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Stereocontrol of 5,5-Spiroketals in the Synthesis of Cephalosporolide H Epimers

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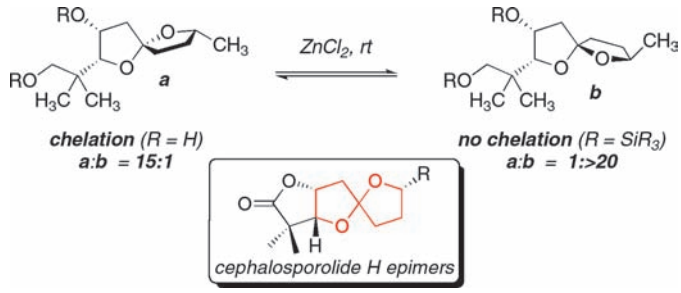
ABSTRACT



A blueprint for controlling the stereochemistry of oxygenated 5,5-spiroketals using chelation effects is provided. Chelation specifically of zinc salts (other protic and Lewis acids were less effective) between the spiroketal oxygen and an appropriately positioned alcohol group overrides normal biases in the preparation of 5,5-spiroketals, as illustrated by the stereocontrolled synthesis of epimeric cephalosporolide H isomers. This study provides new and valuable information for prescribing the chirality of the stereogenic core of 5,5-spiroketals.

Spiroketals are found in many biologically active compounds (cf. Figure 1).[1] The rigid spiroketal framework offers precision orientation of pendant functional groups, which likely supports precise interactions in complex biochemical systems. However, one must be able to install the core spiroketal stereochemistry efficiently in order to take advantage of its rigid three-dimensional shape. For stereocontrol of spiroketals, anomeric effects can be predictably exploited in 6,6- and 5,6-systems,[2] but they are less reliable in 5,5-systems.[3−5]

Consequently, natural 5,5-spiroketals can be extremely challenging targets for stereoselective synthesis. In some cases, such as halichondrin B (Figure 1), the natural epimer

(1) (a) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617. (b) Aho, J. E.; Pihko, P. M.; Rissa, T. K. *Chem. Rev.* **2005**, *105*, 4406. (c) Raju, B. R.; Saikia, A. K. *Molecules* **2008**, *13*, 1942. (d) Blunt, J. W.; Copp, B. R.; Hu, W.-P.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2009**, *26*, 170.

(2) Reviews on anomeric effects: (a) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983. (b) Juaristi, E.; Cuevas, G. *The Anomeric Effect*; CRC Press: Boca Raton, FL, 1994. Selected methods for making 6,6-spiroketals under kinetic and/or chelation control: (c) Reference 1b. (d) Lau, C. K.; Crumpler, S.; Macfarlane, K.; Lee, F.; Berthelette, C. *Synlett* **2004**, 2281. (e) Evans, D. A.; Coleman, P. J.; Dias, L. C. *Angew. Chem., Int. Ed.* **1997**, *36*, 2738.

(3) Anomeric stabilization can be often achieved by either diastereoisomer, compromising the predictive value and preparative utility of anomeric effects for stereocontrol of 5,5-spiroketals. For thoughtful analyses of 5,5-spiroketal stereochemistry in the ritterazine and cephalostatin natural products, see: (a) Taber, D. F.; Joerger, J.-M. *J. Org. Chem.* **2007**, *72*, 3454. (b) Frotner, K. C.; Kato, D.; Tanaka, Y.; Shair, M. D. *J. Am. Chem. Soc.* **2010**, *132*, 275. (c) Kim, S.; Sutton, S. C.; Guo, C.; LaCour, T. G.; Fuchs, P. L. *J. Am. Chem. Soc.* **1999**, *121*, 2056.

(4) Other approaches to controlling the stereochemistry of 5,5-spiroketals: (a) Bueno, A. B.; Hegedus, L. S. *J. Org. Chem.* **1998**, *63*, 684. (b) Cubero, I. I.; Plaza Lopez-Espinosa, M. T.; Kari, N. *Carbohydr. Res.* **1994**, *261*, 231. (c) Sharma, G. V. M.; Chander, A. S.; Goverdhan Reddy, V.; Krishnudu, K.; Ramana Rao, M. H. V.; Kunwar, A. C. *Tetrahedron Lett.* **2000**, *41*, 1997. (d) Yin, B.-L.; Hu, T.-S.; Yue, H.-J.; Gao, Y.; Wu, W.-M.; Wu, Y.-L. *Synlett* **2004**, 306.

