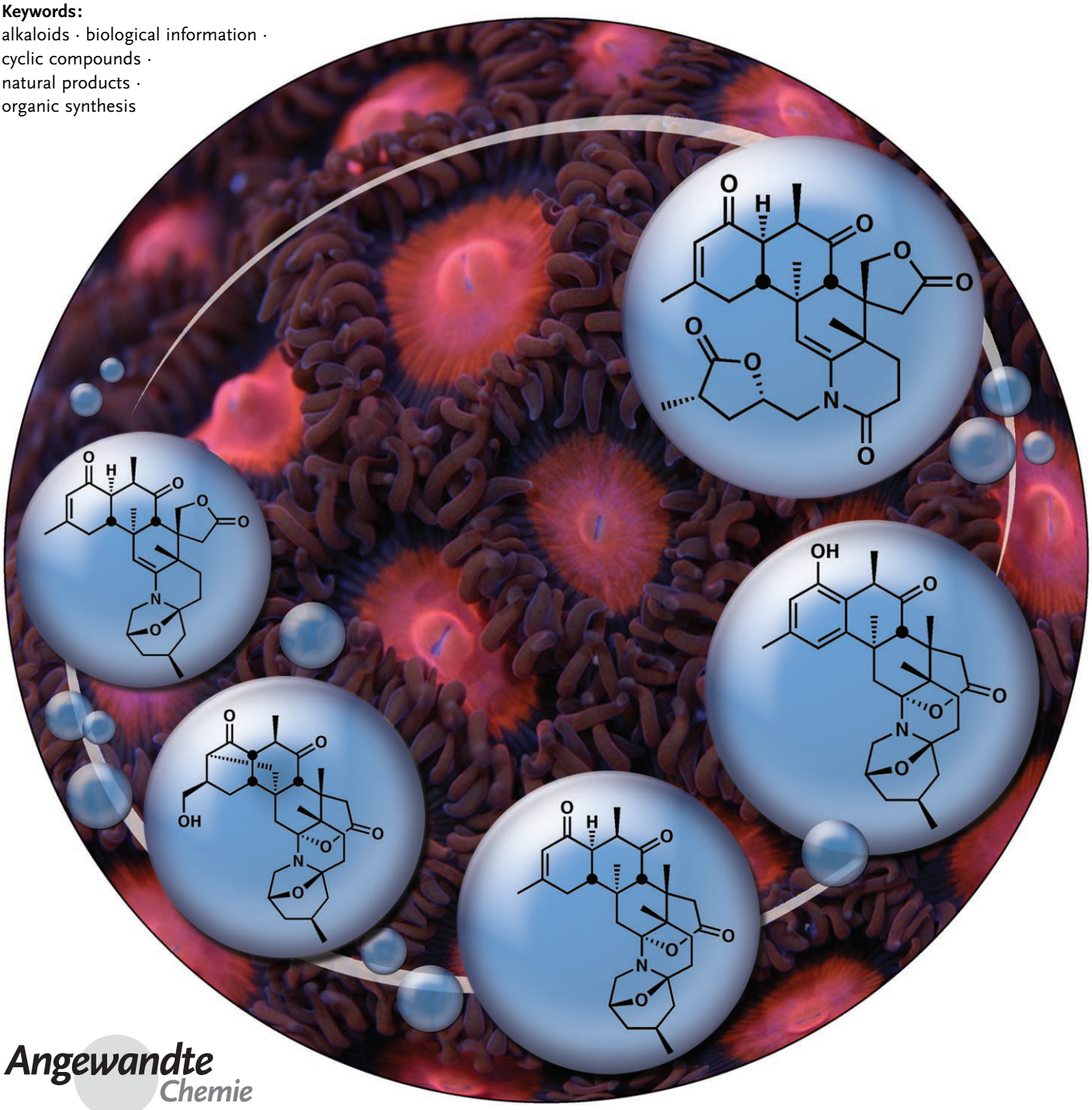
DOI: 10.1002/anie.200703172

Marine Natural Products

The Biology and Chemistry of the Zoanthamine Alkaloids

*Douglas C. Behenna, Jennifer L. Stockdill, and Brian M. Stoltz**

Keywords:
alkaloids · biological information · cyclic compounds · natural products · organic synthesis



© 2008 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Marine natural products have long played an important role in natural products chemistry and drug discovery. Mirroring the rich variety and complicated interactions of the marine environment, the substances isolated from sea creatures tend to be incredibly diverse in both molecular structure and biological activity. The natural products isolated from the polyps of marine zoanthids are no exception. The zoanthamine alkaloids, the first of which were isolated over 20 years ago, are of particular interest to the synthetic community because they feature a novel structural framework and exhibit a broad range of biological activities. In this Review, we summarize the major contributions to understanding the zoanthamine natural products with regard to their isolation and structure determination, as well as studies on their biological activity and total synthesis.

From the Contents

1. Introduction 2366
2. The Zoanthamines 2366
3. Biological Activities of Zoanthamine Alkaloids 2371
4. Synthesis of Zoanthamines 2373
5. Summary and Outlook 2384

1. Introduction

Marine species comprise a vast repository for the isolation of natural products. In this Review, we will focus on the biological and chemical properties of the zoanthamine alkaloids isolated from marine zoanthids. The order zoantharia consists of an intriguing group of marine polyps, which are morphologically classified into at least a dozen genera. Species in this order (Figure 1) are widely dispersed throughout the temperate and tropical littoral regions of the Indian, Pacific, and Atlantic Oceans, and these vibrant soft corals are generally aggressive colonizers of reef environments. In the wild, these stunning organisms reproduce both sexually and asexually.[1] Recently, analysis of their respective mitochondrial DNA has elucidated the relationships between them.[2]

The polyps have a tube-shaped body and are radially symmetrical, and on top of the body are tentacles that guide food to the central orifice for digestion. When alarmed, the polyps contract their tentacles inward, and some species also expel a stream of water laden with powerful toxins from their bodies as a means of defense from predators. For example, the zoanthids from which the zoanthamines were isolated release a severe eye irritant when disturbed.[3] Zoanthids frequently contain symbiotic microalgae, which provide additional energy through photosynthesis. These dinoflagellate algae are thought to play an important role in the biosynthesis of some of the secondary metabolites isolated from the zoanthids.[4]

Figure 1. Selected zoanthids

Diverse natural product archetypes have been isolated from species in the order zoantharia (Scheme 1). Zoanthamine (**1**) is a member of the *Zoanthus* alkaloids, the subject of this Review. Zoanthusterone (**2**) is an ecdysteroid isolated from a *Zoanthus* species.[5] Prostaglandins such as PGA_2 (**3**), isolated from *Palythoa kochii*, stabilize microtubules in a manner similar to paclitaxel.[6] A family of more than a dozen natural products based on the zoanthoxanthin (**4**) skeleton has been isolated from *Parazoanthus axinellae*,[7] and a related structure, parazoanthoxanthin A, shows anticholinesterase activity.[8] Perhaps the best-known isolate from these marine organisms is palytoxin (**5**), which was isolated from *Palythoa* species in the Hawaiian islands and is one of the most toxic compounds known ($LD_{50} = 15\ \mu g\,kg^{-1}$ in mice).[9] The palytoxin structure was determined by Kishi, Uemura, Hirata, and co-workers, and later synthesized by Suh and Kishi.[10]

2. The Zoanthamines

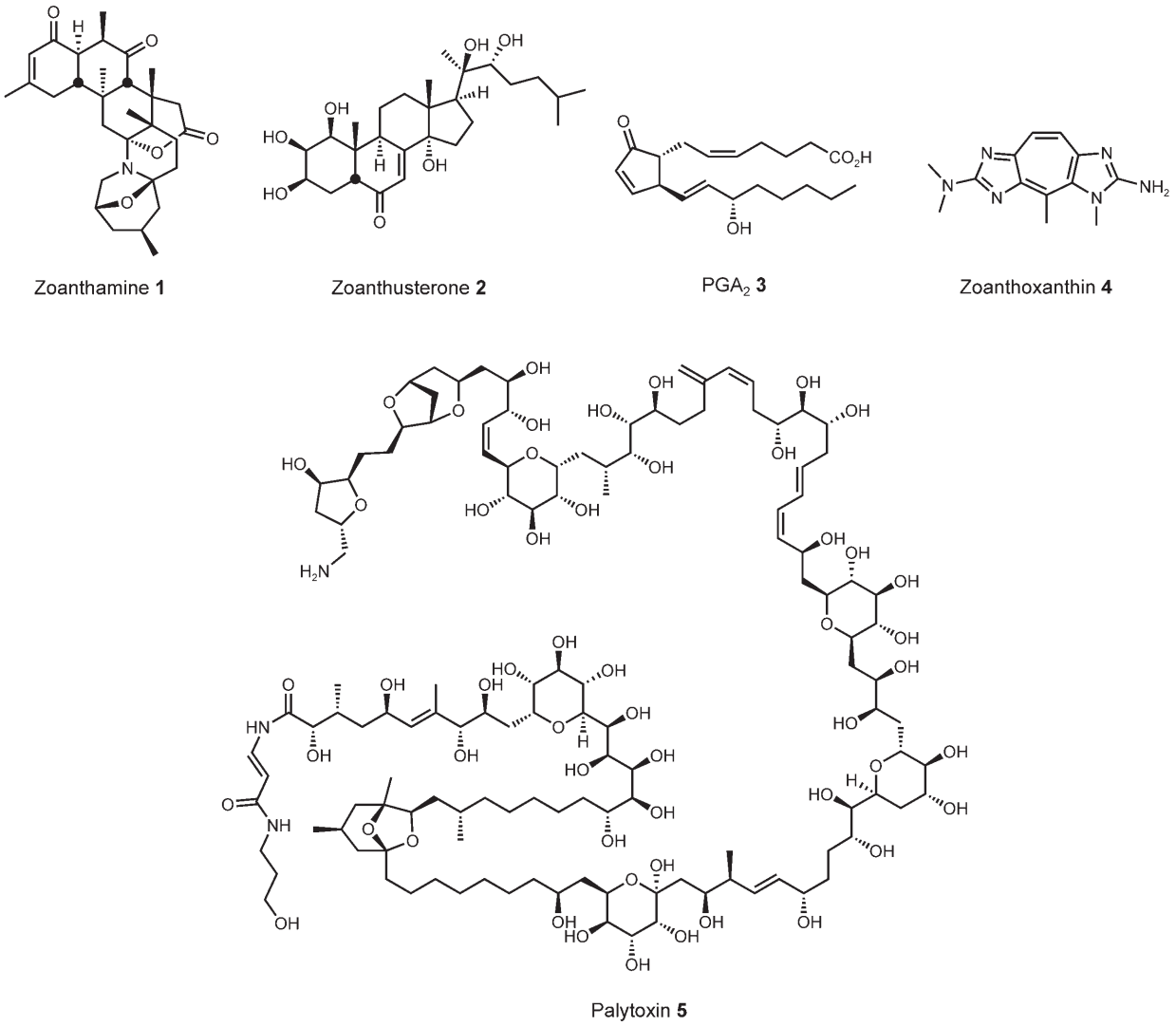
2.1. Isolation and Structural Characterization

In 1984, Rao, Faulkner, and co-workers disclosed the isolation of the natural product zoanthamine (**1**) from a

[*] Dr. D. C. Behenna, J. L. Stockdill, Prof. Dr. B. M. Stoltz
The Arnold and Mabel Beckman Laboratories of Chemical Synthesis
Division of Chemistry and Chemical Engineering
California Institute of Technology
1200 E. California Boulevard, MC 164-30
Pasadena, CA 91125 (USA)
Fax: (+1) 626-564-9297
E-mail: stoltz@caltech.edu
Homepage: http://www.stoltz.caltech.edu

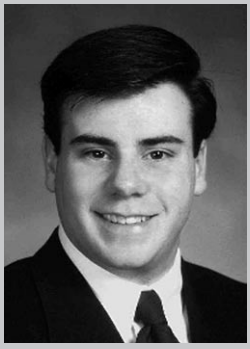
WILEY InterScience DISCOVER SOMETHING GREAT

© 2008 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 1. Natural products isolated from zoanthids.

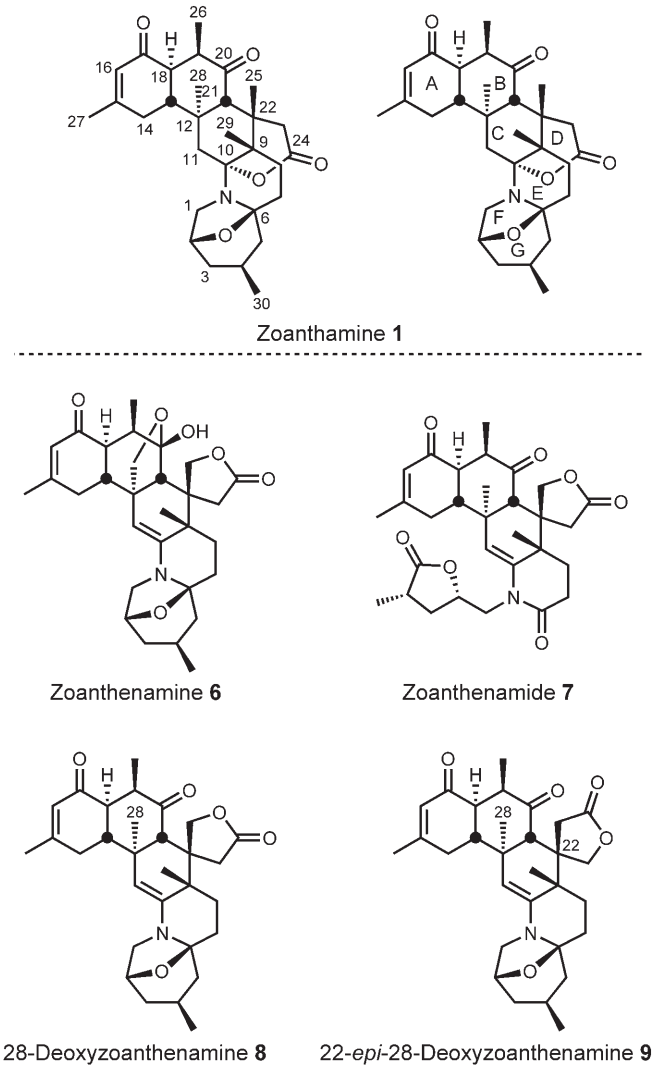
species of the genus *Zoanthus* off the Visakhapatnam coast of India.[3] The connectivity and relative stereochemistry of the previously unknown alkaloid skeleton was unambiguously determined by single-crystal X-ray diffraction studies.[3] (Throughout this Review, the carbon numbering and ring naming will refer to that of zoanthamine (**1**) in Scheme 2.) The initial isolation effort also afforded the related natural products zoanthenamine (**6**) and zoanthenamide (**7**), which were reported in 1985.[11] In 1989, Rao and co-workers isolated 28-deoxyzoanthenamine (**8**) and 22-*epi*-28-deoxyzoanthenamine (**9**) from a *Zoanthus* species in the Bay of Bengal (Scheme 2).[12] The structures of **6**–**9** were deduced by comparison with the spectroscopic data of zoanthamine (**1**). Although these isolation efforts were undertaken in search of



Douglas C. Behenna was born in Norristown, Pennsylvania in 1978. He earned his BA in Chemistry at the University of Pennsylvania in 2000, while working in the group of Professor Dewey G. McCafferty. He completed his PhD in 2006 with Professor Brian M. Stoltz at Caltech (Hertz Fellowship), and is currently pursuing postdoctoral studies in the laboratories of Professor E. J. Corey at Harvard University. His research interests include the synthesis of complex natural products and the development of new synthetic methods.

Jennifer L. Stockdill was born in Mankato, Minnesota, USA in 1981. She obtained a BS in Chemistry at Virginia Polytechnic Institute and State University in 2003, working with Professor Felicia A. Etzkorn and Professor Alan R. Esker. She is currently pursuing a PhD under the direction of Professor Brian M. Stoltz at Caltech as a Novartis Women and Minorities Research Fellow. Her research interests include the total synthesis of biologically relevant natural products and the design and mechanistic investigation of new reaction methods.

