Nonanomeric Spiroketals in Natural Products: Structures, Sources, and Synthetic Strategies

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Contents

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1. Introduction

In every natural product synthesis endeavor, chemists charting their way toward the target molecule have to face both foreseeable problems as well as unexpected difficulties.[1] Of the potential strategic problems immediately obvious to the trained eye, the presence of unstable, fragile, or arduously accessible subunits in the target molecule undoubtedly raises concerns in the minds and hearts of the synthesis team.

This review is about just such structural subunits: the nonanomeric, typically less stable spiroketal isomers, the natural products containing them, and the synthetic strategies that chemists have devised to access these structures. Due to their fragile nature, nonanomeric spiroketals have often been the stumbling blocks of natural product syntheses, and successes in their synthesis have often come only after long, hard work.

Spiroketals are cyclic ketals (acetals) in which two rings are joined by a single atom, the spiro atom, and the two ketal oxygens flanking the spiro atom each belong to one of the rings. The spiroketal ring system is a structural subunit that is often found in naturally occurring substances of marine, insect, bacterial, or plant origin.[2]

1.1. Anomeric Effect and Relative Stabilities of Spiroketal Structures

The term anomeric effect refers to the tendency of an electronegative substituent at the anomeric center (C_1) of a pyranose ring to take an axial rather than equatorial orientation despite unfavorable steric interactions (Scheme 1). The anomeric effect is believed to arise from a stabilizing interaction between one of the lone pairs on oxygen and the antibonding σ^* orbital of the C−O bond. The overlap is efficient only when one of the lone pairs on the oxygen is antiperiplanar to the C−O bond.[3] The lone pair of the exocyclic oxygen can, of course, exert similar effects on the endocyclic oxygen that is part of the pyranose ring; this is called the *exo*-anomeric effect.

The contribution of anomeric stabilization to the total energy has been estimated to be in the range of 1.4−2.4 kcal/mol per interaction.[4] In addition to the anomeric effect, steric interactions, intramolecular hydrogen bonding, and other chelation effects influ-

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Jatta Aho was born in Turku, Finland, in 1979. She received her M.Sc. (Tech) degree in Organic Chemistry from the Helsinki University of Technology in 2004. In the same year she joined the research group of Dr. Petri Pihko as a Ph.D. student and continued working on the total synthesis of pectenotoxins.

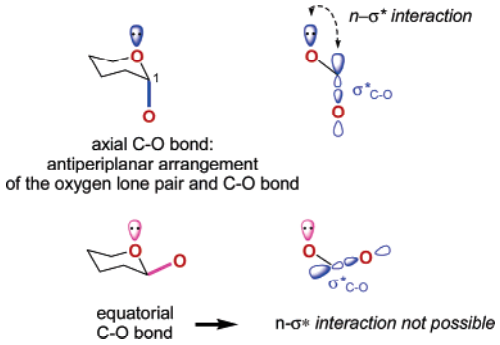
Petri Pihko was born in 1971 in Oulu, Finland, and became interested in chemistry several years before entering the university. He studied chemistry at the University of Oulu and joined the research group of Professor Ari Koskinen, graduating with his Ph.D. degree in 1999. He then spent nearly two years as a postdoctoral associate with Professor K. C. Nicolaou at the Scripps Research Institute in La Jolla, CA, working on the total synthesis of the marine natural product azaspiracid. In 2001 he joined the faculty of Helsinki University of Technology, where he currently holds the post of Senior Lecturer. His current research interests include organocatalysis, catalyst design, and total synthesis.

ence spiroketal conformation.[5] The most stable conformation is the one where the number of anomeric interactions is maximized and unfavorable steric interactions between the substituents are minimized (Scheme 2). Thus, in [6,5]-spiroketal systems two configurations can be identified: the anomeric configuration bearing the axial oxygen substituent and the nonanomeric configuration bearing the equatorial oxygen. In [6,6]-spiroketals four different configurations can be specified, one with two anomeric relationships, two with one nonanomeric relationship, and one with two nonanomeric relationships.

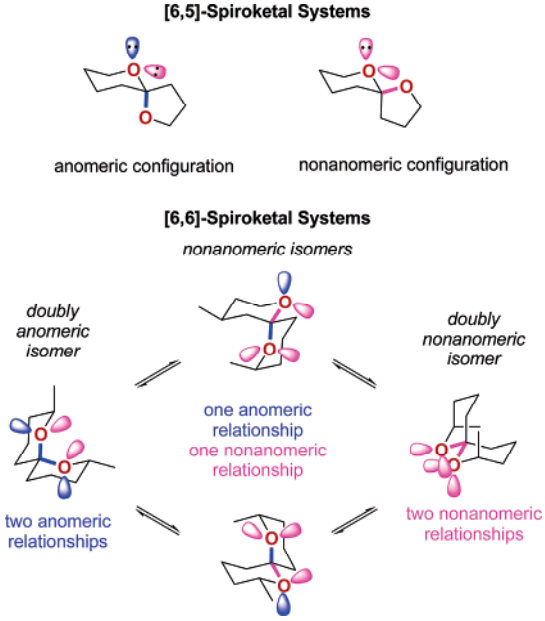
Throughout this review we use the term "nonanomeric" simply as the common descriptor of those spiroketal isomers that have less than the maximum possible number of anomeric interactions. In our view use of the term "contrathermodynamic" in this context should be avoided simply because nonanomeric spiroketals do not always represent the thermodynamically least stable structures (see below).[6]

Terhi Rissa was born in Seinäjoki, Finland, in 1977. She received her M.Sc. (Tech) degree in Organic Chemistry from the Helsinki University of Technology in 2002, initiating the pectenotoxin project. After graduation she joined the research group of Dr. Petri Pihko as a project researcher. In 2004 she worked as a trainee for Novartis Pharma AG in Basel, Switzerland. Since 2005 she has been working at Rautaruukki Oyj as a product development engineer in the field of coil coating.

Scheme 1. Anomeric Effect Stabilizes the Axial Oxygen Substituent Relative to the Equatorial Substituent



Scheme 2. Anomeric and Nonanomeric Relationships in [6,5]- and [6,6]-Spiroketal Systems



1.2. Nonanomeric Spiroketals in Natural Products

In nearly all natural products containing the spiroketal subunit the spiroketal consists of only five-

and six-membered rings, although it is well known that the more strained three- and four-membered ring systems are generally abundant in natural products. For example, the cyclopropane and epoxide rings are important structural units in many classes of natural products.[7] For this reason it is tempting to speculate that perhaps the spiroketal units in natural products are formed in equilibrating conditions, generating the thermodynamically most stable products and favoring only the most stable five- and six-membered rings. This line of thinking appears, at first glance, to be supported by the fact that a number of naturally occurring spiroketal systems also appear to be in the thermodynamically most stable configuration, which typically means that they also possess a maximum number of anomeric effects.

There are, however, a number of naturally occurring spiroketal structures that do not conform to this assumption. Some of them occur as mixtures of fully anomeric and nonanomeric isomers; some of them are apparently purely nonanomeric isomers. These nonanomeric structures have been found in natural products from a wide variety of sources: insect pheromones, different kinds of polyketide antibiotics, and marine toxins.

In addition to being targets of natural product synthesis, spiroketals have been studied extensively as they are excellent systems to study the role of the anomeric effect as a means of controlling the conformation of heterocyclic systems.[8] The anomeric spiroketal unit is very rigid, and it has been suggested that it may be acting as a β-turn mimic in natural products.[9]

The scope of this review covers the structures, occurrence, and synthetic studies of naturally occurring spiroketals bearing nonanomeric relationships. We have also included cases where the natural product was later found to possess an anomeric structure as well as selected cases where the nonanomeric spiroketals were formed as byproducts. Our aim is to focus the attention of the synthetic community to the diversity of nonanomeric spiroketal structures, many of which are still awaiting synthetic access, and also to the advances in the field.

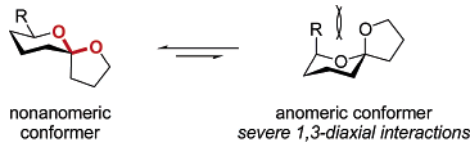
1.3. Conformational Locking Is Required To Stabilize Nonanomeric Structures

The anomeric−nonanomeric configurational dichotomy becomes meaningful only in cases where the following conditions are met. (1) There must be a clear difference between the anomeric (axial or pseudoaxial) and nonanomeric (equatorial or pseudoequatorial) configuration. (2) The ring conformation must be effectively locked to prevent access to the anomeric configuration by simple conformational change (e.g., ring flipping).

Condition 1 applies most clearly to six-membered rings, where the difference between axial and equatorial substituents is clear-cut. Given the rapid pseudorotation in five-membered ring systems,[10] nonanomeric relationships cannot be stabilized in five-membered rings. It is, however, reasonable to assume that suitably substituted seven-membered rings or larger ring systems might display the anomeric−nonanomeric dichotomy. The authors are not aware of any such cases, but the synthesis of such a system would certainly be an interesting exercise in conformational design.

Condition 2 is equally important. Unless the nonanomeric configuration is locked by ring fusion or suitably placed equatorial substituents on the six-membered ring, ring flipping will quickly transform the nonanomeric structure into the more stable anomeric structure. It is perhaps not surprising that nearly all nonanomeric spiroketals bear an alkyl substituent in the 6-position of the tetrahydropyran ring. Ring flipping is prevented in these cases since it would place the substituent and the spiroketal oxygen in a sterically encumbered 1,3-diaxial setting (Scheme 3).

Scheme 3. Unfavorable 1,3-Diaxial Interactions between the Alkyl Substituent in the 6-Position and the Axial Oxygen



In natural products the nonanomeric configuration may be stabilized by additional factors, which override the thermodynamic preference for the anomeric configuration. For example, intramolecular hydrogen bonding may contribute greatly to the stability of the nonanomeric configuration. In addition, the constraints imposed by the macrocyclic structures may favor the nonanomeric configuration.

1.4. General Strategies for the Synthesis of Nonanomeric Spiroketals

Most of the methods that have been used to construct the spiroketal ring system rely on acid-catalyzed spirocyclization, typically accompanied with the release of acid-labile protecting groups. The downside of this method is that it produces a thermodynamic mixture of the spiroketal epimers, favoring the thermodynamically more stable anomeric configuration. Thus, the synthesis of the nonanomeric spiroketal structure might sound like an impossible mission: how to access the *less stable* structure under thermodynamic, equilibrating conditions. One of the methods that has been used to address this problem is to somehow stabilize the nonanomeric structure and thus favor it in the equilibrating mixture. Quite a few synthetic approaches have built upon the utilization of intramolecular hydrogen bonding or related chelation effects with different metal salts. In recent years a number of strategies which are not based on thermodynamic equilibration have also been developed. Many of the methods are still very compound-specific, and few general methods are available. For this reason, in the following discussion, the nonanomeric structures are classified according to their structure and type of compound synthesized. A summary of the methods used to access the nonanomeric spiroketal structures is presented at the end of the review.

2. [6,5]-Spiroketals

The most common nonanomeric spiroketal structure in natural products is the [6,6]-spiroketal, but there are also many natural products that contain the nonanomeric [6,5]-spiroketal. However, natural products containing the nonanomeric [6,5]-spiroketal have attracted much less attention from the synthetic community than the nonanomeric [6,6]-spiroketals.

2.1. Insect Pheromones

A large group of naturally occurring spiroketals have been isolated as pheromones from several insect species.[2,11] These form a diverse set of natural products; among these [5,5]-spiroketal systems **1**, [6,5]-spiroketal systems **2,** [6,6]-spiroketal systems **3**, and [6,7]-spiroketal systems **4** (Figure 1) have all

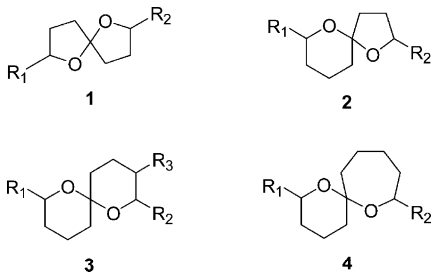
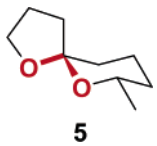


Figure 1. Different insect pheromone systems.

been isolated and characterized. Nonanomeric [6,5]-spiroketal systems have been identified as minor components in different insect pheromones. However, there are few synthetic studies addressing these structures, whereas the corresponding [6,6]-spiroketals have attracted more attention, and there are multiple examples for the synthesis of the nonanomeric structures. These are presented in more detail in section 3.1.

One of the earliest observations for the formation of the nonanomeric [6,5]-spiroketal was reported by Francke et al.[12] They report that very small amounts of the nonanomeric [6,5]-spiroketal **5** were detected by GLC-MS; however, this product was not fully characterized.

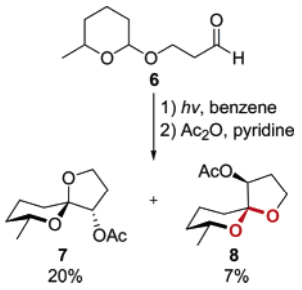


Descotes and co-workers studied the synthesis of insect pheromones bearing the [6,5]-spiroketal structure.[13] Photocyclization of aldehyde **6** followed by acetal protection furnished a 3:1 mixture of anomeric spiroketal **7** and nonanomeric spiroketal **8** in 27% total yield (Scheme 4).

2.2. Polyketide Ionophore Antibiotics with a Nonanomeric [6,5]-Spiroketal Structure

The polyketide ionophore antibiotics[14] are another large group of natural products that contain spiroketals. These microbial metabolites, produced mainly by

Scheme 4. Photocyclization in Spiroketal Synthesis According to Descotes et al.[13]



Streptomyces, have biological properties related to their ability to transport ions across biological and artificial membranes.

The antibiotics of the dianemycin/endusamycin class comprise a group that contains two [6,5]-spiroketal ring systems. Invariably, the AB spiroketal is anomeric, and the CD spiroketal is nonanomeric (Figures 2 and 3). The nonanomeric configuration adopted by the CD ring systems is due to unfavorable steric interactions between the C_{20} and C_{22} methyl groups in the anomeric configuration. In the course of continuous screening a total of 13 antibiotics of this group have been identified: Endusamycin (CP-63,-517), dianemycin, iso-dianemycin, moyukamycin, lenoremycin (A-130A, RO 21-6150), leuseramycin, A-130B, A-130C, CP-53,607 (X-14931A), CP-80,219, X-14934A (CP-47,224), TM-531B, and TM-531C (Figures 2 and 3).[15−17] The structures of these antibiotics have been mainly established by NMR spectroscopy. In selected cases, further X-ray crystallographic analyses of the corresponding rubidium or silver salts have confirmed the structural assignments and allowed the absolute configurations to be established by crystallographic methods. For some of these antibiotics, such as moyukamycin, leuseramycin, and TM-531B-C, the structures are based mainly on NMR spectroscopic studies. However, given their structural similarity to the other members of the group, they are assumed to have the same absolute configuration as dianemycin because of similar optical rotations.[15a]

To date, no total syntheses of any of these natural products have been reported. In addition, the nonanomeric CD spiroketal moiety has not been accessed synthetically.

2.3. [6,5]-Spiroketals of Marine Origin

For several decades marine natural products have been attracting the attention of biologists and chemists, and this has led to the isolation and characterization of a vast array of novel molecules from marine organisms.[18] Marine organisms come from diverse ecological habitats; as a result they produce secondary metabolites which have unique structural features. A number of marine natural products have also shown very promising biological activity. The spiroketal ring system is a relatively common structural feature in marine natural products; however, only two groups of natural products that contain a nonanomeric [6,5]-spiroketal ring system have been identified to date.

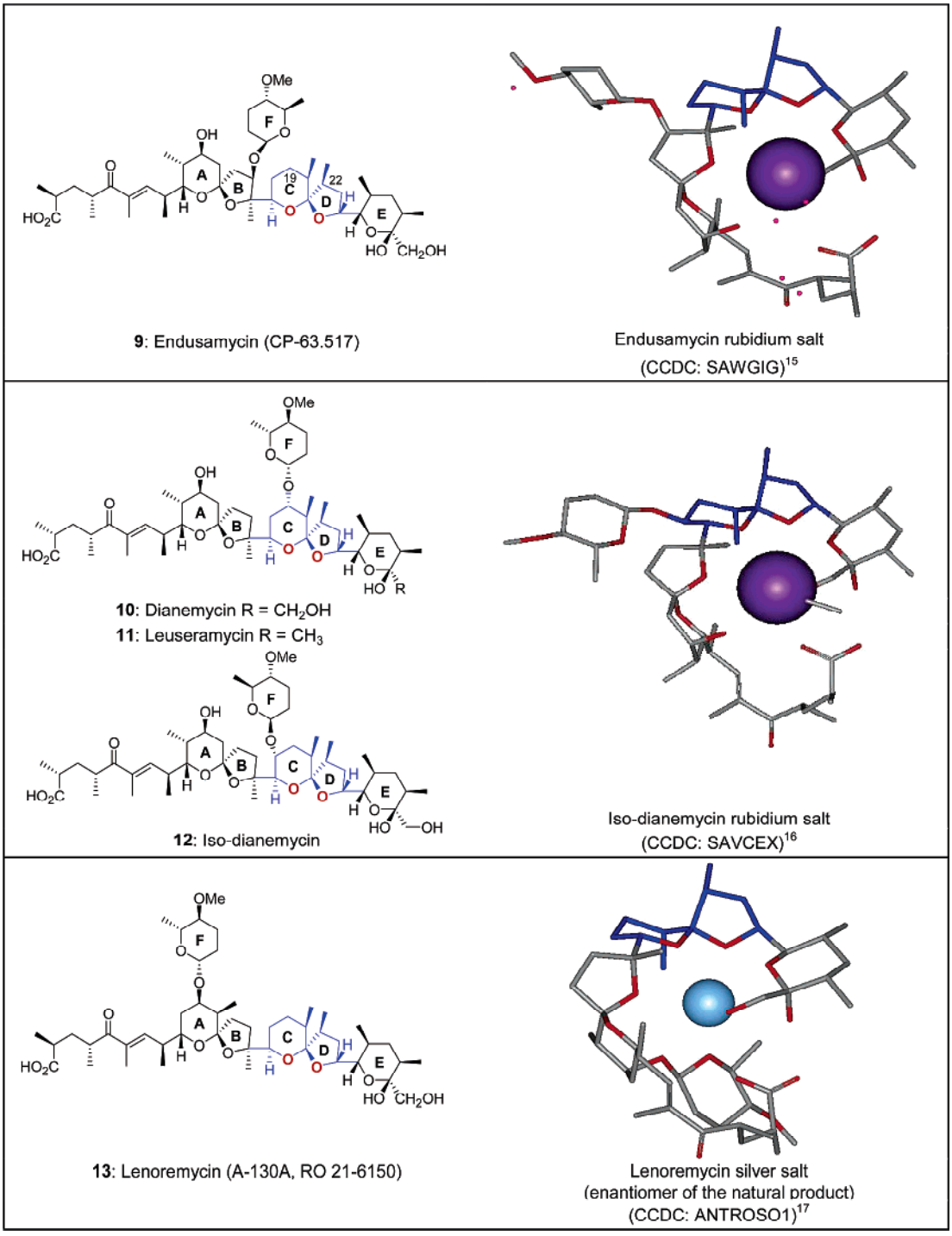


Figure 2. Structures of endusamycin, dianemycin, leuseramycin, and lenoremycin and their crystal structures.[15,16,17]

2.3.1. Spiroketal System of the Ciguatoxins

Ciguatoxin (CTX1B, **21**) and its congeners are the principal toxins associated with ciguatera, one of the most widespread seafood poisons (Figure 4).[19] Ciguatoxins are potent sodium channel activators that bind quasi-irreversibly to site 5 on the voltage-sensitive sodium channels (VSSC) in nerves, heart, and muscle.[20] Thus far, more than 23 ciguatoxins have been identified.[21] Yasumoto and co-workers identified four CTX congeners that contained the same backbone as CTX1B but were assigned to be C_{52} epimers, having a nonanomeric configuration in the LM spiroketal system.[21c,d] It was observed that these epimers underwent isomerization into the epimer containing the anomeric spiro configuration under acidic conditions.

Because of the unique structure of ciguatoxins, accompanied with their exceptionally potent neurotoxicity and their limited availability from nature sources, several research groups have studied the total synthesis of CTXs over the past decade.[22] However, the ciguatoxin congeners bearing the nonanomeric spiroketal system are still awaiting synthetic access, though the nonanomeric subunit has been accessed as the unwanted side product. In the synthesis developed by Hirama and co-workers for

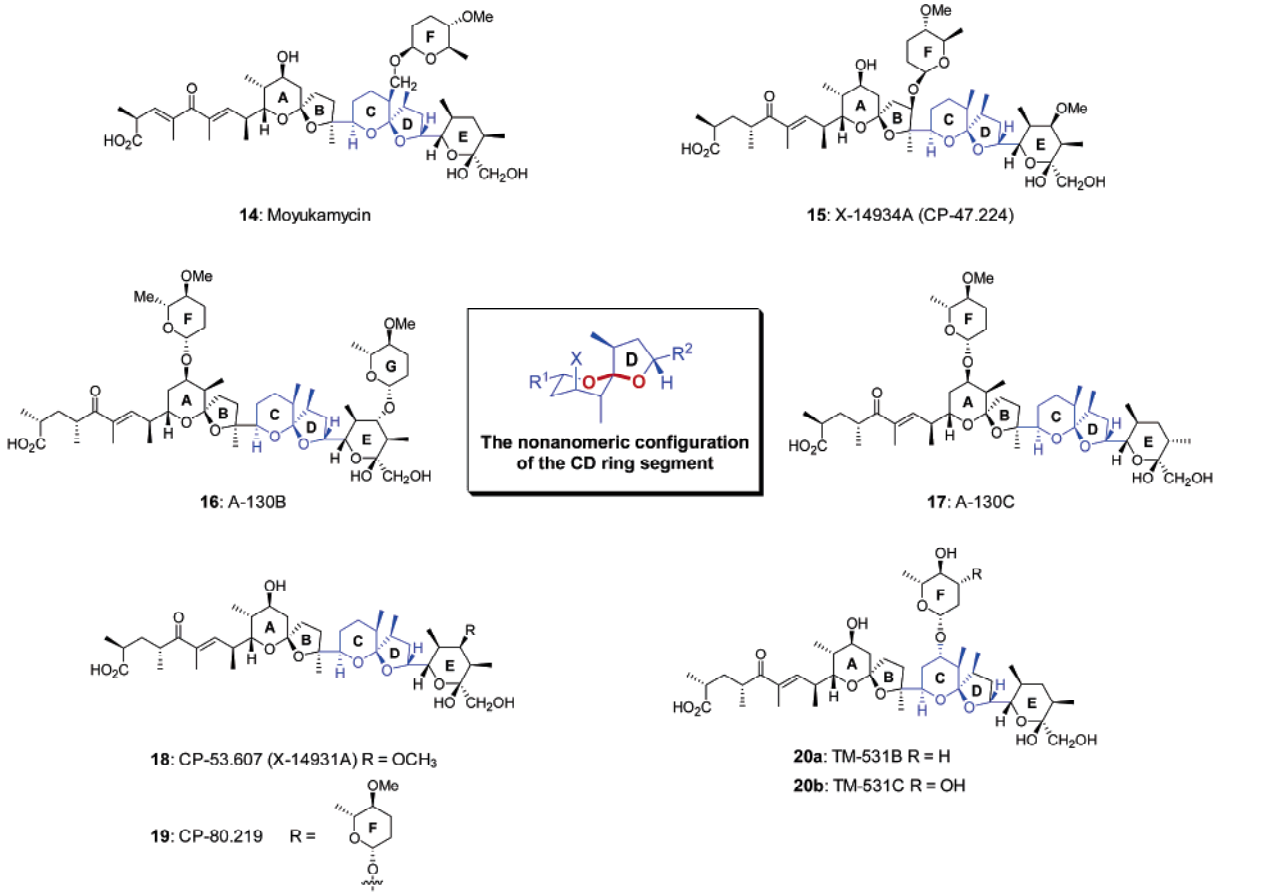


Figure 3. Other polyketide ionophore antibiotics of the dianemycin/endusamycin class with a nonanomeric [6,5]-spiroketal.

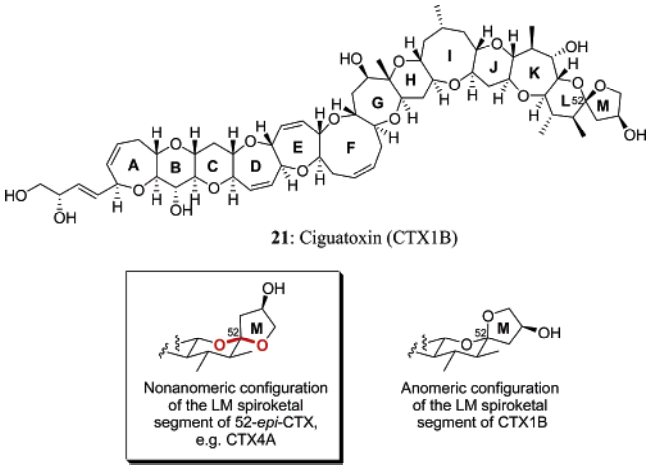
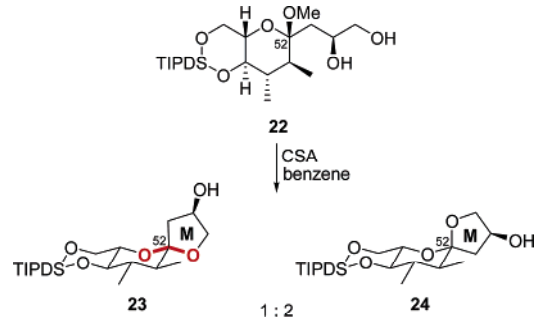


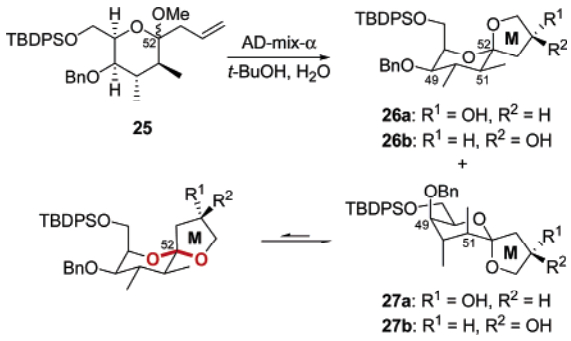
Figure 4. Structure of ciguatoxin (CTX1B).

the LM ring moiety of ciguatoxin, treatment of diol **22** with CSA furnished a 1:2 mixture of nonanomeric spiroketal **23** and anomeric spiroketal **24** (Scheme 5).[23] Here formation of the nonanomeric product is obviously under kinetic control since it was readily converted into the anomeric configuration by heating with CSA. Interestingly, Isobe and co-workers obtained only a mixture of four anomeric diastereomers **26a**,**b** and **27a**,**b** (1:4:4:1) in their synthesis toward the LM ring fragment (Scheme 6).[24] In contrast to the results obtained by Hirama and co-workers, their spiroketalization precursor **25** did not contain a fused ring system (the TIDPS ether ring in **22**). As a consequence, the C_{49} and C_{50} substituents were not

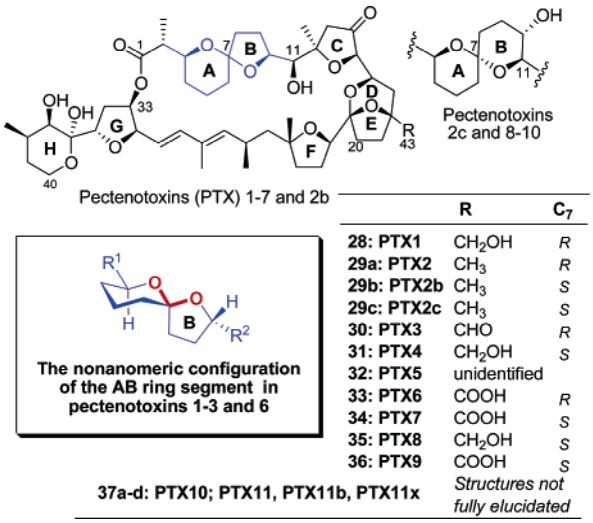
Scheme 5. Synthesis of the LM Spiroketal Moiety of Ciguatoxin According to the Hirama Group[23]



Scheme 6. Synthesis of the LM Spiroketal Moiety of Ciguatoxin According to the Isobe Group[24]



forced to adopt the equatorial positions, and as such the isomers isolated by the Isobe group were all anomeric (Scheme 6).



