Two-Dimensional NMR Analysis of Acetonide Derivatives in the Stereochemical Assignment of Polyol Chains: The Absolute Configurations of Dermostatins A and B

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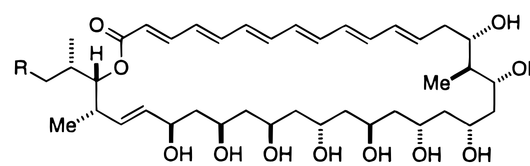
We report a new, integrated strategy for assigning the configuration of 1,3-skipped polyol chains and illustrate the approach with the configurational assignments of both dermostatins A and B. The method is designed around the ^{13}C acetonide analysis, which allows one to reliably determine the relative stereochemistry of an isolated 1,3-diol and is extended using DQF-COSY, HMQC, and ROESY experiments that allow each acetonide of a polyacetonide derivative to be unambiguously assigned as either syn or anti. Using this strategy, the relative configuration of the dermostatin A C13−C32 polyol chain was determined using just two polyacetonide derivatives. The absolute configuration of dermostatin A is 15*S*,16*S*,17*R*,19*R*,21*R*,23*S*,25*S*,27*R*,29*R*,31*R*,34*S*,35*S*, and the configuration of dermostatin B is 15*S*,16*S*,17*R*,19*R*,21*R*,23*S*,25*S*,27*R*,29*R*,31*R*,34*S*,35*S*,36*S*. The 2D ^{13}C acetonide analysis is a very powerful new tool for the stereochemical assignment of alternating polyol chains.

Introduction

The stereochemical assignment of complex 1,3-skipped polyol chains, such as those found in the polyene macrolide antibiotics, has proven to be a difficult and daunting task. The difficulties arise from two facts. First, these compounds exhibit poor crystalline properties, and as a result, only two polyene macrolides have yielded themselves to X-ray crystallographic analysis.[1] Second, these compounds have extremely complex NMR spectra in which most, if not all of the diagnostic resonance's overlap. As a result, only a handful of them have had their stereochemistries assigned on the basis on NMR analysis alone.[2] The stereochemical assignment of most of the compounds in this class have been established by strategies that inevitably involved extensive spectroscopic studies and a laborious combination of chemical degradation and partial synthesis.[3−6] The vast majority of the polyene macrolides have yet to have their full stereochemistry assigned.[7] To date, a simple, direct, and easily applied strategy for the stereochemical assignment of these structures has not been described.[8]

We have recently succeeded in developing a strategy based on the NMR analysis of acetonide derivatives which effectively solves the problem of the stereochemical assignment of polyol chains. Herein we report the full details of this strategy and demonstrate its power by assigning the configurations of both dermostatins A and B.[9]



Dermostatin A (**1**), (R = H)
Dermostatin B (**8**), (R = Me)

[⊗] Abstract published in *Advance ACS Abstracts,* April 1, 1997.

(1) The structure of amphotericin B was determined by X-ray analysis of its *N*-iodoacetyl derivative: (a) Mechlinski, W.; Schaffner, C. P.; Ganis, P.; Avitabile, G. *Tetrahedron Lett.* **1970**, 3873−6. (b) Ganis, P.; Avitabile, G.; Mechlinski, W.; Schaffner, C. P. *J. Am. Chem. Soc.* **1971**, *93*, 4560−4. The structure of roxaticin was determined by X-ray analysis of its heptaacetate derivative: (c) Maehr, H.; Yang, R.; Hong, L. N.; Liu, C. M.; Hatada, M. H.; Todaro, L. J. *J. Org. Chem.* **1989**, *54*, 3816−3819.

(2) Nystatin: (a) Prandi, J.; Beau, J.-M. *Tetrahedron Lett.* **1989**, *30*, 4517−20. (b) Lancelin, J.-M.; Beau, J.-M. *Tetrahedron Lett.* **1989**, *30*, 4521−4. (c) See also: Nicolaou, K. C.; Ahn, K. H. *Tetrahedron Lett.* **1989**, *30*, 1217−20. Vacidin A: (d) Sowinski, P.; Gariboldi, P.; Czerwinski, A.; Borowski, E. *J. Antibiot.* **1989**, *42*, 1631−8. (e) Sowinski, P.; Gariboldi, P.; Pawlak, J. K.; Borowski, E. *J. Antibiot.* **1989**, *42*, 1639−42. Pimaricin: (f) Lancelin, J.-M.; Beau, J.-M. *J. Am. Chem. Soc.* **1990**, *112*, 4060−1. (g) Lancelin, J.-M.; Beau, J.-M. *Bull. Soc. Chim. Fr.* **1995**, *132*, 215−23. Candidin: (h) Pawlak, J.; Sowinski, P.; Borowski, E.; Gariboldi, P. *J. Antibiot.* **1993**, *46*, 1598−1603.

(3) Pentamycin: (a) Oishi T. *Pure Appl. Chem.* **1989**, *61*, 427−30. (b) Nakata, T.; Hata, N.; Suenaga, T.; Oishi, T. *Abstract of Papers*, 30th Symposium on the Chemistry of Natural Products, Fukuoka, Oct 1988, p 540.

(4) Mycoticins A and B: (a) Schreiber, S. L.; Goulet, M. T. *Tetrahedron Lett.* **1987**, *28*, 6001−4. (b) Schreiber, S. L.; Goulet, M. T.; Sammakia, T. *Tetrahedron Lett.* **1987**, *28*, 6005−8. (c) Schreiber, S. L.; Goulet, M. T. *J. Am. Chem. Soc.* **1987**, *109*, 8120−2. (d) Goulet, M. Ph.D. Thesis, Yale University, 1988.

(5) Roflamycoin: (a) Rychnovsky, S. D.; Griesgraber, G.; Schlegel, R. *J. Am. Chem. Soc.* **1994**, *116*, 2623−4. (b) Rychnovsky, S. D.; Griesgraber, G.; Schlegel, R. *J. Am. Chem. Soc.* **1995**, *117*, 197−210.

(6) Filipin III: (a) Rychnovsky, S. D.; Richardson, T. I. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1227−30. (b) Richardson, T. I.; Rychnovsky, S. D. *J. Org. Chem.* **1996**, *61*, 4219−31.

(7) For reviews, see: (a) Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021−40. (b) Beau, J. M. In *Recent Progress in the Chemistry of Synthetic Antibiotics*; Lukacs, G., Ohno, M., Eds.; Springer: Berlin, 1990; pp 135−182. (c) Omura, S.; Tanaka, H. In *Macrolide Antibiotics: Chemistry, Biology, and Practice*; Omura, S., Ed.; Academic Press: New York, 1984; pp 351−404.

(8) Circular dichroism (CD) methods have been developed by both Mori and Nakanishi to assign the absolute configuration of 1,3-skipped polyols. (a) Mori, Y.; Kohchi, Y.; Suzuki, M.; Furukawa, H. *J. Am. Chem. Soc.* **1992**, *114*, 3557−9. (b) Mori, Y.; Sawada, T.; Sasaki, N.; Furukawa, H. *J. Am. Chem. Soc.* **1996**, *118*, 1651−6 and references cited therein. (c) Zhou, P.; Zhao, N.; Rele, D. N.; Berova, N.; Nakanishi, N. *J. Am. Chem. Soc.* **1993**, *115*, 9313−14. (d) Zhao, N.; Zhou, P.; Berova, N.; Nakanishi, K. *Chirality* **1995**, *7*, 636−51. These CD methods are appropriate for determining the absolute configuration of a few centers at the end of a polyol chain, but are not well suited for configurational assignments in the middle of a polyol chain, and to date they have not played a major role in the stereochemical assignment of a polyene macrolide antibiotic. The simple dibenzoate CD method has been used to determine the absolute configuration of a single relationship in a polyol derivative: Pawlak, J.; Nakanishi, K.; Iwashita, T.; Borowski, E. *J. Org. Chem.* **1987**, *52*, 2896−901.

An Integrated Strategy for Polyol Assignments. Our work in this area has focused on the NMR analysis of 1,3-diol acetonides. We first described the ^{13}C acetonide analysis which takes advantage of the unique conformational properties of syn and anti 1,3-diol acetonides.[10] Syn acetonides adopt the expected chair conformation, but anti acetonides adopt a twist-boat conformation to avoid severe 1,3-diaxial interactions present in both possible chair conformations. This difference in conformation can be easily detected from the ^{13}C NMR shifts of the acetonide methyl groups: syn acetonides have an axial methyl group at ca. 30 ppm and an equatorial methyl group at ca. 19 ppm, whereas the anti acetonides have both methyl groups at ca. 25 ppm. Thus the relative configuration of a simple 1,3-diol acetonide can be read directly from its ^{13}C NMR spectrum. This method is particularly well suited for the assignment of relative stereochemistry to a single, isolated 1,3-diol and played a pivotal role in our assignment of stereochemistry to the macrolactins.[11] Indeed, this method has been used by many other groups, not only in the context of structure determination[12] but also in a variety of synthetic endeavors,[13] because it provides a simple and reliable indication of the relative stereochemistry of an isolated 1,3-diol. The ^{13}C acetonide analysis

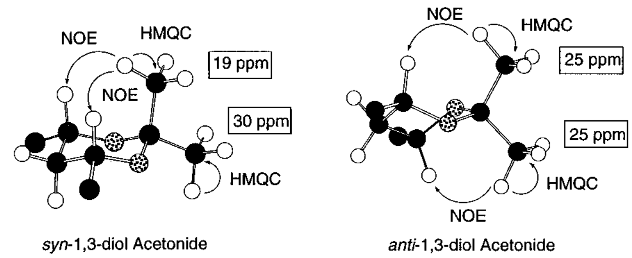


Figure 1. Overview of configurational assignments of polyol chains using ^{13}C acetonide analysis, HMQC correlations, and NOE data.

can also be applied to the 1,3,5...skipped polyol chains of the polyene macrolide antibiotics and was used successfully in our assignment of stereochemistry to roflamycoin[5] and filipin III.[6] However, our experience with these macrolides forced us to confront a serious limitation of the existing method.

