Compounds **2** and **3** (5 mg each) were oxidized with Jones reagent in acetone (1 mL) at 0 °C. Reaction mixtures were purified by preparative TLC (hexane−acetone, 8:2) to obtain 3.0 and 3.3 mg, respectively, of the keto derivative **9** as a yellow oil: $[\alpha]_D^{25}$ −21.0 (*c* 0.10, MeOH); UV (MeOH) λ_{max} (log ϵ) 267 (4.87), 235 (4.86), 2.07 (4.06) nm; IR ($CHCl_3$) ν_{max} 1740, 1683, 1699 cm^{-1}; CD $[\theta]_{214}$ −9452.7, $[\theta]_{270}$ +12861.9, $[\theta]_{336}$ −8186.4; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.81 (2H, m, H-2 and H-3), 4.73 (1H, qd, J = 6.9, 2.2 Hz, H-4), 7.91 (1H, s, H-12), 5.40 (1H, d, J = 13.5 Hz, H-13a), 5.27 (1H, d, J = 13.3 Hz, H-13b), 10.55 (1H, s, H-14), 1.33 (3H, d, J = 6.9 Hz, H-15), 2.10 (H, s, AcO), 4.38 (3H, OCH_3).

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Supporting Information Available: ^{1}H NMR spectra of angulifolide (**1**), angulifolins A−C (**2**−**4**), and triacetylglucosides (**7** and **8)** are available free of charge via the Internet at http://pubs.acs.org.

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