	R	C_7
28: PTX1	CH_2OH	R
29a: PTX2	CH_3	R
29b: PTX2b	CH_3	S
29c: PTX2c	CH_3	S
30: PTX3	CHO	R
31: PTX4	CH_2OH	S
32: PTX5	unidentified	
33: PTX6	COOH	R
34: PTX7	COOH	S
35: PTX8	CH_2OH	S
36: PTX9	COOH	S
	Structures not fully elucidated	

Figure 5. Structures of the pectenotoxins.

2.3.2. Spiroketal System of the Pectenotoxins

The pectenotoxins (PTX) comprise a family of marine natural products isolated from the scallop *Patinopecten yessoensis* (Figure 5). The first members of the family were isolated and characterized by Yasumoto and co-workers in 1985;[25] in subsequent studies a total of 15 pectenotoxin congeners have been found.[26] These compounds have drawn considerable attention[27] as a result of their significant cytotoxicity against a variety of lung, colon, and breast cancer cell lines[28] and their still largely unknown mode of action. PTX2 and PTX6 are known to interact with the actin cytoskeleton at a unique site, effecting depolymerization of F-actin.[29] Structurally, the pectenotoxins share a common carbon skeleton, and the congeners differ from each other in the oxidation state of C_{43} and in the different configurations of the AB spiroketal segment (Figure 5, Figure 6). In PTX1−3 and PTX6 the spiroketal

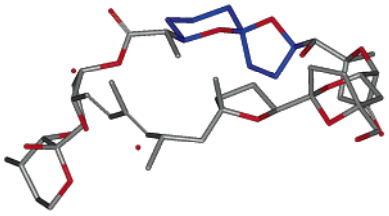
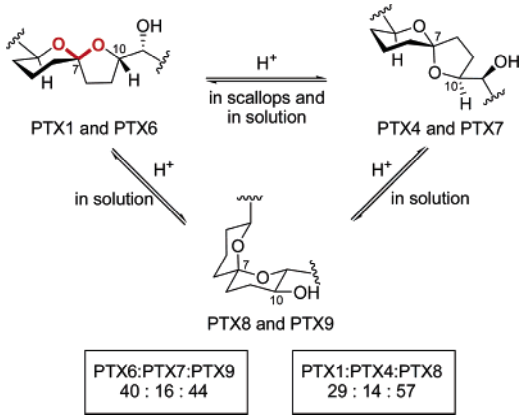


Figure 6. Crystal structure of pectenotoxin-1 (CCDC: DIKHEK). The structure is enantiomeric to that of natural pectenotoxin.[25]

configuration is *R*, corresponding to a spiroketal with no anomeric stabilization. These nonanomeric congeners are the major products obtained after isolation and also appear to be the most cytotoxic. The lethal toxicity of PTX4 is 770 μg/kg, which is approximately one-third that of PTX1.[25a,28,30]

The spiroketal unit of the pectenotoxins has been observed to undergo isomerization under acid catalysis (Scheme 7).[26a] Upon treatment with trifluoroacetic acid, the nonanomeric PTX6 isomerized into an equilibrium mixture of the anomeric isomer PTX7, PTX6, and a third isomer called PTX9. In PTX9 the [6,5]-spiroketal unit was expanded into a [6,6]-

Scheme 7. Acid-Catalyzed Isomerization of the Pectenotoxins[26a]



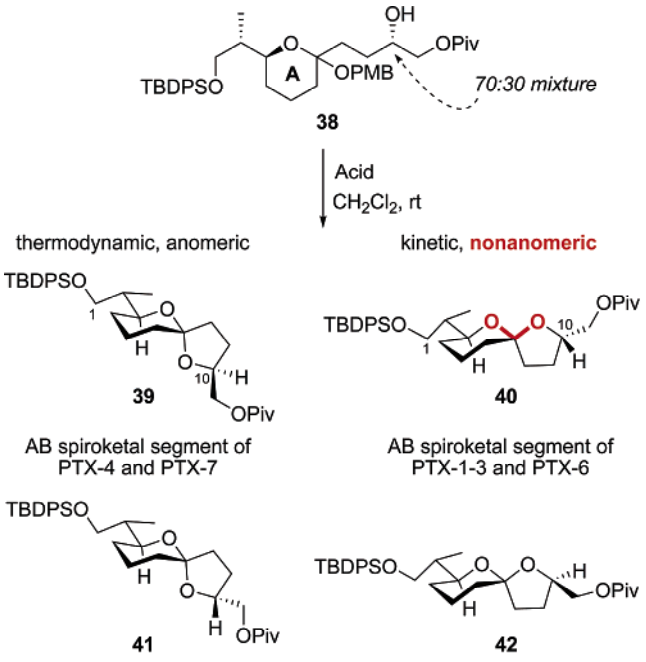
spiroketal system, and it also has the more thermodynamically stable doubly anomeric configuration. The proportions of the different isomers at equilibration were 40:16:44 (PTX6:PTX7:PTX9). Similar results were obtained with PTX1 and PTX4, which yielded a 29:14:57 equilibration mixture of PTX1:PTX4:PTX8. Starting from synthetic PTX4, however, the Evans group later reported that they obtained a ratio of 11:10:79 with PTX1:PTX4:PTX8. Thus, the macrocyclic structure apparently helps in stabilizing the nonanomeric structure enough that it is still detectable after equilibration. Whether this finding could be exploited to access the nonanomeric pectenotoxins synthetically remains an open question. Both Yasumoto and Evans report that they only isolated PTX8 from the equilibrium mixture of PTX1:PTX4:PTX8.[26a,27b]

Pihko (2004). In our own studies we recently developed a method to synthesize the nonanomeric AB spiroketal segment of the pectenotoxins.[31] Acid-catalyzed cyclization of A ring intermediate **38** furnished a mixture of four spiroketal diastereomers **39**−**42** (Scheme 8). Different acid promoters were tested for this key spiroketalization reaction, and by using weak acids (Scheme 8, entries 4−6) the nonanomeric spiroketal ring system **40**, corresponding to the C_1−C_{11} AB spiroketal segment of PTX-1−3 and PTX-6, could be formed as the major product. Formation of the nonanomeric structure appears to be under kinetic control because when stronger acids were used in the spiroketalization the nonanomeric form was detected in the initial stages of the reaction but further equilibration afforded only the anomeric structures **39** and **41** (Scheme 8, entries 2 and 3).

2.4. Other Approaches to the Formation of Nonanomeric [6,5]-Spiroketals

The lituarines A−C are marine toxins isolated from the sea pen *Lituaria australasiae*.[32] The complex cyclic structure of lituarines contains a tricyclic spiroketal fragment in which the [6,5]-spiroketal unit is anomerically stabilized (Figure 7). The Smith group has made intensive studies toward the synthesis of lituarines, and in the synthesis of the spiroketal segment a nonanomeric spiroketal was formed as an undesired product (Scheme 9).[33] By treating ketone **48** containing ca. 10% of cyclic

Scheme 8. Synthesis of the Pectenotoxin AB Spiroketals According to Pihko et al.[31]



Entry	Acid (mol%)	pK_a H_2O (DMSO)	Reaction time	**39** : **41** : **40** (%)
1	PPTS (20)	5.21 (3.4)	10 min	53 : 18 : 29
2	*p*-TsOH (20)	-1.3 (<0)	10 min	51 : 21 : 28
3	*p*-TsOH (20)	-1.3 (<0)	90 min	70 : 30 : <2
4	**$ClCH_2COOH$ (80)**	**2.86**	4 h	**29 : 22 : 49**
5	HCOOH (40)	3.77	4 h	29 : 28 : 43
6	AcOH (200)	4.76 (12.3)	6 h	34 : 26 : 40
7	AcOH (3300)	4.76 (12.3)	21 h	65 : 35 : <2

hemiketals with a catalytic amount of toluenesulfonic acid, a mixture of two anomerically stabilized spiroketals epimeric at C_{16} along with small amounts of a third isomer, the nonanomeric spiroketal **50**, was formed. The amount of nonanomeric spiroketal was highest (10%) when the spiroketalization was carried out in lower concentrations; with longer reaction times **50** was not detected (Scheme 9).

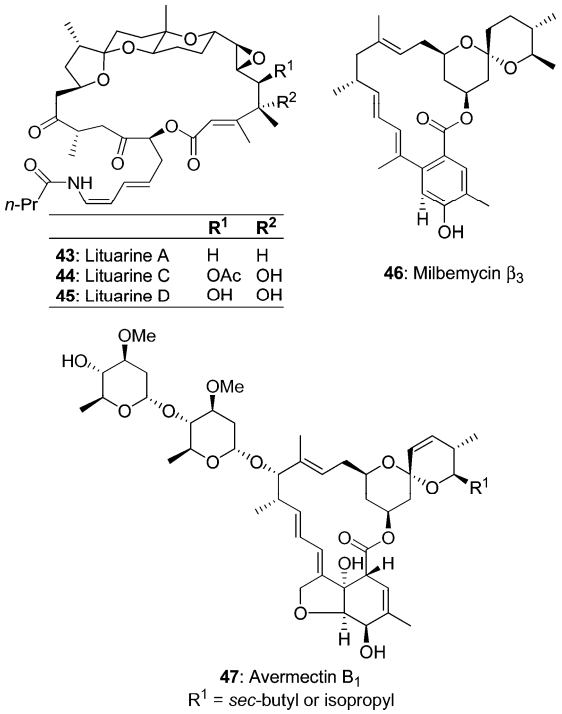
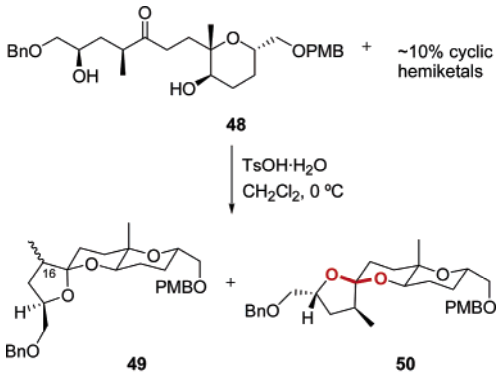


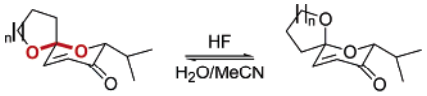
Figure 7. Structures of lituarines A−C, milbemycin β_3, and avermectin B_1.

Scheme 9. Synthesis of the Lituarine Spiroketal According to Smith et al.[33]



Entry	Concentration (M)	Reaction time	**50** (%)
1	0.01M	30 min	10
2	0.3M	25 min	< 5
3	0.3M	1h	0

Scheme 10. Thermodynamic Equilibrium between Anomeric and Nonanomeric Spiroketals According to DeShong et al.[34]

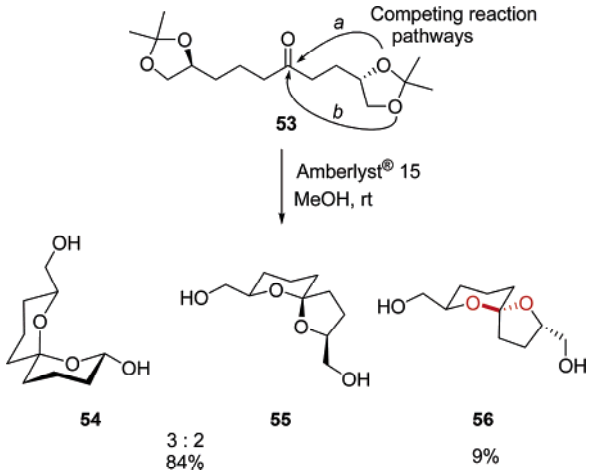


51a: n = 1 **51b**: n = 2 13:87 5:95 **52a**: n = 1 **52b**: n = 2

Sinibaldi and co-workers studied the synthesis of chiral spiroketal skeletons and developed an approach to hydroxyl-substituted [6,6]- and [6,5]-spiroketal systems (Scheme 11).[35] Acetal-protected ketone **53** underwent concomitant deprotection and spiroketalization to form a mixture of spiroketals **54**−**56** from which the nonanomeric product **56** could be isolated in 9% yield. This is an example of a reaction where the competing reaction pathways give rise to both [6,6]- and [6,5]-spiroketals. Quite often in these cases the [6,6]-spiroketals are the major products. This was the case with the isomerization of the pectenotoxins (see above).

DeShong and co-workers studied the synthesis of model systems for the spiroketal moieties found in the avermectins/milbemycins family of antibiotics (Figure 7) and observed the formation of undesired nonanomeric spiroketals.[34] In the case of [6,5]-spiroketals the thermodynamic equilibration gave a mixture of the anomeric spiroketal **52a** and the nonanomeric spiroketal **51a** in a ratio of 87:13, whereas the corresponding [6,6]-spiroketal system furnished a 95:5 mixture (Scheme 10). This illustrates the decrease in the anomeric stabilization in [6,5]-ring systems compared to [6,6]-ring systems. In this case the nearly planar nature of the six-membered pyrone ring diminishes the anomeric effect even further and allows both isomers to be detectable in equilibrium.

Scheme 11. Synthesis of Hydroxyl-Substituted Spiroketal Systems According to Sinibaldi et al.[35]



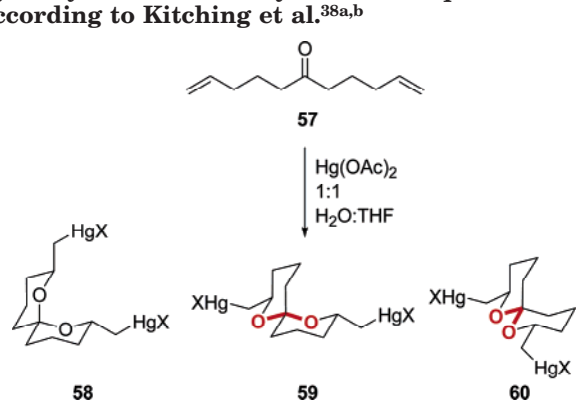
Very recently Rychnovsky and co-workers reported the first synthetic approach that gives access to nonanomeric spiroketal structures as single diastereomers. By using a sequence of stereoselective reductive lithiation followed by cyclization, different kinds of nonanomeric spiroketal structures, including [6,5]-spiroketals, could be formed as single diastereomers.[36] They further applied the reductive cyclization strategy to synthesize the [6,6]-spiroketal segment of spirofungin B.[37] This elegant synthesis is presented in greater detail in section 3.2.1.

3. [6,6]-Spiroketals

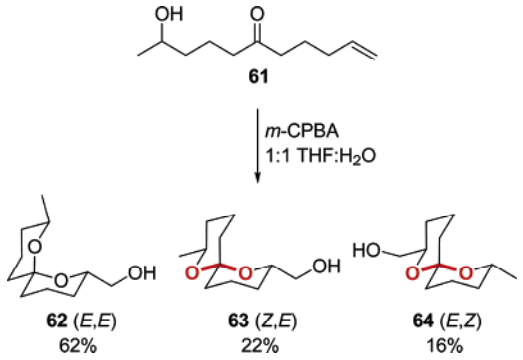
3.1. Insect Pheromones

The Kitching group[38] and the Mori group[39] pioneered this area of spiroketal synthesis.[40] Kitching and co-workers studied different dialkyl- and hydroxyl-substituted spiroketals that are the main components of the pheromones in various fruit flies.[11] In their early synthetic studies racemic spiroketals were formed from dienones and hydroxyenones by a hydroxymercuration−cyclization sequence (Scheme 12).[38a,b] By keeping the reaction times short (<10 min), the nonanomeric mercurocyclization product **59** could be obtained (~40%) along with low levels of a third diastereomer, which was presumed to be the

Scheme 12. Synthesis of Spiroketals by Hydroxymercuration−Cyclization Sequence According to Kitching et al.[38a,b]



Scheme 13. Epoxidation Approach to Spiroketal Systems According to Kitching et al.[38c,d]



doubly nonanomeric isomer **60**. A few years later another strategy was employed in which a mixture of racemic spiroketals **62**−**64** was formed from hydroxyenone **61** by epoxidation followed by acid-catalyzed hydrolysis and cyclization (Scheme 13).[38c,d] Kitching and co-workers also developed a method for the synthesis of each of the six enantiomers of spiroketals **62**−**64** by employing the hydroxymercuration method and using *S*- and *R*-glycerol acetonides as the source of chirality.[38d]

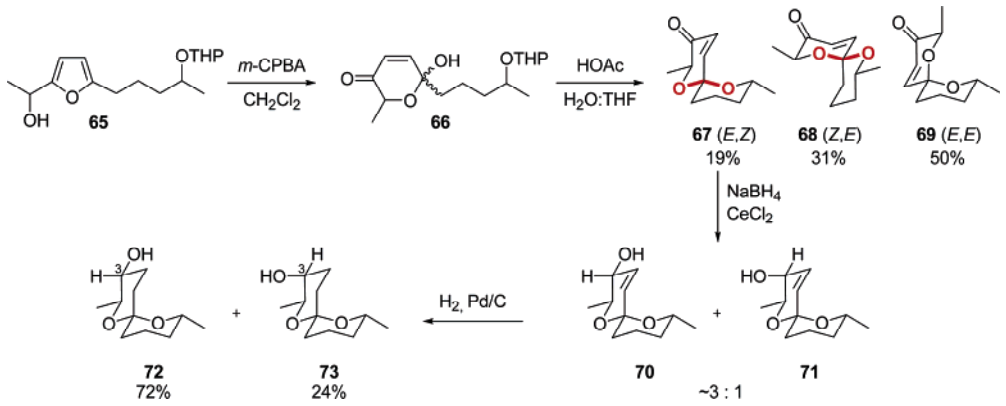
For the synthesis of another hydroxyl-substituted spiroketal **72** (Scheme 14) an alternative approach had to be developed because of the facile isomerization of the [6,6]-spiroketal system to the [5,6]-system under mildly acidic conditions.[38d] A racemic mixture of spiroenone isomers **67**−**69** was prepared in two steps from furan **65** by oxidation to pyranone **66** followed by acid-catalyzed spiroketalization. Luche reduction and hydrogenation of the nonanomeric *E*,*Z* isomer **67** furnished a mixture of racemic spiroketals **72** and **73** in which the major product had an equatorial C_3 hydroxyl group. When the corresponding nonanomeric *Z*,*E* isomer **68** was treated under the same conditions, a more complex mixture of spiroketals was formed.

Kitching and co-workers also synthesized other insect-derived spiroketal structures, but in these syntheses only low levels of the nonanomeric spiroketal structures were formed.[38c]

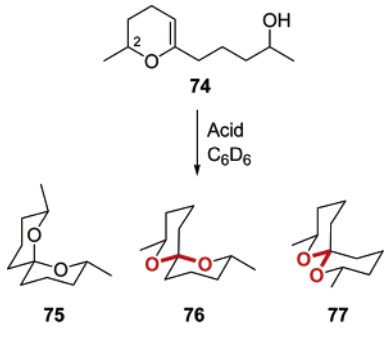
Deslongchamps is one of the pioneers of spiroketal research and has focused on the stereoelectronic aspects of spiroketal formation.[4a,5,41] Deslongchamps and co-workers studied acid-catalyzed cyclizations of different hydroxyenol ethers and presented a thorough explanation for the outcomes using different transition state models.[5b] Upon treatment with trifluoroacetic acid in benzene, dihydropyran **74** formed a 1:1 racemic mixture of the anomeric spiroketal **75** and the nonanomeric spiroketal **76** (Scheme 15). When **74** was treated with acetic acid, a mixture of spiroketals **75**, **76,** and **77** was formed in a ratio of 3:5:2, and upon further treatment with trifluoroacetic acid this mixture was again converted into a 1:1 mixture of spiroketals **75** and **76**.

These results show that different acidic conditions can provide access to either thermodynamically or kinetically controlled cyclization products. Formation

Scheme 14. Synthesis of Nonanomeric Spiroketals through Spiroenones According to Kitching et al.[38d]

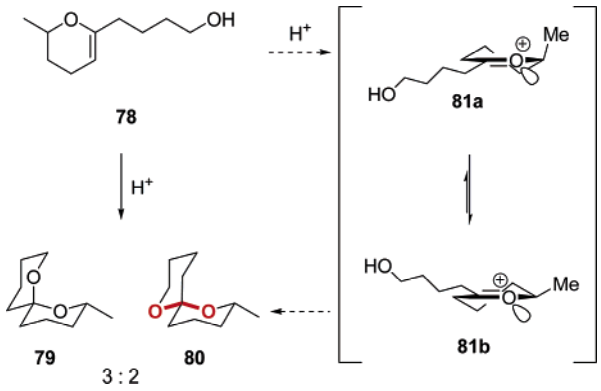


Scheme 15. Acid-Catalyzed Spiroketalization According to Deslongchamps et al.[5b]



Entry	Acid	Ratio	
1	CF_3COOH	**75:76**	1:1
2	AcOH	**75:76:77**	3:5:2

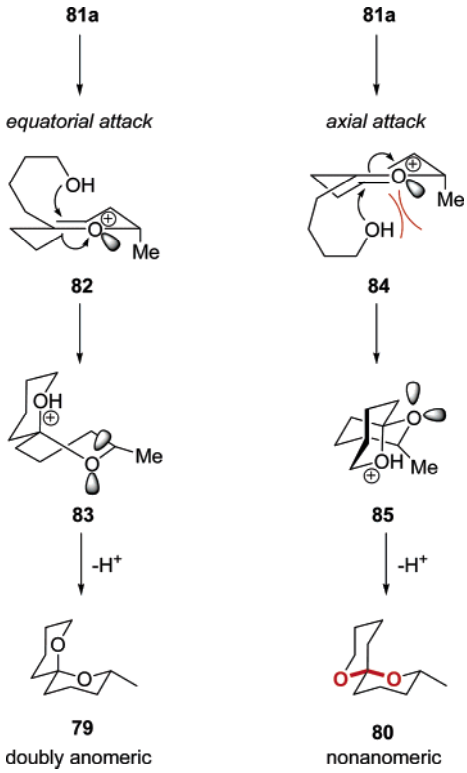
Scheme 16. Acid-Catalyzed Spiroketalization and the Equilibration between the Oxocarbenium Ion Intermediates[5b]



of the nonanomeric structure under kinetic control was explained with an early transition state in which the favorable anomeric interactions are not yet fully developed.[5b] In an acid-catalyzed spiroketalization the hydroxyenol ether **78** forms a mixture of doubly anomeric spiroketal **79** and nonanomeric spiroketal **80** in a ratio of 3:2 (Scheme 16). Protonation of the hydroxyenol ether **78** will produce an oxocarbenium ion, which can have two different conformations **81a** or **81b**, of which conformation **81b** is more stable because of the more favorable pseudoequatorial position of the methyl group (Scheme 16).

The cyclization can occur through either equatorial or axial attack on the oxocarbenium ion. Equatorial

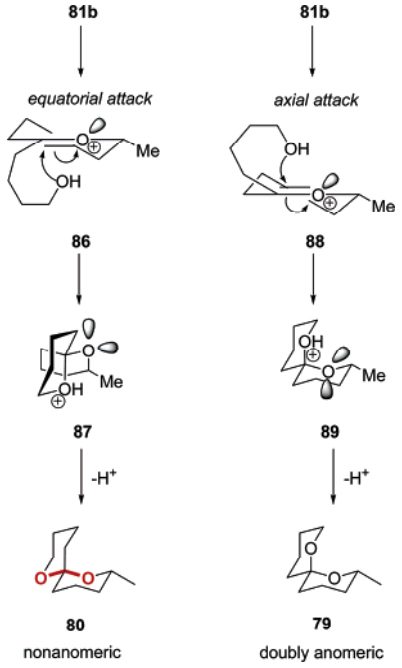
Scheme 17. Axial and Equatorial Attacks on the Oxocarbenium Ion Intermediate 81a with a Pseudoaxial Methyl Group[5b]



attack in conformation **81a** would lead to the doubly anomeric spiroketal **79** through a boatlike intermediate **83**, whereas axial attack would lead to the less stable nonanomeric product **80** through a chairlike intermediate **85** (Scheme 17). With oxocarbenium ion conformation **81b**, equatorial attack would form the nonanomeric product **80** through a boatlike intermediate **87**. Similarly, axial attack would lead to doubly anomeric product **79** through a chairlike intermediate **89** (Scheme 18).

When a late transition state is assumed only doubly anomeric product **79** would form through process **88** → **89** (Scheme 18) since the chairlike intermediates are energetically more favored than the boatlike intermediates. Furthermore, the process **84** → **85** (Scheme 17), which would lead to the nonanomeric product **80** through a chairlike intermediate, suffers from severe steric interactions be-

Scheme 18. Axial and Equatorial Attacks on the Oxocarbenium Ion Intermediate 81b with a Pseudoequatorial Methyl Group[5b]

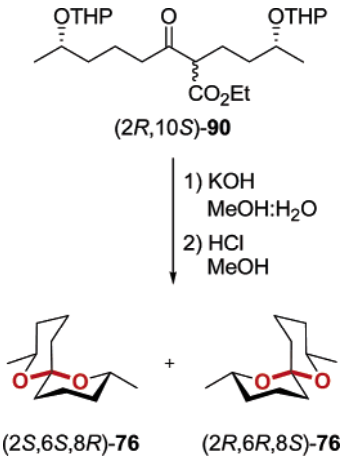


tween the pseudoaxial methyl group and the attacking hydroxyl group.

