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Structural Determination of Montanacin D by Total Synthesis

Shunya Takahashi,* Yayoi Hongo, Yuki Tsukagoshi, and Hiroyuki Koshino

RIKEN (The Institute of Physical and Chemical Research), Wako, Saitama 351-0198, Japan

shunyat@riken.go.jp

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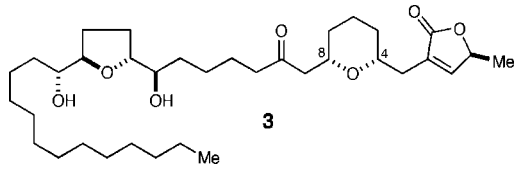
ABSTRACT



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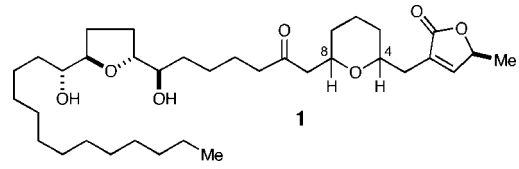
The first total syntheses of acetogenin 3 and its 4*S*,8*R*-isomer are described. The key step involves intermolecular metathesis of an α,β-unsaturated ketone carrying a tetrahydropyranyl lactone with a tetrahydrofuran derivative. Compound 3 has spectroscopic and physical data consistent with those of natural montanacin D, suggesting that the absolute configuration of the natural product is as shown in 3.

The Annonaceous acetogenins from the Annonaceae plants comprise a class of almost 400 natural products that exhibit 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]

In 1999, Qin and Cheng et al. isolated montanacin D from the ethanolic extract of the leaves of *Annona montana*.[3] The structure was elucidated by chemical and spectral means to be **1** possessing a 4,8-*cis* THP ring along with a 16,19-*trans* THF ring (Figure 1).[4] However, the absolute configuration of the THP ring part was not determined. Unlike the other



1

Figure 1. Proposed structure of montanacin D.

approximately 420 acetogenins, the presence of the THP ring adjacent to the butenolide moiety in **1** provides a confor-

(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.; Figadere, 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, and references cited therein.

(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) For recent syntheses of THP−THF acetogenins, see: (a) Evans, P. A.; Cui, J.; Gharpure, S. J.; Polosukhin, A.; Zhang, H.-R. *J. Am. Chem. Soc.* **2003**, *125*, 14702–14703. (b) Yoshimitsu, T.; Makino, T.; Nagaoka, H. *J. Org. Chem.* **2004**, *69*, 1993–1998. (c) Zhu, L.; Mootoo, D. R. *Org. Biomol. Chem.* **2005**, *3*, 2750–2754. (d) Hwang, C. H.; Keum, G.; Sohn, K.; Lee, D. H.; Lee, E. *Tetrahedron Lett.* **2005**, *46*, 6621–6623. (e) Crimmins, M. T.; Zhang, Y.; Diaz, F. A. *Org. Lett.* **2006**, *8*, 2369–2372. (f) Bandur, N. G.; Brückner, D.; Hoffmann, R. W.; Koert, U. *Org. Lett.* **2006**, *8*, 3829–3831. (g) Crisóstomo, F. R. P.; Carrillo, R.; León, L. G.; Martín, T.; Padrón, J. M.; Martín, V. S. *J. Org. Chem.* **2006**, *71*, 2339–2345.