The major limitation of the ^{13}C acetonide analysis is that it only indicates the number of syn and anti acetonides in any one polyacetonide derivative. The method would be much more powerful if it could also determine which acetonides are syn and which are anti. The analysis of filipin III is an excellent example of where the relative stereochemistry of the polyol portion of the molecule could have been proven on a single pair of acetonide derivatives isolated from a short, two-step protection sequence. If we could have explicitly assigned each acetonide as either syn or anti, the relative stereochemistry of filipin III could have been solved using only the two acetonide derivatives that contained all of the relative 1,3-diol relationships. Filipin's stereostructure was solved by further (laborious) chemical degradation and a partial synthesis. To overcome the limitations of the current ^{13}C acetonide analysis, we have taken advantage of the unique conformational properties of 1,3-diol acetonides and analyzed them with several readily available 2D NMR experiments.[14]

The key to analyzing a polyacetonide is to assign each acetonide methyl group in the ^{1}H NMR spectrum. The proton chemical shifts of acetonide methyl groups often overlap in $CDCl_3$, but they are usually well resolved in C_6D_6, while the ^{13}C chemical shifts are essentially unaffected. The proton methyl signals can be easily assigned as syn-axial, syn-equatorial, or anti by inspection of an HMQC spectrum. The methyl protons can then be correlated by through space interactions to the protons of the polyol backbone, using either a NOESY or a ROESY experiment. As illustrated in Figure 1, the axial methyl group in syn acetonides should show NOE cross-peaks to both of the backbone protons on the ring, whereas each anti acetonide methyl group will show a NOE cross-peak to backbone protons on opposite sides of the ring. Indeed this pattern of through space correlation between protons has been used to assign syn or

(9) Dermostatin is an oxopolyene macrolide antibiotic that was isolated from the mycelium of *Streptomyces viridogriseus* Thirum. (a) Thirumalachar, M. J.; Menon, S. K. *Hind. Antibiot. Bull.* **1962**, *4*, 106−8. (b) Bhate, D. S.; Ambekar, G. R.; Bhatnagar, K. K. *Hind. Antibiot. Bull.* **1962**, *4*, 159−162. It consists of two components, dermostatins A and B, whose flat structure have been determined. (a) Pandey, R. C.; Rinehart, K. L., Jr.; Millington, D. S.; Swami, M. B. *J. Antibiot.* **1973**, *26*, 475−7. (b) Narasimhachari, N.; Swami, M. B. *Chemotherapy* **1968**, *13*, 181−7. (c) Narasimhachari, N.; Swami, M. B. *J. Antibiot.* **1970**, *23*, 566. (d) Pandey, R. C.; Rinehart, K. L., Jr.; Millington, D. S. *Hind. Antibiot. Bull.* **1980**, *22*, 47−61. (e) Swamy, M. B.; Sastry, M. K.; Nanda, R. K. *Hind. Antibiot. Bull.* **1994**, *36*, 6−20. Dermostatin shows antifungal activity comparable to that of amphotericin B against a large number of human pathogens including dermatomycosis. Gordee, R. S.; Butler, T. F.; Narasimhachari, N. *J. Antibiot.* **1971**, *24*, 561−5.

(10) (a) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945−8. (b) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099−7102. (c) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511−15.

(11) Rychnovsky, S. D.; Skalitzky, D. J.; Pathirana, C.; Jensen, P. R.; Fenical, W. *J. Am. Chem. Soc.* **1992**, *114*, 671−677.

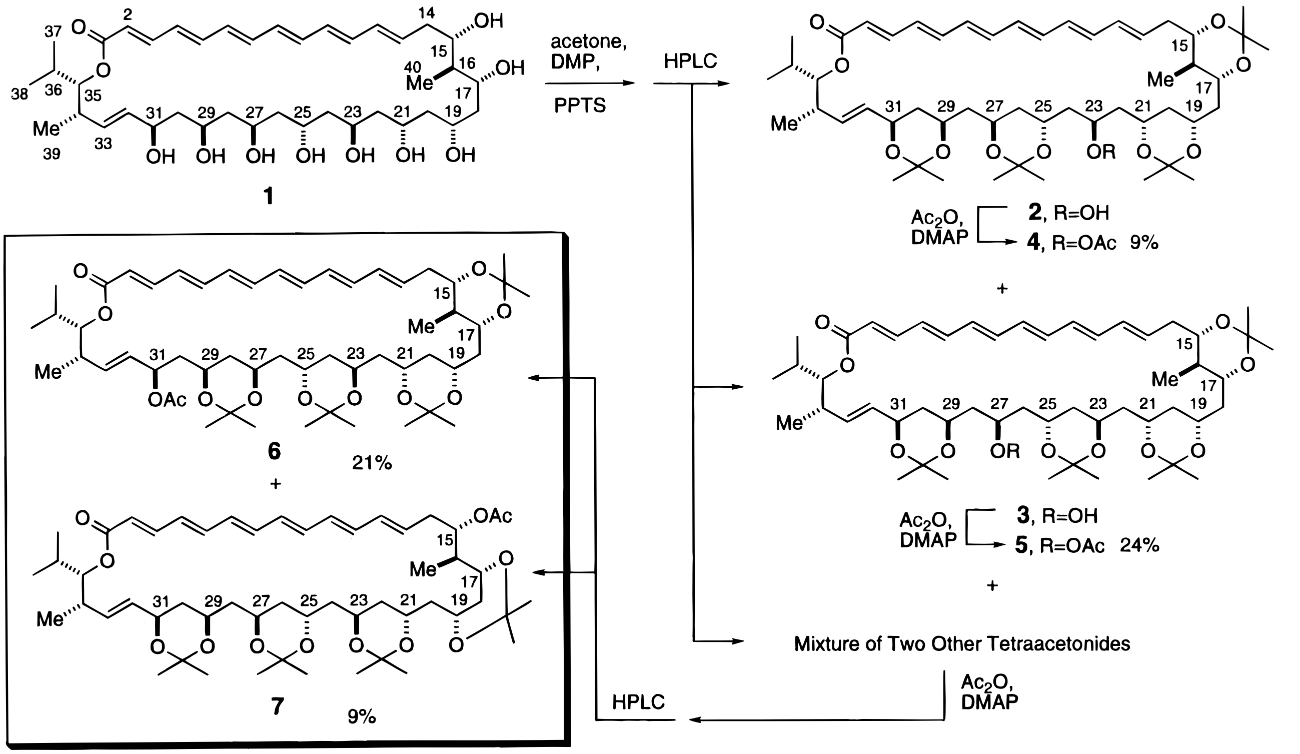
(12) For other examples of ^{13}C acetonide analysis used for structure determination, see: (a) Hoye, T. R.; Jimenez, J. I.; Shier, W. T. *J. Am. Chem. Soc.* **1994**, *116*, 9409−9410. (b) Harmange, J.-C.; Boyle, C. D.; Kishi, Y. *Tetrahedron Lett.* **1994**, *35*, 6819−6822. (c) Golakoti, T.; Ohtani, I.; Patterson, G. M. L.; Moore, R. E.; Corbett, T. H.; Valeriote, F. A.; Demchik, L. *J. Am. Chem. Soc.* **1994**, *116*, 4729−4737. (d) Mori, Y.; Kawajiri, N.; Furukawa, H.; Moore, R. E. *Tetrahedron* **1994**, *50*, 11133−11142. (e) Seki-Asano, M.; Tsuchida, Y.; Hanada, K.; Mizoue, K. *J. Antibiot.* **1994**, *47*, 1234−1241. (f) Murata, H.; Ohama, I.; Harada, K.-I.; Suzuki, M.; Ikemoto, T.; Shibuya, T.; Haneishi, T.; Torikata, A.; Itezono, Y.; Nakayama, N. *J. Antibiot.* **1995**, *48*, 850−62. (g) Golakoti, T.; Ohtani, I.; Heltzel, C. E.; Husebo, T. L.; Jensen, C. M.; Larson, L. K.; Patterson, G. M. L.; Moore, R. E.; Mooberry, S. L.; Corbett, T. H.; Valeriote, F. A. *J. Am. Chem. Soc.* **1995**, *117*, 12030−12049. (h) Searl, P. A.; Richter, R. K.; Molinski, T. F. *J. Org. Chem.* **1996**, *61*, 4073−4079. (i) Suenaga, K.; Mutou, T.; Shibata, T.; Itoh, T.; Kigoshi, H.; Yamada, K. *Tetrahedron Lett.* **1996**, *37*, 6771−6774.

(13) The origional ^{13}C method has been cited in the literature over 100 times. For recent examples, see: (a) Yokokawa, F.; Hamada, Y.; Shiori, T. *Chem. Commun.* **1996**, 871−872. (b) Kim, K. S.; Park, H. B.; Kim, J. Y.; Ahn, Y. H.; Jeong, I. H. *Tetrahedron Lett.* **1996**, *37*, 1249−1252. (c) Paterson, I.; Perkins, M. V. *Tetrahedron* **1996**, *52*, 1811−1834. (d) Travares, F.; Lawson, J. P.; Meyery, A. I. *J. Am. Chem. Soc.* **1996**, *118*, 3303−3304. (e) Szymoniak, J.; Lefranc, H.; Moise, C. *J. Org. Chem.* **1996**, *61*, 3926−3928. (f) Hatakeyama, S.; Fukuyama, H.; Mukugi, Y.; Irie, H. *Tetrahedron Lett.* **1996**, *37*, 4047−4050. (g) Achmatowicz, B.; Jankowski, P.; Wicha, J. *Tetrahedron Lett.* **1996**, *37*, 5589−5592. (h) Scarlato, G. R.; DeMattei, J. A.; Chong, L. S.; Ogawa, A. K.; Lin, M. R.; Armstrong, R. W. *J. Org. Chem.* **1996**, *61*, 6139−6152. (i) Nagasawa, K.; Shimizu, I.; Nakata, T. *Tetrahedron Lett.* **1996**, *37*, 6881−6884. (j) Hamada, Y.; Yokokawa, F.; Kabeya, M.; Hatano, K.; Kurono, Y.; Shioiri, T. *Tetrahedron* **1996**, *52*, 8297−8306. (k) Nacro, K.; Baltas, M.; Escudier, J.-M.; Gorrichon *Tetrahedron* **1996**, *52*, 9047−9056.

(14) We recognized the potential of an integrated HMQC/ROESY/^{13}C acetonide strategy during the structure determination of filipin III. At that time we had already completed the structure determination of filipin III (ref 6) but later reanalyzed several of the complex polyacetonides from that project and demonstrated that the new integrated strategy was successful. This work has been described in a number of seminars beginning with one on December 4, 1995, at U.C. San Diego but has not before appeared in print. The stereochemical assignment of dermostatin A was recently presented: Rychnovsky, S. D.; Richardson, T. I. *Abstract of Papers*, 212th National Meeting of the American Chemical Society, Orlando, FL; American Chemical Society: Washington, DC, 1996; ORG 436.

(15) Examples of 2D NMR analysis of acetonides: (1) Ojika, M.; Nagoya, T.; Yamada, K. *Tetrahedron Lett.* **1995**, *36*, 7491−7494. (2) Lindel, T.; Jensen, P. R.; Fenical, W. *Tetrahedron Lett.* **1996**, *37*, 1327−1330.

Scheme 1



anti relationships in simple acetonide derivatives.[15] The additional data provided by an HMQC spectrum allows each of the acetonide methyl groups to be quickly and unambiguously assigned as syn-axial, syn-equatorial, or anti. In all but the simplest cases these $^{13}C-^{1}H$ acetonide methyl correlation are necessary to definitively assign the configuration of a polyacetonide. This 2D ^{13}C acetonide analysis is demonstrated in the structure determination of dermostatin A presented below.

Results and Discussion

Establishing the Relative Configuration of the C13–C32 Polyol Using 2D NMR Methods. A sample of dermostatin complex was kindly provided by Dr. S. R. Naik from the Hindustan Antibiotics Ltd. A portion of this sample was purified by preparative reversed-phase HPLC to give 59% dermostatin A and 14% dermostatin B. Purified dermostatins A and B were used in the following studies.

