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Synthesis of All Possible Isomers Corresponding to the Proposed Structure of Montanacin E, and Their Antitumor Activity

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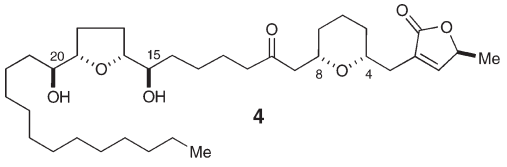

Total synthesis of **4** and its three diastereomers is described. The key steps involve stereoselective formation of the tetrahydrofuran ring by a cascade cyclization of hydroxy tosylate **7** and an intermolecular cross metathesis between a tetrahydrofuran **5** and a γ-lactone **6**. Spectroscopic data of **4** and biosynthetic hypothesis strongly suggest it to be montanacin E. Inhibitory activities of **4** and its isomers against six human solid tumor cell lines were also evaluated.

The rapidly expanding family of annonaceous acetogenins from the Annonaceae plants has recently attracted much attention because of a remarkably broad spectrum of biological properties such as anticancer, antiinfective, immunosuppressive, pesticidal, and antifeedant activities.[1] Structurally, most of these compounds belong to several classic types with an unsubstituted tetrahydrofuran (THF) ring: the mono-THF, the adjacent bis-THF, and the nonadjacent bis-THF acetogenins. Recently, several nonclassical acetogenins have been discovered bearing a tetrahydropyran (THP) ring.[2]

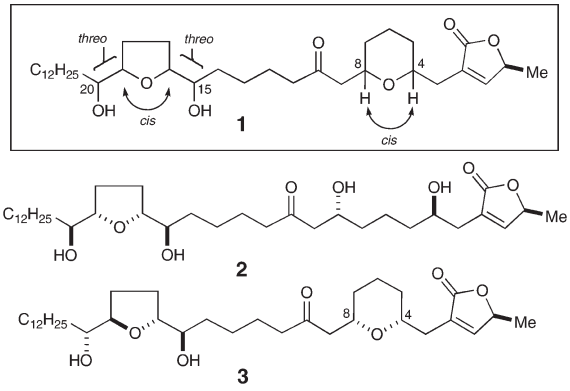

FIGURE 1. Structures of acetogenins from *Annona montana*.

Montanacin E was isolated as a minor component from the ethanolic extract of the leaves of *Annona montana* along with montanacins C (**2**) and D (**3**).[3] The structure of montanacin E was elucidated by spectroscopic methods to be **1** possessing a 4,8-*cis* THP ring[4] along with a 16,19-*cis* THF ring (Figure 1).[5] The relative stereochemistry from C-15 to C-20 was suggested to be *threo*/*cis*/*threo* by comparison of the NMR data of **2**. However, the absolute configuration of the cyclic ether moieties in **1** was not determined because of the lack of a sufficient amount of sample.[6] The antitumor activity was also not evaluated although **1** showed significant cytotoxic activity in a brine shrimp lethality test. As part of our continuing efforts toward synthesis of anticancer THP acetogenins,[7] we describe here total synthesis of all possible isomers corresponding to the proposed structure of montanacin E, and their antitumor activities.

(1) For recent reviews, see: (a) Zafra-Polo, M. C.; Gonzalez, M. C.; Estornell, E.; Sahpaz, S.; Cortes, D. *Phytochemistry* **1996**, *42*, 253–271. (b) Zeng, L.; Ye, Q.; Oberlies, N. H.; Shi, G.; Gu, Z.-M.; He, K.; McLaughlin, J. L. *Nat. Prod. Rep.* **1996**, *13*, 275–306. (c) Zafra-Polo, M. C.; Figadére, B.; Gallardo, T.; Tormo, J. R.; Cortes, D. *Phytochemistry* **1998**, *48*, 1087–1117. (d) Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504–540. (e) Bermejo, A.; Figadére, B.; Zafra-Polo, M.-C.; Barrachina, I.; Estornell, E.; Cortes, D. *Nat. Prod. Rep.* **2005**, *22*, 269–303. (f) McLaughlin, J. L. *J. Nat. Prod.* **2008**, *71*, 1311–1321.