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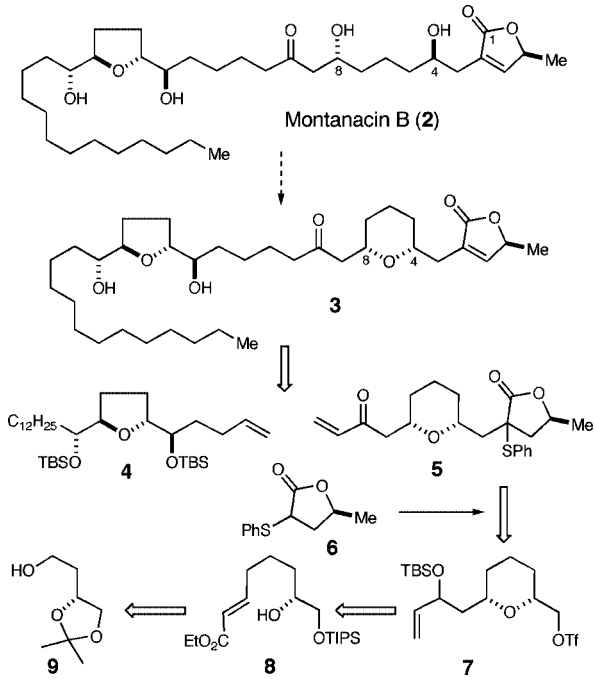
mational rigidity around the lactone ring, an essential domain for several biological activities.[1d] Therefore, compound **1** is regarded as a unique member of this family and is expected to have interesting activity. Recently, we have been engaged in synthetic studies on THP-acetogenins, resulting in the total synthesis of mucocin, jimenezin, muconin, pyranicin, and pyragonicin.[5] As part of our continuing studies in this field, we describe herein the structural determination of montanacin D by total synthesis of (4*R*,8*S*)-montanacin D (**3**) and its 4*S*,8*R*-isomer **27** and a comparison of their analytical data with those reported for montanacin D.

Along with montanacin D, montanacin B (**2**)[3] was also isolated from the same origin by the same authors (Scheme 1). This report prompted us to suppose that montanacin D

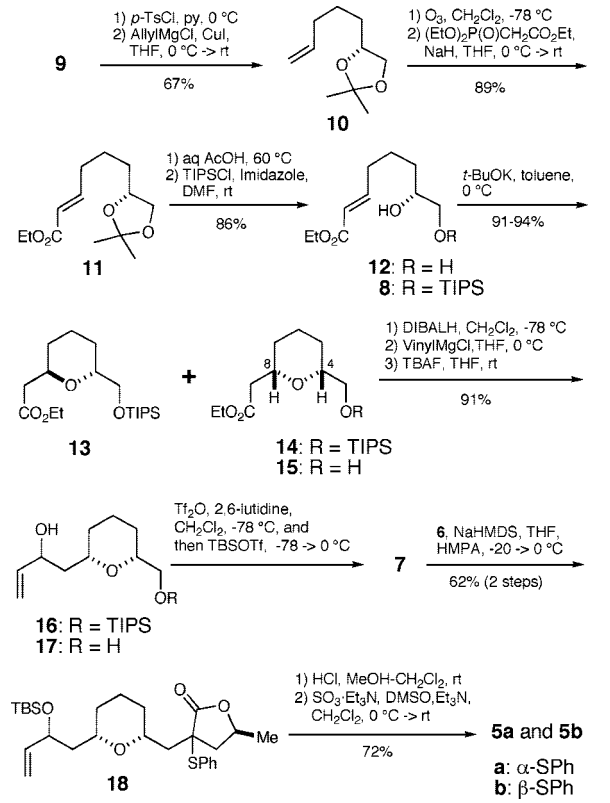
Scheme 1



might be biosynthetically obtained through β-elimination of the C-8 hydroxyl group of **2** followed by oxy-Michael addition of the 4-OH to the resulting olefin. Hence, we initially started synthesis of **3** with the stereochemistry of 4*R*,8*S*. Our synthetic strategy directed toward **3** was based on a convergent process that involved intermolecular metathesis[6] of olefin **4**[7] and enone **5** as illustrated in Scheme 1. The latter might be prepared from γ-lactone **6**[9] and THP derivative **7**. The THP core in **7** would be constructed by an intramolecular oxy-Michael addition of α,β-unsaturated ester **8** having a hydroxyl group. To synthesize **8**, we selected chiral alcohol **9** as the starting material. As **9** and *ent*-**9** are commercially available compounds, this strategy enabled us to prepare both enantiomers of a THP compound such as **7** easily.

Synthesis of **3** began with allylation of the tosylate[10] obtained from **9** (Scheme 2). The resulting olefin **10** was

Scheme 2



ozonolized and then subjected to Wittig−Horner−Emmons reaction to give *E*-olefin **11**. Acid hydrolysis of **11** furnished diol **12**. Cyclization of **12** with NaH at rt for 1.5 h resulted in the stereoselective formation of *cis*-isomer **15**, but partial hydrolysis of the ester moiety decreased the yield of **15** (~50%). The stereochemistry was established by the NMR analyses including NOE experiments. Thus, irradiation of H_8 results in enhancement of the H_4 peak.[11] In the ^{1}H NMR

(5) (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.