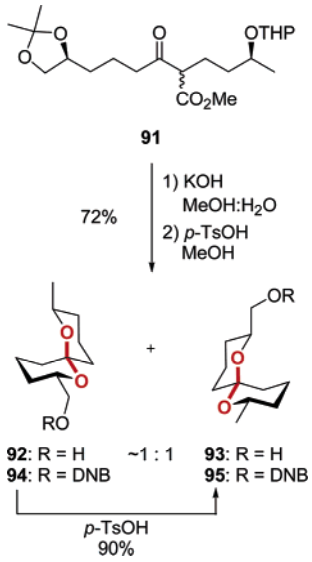
However, the fact that the nonanomeric product is also formed in significant quantities must mean that a late transition state cannot be operating. Deslongchamps and co-workers explain this by proposing an early transition state where formation of the C−O bond is not sufficiently advanced to generate significant energy differences between the equatorial and axial attacks. They further propose that the cyclization would only take place via oxocarbenium ion conformation **81b** (Scheme 18) and that the transition state is closer to **86** and **88** than **87** and **89**. In this scenario the preference for axial attack would be relatively small, perhaps enough to explain the slight bias toward the doubly anomeric product **80**.

In connection with their studies on the pheromones of Andrena species, Mori and co-workers synthesized racemic spiroketal **76**. Starting from keto ester **90**, hydrolysis and decarboxylation followed by deprotection and spiroketalization afforded the nonanomeric spiroketals (2*S*, 6*S*, 8*R*)-**76** and (2*R*, 6*R*, 8*S*)-**76** (Scheme 19).[39a,b] They also developed an efficient synthetic route to the nonanomeric spiroketal system **93** by employing spiroketalization precursors **91** and slightly modified reaction conditions (Scheme 20).[39f] In this way a 1:1 mixture of nonanomeric spiroketal isomers **92** and **93** was formed in 72% yield. After converting spiroketals **92** and **93** into the corresponding 3,5-dinitrobenzoates **94** and **95**, isomerization with a catalytic amount of *p*-TsOH furnished crystalline **95** in 90% yield from **94**. Apparently the equatorial substituents of both rings suffice to stabilize the nonanomeric isomers; the corresponding fully anomeric isomer would suffer from 1,3-diaxial interactions as one of the substituents must be axial. A similar situation is encountered with the CD ring system of the spongistatins (see section 3.3.1)

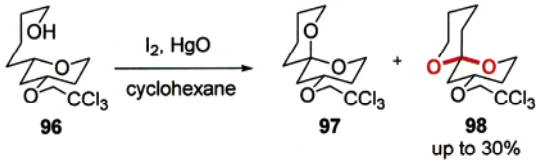
Scheme 19. Synthesis of Nonanomeric Spiroketals According to Mori et al.[39a,b]



Scheme 20. Synthesis of Nonanomeric Spiroketals According to Mori et al.[39f]



Scheme 21. Oxidative Cyclization in Spiroketal Synthesis According to Kay and Williams[42]



Kay and Williams performed some of the first studies into the possibility of synthesizing spiroketals via oxidative cyclization (Scheme 21).[42] Treatment of alcohol **96** with I_2−HgO first forms a hypoiodite intermediate, which then forms spiroketal **97** through a radical pathway along with variable amounts (up to 30%) of nonanomeric spiroketal **98**.

3.2. Polyketide Antibiotics with a Nonanomeric [6,6]-Spiroketal Structure

3.2.1. Spiroketal System of Spirofungin B

Spirofungins A and B are polyketide spiroketal-type antibiotics that were isolated as a ~4:1 mixture from the culture filtrate and extracts of *Streptomyces*

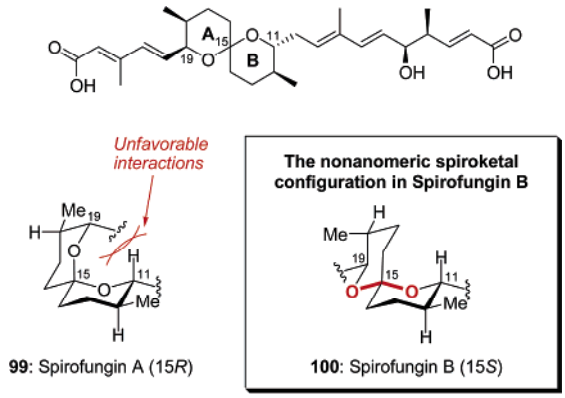
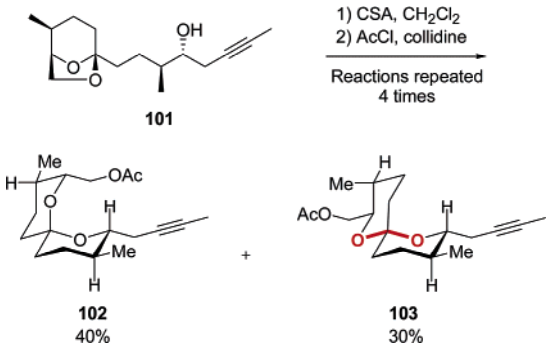


Figure 8. Spirofungins A and B.

violaceusniger Tü 4113 (Figure 8).[43] Initially it was proposed that the spiroketal core in both of the spirofungins A and B possessed doubly anomeric stabilization[44] until Rizzacasa and co-workers recently proposed that the spiroketal core of spirofungin B possessed one less anomeric relationship (Figure 8).[45] Further support for their proposal was found from the previous work published by Shimizu and co-workers in which a ~1.5:1 mixture of doubly anomeric spiroketal **102** and nonanomeric spiroketal **103** was formed under thermodynamic conditions (Scheme 22).[46]

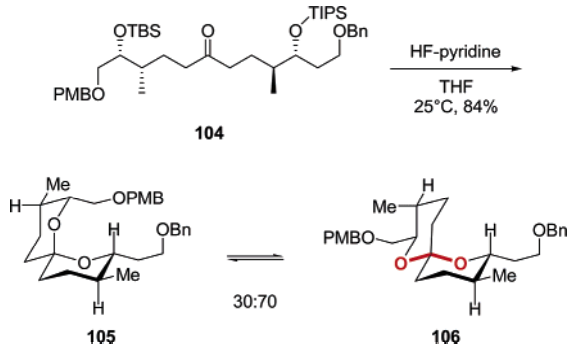
Scheme 22. Synthesis of the Spiroketal Segment of Spirofungins According to Shimizu et al.[46]



The instability of the doubly anomeric structure in spirofungin A is due to unfavorable steric interactions between the axial C_{19} side chain and the C_{11} axial hydrogen (Figure 8). This lowers the energy difference between the doubly anomeric and nonanomeric spiroketal systems, and consequently, the nonanomeric spiroketal is more favored in the thermodynamic equilibration.

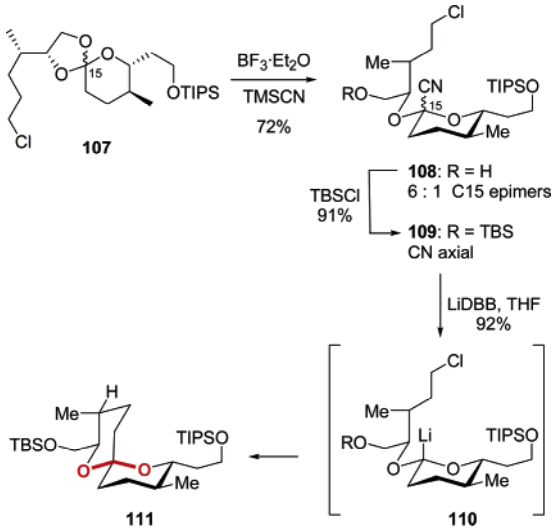
Dias and co-workers showed supporting evidence for the configuration of the epimeric C_{15} carbon in spirofungin B by developing an efficient synthetic method that gives access to both of the spirofungin spiroketals (Scheme 23).[47] Open-chain intermediate **104** was subjected to acid deprotection and concomitant spiroketalization by treatment with HF−pyridine to give a 30:70 mixture of spiroketals **105** and **106**. Most importantly, under these conditions the spiroketal **106**, with only one anomeric relationship, could be isolated as the major product. It was also observed that each isolated pure spiroketal led to the same 30:70 equilibrium mixture under very mild acidic conditions ($CDCl_3$).

Scheme 23. Synthesis of the Spiroketal Segment of Spirofungins A and B by Dias et al.[47]

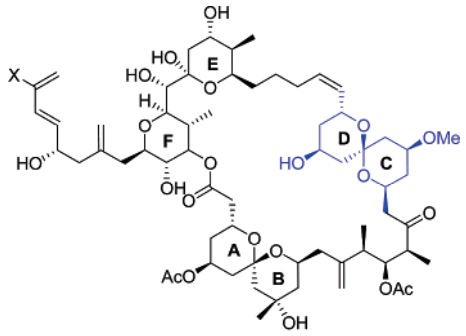


Rychnovsky and co-workers developed a method that constitutes a significant breakthrough in the synthesis of nonanomeric spiroketals.[36] By reversing the usual roles of the nucleophile and electrophile in spiroketal synthesis, the normal preference of the anomeric isomer is effectively suppressed. Upon treatment of the ortho-ester-derived cyanide **109** with lithium di-*tert*-butylbiphenylide (LiDBB), the resulting lithium species **110** retains its axial configuration (Scheme 24).[48] The resulting lithiated acetal can now

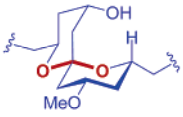
Scheme 24. Reductive Cyclization Approach to Nonanomeric Spiroketals Developed by Rychnovsky et al.[37]



act as a nucleophile, displacing the primary chloride and generating the spiroketal. Using this clever reductive cyclization protocol different kinds of nonanomeric spiroketals can be formed as single diastereomers. This approach was successfully utilized in the synthesis of the spiroketal segment in spirofungin B.[37] A mixture of cyano acetals **108**, epimeric at C_{15}, was synthesized from ortho ester **107** (Scheme 24). The major acetal having the cyano group axial was isolated, followed by TBS protection of the hydroxyl group to give **109** as a single diastereomer. The reductive cyclization protocol, proceeding via the axial lithium species **110**, gave the desired nonanomeric spiroketal **111** in 92% yield and most importantly as a single diastereomer. As could be expected on the grounds of the results published earlier by Dias and co-workers (Scheme 23), rapid formation of



	X
112: Spongistatin 1 = Altohyrtin A	Cl
113: Spongistatin 2 = Altohyrtin C	H
114: Altohyrtin B	Br



The nonanomeric configuration of the CD ring in spongistatins

Figure 9. Structures of the altohyrtins/spongistatins.

a 70:30 equilibrium mixture, favoring the nonanomeric structure **111**, was observed under mildly acidic conditions.

3.3. [6,6]-Spiroketals of Marine Origin

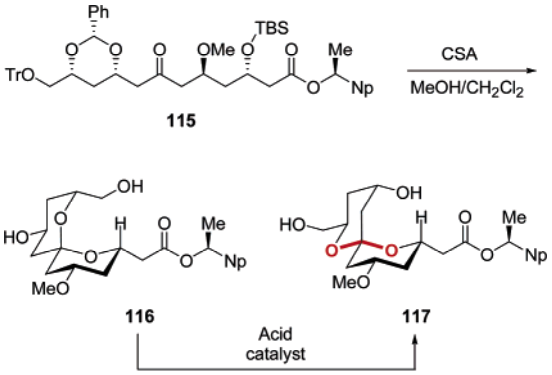
3.3.1. CD Ring System of the Altohyrtins/Spongistatins

In 1993 three research groups independently reported a new class of remarkably cytotoxic marine macrolides. The research led to the identification and structure determination of spongistatins 1−9,[49] cinachyrolide A,[50] altohyrtins A−C, and 5-desacetylaltohyrtin A[51] (Figure 9). The relative and absolute stereochemistries first deduced by Kitagawa and coworkers for the altohyrtins[52] were confirmed through the first total syntheses by Evans et al. (altohyrtin C)[53] and Kishi et al. (altohyrtin A).[54] These excellent syntheses confirmed the long-lasting suspicion that the spongistatins are indeed identical to the altohyrtins and cinachyrolides.

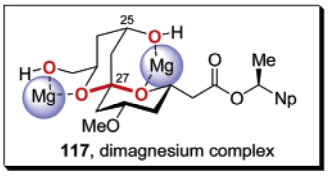
Structurally the spongistatins possess a striking array of diversity, including a 42-membered macrolactone incorporating two spiroketal moieties. A particularly interesting feature is the CD spiroketal unit possessing only one anomeric relationship (Figure 9). In the case of spongistatins it has been proposed that the nonanomeric configuration of the CD spiroketal unit is stabilized by intramolecular hydrogen bonding.[53a] In addition, conformational constraints imposed by the macrocyclic structure most likely favor the nonanomeric configuration.

Because of their exceptional biological activity and intriguing structural feature, seven different research groups have published a total synthesis of one or more of the spongistatins and many advanced synthetic approaches of different key substructures have been developed. In this section all the different approaches leading to the CD spiroketal segment of spongistatins are reviewed. In cases where a single group has published multiple approaches, the route that gives the best selectivity is discussed in more detail.

Scheme 25. Synthesis of the CD Spiroketal Segment of Spongistatin According to Evans et al.[55]



Entry	Acid	Solvent	Time	116:117
1	CSA	$MeOH/CH_2Cl_2$	24h	6:1
2	CSA	CH_2Cl_2	3h	1:1
3	$ZnBr_2$	CH_2Cl_2	1h	1:2.3
4	$Mg(O_2CCF_3)_2$	CH_2Cl_2	3h	1:2.6
5	$ZnCl_2$	CH_2Cl_2	3h	1:4.3



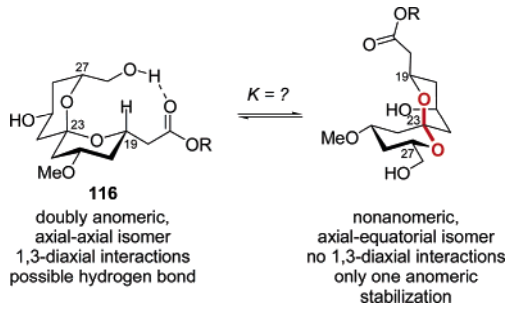
117, dimagnesium complex

Evans (1997). The first total synthesis of the spongistatins was published by Evans and co-workers.[53] In the CD spiroketal synthesis removal of the oxygen protecting groups and spontaneous spirocyclization of **115** furnished a 6:1 mixture of two isomeric spiroketals **116** and **117** (Scheme 25). Formation of the desired nonanomeric spiroketal **117** was accomplished by equilibration of the doubly anomeric spiroketal **116** using different Lewis acid catalysts. A series of conditions was explored to determine ways to control the equilibration (Scheme 25). It was postulated that an internal chelate is formed between the C_{25} hydroxyl group, the metal cation, and the C_{27} anomeric oxygen (**117**, dimagnesium complex), which then stabilizes the nonanomeric structure in the thermodynamic equilibration.[55]

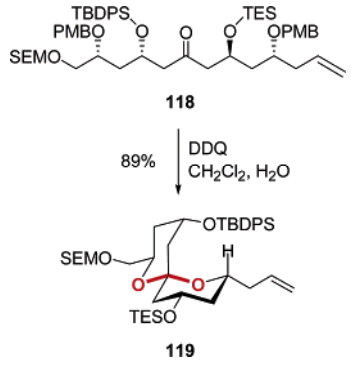
The structure of the undesired CD ring isomer **116** deserves further comment. As a result of unfavorable 1,3-diaxial interactions the preferred conformation of the double anomeric structure might be expected to be axial-equatorial with one less anomeric interaction (Scheme 26). The fact that these effects act in opposing directions may explain why different research groups have obtained the undesired isomer with a very similar structure as the nonanomeric conformer (see below).

Paquette (1997). Perhaps quite surprisingly, the Paquette group appears to have had no difficulties in synthesizing the nonanomeric CD spiroketal system. They report that their spirocyclization substrate

Scheme 26. Two Possible Conformers of the Undesired Isomer of the Spongistatin CD Ring System



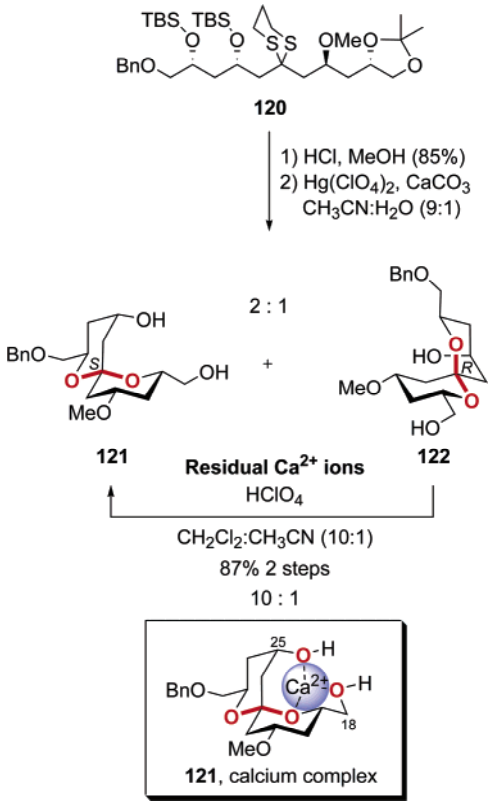
Scheme 27. Synthesis of the CD Spiroketal Segment of Spongistatin According to Paquette et al.[56]



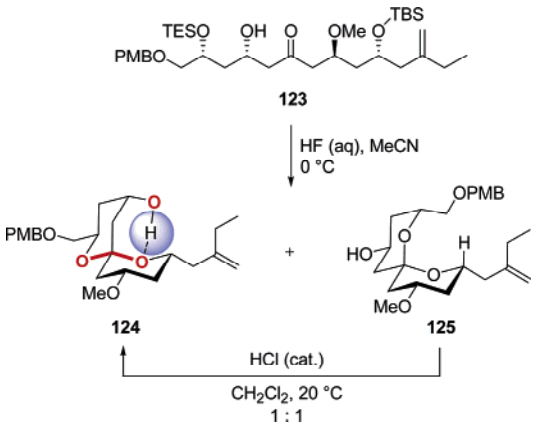
118 underwent an efficient PMB ether deprotection and spontaneous spirocyclization with DDQ to selectively yield the desired nonanomeric spiroketal **119** in 89% yield (Scheme 27).[56] Given the mildness of the conditions employed it is possible that this spirocyclization proceeded under kinetic control. The hydroquinone derived from DDQ might be acting as a mild acid promoter of the spiroketalization in this case.

Smith (1997). Many attempts to synthesize the nonanomeric spiroketal structure of the spongistatins have been inspired by the fact that the configuration is stabilized by intramolecular hydrogen bonding. The Smith group applied this idea by taking advantage of an internal metal chelate in the total syntheses of spongistatins 1 and 2.[57] They observed that Ca^{2+} ions can control an acid-catalyzed epimerization of the doubly anomeric spiroketal to the desired nonanomeric spiroketal. The critical spirocyclization step is presented in Scheme 28. After removing the TBS and acetonide protecting groups from the dithiane adduct **120**, calcium metal-assisted spirocyclization gave a 2:1 mixture of spiroketals **121** and **122**.[57a] They both proved to possess the nonanomeric configuration, and spiroketal **121** had the correct *S* conformation. Most importantly, treatment of this mixture with perchloric acid prior to purification furnished only the desired spiroketal **121**. It was demonstrated that the residual Ca^{2+} ions in the unpurified mixture stabilized the desired spiroketal, which was considered to result from coordination of the Ca^{2+} ion with the hydroxyl groups at C_{18} and C_{25} as well as the C-ring oxygen (**121**, calcium complex, Scheme 28). The use of Ca^{2+} ions proved to be

Scheme 28. Ca^{2+}-Controlled Spirocyclization in the Spongistatin CD Spiroketal Synthesis According to Smith et al.[57a]



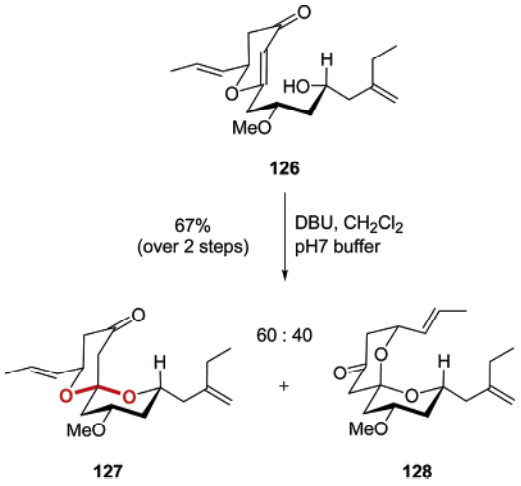
Scheme 29. Synthesis of the CD Spiroketal Segment of Spongistatin According to Paterson et al.[59a]



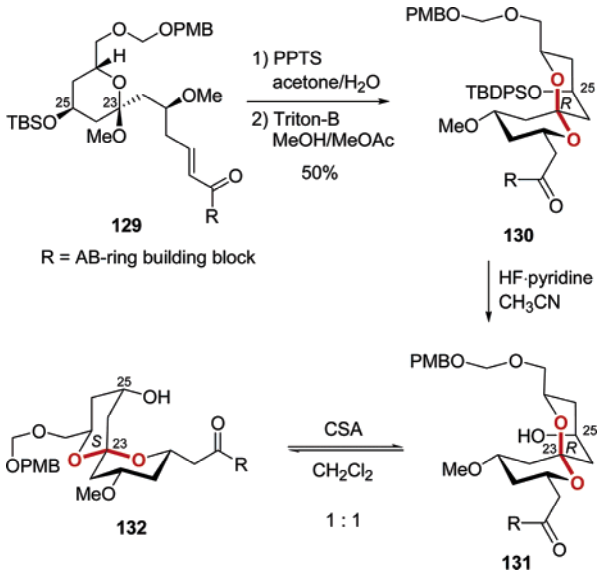
important in the later stages of the synthesis as well. Unfortunately, epimerization of the CD spiroketal occurred under acidic conditions, and the stereochemistry could be corrected by using the preceding Ca^{2+}/perchloric acid equilibration protocol. Interestingly, in this instance the undesired CD ring isomer **122** was in the nonanomeric conformation.

Paterson (1997). The Paterson group also achieved successful total syntheses of spongistatins 1 and 2.[58] Thermodynamic equilibration, assisted by intramolecular hydrogen bonding, was used to obtain the desired CD spiroketal configuration (Scheme 29).[59] Treatment of open-chain ketone precursor **123** with aqueous hydrofluoric acid in acetonitrile led to desilylation and concomitant spirocyclization to give an

Scheme 30. Hetero-Michael Approach in the Synthesis of the CD Spiroketal Segment of Spongistatin According to Paterson et al.[59a]



Scheme 31. Synthesis of the CD Spiroketal Segment of Spongistatin According to Kishi et al.[54a]

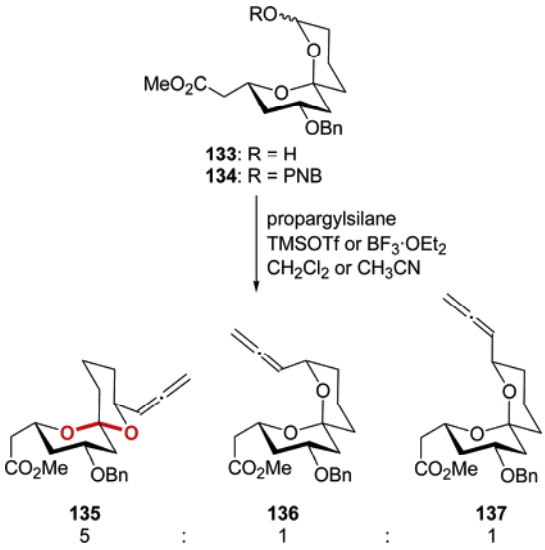


equimolar mixture of spiroketals **124** and **125**. The undesired anomeric isomer **125** could be isolated and reequilibrated to give more of the desired nonanomeric spiroketal **124**.

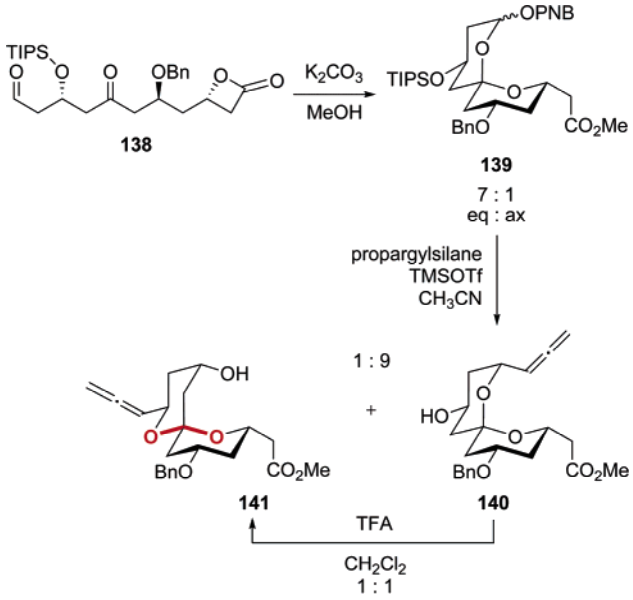
The Paterson group also investigated a complementary strategy for construction of the CD spiroketal subunit in spongistatin.[59a] In contrast to their previous synthesis in which thermodynamic control was employed, the second synthesis is believed to be under kinetic control. The strategy was to form the C ring after the D ring using a hetero-Michael cyclization[60] in which an axial attack would favor the desired nonanomeric structure (Scheme 30). After successful isolation of alcohol intermediate **126**, base-induced hetero-Michael reaction gave the desired nonanomeric spiroketal **127** as the major product.[59a]

Kishi (1998). The strategy employed by Kishi and co-workers in the second total synthesis of spongistatins is distinguished by its unique order of events.[54] Instead of directly synthesizing the CD spiroketal structure from an acyclic precursor, the rings were

Scheme 32. Spirolactol Alkylation Model Studies According to Mead et al.[62]



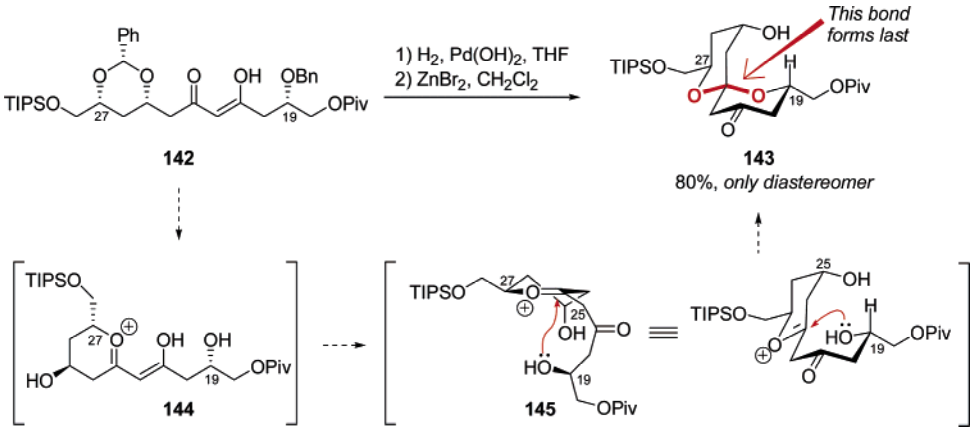
Scheme 33. Spirolactol Alkylation Approach in the Synthesis of the CD Spiroketal Segment of Spongistatin According to Mead et al.[63]



formed consecutively, starting with the D ring. More importantly, the final acid-catalyzed spiroketalization was performed only after the CD and the AB spiroketal building blocks were in place (Scheme 31). However, they also faced difficulties in constructing the nonanomeric spirocenter. After hydrolysis of **129** to the corresponding C_{23} hemiketal, an intramolecular Michael cyclization furnished spiroketal **130**, which had the undesired *R* conformation. In light of work by Heathcock[61] it was assumed that after deprotection of the C_{25} alcohol functionality acid-catalyzed epimerization would provide an equilibrium mixture of the two C_{23} diastereomers. This was indeed the case, and a separable 1:1 mixture of the desired nonanomeric spiroketal **132** and the undesired C_{23} epimer **131** was formed under acidic conditions.