(2) (a) Shi, G.; Alfonso, D.; Fatope, M. O.; Zeng, L.; Gu, Z.-M.; Zhao, G.-X.; He, K.; MacDougal, J. M.; McLaughlin, J. L. *J. Am. Chem. Soc.* **1995**, *117*, 10409–10410. (b) Shi, G.; Kozlowski, J. F.; Schwedler, J. T.; Wood, K. V.; MacDougal, J. M.; McLaughlin, J. L. *J. Org. Chem.* **1996**, *61*, 7988–7989. (c) Alali, F. Q.; Rogers, L.; Zhang, Y.; McLaughlin, J. L. *Tetrahedron* **1998**, *54*, 5833–5844. (d) Chavez, D.; Acevedo, L. A.; Mata, R. *J. Nat. Prod.* **1998**, *61*, 419–421. (e) Fall, D.; Duval, R. A.; Gleye, C.; Laurens, A.; Hocquemiller, R. *J. Nat. Prod.* **2004**, *67*, 1041–1043.

(3) (a) Wang, L.-Q.; Zhao, W.-M.; Qin, G.-W.; Cheng, K.-F.; Yang, R.-Z. *Nat. Prod. Lett.* **1999**, *14*, 83–90. (b) Wang, L.-Q.; Nakamura, N.; Meselhy, M. R.; Hattori, M.; Zhao, W.-M.; Cheng, K.-F.; Yang, R.-Z.; Qin, G.-W. *Chem. Pharm. Bull.* **2000**, *48*, 1109–1113.

(4) Recent syntheses of THP−THF acetogenins: For jimenezin, see: (a) Hwang, C. H.; Keum, G.; Sohn, K.; Lee, D. H.; Lee, E. *Tetrahedron Lett.* **2005**, *46*, 6621–6623. (b) Bandur, N. G.; Brückner, D.; Hoffmann, R. W.; Koert, U. *Org. Lett.* **2006**, *8*, 3829–3831. For mucocin, see: (c) Evans, P. A.; Cui, J.; Gharpure, S. J.; Polosukhin, A.; Zhang, H.-R. *J. Am. Chem. Soc.* **2003**, *125*, 14702–14703. (d) Crimmins, M. T.; Zhang, Y.; Diaz, F. A. *Org. Lett.* **2006**, *8*, 2369–2372. For muconin, see: (e) Yoshimitsu, T.; Makino, T.; Nagaoka, H. *J. Org. Chem.* **2004**, *69*, 1993–1998.

(5) The numbering system of the carbon follows the one employed in ref 3.

(6) The absolute configuration of annonaceous acetogenins has been mainly determined by the modified Mosher's method: Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4093.

(7) (a) Takahashi, S.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 723–726. (b) Takahashi, S.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 727–730. (c) Takahashi, S.; Maeda, K.; Hirota, S.; Nakata, T. *Org. Lett.* **1999**, *1*, 2025–2028. (d) Takahashi, S.; Fujisawa, K.; Sakairi, N.; Nakata, T. *Heterocycles* **2000**, *53*, 1361–1370. (e) Takahashi, S.; Nakata, T. *J. Org. Chem.* **2002**, *67*, 5739–5752. (f) Takahashi, S.; Kubota, A.; Nakata, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 4751–4754. (g) Takahashi, S.; Kubota, A.; Nakata, T. *Tetrahedron Lett.* **2002**, *43*, 8661–8664. (h) Takahashi, S.; Kubota, A.; Nakata, T. *Tetrahedron* **2003**, *59*, 1627–1638. (i) Takahashi, S.; Kubota, A.; Nakata, T. *Org. Lett.* **2003**, *6*, 1353–1356. (j) Takahashi, S.; Ogawa, N.; Koshino, H.; Nakata, T. *Org. Lett.* **2005**, *7*, 2783–2786. (k) Takahashi, S.; Hongo, Y.; Ogawa, N.; Koshino, H.; Nakata, T. *J. Org. Chem.* **2006**, *71*, 6305–6308. (l) Takahashi, S.; Hongo, Y.; Tsukagoshi, Y.; Koshino, H. *Org. Lett.* **2008**, *10*, 4223–4226.