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

(7) This was prepared from a known lactone **19**[8] in three steps (vide infra).

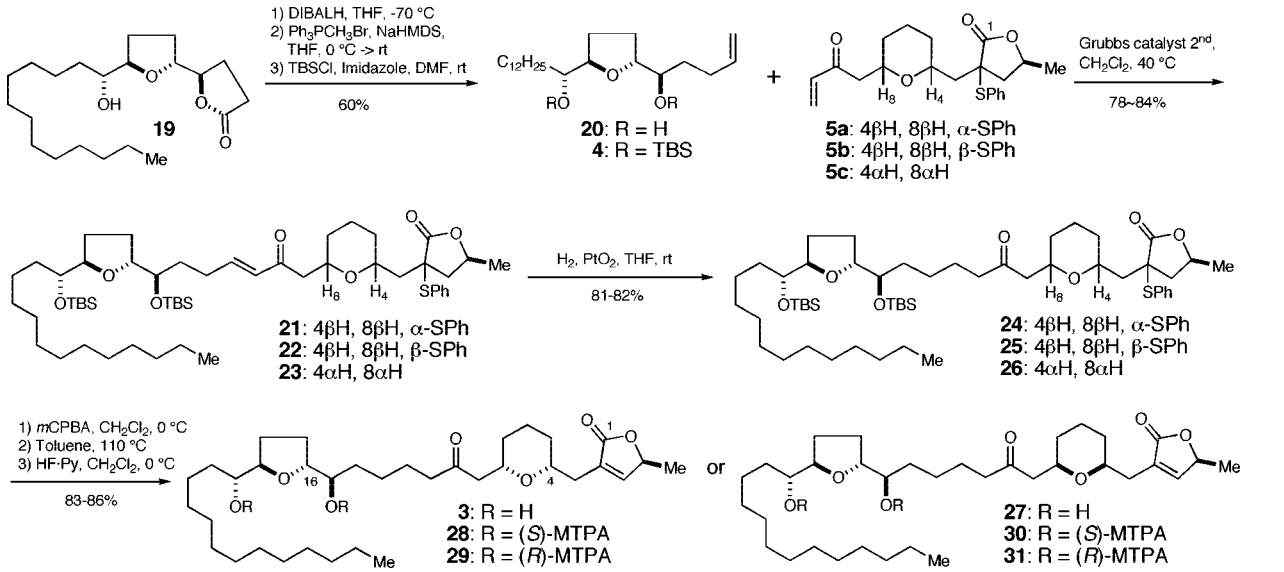
(8) Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* **1993**, *119*, 4891–4892.

(9) White, J. D.; Somers, T. C.; Reddy, G. N. *J. Org. Chem.* **1992**, *57*, 4991–4998.

(10) Koert, U.; Wagner, H.; Pidun, U. *Ber. Chem.* **1994**, *127*, 1447–1457.

(11) The numbering system in ref 3 was adopted.

Scheme 3



($CDCl_3$) spectrum of **15**, the signal corresponding to the proton of C-8 was observed at 3.80 ppm as a doublet of doublet of doublets ($J_{7,8} = 11.1$ Hz). These data are consistent with the proposed structure for **15**. In a similar oxy-Michael reaction, Banwell et al.[12] conducted re-esterification of crude products after cyclization reaction to recover the desired ester. Thus, we introduced a triisopropylsilyl group into the primary OH in **12** in order to suppress the hydrolysis by neighboring group participation and examined the cyclization. Brief treatment (5 min) of silyl ether **8** with *t*-BuOK (0.25 molar equiv) in toluene at 0 °C afforded *trans*-isomer **13** stereoselectively (**13**/**14** = 70/30),[13] while on exposure of **8** to the base for a longer period of time (3 h), the thermodynamic isomer **14** became more prominent (**13**/**14** = 3/97).[14] The isomers could be separated by chromatography on silica gel, and the stereochemistries were confirmed by ^{1}H NMR analyses including NOE experiments.[15] The *cis*-isomer **14** thus obtained was reduced with DIBALH and then alkylated with vinylmagnesium chloride to give alcohol **16** as a diastereomeric mixture (ca. 1:1). Upon treatment with TBAF, **16** led to diol **17**. This was treated successively with triflic anhydride and TBDMSOTf in the presence of 2,6-lutidine at −78 → 0 °C to afford unstable triflate **7**, which reacted with the sodium enolate derived from **6**, giving lactone **18**. Desilylation of **18** and oxidation provided 2*S*-lactone **5b** and 2*R*-isomer **5a** after chromatography on silica gel (**5a**/**5b** = ca. 1/4).[16]