Acetonide derivatives of dermostatin A were prepared in order to assign the relative configuration of the polyol chain (Scheme 1). Exposure of dermostatin A to acetone, DMP, and PPTS for 12 h resulted in a mixture that was cleanly separated by normal-phase HPLC. Three major peaks eluting at 12.6, 15.4, and 22.7 min were isolated. The compounds eluting at 12.6 and 22.7 min were each submitted separately to standard acetylation conditions to give, respectively, tetraacetonide **4** in 9% yield and tetraacetonide **5** in 24% yield. The material eluting at 15.4 min turned out to be a mixture of tetraacetonides which was easily separated by normal-phase HPLC after acetylation to yield tetraacetonide **6** (25.8 min) in 21% yield and tetraacetonide **7** (30.3 min) in 9% yield.

Each of the four tetraacetonides (**4**–**7**) was initially characterized by ^{1}H NMR, FAB HRMS, and DQF-COSY.[16] Analysis of the COSY spectra allowed the acetates of tetraacetonides **6** and **7** to be assigned to the C31 and C15 positions, respectively. Since the acetonide protecting groups of compound **6** are frame shifted by one hydroxyl from compound **7**, these two acetonide derivatives alone provide enough information to uniquely define the relative configuration of each 1,3-diol in the natural product. ROESY[17] and HMQC[18] spectra were collected for each of the four tetraacetonides, but our analysis of the data focused on compounds **6** and **7**. Initially the data was collected using benzene-d_6 as the NMR solvent, but coincidental overlap of several peaks in compound **7** complicated the analysis, *vida infra*. After several solvents were screened, toluene-d_8 was found to give a well-resolved ^{1}H NMR spectrum for compound **7**, and it was used as the NMR solvent for subsequent data collection. The COSY data was used to assign the resonances in the tetraacetonides' spectra, and the assignments for **6** and **7** are summarized in Tables 1 and 2. As discussed below, evaluation of the ROE correlations provided an independent cross-check of these carbinol assignments. The key portions of the ROESY and HMQC data are plotted together in Figure 2 for compound **6** and in Figure 3 for compound **7**. All the necessary information to assign the relative configuration of dermostatin A is contained in Tables 1 and 2 and Figures 2 and 3.[19]

The ROESY and HMQC data for tetraacetonide **6** are shown in Figure 2. Inspection of the HMQC data immediately shows that **6** has one anti acetonide and three syn acetonides. The two anti acetonide methyl groups have chemical shifts at 24–25 ppm, which correspond to peaks e and f in the ^{1}H NMR spectrum. The three syn acetonides each have an axial methyl peak around 19 ppm and an equatorial methyl peak around

(16) Piatini, U.; Sorenson, O. W.; Ernst, R. R. *J. Am. Chem. Soc.* **1982**, *104*, 6800–1.

(17) (a) Bax, A.; Davis, D. G. *J. Magn. Reson.* **1985**, *63*, 207. (b) Bax, A. *J. Magn. Reson.* **1988**, *77*, 134.

(18) Bax, A.; Ikura, M.; Kay, L. E.; Torchia, D. A.; Tschudin, R. *J. Magn. Reson.* **1990**, *86*, 304.

(19) Full spectral data for compounds **4**–**7**, including peak assignments and 2D NMR data, can be found in the Experimental Section or the Supporting Information.

Table 1. Proton Assignments for 6 in Benzene-d_6[a]

carbon no.	δ (ppm)	splitting	J (Hz)
2	5.95	d	15.1
3	7.51	dd	11.2, 15.2
4−13	6.34−6.02	m	
14a	2.47	m	
14b	2.22	ddd	2.6, 10.0, 14.8
15	3.504	dt	3.1, 10.5
16	2.01	tq	10.5, 6.5
17	3.496	dt	3.3, 10.5
18a	1.95	ddd	3.1, 7.3, 15.1
19	4.33	m	
21	4.07	m	
23	4.18	m	
25	4.16	m	
27	4.05	m	
29	3.89	dddd	2.7, 4.2, 8.5, 11.0
30a	2.08	ddd	6.2, 8.7, 13.5
31	5.84	q	7.0
32	5.64	ddd	1.8, 7.0, 15.9
33	6.04	m	
34	2.62	ddq	2.7, 4.5, 7.1
35	5.12	dd	2.7, 8.4
36	1.87	dqq	8.4, 6.6, 6.7
37	0.985	d	6.6
38	0.748	d	6.7
39	1.06	d	7.1
40	0.695	d	6.5
Ac	1.74	s	
Me-synE	1.54	s	
Me-synE	1.53	s	
Me-synE	1.50	s	
Me-synA	1.440	s	
Me-synA	1.440	s	
Me-anti	1.436	s	
Me-anti	1.40	s	
Me-synA	1.30	s	

[a] Spectra were obtained in benzene-d_6 at 500 MHz on a Varian Unity spectrometer. Peaks are referenced to solvent (7.15 ppm). Ac = acetate methyl, Me = methyl of an acetonide, synE = equitorial methyl of a syn acetonide, synA = axial methyl of a syn acetonide, and anti = methyl of an anti acetonide.

Table 2. Proton Assignments of 7 in Toluene-d_8[a]

carbon no.	δ (ppm)	splitting	J (Hz)
2	5.88	d	15.4
3	7.47	dd	11.3, 15.1
4−12	6.17−5.95	m	
13	5.66	ddd	5.2, 10.6, 15.2
14a	2.56	m	
14b	2.46	m	
15	5.54	dt	10.3, 2.9
16	1.94	m	
17	3.79	ddd	2.0, 9.2, 10.9
19	3.59	m	
21	4.21	m	
23	4.05	m	
25	4.05	m	
27	3.88	m	
29	4.09	m	
31	4.28	m	
32	5.61	ddd	1.5, 4.9, 15.9
33	5.88	m	
34	2.48	m	
35	5.02	dd	2.2, 9.9
36	1.80	m	
37	0.953	d	6.6
38	0.705	d	6.7
39	1.06	d	7.0
40	0.878	d	7.1
Ac	1.69	s	
Me-synE	1.54	s	
Me-synE	1.45	s	
Me-anti	1.36	s	
Me-anti	1.35	s	
Me-anti	1.34	s	
Me-synA	1.33	s	
Me-anti	1.30	s	
Me-synA	1.26	s	

[a] Spectra were obtained in toluene-d_8 at 500 MHz on a Varian Unity spectrometer. Peaks are referenced to solvent (7.00 ppm). Ac = acetate methyl, Me = methyl of an acetonide, synE = equitorial methyl of a syn acetonide, synA = axial methyl of a syn acetonide, and anti = methyl of an anti acetonide.

30 ppm. Two of the axial methyl peaks, c and h, overlap, while the third axial methyl peak, a, is well separated from the others. Although methyl peaks c and h overlap, in the ^{1}H NMR spectrum, this does not hinder the analysis. For the syn acetonides, the equatorial methyl peaks, b, d, and g, confirm the number of syn acetonide rings but are of no further use in the analysis since only the axial methyl peaks show through space correlation with backbone protons. The two anti methyls e and f show ROE cross-peaks with the 4.18 multiplet assigned to the C23 and C25 protons. This identifies the position of the lone anti acetonide and by implication identifies the position of the three syn acetonides. Though not entirely necessary, each of the syn acetonides can be unambiguously assigned on the basis of the data available and thus provide additional proof for the stereochemical assignment. To finish the entire evaluation of **6**, the ROE cross-peaks from methyl a to the C15 and C17 protons clearly identify the position of one of the syn methyls, and the other two syn methyls, c and h, show cross-peaks with the C19 and C21 and the C27 and C29 protons, respectively. Assigning the position of the lone anti acetonide is enough to locate all the acetonide rings, but *the combined ROESY/HMQC data allows one to do much more, that is to explicitly assign each acetonide ring in the polyol chain as either syn or anti.* Another piece of information that this acetonide derivative provides is the relative configuration of the C16 methyl. The protons at C15 and C17 of tetraacetonide **6** give rise to two overlapping doublet of triplets in the ^{1}H NMR spectrum with large J_{15-16} and J_{16-17} values of 10.5 Hz that are only consistent with diaxial couplings. Thus the C16 proton is axial and the methyl group is equatorial establishing the C15−C16 and the C16−C17 relationships as anti. The ROESY and HMQC data, combined with the ^{13}C acetonide analysis, allows the relative configuration of four of the eight 1,3-diol relationships to be determined unambiguously using a single tetraacetonide.

The four acetonide rings of **7** incorporate the remaining 1,3-diol relationships necessary to uniquely define the relative configuration of the C13−C32 dermostatin polyol. The initial data for compound **7** was collected in benzene-d_6, which unfortunately lead to overlapping peaks for methyl groups f and h and overlapping backbone protons at C23, C25, and C29.[19] As a result, it was not possible to unambiguously assign each of the acetonide rings as either syn or anti using the benzene data. For the pair of rings at C25−C27 and C29−C31, one was syn and one was anti, but it was not possible to determine which was which. (We did know the *positions* of the acetonide rings from the COSY but had difficulty assigning them as syn or anti.) The benzene-d_6 data were still very informative, and there were two different ways to proceed to solve the structure. One could obtain the remaining relationship by examining the other tetraacetonides, **4** and **5**, or select a solvent to reduce the peak overlap in compound **7**. In order to fully explore the scope of 2D ^{13}C acetonide analysis, we decided to investigate both options.

The ^{1}H NMR spectrum of **7** was acquired in several different solvents, and toluene-d_8 was found to give the best resolution of the methyl acetonide peaks. Generally, ^{13}C chemical shifts are insensitive to solvent, and the ^{13}C

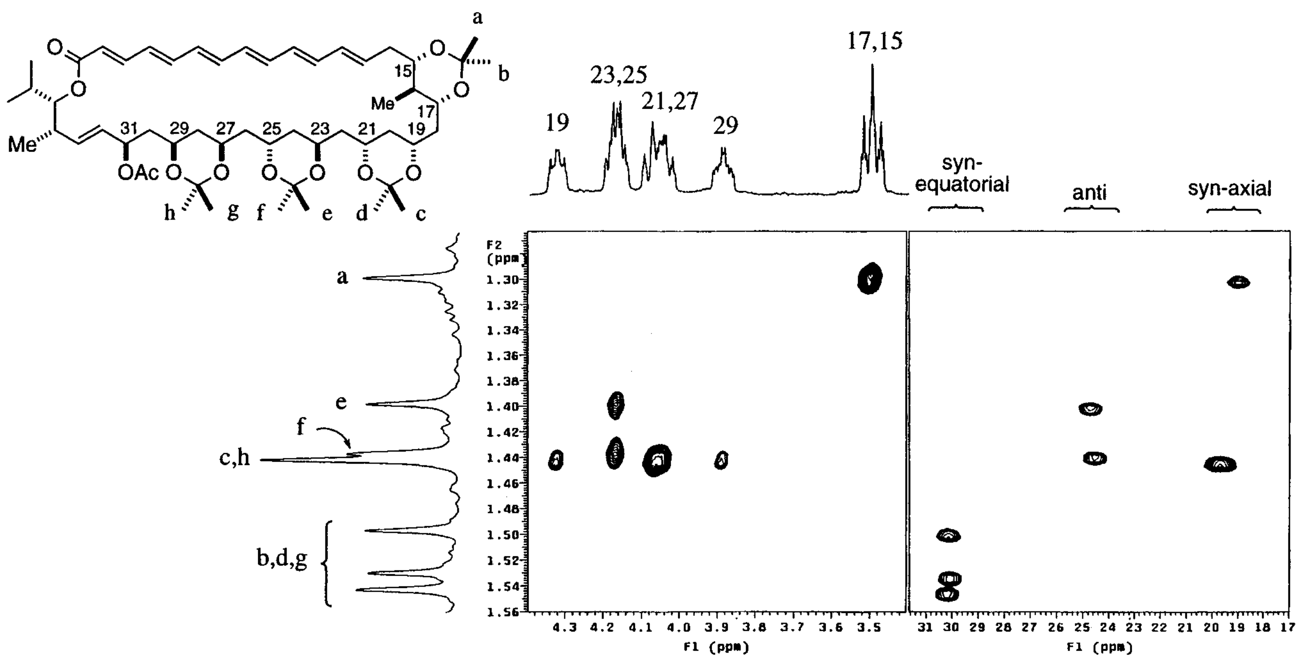


Figure 2. ROESY (left) and HMQC (right) of the acetonide methyl region for compound **6**.