Mead (1998). The Mead group had an original synthetic plan for the synthesis of the CD spiroketal segment of spongistatin that was based on their

Scheme 34. Synthesis of the CD Spiroketal Segment of Spongistatin According to Heathcock et al.[65b]

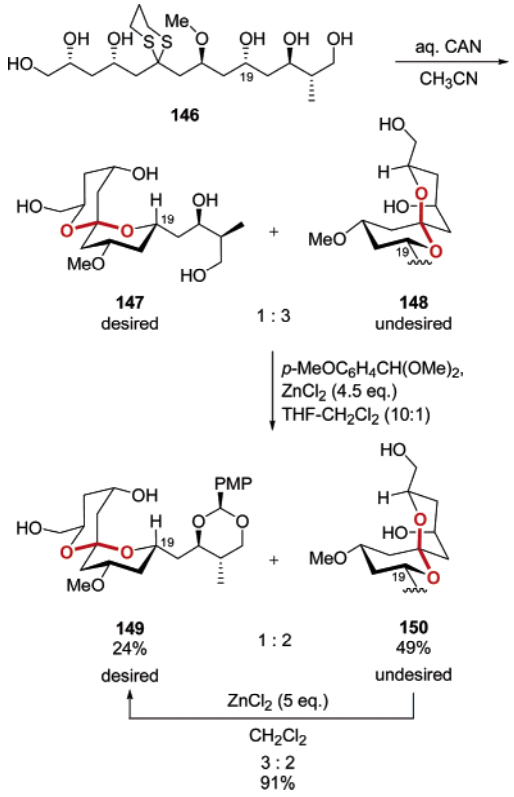


excellent results with a series of model structures. When spirolactols **133** and **134** were alkylated with allyltrimethylsilane in the presence of either TMSOTf or $BF_3{\cdot}OEt_2$, a mixture of nonanomeric spiroketal **135** and doubly anomeric spiroketals **136** and **137** was formed in a ratio 5:1:1 (Scheme 32).[62] Unfortunately, when the corresponding reactions were tested with spirolactol **139**, a precursor of the spongistatin CD ring system, the desired nonanomeric spiroketal **141** was either completely absent or isolated only as the minor product of the reaction (Scheme 33).[63] As for many others before them, they had to turn to the recycling and reequilibration protocol in order to obtain the nonanomeric configuration. TFA conditions developed by Heathcock[61] were utilized to furnish a 1:1 mixture of spiroketals **140** and **141**.

Heathcock (1999). The Heathcock group developed a highly convergent synthetic route to spongistatin 2[64] and an excellent synthesis for the CD spiroketal segment. Already in the first-generation synthesis, published in 1997, the desired nonanomeric spiroketal was favored in a ratio of a 5:1.[61] Subsequent screening of different acid promoters for the spiroketalization reaction revealed that the weak Lewis acid $ZnBr_2$ was a superior reagent.[65] The $ZnBr_2$ protocol afforded the desired nonanomeric spiroketal **143** in greater than 80% yield as the only observed diastereomer (Scheme 34).[65b] A possible reason for the excellent stereoselectivity could lie in the chelation of zinc to the product, a rationalization first suggested by Evans.[55] The authors suggest an alternative explanation where the kinetic preference is a result of basic stereoelectronic effects, causing the C_{19} hydroxyl group to add axially, trans to the C_{27} substituent (**144**, **145**). Since this is the last bond to be formed, this locks the spiroketal system into the desired nonanomeric configuration.[65] In addition, the illustrated mode of attack allows the OH group at C_{25} to take its preferred pseudoaxial position (Scheme 34).[66]

Nakata (2000). Nakata and co-workers also had to rely on equilibration techniques in their synthesis of the CD spiroketal moiety of spongistatin. Removal of the dithioacetalization of **146** with ammonium cerium(IV) nitrate gave, with concomitant spiroketalization, a 1:3 mixture of spiroketals **147** and **148** (Scheme 35).[67] Both possessed the nonanomeric configuration, but only spiroketal **147** corresponded to

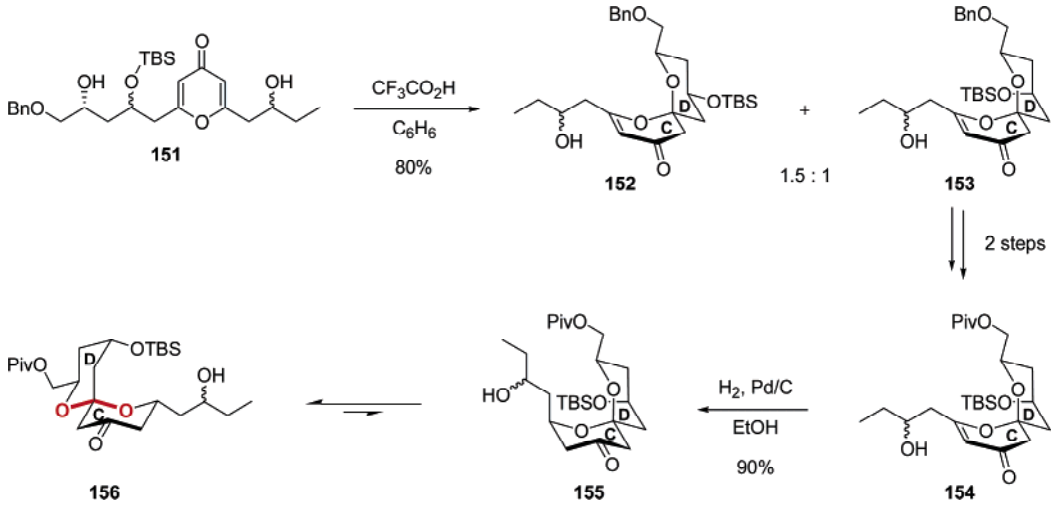
Scheme 35. Synthesis of the CD Spiroketal Segment of Spongistatin According to Nakata et al.[67a]



the natural product. Because the following *p*-methoxybenzylidenation step partially isomerized the anomeric center, the equilibration was left to the final stage. Equilibration of the undesired PMB-protected spiroketal **150** using $ZnCl_2$[55a] furnished a 3:2 mixture of the spiroketals **149** and **150** in 91% combined yield.

Crimmins (2000). One of the most recently published total synthesis of spongistatin 1 is that of Crimmins and co-workers.[68] To avoid the impending selectivity complications with thermodynamic control, the Crimmins group employed a highly elegant approach. Their strategy was to form the desired configuration under kinetic control using a stereoselective hydrogenation of an unsaturated spiroketal as the key step. Exposure of the pyrone adduct mixture **151** to catalytic trifluoroacetic acid afforded a 1.5:1 mixture of spiroenones **152** and **153** in greater

Scheme 36. Stereoselective Hydrogenation Strategy in the Synthesis of the CD Spiroketal Segment of Spongistatin According to Crimmins et al.[68a]

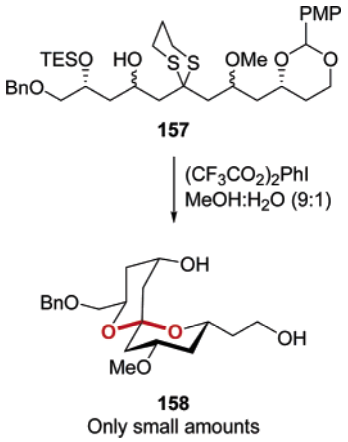


than 80% yield after recycling (Scheme 36).[68a] These two spiroenones could be readily separated by flash chromatography. The benzyl protection of **153** was cleaved, and the resulting primary alcohol group was selectively protected as a pivalate. In the crucial hydrogenation step of the unsaturated spiroketal **154** the hydrogen added only from the convex face, causing the diaxially substituted C ring (**155**) to undergo ring inversion, forming the desired nonanomeric spiroketal **156** in excellent 90% yield. The desired nonanomeric spiroketal could also be formed from the equatorial spiroenone isomer **152** through a slightly different reaction sequence.

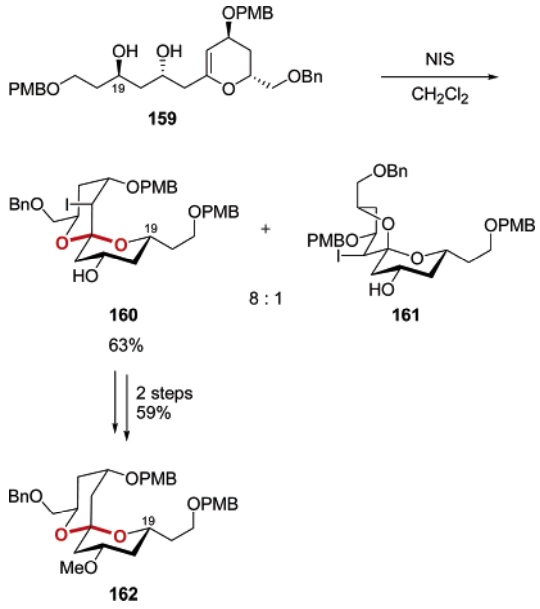
Kitching (2001). The Kitching group reported a synthetic approach to the CD spiroketal system of spongistatin.[69] Spiroketalization precursor **157** was treated with Stork's reagent to furnish a mixture of eight spiroketal diastereomers, which could be separated by reverse-phase HPLC (Scheme 37). However, only very small amounts of the desired spiroketal **158**, containing the stereochemistry of the spongistatin CD spiroketal system, could be isolated from this mixture. It should be noted that in this synthesis only nonanomeric spiroketal isomers were formed.

Roush (2002). The Roush group was also on a quest to avoid the thermodynamic equilibration.[70]

Scheme 37. Synthesis of the CD Spiroketal Segment of Spongistatin According to Kitching et al.[69]



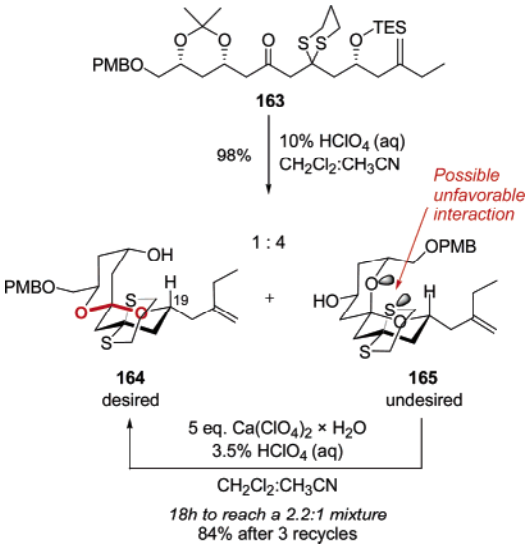
Scheme 38. Intramolecular Iodo−Spiroketalization Approach in the Synthesis of the CD Spiroketal Segment of Spongistatin According to Roush et al.[70]



The desired nonanomeric configuration was obtained with good stereochemical control using a kinetically controlled intramolecular iodo−spiroketalization as the key step. The spirocyclization substrate, glycal **159**, was activated with *N*-iodosuccinimide followed by axial attack of the C_{19} hydroxyl group to provide the desired nonanomeric spiroketal **160** in 63% isolated yield (Scheme 38). Formation of the fully elaborated CD spiroketal structure **162** was accomplished from **160** in 59% yield over two steps.

Ley (2003, 2005). Ley and co-workers used the calcium-mediated epimerization protocol adapted from Smith et al.[57] to synthesize the CD spiroketal segment of spongistatin. Treatment of ketone precursor **163** with perchloric acid furnished spiroketals **164** and **165** as a 1:4 mixture in favor of the undesired doubly anomeric isomer **165** (Scheme 39).[71] Following the Smith protocol the desired nonanomeric spiroketal **164** was formed from **165** in 84% yield after three

Scheme 39. Ca^{2+}-Controlled Spirocyclization in the Synthesis of the CD Spiroketal Segment of Spongistatin According to Ley et al.[71]



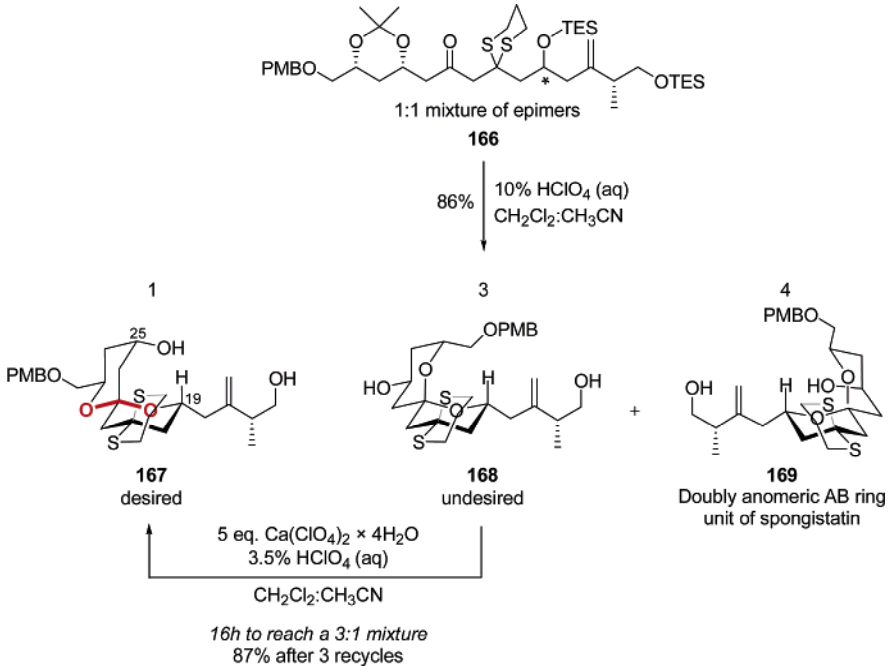
recycles. The dithiane moiety in the spiroketalization precursor appeared to slow the equilibration between the spiroketal isomers. Another interesting observation was that in the Smith synthesis the presence of a C_{17} or C_{18} hydroxyl group was mandatory to give sufficient chelation control (Scheme 28); however, in compound **165** the dithiane moiety enabled equilibrium to occur successfully without a hydroxyl group, possibly due to increased steric hindrance (Scheme 39).

Recently, Ley and co-workers reported a second-generation synthesis for the CD spiroketal segment along with a completion of the total synthesis of spongistatin 1.[72] To decrease the number of steps required to assemble the ABCD ring system of spongistatin, the idea was to access the CD and AB ring systems in the same reaction using an epimeric mixture of the acyclic spiroketalization precursor **166** (Scheme 40). Under the same conditions used previously,[71] a mixture of the desired nonanomeric CD spiroketal **167** and its doubly anomeric isomer **168** along with the doubly anomeric spiroketal **169** (corresponding to the AB spiroketal unit of spongistatin) was obtained in a ratio of 1:3:4. The spiroketal isomers could be separated by preparative HPLC, and the undesired doubly anomeric CD ring system **168** could be converted into the desired nonanomeric spiroketal **167** using the calcium perchlorate epimerization conditions. The authors suggest that the increased proportion of the desired spiroketal isomer after equilibration compared to the earlier CD ring synthesis (3:1 vs 2.2:1, Scheme 39) may be due to the presence of the primary hydroxyl group in the C_{19} side chain. This hydroxyl group may participate in a chelate between the Ca^{2+} ion and the hydroxyl group at C_{25} (see Scheme 29), influencing the stereochemical outcome.

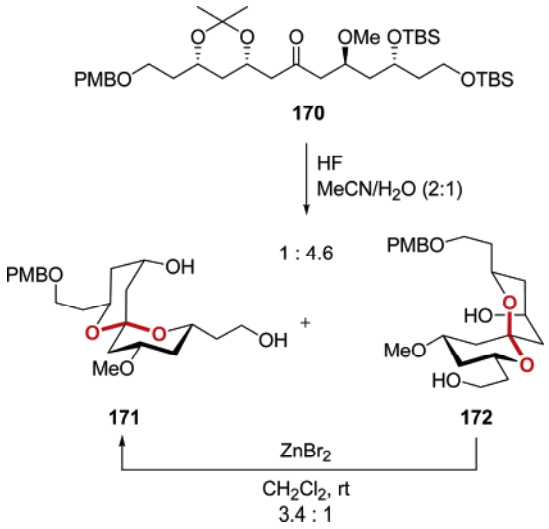
Lau (2004). Lau and co-workers published a synthesis for the CD spiroketal segment of spongistatin where the strategy was simply to utilize Lewis acid catalysis in the equilibration (Scheme 41).[73] Open-chained ketone precursor **170** underwent cyclization when treated with hydrofluoric acid to furnish a mixture of spiroketal isomers **171** and **172** in a ratio of 1:4.6. Upon further treatment with $ZnBr_2$, a reversed ratio of 3.4:1 was achieved, favoring the desired spiroketal **171**.

In summary, the nonanomeric configuration of the CD spiroketal segment of the spongistatins proved to be one of the most challenging struggles in the total syntheses and synthetic approaches for these molecules. Perhaps not surprisingly, very similar strategies and building blocks were used for most of the syntheses. Most research groups relied on ther-

Scheme 40. Second-Generation Synthesis for the CD and AB Spiroketal Segments of Spongistatin According to Ley et al.[72a]



Scheme 41. Synthesis of the CD Spiroketal Segment of Spongistatin According to Lau et al.[73]



modynamic equilibration and recycling to afford reasonable amounts of the desired nonanomeric spiroketal product. In light of this, the exceptionally high selectivities obtained by the Paquette and Heathcock groups in their spiroketal cyclizations are worth mentioning. These may well be the result of kinetic control in the acid-catalyzed spiroketalization step. Equally elegantly, the acid-catalyzed spiroketalization was avoided altogether in the hetero-Michael approach developed by the Paterson group, the stereoselective hydrogenation strategy by the Crimmins group, and the iodo−spiroketalization strategy used by Roush and co-workers.

3.3.2. Spiroketal System of the Aplysiatoxin and Oscillatoxin Families

Aplysiatoxin, oscillatoxins, and their brominated variants are metabolites that have been isolated from the digestive gland of the sea hare *Stylocheilus longicauda*[74] and from a variety of blue-green algae belonging to the class Oscillatoriaceae[75] (Figures 10 and 11). The nonanomeric configuration of the spiroketal unit is due to the destabilizing 1,3-diaxial interactions between the C_4 and C_6 methyl groups that would occur in a doubly anomeric configuration (Scheme 42). Due to their interesting molecular structure, these natural products have been the target of a number of synthetic studies.

Kishi (1987). Kishi and co-workers published elegant total syntheses for aplysiatoxin **173** and debromoaplysiatoxin **174**.[76] Both the spiroketal and the macrocycle were formed at the penultimate step from an open-chain precursor **182** containing all the necessary stereocenters (Scheme 43). By utilizing the macrolactonization method developed earlier by Masamune and co-workers,[77] the desired structure **183**, bearing the correct nonanomeric spiroketal configuration, was formed in 60% yield.

Ireland (1988). Ireland and co-workers developed a synthetic entry to the 3-deoxyaplysiatoxin (**181**) scaffold.[78] The desired spiro configuration was obtained by an acid-catalyzed isomerization where the nonanomeric spiroketal was favored over the doubly

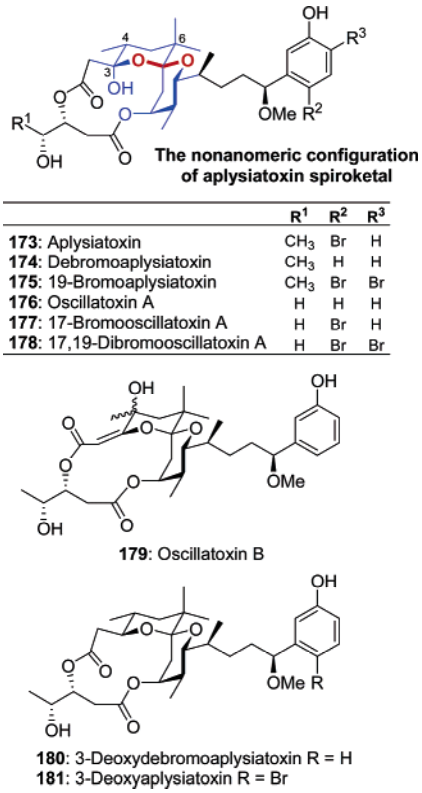


Figure 10. Structures of the aplysiatoxin/oscillatoxin families and their brominated variants.

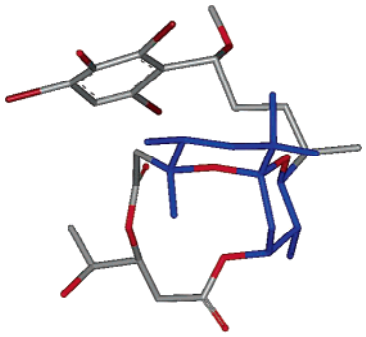
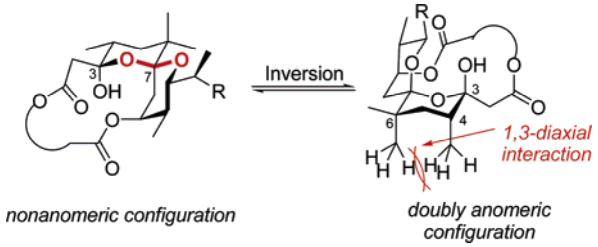


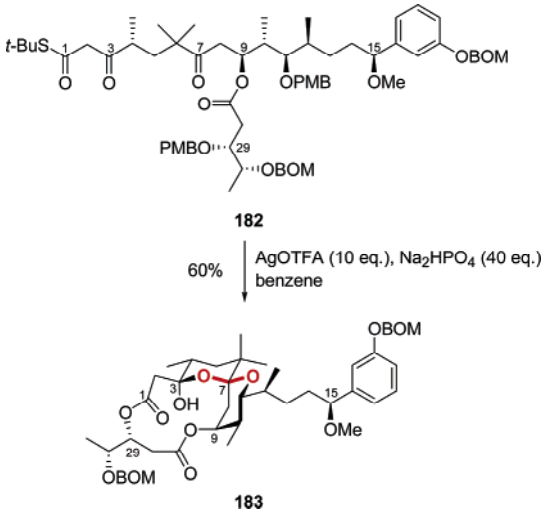
Figure 11. X-ray crystal structure of 19,21-dibromoaplysiatoxin (CCDC: FUBXIJ).[75c]

Scheme 42. Nonanomeric Configuration of the Aplysiatoxins and Its Inversion to the Doubly Anomeric Configuration



anomeric spiroketal because of steric strain. The hetero-Diels−Alder reaction between **184** and **185** afforded enol ether **186**, which underwent hydroboration and benzoate protection to furnish doubly anomeric spiroketal **187** (Scheme 44). Treatment of **187** with HCl formed a 70:30 equilibrium mixture of spiroketals **188** and **187**, in favor of the desired nonanomeric spiroketal **188**. This equilibration ratio was explained by considering individual stabilizing

Scheme 43. Synthesis of Debromoaplysiatoxin According to Kishi et al.[76]



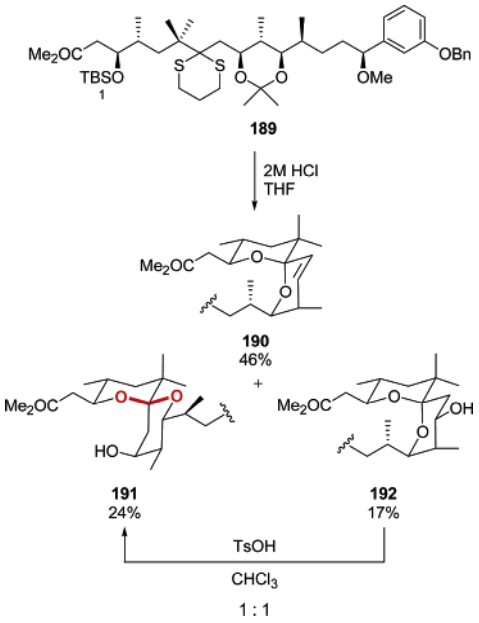
effects; while spiroketal **187** has two stabilizing anomeric relationships, other sterically destabilizing effects, for example, 1,3-diaxial interactions, render it slightly less stable than the nonanomeric configuration **188**.[79]

Yamamura (1989). Yamamura and co-workers developed a synthesis of 3-deoxydebromoaplysiatoxin **180**.[80] The desired nonanomeric configuration of the spiroketal unit was once again formed by repeating an acid-catalyzed equilibration reaction between the corresponding doubly anomeric and nonanomeric spiroketals. Ester **189** was used as the spiroketalization precursor, which under acidic conditions cyclized to form a mixture of spiroketals **190**−**192** (Scheme 45). Unfortunately, the dehydration product **190** was formed as the major product. Equilibration of the undesired doubly anomeric spiroketal **192** using TsOH furnished a separable 1:1 mixture of **192** and the desired nonanomeric spiroketal **191**.

3.4. Other Approaches to the Formation of Nonanomeric [6,6]-Spiroketals

Reveromycins A−D are a family of polyketide-type antibiotics isolated from the genus *Streptomyces*

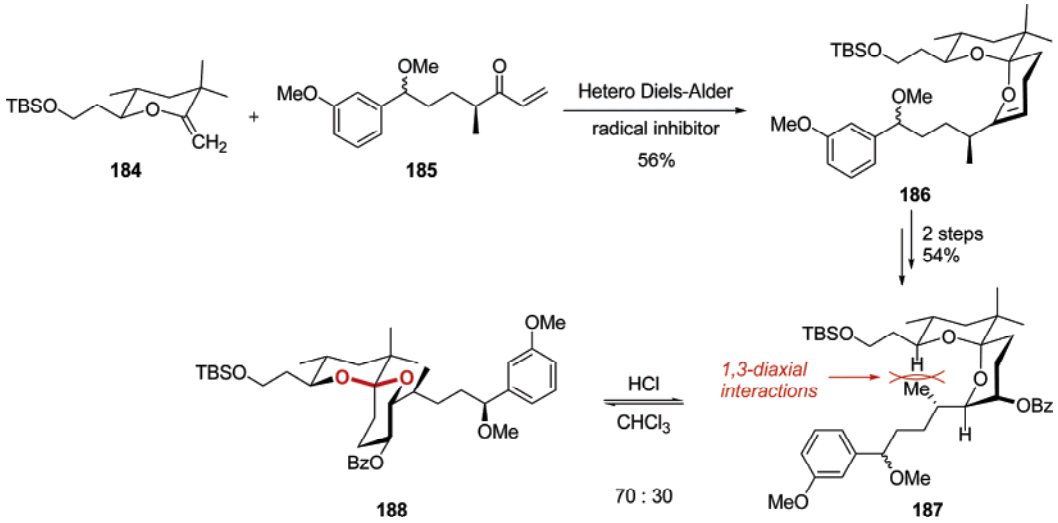
Scheme 45. Synthesis of the 3-Deoxydebromoaplysiatoxin Spiroketal System According to Yamamura et al.[80]



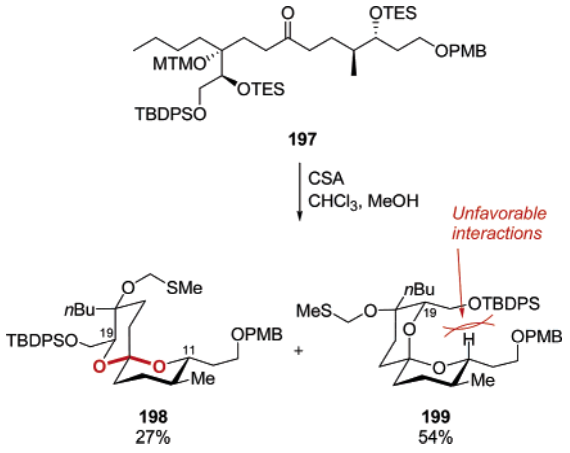
(Figure 12).[81] The spiroketal structures in reveromycins are not nonanomeric, but it has been discovered that the doubly anomeric [6,6]-spiroketal system can easily undergo acid-catalyzed isomerization into the nonanomeric [6,6]-spiroketal system. This isomerization is a consequence of the decreased energy difference between the spiroketal isomers, ultimately resulting from 1,3-diaxial interactions in the doubly anomeric AB ring system.