The left-half-segment **4** was prepared from the known lactone **19** in three steps: (1) DIBALH reduction of **19**, (2) Wittig reaction, and (3) silylation of **20** (Scheme 3). Intermolecular olefin metathesis of **4** with the major lactone **5b** in the presence of Grubbs second generation catalyst proceeded nicely to give *E*-olefin **22** in 84% yield. The coupling reaction of TBS ether **18** or its corresponding alcohol with **4** gave unsatisfactory results. Hydrogenation of the enone moiety in **22** was achieved by using PtO_2 in THF to afford saturated ketone **25** in 82% yield. Oxidation of the phenyl sulfide moiety with *m*-CPBA followed by thermolysis and a final deprotection provided the target molecule **3** in 83% overall yield. Similarly, minor isomer **5a** was smoothly coupled with **4**, affording **21** (82%). The enone **21** was hydrogenated and the resulting ketone **24** was transformed into **3** in good overall yield. The physical and spectral data ($[\alpha]_D$, ^{1}H and ^{13}C NMR) of **3**[18] were well matched with those of natural montanacin D. The THP core is located apart from the other stereogenic regions so that the effect of this domain on the chemical shift seemed to be small in the NMR spectra. Hence, for unambiguous establishment of the structure of montanacin D, the data of 4*S*,8*R*-isomer **27** was also required.

In a similar manner, enone **5c**[19] was prepared from *ent*-diol **17** in 36% overall yield. Cross-metathesis of **5c** with **4** afforded **23**, which was reduced to give **26** in 62% yield (2 steps). Finally, butenolide formation in **26** and desilylation

(12) Banwell, M. G.; Bui, C. T.; Simpson, G. W. *J. Chem. Soc., Perkin Trans. 1* **1998**, 791–799.

(13) The ratio was determined by ^{1}H NMR analysis.

(14) For an example of oxy-Michael cyclization by using NaH as a base, see: Edmunds, A. J. F.; Trueb, W. *Tetrahedron Lett.* **1997**, *38*, 1009–1012.

(15) Irradiation of C*H*CO_2Et in **13** caused an NOE of the proton at the C-4 position. In **14**, a strong NOE was observed for the signal of H_8 upon irradiation of H_4.

(16) The stereochemistries of each were deduced by the ^{1}H NMR analyses. In the ^{1}H NMR spectra, the methyl group of **5b** was observed at δ 1.16 (d, $J = 6.3$ Hz) while the minor isomer **5a** showed a doublet at 1.39 ppm. The data were consistent with those reported in the literature.[8,17]

(17) Sinha, A.; Sinha, S. C.; Sinha, S. C.; Keinan, E. *J. Org. Chem.* **1999**, *64*, 2381–2386, references cited therein.

(18) Physical and spectroscopic data for **3**: $[\alpha]^{24}_D = +14.3$ (*c* 0.12, MeOH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.29, 174.14, 151.27, 130.57, 82.70, 82.53, 77.78, 75.59, 74.05, 74.03, 73.72, 49.13, 43.78, 33.49, 33.26, 31.91, 31.78, 31.15, 31.06, 29.70, 29.66, 29.64, 29.63, 29.61, 29.58, 29.34, 28.71, 28.70, 25.60, 25.20, 23.54, 23.28, 22.67, 19.09, 14.10.

(19) This compound was obtained as an inseparable mixture of diastereomers with regard to the SPh group.