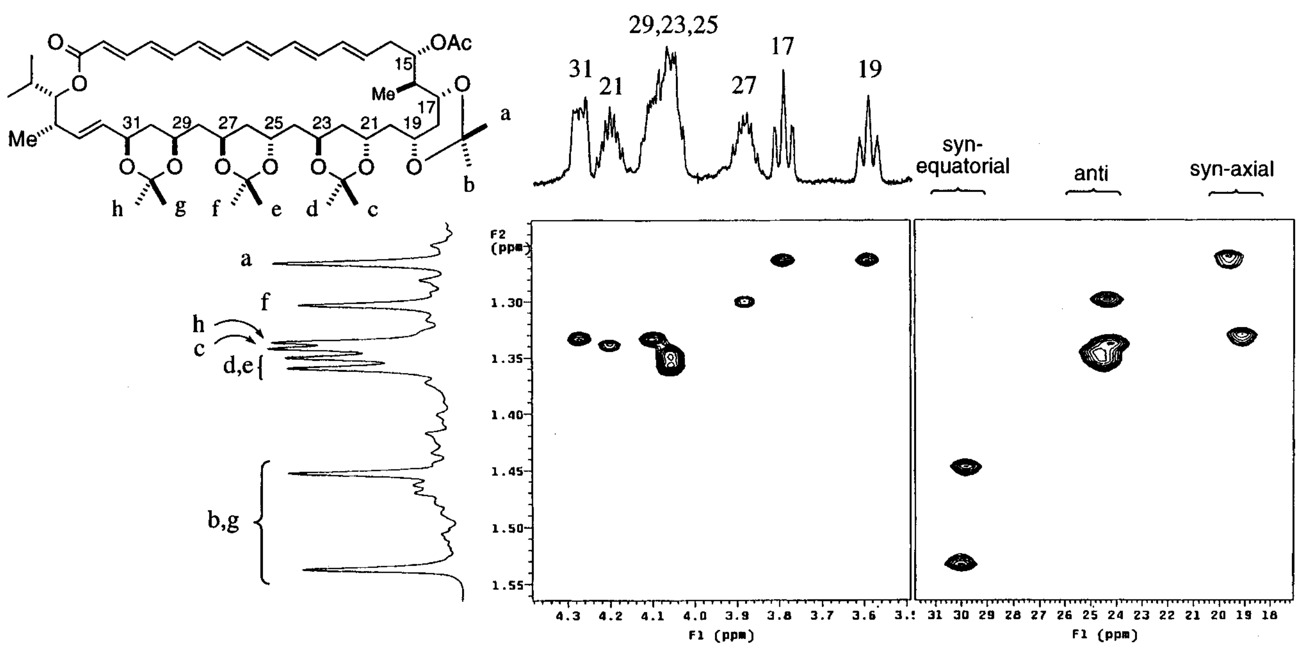


Figure 3. ROESY (left) and HMQC (right) of the acetonide methyl region for compound **7**.

acetonide analysis works well in many different solvents including $CDCl_3$, benzene-d_6, CD_2Cl_2, and toluene-d_8. The ROESY and HMQC data for tetraacetonide **7** in toluene-d_8 is plotted in Figure 3. Inspection of the HMQC shows that tetraacetonide **7** has two syn acetonide rings and two anti acetonide rings. The syn-axial methyl groups have signals around 19 ppm and can be identified as a and h in the proton NMR spectrum. The anti methyl signals show up at 24−25 ppm and were identified as c, d, e, and f. Methyl a shows ROE cross-peaks with the C17 and C19 protons, thus determining the position of one of the syn acetonide rings. Methyl h shows ROE cross-peaks with C31 and one of the peaks in the C23, C25, and C29 set at 4.09 ppm, thus determining the position of the other syn acetonide as C29−C31. The anti methyls d and e have cross-peaks in the C23, C25, and C29 peak, with complementary cross-peaks from c and f to the C21 and C27 protons, respectively; thus the two anti rings are located at C21−C23 and C25−C27. Using the toluene-d_8 NMR data, each and every acetonide ring in compound **7** can be explicitly assigned as either syn or anti. When the methyl acetonide peaks are resolved, assignment of the configuration of complex polyol acetonides using the 2D ^{13}C acetonide method is simply a matter of connecting the dots. The relative configuration of the entire polyol section of dermostatin can be fully assigned using only two acetonide derivatives.

Configurational assignment could also be made by examination of tetraacetonides **4** and **5** (data not shown).[19] Analysis of the benzene-d_6 data for tetraacetonide **7** left unassigned the configurations at C25−C27 and C29−C31. One ring was syn and the other was anti, but a simple analysis did not reveal which was which. Inspection of the data for compound **4** showed that the isolated C29 proton at 4.08 ppm had a ROE cross-peak with the methyl at 1.35 ppm. That methyl signal also showed a

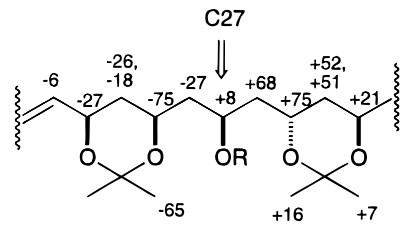


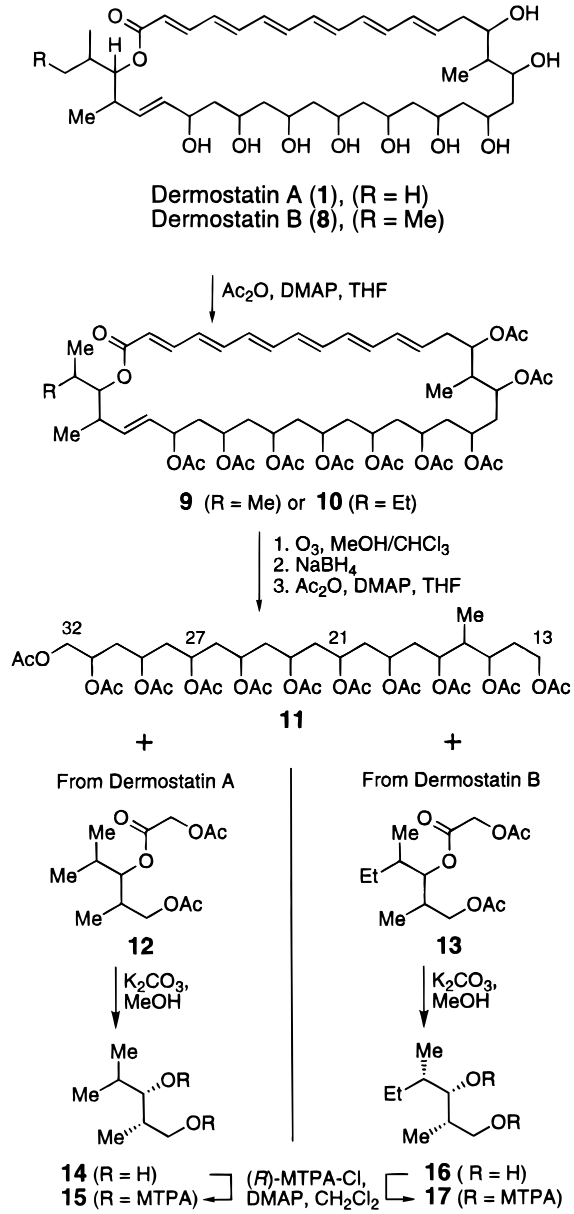
Figure 4. Advanced Mosher ester analysis of the C27 position of tetraacetonide **3**. The ΔδH values (in hertz at 500 MHz) are shown for each proton.

cross-peak with the C19 and C31 peak at 4.3 ppm and had an HMQC cross-peak at 19.5 ppm. Thus the C29−C31 ring was syn, the C25−C27 ring was therefore anti, and the C13−C32 relative configuration of dermostatin A was assigned. The same information can be found in the NMR data for tetraacetonide **5**. Indeed, the methyl peaks in both **4** and **5** are well resolved, and the location of every syn and anti ring can be explicitly assigned from the ROESY and HMQC data. Analysis of the four acetonide derivatives that were prepared from dermostatin A using the 2D ^{13}C acetonide analysis results in an overdetermination of the C13−C32 configuration, which increases the confidence level of the stereochemical assignment.

Absolute Configuration of the Polyol Region. Additional information was needed to assign the absolute configuration of the polyol portion of dermostatin A. The major acetonide formed in the protection of dermostatin A was tetraacetonide **3** (Scheme 1), which was isolated as a single compound by HPLC. Advanced Mosher ester analysis[20] was carried out on the C27 alcohol of **3** by preparing the *R* and *S* Mosher esters and assigning their ^{1}H NMR spectra using both DQF-COSY and ROESY spectra. The $\Delta\delta$ values ($\Delta\delta = \delta S - \delta R$) are shown in Figure 4 for the protons around the C27 position of **3**. With the simple pattern of negative values on the left and positive values on the right, the absolute configuration of the C27 stereogenic center can be confidently assigned as *R* (beta). This single assignment of absolute stereochemistry in the middle of the C15−C32 polyol section combined with the relative stereochemistry assigned above determines the absolute stereochemistry of the entire C13−C32 polyol chain of dermostatin A.

Degradation Studies. The first goal of the degradation work was to determine if the polyol portions of dermostatins A and B were identical. Dermostatin A nonaacetate was cleanly prepared upon treatment with Ac_2O and DMAP as illustrated in Scheme 2. The resulting nonaacetate **9** was subjected to an ozonolysis, reduction ($NaBH_4$), and acetylation sequence to deliver undecaacetate **11** of the C13−C32 polyol and diacetate **12** containing C34−C36 of the natural product. Dermostatin B was independently treated under acetate-forming conditions to give nonaacetate **10** (Scheme 2). The dermostatin B nonaacetate was subjected to the same sequence of ozonolysis, reduction ($NaBH_4$), and acetylation as the dermostatin A derived acetate to give undecaacetate **11** and a different diacetate **13**. The initial samples of **11** were contaminated with an unidentified impurity, so samples of **11** from both dermostatins A and B were purified by reversed-phase HPLC. The purified samples showed identical ^{1}H NMR and DQF-COSY spectrum, as well as HPLC and TLC mobility, so it was

Scheme 2



established that dermostatins A and B had the same polyol configuration.[21] The CD spectra of the purified polyacetate samples were also identical, demonstrating that both had the same absolute configuration.[22] All of the data suggested that the two samples were identical, indicating absolute stereochemical homology of the 1,3-polyol segment (C13-C32) of dermostatins A and B.