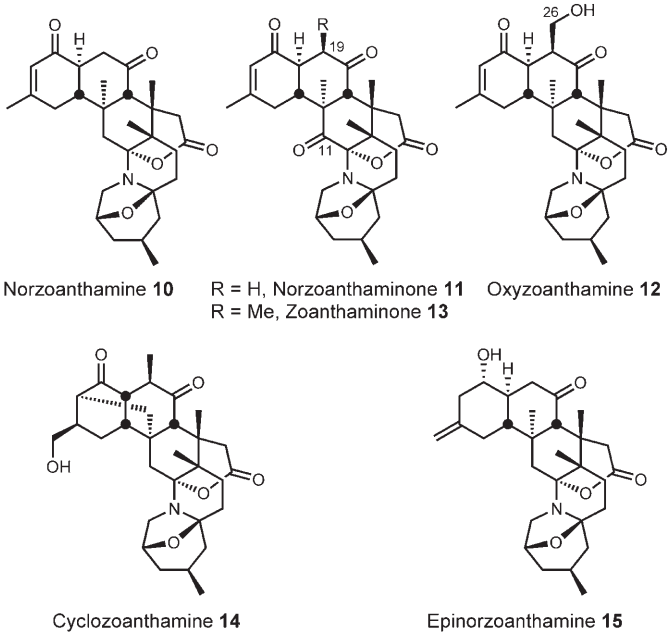
 © 2008 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 2. Zoanthamine natural products isolated by the research groups of Rao and Faulkner.

a known eye irritant produced by the *Zoanthus* species, all five of the isolated alkaloids showed inhibition of inflammation induced by phorbol myristate acetate (PMA) in mouse ears.[3,11]

In 1995, Uemura and co-workers identified five new zoanthamine natural products isolated from a *Zoanthus* species collected off the Ayamaru coast of the Amami Islands south of Japan.[13] These isolates displayed structural variations including compounds lacking a substituent at C19, such as norzoanthamine (**10**) and norzoanthaminone (**11**), which is also oxidized at C11 (Scheme 3). Oxyzoanthamine (**12**) is unique in that it displays C26 oxidation. The relative configuration of norzoanthamine was confirmed by X-ray diffraction studies.[13] The absolute configuration of norzoanthamine was later determined by NMR analysis of MTPA derivatives to be as shown in Scheme 3.[14] Zoanthaminone (**13**) contains 30 carbon atoms and is oxidized at C11; its X-ray crystal structure was disclosed by Clardy and coworkers.[15] Cyclozoanthamine (**14**) and epinorzoanthamine (**15**) display intriguing modifications to the A-ring enone functionality. Both structures were assigned by extensive NOE experiments.[13]

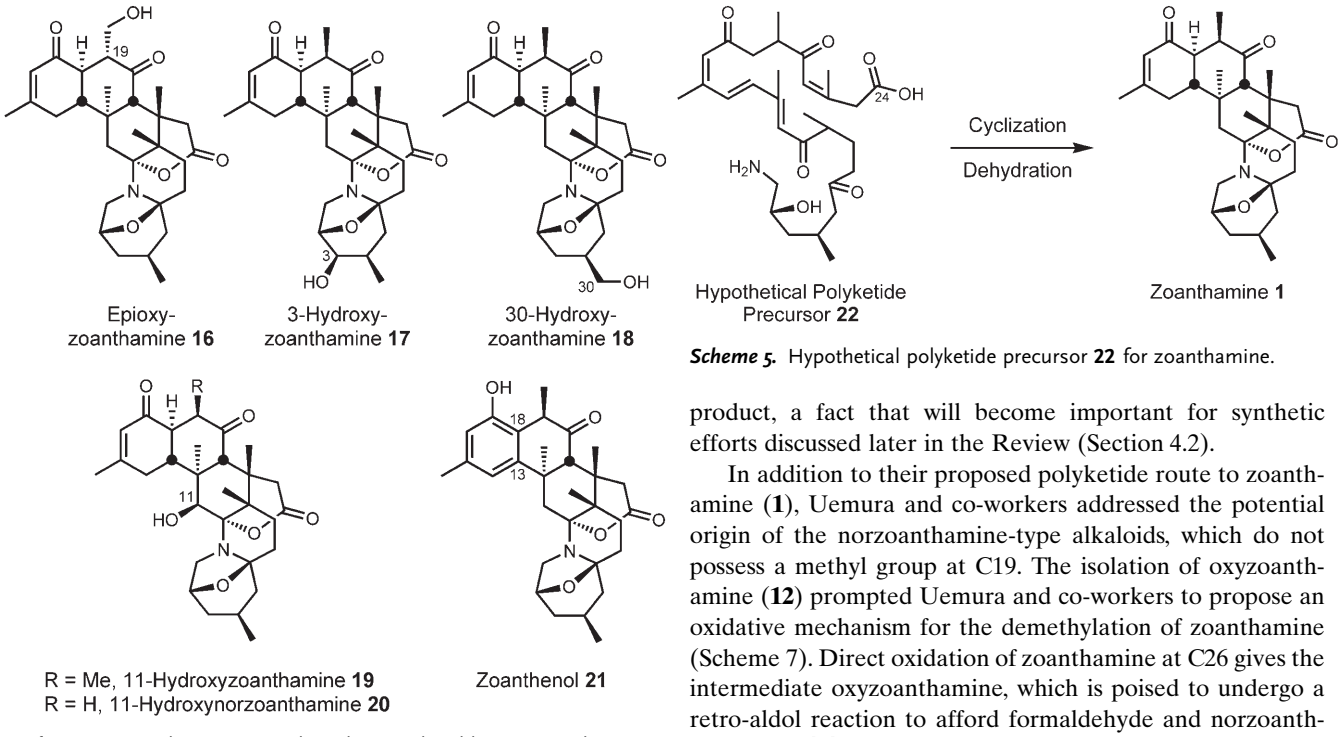


Scheme 3. Zoanthamine natural products isolated by the research groups of Uemura and Clardy.

In 1996, Norte and co-workers isolated a number of zoanthamine alkaloids with interesting oxidation patterns from zoanthids in the Canary Islands (Scheme 4). Epioxyzoanthamine (**16**) is unique in its C19 configuration, which was determined by comparison with NMR data of oxyzoanthamine (**12**).[16] 3-Hydroxyzoanthamine (**17**) and 30-hydroxyzoanthamine (**18**) show novel sites of oxidation, while 11-hydroxyzoanthamine (**19**) and 11-hydroxynorzoanthamine (**20**) are presumably related to zoanthaminone and norzoanthaminone, respectively. Zoanthenol (**21**) has a unique oxidized aromatic A ring, which removes the C13 and C18 stereocenters. As a result of the structural change, extensive

Brian M. Stoltz was born in Philadelphia, Pennsylvania in 1970. After spending a year at the Ludwig Maximilians Universität in München, Germany, he obtained his BS in Chemistry and BA in German from Indiana University of Pennsylvania (1993). He then earned his PhD in 1997 under the direction of Professor John L. Wood at Yale University. After postdoctoral research with Professor E. J. Corey at Harvard University (1998–2000, NIH fellowship), he joined the faculty at Caltech in 2000 where he is currently a Professor of Chemistry. His research focuses on the design and implementation of new synthetic strategies for the synthesis of complex molecules with important biological properties, and the development of new synthetic methods including asymmetric catalysis and cascade processes.

 © 2008 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 4. Zoanthamine natural products isolated by Norte and co-workers.

Scheme 5. Hypothetical polyketide precursor **22** for zoanthamine.

HMBC and ROESY correlation experiments were performed to confirm its structure and relative configuration.[17]

2.2. Biosynthesis of the Zoanthamines

Despite their history of more than 20 years, relatively little is known about the biosynthesis of the zoanthamine natural products. Rao et al. noted in 1984 that elements of the 30-atom zoanthamine carbon skeleton suggest a triterpene origin; however, they were unable to identify normal head-to-tail linkages to account for the zoanthamine skeleton.[3] More recently, Uemura and co-workers have proposed that the zoanthamines may arise from polyketide precursor **22** (Scheme 5),[14,18] with polyketide biosynthesis beginning at the C24 carboxylate,[4] but further details of the pathway were not given. Nevertheless, proposed intermediate **22** accounts for most of the oxygenation found in the zoanthamines, and it does readily lead to the zoanthamine structure following standard organic reaction mechanisms (Scheme 6).

A mechanism for the conversion of **22** into **1** begins with tautomerization, an electrocyclization, and a Diels–Alder reaction to form intermediate **23**. Tautomerization and activation of the carbonyl group in **23** yields **24**, which then undergoes 6-*exo* alcohol attack and protonation to form intermediate **25**. Formation of the oxocarbenium ion with loss of water gives **26**, which undergoes a subsequent amine attack and proton transfer to give intermediate **27**. Release of water provides iminium ion **28**, then carboxylic acid attack and a subsequent deprotonation provides zoanthamine (**1**). The reversibility of each step in the formation of the DEFG ring system allows formation of the thermodynamically favored product, a fact that will become important for synthetic efforts discussed later in the Review (Section 4.2).

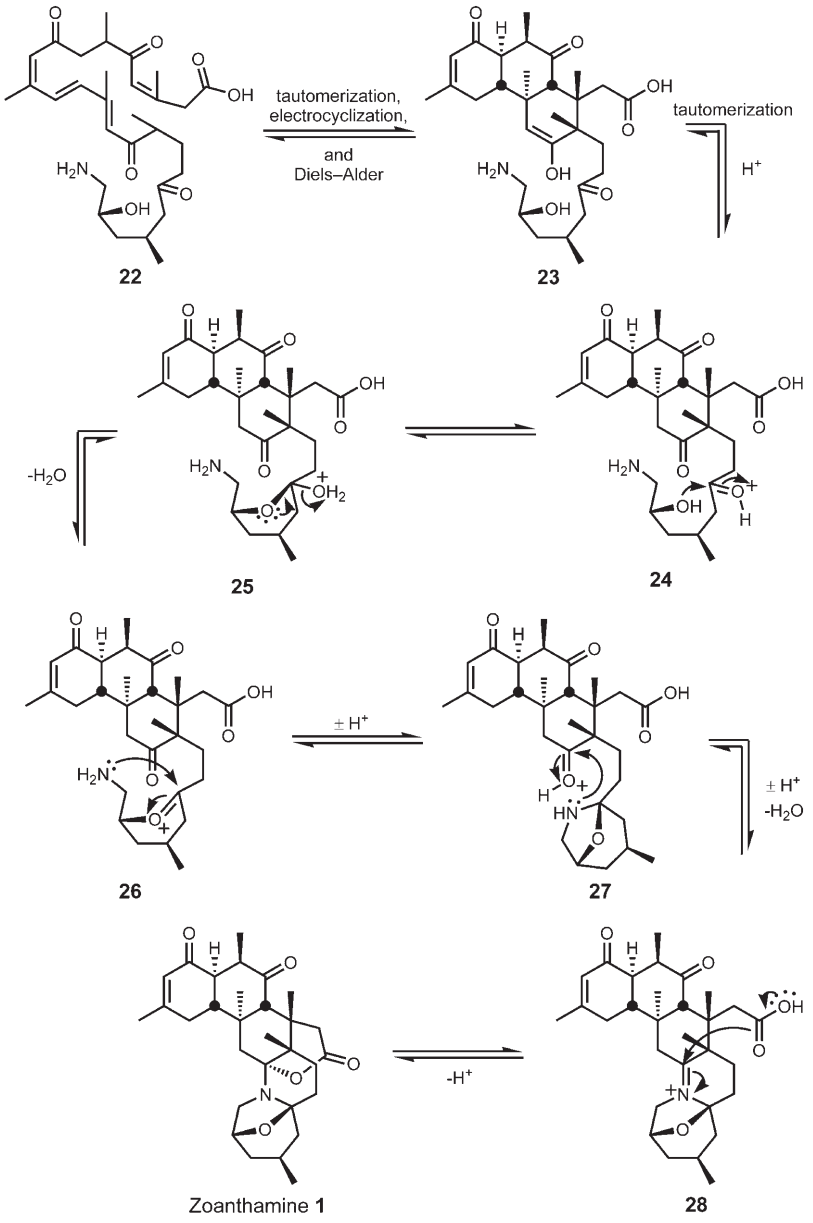
In addition to their proposed polyketide route to zoanthamine (**1**), Uemura and co-workers addressed the potential origin of the norzoanthamine-type alkaloids, which do not possess a methyl group at C19. The isolation of oxyzoanthamine (**12**) prompted Uemura and co-workers to propose an oxidative mechanism for the demethylation of zoanthamine (Scheme 7). Direct oxidation of zoanthamine at C26 gives the intermediate oxyzoanthamine, which is poised to undergo a retro-aldol reaction to afford formaldehyde and norzoanthamine (**10**).[13] It is unclear why Uemura and co-workers do not propose substitution of an acetate unit for the relevant propionate unit. Such a modification of 22 (Scheme 5) would allow direct access to the zoanthamines lacking C26, such as norzoanthamine (**10**), while direct oxidation of C26 itself could still explain the formation of oxyzoanthamine (**12**).

Another factor complicating the understanding of the biosynthesis of the zoanthamine alkaloids is the role of the symbiotic dinoflagellate algae that are commonly contained in zoanthids. Algae of the genus *Symbiodinium* have been isolated from zoanthids of the genus *Zoanthus*.[19] Although such symbiotic strains are difficult to culture axenically,[*] Nakamura et al. have been able to produce quantities of *Symbiodinium* species free of zoanthids.[4] While the algae produced different distributions of metabolites depending on the media used, significant experimentation with culture conditions allowed the Nakamura research group to isolate the new C_{30} alkaloid zooxanthellamine (**29**). Zooxanthellamine exists as an equilibrium between a hemiaminal lactone and an iminium carboxylate (Scheme 8). Its structure and relative configuration were established by extensive NMR studies. Zooxanthellamine (**29**) has the same absolute configuration as the zoanthamine alkaloids, as demonstrated by comparison of the NMR data of its MTPA ester.[4]

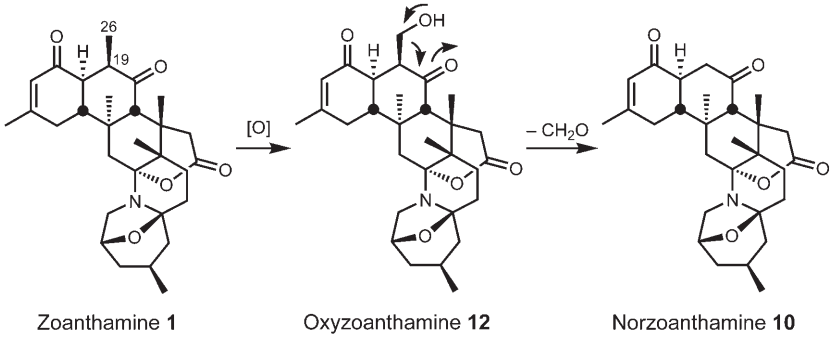
The remarkable similarity between zooxanthellamine (**29**) and zoanthamine (**1**) has called into question the role of the zoanthids in producing the zoanthamine natural products.[20] It may be that the zoanthids play only a small role in the biosynthesis, such as adjusting the oxidation state of the completed zoanthamine skeleton. The subtle variations in the alkaloid structures could be determined by factors in the

[*] An axenic culture is one that is prepared completely free from any other living organisms, including contamination or, in this case, the host zoanthid.

 © 2008 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 6. Mechanism for the cyclization of the hypothetical polyketide precursor **22** to form zoanthamine.



Scheme 7. Proposed biosynthesis of norzoanthamine.

marine environment or by the host zoanthid species. Alternatively, different species of algae may be involved in the production of different zoanthamines.

To date, there has been only one published attempt at a study directed toward the elucidation of the biogenesis of the zoanthamines. Norte and co-workers conducted a feeding study, during which labeled sodium acetate, glycine, and glucose were fed to small colonies of *Zoanthus* species.[7] Although the levels of incorporation of the labeled atoms were higher than 10% for all cases, the incorporation appeared to be random, thus leaving the question of the biosynthesis of the zoanthamines unanswered.

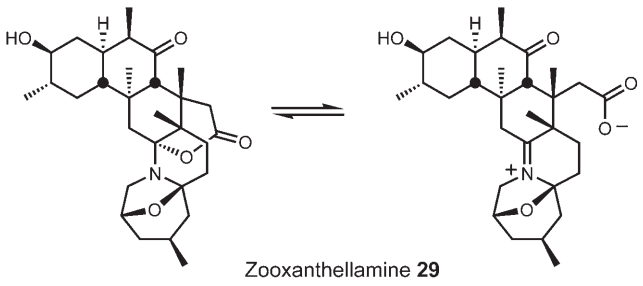
Perhaps the clearest insight offered by these biosynthetic proposals is that there is a definite need for further experimental studies elucidating the biogenesis of these compounds. Without such experimental data, no proposal can be either soundly supported or rationally refuted.