(5) There is some inconsistency relating to common spiroketal numbering (i.e., [4.4]-spiroketal vs 5,5-spiroketal), likely arising from conflicting desires to conform partially to IUPAC spirocycle nomenclature versus to adhere to the common practice of counting the ring sizes independently. We are following the common practice of identifying the ring sizes independently, separated by a comma: 5,5-spiroketal refers to spiro-fused THF rings, and 6,6-spiroketal refers to spiro-fused THP (oxane) rings.

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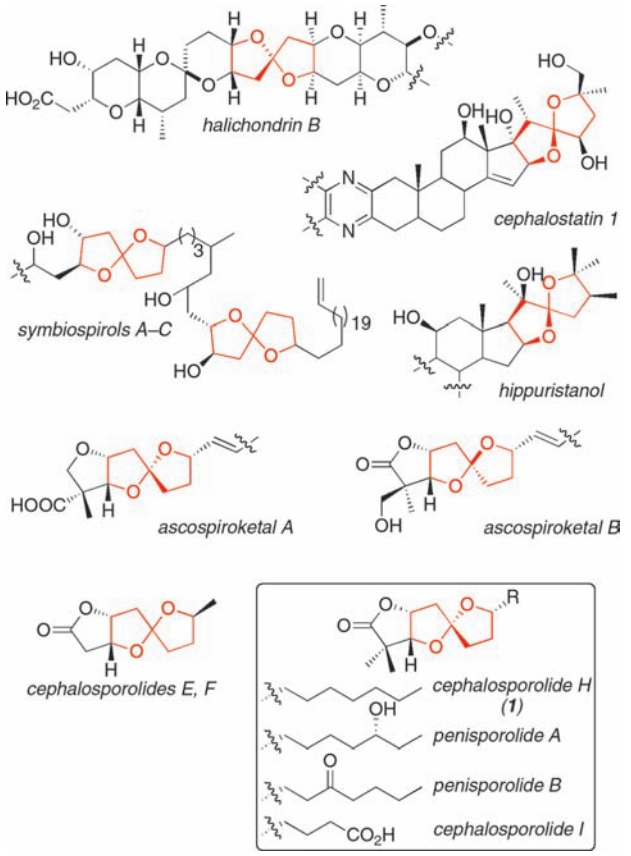


Figure 1. Reported (truncated) structures of some 5,5-spiroketal natural products.[3−5]

is preferred, but such substrate biases are not always clear at the outset. The related cephalostatins and ritterazines, for example, feature contra-thermodynamic 5,5-spiroketals, as addressed in thoughtful studies by Shair, Taber, and Fuchs.[3] Deslongchamps just reported the synthesis of the natural 5,5-spiroketal hippuristanol, the thermodynamics of which are solvent-dependent.[6] In many cases, however, both 5,5-spiroketals epimers are encountered within the same natural product family (cf. symbiospirols, ascospiroketals, and cephalosporolides).

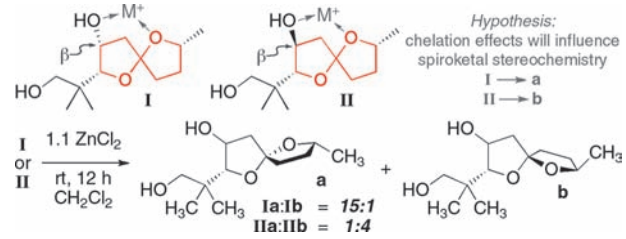
Our studies focus on cephalosporolide H, which is isolated as a single spiroketal epimer from the culture broth of the marine fungus *Penicillium* sp.[7] Cephalosporolide H has potential as an anti-inflammatory agent by virtue of its inhibitory activity against 3α-hydroxysteroid dehydrogenase (3α-HSD).[8]