The other objective of the degradation studies of dermostatins A and B was to determine the absolute configuration of the C34−C36 fragment of both compounds. To this end, the diacetates **12** and **13** derived from dermostatins A and B respectively were independently saponified by treatment with methanolic potassium carbonate to give diols **14** and **16** respectively (Scheme 2). Mosher ester derivatives **15** and **17** were prepared for each compound by treatment with Mosher acid chloride to aid in the assignment of its absolute configuration and serve as targets for synthetic studies.

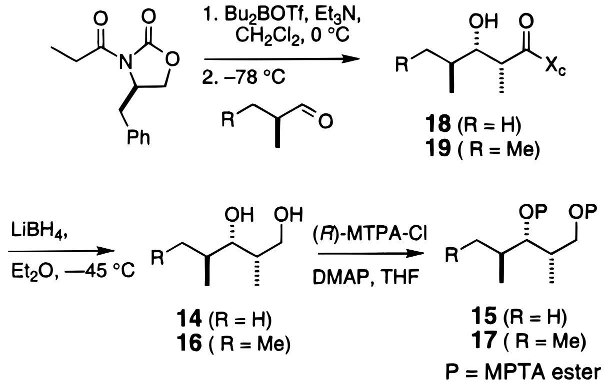
Authentic samples of diols **14** and **16** and Mosher esters **15** and **17** were prepared by the route outlined in

(20) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−6.

(21) Proton NMR analysis of a combined sample of **11** showed no peak doubling.

(22) For CD spectra, see Supporting Information.

Scheme 3



Scheme 3. The aldehydes underwent aldol condensations with propionyloxazolidinone to give **18** and **19** in good yield and diastereoselectivity. Reduction ($LiBH_4$) of the resulting aldol adducts provided synthetic diols **14** and **16** which were shown to be identical by TLC and NMR to the dermostatin-derived diols. The Mosher esters of each were synthesized as described before to give esters **15** and **17** which were also identical by NMR and TLC to the compounds derived from the natural products.[23] This is the same strategy used by Schreiber and Goulet in their configurational assignment of the C30−C33 portion of mycoticins A and B,[4] and is based on very reliable Evans aldol condensations.[24] Since the synthetic diols and their MTPA esters were identical with the naturally derived degradation fragments by ^{1}H NMR analysis and TLC, the relative and absolute configurations of the C33−C36 fragments for both dermostatin A and dermostatin B were established.

Absolute Configuration of Dermostatins A and B. Compiling the information that has been presented allows for the full stereochemical assignment of dermostatins A and B. As described in the Mosher analysis above, the configuration at C27 was assigned as *R*, and thus the absolute configuration of dermostatin A is 15*S*,16*S*,17*R*,19*R*,21*R*,23*S*,25*S*,27*R*,29*R*,31*R*,34*S*,35*S*. The configuration of dermostatin B is 15*S*,16*S*,17*R*,19*R*,21*R*, 23*S*,25*S*,27*R*,29*R*,31*R*,34*S*,35*S*,36*S*. The 2D ^{13}C acetonide analysis was carried out using only 35 mg of purified dermostatin A, and the degradation work was carried out with 10−15 mg each of dermostatins A and B. Since acetonide formation is a nondestructive technique, if needed, the natural product can be regenerated by deprotection. The complete structure assignment of dermostatins A and B was carried out in just 1 month.

Discussion

The ^{13}C acetonide analysis combined with ROESY and HMQC experiments makes the explicit assignment of syn and anti relative configuration along a polyol chain simple. One potential problem, overlapping acetonide methyl peaks in the ^{1}H NMR spectrum, can be overcome by using different solvents. Of the four tetraacetonides **4**−**7**, the position and relative configuration of all of the acetonide rings could be determined for three of them using the first solvent tried, benzene-d_6. The remaining tetraacetonide could be assigned by collecting data in toluene-d_8. This 2D ^{13}C acetonide method is an extremely powerful strategy for determining the configuration of polyol chains and should find widespread use in the structure determination of natural products.

In the preparation of polyacetonide derivatives, one makes several choices that affect the analysis. Should vigorous conditions be used in the acetonide formation? Should one use ^{13}C-enriched acetone? We have found that a mixture of acetone and 2,2-dimethoxypropane (DMP) with PPTS catalysis is usually vigorous enough to give satisfactory yields of polyacetonides. In the case of dermostatin there are nine free hydroxyls, so these conditions should result in *a mixture* of tetraacetonides. In most degradation chemistry, mixtures are to be avoided, but in the ^{13}C acetonide analysis, each additional polyacetonide provides information on different stereochemical relationships. Therefore, a mixture of *separable* polyacetonides is highly desirable.

The use of ^{13}C-enriched acetone provides some advantages in the analysis but is by no means essential. The dermostatin tetraacetonides in Scheme 1 were analyzed with approximately 10% ^{13}C enrichment of the acetonide methyls, which allowed us to obtain better quality HMQC data using less instrument time and less material. The ^{13}C enrichment has no advantage for the collection of other spectra, DQF-COSY and ROESY, and high levels of enrichment actually complicate the analysis due to ^{1}H−^{13}C couplings observable in the proton spectrum. Because of the small reaction volumes, modest levels of ^{13}C enrichment can be achieved using small amounts of 1,3-$^{13}C_2$-acetone. For example, only 50 μL (ca. \$25)[25] of 98% 1,3-$^{13}C_2$-acetone would be needed to achieve 10% ^{13}C enrichment in a typical derivatization reaction using 0.5 mL of acetone. Certainly ^{13}C enrichment provides a sometimes needed boost in sensitivity, but the increased sensitivity of modern NMR instruments using an indirect detection pulse sequence like an HMQC experiment makes ^{13}C enrichment optional.

Comparison with the Standard ^{13}C Acetonide Analysis. The 2D ^{13}C acetonide method allows each acetonide of a polyacetonide to be unambiguously assigned either as syn or anti. Although earlier versions of the ^{13}C acetonide analysis[5,6,10,11] did not allow for the *assignment* of each acetonide as either syn or anti, it could be used to unambiguously determine the *number* of syn and anti acetonide rings in each polyacetonide. As alluded to earlier, the entire polyol of filipin III could have been determined on just two acetonide derivatives that were made in the first reaction sequence. It was possible to determine the stereochemistry through degradation and additional analog synthesis, but the method presented in this paper would have rendered the filipin analysis trivial. It is instructive to compare the old method of analysis to the current structure determination of dermostatin A. Dermostatin A is an extremely challenging case for the traditional ^{13}C acetonide approach. Using the standard ^{13}C acetonide analysis, the four tetraacetonides **4**−**7** reduce the number of possible diastereomers from 256 to six. Other constraints could reduce it further, such as using ^{1}H NMR coupling constants to assign the C15−C17 relationship as syn, which would reduce the number of possible stereoisomers from six to five. Other possible dermostatin A acetonide derivatives could be prepared, but we have not been able to identify any plausible derivatives that would lead to a unique solution. One could synthesize the remaining

(23) See the Supporting Information for comparative NMR's of the Mosher esters **15** and **17**.

(24) Gage, J. R.; Evans, D. A. *Org. Synth.* **1989**, *68*, 83−90 and references cited therein.

(25) Aldrich list 98% enriched 1,3-$^{13}C_2$-acetone (#29,918-9) at \$438 for 1 g.

five or six diastereomers of compound **11**, but that is a very labor-intensive strategy. The standard ^{13}C acetonide analysis does not lead to a solution for the configuration of dermostatin A. Although the standard ^{13}C acetonide analysis is very useful, it pales in comparison to the power of the 2D ^{13}C acetonide method. The ^{13}C acetonide analysis augmented by ROESY and HMQC data allowed the correct polyol diastereomer of dermostatin A to be unambiguously assigned using just two tetraacetonide derivatives. There are many isolated techniques that could make headway in a structural determination of dermostatin, but we are not aware of any strategy, other than X-ray crystallography, that would reliably lead to a configurational assignment of the dermostatin polyol region.

Conclusions

We have outlined a comprehensive strategy for assigning the configuration to polyol chains. The method is designed around the ^{13}C acetonide analysis, which allows one to reliably determine the number of syn and anti rings in a complex polyacetonide and is extended using DQF-COSY, HMQC, and ROESY experiments allowing each acetonide to be assigned as either syn or anti. *Using this strategy the relative configuration of the dermostatin A C13−C32 polyol chain could be determined using just two polyacetonide derivatives.* For comparison, the standard ^{13}C acetonide analysis of dermostatin A did not led to a unique solution; it did, however, narrow the number of diastereomers of the polyol region to six. The 2D ^{13}C acetonide analysis is the most powerful method that has been reported to date for determining the configuration of alternating polyol chains, and this strategy will be an important new tool for the stereochemical assignment of polyene macrolide antibiotics and other 1,3-polyol-containing compounds.[26]

Experimental Section[27]

Dermostatin A (1) and Dermostatin B (8). Dermostatin complex (kindly donated to us by Hindustatin Antibiotics) (100 mg) was dissolved in DMF (1 mL) and DMSO (1 mL) to make a 50 mg/mL solution. This solution was injected (200−400 μL per injection) onto a reversed-phase HPLC column[28] and eluted with 80% MeOH/20% H_2O at 21 mL/min.[29] Two major peaks eluting at 16.1 min (dermostatin A, 57.9 mg) and 19.7 min (dermostatin B, 13.6 mg) were collected and isolated as yellow amorphous solids.

Dermostatin A (1): t_R 16.1 min; UV−vis (CH_3OH/H_2O) λ_{max} 282 (250 mAU), 390 nm (2150 mAU); IR (KBr) 3396, 2941, 1690, 1619, 1561, 1430, 1379, 1250, 1133, 1081, 1013 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 7.30 (dd, J = 15.0, 11.5 Hz, 1 H), 6.71 (dd, J = 14.5, 11.2 Hz, 1 H), 6.52 (dd, J = 14.5, 11.0 Hz, 1 H), 6.45−6.21 (m, 6 H), 6.16 (ddd, J = 15.1, 10.4, 1.7 Hz, 1 H), 5.90 (d, J = 15.1 Hz, 1 H), 5.82 (ddd, J = 15.1, 4.6, 4.4 Hz, 1 H), 5.57 (ddd, J = 15.9, 5.3, 0.6 Hz, 1 H), 5.48 (ddd, J = 15.9, 5.1, 1.0 Hz, 1 H), 4.83 (m, 1 H), 4.27 (dt, J = 10.6, 3.1 Hz, 1 H), 4.14−3.88 (m, 7 H), 3.56 (m, 1 H), 2.61 (m, 1 H), 2.43 (m, 1 H), 2.38 (m, 1 H), 1.91−1.12 (m, 16 H), 1.01 (d, J = 6.9 Hz, 3 H), 0.95 (d, J = 6.7 Hz, 3 H), 0.87 (d, J = 6.9 Hz, 3 H), 0.86 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO) δ 166.7, 145.1, 141.6, 138.1, 136.3, 135.2, 134.8, 133.3, 132.4, 132.1, 131.3, 131.1, 130.9, 130.0, 120.6, 80.3, 70.4, 69.6, 69.4, 68.8, 68.4, 67.8, 67.7, 62.9, 62.4, 47.3, 47.0, 46.8, 46.4, 45.2, 44.6, 44.1, 42.8, 35.8, 29.4, 29.3, 20.1, 18.8, 11.2, 10.4; HRMS (FAB) calcd for $C_{40}H_{65}O_{11}$ 721.4526, found 721.4524 (M + H).