2.3. Reactivity of Norzoanthamine

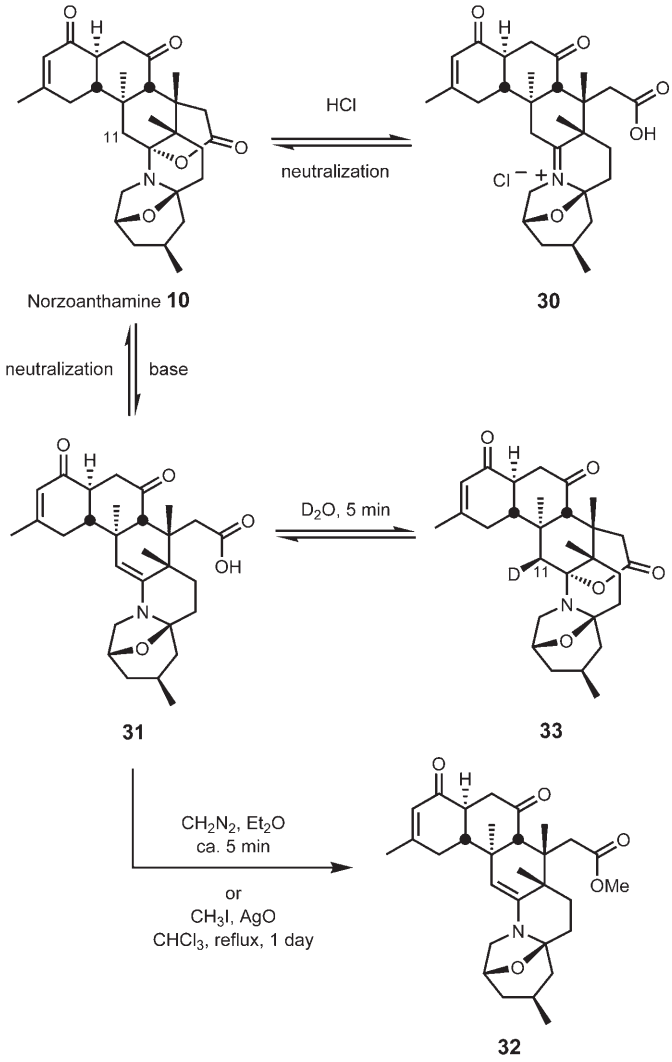
Following its isolation, norzoanthamine (**10**) was subjected to a number of reaction conditions to aid in the formation of hypotheses about its mechanism of action for various biological activities.

An equilibrium between the lactone and iminium forms—similar to that of zooxanthellamine (Scheme 8)—has been demonstrated in several zoanthamine natural products (Scheme 9). Norzoanthamine (**10**) forms iminium **30** under acidic conditions and is reformed upon neutralization.[18] Under neutral to basic conditions, elimination occurs to form enamine **31**. The equilibrium between norzoanthamine (**10**) and enamine **31** was demonstrated by the conversion of norzoanthamine into methyl ester **32** within minutes upon exposure to diazomethane.[18] Furthermore, the NMR spectra of norzoanthamine (**10**) recorded in D_2O show specific and complete deuterium incorporation at the 11β-position to give deuteride **33**.[16,17] Similar rates of deuterium incorporation were observed with zoanthenol (**21**), 3-hydroxynorzoanthamine, and 30-hydroxnorzoanthamine. In contrast, the 11β-hydroxyzoanthamines did not show significant deuterium incorporation, which suggests that the elimination to an enamine is inaccessible.[17] This dynamic behavior in aqueous media at physiologically relevant

 © 2008 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 8. Structure of zooxanthellamine.



Scheme 9. Equilibria between lactone and enamine forms of norzoanthamine.

pH values may play an important role in determining the bioactivities of these molecules.

The hemiaminal region of the zoanthamine alkaloids also shows intriguing reactivity under reductive conditions. Treatment of norzoanthamine (**10**) with sodium borohydride generates two anomalous products: enone **34** and allylic alcohol **35** (Scheme 10).[14,18] The formation of these products may be explained by an opening of the hemiaminal to form iminium **36**. Deprotonation leads to enamine **37**, which is believed to attack the lactone in an intramolecular fashion to afford the keto-iminium intermediate **38**. Dehydration generates iminium **39**, which undergoes reduction to give enone **34**. Further reduction affords allylic alcohol **35**.

3. Biological Activities of Zoanthamine Alkaloids

3.1. Antiosteoporotic Activity

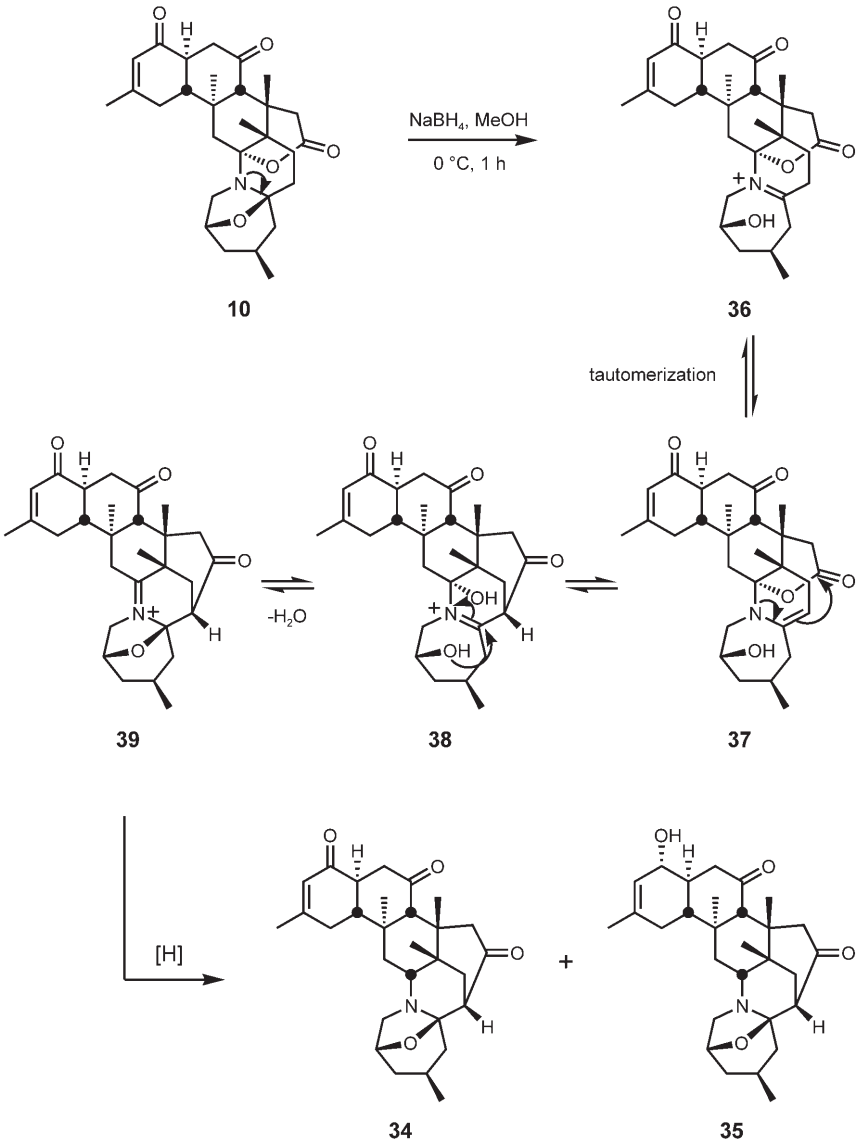
Perhaps the best-studied and most well-known biological activity of the zoanthamine alkaloids is the antiosteoporotic effect first reported by Uemura and co-workers in 1996.[21] Osteoporosis is a loss of bone mineral density that often results when osteoclasts reabsorb bone tissue at a rate faster than it is regenerated.[22] Norzoanthamine (**10**) and its hydrochloride salt (**30**) have been shown to prevent the symptoms of osteoporosis in vivo in ovariectomized mice, a pharmaceutical model for postmenopausal osteoporosis.[21] Ovariectomized mice, which are inherently deficient in estrogen, quickly lose bone mass and strength. However, at doses of 0.08–2.0 $mg\,kg^{-1}\,day^{-1}$ (five days a week for four weeks, p.o.) of norzoanthamine hydrochloride, these mice retained femur weight at statistically higher rates than the untreated ovariectomized mice.[18,21] With 0.4 $mg\,kg^{-1}\,day^{-1}$ of norzoanthamine hydrochloride (**30**), the femurs of ovariectomized mice maintained their strength, as measured by failure load, at nearly comparable levels to non-ovariectomized control mice.[18,21] Mice treated with norzoanthamine hydrochloride (**30**) possessed cortical bone that is significantly thicker than that found in the control animals.[23]

In analogy to estrogen replacement therapy in postmenopausal women, treatment with 17β-estradiol reverses the effects of osteoporosis in ovariectomized mice. However, treatment with norzoanthamine hydrochloride (**30**) shows interesting differences from estrogen therapy: 17β-estradiol causes a dose-dependent increase in uterine weight in treated mice, while mice treated with norzoanthamine hydrochloride did not exhibit this side effect.[23]

The origin of the antiosteoporotic effect of norzoanthamine (**10**)—like estrogen[24]—may lie in its ability to suppress the production of interleukin 6 (IL-6). IL-6 is involved in stimulating the generation of osteoclasts, which reabsorb bone tissue. Norzoanthamine (**10**) and its hydrochloride salt (**30**) suppress the excretion of IL-6 from preosteoblastic cells at concentrations of 13 and 4.6 $\mu g\,mL^{-1}$, respectively, in vitro.[25] However, in vitro studies with norzoanthamine hydrochloride (**30**) showed no effect on the formation of osteoclasts, and suppression of IL-6 secretion has not yet been demonstrated in vivo.[23] These last two points, together with the lack of uterine weight gain in ovariectomized mice, suggest that the zoanthamine alkaloids may act by a mechanism distinct from estrogen therapies,[26] and thus they may offer treatments for postmenopausal osteoporosis with fewer side effects.

The need to find non-estrogen osteoporosis therapies has spurred considerable effort to define a structure–activity relationship (SAR) for the antiosteoporotic effects of nor-

 © 2008 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 10. Unexpected reduction of norzoanthamine.

zoanthamine (**10**). Uemura and co-workers used semisynthesis to produce a number of zoanthamine derivatives (Scheme 11). Each compound was then tested for IL-6 inhibitory activity.[18,25] It should be noted that all of the derivatives assayed were significantly less efficacious (higher IC_{50} values) in limiting IL-6 production than norzoanthamine (**10**).[27] The studies revealed that the removal of the olefinic double bond (such as in ketone **41** and diol **42**) caused some loss in activity. Furthermore, disruption of the lactone/hemiaminal functionality (in carboxylic acid **43** and ester **32**) also resulted in a drop in activity.[18]

More recently, Hirama and co-workers have conducted an SAR study of zoanthamine-related molecules to determine the structural features needed to inhibit the growth of IL-6-dependent MH-60 cells (Scheme 12).[28] In their assays, the hydrochloride salts **30** and **44** showed the greatest inhibition of MH-60 cell growth (IC_{50}: 13 and 26 μM, respectively). The model compounds **45**, for the "northern" carbocyclic region of zoanthenol, and **46**, for the "southern" heterocyclic region, both showed very poor activity. However, iminium **47**, demonstrated activity approaching that of the zoanthamine hydrochlorides. This result provides further support for two trends: 1) the hydrochloride salt form of a zoanthamine-related molecule is typically a more active inhibitor of IL-6 production than the natural product, and 2) the heterocyclic portion of the molecule is likely important in the pharmacophore for IL-6 inhibition.

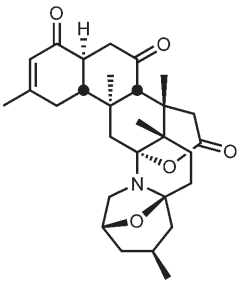
3.2. Miscellaneous Biological Activities

A variety of other biological activities have been reported for molecules in the zoanthamine family. As mentioned in Section 2.1, zoanthamine (**1**), zoanthenamine (**6**), and zoanthenamide (**7**) were found to be inhibitors of PMA-induced ear inflammation in mice.[3,11] Uemura and co-workers reported that norzoanthamine (**10**), norzoanthaminone (**11**), oxyzoanthamine (**12**), cyclozoanthamine (**14**), and epinorzoanthamine (**15**) display significant cytotoxicity against P388 murine leukemia cells (Table 1).[13] The most potent cytotoxicity was displayed by norzoanthaminone (**11**) and oxyzoanthamine (**12**).

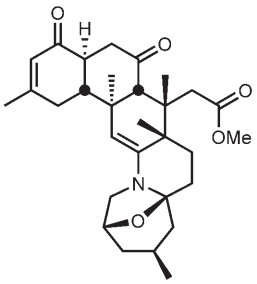
The antibacterial properties of zoanthamine (**11**) and several of its reduced derivatives have also been investigated.[29] In disk susceptibility experiments, the zoanthamine alkaloids showed activity against both Gram-negative and Gram-positive bacteria (Table 2).

More recently, the effect of zoanthamine alkaloids on human platelet aggregation has been investigated.[30] These experiments showed that at concentrations of 0.5 mM, 11β-hydroxyzoanthamine (**19**) and related methyl ester **32** inhibit platelet aggregation caused by collagen, arachidonic acid, and thrombin. Oxyzoanthamine (**12**) and zoanthenol (**21**) were highly selective inhibitors, showing inhibition of aggregation in the presence of collagen at 0.5 mM, but showing almost no activity in the presence of arachidonic acid or thrombin. Such selective activity is important in the potential treatment of cardiovascular disease. The formation of a thrombus as a result of abnormal platelet aggregation can lead to the obstruction of a vein or artery, thus causing an infarction or stroke.[31] Several antithrombotic agents are already in use for treating cardiovascular disease; however, their efficacy is limited by weak antithrombotic effects at the administered dosage and/or deleterious side effects such as the inhibition of haemostasis, which leads to significant abnormal bleeding.[32]

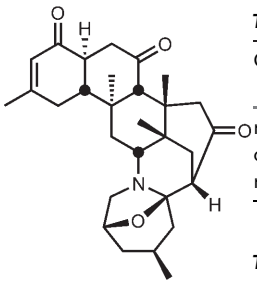
 © 2008 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



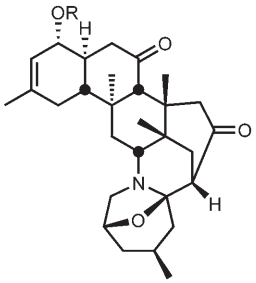
Norzoanthamine **10**
13 μg mL^{-1} (HCl salt)



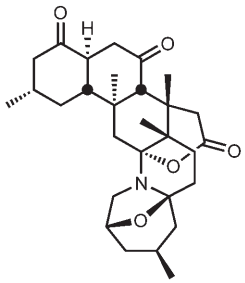
32, >100 μg mL^{-1}



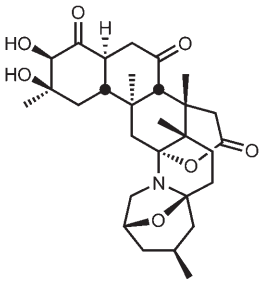
38, 25 μg mL^{-1}



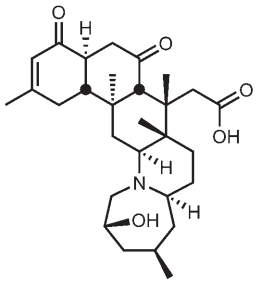
39, R = H, 30 μg mL^{-1}
40, R = OAc, 23 μg mL^{-1} [1]



41, 45 μg mL^{-1}

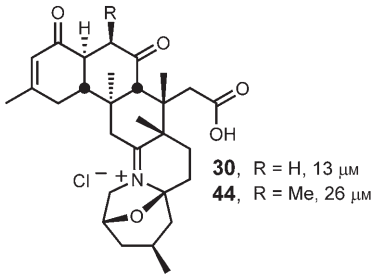


42, 35 μg mL^{-1}

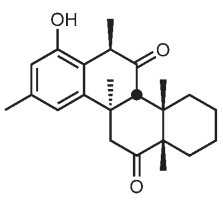


43, 42 μg mL^{-1}

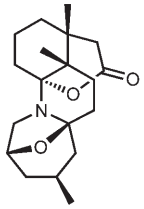
Scheme 11. IC_{50} values for the inhibition of IL-6 production in the SAR study by Uemura and co-workers.



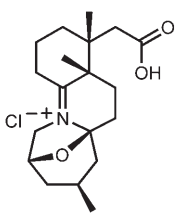
30, R = H, 13 μM
44, R = Me, 26 μM



45, >100 μM



46, >100 μM



47, 70 μM

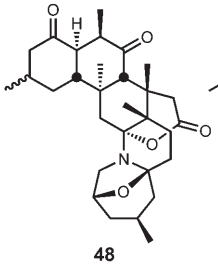
Scheme 12. IC_{50} values for the inhibition of IL-6-dependent cell growth for various structures in the SAR study by Hirama and co-workers.

Table 1: IC_{50} values for the inhibition of P388 murine leukemia cells.