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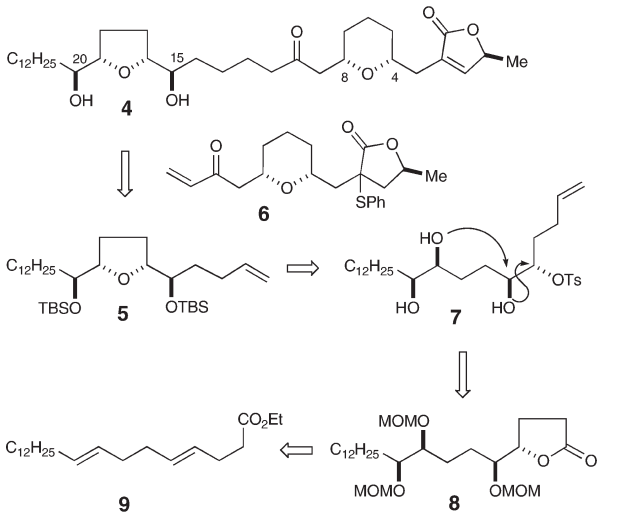
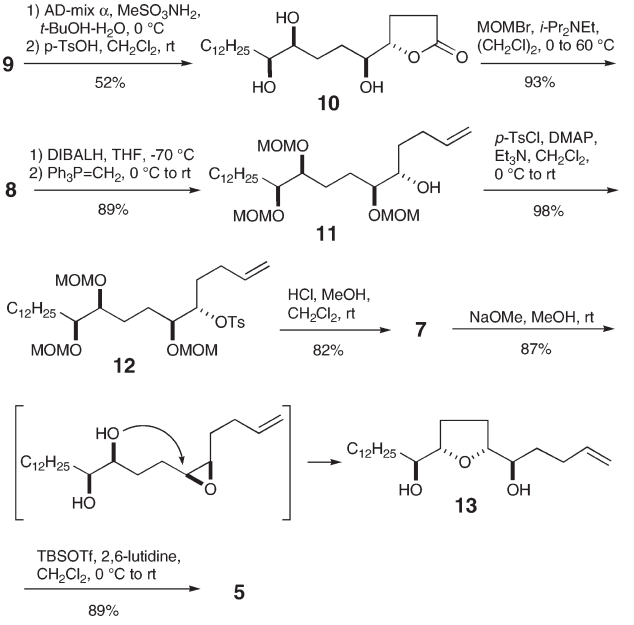
SCHEME 1. Retrosynthetic Analysis of Acetogenin 4[5]



SCHEME 2. Synthesis of THF Segment 5



In an analogy with the case of montanacin D (**3**), we hypothesized that montanacin E might be biosynthetically obtained from **2**. Hence we initially started synthesis of **4** with the stereochemistry of 4*R*,8*S*,15*R*,20*S*. Our synthetic strategy directed toward **4** was based on a convergent process that involved intermolecular metathesis[8] of olefin **5** and enone **6**[7l] as illustrated in Scheme 1. The THF ring in **5** might be constructed by an intramolecular cascade cyclization of tosylate **7**. Oxidative cleavage of the one-carbon unit in **7** leads to γ-lactone **8**. This would be obtained by the Sharpless AD reaction[9] with unsaturated ester **9**. By changing the chiral reagent, preparation of *ent*-**5** is also feasible. Since we have already developed the method for preparation of **6** and its diastereomer **21**, this strategy also enables us to synthesize diastereomers of **4** in regard to the cyclic-ether moieties easily.

Synthesis of **5** began with preparation of lactone **10** by Sinha and Keinan's method (Scheme 2).[10] The hydroxyl groups in **10** were protected as methoxymethyl (MOM) ether. The MOM ether **8** obtained was treated with DIBAL-H and the resulting hemiacetal was reacted with methylenetriphenyl phosphorane to give olefin **11**. Sulfonylation of **11** with *p*-TsCl and triethylamine in the presence of DMAP gave the corresponding tosylate **12**. Upon treatment with HCl in methanol−dichloromethane, **12** afforded **7**, which was treated with sodium methoxide in methanol. The key cyclization proceeded nicely to provide THF ether **13** in good yield. Both hydroxyl groups in **13** were silylated, giving bis TBS ether **5**.