Dermostatin B (8): t_R 19.7 min; UV−vis (CH_3OH/H_2O) λ_{max} 282 (250 mAU), 390 nm (2150 mAU); ^{1}H NMR (500 MHz, CD_3OD) δ 7.30 (dd, J = 14.9, 11.5 Hz, 1 H), 6.71 (dd, J = 14.5, 11.1 Hz, 1 H), 6.53 (dd, J = 14.5, 10.9 Hz, 1 H), 6.45−6.30 (m, 6 H), 6.14 (ddd, J = 15.0, 10.3, 1.6 Hz, 1 H), 5.88 (d, J = 15.0 Hz, 1 H), 5.82 (ddd, J = 15.1, 10.6, 4.4 Hz, 1 H), 5.56 (ddd, J = 15.9, 5.3, 1.0 Hz, 1 H), 5.47 (ddd, J = 15.9, 5.1, 1.2 Hz, 1 H), 4.84 (m, 1 H), 4.27 (dt, J = 10.6, 3.1 Hz, 1 H), 4.14−3.90 (m, 7 H), 3.57 (m, 1 H), 2.60 (m, 1 H), 2.42 (m, 1 H), 2.38 (m, 1 H), 1.71−1.01 (m, 18 H), 1.01 (d, J = 6.9 Hz, 3 H), 0.92 (d, J = 6.8 Hz, 3 H), 0.87 (d, J = 7.1 Hz, 3 H), 0.86 (t, J = 7.6 Hz, 3 H); HRMS (FAB) calcd for $C_{41}H_{66}O_{11}Na$ 757.4502, found 757.4490 (M + Na).

23-*O*-Acetyl-15,17:19,21:25,27:29,31-tetra-*O*-(1-methylethylidene)dermostatin A (4), 27-*O*-Acetyl-15,17:19,21:23,25:29,31-tetra-*O*-(1-methylethylidene)dermostatin A (5), 31-*O*-Acetyl-15,17:19,21:23,25:27,29-tetra-*O*-(1-methylethylidene)dermostatin A (6), and 15-*O*-Acetyl-17,19:21,23:25,27:29,31-tetra-*O*-(1-methylethylidene)dermostatin A (7). Dermostatin A (10 mg, 14 μmol) was added to a solution of acetone (0.5 mL), DMP (0.25 mL), and PPTS (4.0 mg, 15 μmol). The solution was stirred in the dark under argon for 12 h and then quenched with 4 μL of Et_3N. The solution was concentrated under reduced pressure to give a yellow oil. The mixture was passed through a plug of silica gel eluting with 50% EtOAc/hexanes and then separated by normal phase semipreparative HPLC (Alltech Econosil SI 10U 250 × 10 mm) eluting with 40% EtOAc at 4 mL/min. Three major peaks eluting at 12.6, 15.4, and 22.7 min were collected.

The substance eluting at 12.6 min was taken up in THF (1 mL). Acetic anhydride (10 μL, 106 μmol) and DMAP (15 mg, 122 μmol) were added. The reaction was stirred under argon in the dark for 30 min and then quenched with 20 μL of MeOH. The solution was diluted with 20 of mL EtOAc, washed with saturated $NaHCO_3$, water, and brine, dried ($MgSO_4$), and then concentrated under reduced pressure to give a yellow oil. The product was purified by silica gel flash chromatography (1 × 5 cm) eluting with 30% EtOAc/hexanes to yield 2.8 mg (3.1 μmol, 24%) of tetraacetonide **4** as a yellow glass.

The substance eluting at 22.7 min was subjected to the same acetylation conditions described above. The product was purified by silica gel flash chromatography (1 × 5 cm) eluting with 30% EtOAc/hexanes to give 1.2 mg (1.3 μmol, 9%) of tetraacetonide **5** as a yellow glass.

The substance eluting at 15.4 min was subjected to the same acetylation conditions described above. The resulting mixture was passed through a plug of silica gel eluting with 30% EtOAc/hexanes and then separated by normal phase semipreparative HPLC eluting with 20% EtOAc at 4 mL/min. Two major peaks eluting at 25.8 and 30.3 min, respectively, were collected to provide 2.7 mg of tetraacetonide **6** (3.0 μmol, 21%) and 1.2 mg of tetraacetonide **7** (1.3 μmol, 9%) as a yellow glass.

Tetraacetonide 4: ^{1}H NMR (500 MHz, C_6D_6) δ 7.48 (dd, J = 10.9, 14.9 Hz, 1 H), 6.27−5.89 (m, 12 H), 5.62 (ddd, J = 1.7, 5.0, 15.7 Hz, 1 H), 5.46 (dtd, J = 3.1, 6.7, 9.9 Hz, 1H), 5.10 (dd, J = 2.8, 9.0 Hz, 1 H), 4.32−4.21 (m, 2 H), 4.06 (dtd, J = 2.4, 6.4, 10.7 Hz, 1 H), 3.99−3.90 (m, 2 H), 3.74−3.70 (m, 1 H), 3.51−3.43 (m, 2 H), 2.53−2.59 (m, 1 H), 2.50−2.46 (m, 1 H), 2.25 (ddd, J = 2.8, 10.3, 14.4 Hz, 1 H), 2.21−1.01 (m, 16 H), 1.76 (s, 3 H), 1.57 (s, 3 H),1.55 (s, 3 H),1.47 (s, 3 H),1.42 (s, 3 H),1.37 (s, 3 H),1.34 (s, 3 H),1.33 (s, 3 H),1.26 (s, 3 H), 1.12 (d, J = 7.0 Hz, 3 H), 1.03 (d, J = 6.6 Hz, 3 H), 0.759 (d, J = 6.7 Hz, 3 H), 0.693 (d, J = 6.5 Hz, 3 H); HRMS (FAB) calcd for $C_{54}H_{82}O_{12}$ 922.5806, found 922.5818 (M^+).

Tetraacetonide 5: ^{1}H NMR (500 MHz, C_6D_6) δ 7.43 (dd, J = 11.0, 14.8 Hz, 1 H), 6.26−6.06 (m, 8 H), 5.99 (d, J = 15.0 Hz, 1 H), 5.97−5.87 (m, 3 H), 5.59 (ddd, J = 1.5, 4.8, 15.7 Hz, 1 H), 5.50 (tt, J = 3.2, 9.3 Hz), 5.12 (dd, J = 2.6, 8.9 Hz, 1 H), 4.37−4.31 (m, 2 H), 4.16−4.09 (m, 1 H), 4.01−3.92 (m, 2 H),

(26) Possible applications of this exciting new tool would be in the configurational assignments of polyol natural products such as aflastatin A, linearmycin, or RK-397. (a) Sakuda, S.; Ono, M.; Furihata, K.; Nakayama, J.; Suzuki, A.; Isogai, A. *J. Am. Chem. Soc.* **1996**, *118*, 7855−7856. (b) Sakuda, S.; Gucebigol, U.; Itoh, M.; Nishimura, T.; Yamada, Y. *Tetrahedron Lett.* **1995**, *36*, 2777−80. (c) Koshino, H.; Kobinata, K.; Isono, K.; Osada, H. *J. Antibiot.* **1993**, *46*, 1619−21.

(27) For a general experimental section and NMR parameters, see Supporting Information.

(28) Column used was a 21.4 mm × 25 cm Rainin Microsorb C18 reversed phase Dynamax column.

(29) (a) Pandey, R. C. U.S. Patent 5,210,226, 1993. (b) Pandey, R. C. U.S. Patent 5,159,002, 1992.

3.88−3.82 (m, 1 H), 3.53−3.46 (m, 2 H), 2.59−2.48 (m, 2 H), 2.32−2.21 (m, 1 H), 2.05 (tq, J = 10.6, 6.4 Hz, 1 H), 1.96−1.06 (m, 15 H), 1.75 (s, 3 H), 1.57 (s, 3 H), 1.54 (s, 3 H), 1.50 (s, 3 H), 1.45 (s, 3 H), 1.41 (s, 3 H), 1.39 (s, 3 H), 1.34 (s, 3 H), 1.33 (s, 3 H), 1.03 (d, J = 7.0 Hz, 3 H), 0.999 (d, J = 6.7 Hz, 3 H), 0.726 (d, J = 6.8 Hz, 3 H), 0.721 (d, J = 6.4 Hz, 3 H); HRMS (FAB) calcd for $C_{54}H_{82}O_{12}$ 922.5806, found 922.5814 (M^+).

Tetraacetonide 6: ^1H NMR (500 MHz, C_6D_6) δ 7.51 (dd, J = 11.2, 15.2 Hz, 1 H), 6.34 (dd, J = 9.6, 16.2 Hz, 1 H), 6.26−6.02 (m, 10 H), 5.95 (d, J = 15.1 Hz, 1 H), 5.84 (q, J = 7.0 Hz, 1 H), 5.64 (ddd, J = 1.8, 7.0, 15.9 Hz, 1 H), 5.12 (dd, J = 2.7, 8.4 Hz, 1 H), 4.35−4.30 (m, 1 H), 4.20−4.14 (m, 2 H), 4.10−4.02 (m, 2 H), 3.89 (dddd, J = 2.7, 4.2, 8.5, 11.0 Hz, 1 H), 3.53−3.47 (m, 2 H), 2.62 (ddq, J = 2.7, 4.5, 7.1 Hz, 1 H), 2.51−2.43 (m, 1 H), 2.22 (ddd, J = 2.6, 10.0, 14.8 Hz, 1 H), 2.08 (ddd, J = 6.2, 8.7, 13.5 Hz, 1 H), 2.01 (tq, J =10.5, 6.5 Hz, 1 H), 1.95 (ddd, J = 3.1, 7.3, 15.1 Hz, 1 H), 1.87 (dqq, J = 8.4, 6.6, 6.7 Hz, 1 H), 1.70−1.10 (m, 12 H), 1.74 (s, 3 H), 1.54 (s, 3 H), 1.53 (s, 3 H), 1.50 (s, 3 H), 1.440 (s, 6 H), 1.436 (s, 3 H), 1.40 (s, 3 H), 1.30 (s, 3 H), 1.06 (d, J = 7.1 Hz, 3 H), 0.985 (d, J = 6.6 Hz, 3 H), 0.748 (d, J = 6.7 Hz, 3 H), 0.695 (d, J = 6.5 Hz, 3 H); HRMS (FAB) calcd for $C_{54}H_{82}O_{12}$ 922.5806, found 922.5809 (M^+).