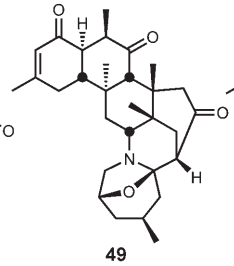
Compound	IC_{50} [μg mL^{-1}]	Compound	IC_{50} [μg mL^{-1}]
norzoanthamine (**10**)	24.0	cyclozoanthamine (**14**)	24.0
oxyzoanthamine (**12**)	1.0	epinorzoanthamine (**15**)	2.6
norzoanthaminone (**11**)	7.0		

Table 2: Antibacterial activities of some zoanthamine alkaloids as specified as the diameter of the inhibition zone in mm.

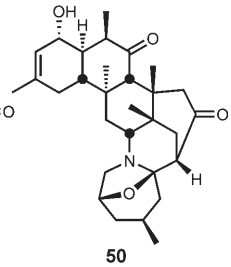
Compound	Gram negative		Gram positive	
	S. typhimurium	*E. coli*	*B. sphaericus*	*S. aureus*
1	6	6	8	7
48	12	6	8	10
49	7	6	8	10
50	6	7	7	9



48



49



50

Experimental and clinical evidence indicate that a selective collagen receptor antagonist will result in only a very small change in haemostasis, thus meaning a safer, yet still potent drug.[32]

4. Synthesis of Zoanthamines

4.1. General Remarks

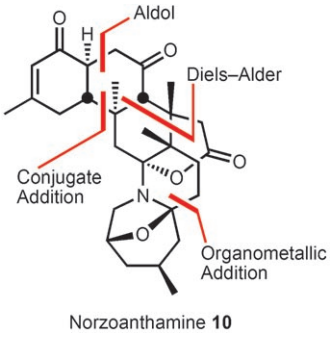
The intriguing diversity of biological activities and the densely functionalized structures of the zoanthamine alkaloids have inspired a host of research groups to publish strategies toward the total syntheses of these molecules. Many researchers have focused their efforts on the synthesis of the tricyclic ABC ring system, which poses a significant synthetic challenge because of the large number of stereocenters. For example, the C ring contains three quaternary stereocenters in vicinal and nonvicinal relationships. In addition to the difficulty of synthesizing quaternary centers, the steric bulk of the substituents renders even routine transformations on nearby functional groups troublesome. Other researchers have focused on the synthesis of the heterocyclic DEFG rings. This ring system presents the challenge of forming the heterocycles with the correct hemiaminal connectivity and configuration.

4.2. Miyashita's Synthesis of Norzoanthamine

Twenty years after the isolation of the first zoanthamine alkaloids, Miyashita et al. reported the first and, as yet, only

© 2008 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

completed total synthesis of a zoanthamine alkaloid.[33] The general synthetic plan for their synthesis of norzoanthamine (**10**) is illustrated in Scheme 13. This impressive 41-step

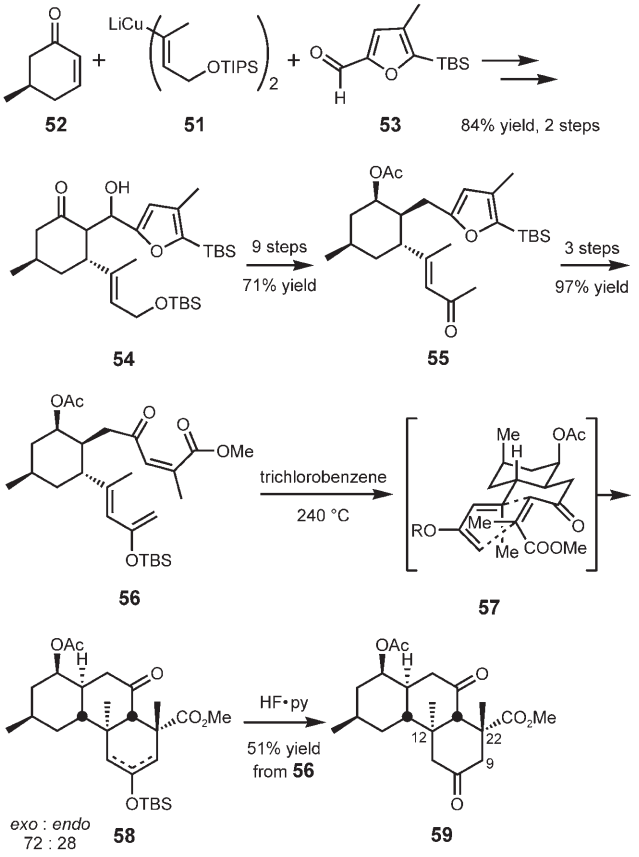


Scheme 13. Retrosynthetic analysis of norzoanthamine according to Miyashita and co-workers.

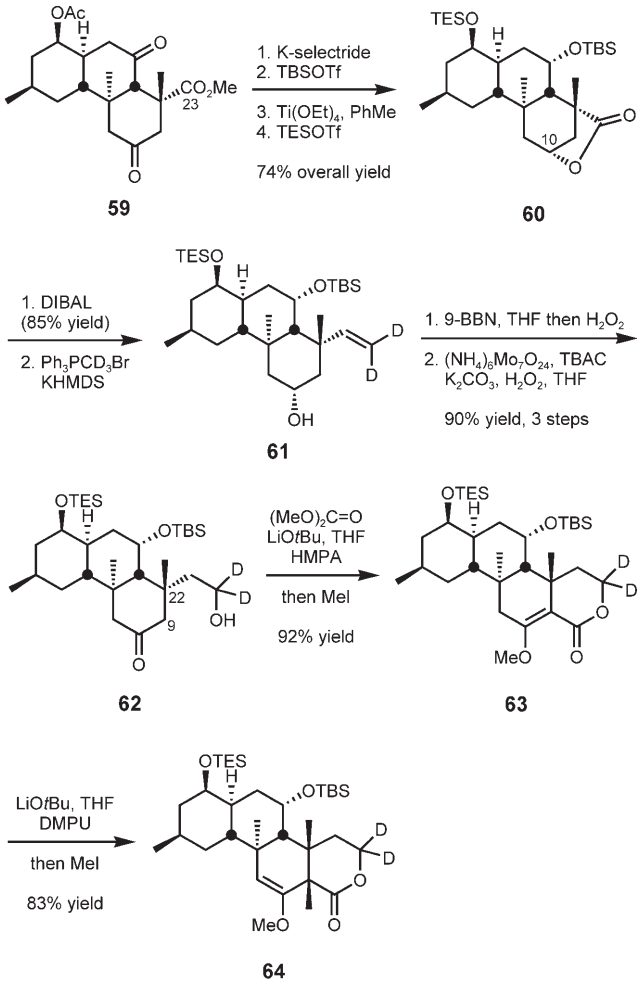
synthesis included several creative solutions to problems that likely arose during the execution of the synthesis. Their Diels–Alder strategy for the construction of the ABC ring system of norzoanthamine (**10**) was disclosed in 2002 (Scheme 14).[34]

The synthesis began with the addition of cuprate **51** to the enantiopure enone **52**, followed by an aldol reaction with aldehyde **53** to provide ketone **54**. This efficient sequence set the absolute configuration at C13, from which the remaining stereocenters were derived. Following several functional group manipulations, furan **55** was photochemically oxidized using the conditions developed by Katsumura. Subsequent formation of a silyl enol ether provided Diels–Alder substrate **56**, which upon heating to 240 °C reacted predominantly through the desired *exo* transition state **57** to give a mixture of silyl enol ether isomers **58**. After cleavage of the silyl group, diastereomerically pure ketone **59** was isolated in 51 % yield over the two steps. This Diels–Alder reaction sets both the C12 and C22 quaternary centers of norzoanthamine (**10**) with the correct absolute configuration.

At this point, a number of functional-group manipulations were undertaken to allow homologation at C23 and installation of the final quaternary center at C9 (Scheme 15). The diastereoselective reduction of both ketones in **59** was accomplished by the addition of K-selectride from the convex face of the molecule, thereby resulting in the formation of the desired lactone at the newly formed C10 hydroxy group. Silylation with TBSOTf, then conversion of the phenolic acetate into a TES group afforded protected lactone **60**. Reduction of the lactone to the lactol followed by a Wittig reaction provided dideuterated olefin **61**. Hydro-



Scheme 14. Construction of the ABC core by a Diels–Alder reaction according to Miyashita and co-workers.

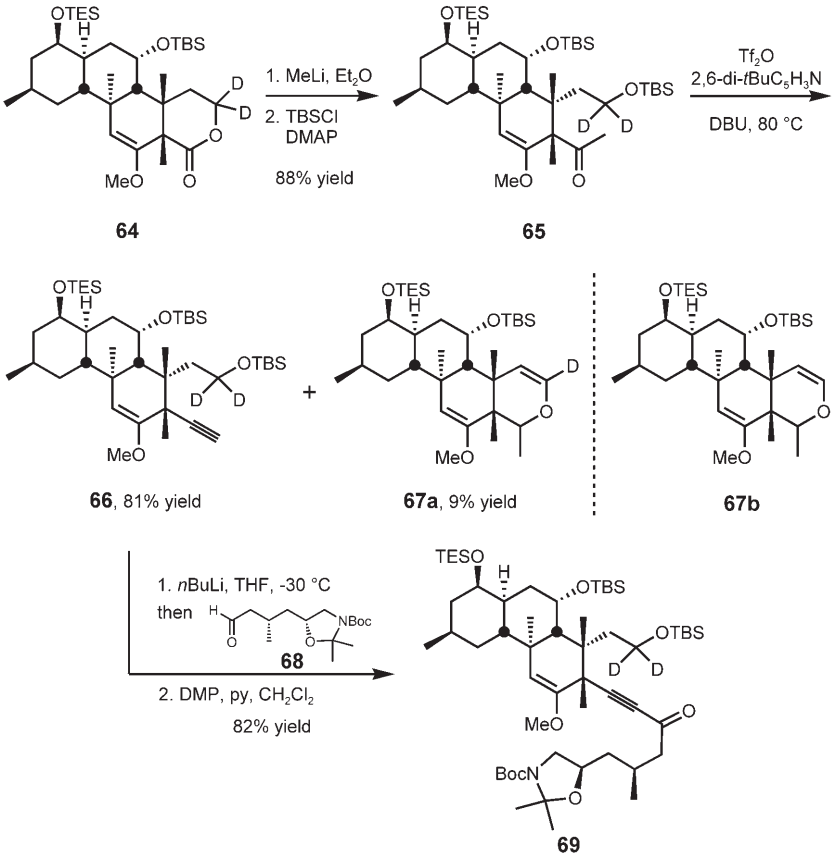


Scheme 15. Functionalization of the ABC core.

© 2008 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

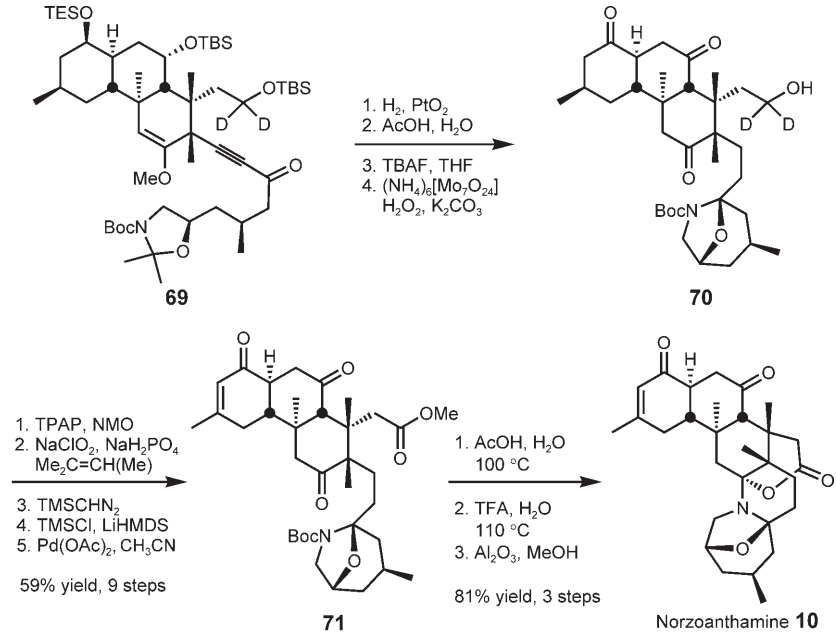
boration and oxidation provided ketone **62**, which was poised for the formation of the C9 quaternary center. To that end, acylation of **62** with dimethyl carbonate and lithium *tert*-butoxide proceeded regioselectively, presumably through an initial acylation of the alcohol and subsequent formation of a lactone by C acylation of the enolate. This series of events was followed by quenching with methyl iodide to give lactone **63**. Upon treatment with lithium *tert*-butoxide and methyl iodide in DMPU, lactone **63** underwent C alkylation to give quaternized δ-lactone **64**. Impressively, this difficult transformation provided a single diastereomer in 83% yield.

The synthesis of the "southern" portion of norzoanthamine (**10**) began with conversion of the C8 lactone into an alkyne followed by addition of the side chain (Scheme 16). Addition of methyl lithium to lactone **64** followed by the introduction of a silyl protecting group provided methyl-substituted ketone **65**, which was converted into alkyne **66** by treatment with triflic anhydride and DBU. This conversion was accompanied by the formation of a small amount of by-product **67a**. In the corresponding non-deuterated substrate, the by-product **67b** was formed in 30% yield, thereby reducing the yield of the desired alkyne to 66%. The carbon skeleton of norzoanthamine (**10**) was completed by the addition of aldehyde **68** to the lithium salt of alkyne **66** and oxidation of the resulting alcohol to ynone **69**.



Scheme 16. Attaching the side chain for the "southern" structural unit.

Completion of the target required a further twelve steps of deprotection, oxidation state adjustment, and dehydration (Scheme 17). From **69**, reduction of the alkyne, cleavage of the enol ether and acetal under acidic conditions, global desilylation, and oxidation of the secondary alcohol provided **70**. Sequential oxidation of the primary alcohol provided the carboxylic acid, which was esterified with trimethylsilyldiazomethane. A Saegusa–Ito oxidation installed the A-ring enone to give **71**. Treatment of **71** with hot aqueous acetic acid resulted in cleavage of the carbamate group and formation of an iminium ion. Upon being subjected to aqueous TFA at 110 °C, the methyl ester added into the iminium ion, thereby forming the trifluoroacetate of norzoanthamine. Treatment of the salt with basic alumina in methanol revealed the natural product. This impressive synthetic accomplishment also served to unambiguously confirm the absolute configuration of norzoanthamine (**10**), which had previously been deduced from NMR experiments.

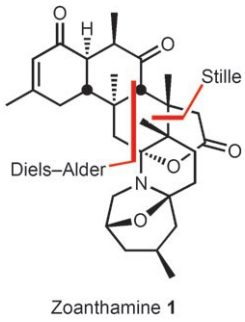


Scheme 17. Final steps in the synthesis of norzoanthamine.

 © 2008 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

4.3. Tanner's Diels–Alder Approach to the Zoanthamine ABC Ring System

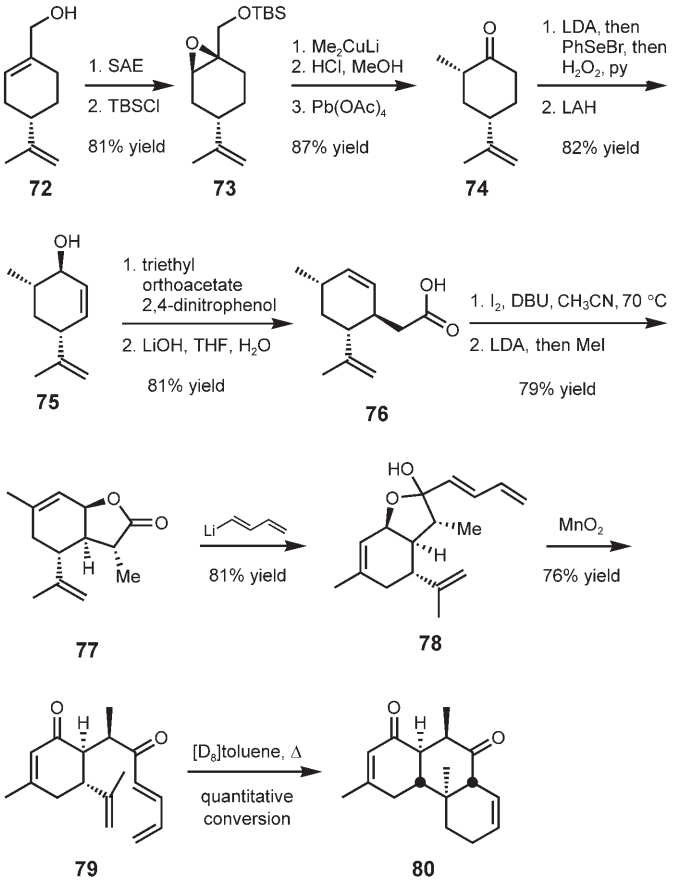
Tanner and co-workers also chose to assemble the ABC rings by using a Diels–Alder approach (Scheme 18). A Stille coupling was planned for the synthesis of the Diels–Alder precursor, and the synthesis would begin with perillyl alcohol, both enantiomers of which are available. The configuration of all the remaining stereocenters would then be set by diastereoselective transformations.