Construction of the complete carbon backbone was accomplished by our previously reported method.[7l] Thus, a mixture of **5** and enone **6** in dichloromethane was heated at 40 °C in the presence of Grubbs catalyst second generation to give *E*-olefin **14** in high yield (Scheme 3). This compound was hydrogenated over 5% PtO_2 to provide ketone **16**. Oxidation of the SPh group followed by elimination reaction gave **4** after treatment with HF·pyridine complex in good overall yield.

After establishing the method for the synthesis of **4**, we next turned to preparation of other diastereomers of **4**. Initially, *ent*-**5** was synthesized from *ent*-**10**[10] according to the method described above. The coupling reaction of *ent*-**5** with **6** led to **15**. Hydrogenation of **15** afforded **17** from which **18** was synthesized through a butenolide formation and deprotection reaction. Similarly, both **5** and *ent*-**5** were coupled with lactone **21**,[7l] giving **22** and **23**, respectively (Scheme 4). These compounds were transformed into a couple of acetogenins **26** and **27** via **24** and **25**, respectively.

The four isomers thus obtained were submitted to extensive NMR analyses and the results are shown in Table 1. The ^{1}H and ^{13}C NMR data of both **4** and **18** were consistent with those reported for montanacin E. On the other hand, the data of **26** and **27** were not so consistent. The characteristic difference is in the chemical shift of protons in the terminal butenolide residue: the ^{1}H NMR spectra of **26** and **27** in $CDCl_3$ showed an olefinic proton of C-33 at 7.17 ppm, whereas H-33 of the natural montanacin E was observed at δ 7.14. The methyl group at C-34 of **26** and **27** showed a slight upfield shift rather than that of natural montanacin E (1.38 ppm vs. 1.41 ppm). Since we could not discriminate between **4** and **18** in the ^{1}H and ^{13}C NMR spectra,[11] the corresponding MTPA derivatives **19** and **20** were prepared. As shown in Table 1, each MTPA ester showed clearly different spectra. It should be mentioned that the chemical shifts of H-15−21, -33, and -34 were markedly different. Due to the unavailability of natural product,[12] a direct comparison of our samples with a natural type was impossible. If derivation of a natural sample into the corresponding MTPA ester is possible, an unambiguous assignment of absolute stereochemistry of montanacin E can be performed.

(8) Grubbs, R. H. In *Handbook of Metathesis*; Wiley-VCH: New York, 2003; Vols. 1−3.

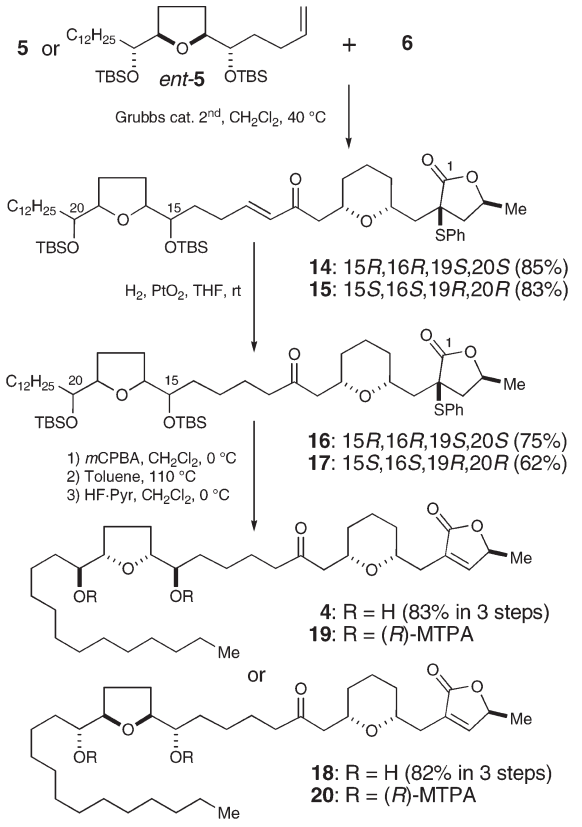
(9) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.

(10) Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* **1993**, *115*, 4891–4892.