Tetraacetonide 7: ^1H NMR (500 MHz, C_6D_6) δ 7.58 (dd, J = 11.2, 15.1 Hz, 1 H), 6.19−5.96 (m, 11 H), 5.71 (ddd, J = 4.7, 10.4, 15.1 Hz, 1 H), 5.69−5.62 (m, 2 H), 5.11 (dd, J = 2.2, 9.9, 1 H), 4.35−4.27 (m, 2 H), 4.19−4.11 (m, 3H), 4.02−3.95 (m, 1 H), 3.83 (ddd, J = 2.1, 10.8, 11.1 Hz, 1 H), 3.69−3.63 (m, 1 H), 2.64−2.58 (m, 1 H), 2.55−2.47 (m, 2 H), 2.13−1.97 (m, 3 H), 1.82 (dqq, J = 9.9. 6.6, 6.7 Hz, 1 H), 1.76−1.10 (m, 12 H), 1.69 (s, 3 H), 1.59 (s, 3 H), 1.51 (s, 3 H), 1.40 (s, 3 H), 1.39 (s, 3 H), 1.38 (s, 3 H), 1.34 (s, 6 H), 1.30 (s, 3 H), 1.08 (d, J = 7.0 Hz, 3 H), 0.986 (d, J = 6.6 Hz, 3 H), 0.877 (d, J = 7.1 Hz, 3 H), 0.688 (d, J = 6.7 Hz, 3 H); ^1H NMR (500 MHz, $C_6D_5CD_3$) δ 7.47 (dd, J = 11.3, 15.1 Hz, 1 H), 6.17−5.95 (m, 9 H), 5.89 (dd, J = 15.8, 1.2 Hz, 1 H), 5.88 (d, J = 15.4 Hz, 1 H), 5.66 (ddd, J = 5.2, 10.6, 15.2 Hz, 1 H), 5.61 (ddd, J = 1.5, 4.9, 15.9 Hz, 1 H), 5.54 (dt, J = 10.3, 2.9 Hz, 1 H), 5.02 (dd, J = 2.2, 9.9 Hz, 1 H), 4.28 (m, 1 H), 4.21 (m, 1 H), 4.13−4.02 (m, 3 H), 3.88 (m, 1 H), 3.79 (ddd, J = 2.0, 9.2, 10.9), 3.59 (m, 1 H), 2.56 (m, 1 H), 2.50−2.48 (m, 1 H), 2.05−1.17 (m, 16 H), 1.69 (s, 3 H), 1.54 (s, 3 H), 1.45 (s, 3 H), 1.36 (s, 3 H), 1.35 (s, 3 H), 1.34 (s, 3 H), 1.33 (s, 3 H), 1.30 (s, 3 H), 1.26 (s, 3 H), 1.06 (d, J = 7.0 Hz, 3 H), 0.953 (d, J = 6.6 Hz, 3 H), 0.878 (d, J = 7.1 Hz, 3 H), 0.705 (d, J = 6.7 Hz, 3 H);HRMS (FAB) calcd for $C_{54}H_{82}O_{12}$ 922.5806, found 922.5819 (M^+).

27-*O*-[(*S*)-α-Methoxy-α-(trifluoromethyl)phenylacetyl]-15,17:19,21:23,25:29,31-tetra-*O*-(1-methylethylidene)dermostatin A (8S) and 27-*O*-[(*R*)-α-Methoxy-α-(trifluoromethyl)phenylacetyl]-15,17:19,21:23,25:29,31-tetra-*O*-(1-methylethylidene)dermostatin A (3R). A solution of 27-hydroxy-15,17:19,21:23,25:29,31-tetra-*O*-(1-methylethylidine-)dermostatin A (**3**) (3 mg, 3.4 mmol) in 2 mL of CH_2Cl_2 was split into two equal halves and placed into separate reaction flasks. To these solutions were added DMAP and then (*R*)- or (*S*)-MTPACl (10 μL, 53 μmol). After 30 min, each reaction was quenched with 4 mL of saturated $NaHCO_3$. The aqueous layer was extracted (3 × 5 mL) with CH_2Cl_2. The combined organic extractions were dried (Na_2SO_4) and then concentrated under reduced pressure. The products were purified by silica gel flash chromatography (1 × 5 cm) eluting with 30% EtOAc/hexanes to yield 1.5 mg (1.4 μmol, 82%) and 1.6 mg (1.5 μmol, 86%) of (*S*)- and (*R*)-MTPA esters **3S** and **3R**, respectively, as yellow glass.

MTPA ester 3S: ^1H NMR (500 MHz, C_6D_6) δ 7.78 (m, 2 H), 7.46 (dd, J = 11.2, 15.1 Hz, 1 H), 7.13−6.98 (m, 3 H), 6.28−6.05 (m, 8 H), 6.00 (d, J = 15.2 Hz, 1 H), 6.01−5.90 (m, 3 H), 5.65 (m, 1 H), 5.58 (ddd, J = 1.6, 4.9, 15.8 Hz, 1 H), 5.12 (dd, J = 2.7, 8.9 Hz, 1 H), 4.35 (m, 1 H), 4.25 (m, 1 H), 4.13 (m, 1 H), 4.00 (m, 1 H), 3.94 (m, 1 H), 3.76 (m, 1 H), 3.53−3.46 (m, 2 H), 3.45 (s, 3 H), 2.58 (m, 1 H), 2.50 (m, 1 H), 2.26 (m, 1 H), 2.04 (tq, J = 10.7, 6.4), 1.95−1.85 (m, 2 H), 1.72−1.12 (m, 13 H), 1.57 (s, 3 H), 1.48 (s, 3 H), 1.47 (s, 3 H), 1.44 (s, 6 H), 1.35 (s, 3 H), 1.33 (s, 3 H), 1.20 (s, 3 H), 1.06 (d, J = 7.0 Hz, 3 H), 1.02 (d, J = 6.6 Hz, 3 H),0.747 (d, J = 6.7 Hz, 3 H),0.713 (d, J = 6.4 Hz, 3 H); HRMS (FAB) calcd for $C_{62}H_{87}O_{13}F_3$ 1096.6098, found 1096.6129 (M^+).

MTPA ester 3R: ^1H NMR (500 MHz, C_6D_6) δ 7.79 (m, 2 H), 7.44 (dd, J = 11.2, 15.1 Hz, 1 H), 7.14−6.98 (m, 3 H), 6.27−6.05 (m, 8 H), 5.99 (d, J = 15.2 Hz, 1 H), 5.98 −5.89 (m, 3 H), 5.64 (m, 1 H), 5.57 (ddd, J = 1.6, 5.1, 15.8 Hz, 1 H), 5.11 (dd, J = 2.7, 8.9 Hz, 1 H), 4.36 (m, 1 H), 4.30 (m, 1 H), 4.09 (m, 1 H), 4.00 (m, 1 H), 3.91 (m, 1 H),3.79 (m, 1 H), 3.55−3.47 (m, 2 H), 3.50 (s, 3 H), 2.57 (m, 1 H), 2.50 (m, 1 H), 2.32−2.23 (m, 1 H), 2.13−1.88 (m, 5 H), 1.72−1.10 (m, 11 H), 1.57 (s, 3 H), 1.52 (s, 3 H), 1.47 (s, 3 H), 1.45 (s, 3 H), 1.41 (s, 3 H), 1.33 (s, 9 H), 1.04 (d, J = 6.9 Hz, 3 H), 0.949 (d, J = 6.6 Hz, 3 H), 0.740 (d, J = 6.8 Hz, 3 H), 0.713 (d, J = 6.4 Hz, 3 H); HRMS (FAB) calcd for $C_{62}H_{87}O_{13}F_3$ 1096.6098, found 1096.6096 (M^+).

Dermostatin A Nonaacetate (9). To a suspension of dermostatin A (**1**) (16.3 mg, 0.023 mmol, 1 equiv) in dry THF (10 mL) under argon were added DMAP (100 mg, 0.82 mmol, 36 equiv) and Ac_2O (80 μL, 0.73 mmol, 32 equiv). The solution was allowed to stir at room temperature in the dark for 1 h at which time it was quenched with MeOH (100 μL). The reaction mixture was diluted with EtOAc (30 mL) and washed with 0.05 M H_2SO_4 (2 × 5 mL) and brine (5 mL). The organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. The crude yellow solid was purified on a SiO_2 gel column eluting with 50% acetone/hexanes to afford dermostatin A nonaacetate (22.6 mg, 0.021 mmol, 91%) as a yellow amorphous solid: R_f 0.5 (SiO_2, 50% acetone/hexanes); UV−vis (CH_3OH/H_2O) λ_{max} 282 (8 mAU), 383 nm (61 mAU); IR (KBr) 2925, 2855, 1745, 1702, 1373, 1250, 1132, 1036 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.27 (dd, J = 15.2, 11.5 Hz, 1 H), 6.59 (dd, J = 15.7, 11.1 Hz, 1 H), 6.48−6.12 (m, 8 H), 5.85 (d, J = 15.2 Hz, 1 H), 5.71 (m, 1 H), 5.59 (dd, J = 15.8, 5.3 Hz, 1 H), 5.36 (dd, J = 15.7, 5.5 Hz, 1 H), 5.19 (m 1 H), 4.92−4.68 (m, 4 H), 4.60−4.40 (m, 5 H), 2.52−2.48 (m, 2 H), 2.80 (m, 1 H), 2.07 (s, 3 H), 2.03 (s, 3 H), 2.01 (s, 3 H), 2.00 (s, 9 H), 1.98 (s, 3 H), 1.96 (s, 3 H), 1.95 (s, 3 H), 2.20−1.45 (m, 16 H), 1.00 (d, J = 6.9 Hz, 3 H), 0.93 (d, J = 7.1 Hz, 3 H), 0.92 (d, J = 6.7 Hz, 3 H), 0.88 (d, J = 6.4 Hz, 3 H); HRMS (FAB) calcd for $C_{58}H_{82}O_{20}Na$ 1121.5297, found 1121.5295 (M + Na).

Dermostatin B Nonaacetate (10). Dermostatin B (**8**) (13.5 mg, 0.018 mmol) was subjected to the acetate-forming conditions described previously for dermostatin A to provide dermostatin B nonaacetate as a yellow solid. The crude yellow solid was purified on a SiO_2 gel column eluting with 50% acetone/hexanes to afford dermostatin B nonaacetate (18.9 mg, 0.017 mmol, 94%) as a yellow amorphous solid: R_f 0.53 (SiO_2 gel, 50% acetone/hexanes); UV−vis (CH_3OH/H_2O) λ_{max} 282 (60 mAU), 388 nm (500 mAU); IR (KBr) 2972, 2926, 1741, 1702, 1373, 1248, 1132, 1034 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, TMS) δ 7.27 (m, 1 H), 6.60 (dd, J = 14.7, 11.0 Hz, 1 H), 6.49−6.13 (m, 8 H), 5.87 (d, J = 15.1 Hz, 1 H), 5.73 (m, 1 H), 5.60 (ddd, J = 14.8, 5.2, 1.1 Hz, 1 H), 5.39 (ddd, J = 14.3, 5.3, 1.6 Hz, 1 H), 5.10 (m 1 H), 4.98−4.72 (m, 8 H), 2.58 (m, 2 H), 2.42 (m, 1 H), 2.10 (s, 3 H), 2.04 (s, 3 H), 2.03 (s, 3 H), 2.02 (s, 3 H), 2.01 (s, 6 H), 1.99 (s, 3 H), 1.98 (s, 3 H), 1.97 (s, 3 H), 2.20−1.45 (m, 19 H), 1.00 (d, J = 6.9 Hz, 3 H), 0.95 (d, J = 7.1 Hz, 3 H), 0.89 (d, J = 6.8 Hz, 3 H), 0.886 (t, J = 7.5 Hz, 3 H); HRMS (FAB) calcd for $C_{59}H_{84}O_{20}Na$ 1135.5453, found 1135.5457 (M + Na).

Dermostatin A Derived Bisacetate (12) and Undecaacetate (11). In an argon-purged flask, dermostatin A nonaacetate (**9**) (31.8 mg, 0.029 mmol, 1.0 equiv) was dissolved in $CHCl_3$ (2.0 mL) and MeOH (4.0 mL) and cooled to −78 °C. Ozone was bubbled through the yellow solution until a blue color persisted. Argon was then bubbled through the solution until it was colorless. Sodium borohydride (35 mg, 0.93 mmol, 32 equiv) was added, and the cold bath was removed allowing the solution to warm slowly over 15 min. The reaction was then quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc (3 × 10 mL). The combine organics were washed with brine (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give a colorless oil (29.6 mg). The resulting oil was dissolved in dry THF (12 mL) and treated with DMAP (150 mg, 1.23 mmol) and Ac_2O (110 μL, 1.15 mmol) at room temperature for 3 h, under argon. Following the addition of methanol (150 μL), H_2O (5 mL) was added and the solution was extracted with EtOAc (35 mL). The organic layer was washed with brine (5 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give a colorless oil. Chromatography (SiO_2 gel, 25% acetone/hexane and then 50% acetone/hexane) gave the small bisacetate (3.1 mg, 0.011 mmol, R_f 0.6 (SiO_2, 50% acetone/hexanes) as a colorless oil, and the large undecaacetate (15.3 mg, 0.016 mmol, R_f 0.3 (SiO_2 gel, 50% acetone/hexanes), also as a colorless oil.

Bisacetate derived from dermostatin A (12): $[\alpha]^{24}_{D}$ +1 (*c* 0.4, $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6) δ 4.99 (dd, J = 7.9, 4.1 Hz, 1 H), 4.35 (d, J = 15.7 Hz, 1 H), 4.26 (d, J = 15.7 Hz, 1 H), 3.98 (dd, J = 11.0, 7.4, 1 H), 3.77 (dd, J = 11.1, 6.1 Hz, 1 H), 1.93 (m, 1 H), 1.71 (s, 3 H, OC(O)CH_3), 1.66 (s, 3 H, OC(O)CH_3), 1.63 (m, 1 H), 0.82 (d, J = 6.7 Hz, 3 H), 0.74 (d, J = 7.1 Hz, 3 H), 0.60 (d, J = 6.7 Hz, 3 H); HRMS (CI) calcd for $C_{13}H_{23}O_6$ 275.1494, found 275.1486 (M + H).

Undecaacetate Derived from Dermostatin A (11). Further purification was achieved by reversed-phase HPLC[28] eluting with a gradient of 100% H_2O to 100% acetonitrile over 30 min at 21 mL/min. The major peak (t_R 18.2 min) was isolated as a colorless oil: ^{1}H NMR (500 MHz, C_6D_6) δ 5.31−5.09 (m, 9 H), 4.25 (dd, J = 12.1, 3.3 Hz, 1 H), 4.11−4.03 (m, 2 H), 4.01 (dd, J = 12.1, 6.3 Hz, 1 H), 1.91 (s, 3 H), 1.90 (s, 3 H), 1.88 (s, 3 H), 1.87 (s, 3 H), 1.82 (s, 3 H), 1.81 (s, 3 H), 1.77 (s, 6 H), 1.75 (s, 3 H), 1.71 (s, 3 H), 1.68 (s, 3 H), 2.04−1.50 (m, 15 H), 0.72 (d, J = 7.2 Hz, 3 H); HRMS (FAB) calcd for $C_{43}H_{66}O_{22}$Na 957.3943, found 957.3937 (M + Na).

Dermostatin B Derived Bisacetate (13) and Undecaacetate (11). The dermostatin B derived nonaacetate (**10**) was subjected to the previously described ozonolysis, $NaBH_4$ reduction, and acetylation sequence to provide the small bisacetate (1.1 mg, 0.004 mmol, R_f 0.6 (SiO_2, 50% acetone/hexanes) as a colorless oil and the large undecaacetate (7.5 mg, 0.008 mmol, R_f 0.3 (SiO_2, 50% acetone/hexanes), also as a colorless oil.

Bisacetate derived from dermostatin B (13): $[\alpha]^{24}_{D}$ −33 (*c* 0.15, $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6) δ 5.07 (dd, J = 8.4, 3.6 Hz, 1 H), 4.35 (d, J = 15.8 Hz, 1 H), 4.26 (d, J = 15.6 Hz, 1 H), 4.00 (dd, J = 11.1, 7.8 Hz, 1 H), 3.80 (dd, J = 11.1, 6.0 Hz, 1 H), 1.95 (m, 1 H), 1.72 (s, 3 H, OC(O)CH_3), 1.66 (s, 3 H, OC(O)CH_3), 1.50 (m, 1 H), 1.45 (m, 1 H), 1.05 (m, 1 H), 0.77 (t, J = 7.4 Hz, 3 H), 0.75 (d, J = 6.8 Hz, 3 H), 0.62 (d, J = 6.8 Hz, 3 H); HRMS (CI) calcd for $C_{14}H_{24}O_6$ 289.1651, found 289.1648 (M + H).

Undecaacetate Derived from Dermostatin B (11). Further purification was achieved by reversed-phase HPLC[28] eluting with a gradient of 100% H_2O to 100% acetonitrile over 30 min at 21 mL/min The major peak (t_R 18.4 min)[30] was isolated as a colorless oil: ^{1}H NMR (500 MHz, C_6D_6) δ ^{1}H NMR (500 MHz, C_6D_6) δ 5.31−5.09 (m, 9 H), 4.25 (dd, J = 12.2, 3.2 Hz, 1 H), 4.11−4.03 (m, 2 H), 4.01 (m, 1 H), 1.91 (s, 3 H), 1.90 (s, 3 H), 1.88 (s, 3 H), 1.87 (s, 3 H), 1.82 (s, 3 H), 1.81 (s, 3 H), 1.77 (s, 6 H), 1.75 (s, 3 H), 1.71 (s, 3 H), 1.68 (s, 3 H), 2.04−1.50 (m, 15 H), 0.72 (d, J = 7.2 Hz, 3 H); HRMS (FAB) calcd for $C_{43}H_{66}O_{22}$Na 957.3943, found 957.3942 (M + Na).

Dermostatin A Derived Diol (14). To a solution of the dermostatin A derived bisacetate (**12**) (2.5 mg, 0.009 mmol) in MeOH (0.5 mL) under argon was added a few crystals of K_2CO_3. The reaction was allowed to stir at room temperature overnight, at which time the MeOH was removed under reduced pressure to give a white solid. The solid was dissolved in a minimum amount of 75% EtOAc/hexanes and passed through a short plug of SiO_2 gel eluting with 75% EtOAc/hexane to give a white amorphous solid (ca. 0.6 mg, 0.005 mmol): R_f 0.31 (SiO_2 gel, 75% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 3.74 (m, 1 H), 3.42 (m, 1 H), 2.04 (m, 2 H), 1.86 (m, 1 H), 1.71 (dddd, J = 13.2, 8.8, 6.7, 6.5 Hz, 1 H), 1.01 (d, J = 6.8 Hz, 3 H), 0.96 (d, J = 7.2 Hz, 3 H), 0.86 (d, J = 6.8 Hz, 3 H).

Dermostatin A Derived (*S*)-MTPA Ester (15). To a solution of the dermostatin A derived diol (**14**) (0.6 mg, 0.005 mmol) in CH_2Cl_2 (1.0 mL) under argon was added DMAP (8.1 mg, 65 μmol, 15 equiv) followed by addition of (*R*)-MTPACl (8.0 μL, 42 μmol, 10 equiv). The reaction was allowed to stir at room temperature for 1 h at which time it was quenched with saturated $NaHCO_3$ (2 mL) and extracted into CH_2Cl_2 (2 × 3 mL). The combine organics were washed with brine (3 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography (SiO_2 gel, 10% EtOAc/hexane and then 25% EtOAc/hexane) gave the desired bis ester (ca. 1.1 mg, 0.002 mmol) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz, TMS) δ 7.53 (m, 4 H), 7.41 (m, 6 H), 4.93 (dd, J = 7.5, 3.6 Hz, 1 H), 4.10 (dd, J = 11.1, 6.3 Hz, 1 H), 3.97 (dd, J = 11.0, 7.4 Hz, 1 H), 3.55 (s, 3 H, OCH_3), 3.49 (s, 3 H, OCH_3), 2.20 (m, 1 H), 0.85 (d, J = 6.9 Hz, 3 H), 0.82 (d, J = 6.9 Hz, 3 H), 0.81 (d, J = 6.6 Hz, 3 H); HRMS (FAB) calcd for $C_{27}H_{30}F_6O_6$Na 587.1844, found 587.1861 (M + Na).

Dermostatin B Derived Diol (16). The dermostatin A derived bisacetate (**13**) was saponified as described for **12** to give, after purification, a white amorphous solid (ca. 0.4 mg, 0.003 mmol): R_f 0.36 (SiO_2 gel, 75% EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$ TMS) δ 3.75 (m, 2 H), 3.52 (m, 1 H), 2.03 (m, 2 H), 1.85 (m, 1 H), 1.74 (m, 1 H), 1.25 (brs, 1 H), 1.16 (m, 1 H), 0.95 (d, J = 7.0 Hz, 3 H), 0.92 (t, J = 7.5 Hz, 3 H), 0.82 (d, J = 6.7 Hz, 3 H).

Dermostatin B Derived (*S*)-MTPA Ester (17). Dermostatin B derived diol (**16**) (ca. 0.4 mg) was subjected to the (*S*)−MTPA ester forming conditions described for **15** to give, after purification, bis ester (**17**), (ca 1.0 mg, 0.002 μmol) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz, TMS) δ 7.55 (m, 4 H), 7,41 (m, 6 H), 5.00 (dd, J = 7.9, 3.2 Hz, 1 H), 4.08 (dd, J = 11.1, 6.3 Hz, 1 H), 3.97 (dd, J = 11.0, 7.7 Hz, 1 H), 3.55 (s, 3 H, OCH_3), 3.50 (s, 3 H, OCH_3), 2.21 (m, 1 H), 1.63 (m, 1 H), 1.31 (m, 1 H), 1.01 (m, 1 H), 0.85 (d, J = 7.1 Hz, 3 H), 0.78 (m, 6 H); HRMS (FAB) calcd for $C_{28}H_{32}F_6O_6$Na 601.2001, found 601.2011 (M + Na).

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Supporting Information Available: Sample experimental procedures for compounds **14**−**19** and spectroscopic data for compounds **4**−**7**, **11**, and **14**−**17** (31 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(30) When the nonaacetates from dermostatins A and B were combined and analyzed by HPLC, a single peak was observed.