Scheme 18. Retrosynthetic analysis of zoanthamine according to Tanner and co-workers.

The synthesis began with an asymmetric Sharpless epoxidation of known perillyl alcohol **72** followed by silylation to provide epoxide **73** (Scheme 19).[35] The methyl group was installed at C15 by diastereoselective addition of Gilman's reagent to the epoxide. Removal of the silyl group and subsequent treatment with lead tetraacetate led to the desired methyl-substituted ketone **74**. Trapping of the kinetic enolate with PhSeBr and peroxide oxidation allowed for installation of the enone. Subsequent reduction with lithium aluminium hydride (LAH) led to allylic alcohol **75** as a single diastereomer. Alkylation with Claisen rearrangement was affected using triethyl orthoacetate and catalytic amounts of 2,4-dinitrophenol. This was followed by saponification with LiOH to form **76**. Iodolactonization occurred to give a mixture of five- and six-membered iodolactones that equilibrated upon heating. The addition of DBU to the reaction mixture resulted in the elimination of HI, irreversibly trapping the thermodynamically favored product. Diastereoselective alkylation of this enol lactone with MeI provided **77**, which was subjected to lithiobutadiene to yield hemiacetal **78**. Oxidation with manganese dioxide provided the Diels–Alder precursor **79**, which upon heating in [D_8]toluene provided tricycle **80** quantitatively.

Encouraged by the success of this Diels–Alder cycloaddition, the Tanner research group set out to synthesize more functionalized model substrates derived from (−)-carvone to more readily probe the limitations of the reaction. The first model substrate (**81**, Scheme 20) led to a disappointing, but critical, discovery: no reaction was observed on heating in toluene for several days. It was determined that the extra electron density in the diene rendered the desired inverse-electron demand Diels–Alder ineffective. Thus, Diels–Alder substrate **83** (R = TBS) was synthesized. Upon



Scheme 19. Approach of Tanner and co-workers to a model ABC ring system.

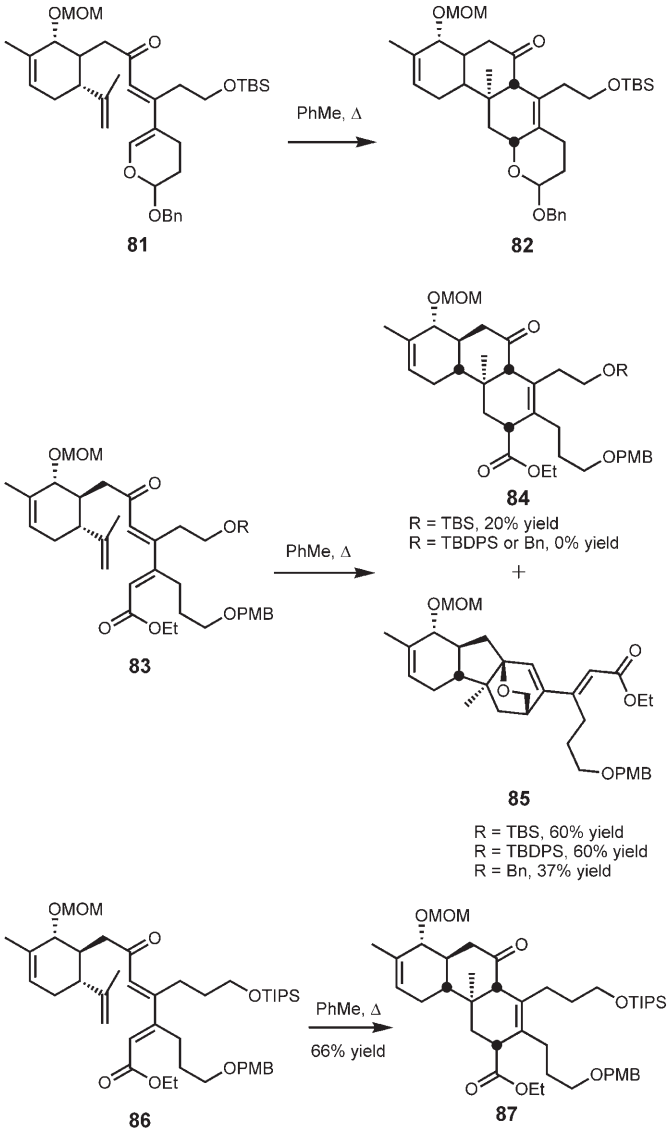
heating, two products were observed: the desired Diels–Alder adduct **84** and the unusual product **85**. When the nature of the protecting group (R) was varied, **85** was the sole product. However, a lengthening of the chain at C22 by a methylene group (**86**) was sufficient to avoid the formation of the side product and provided a 66% yield of **87** with the correct configuration for the synthesis of zoanthamine (**1**).

This final modification confirmed the mechanistic hypothesis illustrated in Scheme 21. A [1,5]-sigmatropic rearrangement of the Diels–Alder substrate (**83**) leads to extended enol **88**, loss of ROH (R = TBS, TBDPS, Bn) then gives terminal olefin **89**. A 6π electrocyclization provides pyran **90**, which then undergoes an intramolecular Diels–Alder reaction to form the side product **85**.

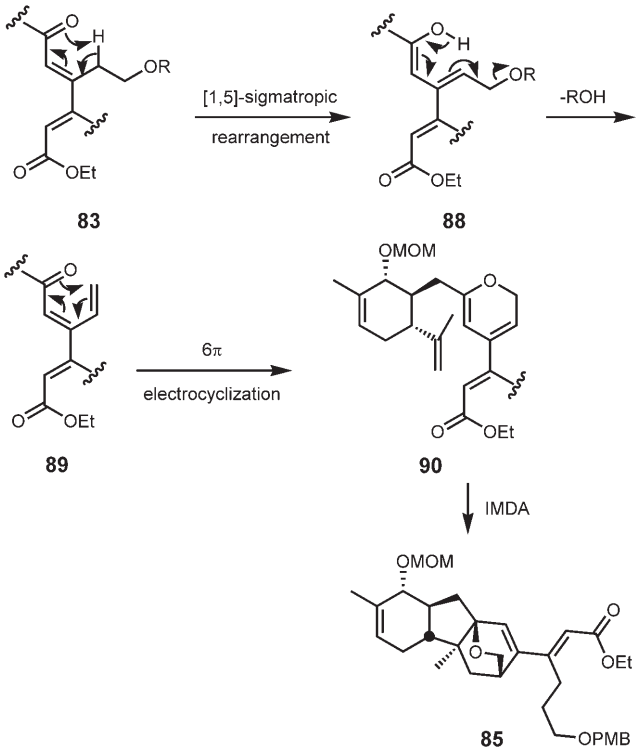
Armed with this information, perillyl alcohol was converted into vinyl iodide **91** (Scheme 22).[36] Stille coupling with stannane **92** proved difficult and required the conditions reported by Corey and co-workers to afford reasonable yields of the Diels–Alder substrate **93**.[37–39] Diels–Alder cyclization proceeded with high diastereoselectivity to afford β,γ-unsaturated ester **94**, albeit in a modest 14% yield. The major product, tetrahydrofuran **95**, was isolated in 31% yield.

Upon examining the differences between this perillyl alcohol derived substrate and the corresponding carvone-derived substrate (reaction not shown), Tanner and co-workers noted that the allylic MOM-protected allyl alcohol was arranged in a pseudoaxial orientation in the Diels–Alder

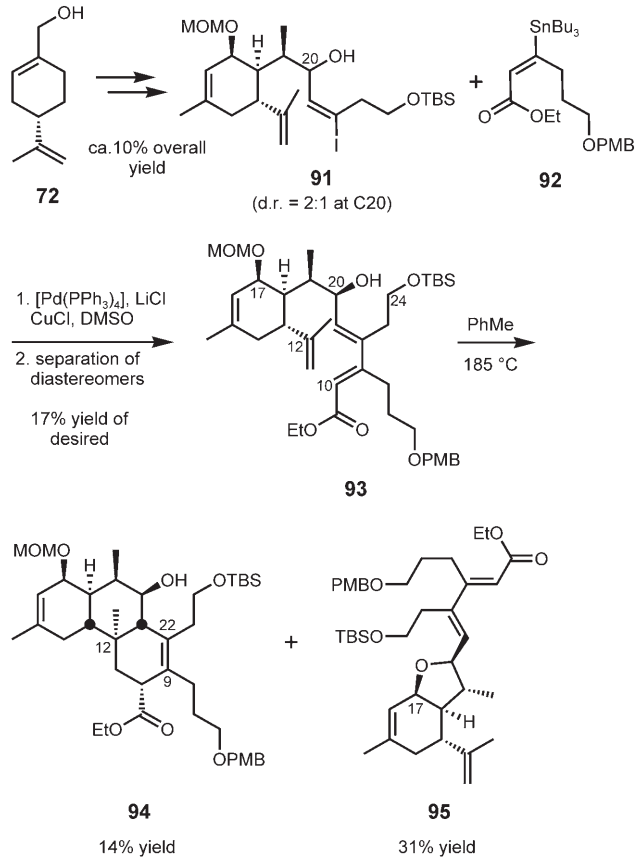
 © 2008 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 20. Cyclizations of model compounds derived from (−)-carvone.



Scheme 21. Proposed mechanism for the formation of undesired products **85**.



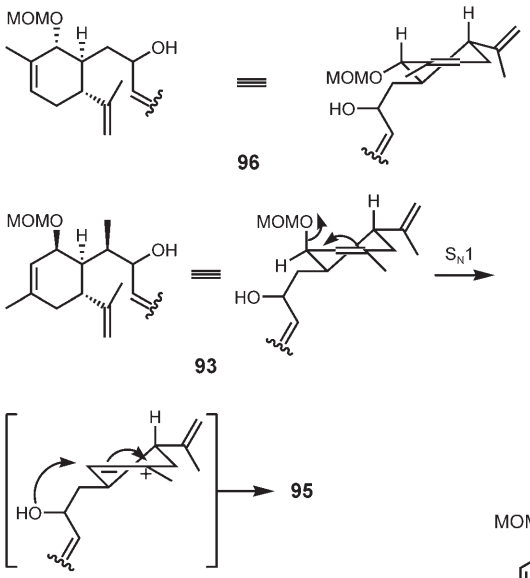
Scheme 22. Approach used by Tanner and co-workers for the synthesis of the functionalized ABC ring system.

precursor **93**, whereas model substrate **96** possesses a pseudoequatorial MOM ether (Scheme 23). It is believed that this difference allows for S_N1-type displacement and cyclization to form tetrahydrofuran **95**.

Based on this rationale, substrate **97** was synthesized and cyclized by treatment with toluene at 205 °C (Scheme 24).[40] Gratifyingly, the Diels–Alder reaction proceeded smoothly through an *exo* transition state to provide tricycle **98** in 85% yield. Protection of the C20 alcohol as the MOM ether (**98**→**99**) was followed by an oxidative cleavage sequence to afford enone **100**. Subsequent removal of the PMB ether and oxidation provided aldehyde **101**. Treatment of side chain **102** with *tert*-butyllithium, addition of aldehyde **101**, and oxidation of the resulting alcohol afforded advanced intermediate **103**.

While this Diels–Alder strategy nicely establishes the quaternary center at C12, it requires the formation of the difficult vicinal C9 and C22 quaternary centers at a late stage

 © 2008 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 23. Mechanism for the formation of by-product **95**.

in the synthesis. The Tanner research group is poised to begin their installation, which they hope to achieve by Michael addition and alkylation. Once the quaternary centers are installed, only oxidation at C24 and cyclization of the side chain to form the DEFG rings remain to complete the total synthesis of norzoanthamine (**10**).

4.4. Uemura's Approach to the Norzoanthamine ABC Ring System

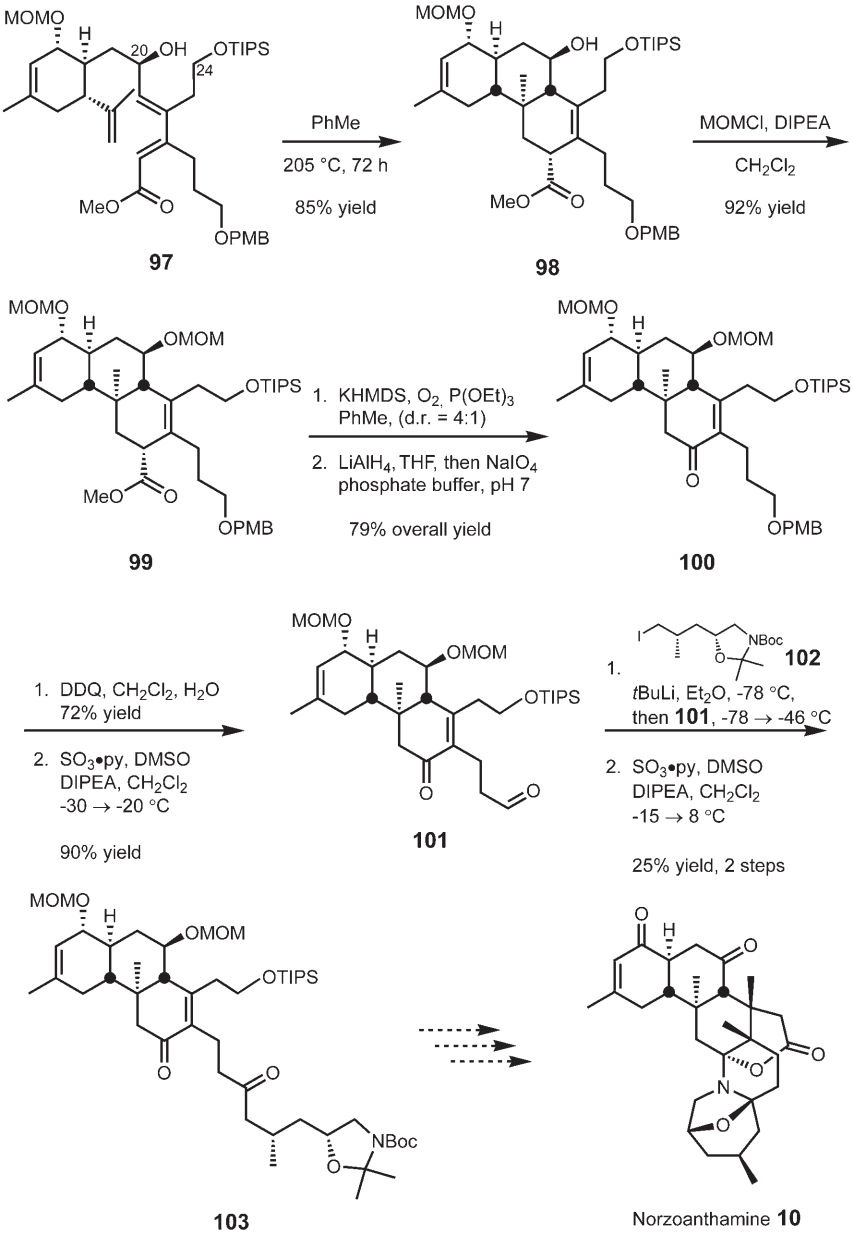
Recently, Uemura and co-workers reported a synthetic strategy based on their biosynthetic hypothesis (see Section 2.2), which purports that the zoanthamine alkaloids arise from a linear polyketide skeleton, which then undergoes numerous pericyclic reactions.[41] To support this hypothesis, they endeavored to synthesize and cyclize polyene **104** en route to the natural product (Scheme 25).

Vinyl iodide **105** and alkyne **106** were efficiently assembled then united by Sonogashira coupling.[42] Conversion into enyne **107** was completed by oxidation and methylation (Scheme 26). To date, no report has appeared on the selective reduction of enyne **107** to the linear polyene **104** or on attempts to cyclize either **104** or **107**.

4.5. Williams's Approach to the Norzoanthamine AB and EFG Ring Systems

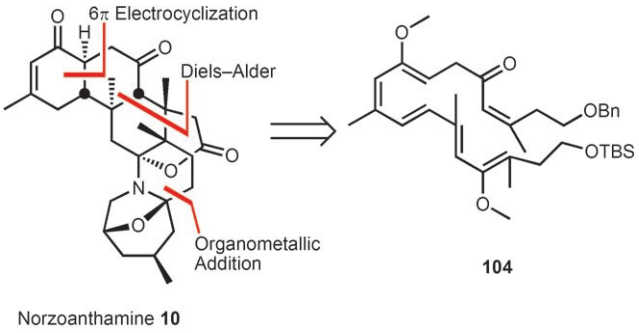
Williams and co-workers have explored approaches to the synthesis of both the carbocyclic AB rings and the heterocyclic EFG rings of norzoanthamine and zoanthenol. An intramolecular Diels–Alder cyclization constructs the AB rings, which will be followed by appending the C ring (Scheme 27).[43] The EFG ring system is formed by conjugate addition of an enamine to a functionalized linear enone then cyclization to form the configuration and connectivity observed in the natural products.