The inherent instability of the doubly anomeric structure has caused difficulties in many synthetic studies toward reveromycins. In the total synthesis of reveromycin A, Nakata and co-workers obtained a 1:2 mixture of the nonanomeric spiroketal **198** and the doubly anomeric spiroketal **199** (Scheme 46).[82] This result was actually expected based on MM2 calculations, predicting an energy difference of 0.44 kcal/mol between the corresponding spiroketals, corresponding to a 1:2.3 product ratio. In a similar vein, Theodorakis and co-workers obtained a mixture of

Scheme 44. Synthesis of the Deoxyaplysiatoxin Spiroketal System According to Ireland et al.[78]



Scheme 46. Synthesis of the Reveromycin Spiroketal System According to Nakata et al.[82]



nonanomeric and doubly anomeric spiroketals in a ratio of 1:1.5 using modified conditions and a different cyclization precursor.[83]

In the studies toward the synthesis of milbemycin (Figure 7), Williams and Barner reported an interesting *base-induced* isomerization of spiroketals.[84] Spiroketal **201**, bearing an axial hydroxymethyl substituent at C_2, undergoes isomerization with lithium hydroxide to give a 2:1 mixture of **201** and the nonanomeric spiroketal **202** (Scheme 47). The thermodynamically most stable spiroketal isomer **200**, with an equatorial hydroxymethyl substituent, does not undergo isomerization and neither of the spiroketal isomers **201** and **202** appear to interconvert to **200** under the reaction conditions. The authors propose that cleavage of either of the spiro bonds in **201**, followed by attack at the opposite face of the dihydropyrone intermediate (**203**), forms the nonanomeric structure. It is interesting to note that the second Paterson synthesis of the spongistatin CD ring spiroketal afforded a very similar product ratio starting from the pyrone intermediate (Scheme 30).

Kocienski and co-workers also studied the synthesis of the spiroketal unit of the milbemycin (Figure 7). They proposed that a dioxonium ion such as **207** acts as an intermediate in the formation of the natural double anomeric spiroketal of milbemycin

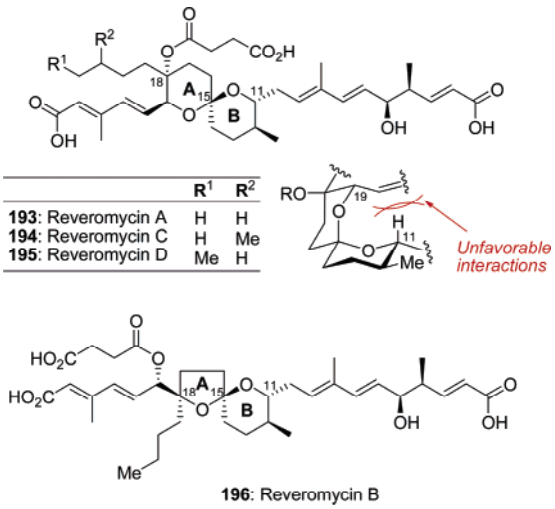
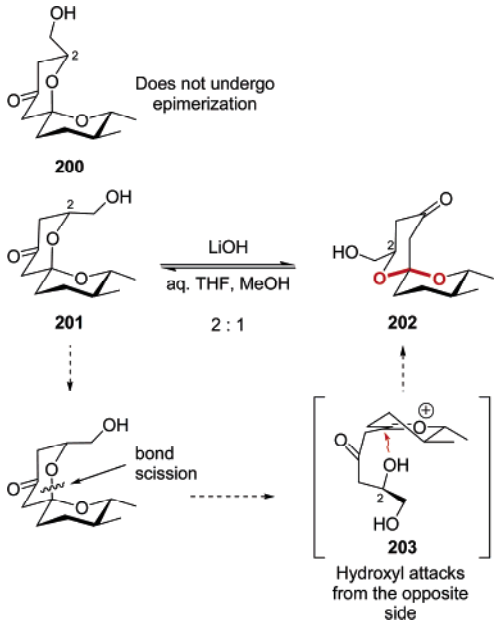
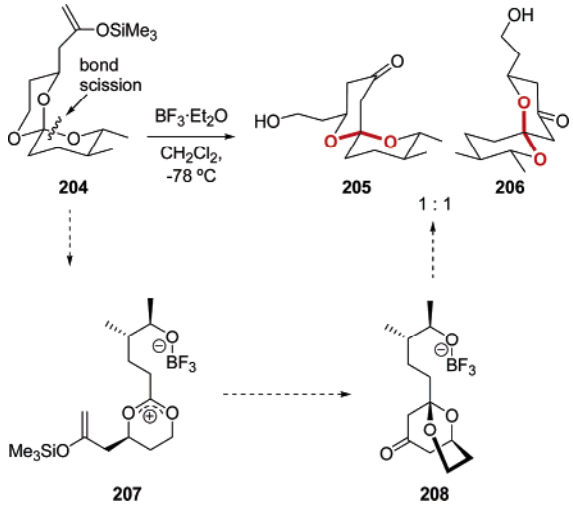


Figure 12. Structures of the reveromycins.

Scheme 47. Base-Induced Isomerization of Spiroketals According to Williams and Barner[84]



Scheme 48. Synthesis of Nonanomeric Spiroketals by Kocienski et al.[85]

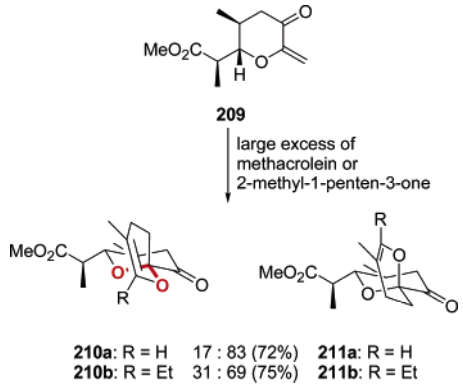


(Scheme 48).[85] To obtain further support for their proposal, they also performed studies which would lead to the nonanomeric product.[85] Using ortholactone **204** as a starting material in the intramolecular Mukaiyama reaction, a mixture of nonanomeric spiroketals **205** and **206** was formed in a ratio of ca. 1:1 (Scheme 48). The authors suggest that cleavage of the spiro bond forms a dioxonium ion **207**, which then cyclizes to give the bicyclic acetal intermediate **208** before equilibrating to give spiroketals **205** and **206**.

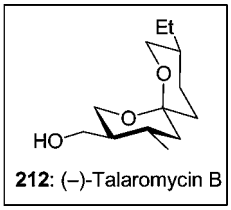
Ireland and co-workers also observed formation of an undesired nonanomeric spiroketal in their synthetic studies toward macrolide antibiotics.[86] A hetero-Diels–Alder reaction between keto–enol ether **209** and either 2-methyl-1-penten-3-one or methacrolein was used to form a mixture of spiroketal products that contained 17–31% of the nonanomeric spiroketal adducts **210a** and **210b** (Scheme 49).[86a]

Similar results were published later by Tietze,[87] who also used a hetero-Diels–Alder reaction to

Scheme 49. Formation of Nonanomeric Spiroketals in a Hetero-Diels–Alder Reaction According to Ireland et al.[86a]



synthesize (−)-talaromycin B, **212**. The cycloaddition between methyl *O*-benzoyldiformyl acetate **213** and vinyl ether **214** furnished a mixture of four spiroketal diastereomers **215**, **216**, **217**, and **218** in a ratio of 1.5:1:3:2. It should be noted that the products **215**–**218** are conformationally flexible[87] due to the presence of the double bond, and as a result, ring flipping readily interconverts the nonanomeric and anomeric conformers (Scheme 50).



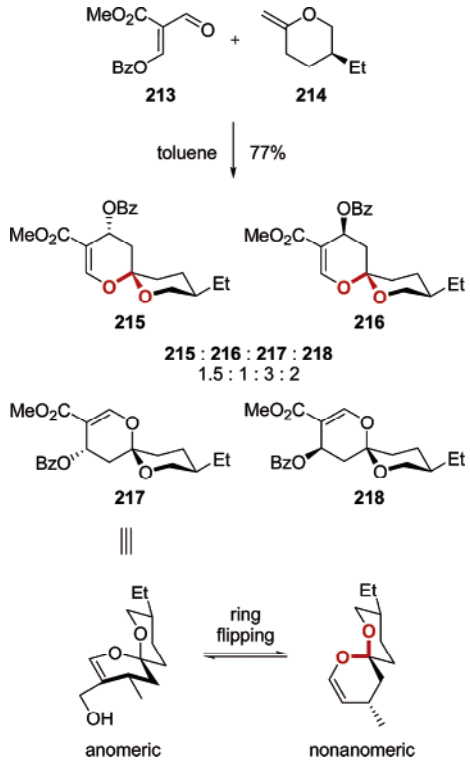
4. Tricyclic Spiroketal Systems

In recent years a number of compounds containing tricyclic spiroketal systems have been isolated from Nature. Like the simpler bicyclic spiroketal systems introduced in previous sections, these dispiroketals have also sparked interest in the synthetic community.[88]

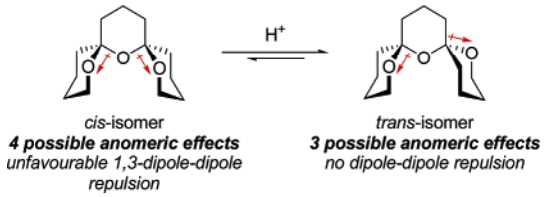
The thermodynamic stability of spiroketals is mainly influenced by three factors: anomeric effects, steric influences, and chelation effects including intramolecular hydrogen bonding. In the case of dispiroketals, an additional factor, dipole–dipole interactions, has to be taken into consideration when predicting stability (Scheme 51). One could easily assume that the cis-isomer, incorporating the maximum amount of anomeric stabilization, would be more stable than the corresponding trans-isomer, with a maximum of three anomeric effects. However, because of dipole–dipole repulsion between the two 1,3-diaxial oxygens, the cis-isomer is estimated to be 0.3–0.7 kcal/mol less stable.[3,89] The fact that the overall stability is a sum of all four factors has led to many interesting results in the syntheses of dispiroketal structures.

Tricyclic spiroketal systems that do not possess maximum anomeric stabilization are only found in the narasin–salinomycin class of natural products. In this section the structures and synthetic strategies toward nonanomeric tricyclic spiroketals, such as the narasin–salinomycin polyketides, pinnatoxins, and

Scheme 50. Formation of the Nonanomeric Spiroketal in Hetero-Diels–Alder Reaction According to the Tietze Group[87]



Scheme 51. Dipole–Dipole Repulsions Affect the Stability of Trioxaspiroketals



azaspiracids, are discussed. Some of the earlier syntheses of tricyclic spiroketals have been partially covered in previous reviews.[88,90] In the following discussion only the syntheses which result in the formation of the nonanomeric spiroketal isomers are discussed in detail to allow a full comparison of the strategies used for their synthesis.

4.1. Polyketide Antibiotics

4.1.1. Narasin–Salinomycin Class of Natural Products

Since the discovery of salinomycin in 1973[91] eight polyether antibiotics bearing the same trioxadispiroketal moiety have been found (Figure 13).[92,93] These narasin–salinomycin class antibiotics play an important role in the poultry industry and are used as feed additives to improve feed utilization in cattle, sheep, and goats.

None of the trioxadispiroketal structures of the narasin–salinomycin class of natural products have maximum anomeric stabilization. The four possible diastereomers of the ring system are illustrated in Figure 14.[94] When only anomeric effects are considered, the thermodynamically least stable structure would be 21-*epi*-salinomycin **B**, as it has only one

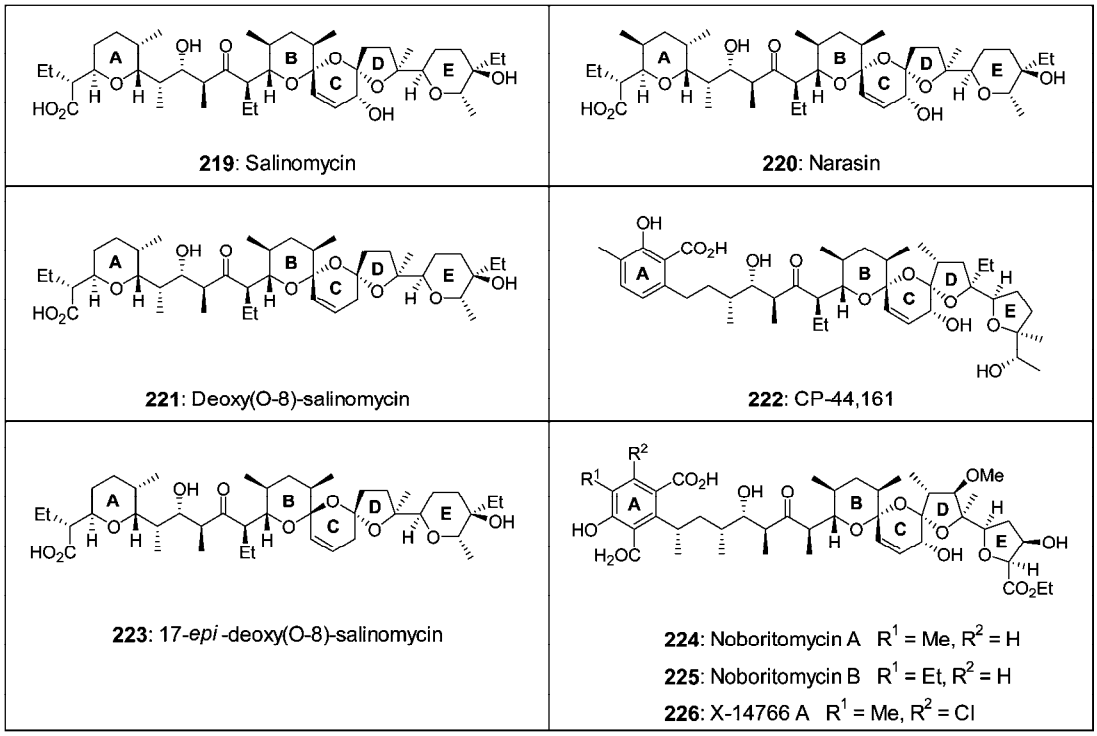


Figure 13. Structures of the narasin−salinomycin class of polyketide antibiotics.

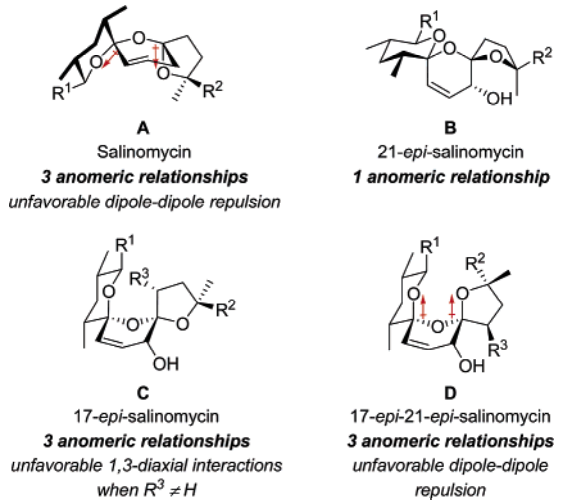


Figure 14. Four possible diastereomers of the salinomycin dispiroketal ring system.

anomeric stabilization whereas structures **A**, **C**, and **D** have three. The thermodynamically most stable structure must be 17-*epi*-salinomycin **C** because although it exhibits unfavorable 1,3-diaxial interactions (when R^3 = Me, antibiotics **222** and **224**−**226**), it does not suffer from the unfavorable 1,3-dipole−dipole repulsions like **A** and **D**. Diastereomer **A** depicts the stereochemistry adopted by natural salinomycin, and it has been suggested that the conformation is stabilized by long-distance hydrogen bonding between the ether oxygen (C_{20}) in the five-membered ring and the C_9 hydroxyl group (Figure 15).[95]

To date, three total syntheses of salinomycin have been reported independently by Kishi, Yonemitsu, and Kocienski. All of these groups had very elegant and original ideas, but in the end all of them had to assemble the correct dispiroketal configuration in a similar manner using thermodynamically controlled epimerization. In addition to the salinomycin spiroketal structure, also the other epimers of the ring system have drawn considerable attention.[88]

Kishi (1982). Kishi and co-workers were the first to report total syntheses of salinomycin and narasin.[95] After extensive research they observed that in the case of dispiroketal intermediates precursors bearing the 17-*epi*-configuration (**229**, R = H) are favored over those bearing the salinomycin configuration (**230**, R = H) upon acid equilibration (Scheme 52). When the natural products themselves were equilibrated, however, the natural salinomycin configuration **219** was favored over 17-*epi*-salinomycin **231**.

The last critical steps of the salinomycin synthesis by Kishi and co-workers are presented in Scheme 52. The dispiroketal **228**, with the 17-*epi*-configuration, was synthesized from acetylene intermediate **227** by reduction and subsequent acid-catalyzed intramolecular cyclization. A few modifications on the left-hand side chain and reprotection of the allylic hydroxyl group gave the dispiroketal **229**. Aldol coupling of **229** with the A ring fragment furnished, after desilylation, a single isomer of **231** corresponding to 17-*epi*-salinomycin. Fortunately, **231** could be equilibrated under acid catalysis to furnish a 7:1 mixture of dispiroketals **219** and **231**, favoring the natural configuration of salinomycin. The idea that the long-distance hydrogen bond stabilizes the natural configuration received further support from the result obtained by Kishi and co-workers since in the case of the structures where the C_{20} hydroxyl group was acetal protected (see tables in Scheme 52) the 17-*epi*-configuration was always favored over the natural configuration.

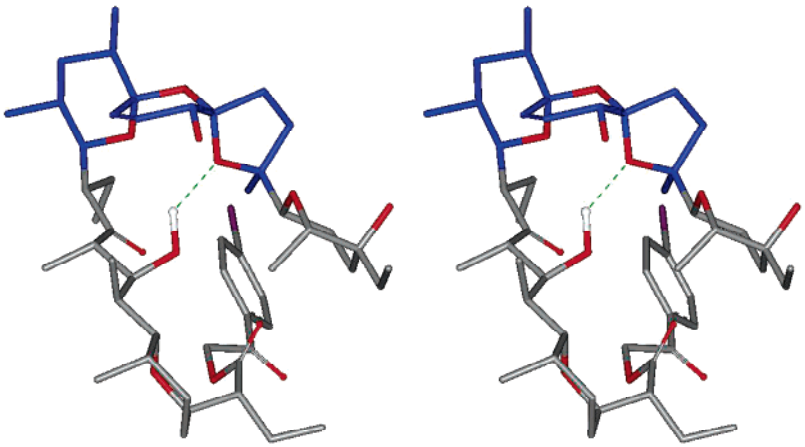
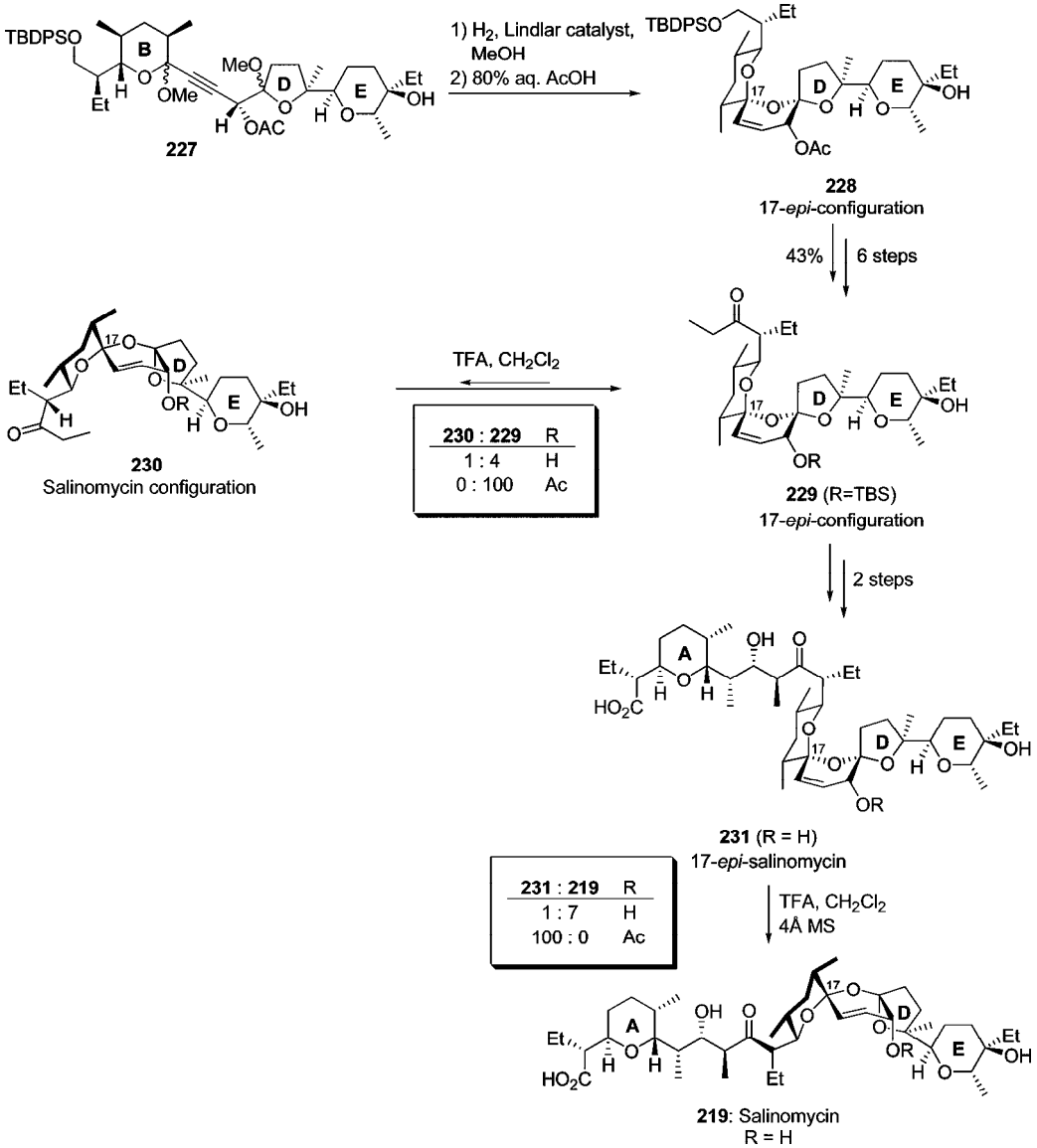


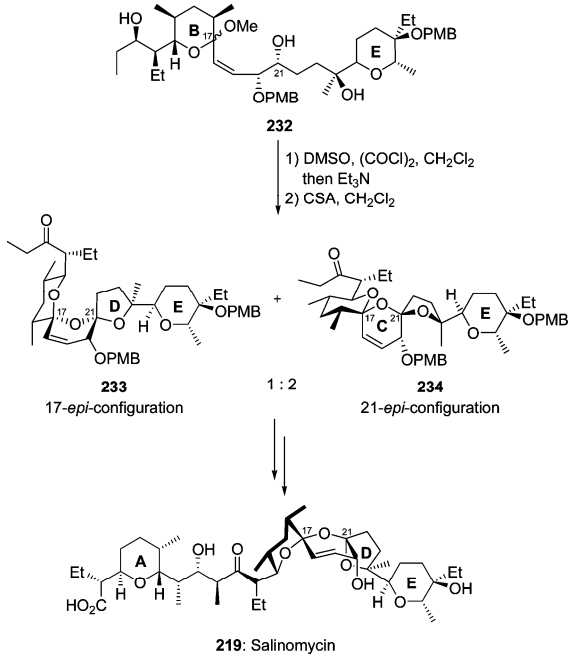
Figure 15. Stereoview of the X-ray crystal structure of salinomycin *p*-iodophenacyl ester (CCDC: IPMSAL10). The trioxadispiroketal system is shown in blue. The green dots identify the hydrogen bond between the C_9 hydroxyl and one of the spiroketal oxygens. [92c]

Scheme 52. Synthesis of Salinomycin According to Kishi et al.[95]



Yonemitsu (1987). The Yonemitsu group was the second to accomplish a total synthesis of salinomycin.[96] The desired spiro configuration was constructed in a manner similar to that used by Kishi et al.[96a−c] The Yonemitsu group also published a second-generation synthesis for salinomycin. In this synthesis the spirocyclization step was carried out with intermediate **232** in which the D ring had not yet

Scheme 53. Synthesis of Salinomycin According to Yonemitsu et al.[96e]

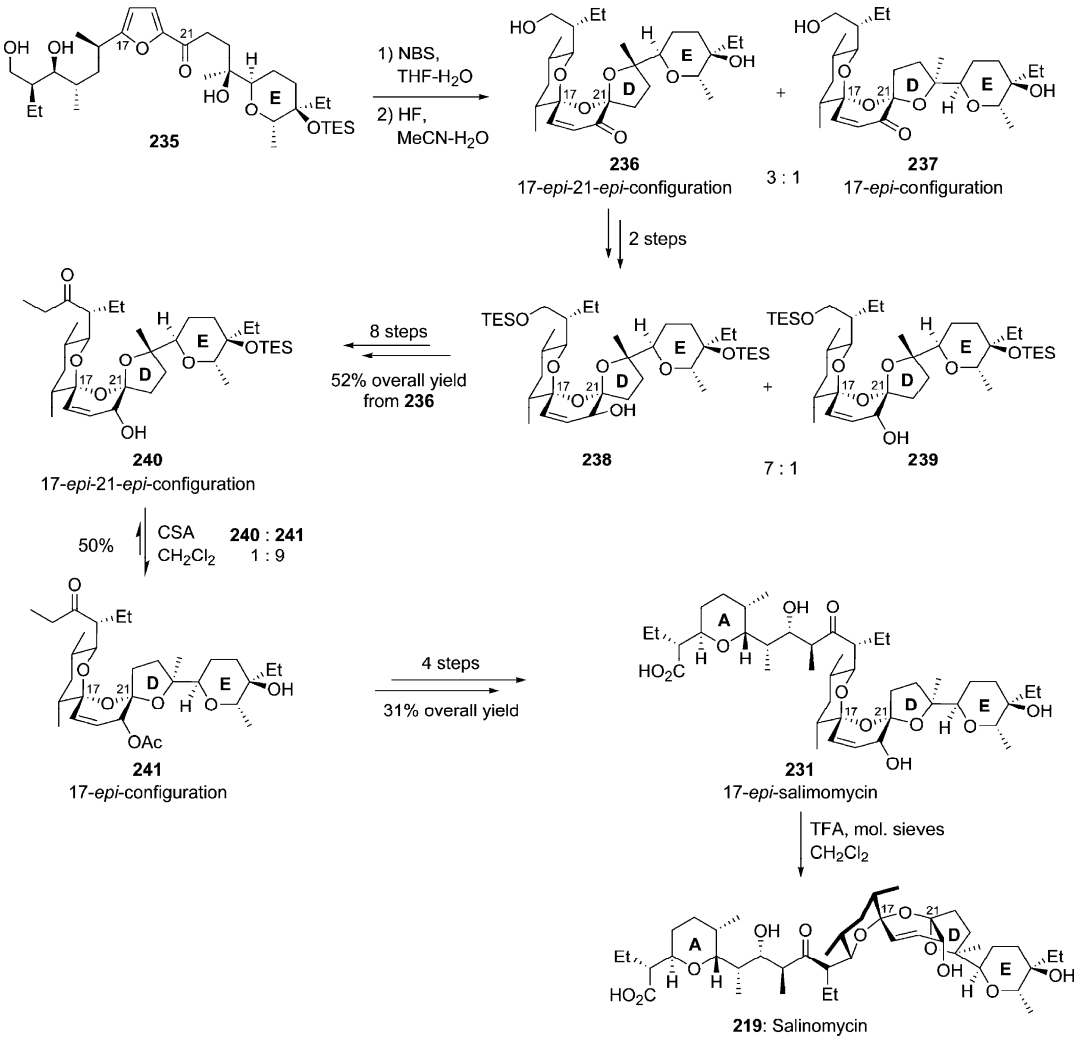


been constructed (Scheme 53).[97] Oxidation of the secondary hydroxyl group followed by treatment with CSA furnished a 1:2 mixture of 17-*epi*-structure **233** and 21-*epi*-structure **234**. This mixture could then be converted into salinomycin **219** after condensation with the left-hand side precursor by the method developed by Kishi et al.[95]

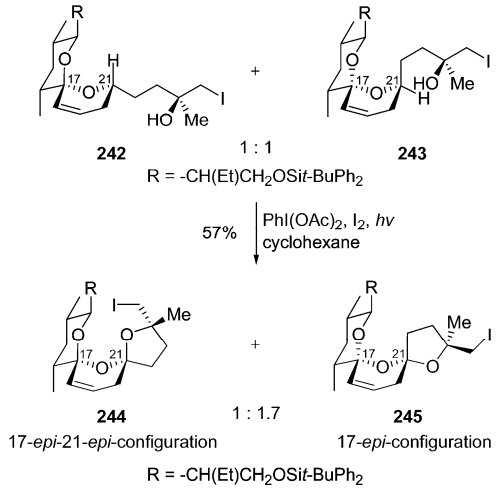
Brown and Kocienski (1994). The third total synthesis of salinomycin by Brown and Kocienski was a real test of endurance.[98] It seemed that every spiroketalization attempt led to formation of the 17-*epi*-21-*epi*-configuration, and worst of all, the attempts to rearrange the configuration all ended in decomposition. Ultimately, they resorted to the method used earlier by both Kishi and Yonemitsu. The essential steps of the eventually successful synthesis are described in Scheme 54.