This Letter provides (i) a blueprint for controlling the stereochemistry of oxygenated 5,5-spiroketals using chelation effects and (ii) practical demonstration in target-oriented synthesis. Prescribed access to 5,5-spiroketals will greatly facilitate the synthesis of complex and contra-thermodynamic 5,5-spiroketals. The ability to *design* substrate preferences for either 5,5-spiroketal epimer will offer entry into new regions of chemical space.[9]

We envisioned a strategy in which chelation of metal salts across the two rings is used to control spiroketal stereochemistry. Such metal-chelation effects have been documented in 6,6-spiroketals[2] but to our knowledge not in 5,5-spiroketals.[10] Preliminary development of such a strategy for controlling the stereochemistry of 5,5-spiroketals is described herein. Finally, application of this strategy to the synthesis of both spiroketal epimers of cephalosporolide H is presented.[11]

The central hypothesis, that chelation between a free alcohol and the spiroketal oxygen of the adjoining ring will override steric effects and determine which core diastereomer predominates, and initial corroborating observations are outlined in Scheme 1.

Scheme 1. Epimerization of β-Hydroxylated 5,5-Spiroketals[a]



[a] Spiroketals **I** and **II** were epimerized using zinc chloride and equilibrium ratios established by ^{1}H NMR analysis. Other protic and Lewis acids either promoted decomposition (camphorsulfonic acid, $TiCl_4$, $BF_3{\cdot}OEt_2$) or failed to induce epimerization ($MgCl_2$).

Initial experiments involved treating β-oxygenated 5,5-spiroketals[12] **I** and **II** with various protic and Lewis acids (Scheme 1). Mild Lewis acids such as $MgCl_2$ did not induce epimerization, and strong Lewis acids including $BF_3{\cdot}OEt_2$ and $TiCl_4$ promoted double elimination to furan and/or general decomposition. Protic acids has similar effects. In contrast, zinc chloride ($ZnCl_2$) effectively catalyzed the equilibration between isomers **a** and **b**. In each case, the major isomer (**Ia** and **IIb**)[13] was the one capable of participating in the hypothesized chelation interaction.

The role of chelation clearly emerges from experiments on spiroketal **I** (Table 1), the alcohol stereochemistry of which corresponds to cephalosporolide H. *Either spiroketal epimer (***a** or **b**) can be produced in ≥15:1 dr by enabling or

(6) Ravindar, K.; Reddy, M. S.; Lindqvist, L.; Pelletier, J.; Deslongchamps, P. *Org. Lett.* **2010**, published ASAP ahead of print, DOI: 10.102/ol1019663.

(7) Li, X.; Yao, Y.; Zheng, Y.; Sattler, I.; Lin, W. *Arch. Pharm. Res.* **2007**, *30*, 812.

(8) Penning, T. M. *J. Pharm. Sci.* **1985**, *74*, 651.

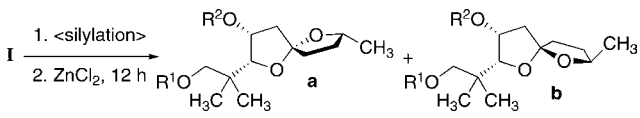
(9) For diversity-oriented synthesis of 6,6-spiroketals in which chelation effects are cited, see: Moilanen, S. B.; Potuzak, J. S.; Tan, D. S. *J. Am. Chem. Soc.* **2006**, *128*, 1792, and references therein.

(10) We speculate that this discrepancy arises from the tendency of oxygenated 5,5-spiroketals to undergo acid-catalyzed dehydration to furans, an issue that we address herein.

(11) Synthesis of the spiroketal core of the cephalosporolides has been reported twice, each time in a roughly 2:1 mixture: (a) Ramana, C. V.; Suryawanshi, S. B.; Gonnade, R. G. *J. Org. Chem.* **2009**, *74*, 2842. (b) Fernandes, R. A.; Ingle, A. B. *Synlett* **2010**, 158.

(12) The synthesis of spiroketals **I** and **II** follows closely the synthesis of cephalosporolide H (vide infra). See Supporting Information.

Table 1. Role of Chelation in the Stereoselective Epimerization of **I**[a]



entry	substrate	R^1	R^2	ratio (**a**:**b**)
1	**I**	H	H	15:1
2	**I-2**	TBDPS	H	3:1
3	**I-3**	H	TBS	1:10
4	**I-4**	TBDPS	TBS	1:>20

[a] Spiroketal **I** was selectively silylated at either or both hydroxy groups and then epimerized using zinc chloride, and the equilibrium ratios were established by ^{1}H NMR analysis. See Supporting Information and ref 13.

blocking chelation (entries 1 and 4). Note that isomer **a** is not observed when silyl groups are positioned to disrupt chelation effects (entry 4), indicating that the reported structure of cephalosporolide H may be contra-thermodynamic.[14] Considering the experiments recounted in entries 2 and 3, we conclude that a free hydroxyl group on the spiroketal ring (R^2 = H) provides the dominant chelation interaction, with a side-chain alcohol providing a secondary, reinforcing role. Perhaps most instructive is to compare entries 2 and 4: silylation changes the selectivity from predominantly isomer **a** to exclusively isomer **b**. What emerges from this study is a strategy for preparing either isomer of the reported cephalosporolide H spiroketal core, as described below.

The synthesis of epimeric cephalosporolide H spiroketals began with alcohol **2**[15] (Scheme 2): Swern oxidation and propynyl Grignard addition gave alcohol **3** as the minor diastereomer in a 1:3 mixture. Note that this Grignard addition is an unusual example of Felkin selectivity in which the quaternary carbon is acting as the "medium" substituent, despite the potential for chelation-control involving the acetal oxygen (Figure 2).[16] Reoxidation and matched asymmetric

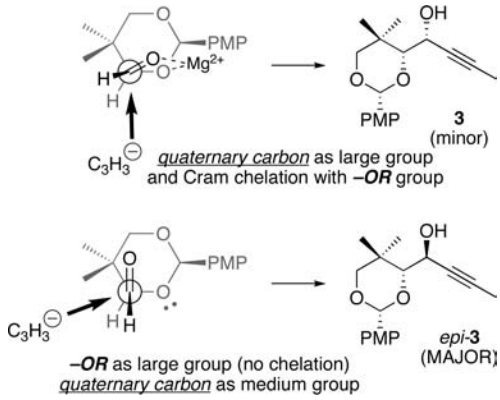


Figure 2. Felkin−Anh models for formation of **3** (desired) and *epi*-**3**.

reduction with (*S*)-CBS reagent[17] provided alcohol **3** exclusively; the overall yield for the four-step sequence **2** → **3** was 63%.

Propargyl alcohol **3** was subjected to the alkyne zipper reaction[18] and protected as a TBS ether to give terminal alkyne **4**. Coupling[19] with (*R*)-1,2-epoxynonane (**5**)[20] gave internal alkyne **6**, a key intermediate in the synthesis.

After considerable optimization (the details of which will be reported elsewhere), it was found that gold(I) chloride in MeOH[21c] induced cycloisomerization[21] of alkyne **6** with concomitant cleavage of the PMP acetal and TBS ether to give 5,5-spiroketal **7** in 80% yield, but as a ca. 1:1 mixture with spiroketal epimer **9**. Notably, *exposure of this mixture to zinc chloride chelation effects for 8 h delivered spiroketal 7 as a single diastereomer in 86% yield*. Magnesium oxide was included in this case as a protic acid scavenger.[22] The protic acid scavanger helps suppress acid-catalyzed dehydration to furan byproduct, which otherwise were detected in small quantities.

Oxidation of spiroketal diol **7** (cf. Scheme 1, isomer **a**) was expected to provide cephalosporolide H, but spectroscopic data for lactone **1** did not match that reported for the natural product.[7]

Retreating in the synthetic sequence to internal alkyne **6**, cycloisomerization with bis-acetonitrile palladium(II) chloride in CH_3CN provided 5,5-spiroketal **8** with the TBS ether intact, this time as a 9:1 mixture favoring the opposite (thermodynamic) spiroketal stereochemistry (cf. Scheme 1, isomer **b**). Desilylation with TBAF provided spiroketal **9**, still in a 9:1 ratio over **7**. TEMPO-catalyzed oxidation gave

(13) Spiroketal stereochemistry assigned by ^{1}H NMR using diagnostic NMR resonances of the spiroketal methyl group. To quote from ref 13c (below), "CH_3... when *cis* to the oxygen of the second ring resonates at lower field than when *trans* to the oxygen... of the second ring." For further discussion and analysis of this spectroscopic trend, see Supporting Information, ref 11a and (a) Brimble, M. A.; Bryant, C. J. *Chem. Commum.* **2006**, 4506. (b) Occhiato, E. G.; Guarna, A.; De Sarlo, F.; Scarpi, D. *Tetrahedron: Asymmetry* **1995**, *6*, 2971. (c) Nishiyama, T.; Woodhall, J. F.; Lawson, E. N.; Kitching, W. *J. Org. Chem.* **1989**, *54*, 2183. For the seminal identification of this NMR correlation, see: (d) Francke, W.; Reith, W.; Sinnwell, V. *Chem. Ber.* **1980**, *113*, 2686. For independent confirmation of this trend by X-ray analysis, see ref 11a.

(14) This preference for the large *tert*-alkyl group to orient *trans* to the spiroketal oxygen is not unusual in 5,5-spiroketal systems, although this trend is not sufficiently reliable as to be predictive. See ref 13a−c.

(15) Alcohol **2** is available in two steps from (−)-pantolactone; see: Shiina, I.; Shibata, J.; Ibuka, R.; Imai, Y.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 113.

(16) (a) Tlais, S. F.; Clark, R. J.; Dudley, G. B. *Molecules* **2009**, *14*, 5216. (b) Changing the reaction solvent from THF to ethyl ether did not alter the product ratio significantly.

(17) Parker, K. A.; Ledeboer, M. W. *J. Org. Chem.* **1996**, *61*, 3214.

(18) Scheerer, J. R.; Lawrence, J. F.; Wang, G. C.; Evans, D. A. *J. Am. Chem. Soc.* **2007**, *129*, 8968.

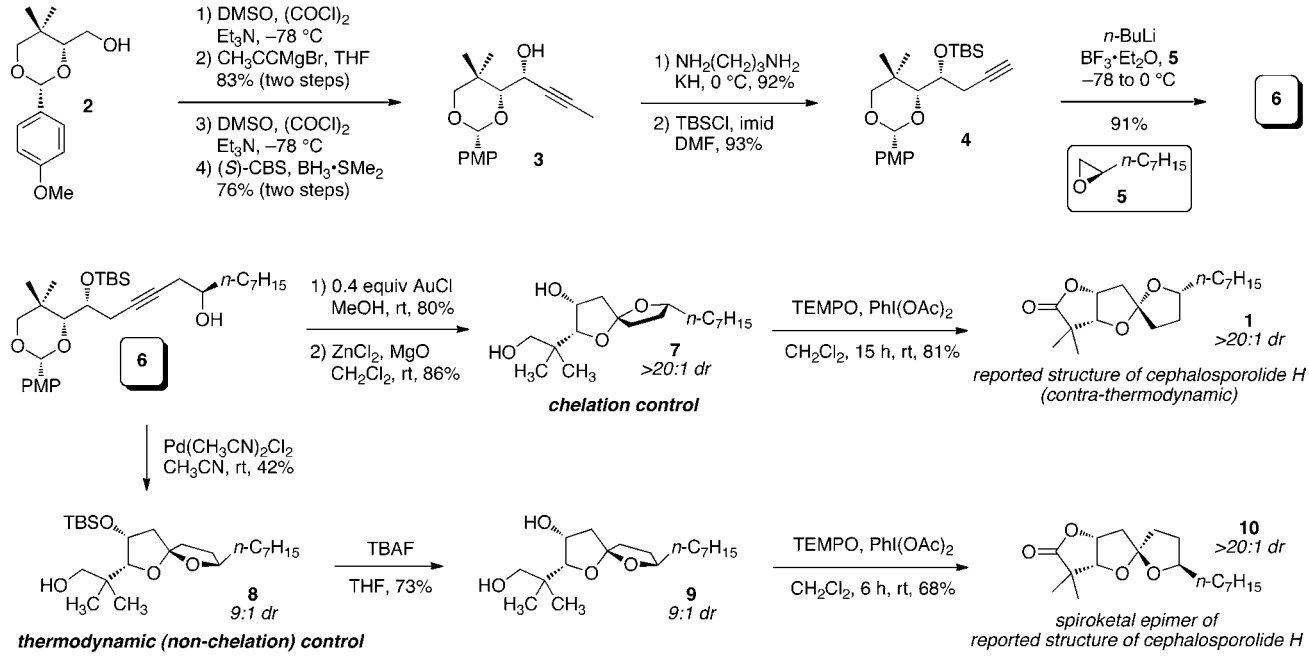
(19) Trost, B. M.; Weiss, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 7664.

(20) (a) Frost, C. G.; Penrose, S. D.; Gleave, R. *Org. Biomol. Chem.* **2008**, *6*, 4340. (b) Savle, P. S.; Lamoreaux, M. J.; Berry, F.; Gandour, R. D. *Tetrahedron: Asymmetry* **1998**, *9*, 1843.

(21) (a) Utimoto, K. *Pure. Appl. Chem.* **1983**, *55*, 1845. (b) Liu, B.; De Brabander, J. K. *Org. Lett.* **2006**, *8*, 4907. (c) Li, Y.; Zhou, F.; Forsyth, C. *Angew. Chem., Int. Ed.* **2007**, *46*, 279. (d) Aponick, A.; Li, C.-Y.; Palmes, J. A. *Org. Lett.* **2008**, *11*, 121.

(22) For previous applications of magnesium oxide as an acid scavenger, see: (a) Espino, C. G.; Wehn, P. M.; Chow, J.; DuBois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935. (b) Poon, K. W. C.; Dudley, G. B. *J. Org. Chem.* **2006**, *71*, 3923.

Scheme 2. Synthesis of the Reported Structure of Cephalosporolide H (**1**) and Its Spiroketal Epimer (**10**)[a]



[a] See Supporting Information for details.

rise to diastereomerically pure lactone **10**[23] in 68% yield; spectroscopic data aligned better with data reported for cephalosporolide H.[24,25] Accordingly, we suggest that the reported stereochemical assignment for cephalosporolide H is incorrect and that the spiroketal stereochemistry for cephalosporolide I[7] and the penisporolides[26] should also be reconsidered.

To summarize, we have shown that chelation of zinc salts between the spiroketal oxygen and an appropriately positioned alcohol group overrides normal biases in the preparation of 5,5-spiroketals, as illustrated by the stereocontrolled synthesis of both the reported structure of cephalosporolide H (**1**) and its spiroketal epimer (**10**). The use of zinc salts is important: weaker acids do not enable isomerization, and stronger acids promote decomposition, including especially elimination to furans. This study provides new and valuable information for prescribing the chirality of the stereogenic core of 5,5-spiroketals.

Acknowledgment. This research is supported by a grant from the National Science Foundation (NSF-CHE 0749918). We thank Dr. Tom Gedris (FSU) for assistance with NMR analysis.

Supporting Information Available: Experimental procedures, characterization data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) The oxidation **9** → **10** is significantly faster than the oxidation **7** → **1**, facilitating production of the more stable lactone (**10**). For a related example, see: Dudley, G. B.; Engel, D. A.; Ghiviriga, I.; Lam, H.; Poon, K. W. C.; Singletary, J. A. *Org. Lett.* **2007**, *9*, 2839.

(24) Our data for **10** are in close agreement with the data reported for the natural product, and our data for synthetic **1** are not. However, attempts to secure an authentic sample and/or copies of original NMR spectra were unsuccessful, so positive conclusions on the correct structure of natural cephalosporolide H cannot be made at this time. See Supporting Information for a table comparing the various NMR data.

(25) Our stereochemical assignment of spiroketals **1** and **10** is based on NMR correlations with the spiroketal resonances of cephalosporolides E and F, for which X-ray crystallographic data is available, and by analogy to the model systems **I** and **II** (see ref 13). Direct spectroscopic analysis using NOE and NOESY experiments conducted on both spiroketal epimers was inconclusive. The original spiroketal stereochemical assignment of cephalosporolide H (ref 7) was made on the basis of NOESY crosspeaks that we observe in both epimers. A full analysis of the factors supporting our structural conclusions is provided in Supporting Information.

(26) Li, X.; Sattler, I.; Lin, W. *J. Antibiot.* **2007**, *60*, 191.