In the key Diels–Alder reaction, nitroalkene **108** underwent reaction in benzene at reflux via an *endo* transition state to afford decalin **109** in good yield and 10:1 d.r. (Scheme 28). A Nef reaction[44] converted the nitro moiety into the desired ketone and facilitated migration of the olefinic double bond. The product enone **110** has the correct configuration and necessary functionality for annulation of the C ring.

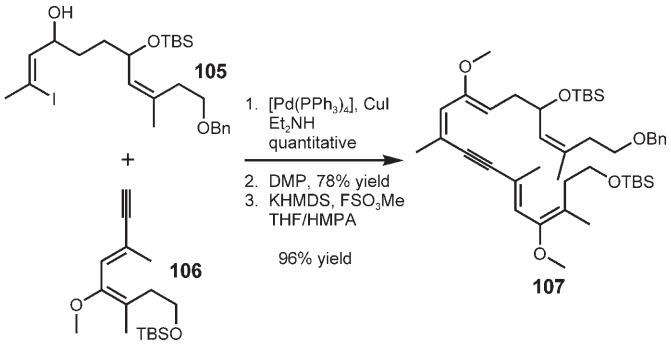


Scheme 24. Diels–Alder cyclization and modification of the cycloadduct according to Tanner and co-workers.

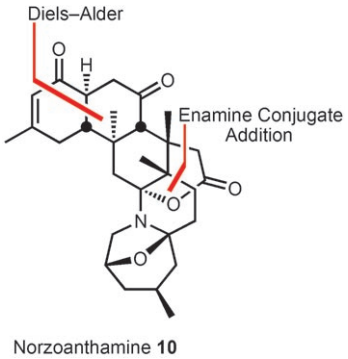
 © 2008 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 25. Retrosynthetic analysis of norzoanthamine according to Uemura and co-workers.



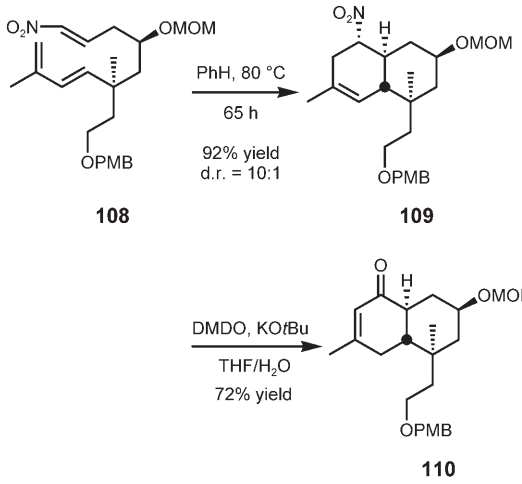
Scheme 26. Approach used by Uemura and co-workers for the synthesis of norzoanthamine.



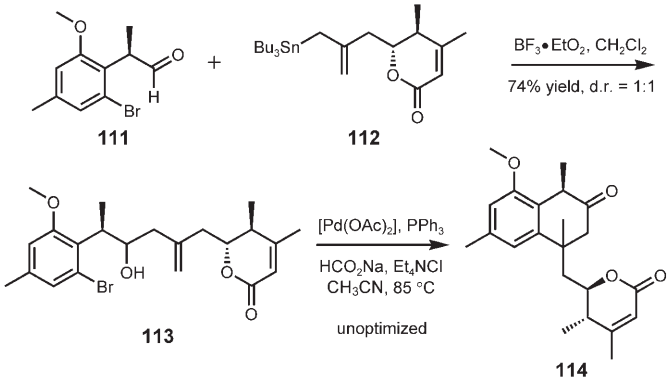
Scheme 27. Retrosynthetic analysis of norzoanthamine according to Williams and co-workers.

The Williams research group has recently published an interesting approach to the zoanthenol AB rings through allylation of aldehyde **111** with stannane **112** (Scheme 29).[45] Upon treatment with $BF_3{\cdot}Et_2O$, alcohol **113** was formed as a 1:1 mixture of diastereomers. Although the conditions remain unoptimized, the desired product **114** resulting from Pd insertion and intramolecular Heck coupling has been isolated, with good recovery of starting material.

In addition, Williams and Cortez demonstrated an efficient strategy to append the C1–C8 (EFG) fragment to the ABC ring system and stereospecifically establish the C9 quaternary center.[46] When heated in the presence of zinc(II) chloride, chiral imine **115** partially tautomerizes to enamine **116** (Scheme 30). The resulting equilibration is driven by the



Scheme 28. Early efforts toward the synthesis of the norzoanthamine AB rings by Williams and co-workers.



Scheme 29. Recent efforts by Williams and co-workers toward the synthesis of the norzoanthamine AB rings.

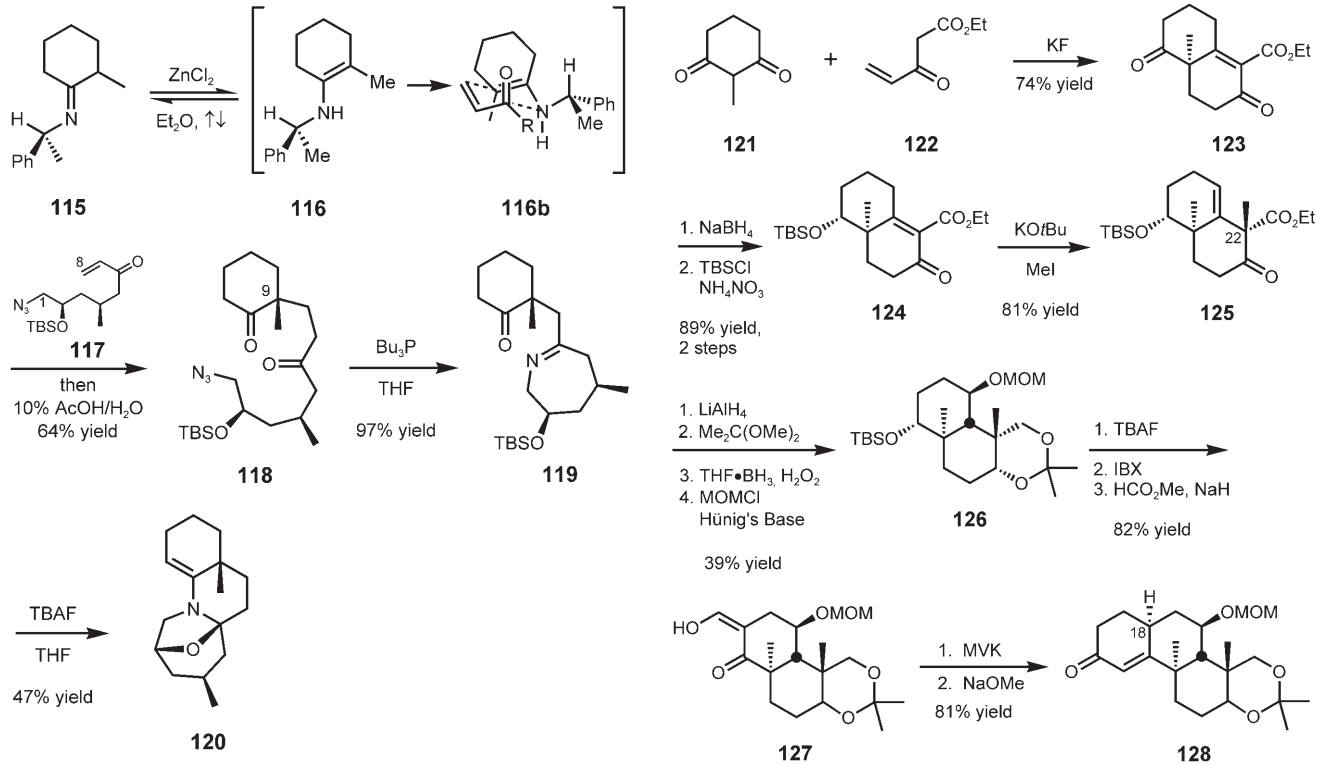
conjugate addition of enamine **116** to enone **117** from the β face (as seen in the energy-minimized conformation of **116b**).[47] Enone **117** was prepared in an enantioenriched form using Evans chiral oxazolidinone.[48] Hydrolysis of the intermediate iminium intermediate affords diketone **118** with excellent diastereoselectivity (22:1). A Staudinger reduction of azide **118** provides imine **119**. Treatment with TBAF cleaves the silyl ether and the free alcohol attacks the imine. The resultant amine condenses onto the ketone to give the EFG model enamine **120**.

4.6. Theodorakis's Annulation Approach to the Norzoanthamine ABC Ring System

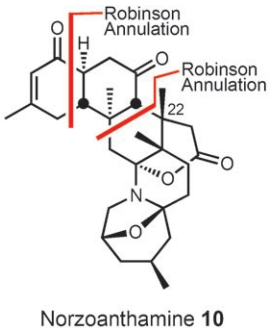
Theodorakis and co-workers proposed a unique annulation strategy that begins with an intact B ring and sequentially appends the C and A rings.[49] Robinson annulations are applied for the synthesis of both rings (Scheme 31).

The synthesis commenced with condensation of *meso*-diketone **121** and ketoester **122** in the presence of potassium fluoride to afford enone **123** (Scheme 32).[50] Reduction with

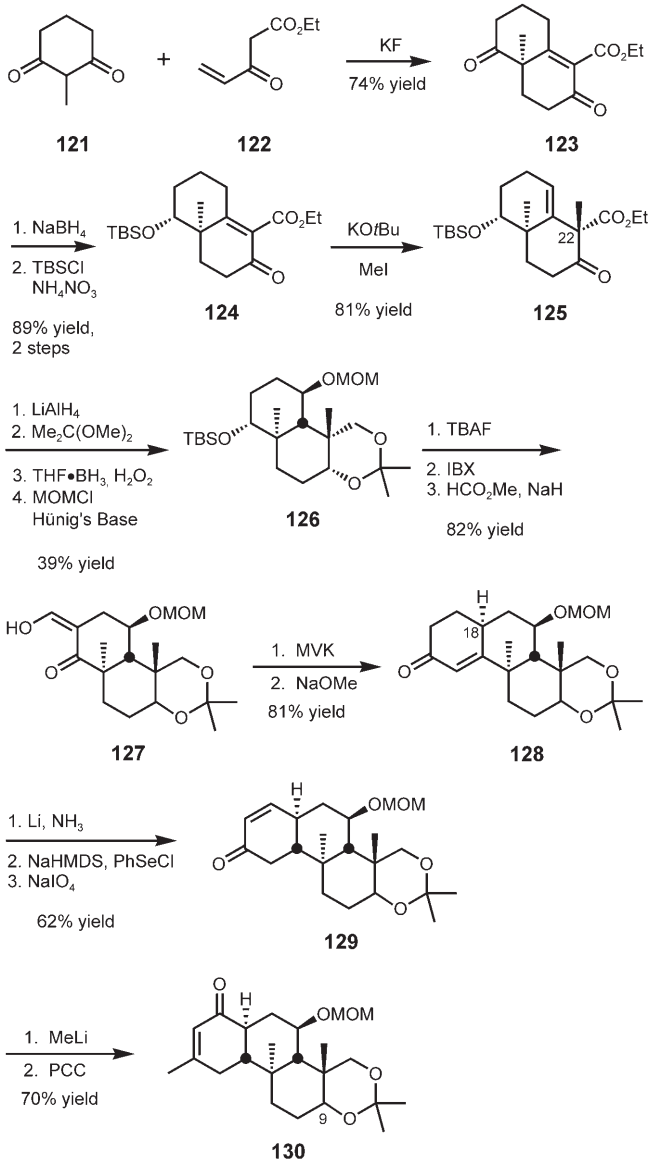
 © 2008 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 30. Synthesis of a model EFG ring system by Williams and co-workers.



Scheme 31. Retrosynthetic analysis of norzoanthamine according to Theodorakis and co-workers.



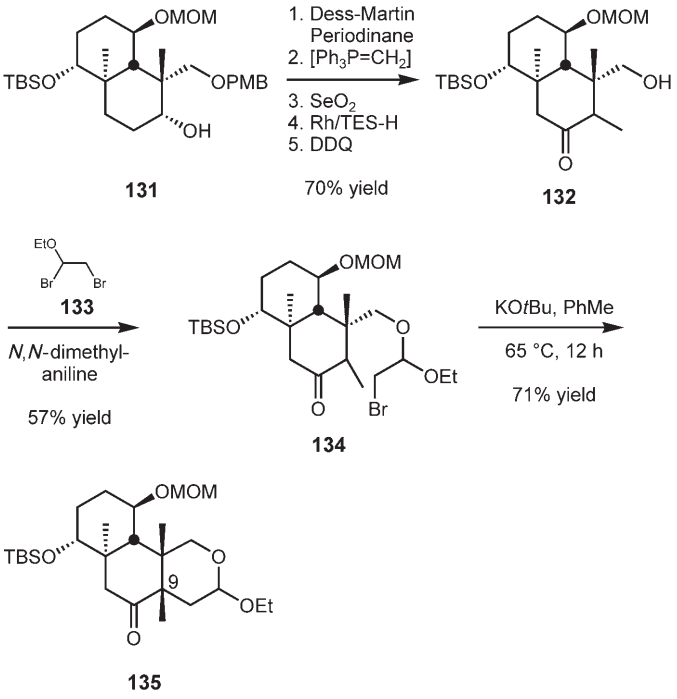
Scheme 32. Approach used by Theodorakis and co-workers for the synthesis of the ABC ring system.

sodium borohydride and silylation provided α,β-unsaturated ketoester **124**. Treatment of **124** with potassium *tert*-butoxide and methyl iodide produced the quaternized ketoester **125** with complete diastereomeric control. Exhaustive reduction with lithium aluminium hydride produced a diol, which was then protected as the acetonide. Hydroboration and oxidation followed by formation of the MOM ether provided **126**. Desilylation, oxidation, and alkylation with methyl formate provided hydroxyenone **127**. A two-step Robinson annulation[51] gave enone **128** as a single isomer. Enone **128** was then reduced to the corresponding ketone, and subsequent olefin installation provided **129**. Addition of methyl lithium and oxidation with PCC afforded the transposed enone **130**, which contained all the functionality and stereochemical features of the AB rings.

In a related study, Theodorakis and co-workers demonstrated that the installation of the difficult C9 quaternary center was possible from selectively protected alcohol **131** (Scheme 33).[52] Oxidation to the corresponding ketone and olefination, followed by allylic oxidation provided an exocyclic enone. Conjugate reduction and cleavage of the PMB ether then provided methyl-substituted ketone **132**. Acetal formation between Stork's 1,2-dibromo-diethyl ether reagent (**133**)[53] and the alcohol moiety of ketone **132** produced bromide **134**. Exposure of bromide **134** to base gave intramolecular alkylation product **135** in 71% yield. The efficiency of this protocol is impressive given the difficulty of establishing vicinal quaternary centers. Furthermore, the alkylation gave complete selectivity for the desired C9 epimer of acetal **135**, as confirmed by X-ray structure determination.

Taken in conjunction with other studies from the Theodorakis research group, this strategy solves the difficult

 © 2008 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

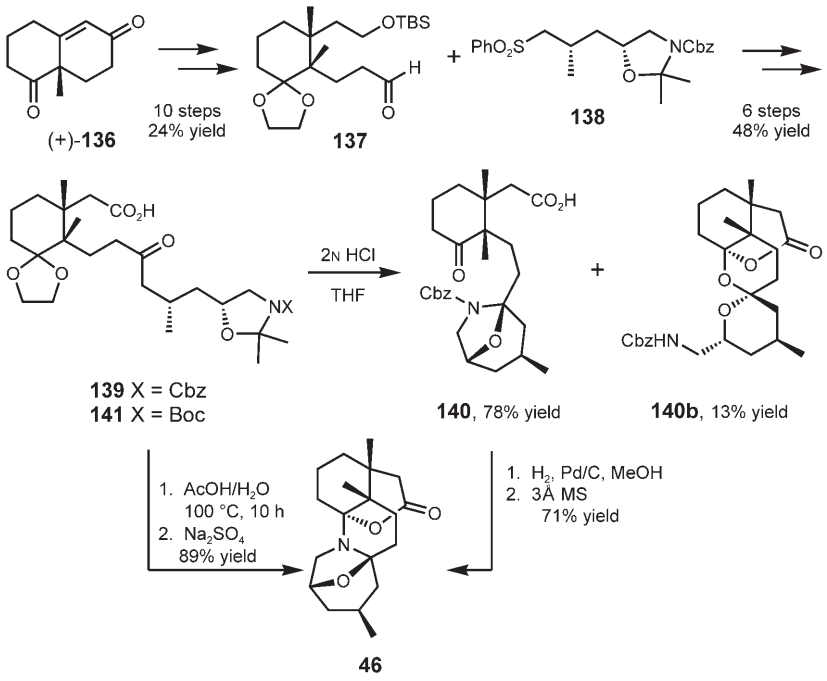


Scheme 33. Installation of the C9 quaternary center by Theodorakis and co-workers.

problem of generating all three of the C-ring quaternary centers and produces a norzoanthamine ABC ring system well poised for the completion of the total synthesis.