One of the ways in which they obtained the dispiroketal moiety bearing the undesired 17-*epi*-21-*epi*-salinomycin configuration was by oxidative rearrangement of acylfuran **235** with *N*-bromosuccinimide[99] followed by treatment with hydrofluoric acid.[98c] In this way a 3:1 separable mixture of dispiroketal **236** and the corresponding C_{21} epimer **237** was formed. Since the 17-*epi*-structure **237** could not be accessed as the major product with any of the methods tried, it was decided that both of the incorrect stereocenters of the 17-*epi*-21-*epi*-structure **236** could be rearranged at a later stage of the

Scheme 54. Synthesis of Salinomycin According to Brown and Kocienski[98c]



Scheme 55. Synthesis of 17-*epi*- and 17-*epi*-21-*epi*-Salinomycin Dispiroketal Ring Systems According to Brimble et al.[100e]

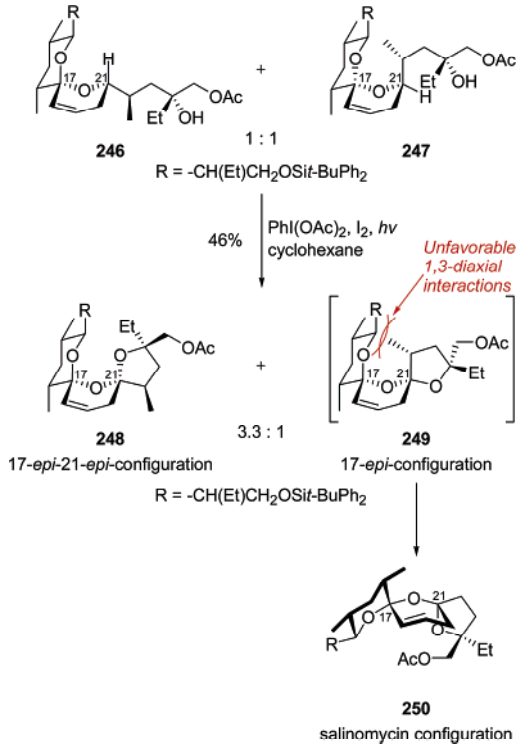


synthesis. Thus, the hydroxyl groups of **236** were protected as a triethylsilyl ether, and the allylic ketone was stereoselectively reduced to form a 7:1 mixture of allylic alcohols **238** and **239**. The authors encountered difficulty again at this stage since the major product had the incorrect stereochemistry at C_{20}. The following steps protected the newly formed C_{20} hydroxyl group, selectively deprotected the primary triethylsilyl ether, and formed the side chain ketone. After hydrolysis the major isomer, bearing the incorrect C_{20} stereochemistry, could then be converted to **240** by a Mitsunobu inversion. This dispiroketal structure now had the correct stereochemistry at C_{20} but still had the incorrect configuration at C_{17} and C_{21}. After the allylic alcohol was protected as an acetate, treatment with camphorsulfonic acid caused epimerization at C_{21} to give dispiroketal **241**, with incorrect stereochemistry only at C_{17}. Acetate protection of the allylic alcohol was changed to a TES ether, and the following aldol condensation with the left-hand side precursor furnished 17-*epi*-salinomycin **231**. After removal of the triethylsilyl protecting groups the crude product was immediately treated with trifluoroacetic acid to give salinomycin **219**.

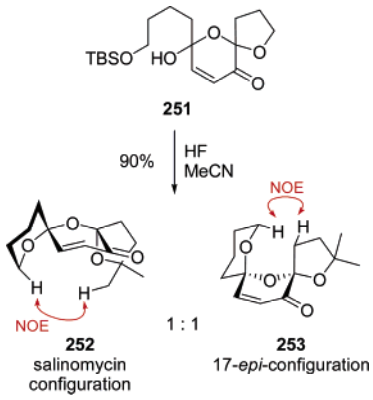
Brimble and Baker also studied the synthesis of the dispiroketal systems present in the salinomycin family of antibiotics.[100] Utilizing Suárez modification of the photochemical hypoiodite oxidation[101] Brimble and Baker obtained very nice results in the synthesis of different kinds of dispiroketal structures. This method was also used to synthesize dispiroketal systems that possess 17-*epi*-salinomycin, 17-*epi*-21-*epi*-salinomycin, and salinomycin (CP44,161) stereochemistries (Schemes 55 and 56). In studies toward the synthesis of the dispiroketal moiety in 17-*epi*-deoxy-(O-8)-salinomycin **223**, a 1:1.7 mixture of dispiroketals **244** and **245** was formed using a mixture of iodides **242** and **243** in the oxidative cyclization (Scheme 55).[100e]

In more recent studies toward the synthesis of the dispiroketal moiety in CP44,161 **222** the oxidative cyclization approach, using a mixture of acetates **246** and **247**, provided a reversed 3.3:1 ratio of the

Scheme 56. Synthesis of 17-*epi*-21-*epi*-Salinomycin and CP44,161 (salinomycin) Dispiroketal Ring Systems According to Brimble et al.[100j]



Scheme 57. Synthesis of Salinomycin and 17-*epi*-Salinomycin Dispiroketal Ring Systems According to Albizati and Perron[102]



corresponding dispiroketals **248** and **250** (Scheme 56).[100i,j] The authors suggest that the minor isomer **250**, which has the correct spiroketal stereochemistry for salinomycin and CP44,161, arises via the 17-*epi*-configuration **249**. The reversed ratio and formation of isomer **250** are a consequence of unfavorable 1,3-diaxial interactions imposed by an additional methyl group in the D ring.

Albizati and Perron also developed an approach to the salinomycin dispiroketal ring systems (Scheme 57).[102] Deprotection and spontaneous cyclization of lactol **251** afforded a 1:1 mixture of dispiroketals **252** and **253**, which possessed the salinomycin and the 17-*epi*-salinomycin configurations. It should be noted that the NOE data presented in the paper do not exclude the possibility that the products might also be the corresponding 17-*epi*-salinomycin and 17-*epi*-21-*epi*-salinomycin spiroketals.

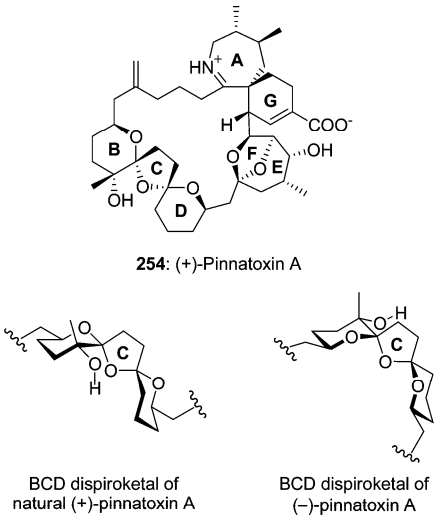


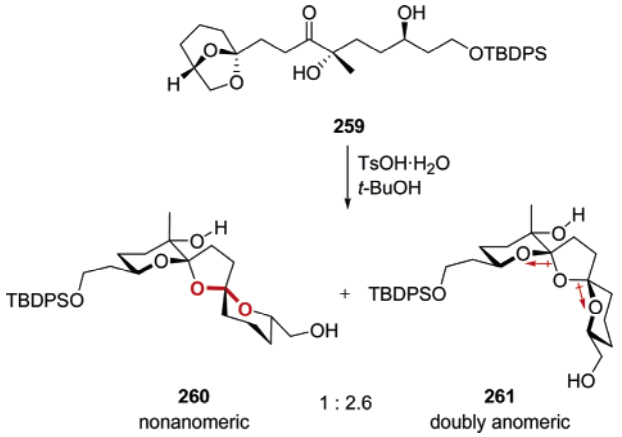
Figure 16. Pinnatoxin A and the BCD dispiroketal structures.

4.2. Tricyclic Spiroketals of Marine Origin

4.2.1. Pinnatoxins: Formation of the Undesired Nonanomeric Isomer

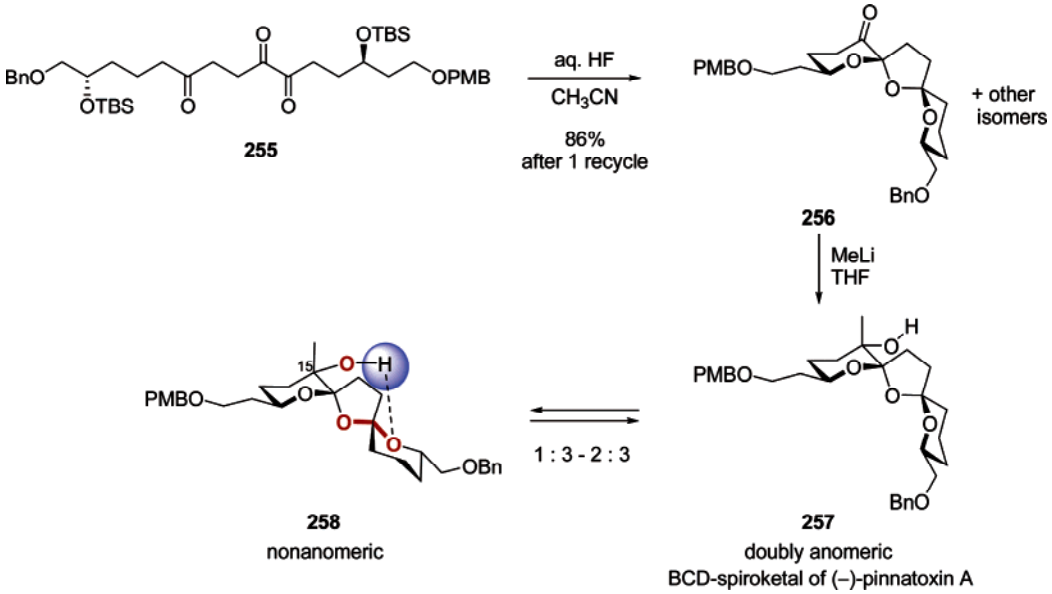
Pinnatoxins are a group of marine-derived macrocycle toxins that were isolated from the shellfish *Pinna muricata* and characterized by Uemura and co-workers in 1995.[103] As a result of their unique molecular structures and pronounced biological activities as Ca^{2+} channel activators, a number of approaches toward the synthesis of pinnatoxins have been described. The first total synthesis of (−)-pinnatoxin A, published by Kishi and co-workers in 1998, also established the absolute stereochemistry of the natural (+)-pinnatoxin A, **254** (Figure 16).[104] Recently, Hirama and co-workers published a formal total synthesis of (+)-pinnatoxin A.[105] As with the natural products discussed earlier, the BCD spiroketal system has presented a major challenge in all of the syntheses of the pinnatoxins. In the natural pinnatoxins the dispiroketal structure has the maximum anomeric stabilization, so it might be assumed that access to the natural spiroisomer would be straightforward. In total syntheses such predictions are always dangerous, and indeed four research groups independently observed that under different conditions an unwanted dispiroketal configuration with one less anomeric stabilization was formed.

Scheme 59. Synthesis of the BCD Dispiroketal Segment of (−)-Pinnatoxin A According to Hirama et al.[105b]

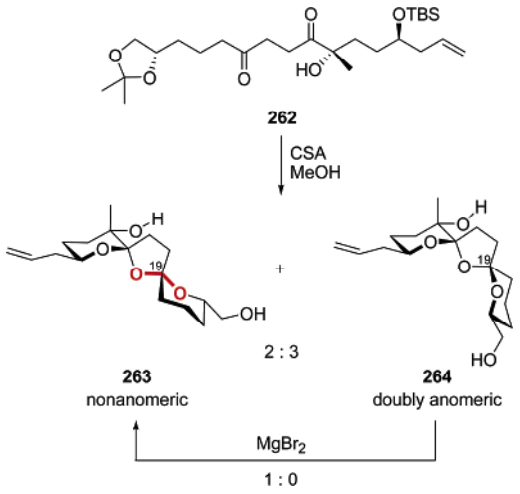


Murai (1997). The first synthesis of the BCD dispiroketal moiety of (−)-pinnatoxin A was reported by Murai and co-workers.[106] The desired dispiroketal structure, having the natural relative stereochemistry, was formed via acid-catalyzed cyclization of an open-chain triketone **255** (Scheme 58). Exposure of **255** to aqueous hydrofluoric acid in acetonitrile first cleaved the TBS ether protecting groups, and subsequent cyclization gave the desired tricyclic keto−acetal **256** along with several isomers. The undesired isomers could be converted to **256** under the same conditions. Stereoselective methylation then afforded the desired alcohol **257** in 82% yield as a single stereoisomer. Though the keto−acetal **256** was quite stable, the methylated form **257** isomerized in the presence of acid to form a less anomerically stabilized

Scheme 58. Synthesis of the BCD Dispiroketal Segment of (−)-Pinnatoxin A According to Murai et al.[106a,107]



Scheme 60. Synthesis of the BCD Dispiroketal Segment of (−)-Pinnatoxin A According to Kishi et al.[104]



and undesired isomer **258**. In light of these interesting results, to investigate the stability of these dispiroketal structures a more detailed study was conducted.[107] Exposure of **257** to different acids provided a mixture of spiroketals **257** and **258** in varying ratios (3:1−3:2). Because acidic treatment of spiroketal **258** also furnished a mixture of these two isomers in the corresponding ratios, the isomerization is obviously under thermodynamic control. It was considered that the equatorial hydroxyl group at C_{15} could stabilize the nonanomeric structure **258** as a consequence of internal hydrogen bonding with the tetrahydropyranol oxygen in the D ring.[107]

Hirama (1998). Hirama and co-workers introduced another synthesis for the BCD dispiroketal moiety of (−)-pinnatoxin A.[105] It was predicted that acid-catalyzed spiroketalization of open-chain precursor **259** would predominantly form the desired doubly anomeric dispiroketal **261** based on MM2* calculations and the fact that **261** has the maximum amount of anomeric stabilization (Scheme 59).[105b,108] However, when the reaction was performed a mixture of the undesired nonanomeric dispiroketal **260** and the desired dispiroketal **261** was formed in a ratio of 1:2.6. This equilibrium ratio and the instability of the doubly anomeric configuration was proposed to derive from unfavorable dipole interactions between the C−O bonds in the B and D rings.

Kishi (1998). In the first total synthesis of (−)-pinnatoxin A Kishi and co-workers used an acid-catalyzed cyclization of a diketone intermediate **262** to form the BCD dispiroketal unit (Scheme 60).[104] Again, the desired dispiroketal **264** with maximum anomeric stabilization could not be selectively accessed. The reaction gave a 2:3 mixture of the undesired nonanomeric spiroketal **263** and the desired doubly anomeric spiroketal **264**. This ratio could be altered by the choice of the acid, solvent, and addition of metal ions. For example, in the presence of magnesium bromide the desired doubly anomeric dispiroketal **264** completely epimerized to the undesired nonanomeric dispiroketal **263**.

Hashimoto (2001). Hashimoto and co-workers developed a highly stereoselective synthesis for construction of the BCD dispiroketal system of (+)-pinnatoxin A.[109] In addition, they conducted extensive studies addressing the dispiroketal formation and offered comprehensive mechanistic explanations for the stereochemical outcome.[109b] These exceptional results clearly show the versatility of dispiroketal structures.

While in all of the pinnatoxin dispiroketal syntheses presented above an acid-catalyzed spiroketalization of an open-chain ketone precursor is used, Hashimoto and co-workers made an exception by using a different approach. They envisaged using a hemiketal formation followed by intramolecular hetero-Michael addition as key steps in the dispiroketalization process.[109] Although the overall strategy worked very smoothly, the authors were still unable to avoid formation of the unwanted dispiroketal configuration with one less anomeric stabilization.

Triketone **265** was used as a substrate for the spiroketalization studies (Scheme 61). When **265** was treated with hydrochloride acid, the C_{12} TES protection was selectively cleaved and an equilibrium mixture was formed, containing the corresponding unprotected triketone **266** and stereoisomers of two different hemiketals **267** and **268**. Submission of this equilibrium mixture to different bases furnished four dispiroketal isomers **269**−**272** in a variety of ratios, dependent on the reaction time and temperature (Scheme 61).

It was discovered that this reaction sequence predominantly forms the undesired nonanomeric dispiroketal **270**, which slowly isomerizes to form the desired doubly anomeric dispiroketal **269** as the major product (Scheme 61, entries 2 and 3). When the reaction was carried out at −50 °C, a 1:4−1:3 mixture of dispiroketals **269** and **270** was formed with no trace amount of dispiroketals **271** and **272**. Most importantly, no isomerization of **270** to **269** was observed at this temperature. These results clearly indicate that formation of isomers **269** and **270** is a result of kinetic control.

To explain the significant kinetic preference for formation of the nonanomeric structure **270**, the authors propose that the hetero-Michael cyclization can occur through two different hemiketal conformations **273a** and **273b** (Scheme 62).[109b] These conformations give rise to four different transitions-state models **274**−**277**; of these the models **275** and **277** are disfavored because of severe steric interactions between the C_{18} and C_{23} hydrogens. In addition, the transition-state model **274**, which would lead to the desired doubly anomeric product **269**, also suffers from steric interaction between the C_{12} and C_{23} side chains. Therefore, the nonanomeric product **270**, produced via transition-state **276**, is favored in the equilibrium.

4.2.2. Azaspiracid: Mistakenly Believed To Possess a Nonanomeric Structure

Azaspiracid 1[110] and its congeners, azaspiracids 2−5,[111] are a class of natural products that possess a complex structural framework and present serious environmental and human health hazards. Since the initial isolation of azaspiracid 1 from mussels culti-

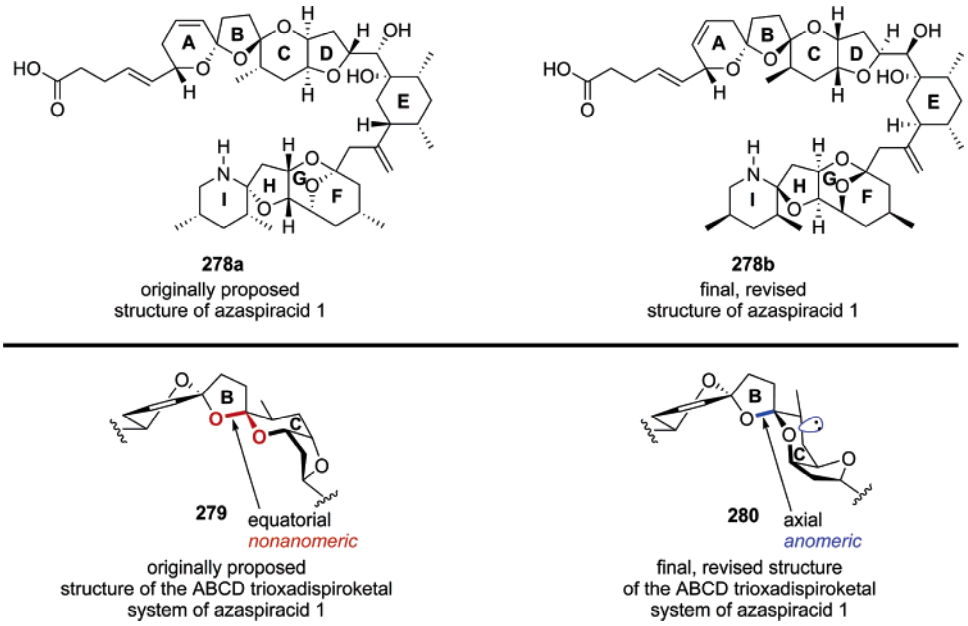
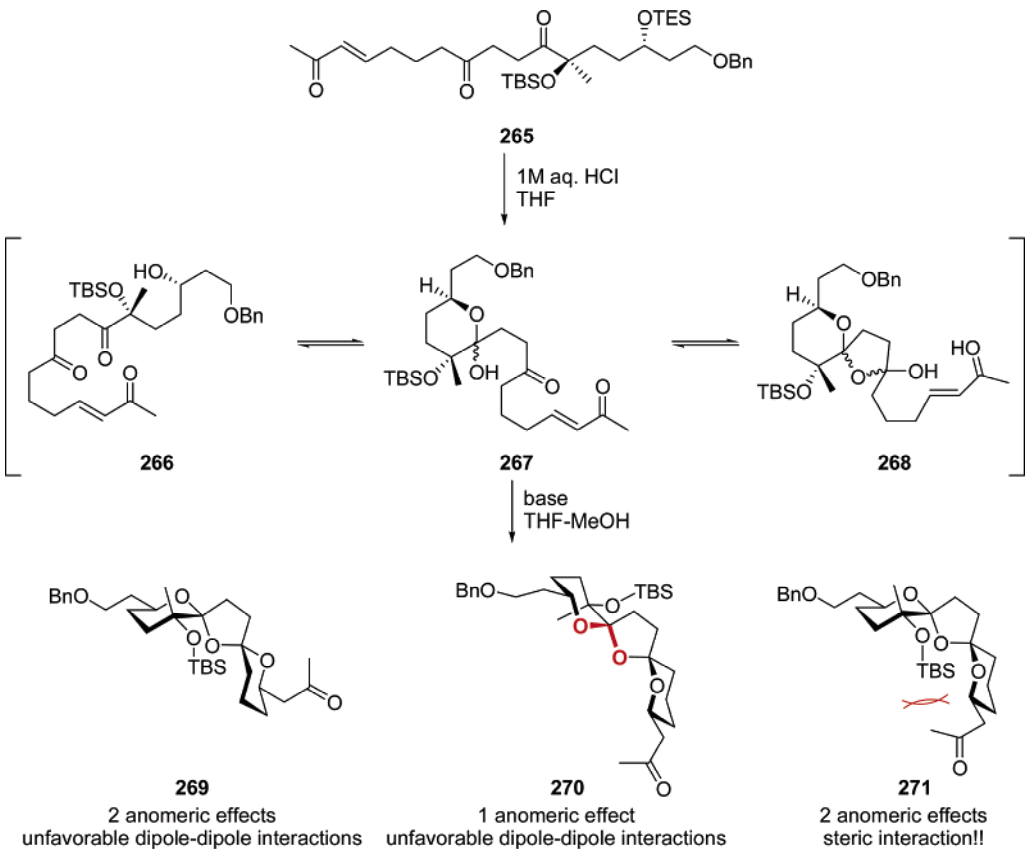


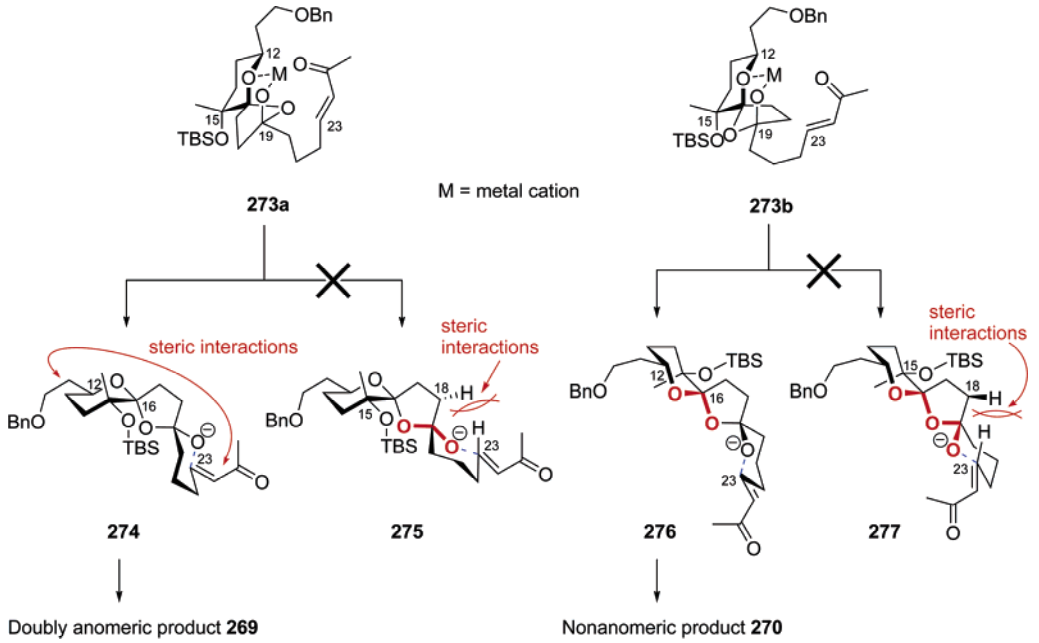
Figure 17. Original and revised structures of azaspiracid 1 and its ABCD trioxadispiroketal moiety.