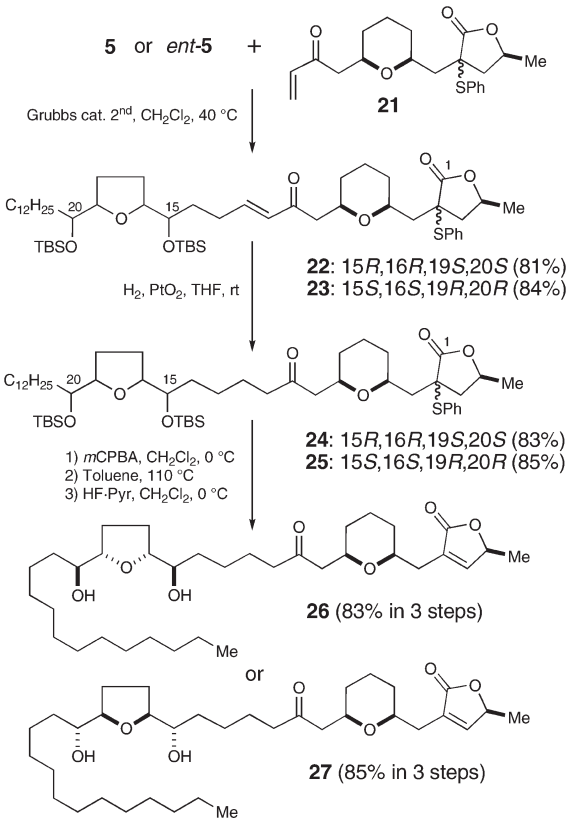
(11) Comparison of $[\alpha]_D$ between **4** or **18** and natural montanacin E provided no reliable information because of the small values and low concentrations reported.

(12) Private communication from Prof. G. W. Qin.

SCHEME 3. Total Synthesis of Acetogenins 4 and 18[5]



SCHEME 4. Total Synthesis of Acetogenins 26 and 27[5]



However, we propose that natural montanacin E might be **4** rather than **18** based on the standpoint of biosynthesis.

The antitumor activities of **3**, **4**, **18**, **26**, **27**, and the 4*S*, 8*R*-epimer **28**[71] of **3** were evaluated. As shown in Table 2, all compounds employed showed significant cytotoxicity toward six human solid tumor cell lines[13] with adriamycin as the positive control. No remarkable difference of inhibitory activity between **4** and **18** was observed.

In conclusion, the synthesis of all possible isomers corresponding to montanacin E was achieved. The analysis of the data allowed diastereomers **26** and **27** to be eliminated, and that biosynthetic considerations favored structure **4** as the natural product.

Experimental Section

(3*S*,5*S*,2′*R*,6′*S*,13′*R*,14′*R*,17′*S*,18′*S*)-[13′,18′-Di(*tert*-butyldimethylsilyloxy)-2′,6′:14′,17′-dioxido-8′-oxo-9′-triacontenyl]-5-methyl-3-(phenylthio)tetrahydrofuran-2-one (14). To a stirred mixture of **5** (50.1 mg, 85.9 μmol) and **6** (20.0 mg, 53.4 μmol) in dichloromethane (2.0 mL) was added Grubbs' second-generation catalyst (8.3 mg, 9.8 μmol). The mixture was stirred at rt for 10 min and at 40 °C for 2 h, then cooled to rt. Florisil was added with stirring, and the resulting mixture was filtered through a pad of Celite. The filtrate was concentrated to give a syrup, which was chromatographed on silica gel (*n*-hexane−ethyl acetate = 20:1 → 4:1) to give **14** (42.1 mg, 85% from **6**) as a colorless syrup; $[\alpha]^{24}_{D}$ −18.9 (*c* 0.12, $CHCl_3$); IR (ZnSe) 2924, 2853, 1767, 1671, 1629, 1461, 1340, 1250, 1185, 1068, 834 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.56−7.52 (2H, m), 7.41−7.30 (3H, m), 6.82 (1H, dt, *J* = 15.9, 6.8 Hz), 6.08 (1H, d, *J* = 15.9 Hz), 4.37 (1H, m), 3.89 (1H, m), 3.85−3.75 (2H, m), 3.73 (1H, m), 3.66 (1H, m), 3.61 (1H, m), 2.79 (1H, dd, *J* = 16.4, 7.6 Hz), 2.76 (1H, *J* = 14.2, 7.6 Hz), 2.46 (1H, *J* = 16.4, 4.9 Hz), 2.35 (1H, m), 2.24 (1H, m), 2.00 (1H, dd, *J* = 14.2, 10.0 Hz), 1.85−1.20 (36H, m), 1.18 (3H, d, *J* = 6.1 Hz), 0.88 (9H, s), 0.87 (12H, m), 0.07 (3H, s), 0.06 (3H, s), 0.04 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.5, 177.6, 148.2, 137.0, 130.8, 130.4, 129.7, 128.9, 81.7, 81.5, 74.3, 74.2, 74.0, 73.8, 73.2, 54.4, 45.8, 41.6, 38.6, 32.8, 31.9, 31.3, 31.2, 30.9, 29.8, 29.7, 29.6, 29.3, 28.8, 26.9, 26.8, 25.9, 25.7, 23.4, 22.7, 21.3, 18.2, 18.1, 14.1, −4.2, −4.3, −4.6, −4.7; HRMS (ESI) calcd for $C_{53}H_{92}O_7Si_2SNa$ $[M + Na]^+$ 951.6000, found 951.5959.

(3*S*,5*S*,2′*R*,6′*S*,13′*R*,14′*R*,17′*S*,18′*S*)-[13′,18′-Di(*tert*-butyldimethylsilyloxy)-2′,6′:14′,17′-dioxido-8′-oxo-triacontanyl]-5-methyl-3-(phenylthio)tetrahydrofuran-2-one (16). A mixture of **14** (23.2 mg, 24.9 μmol) and PtO_2 (6.8 mg) in THF (1.2 mL) was vigorously stirred at rt under H_2 atmosphere for 12 h, filtered through a pad of Celite, and concentrated. The residue was purified by preparative TLC (*n*-hexane−ethyl acetate 8:1, 6 developments) to give **16** (17.4 mg, 75%) as a colorless syrup; $[\alpha]^{22}_{D}$ −16.8 (*c* 0.32, $CHCl_3$); IR (ZnSe) 2925, 2854, 1772, 1716, 1456, 1376, 1233, 1187, 1081, 835 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.56−7.53 (2H, m), 7.39−7.31 (3H, m), 4.35 (1H, m), 3.86 (1H, m), 3.81−3.76 (2H, m), 3.67 (1H, m), 3.61 (2H, m), 2.71 (1H, dd, *J* = 14.2, 7.6 Hz), 2.63 (1H, dd, *J* = 16.1, 8.5 Hz), 2.51−2.37 (2H, m), 2.25 (1H, dd, *J* = 16.1, 3.9 Hz), 2.03 (1H, dd, *J* = 14.2, 10.3 Hz), 1.87−1.20 (40H, m), 1.19 (3H, d, *J* = 6.4 Hz), 0.88 (9H, s), 0.87 (12H, m), 0.05 (9H, s), 0.04 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.3, 177.4, 137.0, 130.5, 129.6, 128.8, 81.8, 81.7, 74.4, 74.3, 74.1, 73.7, 73.0, 54.1, 48.6, 44.3, 42.3, 38.6, 32.8, 32.7, 31.9, 31.2, 30.7, 29.8, 29.7, 29.6, 29.3, 27.0, 26.9, 25.9, 25.7, 25.3, 23.7, 23.3, 22.7, 21.4, 18.2, 14.1, −4.3, −4.6; HRMS (ESI) calcd for $C_{53}H_{94}O_7Si_2SNa$ $[M + Na]^+$ 953.6157, found 953.6137.

(13) Shi, G.; Zeng, L.; Gu, Z.-M.; MacDougal, J. M.; McLaughlin, J. L. *Heterocycles* **1995**, *41*, 1785–1796.

TABLE 1. ^{1}H NMR (600 or 500 MHz) Data (δ) for Compounds 1, 4, 18, 19, 20, 26, and 27

no.[a]	natural **1**[b]	**4**	**18**	**26**	**27**	**19**	**20**
3	2.36 d (6.0)	2.35 m	2.36 m	2.35 m	2.35 m	2.36 m	2.36 m
4	3.59 m	3.58 m	3.58 m	3.56 m	3.56 m	3.58 m	3.56 m
5−7	1.26−1.64 m	1.23−1.84 m	1.23−1.84 m	1.23−1.84 m	1.23−1.84 m	1.25−1.84 m	1.23−1.84 m
8	3.85 m	3.83 m	3.83 m	3.82 m	3.83 m	3.83 m	3.80 m
9	2.63 dd (15.0, 9.0)	2.62 dd (15.6, 9.1)	2.63 dd (15.6, 9.1)	2.63 dd (15.6, 9.1)	2.63 dd (15.6, 9.1)	2.61 dd (15.9, 8.8)	2.60 dd (15.9, 8.8)
	2.37[c] dd (15.0, 6.6)	2.37 dd (15.6, 3.5)	2.37 dd (15.6, 4.0)	2.37 dd (15.6, 4.0)	2.37 dd (15.6, 4.0)	2.37 dd (15.9, 4.0)	2.35 m
11	2.41[c] m	2.41 t (7.1)	2.41 t (7.3)	2.41 t (7.3)	2.41 t (7.3)	2.30 t (7.6)	2.31−2.37 m
12	1.26−1.87 m	1.52 m, 1.58 m	1.52 m, 1.58 m	1.52 m, 1.56 m	1.52 m, 1.58 m	1.38 m, 1.52 m	1.48 m
13	1.26−1.87 m	1.35 m, 1.48 m	1.34 m, 1.46 m	1.35 m, 1.48 m	1.36 m, 1.48 m	1.12 m, 1.17 m	1.28 m
14	1.47 m	1.46 m	1.46 m	1.46 m	1.46 m	1.34 m	1.66 m, 1.71 m
15	3.40 m	3.40 m	3.41 m	3.41 m	3.41 m	5.06 ddd (8.0, 7.5, 3.5)	4.91 ddd (7.0, 6.5, 3.0)
16	3.80 m	3.81 m	3.81 m	3.81 m	3.81 m	3.87 m	4.08 ddd (7.0, 4.6, 3.5)
17	1.75 m, 1.95 m	1.75 m, 1.93 m	1.76 m, 1.93 m	1.75 m, 1.93 m	1.76 m, 1.93 m	0.90 m, 1.48 m	1.36 m, 1.82 m
18	1.75 m, 1.95 m	1.75 m, 1.93 m	1.76 m, 1.93 m	1.75 m, 1.93 m	1.76 m, 1.93 m	1.38 m, 1.82 m	0.86 m, 1.44 m
19	3.80 m	3.81 m	3.81 m	3.81 m	3.81 m	4.09 m	3.87 ddd (8.1, 8.0, 7.0)
20	3.40 m	3.42 m	3.42 m	3.42 m	3.42 m	4.93 m	5.07 ddd (9.1, 8.0, 3.5)
21	1.47 m	1.46 m	1.46 m	1.46 m	1.46 m	1.64 m, 1.68 m	1.27 m, 1.35 m
32	0.88 t (7.0)	0.87 t (7.1)	0.88 t (6.8)	0.87 t (7.1)	0.88 t (7.1)	0.88 t (7.1)	0.89 t (7.1)
33	7.14 d (1.6)	7.14 m	7.14 m	7.17 m	7.17 m	7.13 m	7.14 m
34	4.99 dq (1.6, 6.8)	4.98 dq (1.5, 6.6)	4.98 dq (1.5, 6.6)	4.98 dq (1.4, 6.6)	4.98 dq (1.5, 6.6)	4.94 m	4.96 m
35	1.41 d (6.8)	1.40 d (6.6)	1.40 d (6.6)	1.39 d (6.6)	1.39 d (6.6)	1.38 d (7.1)	1.39 d (7.1)

[a]Reference 5. [b]Reference 3b (500 MHz). [c]Obtained from the copies of the original NMR spectra kindly provided by Prof. Qin. The original data denoted in ref 3b were opposite.

TABLE 2. ED_{50} (μg/mL) Values of 3, 4, 18, 26, 27, and 28 against Six Human Tumor Cell Lines[a]

	ACHN	MCF-7	PC-3	HT-29	PACA	A-549
4	5.8×10^{-1}	7.2×10^{-1}	8.8×10^{-1}	3.2	3.3	1.3
18	1.4	1.6	1.3	>10	4.7	3.1
26	4.4×10^{-1}	4.3×10^{-1}	7.5×10^{-1}	>10	3.3	7.9×10^{-1}
27	5.4	2.6	1.6	8.4	6.0	3.2
3 (montanacin D)	4.5×10^{-1}	1.0	1.0	3.2	3.5	1.6
28	3.7×10^{-1}	5.4×10^{-1}	7.8×10^{-1}	2.1	3.2	9.6×10^{-1}
Adr[b]	9.0×10^{-2}	1.0×10^{-2}	1.2×10^{-1}	3.0×10^{-2}	3.7×10^{-3}	9.0×10^{-3}

[a]ACHN (renal carcinoma), MCF-7 (breast carcinoma), PC-3 (prostate adenocarcinoma), HT-29 (colon adenocarcinoma), PACA (pancreas carcinoma), and A-549 (lung carcinoma). [b]Adriamycin was used for the standard positive control.

(5*S*,2′*R*,6′*S*,13′*R*,14′*R*,17′*S*,18′*S*)-[13′,18′-Dihydroxy-2′,6′:14′,17′-dioxido-8′-oxotriacontanyl]-5-methylfuran-2(5*H*)-one (4). To a stirred solution of **16** (14.1 mg, 15.1 μmol) in dichloromethane (1.0 mL) was added mCPBA (70−75% assay; 3.7 mg, ca. 15.1 μmol) at 0 °C. After 30 min, aqueous saturated $NaHCO_3$/$Na_2S_2O_3$ (1:1) was added, and the resulting mixture was extracted with ether. The extracts were washed with aqueous saturated $Na_2S_2O_3$, water, and brine, dried, and concentrated. The residue was dissolved in toluene (1.0 mL). The solution was heated at 100−105 °C for 1 h with stirring, then concentrated to give a crude butenolide (22.9 mg). To a stirred solution of the butenolide (22.9 mg) in dichloromethane (0.7 mL) was added a HF·pyridine complex (50 μL) at 0 °C, then the mixture was stirred at 0 °C for 30 min. After addition of aqueous saturated $NaHCO_3$, the resulting mixture was stirred at 0 °C for 10 min and extracted with ethyl acetate. The extracts were washed with water and brine, dried, and then concentrated. The residue was purified by preparative TLC (ethyl acetate, 2 developments) to give **4** (7.4 mg, 83% from **16**) as a white powder; $[\alpha]^{22}_D$ + 1.6 (*c* 0.32, methanol); IR (ZnSe) 3407, 2916, 2848, 1756, 1734, 1698, 1461, 1405, 1318, 1300, 1196, 1139, 1018 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.14 (1H, m), 4.98 (1H, brdq, J = 1.5, 6.6 Hz), 3.83 (1H, m), 3.81 (2H, m), 3.58 (1H, m), 3.42 (1H, m), 3.40 (1H, m), 2.62 (1H, dd, J = 15.6, 9.1 Hz), 2.41 (2H, t, J = 7.2 Hz), 2.37 (1H, dd, J = 15.6, 3.5 Hz), 2.35 (2H, m), 1.93 (2H, m), 1.84 (1H, m), 1.75 (2H, m), 1.58 (3H, m), 1.56 (1H, m), 1.52 (1H, m), 1.48 (2H, m), 1.46 (4H, m), 1.40 (3H, d, J = 6.6 Hz), 1.35 (2H, m), 1.28 (2H, m), 1.25 (17H, m), 1.23 (1H, m), 0.87 (3H, t, J = 7.1 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.37, 174.17, 151.32, 130.56, 82.66, 82.60, 77.81, 75.55, 74.29, 74.05, 74.00, 49.13, 43.72, 34.15, 33.81, 31.91, 31.79, 31.15, 31.05, 29.68, 29.65, 29.62, 29.60, 29.33, 28.10, 25.71, 25.27, 23.50, 23.28, 22.67, 19.08, 14.09; HRMS (ESI) calcd for $C_{35}H_{60}O_7Na$ $[M + Na]^+$ 615.4237, found 615.4209.

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Supporting Information Available: Experimental procedures and NMR spectra of **4**, **5**, **7**, **8**, **10**−**18**, and **22**−**27**. This material is available free of charge via the Internet at http://pubs.acs.org.