4.7. Kobayashi's Synthesis of the Heterocyclic CDEFG Zoanthamine Ring System

In 1998, Kobayashi and co-workers disclosed an enantioselective route to the CDEFG ring system.[54] The Wieland–Miescher ketone (**136**)[55] served as the starting material to produce aldehyde **137** (Scheme 34). The coupling of the lithium salt of sulfone **138** to aldehyde **137** and adjustment of the oxidation state completed the Cbz-protected cyclization substrate **139**. Treatment with hydrochloric acid removed the acetonide and formed the FG rings in good yield (**140**) but was accompanied by the formation of an acetal by-product **140b** in 13% yield. Resubjecting this by-product to acidic conditions did not form a hemiaminal-containing product. Tricyclic intermediate **140** was hydrogenolyzed and dehydrated to furnish pentacyclic hemiaminal ether **46**. A one-pot protocol for cyclization was subsequently investigated using Boc-protected substrate **141** in acidic conditions and gave an excellent yield of the hemiaminal lactone **46**.[56]



Scheme 34. Sulfone approach used by Kobayashi and co-workers for the synthesis of the CDEFG ring system.

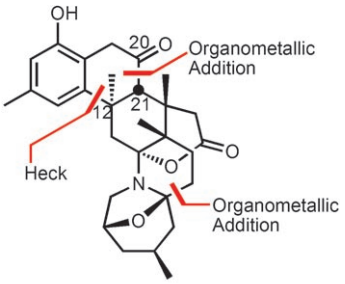
4.8. Hirama's Strategy for the Zoanthenol ABC Ring System

The strategy proposed by Hirama and co-workers is specifically geared toward the synthesis of zoanthenol's ABC ring system. The key Heck[57] disconnection of C12 and C13 relies on the aromatic A ring unique to zoanthenol (Scheme 35). Addition of a stannane into an enone was envisioned for the formation of the C20–C21 bond.

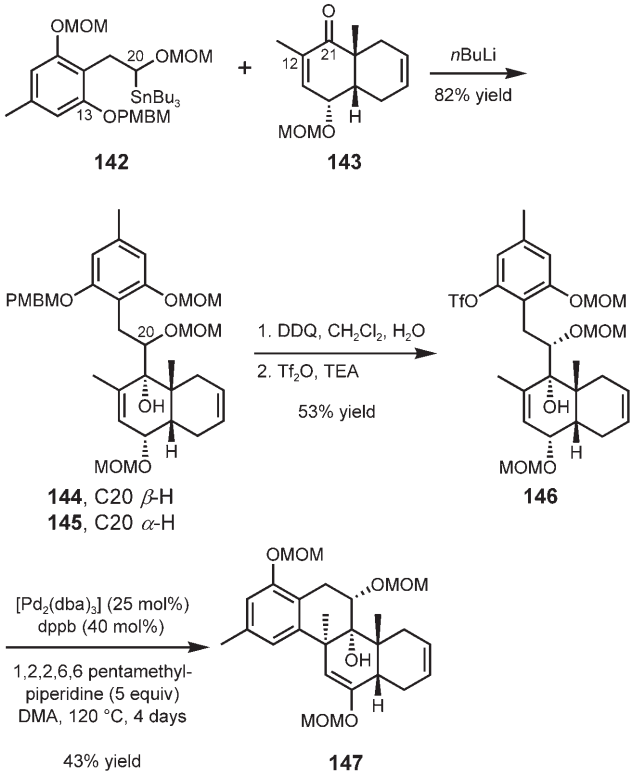
Transmetalation of stannane **142** and addition to enone **143**, derived from an asymmetric quinone Diels–Alder reaction,[58] afforded tertiary alcohols **144** and **145** as a mixture of epimers at C20 (Scheme 36). Cleavage of the PMBM ether followed by formation of a triflate provided aryl triflate **146** and allowed for the investigation of the key intramolecular Heck reaction. After significant optimization, conditions were developed to produce the desired enol ether **147** in modest yield.[59] Although the reaction did proceed with excellent diastereoselectivity, it had several drawbacks, including high palladium loading, long reaction times, and side products arising from the simple reduction of the triflate substrate.

Heck substrate **146** was modified to enone **148** to increase the electrophilicity of the accepting olefinic double bond (Scheme 37). Exposure of enone **148** to reductive Heck conditions produced ketone **149** in excellent yield, and with the difficult C12 stereocenter established, the C-ring ketone was selectively reduced with L-Selectride then silylated. The next goal was the reduction of the tertiary alcohol moiety of **149**. Reductive cleavage of the BOM ether and oxidation provided **150**, which was treated with samarium(II) iodide to give the reduced ketone **151** in good yield as a single diastereomer, as well as epimeric alcohol **152** in 17% yield.[60]

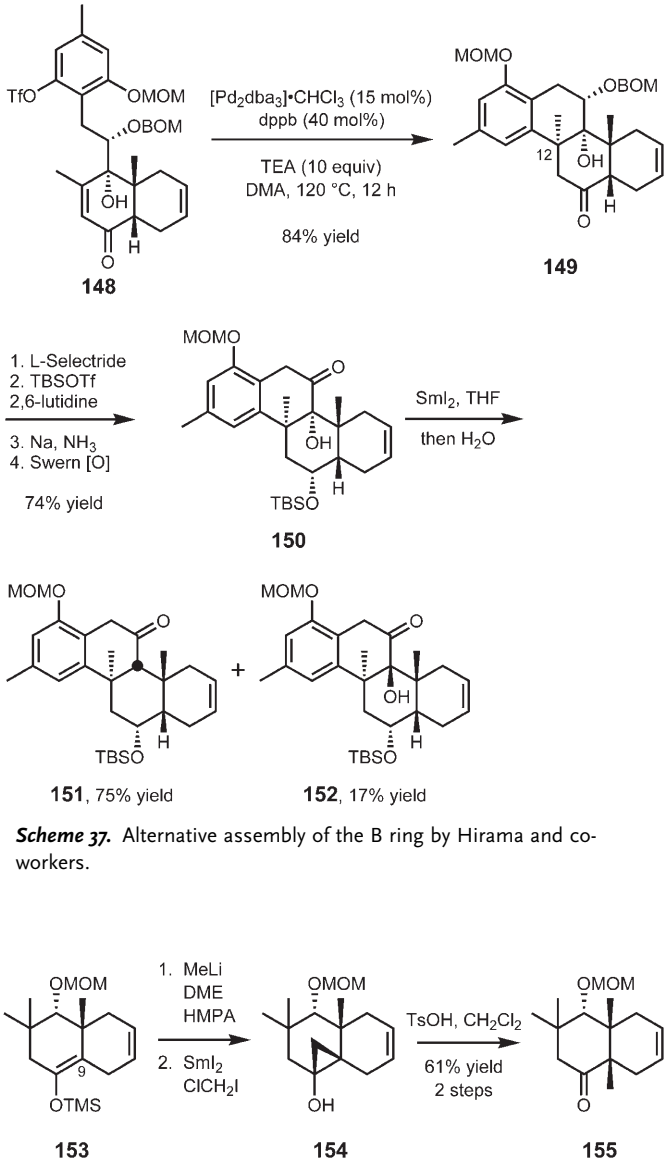
 © 2008 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 35. Retrosynthetic analysis of zoanthenol according to Hirama and co-workers.



Scheme 36. Heck strategy used by Hirama and co-workers for the synthesis of the zoanthenol ABC ring system.



Scheme 37. Alternative assembly of the B ring by Hirama and co-workers.

Scheme 38. Installation of the C9 methyl group according to Hirama and co-workers.

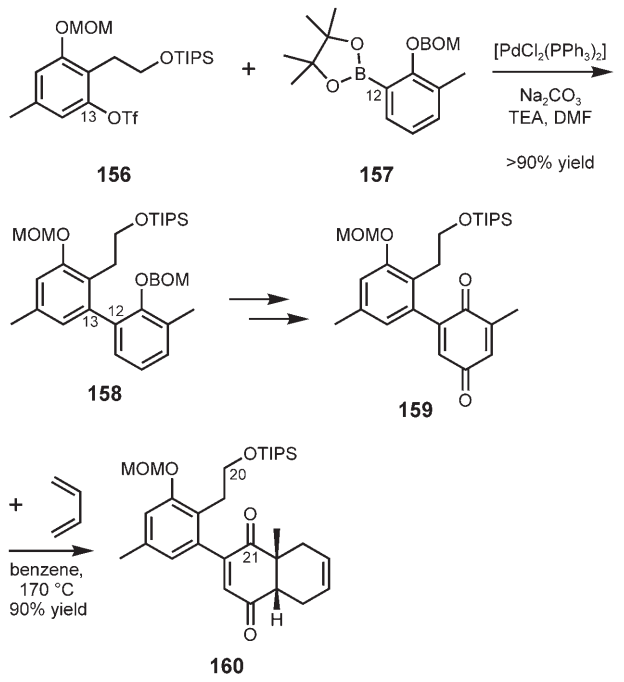
The greatest challenge that remains in Hirama's synthesis is the establishment of the C9 quaternary stereocenter. However, his research group has already demonstrated a highly diastereoselective methylation of silyl enol ether **153** as a model reaction for the methylation at C9 (Scheme 38).[61] The methylation was achieved by a samarium(II) iodide promoted cyclopropanation and acid-mediated ring opening to give methyl-substituted ketone **155** and its C9 epimer with a favorable 3:1 ratio.

Recently, Hirama and co-workers disclosed an alternate strategy for the assembly of the ABC ring system of zoanthenol (**1**). This strategy reverses the order in which the B-ring bonds are formed (Scheme 39).[62] Suzuki coupling of aryl triflate **156** and borane **157** unites the A- and C-ring building blocks through formation of the C12–C13 bond to yield biaryl **158**. Removal of the BOM group and oxidation provided quinone **159**, which was heated with butadiene to form **160**. After elaboration of Diels–Alder adduct **160**, the final B-ring bond (C20–C21) could be constructed by an organometallic addition (analogous to the synthesis of tertiary alcohols **144**/**145** and **148**) or by a pinacol-type coupling of a C20 aldehyde.

4.9. Stoltz's Approach to the Carbocyclic Core of Zoanthenol

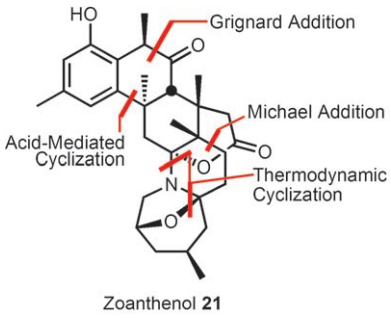
Our research group has recently reported efforts toward the zoanthenol ABC ring system.[63] Our approach is unique in that it forms the quaternary center at the B–C ring junction

 © 2008 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



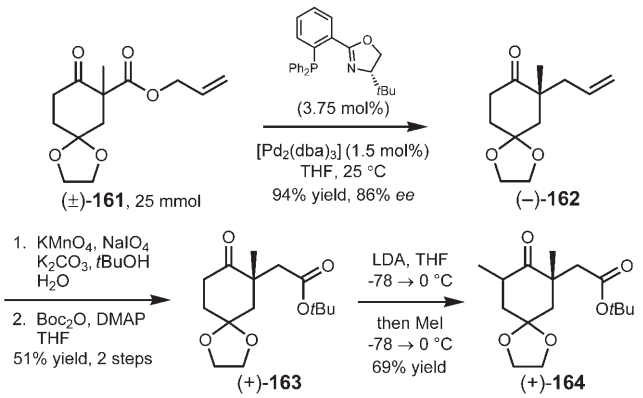
Scheme 39. Modified strategy used by Hirama and co-workers.

using an acid-mediated Friedel–Crafts alkylation. The route also features a selective Grignard addition to tether the A and C rings. The "southern" portion of the molecule is projected to arise from a Michael addition of a C-ring methyl-substituted ketone to an enone that is suitably functionalized for thermodynamic cyclization to form the DEFG ring system (Scheme 40).

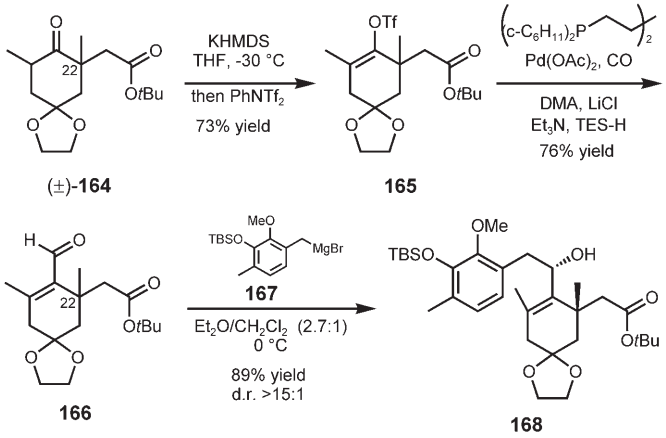


Scheme 40. Retrosynthetic analysis of zoanthenol according to Stoltz and co-workers.

Beginning with racemic β-ketoester **161**, an enantioconvergent allylation reaction yielded enantioenriched α-quaternary ketone (−)-**162** in high yield and could be performed on a 25-mmol scale (Scheme 41).[64] The terminal olefin was then oxidatively cleaved to the carboxylic acid and esterified with Boc_2O to yield *tert*-butyl ester (+)-**163**. Deprotonation with LDA and trapping with methyl iodide afforded enantioenriched methyl-substituted ketone (+)-**164** as a mixture of diastereomers. This ketone was then enolized and trapped as triflate **165**, which was subjected to highly optimized reductive carbonylation conditions to form enal **166** (Scheme 42). Addition of Grignard reagent **167** to enal **166** was accomplished in high yield and excellent selectivity to provide the desired diastereomer of alcohol **168**.



Scheme 41. Enantioselective allylation route to the C-ring building block.

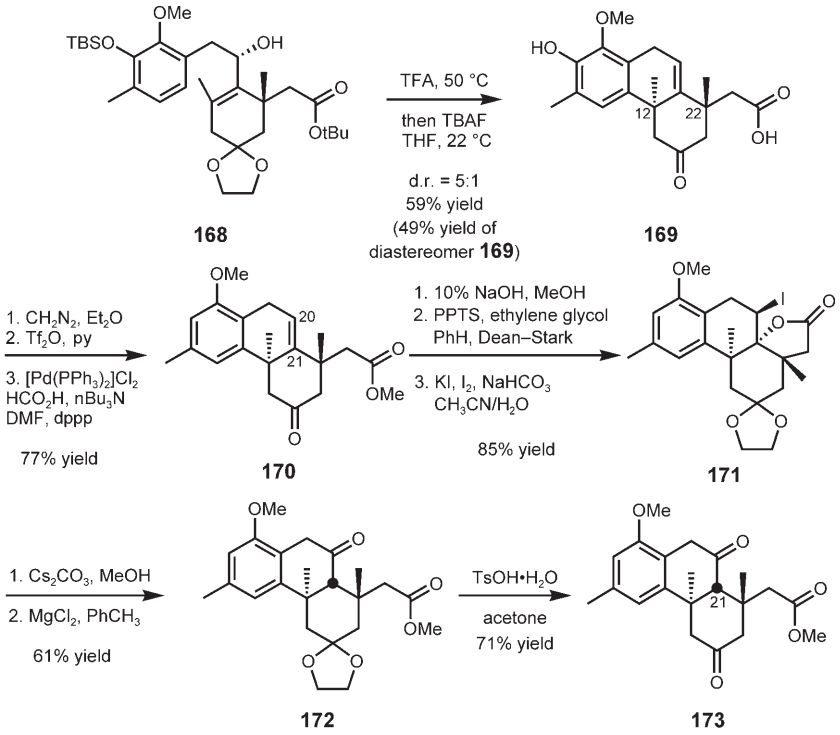


Scheme 42. Coupling of the A and C rings through a diastereoselective Grignard addition.

At this point, we were poised to attempt the acid-mediated cyclization to form the B ring and C12 quaternary stereocenter of zoanthenol (**1**). Subjecting allylic alcohol **168** to neat trifluoroacetic acid at 50 °C followed by TBAF to remove any residual TBS ether linkages resulted in a 49% yield of the desired diastereomer of tricycle **169** (Scheme 43). Interestingly, this reaction is believed to proceed by an S_N'-type 6-*endo* cyclization mechanism. Migration of the double bond to form a C-ring endocyclic enone followed by 6-*exo* cyclization and dehydration is not observed.