Scheme 61. Synthesis of the BCD Dispiroketal Segment of (+)-Pinnatoxin A According to Hashimoto et al.[109]

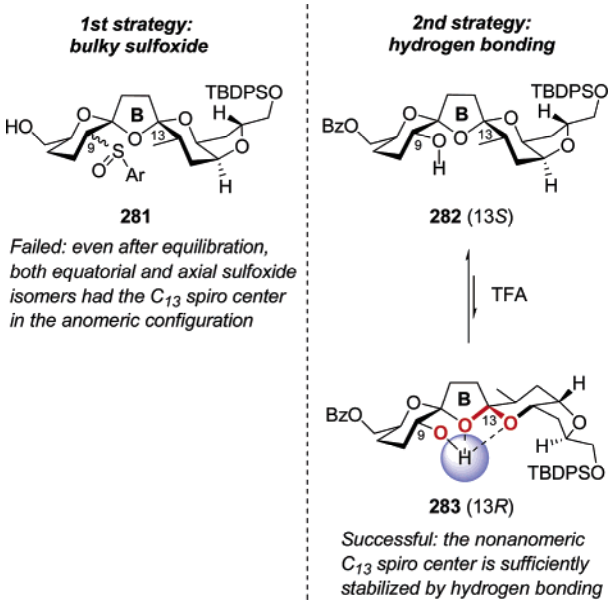


Entry	Base	T	Time	269:270:271:272
1	NaOMe	0 ºC	1h	77:8:10:5
2	LiOMe	rt	10s	33:64:0:3
3	LiOMe	rt	48h	82:8:6:4
4	LiOMe	-50 ºC	8h	20:80:0:0
5	NaOMe	-50 ºC	1.5h	24:76:0:0

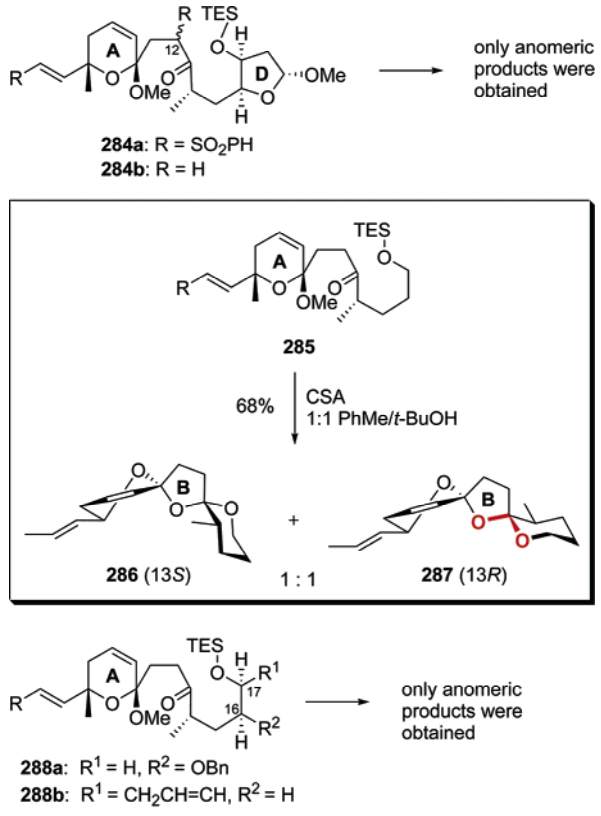
Scheme 62. Transition-State Models for the Hetero-Michael Addition in the Synthesis of the BCD Dispiroketal Segment of (+)-Pinnatoxin A Proposed by Hashimoto et al.[109b]



Scheme 63. Strategies Used To Synthesize the Nonanomeric ABCD Moiety of the Azaspiracids According to Nicolaou et al.[114]



Scheme 64. Synthesis of the Nonanomeric ABCD Moiety of the Azaspiracids According to Carter et al.[115]



vated *Mytilus edulis*,[112] azaspiracids have been the focus of intensive synthetic study. The original structure of azaspiracid 1 (**278a**; Figure 17), proposed by Yasumoto, has been revised twice. The corrected structure came to light in 2004 by the remarkable total synthesis by Nicolaou and co-workers[113] (**278b**, Figure 17). Before the final structural revision the dispiroketal moiety was proposed to possess a transoidal nonanomeric stereochemistry **279** (Figure 17) where the B ring oxygen atom is in an equatorial orientation with respect to the C ring oxygen. Even if it seemed to be an almost impossible mission, many groups studied intensively for ways to construct this nonanomeric structure, and a few also succeeded in it.

Nicolaou (2001). Nicolaou and co-workers were the first to accomplish the synthesis of the unnatural nonanomeric ABCD ring moiety of the azaspiracids.[114] The first strategy was to use a tolyl sulfoxide group at C_9 (**281**), which, by virtue of its steric bulk, was expected to force the spiroketal into the desired nonanomeric configuration (Scheme 63). Interestingly, the steric bulk of the sulfoxide was not enough to overcome the anomeric effect, and an alternative

Table 1. Methods Used To Access Nonanomeric Spiroketal Structures

Acid-Catalyzed Spiroketalization

A. Thermodynamic Methods

reason for the stability of the nonanomeric isomer			
Lewis-acid/metal chelation	hydrogen bonding	steric effects	other reasons
Evans (spongistatin)[55]	Paterson (spongistatin)[59a]	Shimizu (spirofungin)[46]	DeShong (avermectin)[34]
Smith (spongistatin)[57a]	Kishi (spongistatin)[54a]	Dias (spirofungin)[47]	Sinibaldi (reveromycin)[35]
Nakata (spongistatin)[67a]	Mead (spongistatin)[63]	Ley (spongistatin)[71,72a]	Kishi (salinomycin)[95]
Lau (spongistatin)[73]	Yamamura (aplysiatoxin)[80]	Ireland (aplysiatoxin)[78]	Yonemitsu (salinomycin)[96e]
Kishi (pinnatoxin)[104]	Murai (pinnatoxin)[106a,107]	Nakata (reveromycin)[82]	Brown/Kocienski (salinomycin)[98c]
	Hirama (pinnatoxin)[105b]	Theodorakis (reveromycin)[83]	Albizati/Perron (salinomycin)[102]
	Nicolaou (azaspiracid)[114]		Carter (azaspiracid)[115]

B. Kinetic Methods[a]

Smith (lituarine)[b,33]
Pihko (pectenotoxin)[31]
Kitching (insect pheromones)[38c,d]
Mori (insect pheromones)[39]
Deslongchamps (insect pheromone)[5b]
Heathcock (spongistatin)[65b]
Paquette (spongistatin)[56]

Other Spiroketalization Methods

A. Direct Methods

oxidative cyclization
Kay/Williams (insect pheromones)[42]
Brimble (salinomycin)[100]

hetero-Diels–Alder
Ireland (macrolide antibiotics)[86a]
Tietze (talaromycin)[87]

hetero-Michael
Paterson (spongistatin)[59a]
Hashimoto (pinnatoxin)[109]

reductive lithiation, Rychnovsky (spirofungin)[37]
reductive removal of sulfur linkage, Nishiyama (azaspiracid)[116a]
macrolactonization, Kishi (aplysiatoxin)[76]

B. Electrophile-Mediated Spirocyclizations

iodo-spiroketalization, Roush (spongistatin)[70]
hydroxymercuration, Kitching (insect pheromones)[38a,b]

C. Indirect Methods

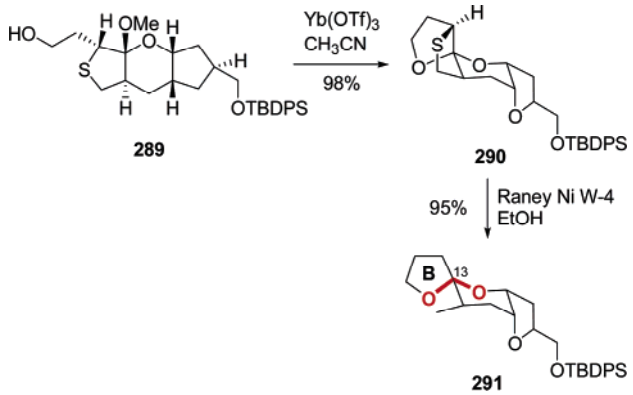
stereoselective hydrogenation, Crimmins (spongistatin)[68a]
base-induced epimerization, Williams/Barner (milbemycin)[84]
Mukaiyama reaction, Kocienski (milbemycin)[85]

[a] Thermodynamic equilibration experiments have not been reported in all cases. [b] Only very minor amounts of nonanomeric isomer formed.

approach had to be developed. Encouraged by the results published by Murai[107] (Scheme 58), Paterson[59a] (Scheme 29), and Heathcock,[64] the group developed a new strategy where the spirocyclization to give the desired nonanomeric 13*R* configuration was controlled by intramolecular interactions. The idea was to invert the anomeric 13*S* configuration to the nonanomeric configuration using the hydrogen-bonding ability of a free hydroxyl group at C_9 (Scheme 63). For this purpose tetracycle **282** was synthesized, from which the desired spiroketal **283**, bearing the nonanomeric C_{13} spiro center, was readily obtained in 56% yield via acid-catalyzed epimerization along with 44% of the recovered starting material **282**.

Carter (2002). The Carter group investigated multiple strategies, such as solvent effects and steric effects (C_{12} sulfone in **284a**), for construction of the transoidal nonanomeric dispiroketal structure of azaspiracids (Scheme 64).[115] Finally, it was found that the nonanomeric dispiroketal could be formed by removing the D ring functionality from the spiroketalization precursor (**284** vs **285**).[115b] Acid-catalyzed spirocyclization of **285** furnished a 1:1 mixture of dispiroketals **286** and **287** in 68% yield. An identical equilibrium mixture was formed when the undesired anomeric dispiroketal **286** was resubmitted to the same acidic reaction conditions. The desired nonanomeric dispiroketal **287** could be obtained in 62% overall yield using one equilibration cycle. Interestingly, when the same reaction was tested with precursors containing C_{16} or C_{17} substitution (**288a**,**b**), again only anomeric dispiroketal products were formed.

Scheme 65. Synthesis of the Nonanomeric BCD Moiety of Azaspiracid According to Nishiyama et al.[116a]



Nishiyama (2004). Nishiyama and co-workers also succeeded in construction of the nonanomeric BCD ring system of the azaspiracids.[116] The stereochemistry of the C_{13} spirocenter was controlled by connecting the B and C rings with a sulfur atom (Scheme 65). The synthetic effort required to access sulfur-containing substrate **289** was rewarded by an excellent selectivity and yield of the desired nonanomeric spiroketal **291**. A similar procedure was later

used successfully in the synthesis of the nonanomeric ABCD ring system of azaspiracids.

5. Conclusion

One of the purposes of this review is to attract the attention of the synthetic community to the successes and failures that have accompanied the routes toward nonanomeric spiroketals and also to unsolved synthetic challenges, such as the nonanomeric CD spiroketal system of the dianemycin/endusamycin antibiotics. We can also reasonably expect that more natural products bearing the nonanomeric spiroketal structure will be discovered in the future.

Table 1 summarizes the methods that have been used to access the nonanomeric spiroketal structures. A striking feature that is immediately apparent is that thermodynamic equilibration is still considered to be the method of choice in many instances. In view of this, it is quite surprising that computational methods have been used only rarely to estimate (and predict) the relative ratios of the isomers in equilibrium conditions. Of course, this most likely reflects the fact that the different isomers are often very close in energy, well within the error limits of most computational approaches. Given the somewhat unpredictable nature of spiroketal systems, especially the tricyclic spiroketals, it is not surprising that nearly all research groups have had to struggle very hard to secure the desired result. It is obvious that we need to learn much more about spiroketals before fully rational approaches to the desired spiroketal isomers can be envisaged.

6. Acknowledgments

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7. Note Added in Proof

Tan and co-workers recently reported a novel kinetic spiroketalization study of glycal-derived epoxides that allows the synthesis of either nonanomeric or anomeric spiroketals. In MeOH, the epoxide opening-spiroketalization reaction proceeded under kinetic control, affording the nonanomeric spiroketal in excellent selectivity. Addition of *p*-TsOH, in turn, afforded the corresponding thermodynamic, anomeric isomers.[117]

9. Note Added after ASAP Publication

This review was posted ASAP on November 30, 2005. Structure 54 in Scheme 11 has been revised. This review was reposted on December 5, 2005.

9. References

(1) For lucid accounts on the adventurous nature of total synthesis, see: (a) Sierra, M. A.; de la Torre, M. C. *Dead Ends and Detours: Direct Ways to Successful Total Synthesis*; Wiley-VCH: Weinheim, 2004. (b) Nicolaou, K. C.; Snyder, S. A. *Classics in Total Synthesis II*: *More Targets, Strategies, Methods*; Wiley-VCH: Weinheim, 2003.

(2) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617.

(3) (a) For extensive reviews on stereoelectronic effects, see: (a) Kirby, A. J. *The anomeric effect and related stereoelectronic effects at oxygen*; Springer-Verlag: New York, 1983. (b) Deslongchamps, P. *Stereoelectronic effects in organic chemistry*; Pergamon Press: Oxford, 1983. (c) Thatcher, G. R. J. *The Anomeric Effect and Associated Stereoelectronic Effects*; ACS Symposium Series 539; American Chemical Society: Washington, DC, 1985. (d) Juaristi, E.; Cuevas, G. *The Anomeric Effect*; CRC Press: Boca Raton, FL, 1995.

(4) (a) Deslongchamps, P.; Rowan, D. D.; Pothier, N.; Sauve, T.; Saunders, J. K. *Can. J. Chem.* **1981**, *59*, 1105. (b) Descotes, G.; Lissac, M.; Delmau, J.; Duplau, J. *C. R. Acad. Sci. Ser. C* **1968**, *267*, 1240.

(5) (a) Deslongchamps, P.; Pothier, N. *Can. J. Chem.* **1987**, *68*, 597. (b) Pothier, N.; Goldstein, S.; Deslongchamps, P. *Helv. Chim. Acta* **1992**, *75*, 604.

(6) In addition, the word "contrathermodynamic", if read literally, means something that stands in opposition to the laws of thermodynamics. This is obviously not possible.

(7) Cyclopropanes: (a) Liu, H.-W.; Walsh, C. T. *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; John Wiley & Sons Ltd.: New York, 1987. (b) Wessjohann, C. A.; Brandt, W. *Chem. Rev.* **2003**, *103*, 1625. (c) Epoxides: Marco-Contelles, J.; Molina, M. T.; Anjum, S. *Chem. Rev.* **2004**, *104*, 2857.

(8) For reviews on the synthesis of spiroketals, see ref 2 and (a) Kluge, A. F. *Heterocycles* **1986**, *24*, 1699. (b) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309. (c) Jacobs, M. F.; Kitching, W. B. *Curr. Org. Chem.* **1998**, *2*, 395. (d) Ley, S. V.; Baeschlin, D. K.; Dixon, D. J.; Foster, A. C.; Ince, S. J.; Priepke, H. W. M.; Reynolds, D. J. *Chem. Rev.* **2001**, *101*, 53. (f) Mead, K. T.; Brewer, B. N. *Curr. Org. Chem.* **2003**, *7*, 227.

(9) As an example, the spiroketal subunits of the calyculins and okadaic acid, both inhibitors of serine/threonine protein phosphatases, have been proposed to act as a β-turn mimics: (a) Gauss, C. M.; Sheppeck, J.; Chamberlin, A. R. *Bioorg. Med. Chem.* **1997**, *5*, 1739. (b) Lindvall, M. K.; Pihko, P. M.; Koskinen, A. M. P. *J. Biol. Chem.* **1997**, *272*, 23312.

(10) For discussions, see: Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; John Wiley & Sons Ltd.: New York, 1994; p 758.

(11) (a) Francke, W.; Heeman, V.; Gerken, B.; Renwick, J. A. A.; Vite, J. P. *Naturwissenschaften* **1977**, *64*, 590. (b) Francke, W.; Hindorf, G.; Reith, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 862. (c) Francke, W.; Reith, W. *Liebigs Ann. Chem.* **1979**, 1. (d) Francke, W.; Hindorf, G.; Reith, W. *Naturwissenschaften* **1979**, *66*, 618. (e) Francke, W.; Reith, W.; Bergström, G.; Tengö, J. *Naturwissenschaften* **1980**, *67*, 149. (f) Baker, R.; Herbert, R.; Howse, P. E.; Jones, O. T.; Francke, W.; Reith, W. *J. Chem. Soc., Chem. Commun.* **1980**, 52. (g) Francke, W.; Reith, W.; Bergström, G.; Tengö, J. *Z. Naturforsch.* **1981**, *36*, 928. (h) Baker, R.; Herbert, R. H.; Parton, A. H. *J. Chem. Soc., Chem. Commun.* **1982**, 601.

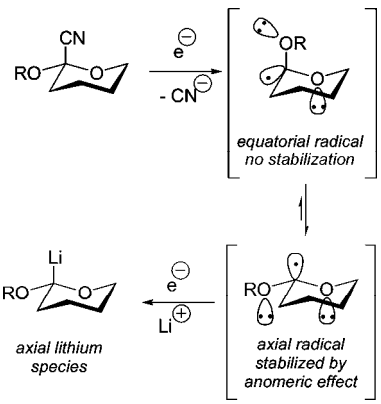
(12) Francke, W.; Reith, W.; Sinnwell, V. *Chem. Ber.* **1980**, *113*, 2686.

(13) Koźluk, T.; Cottier, L.; Descotes, G. *Tetrahedron* **1981**, *37*, 1875.

(14) Westley, J. W. *Polyether Antibiotics*; Marcel Dekker: New York, 1982.

(15) (a) For an excellent introduction to the structures of the dianemycin class and for the structure of endusamycin, see: Oscarson, J. R.; Bordner, J.; Celmer, W. D.; Cullen, W. P.; Huang, L. H.; Maeda, H.; Moshier, P. M.; Nishiyama, S.; Presseau, L.; Shibakawa, R.; Tone, J. *J. Antibiot.* **1989**, *42*, 37. For the isolation and characterization of other members of the dianemycin class, see: (b) Dianemycin: Hamill, R. L.; Hoehn, M. M.; Pittenger, G. E.; Chamberlin, J.; Gorman, M. *J. Antibiot.* **1969**, *22*, 161. (c) Leuseramycin: Mizutani, T.; Yamagishi, M.; Hara, H.; Kawashima, A.; Ômura, S.; Ôzeki, M.; Mizoue, K.; Seto, H.; Ôtake, N. *J. Antibiot.* **1980**, *33*, 137. (d) Lenoremycin (A-130A, Ro 21-6150): Blount, J. F.; Evans, R. H.; Liu, C.-M.; Hermann, T.; Westley, J. W. *J. Chem. Soc., Chem. Commun.* **1975**, 853. For the origin of the name lenoremycin, see: (e) Anteunis, M. J. O.; Rodios, N. A.; Verhegge, G. *Bull. Soc. Chim. Belg.* **1977**, *86*, 609. (f) Moyukamycin: Nakayama, H.; Seto, H.; Ôtake, N.; Yamagishi, M.; Kawashima, A.; Mizutani, T.; Ômura, S. *J. Antibiot.* **1985**, *38*, 1433. (g) X-14934A (CP-47,224): Celmer, W. D.; Moppett, C. E.; Cullen, W. P.; Oscarson, J. R.; Huang, L. H.; Shibakawa, R.; Tone, J. U.S. Patent 4,150,152, 1979. (h) A-130B and A-130C: Tsuji, N.; Terui, K.; Nagashima, K.; Tori, K.; Johnson, L. F. *J. Antibiot.* **1980**, *33*, 94. (i) CP-53,607 (X-14931A): Westley, J. W.; Liu, C.; Sello, L. H.; Troupe, N.; Blount, J. F.; Chiu, A.-M.; Todaro, L. J.; Miller, P. A.; Liu, M. *J. Antibiot.* **1984**, *37*, 813. (j) CP-80,219: Dirlam, J. P.; Presseau-Linabury, L.; Koss, D. A. *J. Antibiot.* **1990**, *43*, 727. (k) TM-531B and TM-

531C: Mizutani, T.; Yamagishi, M.; Mizoue, K.; Kawashima, A.; Ômura, S.; Ôzeki, M.; Seto, H.; Ôtake, N. *J. Antibiot.* **1981,** *34*, 1369.
(16) Hauske, J. R.; Kostek, G. *J. Org. Chem.* **1989**, *54*, 3500.
(17) Koyama, H.; Utsumi-Oda, K. *J. Chem. Soc., Perkin. Trans. 2* **1977**, 1531.
(18) (a) Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2005**, *22*, 15. (b) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897.
(19) For reviews on ciguatoxin and related marine toxins, see: (a) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897. (b) Yasumoto, T. *Chem. Rec.* **2001**, *1*, 228.
(20) (a) Bidard, J.-N.; Vijverberg, H. P. M.; Frelin, C.; Chungue, E.; Legrand, A. M.; Bagnis, R.; Lazdunski, M. *J. Biol. Chem.* **1984**, *259*, 8353. (b) Lombet, A.; Bidard, J.-N.; Lazdunski, M. *FEBS Lett*. **1987**, *219*, 355. (c) Dechraoui, M.-Y.; Naar, J.; Pauillac, S.; Legrand, A.-M. *Toxicon* **1999**, *37*, 125. (d) Anger, T.; Madge, D. J.; Mulla, M.; Riddal, D. *J. Med. Chem.* **2001**, *44*, 115.
(21) (a) Murata, M.; Legrand, A.-M.; Ishibashi, Y.; Yasumoto, T. *J. Am. Chem. Soc.* **1989**, *111*, 8929. (b) Satake, M.; Murata, M.; Yasumoto, T. *Tetrahedron Lett.* **1993**, *34*, 1975. (c) Satake, M.; Ishibashi, Y.; Legrand, A.-M.; Yasumoto, T. *Biosci. Biotechnol. Biochem.* **1997**, *60*, 2103. (d) Yasumoto, T.; Igarashi, T.; Legrand, A.-M.; Cruchet, P.; Chinain, M.; Fujita, T.; Naoki, H. *J. Am. Chem. Soc.* **2000**, *122*, 4988.
(22) For leading references, see: (a) Inoue, M.; Uehara, H.; Maruyama, M.; Hirama, M. *Org. Lett.* **2002**, *4*, 4551. (b) Inoue, M.; Hirama, M. *Synlett* **2004**, 57.
(23) Oishi, T.; Shoji, M.; Kumahara, N.; Hirama, M. *Chem. Lett.* **1997**, 845.
(24) Baba, T.; Huang, G.; Isobe, M. *Tetrahedron* **2003**, *59*, 6851.
(25) Yasumoto, T.; Murata, M.; Oshima, Y.; Sano, M.; Matsumoto, G. K.; Clardy, J. *Tetrahedron* **1985**, *41*, 1019.
(26) (a) Sasaki, K.; Wright, J. L. C.; Yasumoto, T. *J. Org. Chem.* **1998**, *63*, 2475. (b) Daiguji, M.; Satake, M.; James, K. J.; Bishop, A.; Mackenzie, L.; Naoki, H.; Yasumoto, T. *Chem. Lett.* **1998**, *7*, 653. (c) Suzuki, T.; Beuzenberg, V.; Mackenzie, K.; Quilliam, M. A. *J. Chromatogr. A* **2003**, *992*, 141. In addition, two PTX-related seco acids have been isolated, see: (d) Daiguji, M.; Satake, M.; James, K. J.; Bishop, A.; Mackenzie, L.; Naoki, H.; Yasumoto, T. *Chem. Lett.* **1998**, *7*, 653.
(27) For the total synthesis of PTX4, see: (a) Evans, D. A.; Rajapakse, H. A.; Stenkamp, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 4569. (b) Evans, D. A.; Rajapakse, H. A.; Chiu, A.; Stenkamp, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 4573. For synthetic efforts toward the pectenotoxins, see: (c) Amano, S.; Fujiwara, K.; Murai, A. *Synlett* **1997**, 1300. (d) Awakura, D.; Fujiwara, K.; Murai, A. *Synlett* **2000**, 1733. (e) Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2001**, *3*, 1949. (f) Paquette, L. A.; Peng, X.; Bondar, D. *Org. Lett.* **2002**, *4*, 937. (g) Bondar, D.; Liu, J.; Müller, T.; Paquette, L. A. *Org. Lett.* **2005**, *7*, 1813.
(28) Jung, J. H.; Sim, C. J.; Lee, C.-O. *J. Nat. Prod.* **1995**, *58*, 1722.
(29) (a) Spector, I.; Braet, F.; Schochet, N. R.; Bubb, M. R. *Microscop. Res. Technol.* **1999**, *47*, 18. (b) Leira, F.; Cabadon, A. G.; Vieytes, M. R.; Roman, Y.; Alfonso, A.; Botana, L. M.; Yasumoto, T.; Malaguti, C.; Rossini, G. P. *Biochem. Pharmacol.* **2002**, *63*, 1979.
(30) Yasumoto, T.; Murata, M.; Lee, J.-S.; Torigoe, K. *Bioactive Molecules: Mycotoxins and Phycotoxins'88*; Natori, S., Hashimoto, K., Ueno, Y., Eds.; Elsevier: New York, 1989; Vol. 10, p 375.
(31) Pihko, P. M.; Aho, J. E. *Org. Lett.* **2004**, *6*, 3849.
(32) Vidal, J.-P.; Escale, R.; Girard, J.-P.; Rossi, J.-C.; Chantraine, J.-M.; Aumelas, A. *J. Org. Chem.* **1992**, *57*, 5857.
(33) Smith, A. B., III; Frohn, M. *Org. Lett.* **2001**, *3*, 3979.
(34) DeShong, P.; Waltermire, R. E.; Ammon, H. L. *J. Am. Chem. Soc.* **1988**, *110*, 1901.
(35) Tursun, A.; Canet, I.; Aboab, B.; Sinibaldi, M.-E. *Tetrahedron Lett.* **2005**, *46*, 2291.
(36) Takaoka, L. R.; Buckmelter, A. J.; La Cruz, T. E.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2005**, *127*, 528.
(37) La Cruz, T. E.; Rychnovsky, S. D. *Org. Lett.* **2005**, *7*, 1873.
(38) (a) Kitching, W.; Lewis, J. A.; Fletcher, M. T.; De Voss, J. J.; Drew, R. A. I.; Moore, C. J. *J. Chem. Soc., Chem. Commun.* **1986**, 855. (b) Kitching, W.; Lewis, J. A.; Perkins, M. V.; Drew, R.; Moore, C. J.; Schurig, V.; König, W. A.; Francke, W. *J. Org. Chem*. **1989**, *54*, 3893. (c) Perkins, M. V.; Kitching, W. *J. Chem. Soc., Perkin. Trans. 1* **1990**, 2501. (d) Perkins, M. V.; Jacobs, M. F.; Kitching, W.; Cassidy, P. J.; Lewis, J. A.; Drew, R. A. I. *J. Org. Chem.* **1992**, *57*, 3365. (e) Chen, J.; Fletcher, M. T.; Kitching, W. *Tetrahedron: Asymmetry* **1995**, *6*, 967.
(39) (a) Mori, K.; Tanida, K. *Heterocycles* **1981**, *15*, 1171. (b) Mori, K.; Tanida, K. *Tetrahedron* **1981**, *37*, 3221. (c) Mori, K.; Ikunaka, M. *Tetrahedron* **1984**, *40*, 3471. (d) Mori, K.; Uematsu, T.; Watanabe, H.; Yanagi, K.; Minobe, M. *Tetrahedron Lett.* **1984**, *25*, 3875. (e) Mori, K.; Watanabe, H.; Yanagi, K.; Minobe, M. *Tetrahedron* **1985**, *41*, 3663. (f) Mori, K.; Watanabe, H. *Tetrahedron* **1986**, *42*, 295.
(40) For examples of other studies concerning insect pheromones (anomeric), see: (a) Ley, S. V.; Lygo, B. *Tetrahedron Lett.* **1982**, *23*, 4625. (b) Amouroux, R. *Heterocycles* **1984**, *22*, 1489.
(41) Deslongchamps, P.; Rowan, D. D.; Pothier, N.; Saunders, J. K. *Can. J. Chem.* **1981**, *59*, 1122.
(42) Kay, I. T.; Williams, E. G. *Tetrahedron Lett.* **1983**, *24*, 5915.
(43) Holtzel, A.; Kempter, C.; Metzger, J. W.; Jung, G.; Groyh, I.; Fritz, T.; Fiedler, H.-P. *J. Antibiot.* **1998**, *51*, 699.
(44) (a) Takahashi, H.; Osada, H.; Koshino, H.; Kudo, T.; Amano, S.; Shimizu, S.; Yoshihama, M.; Isono, K. *J. Antibiot.* **1992**, *45*, 1409. (b) Takahashi, H.; Osada, H.; Koshino, H.; Sasaki, M.; Onose, R.; Nakakoshi, M.; Yoshihama, M.; Isono, K. *J. Antibiot.* **1992**, *45*, 1414.
(45) Zanatta, S. D.; White, J. M.; Rizzacasa, M. A. *Org. Lett.* **2004**, *6*, 1041.
(46) Shimizu, T.; Kusaka, J.; Ishiyama, H.; Nakata, T. *Tetrahedron Lett.* **2003**, *44*, 4965.
(47) Dias, L. C.; de Oliveira, L. G. *Org. Lett.* **2004**, *6*, 2587.
(48) The Rychnovsky approach is a very clever example of the generality and utility of the anomeric effect. Presumably, the radical intermediate generated by the reduction of the oxonium cation derived from **109** can still undergo inversion of stereochemistry. The axial radical is preferred, apparently as a result of the anomeric effect (for discussions, see: Rychnovsky, S. D.; Powers, J. P.; LePage, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 8375), see below. When the second electron is added in the reduction, the resulting anion can no longer undergo inversion and therefore remains locked in the axial configuration! The configurational stability of α-oxygenated alkyllithiums is well documented: Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980***, 102,* 1201.



(49) (a) Pettit, G. R.; Cichacz, Z. A.; Gao, F.; Herald, C. L.; Boyd, M. R.; Schmidt, J. M.; Hooper, J. N. A. *J. Org. Chem.* **1993**, *58*, 1302. (b) Pettit, G. R.; Cichacz, Z. A.; Gao, F.; Herald, C. L.; Boyd, M. R. *J. Chem. Soc., Chem. Commun.* **1993**, 1166. (c) Pettit, G. R.; Herald, C. L.; Cichacz, Z. A.; Gao, F.; Schmidt, J. M.; Boyd, M. R.; Christie, N. D.; Boettner, F. E. *J. Chem. Soc., Chem. Commun.* **1993**, 1805. (d) Pettit, G. R.; Herald, C. L.; Cichacz, Z. A.; Gao, F.; Boyd, M. R.; Christie, N. D.; Schmidt, J. M. *Nat. Prod. Lett.* **1993**, *3*, 239. (e) Pettit, G. R.; Cichacz, Z. A.; Herald, C. L.; Gao, F.; Boyd, M. R.; Schmidt, J. M.; Hamel, E.; Bai, R. *J. Chem. Soc., Chem. Commun.* **1994**, 1605.
(50) Fusetani, N.; Shinoda, K.; Matsunaga, S. *J. Am. Chem. Soc.* **1993**, *115*, 3977.
(51) (a) Kobayashi, M.; Aoki, S.; Sakai, H.; Kawazoe, K.; Kihara, N.; Sasaki, T.; Kitagawa, I. *Tetrahedron Lett.* **1993**, *34*, 2795. (b) Kobayashi, M.; Aoki, S.; Sakai, H.; Kihara, N.; Sasaki, T.; Kitagawa, I. *Chem. Pharm. Bull.* **1993**, *41*, 989.
(52) (a) Kobayashi, M.; Aoki, S.; Kitagawa, I. *Tetrahedron Lett.* **1994**, *35*, 1243. (b) Kobayashi, M.; Aoki, S.; Gato, K.; Kitagawa, I. *Chem. Pharm. Bull.* **1996**, *44*, 2142.
(53) (a) Evans, D. A.; Coleman, P. J.; Diaz, L. C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2737. (b) Evans, D. A.; Trotter, B. W.; Côté, B.; Coleman, P. J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2741. (c) Evans, D. A.; Trotter, B. W.; Côté, B.; Coleman, P. J.; Dias, L. C.; Tyler, A. N. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2744.
(54) (a) Guo, J.; Duffy, K. J.; Stevens, K. L.; Dalko, P. I.; Roth, R. M.; Hayward, M. M.; Kishi, Y. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 187. (b) Hayward, M. M.; Roth, R. M.; Duffy, K. J.; Dalko, P. I.; Stevens, K. L.; Guo, J.; Kishi, Y. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 190.
(55) See ref 53a and (a) Evans, D. A.; Trotter, B. W.; Coleman, P. J.; Côtè, B.; Dias, L. C.; Rajapakse, H. A.; Tyler, A. N. *Tetrahedron* **1999**, *55*, 8671.
(56) Paquette, L. A.; Braun, A. *Tetrahedron Lett.* **1997**, 38, 5119.
(57) (a) Smith A. B., III; Doughty, V. A.; Lin, Q.; Zhuang, L.; McBriar, M. D.; Boldi, A. M.; Moser, W. H.; Murase, N.; Nakayama, K.; Sobukawa, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 191. (b) Smith,

A. B., III; Lin, Q.; Doughty, V. A.; Zhuang, L.; McBriar, M. D.; Kerns, J. K.; Brook, C. S.; Murase, N.; Nakayama, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 196. (c) Smith, A. B., III; Doughty, V. A.; Sfouggatakis, C.; Bennett, C. S.; Koyanagi, J.; Takeuchi, M. *Org. Lett.* **2002**, *4*, 783. For the first studies of the Ca^{2+}-controlled spirocyclizations, see: (d) Smith, A. B., III; Zhuang, L.; Brook, C. S.; Lin, Q.; Moser, W. H.; Trout, R. E. L.; Boldi, A. M. *Tetrahedron Lett*. **1997**, *38*, 8671.

(58) Paterson, I.; Chen, D. Y.-K.; Coster, M. J.; Aceña, J. L.; Bach, J.; Gibson, K. R.; Keown, L. E.; Oballa, R. M.; Trieselmann, T.; Wallace, D. J.; Norcross, R. D. *Angew. Chem., Int. Ed.* **2001**, *40*, 4055.

(59) (a) Paterson, I.; Wallace, D. J.; Gibson, K. R. *Tetrahedron Lett.* **1997**, *38*, 8911. For a more recent and a slightly modified CD spiroketal synthesis, see: (b) Paterson, I.; Coster, M. J. *Tetrahedron Lett.* **2002**, *43*, 3285.

(60) Negri, D. P.; Kishi, Y. *Tetrahedron Lett.* **1987**, *28*, 1063.

(61) Hayes, C. J.; Heathcock, C. H. *J. Org Chem.* **1997,** *62*, 2678.

(62) Zemribo, R.; Mead, K. T. *Tetrahedron Lett*. **1998**, *39*, 3891.

(63) Zemribo, R.; Mead, K. T. *Tetrahedron Lett*. **1998**, *39*, 3895.

(64) (a) Heathcock, C. H.; McLaughlin, M.; Medina, J.; Hubbs, J. L.; Wallace, G. A.; Scott, R.; Claffey, M. M.; Hayes, C. J.; Ott, G. R. *J. Am. Chem. Soc.* **2003**, *125*, 12844. (b) Wallace, G. A.; Scott, R.; Heathcock, C. H. *J. Org. Chem.* **2000**, *65*, 4145. (c) Ott, G. R.; Heathcock, C. H. *Org. Lett.* **1999**, *1*, 1475. (d) Claffey, M. M.; Heathcock, C. H. *J. Org. Chem.* **1996**, *61*, 7646.

(65) (a) Claffey, M. M.; Hayes, C. J.; Heathcock, C. H. *J. Org. Chem.* **1999**, *64*, 8267. (b) Hubbs, J. L.; Heathcock, C. H. *J. Am. Chem. Soc.* **2003**, *125*, 12836.

(66) Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 168.

(67) (a) Terauchi, T.; Sato, I.; Tsukada, T.; Kanoh, N.; Nakata, M. *Tetrahedron Lett.* **2000**, *41*, 2649. For the formal total synthesis of spongistatin 2, see: (b) Terauchi, T.; Terauchi, T.; Sato, I.; Shoji, W.; Tsukada, T.; Tsunoda, T.; Kanoh, N.; Nakata, M. *Tetrahedron Lett.* **2003**, *44*, 7741. (c) Terauchi, T.; Tanaka, T.; Terauchi, T.; Morita, M.; Kimijima, K.; Sato, I.; Shoji, W.; Nakamura, Y.; Tsukada, T.; Tsunoda, T.; Hayashi, G.; Kanoh, N.; Nakata, M. *Tetrahedron Lett.* **2003**, *44*, 7747.

(68) For the synthesis of the CD spiroketal, see: (a) Crimmins, M. T.; Katz, J. D. *Org. Lett*. **2000**, *2*, 957. For the total synthesis, see: (b) Crimmins, M. T.; Katz, J. D.; Washburn, D. G.; Allwein, S. P.; McAtee, L. F. *J. Am. Chem. Soc*. **2002**, *124*, 5661.

(69) Jacobs, M. F.; Glenn, M. P.; McGrath, M. J.; Zhang, H.; Brereton, I.; Kitching, W. *Arkivoc General Papers*, 2001, ms. 114−137.

(70) Holson, E. B.; Roush, W. R. *Org. Lett.* **2002**, *4*, 3719.

(71) Gaunt, M. J.; Hook, D. F.; Tanner, H. R.; Ley, S. V. *Org. Lett.* **2003**, *5*, 4815.

(72) (a) Ball, M.; Gaunt, M. J.; Hook, D. F.; Jessiman, A. S.; Kawahara, S.; Orsini, P.; Scolaro, A.; Talbot, A. C.; Tanner, H. R.; Yamanoi, S.; Ley, S. V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5433. (b) Kawahara, S.; Gaunt, M. J.; Scolaro, A.; Yamanoi, S.; Ley, S. V. *Synlett* **2005**, 2031.

(73) Lau, C. K.; Crumpler, S.; Macfarlane, K.; Lee, F.; Berthelette, C. *Synlett* **2004**, 2281.

(74) (a) Kato, Y.; Scheuer, P. J. *J. Am. Chem. Soc.* **1974**, *96*, 2245. (b) Kato, Y.; Scheuer, P. J. *Pure Appl. Chem.* **1975**, *41*, 1. (c) Kato, Y.; Scheuer, P. J. *Pure Appl. Chem.* **1976**, *48*, 29.

(75) (a) Mynderse, J. S.; Moore, R. E. *J. Org. Chem.* **1978**, *43*, 2301. (b) Moore, R. E. *Pure Appl. Chem.* **1982**, *54*, 1919. (c) Moore, R. E.; Blackman, A. J.; Cheuk, C. E.; Mynderse, J. S.; Matsumoto, G. K.; Clardy, J.; Wooward, R. W.; Craig, J. C. *J. Org. Chem.* **1984**, *49*, 2484. (d) Entzeroth, M.; Blackman, A. J.; Mynderse, J. S.; Moore, R. E. *J. Org. Chem.* **1985**, *50*, 1255.

(76) Park, P.-U.; Broka, C. A.; Johnson, B. F.; Kishi, Y. *J. Am. Chem. Soc.* **1987**, *109*, 6205.

(77) Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585.

(78) Ireland, R. E.; Thaisrivongs, S.; Dussault, P. H. *J. Am. Chem. Soc.* **1988**, *110*, 5768.

(79) For precise discussion and further information, see refs 78 and 3b.

(80) Toshima, H.; Suzuki, T.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1989**, *30*, 6725.

(81) (a) Osada, H.; Koshino, H.; Isono, K.; Takahashi, H.; Kawanishi, G. *J. Antibiot.* **1991**, *44*, 259. (b) Takahashi, H.; Osada, H.; Koshino, H.; Kudo, T.; Amano, S.; Shimizu, S.; Yoshihama, M.; Isono, K. *J. Antibiot.* **1992**, *45*, 1409. (c) Takahashi, H.; Osada, H.; Koshino, H.; Sasaki, M.; Onose, R.; Nakakoshi, M.; Yoshihama, M.; Isono, K. *J. Antibiot.* **1992**, *45*, 1414. (d) Koshino, H.; Takahashi, H.; Osada, H.; Isono, K. *J. Antibiot.* **1992**, *45*, 1420.

(82) Shimizu, T.; Masuda, T.; Hiramoto, K.; Nakata, T. *Org. Lett.* **2000**, *2*, 2153.

(83) Drouet, K. E.; Ling, T.; Tran, H. V.; Theodorakis, E. A. *Org. Lett*. **2000**, *2*, 207.

(84) Williams, D. R.; Barner, B. A. *Tetrahedron Lett.* **1983**, *24*, 427.

(85) Kocienski, P.; Street, S. D. A. *J. Chem. Soc., Chem. Commun.* **1984**, 571.

(86) (a) Ireland, R. E.; Daub, J. P. *J. Org. Chem.* **1983**, *48*, 1303. (b) Ireland, R. E.; Daub, J. P. *J. Org. Chem.* **1983**, *48*, 1312.

(87) Tietze, L. F.; Schneider, C. *J. Org. Chem.* **1991**, *56*, 2476.

(88) For reviews on the chemistry and synthesis of tricyclic spiroketal systems, see: (a) Brimble, M. A.; Fares, F. A. *Tetrahedron* **1999**, *55*, 7661. (b) Brimble, M. A.; Furkert, D. P. *Curr. Org. Chem.* **2003**, *7*, 1461.

(89) For studies on dispiroketals, see: (a) Brimble, M. A.; Rush, C. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 497. (b) McGarvey, G. J.; Stepanian, M. W.; Bressette, A. R.; Ellena, J. F. *Tetrahedron Lett.* **1996**, *37*, 5461. (c) McGarvey, G. J.; Stepanian, M. W.; Bressette, A. R.; Ellena, J. F. *Tetrahedron Lett.* **1996**, *37*, 5465.

(90) Faul, M. M.; Huff, B. E. *Chem. Rev.* **2000**, *100*, 2407.

(91) (a) Miyazaki, Y.; Shibuya, M.; Sugawara, H.; Kawaguchi, O.; Hirose, C.; Nagatsu, J. *J. Antibiot.* **1974**, *27*, 814. (b) Kinashi, H.; Otake, N.; Yonehara, H.; Sato, S.; Saito, Y. *Tetrahedron Lett.* **1973**, 4955. (c) Kinashi, H.; Otake, N.; Yonehara, H.; Sato, S.; Saito, Y. *Acta Crystallogr.* **1975**, *31*, 2411.

(92) (a) Westley, J. W.; Blount, J. F.; Evans, R. H.; Liu, C. *J. Antibiot.* **1977**, *30*, 610. (b) Berg, D. H.; Hamill, R. L. *J. Antibiot.* **1978**, *38*, 1. (c) Occolowitz, J. L.; Berg, D. H.; DeBuno, M.; Hamill, R. L. *Biomed. Mass Spectrom.* **1976**, *3*, 272. (d) Seto, H.; Yahagi, T.; Miyazaki, Y.; Otake, N. *J. Antibiot.* **1977**, *30*, 530. (e) Keller-Juslen, C.; King, H. D.; Kuhn, M.; Loosli, H.; Von Wartburg, A. *J. Antibiot.* **1978**, *31*, 820. (f) Westley, J. W.; Evans, R. H.; Sello, L. H.; Troupe, N.; Liu, C.; Blount, J. F.; Pitcher, R. G.; Williams, T. H.; Miller, P. A. *J. Antibiot.* **1981**, *34*, 139.

(93) For a comprehensive review on the chemistry and biology of polyether antibiotics including salinomycin, see: Westley, J. W. *Polyether Antibiotics*; Marcel Dekker: New York, 1983.

(94) See ref 3b and 8b and references therein.

(95) See ref 91b,c and (a) Kishi, Y.; Hatakeyama, S.; Lewis, M. D. Total synthesis of narasin and salinomycin. In *Frontiers of Chemistry*; Pergamon Press: Oxford, 1982; p 287. (b) Mronga, S.; Muller, G.; Fischer, J.; Ridell, F. *J. Am. Chem. Soc*. **1993**, *115*, 8414.

(96) (a) Horita, K.; Nakato, S.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron Lett.* **1987**, *288*, 3253. (b) Horita, K.; Oikawa, Y.; Nakato, S.; Yonemitsu, O. *Tetrahedron Lett.* **1988**, *29*, 5143. (c) Horita, K.; Oikawa, Y.; Yonemitsu, O. *Chem. Pharm. Bull.* **1989**, *37*, 1698. (d) Horita, K.; Nagato, S.; Oikawa, Y.; Yonemitsu, O. *Chem. Pharm. Bull.* **1989**, *37*, 1705. (e) Horita, K.; Oikawa, Y.; Nagato, S.; Yonemitsu, O. *Chem. Pharm. Bull.* **1989**, *37*, 1717. (f) Horita, K.; Nagato, S.; Oikawa, Y.; Yonemitsu, O. *Chem. Pharm. Bull.* **1989**, *37*, 1726.

(97) See ref 96 and (a) Horita, K.; Oikawa, Y.; Nakato, S.; Yonemitsu, O. *Tetrahedron Lett.* **1988**, *29*, 5143.

(98) (a) Brown, R. C. D.; Kocienski, P. J. *Synlett* **1994**, 415. (b) Brown, R. C. D.; Kocienski, P. J. *Synlett* **1994**, 417. (c) Kocienski, P. J.; Brown, R. C. D. *J. Chem. Soc., Perkin Trans.* **1998**, *1*, 9.

(99) For earlier studies on oxidative rearrangements in spiroketal synthesis, see: Kocienski, P.; Fall, Y.; Whitby, R. *J. Chem. Soc., Perkin Trans. 1* **1989**, 841.

(100) (a) Baker, R.; Brimble, M. A. *J. Chem. Soc., Chem. Commun*. **1985**, 78. (b) Baker, R.; Brimble, M. A.; Robinson, J. A. *Tetrahedron Lett.* **1985**, *26*, 2115. (c) Baker, R.; Brimble, M. A. *J. Chem. Soc., Perkin Trans. 1* **1988**, 125. (d) Brimble, M. A.; Williams, G. M.; Baker, R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2221. (e) Brimble, M. A.; Williams, G. M. *J. Org. Chem.* **1992**, *57*, 5818. (f) Allen, P. R.; Brimble, M. A.; Fares, F. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2403. (g) Brimble, M. A.; Fares, F. A.; Turner, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 677. (h) Brimble, M. A. *J. Heterocycl. Chem.* **1999**, *36*, 1373. (i) Allen, P. R.; Brimble, M. A.; Prabaharan, H. *Synlett* **1999**, 295. (j) Allen, P. R.; Brimble, M. A.; Prabaharan, H. *J. Chem. Soc., Perkin Trans. 1* **2001**, 379. (k) Brimble, M. A. *Molecules* **2004**, *9*, 394.

(101) (a) Kalvoda, J.; Heusler, K. *Synthesis* **1971**, 501. (b) Francisco, C. G.; Freire, R.; Hernández, R.; Medina, M. C.; Suárez, E. *Tetrahedron Lett.* **1983**, *24*, 4621. (c) Concepción, J. I.; Francisco, C. G.; Hernández, R.; Salazar, J. A.; Suárez, E. *Tetrahedron Lett.* **1984**, *25*, 1953. (d) Majetich, G.; Wheless, K. *Tetrahedron* **1995**, *51*, 7095.

(102) Perron, F.; Albizati, K. F. *J. Org. Chem.* **1989**, *54*, 2044.

(103) Uemura, D.; Chou, T.; Haino, T.; Nagatsu, A.; Fukuzawa, S.; Zheng, S. Z.; Chen, H. S. *J. Am. Chem. Soc*. **1995**, *117*, 1155.

(104) McCauley, J. A.; Nagasawa, K.; Lander, P. A.; Mischke, S. G.; Semones, M. A.; Kishi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 7647.

(105) For the formal total synthesis, see: (a) Sakamoto, S.; Sakazaki, H.; Hagiwara, K.; Kamada, K.; Ishii, K.; Noda, T.; Inoue, M.; Hirama, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 6505. For the synthesis of the BCD dispiroketal moiety, see: (b) Noda, T.; Ishiwata, A.; Uemura, S.; Sakamoto, S.; Hirama, M. *Synlett* **1998**, 298. For other synthetic studies of pinnatoxin A, see: (c) Ishiwata, A.; Sakamoto, S.; Noda, T.; Hirama, M. *Synlett* **1999**, 692. (d) Nitta, A.; Ishiwata, A.; Noda, T.; Hirama, M. *Synlett* **1999**, 695. (e) Wang, J.; Sakamoto, S.; Kamada, K.; Nitta, A.; Noda, T.; Oguri, H.; Hirama, M. *Synlett* **2003**, 891.

(106) (a) Sugimoto, T.; Ishihara, J.; Murai, A. *Tetrahedron Lett.* **1997**, *38*, 7379. (b) Sugimoto, T.; Ishihara, J.; Murai, A. *Synlett* **1999**,

541. (c) Ishihara, J.; Tojo, S.; Kamikawa, A.; Murai, A. *Chem. Commun.* **2001**, 1392.
(107) Ishihara, J.; Sugimoto, T.; Murai, A. *Synlett* **1998**, 603.
(108) This result underscores the difficulties associated with computational modeling of structures stabilized by hydrogen bonding. For further discussion, see: Gilli, G.; Gilli, P. *J. Mol. Struct.* **2000**, *552*, 1.
(109) (a) Nakamura, S.; Inagaki, J.; Sugimoto, T.; Kudo, M.; Nakajima, M.; Hashimoto, S. *Org. Lett.* **2001**, *3*, 4075. For detailed consideration of the stereochemical models, see: (b) Nakamura, S.; Inagaki, J.; Kudo, M.; Sugimoto, T.; Obara, K.; Nakajima, M.; Hashimoto, S. *Tetrahedron* **2002**, *58*, 10353.
(110) Satake, M.; Ofuji, K.; Naoki, H.; James, K. J.; Furey, A.; McMahon, T.; Silke, J.; Yasumoto, T. *J. Am. Chem. Soc.* **1998**, *120*, 9967.
(111) (a) Ofuji, K.; Satake, M.; McMahon, T.; Silke, J.; James, K. J.; Naoki, H.; Oshima, Y.; Yasumoto, T. *Nat. Toxins* **1999**, *7*, 99. (b) Ofuji, K.; Satake, M.; McMahon, T.; James, K. J.; Naoki, H.; Oshima, Y.; Yasumoto, T. *Biosci. Biotechnol. Biochem.* **2001**, *65*, 740.
(112) McMahon, T.; Silke, J. *Harmful Algae News* **1996**, *14*, 2.
(113) (a) Nicolaou, K. C.; Vyskocil, S.; Koftis, T. V.; Yamada, Y. M. A.; Ling, T.; Chen, D. Y.-K.; Tang, W.; Petrovic, G.; Frederick, M. O.; Satake, Y. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4312. (b) Nicolaou, K. C.; Koftis, T. V.; Vyskocil, S.; Petrovic, G.; Ling, T.; Yamada, Y. M. A.; Tang, W.; Frederick, M. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 4318. For other publications covering the structural revision, see: (c) Nicolaou, K. C.; Li, Y.; Uesaka, N.; Koftis, T. V.; Vyskocil, S.; Ling, T.; Govindasamy, M.; Qian, W.; Bernal, F.; Chen, D. Y.-K. *Angew. Chem., Int. Ed.* **2003**, *42*, 3643. (d) Nicolaou, K. C.; Chen, D. Y.-K.; Li, Y.; Qian, W.; Ling, T.; Vyskocil, S.; Koftis, T. V.; Govindasamy, M.; Uesaka, N. (e) Nicolaou, K. C.; Snyder, S. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1012.
(114) Nicolaou, K. C.; Qian, W.; Bernal, F.; Uesaka, N.; Pihko, P. M.; Hinrichs, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4068.
(115) (a) Carter, R. G.; Graves, D. E. *Tetrahedron Lett.* **2001**, *42*, 6035. (b) Carter, R. C.; Bourland, T. C.; Graves, D. E. *Org. Lett.* **2002**, *4*, 2177. (c) Carter, R. G.; Graves, D. E.; Gronemeyer, M. A.; Tschumper, G. S. *Org. Lett.* **2002**, *4*, 2181. (d) Carter, R. G.; Bourland, T. C.; Zhou, X.-T.; Gronemeyer, M. A. *Tetrahedron* **2003**, *59*, 8963. (e) Zhou, X.-T.; Carter, R. G. *Chem. Commun.* **2004**, 2138.
(116) (a) Ishikawa, Y.; Nishiyama, S. *Tetrahedron Lett.* **2004**, *45*, 351. (b) Ishikawa, Y.; Nishiyama, S. *Heterocycles* **2004**, *63*, 539. (c) Ishikawa, Y.; Nishiyama, S. *Heterocycles* **2004**, *63*, 885.
(117) Potuzak, J. S.; Moilanen, S. B.; Tan, D. S. *J. Am. Chem. Soc.* **2005**, *127*, 13796.

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