Table 1. Selected ^{1}H NMR data (δ) for Natural Compound, **3**, **27**, and Their MTPA Esters

				(*S*)-MTPA ester			(*R*)-MTPA ester		
position	natural	**3**	**27**	natural	**28**	**30**	natural	**29**	**31**
3	2.36 (d, 6.0)[a]	2.35 (m)[b]	2.36 (m)[b]						
4	3.59 (m)	3.58 (m)	3.56 (m)	3.566	3.570	3.561	3.564	3.568	3.557
8	3.85 (m)	3.82 (m)	3.82 (m)	3.818	3.810	3.810	3.813	3.809	3.805
9	2.63 (dd, 15.0, 9.0)	2.62 (dd, 15.9, 8.8)	2.63 (dd, 15.9, 8.8)	2.600	2.600	2.603	2.589	2.587	2.590
	2.41 (dd, 15.0, 6.6)	2.37 (dd, 15.9, 3.9)	2.37 (dd, 15.9, 3.3)	2.360	2.340	2.355	2.342	2.340	2.337
11	2.37 (m)	2.41 (t, 7.2)	2.41 (t, 7.2)						
14	1.40 (m)	1.39 (m)	1.39 (m)	1.562	1.580	1.580	1.519	1.530	1.530
15	3.40 (m)	3.38 (m)	3.38 (m)						
16	3.80 (m)	3.79 (m)	3.79 (m)	3.918	3.919	3.918	3.998	3.999	4.001
17,18				1.650	1.650	1.650	1.890	1.910	1.920
				1.382	1.370	1.370	1.560	1.570	1.560
19	3.80 (m)	3.79 (m)	3.79 (m)	3.918	3.919	3.918	3.998	3.999	4.001
20	3.40 (m)	3.40 (m)	3.40 (m)						
21	1.40 (m)	1.39 (m)	1.39 (m)	1.562	1.540	1.550	1.519	1.530	1.530
32	0.88 (t, 7.0)	0.87 (t, 6.9)	0.87 (t, 7.1)						
33	7.14 (d, 1.6)	7.14 (m)	7.17 (m)	7.136[c]	7.130	7.149	7.132[c]	7.126	7.154
34	4.99 (dq, 6.8, 1.6)	4.98 (brq, 6.6)	4.98 (brq, 6.6)	4.962[c]	4.954	4.958	4.959[c]	4.959	4.959
35	1.41 (d, 6.8)	1.40 (d, 6.6)	1.38 (d, 6.6)	1.390[c]	1.384	1.360	1.390[c]	1.384	1.364

[a] 500 MHz. [b] 600 MHz. [c] Obtained from the copies of the original NMR spectra kindly provided by Prof. Qin.

yielded the second target **27** (78% yield).[20] The spectroscopic and physical properties of the synthetic material **27** were found to differ from those of natural montanacin D. In particular, the specific rotation of **27** [$[\alpha]^{24}_D = +26.9$ (*c* 0.12, MeOH)] was higher than the reported value of natural montanacin D [$[\alpha]^{25}_D = +12.4$ (*c* 0.1, MeOH)]. In addition, the synthetic product **27** contained three signals at δ 1.38 (H-35), 3.56 (H-4), and 7.17 (H-33), which were observed at 1.41, 3.59, and 7.14 ppm, respectively, in the ^{1}H NMR spectrum of the natural product (Table 1).

We also prepared MTPA esters of **3** and **27** and carried out extensive NMR analyses of the compounds **28**−**31**. Table 1 lists the comparisons of ^{1}H NMR data. In analogy with the case of OH-free compounds, we found that the data from MTPA derivatives of **3** closely resembled those of natural montanacin D. In contrast, the two signals for H-33 and -35 of the synthetic materials **30** and **31** deviated by 0.01−0.03 ppm compared to the respective signals of the natural compounds in the ^{1}H NMR spectra.[21] Based on the results of these synthetic studies, we concluded that the structure of natural montanacin D is **3**.

In summary, we succeeded in a convergent synthesis of two possible isomers proposed to montanacin D based on cross-metathesis as a key step, showing that the structure of natural montanacin D is **3** not **27**.

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Supporting Information Available: Experimental procedures, NMR spectra of **3**−**5c**, **8**, **10**−**18**, and **20**−**31**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Spectroscopic data for **27**: ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.27, 174.15, 151.43, 130.55, 82.69, 82.51, 77.76, 75.66, 74.02, 73.97, 73.69, 49.17, 43.70, 33.48, 33.23, 31.90, 31.74, 31.17, 31.05, 29.70, 29.66, 29.64, 29.63, 29.61, 29.58, 29.34, 28.70, 25.59, 25.19, 23.50, 23.28, 22.67, 19.03, 14.10.

(21) The difference seemed to be due to the THP ring not flanking both MTPA esters since the butenolide unit and the THF region are separated by a long carbon chain.