Tricycle **169** was advanced to methyl ester **170** by esterification, formation of the aryl triflate, and then treatment with palladium(II) under reducing conditions. Although formation of tricycle **169** resulted in elimination of the C20 oxygenation, the ketone could be readily reinstalled beginning with saponification of the methyl ester, ketalization, and iodolactonization to form **171**. Lactone methanolysis, epox-

 © 2008 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 43. Synthesis of the carbocyclic zoanthenol core by Stoltz and co-workers.

idation, and a 1,2-hydride shift provided the necessary ketone **172**. Removal of the ketal afforded crystalline diketone **173**, which allowed for confirmation of the stereochemical assignment of the newly formed C12 and C22 quaternary centers by X-ray crystallography.[63]

5. Summary and Outlook

The zoanthamine alkaloids are a structurally unique family of natural products. Although they are isolated from soft coral of the order zoantharia, it may be that symbiotic algae play a large role in their biosynthesis. Their biosynthesis is believed to involve a polyketide pathway, but no specifics of the route are known. The benefit of these complicated natural products to the producing organisms is unknown, but the isolation of various zoanthamine alkaloids in the Indian, Pacific, and Atlantic Oceans suggests that these widespread metabolites may have an important function. Antiosteoporotic, antibiotic, anti-inflammatory, and cytotoxic biological activities have been observed for various zoanthamines. As a result, these molecules have garnered increasing attention from synthetic chemists.

As synthetic targets, the zoanthamine alkaloids are a challenge to current synthetic methods and an inspiration for the creation of new reactions. In the contemporary era, it is common for newly isolated natural products with interesting structures or biological significance to succumb to total synthesis within one to two years of their isolation. By comparison, 20 years passed between the isolation of zoanthamine and the total synthesis of norzoanthamine in 2004 by Miyashita and co-workers. Any successful synthesis of these alkaloids requires expertise in both carbocyclic and heterocyclic chemistry. Construction of the carbocyclic ABC rings is hindered by the number of stereochemical features of this region of the molecule—in particular, the three quaternary centers of the C ring present a formidable challenge. This architecture has inspired a number of creative annulation strategies that utilize Diels–Alder, Heck, Friedel–Crafts, and Robinson annulation reactions. The heterocyclic DEFG rings are topographically complex and contain a number of sensitive functional groups. Pioneering syntheses of the heterocyclic region of these molecules have determined the feasibility of different cyclization strategies.

For over two decades, the novel bioactivities and synthetic challenges of the zoanthamine natural products have generated a significant body of research. With many questions as yet unanswered, interest in the zoanthamine alkaloids is likely to increase for the foreseeable future.

Abbreviations List

Boc	*tert*-butoxycarbonyl
Cbz	benzyloxycarbonyl
dba	*trans*,*trans*-dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMA	*N*,*N*-dimethylacetamide
DMDO	dimethyldioxirane
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess–Martin periodinane
d.r.	diastereomeric ratio
HMBC	heteronuclear multiple bond coherence
HMDS	hexamethyldisilazide or hexamethyldisilazane
HMPA	hexamethylphosphoramide
IC_{50}	inhibitory concentration for 50% of the test population
IL-6	interleukin 6
LD_{50}	lethal dosage to kill 50% of test population
MH-60	mouse myelohybridoma cells
MOM	methoxymethyl
MTPA	α-methoxy-α-(trifluoromethyl)phenylacetic acid
MVK	methyl vinyl ketone
NOE	nuclear Overhauser effect
PCC	pyridinium chlorochromate
PG	prostaglandin

 © 2008 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

PMA	phorbol myristate acetate
PMB	*para*-methoxybenzyl
PMBM	*para*-methoxybenzyloxymethyl
p.o.	per os (oral application)
py	pyridine
ROESY	rotating-frame Overhauser effect spectroscopy
SAR	structure–activity relationship
TEA	triethylamine
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
TIPS	triisopropylsilyl
Ts	*para*-toluenesulfonyl

We thank www.zoaid.com for the use of pictures of zoanthids throughout this Review, and Teresa Barth for assistance with the design of the graphics and frontispiece.

Received: July 16, 2007
Published online: February 28, 2007

[1] a) S. Ono, J. D. Reimer, J. Tsukahara, *Zool. Sci.* **2005**, *22*, 247–255; b) J. S. Ryland, *Invert. Rep. Develop.* **1997**, *31*, 177–188.
[2] F. Sinniger, J. I. Montoya-Burgos, P. Chevaldonné, J. Pawlowski, *Mar. Biol.* **2005**, *147*, 1121–1128.
[3] C. B. Rao, A. S. R. Anjaneyulu, N. S. Sarma, Y. Venkateswarlu, R. M. Rosser, D. J. Faulkner, M. H. M. Chen, J. Clardy, *J. Am. Chem. Soc.* **1984**, *106*, 7983–7984.
[4] H. Nakamura, Y. Kawase, K. Maruyama, A. Muria, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 781–787.
[5] a) A. Suksamrarn, A. Jankam, B. Tarnchompoo, S. Putchakarn, *J. Nat. Prod.* **2002**, *65*, 1194–1197; b) H. Shigemori, Y. Sato, T. Kagata, J. Kobayashi, *J. Nat. Prod.* **1999**, *62*, 372–374.
[6] C. Han, J. Qi, X. Shi, Y. Sakagami, T. Shibata, K. Uchida, M. Ojika, *Biosci. Biotechnol. Biochem.* **2006**, *70*, 706–711.
[7] J. J. Fernández, M. L. Souto, A. H. Daranas, M. Norte, *Curr. Top. Phytochem.* **2000**, *4*, 106–119.
[8] K. Sepcic, T. Turk, P. Macek, *Toxicon* **1998**, *36*, 937–940.
[9] R. E. Moore, P. J. Scheuer, *Science* **1971**, *172*, 495–498.
[10] For structure determination, see J. K. Cha, W. J. Christ, J. M. Finan, H. Fujioka, Y. Kishi, L. L. Klein, S. S. Ko, J. Leder, W. W. McWhorter, K.-P. Pfaff, M. Yonaga, D. Uemura, Y. Hirata, *J. Am. Chem. Soc.* **1982**, *104*, 7369–7371; for total synthesis, see E. M. Suh, Y. Kishi, *J. Am. Chem. Soc.* **1994**, *116*, 11205–11206.
[11] C. B. Rao, A. S. R. Anjaneyula, N. S. Sarma, Y. Venkatateswarlu, R. M. Rosser, D. J. Faulkner, *J. Org. Chem.* **1985**, *50*, 3757–3760.
[12] C. B. Rao, D. V. Roa, V. S. N. Raju, *Heterocycles* **1989**, *28*, 103–106.
[13] S. Fukuzawa, Y. Hayashi, D. Uemura, A. Nagatsu, K. Yamada, Y. Ijuin, *Heterocycl. Commun.* **1995**, *1*, 207–214.
[14] M. Kuramoto, K. Hayashi, Y. Fujitani, K. Yamaguchi, T. Tsuji, K. Yamada, Y. Ijuin, D. Uemura, *Tetrahedron Lett.* **1997**, *38*, 5683–5686.
[15] Atta-ur-Rahman, K. A. Alvi, S. A. Abbas, M. I. Choudhary, J. Clardy, *Tetrahedron Lett.* **1989**, *30*, 6825–6828.
[16] A. H. Daranas, J. J. Fernández, J. A. Gavín, M. Norte, *Tetrahedron* **1998**, *54*, 7891–7896.
[17] A. H. Daranas, J. J. Fernández, J. A. Gavín, M. Norte, *Tetrahedron* **1999**, *55*, 5539–5546.
[18] a) M. Kuramoto, K. Hayashi, K. Yamaguchi, M. Yada, T. Tsuji, D. Uemura, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 771–779; b) D. Uemura, *Chem. Rec.* **2006**, *6*, 235–248.
[19] R. K. Trench, *Pure Appl. Chem.* **1981**, *53*, 819–835.
[20] Also in this study, zooxanthellatoxin, a molecule closely related to palytoxin, was isolated; see Ref. [4] for details.
[21] M. Kuramoto, H. Arimoto, K. Hayashi, I. Hayakawa, D. Uemura, T. Chou, K. Yamada, T. Tsuji, K. Yamaguchi, K. Yazawa, Symposium Papers, 38th Symposium on the Chemistry of Natural Products **1996**, 79–84.
[22] T. J. Chambers, *J. Cell Sci.* **1982**, *57*, 247–260.
[23] K. Yamaguchi, M. Yada, T. Tsuji, M. Kuramoto, D. Uemura, *Biol. Pharm. Bull.* **1999**, *22*, 920–924.
[24] P. V. N. Bodine, H. A. Harris, B. S. Komm, *Endocrinology* **1999**, *140*, 2439–2451.
[25] K. Kuramoto, K. Yamaguchi, T. Tsuji, D. Uemura in *Drugs from the Sea* (Ed.: N. Fusetani), Karger, Basel, **2000**, pp. 98–106.
[26] For other descriptions of this activity, see a) M. Kuramoto, H. Arimoto, D. Uemura, *J. Synth. Org. Chem. Jpn.* **2003**, *61*, 59–65; b) M. Kuramoto, H. Arimoto, D. Uemura, *Mar. Drugs* **2004**, *1*, 39–54; c) M. Kita, D. Uemura, *Chem. Lett.* **2005**, *34*, 454–459; d) K. Yamada, M. Kuramoto, D. Uemura, *Recent Res. Dev. Pure Appl. Chem.* **1999**, *3*, 245–254.
[27] The IC_{50} values are for the inhibition of IL-6 production from preosteoblastic MC3T3-E1 cells stimulated by parathyroid hormone; see Ref. [25].
[28] G. Hirai, H. Oguri, M. Hayashi, K. Koyama, Y. Koizumi, S. M. Moharram, M. Hirama, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2647–2651.
[29] Y. Venkateswarlu, N. S. Reddy, P. Ramesh, P. S. Reddy, K. Jamil, *Heterocycl. Commun.* **1998**, *4*, 575–580.
[30] R. M. Villar, J. Gil-Longo, A. H. Daranas, M. L. Souto, J. J. Fernández, S. Peixinho, M. A. Barral, G. Santafé, J. Rodríguez, C. Jiménez, *Bioorg. Med. Chem.* **2003**, *11*, 2301–2306.
[31] N. L. Benowitz, *Prog. Cardiovasc. Dis.* **2003**, *46*, 91–111.
[32] S. P. Jackson, S. M. Schoenwalder, *Nat. Rev.* **2003**, *2*, 1–15.
[33] M. Miyashita, M. Sasaki, I. Hattori, M. Sakai, K. Tanino, *Science* **2004**, *305*, 495–499; M. Miyashita, *Pure Appl. Chem.* **2007**, *79*, 651–665.
[34] M. Sakai, M. Sasaki, K. Tanino, M. Miyashita, *Tetrahedron Lett.* **2002**, *43*, 1705–1708.
[35] D. Tanner, P. G. Anderson, L. Tedenborg, P. Somfai, *Tetrahedron* **1994**, *50*, 9135–9144.
[36] a) D. Tanner, L. Tedenborg, P. Somfai, *Acta Chem. Scand.* **1997**, *51*, 1217–1223; b) T. E. Nielsen, D. Tanner, *J. Org. Chem.* **2002**, *67*, 6366–6371.
[37] T. E. Nielsen, S. Le Quement, M. Juhl, D. Tanner, *Tetrahedron* **2005**, *61*, 8013–8024.
[38] X. Han, B. M. Stoltz, E. J. Corey, *J. Am. Chem. Soc.* **1999**, *121*, 7600–7605.
[39] M. Juhl, T. E. Nielsen, S. Le Quement, D. Tanner, *J. Org. Chem.* **2006**, *71*, 265–280.
[40] M. Juhl, R. Monrad, I. Søtofte, D. Tanner, *J. Org. Chem.* **2007**, *72*, 4644–4654.
[41] T. Irifune, T. Ohashi, T. Ichino, E. Sakia, K. Suenaga, D. Uemura, *Chem. Lett.* **2005**, *34*, 1058–1059.
[42] K. Sonogashira, Y. Tohdo, N. Hagihara, *Tetrahedron Lett.* **1975**, *16*, 4467–4470.
[43] D. R. Williams, T. A. Brugel, *Org. Lett.* **2000**, *2*, 1023–1026.
[44] For a review of Nef reactions, see H. W. Pinnick, *Org. React.* **1990**, *38*, 655–792.
[45] D. R. Williams, D. C. Ihle, T. A. Brugel, S. Patanaik, *Heterocycles* **2006**, *70*, 77–82.
[46] D. R. Williams, G. A. Cortez, *Tetrahedron Lett.* **1998**, *39*, 2675–2678.
[47] a) J. d'Angelo, D. Desmaële, F. Dumas, A. Guingant, *Tetrahedron: Asymmetry* **1992**, *3*, 459–505; b) P. W. Hickmott, *Tetrahedron* **1984**, *40*, 2989–3051.
[48] For a review of Evans aldol methodology, see D. J. Ager, I. Prakash, D. R. Schaad, *Aldrichimica Acta* **1997**, *30*, 3–12.

 © 2008 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

[49] S. Ghosh, F. Rivas, D. Fischer, M. A. González, E. A. Theodorakis, *Org. Lett.* **2004**, *6*, 941 – 944.
[50] a) T. Ling, C. Chowdhury, B. A. Kramer, B. G. Vong, M. A. Palladino, E. A. Theodorakis, *J. Org. Chem.* **2001**, *66*, 8843 – 8853; b) T. Ling, B. A. Kramer, M. A. Palladino, E. A. Theodorakis, *Org. Lett.* **2000**, *2*, 2073 – 2076.
[51] For a review of Robinson annulations, see R. E. Gawley, *Synthesis* **1976**, 777 – 794.
[52] F. Rivas, S. Ghosh, E. A. Theodorakis, *Tetrahedron Lett.* **2005**, *46*, 5281 – 5284.
[53] The use of dibromide **133** for radical cyclizations was explored, see a) G. Stork, R. Mook, S. A. Biller, S. D. Rychnovsky, *J. Am. Chem. Soc.* **1983**, *105*, 3741 – 3742; b) G. Stork, P. M. Sher, *J. Am. Chem. Soc.* **1983**, *105*, 6765 – 6766.
[54] a) N. Hikage, H. Furukawa, K. Takao, S. Kobayashi, *Tetrahedron Lett.* **1998**, *39*, 6237 – 6240; b) N. Hikage, H. Furukawa, K. Takao, S. Kobayashi, *Tetrahedron Lett.* **1998**, *39*, 6241 – 6244.
[55] a) P. Wieland, K. Miescher, *Helv. Chim. Acta* **1950**, *33*, 2215 – 2228; b) for the enantioselective preparation, see P. Buchschacher, A. Fürst, J. Gutzwiller, *Org. Synth.* **1985**, *63*, 37 – 43.
[56] N. Hikage, H. Furukawa, K. Takao, S. Kobayashi, *Chem. Pharm. Bull.* **2000**, *48*, 1370 – 1372.
[57] a) R. F. Heck, J. P. Nolley, *J. Am. Chem. Soc.* **1968**, *90*, 5518 – 5526; b) R. F. Heck, *Acc. Chem. Res.* **1979**, *12*, 146 – 151; c) R. F. Heck, *Org. React.* **1982**, *27*, 345 – 390.
[58] S. M. Moharram, G. Hirai, K. Koyama, H. Oguri, M. Hirama, *Tetrahedron Lett.* **2000**, *41*, 6669 – 6673.
[59] G. Hirai, H. Oguri, S. M. Moharram, K. Koyama, M. Hirama, *Tetrahedron Lett.* **2001**, *42*, 5783 – 5787.
[60] G. Hirai, Y. Koizumi, S. M. Moharram, H. Oguri, M. Hirama, *Org. Lett.* **2002**, *4*, 1627 – 1630.
[61] G. Hirai, H. Oguri, M. Hirama, *Chem. Lett.* **1999**, 141 – 142.
[62] S. M. Moharram, H. Oguri, M. Hirama, *Egypt. J. Pharm. Sci.* **2003**, *44*, 177 – 193.
[63] D. C. Behenna, J. L. Stockdill, B. M. Stoltz, *Angew. Chem.* **2007**, *119*, 4155 – 4158; *Angew. Chem. Int. Ed.* **2007**, *46*, 4077 – 4080.
[64] a) D. C. Behenna, B. M. Stoltz, *J. Am. Chem. Soc.* **2004**, *126*, 15044 – 15045; b) J. T. Mohr, D. C. Behenna, A. M. Harned, B. M. Stoltz, *Angew. Chem.* **2005**, *117*, 7084 – 7087; *Angew. Chem. Int. Ed.* **2005**, *44*, 6924 – 6927; c) R. M. McFadden, B. M. Stoltz, *J. Am. Chem. Soc.* **2006**, *128*, 7738 – 7739.

 © 2008 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim