CHAPTER ONE

The Biology and Chemistry of the Zoanthamine Alkaloids

1.1.1 Introduction[1]

Marine species comprise a vast repository for natural products isolation. In this chapter, we will focus on the biology and chemistry of the zoanthamine alkaloids, isolates from marine zoanthids. The order zoantharia consists of an intriguing group of marine polyps, morphologically classified into at least a dozen genera. Species in this order are widely dispersed throughout the temperate and tropical 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 (Figure 1.1.1) reproduce both sexually and asexually.[2] Recently, analysis of their respective mitochondrial DNA has elucidated the relationships between them.[3]

Figure 1.1.1 Representative zoanthids.

The polyps have a tube-shaped body and are radially symmetrical. Atop 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.[4] Zoanthids frequently contain symbiotic microalgae, which provide additional energy via photosynthesis. These dinoflagellate algae are thought to play an important role in the biosynthesis of some of the secondary metabolites isolated from the zoanthids.[5]

Diverse natural product archetypes have been isolated from species in the order zoantharia (Figure 1.1.2). Zoanthamine (**1**) is a member of the *Zoanthus* alkaloids, the subject of this chapter. Zoanthusterone (**2**) is an ecdysteroid isolated from a *Zoanthus sp*.[6] Prostaglandins like PGA_2 (**3**), isolated from *Palythoa kochii*, stabilize microtubules in a manner similar to paclitaxel.[7] A family of more than a dozen natural products based on the zoanthoxanthin (**4**) skeleton has been isolated from *Parazoanthus axinellae*.[8] A related structure, parazoanthoxanthin A, shows anticholinesterase activity.[9] Perhaps the best-known isolate from these marine organisms is palytoxin (**5**). Isolated from *Palythoa sp*. in the Hawaiian islands, palytoxin is one of the most toxic compounds known, with an LD_{50} of 15 μg/kg in mice.[10] The palytoxin structure was determined by Kishi, Uemura, and Hirata, and later synthesized by Kishi.[11]

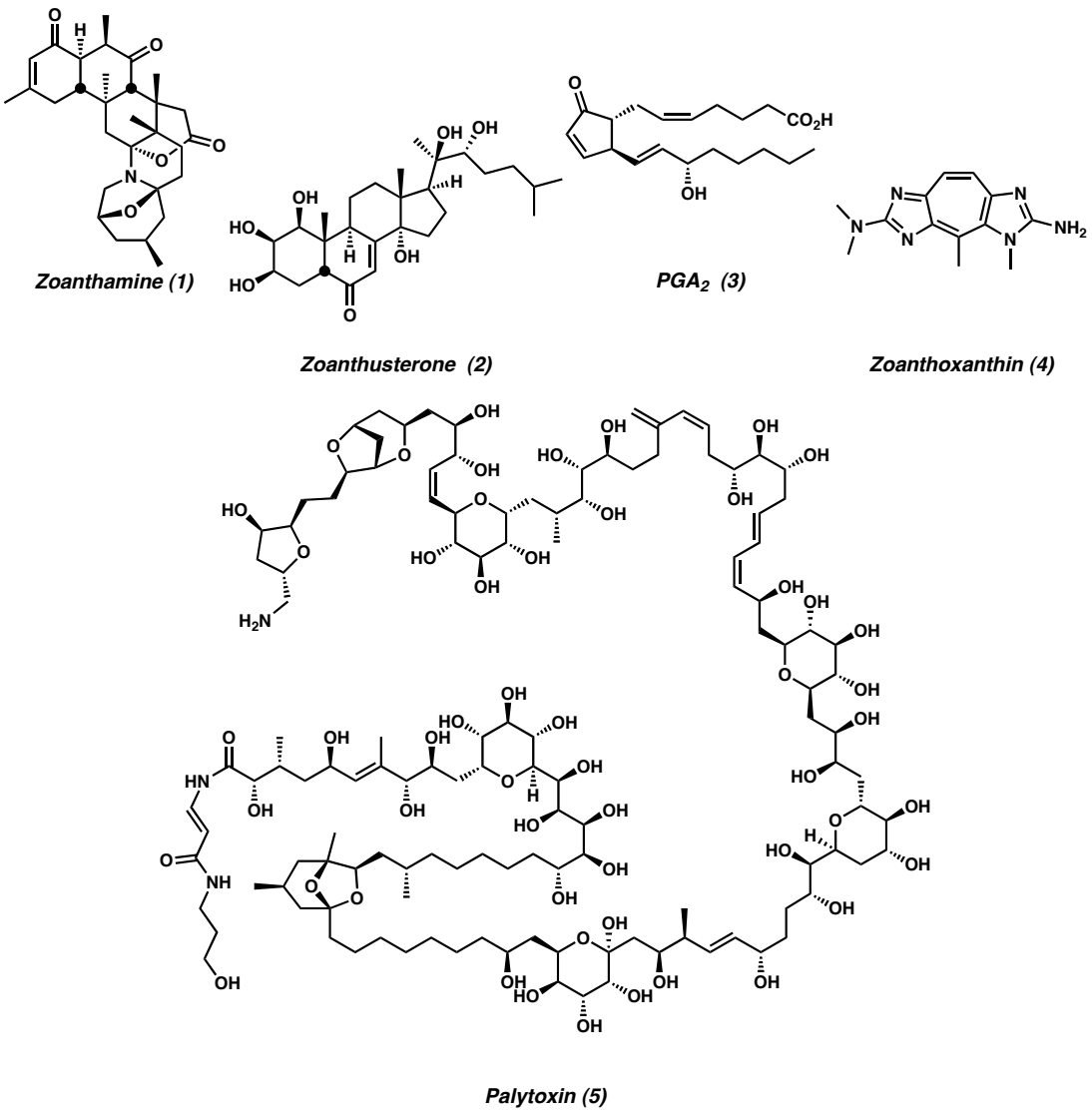


Figure 1.1.2 Natural products isolated from zoanthids.

1.2 The Zoanthamine Natural Products

1.2.1 Isolation and Structural Characterization of the Zoanthamine Natural Products

In 1984, Rao and coworkers disclosed the isolation of the natural product zoanthamine (**1**) from a species of the genus *Zoanthus* off the Visakhapatnam coast of India.[4] The connectivity and relative stereochemistry of the previously unknown alkaloid skeleton was unambiguously determined by single-crystal X-ray diffraction.[4] Throughout this thesis, carbon numbering and ring naming will refer to that of

zoanthamine (Figure 1.2.1). The initial isolation effort also afforded the related natural products zoanthenamine (**6**) and zoanthenamide (**7**), which were reported in 1985.[12] In 1989, Rao and coworkers isolated 28-deoxyzoanthenamine (**8**) and 22-*epi*-28-deoxyzoanthenamine (**9**) from a *Zoanthus* species in the Bay of Bengal.[13] Structures **6**–**9** were deduced by comparison with zoanthamine's spectroscopic data. Although these isolation efforts were undertaken in search of a known eye irritant produced by the *Zoanthus* species, all five of the isolated alkaloids showed inhibition of phorbol myristate acetate (PMA)-induced inflammation in mouse ears.[4,12]

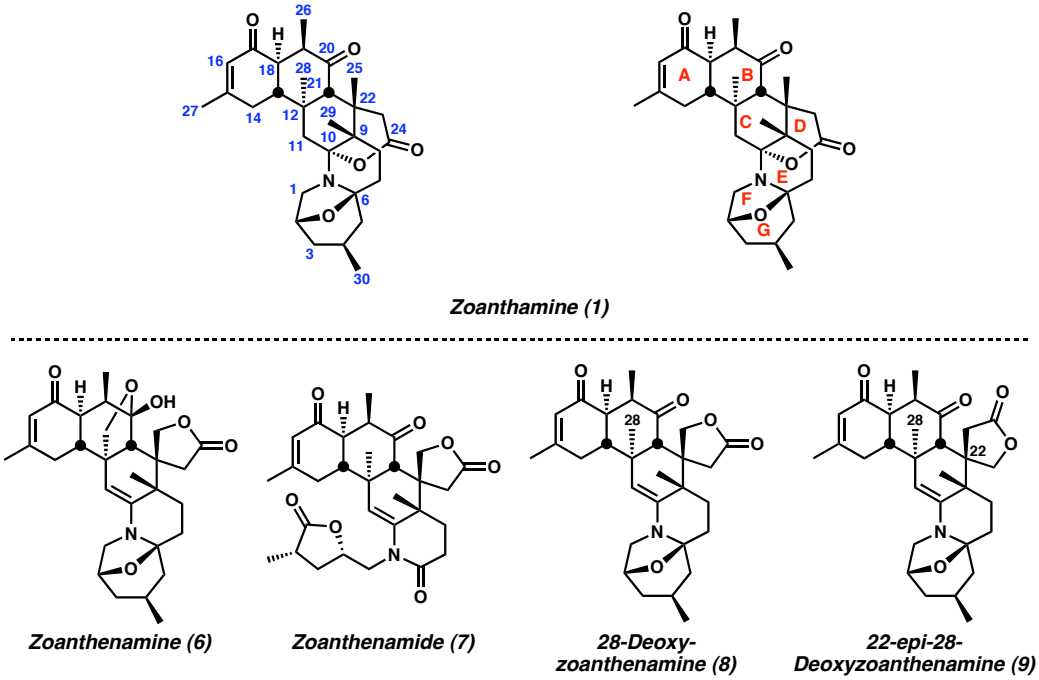


Figure 1.2.1 Zoanthamine natural products isolated by Rao.

In 1995, Uemura identified five new zoanthamine natural products isolated from a *Zoanthus* species collected off the Ayamaru coast of the Amami Islands south of Japan.[14] These isolates displayed structural variations including compounds lacking functionality at C(19) such as norzoanthamine (**10**) and norzoanthaminone (**11**), which is also oxidized at C(11). Oxyzoanthamine (**12**) is unique in displaying C(26) oxidation (Figure 1.2.2). The relative configuration of norzoanthamine was confirmed by X-ray

diffraction.[14] The absolute configuration of norzoanthamine was later determined by NMR analysis of MTPA derivatives to be as shown.[15] Zoanthaminone (**13**) is a 30-carbon alkaloid possessing C(11) oxidation, and its X-ray crystal structure was disclosed by Clardy.[16] Cyclozoanthamine (**14**) and epinorzoanthamine (**15**) display intriguing modifications to the A ring enone functionality. Both structures were assigned by extensive nOe experiments. [14]

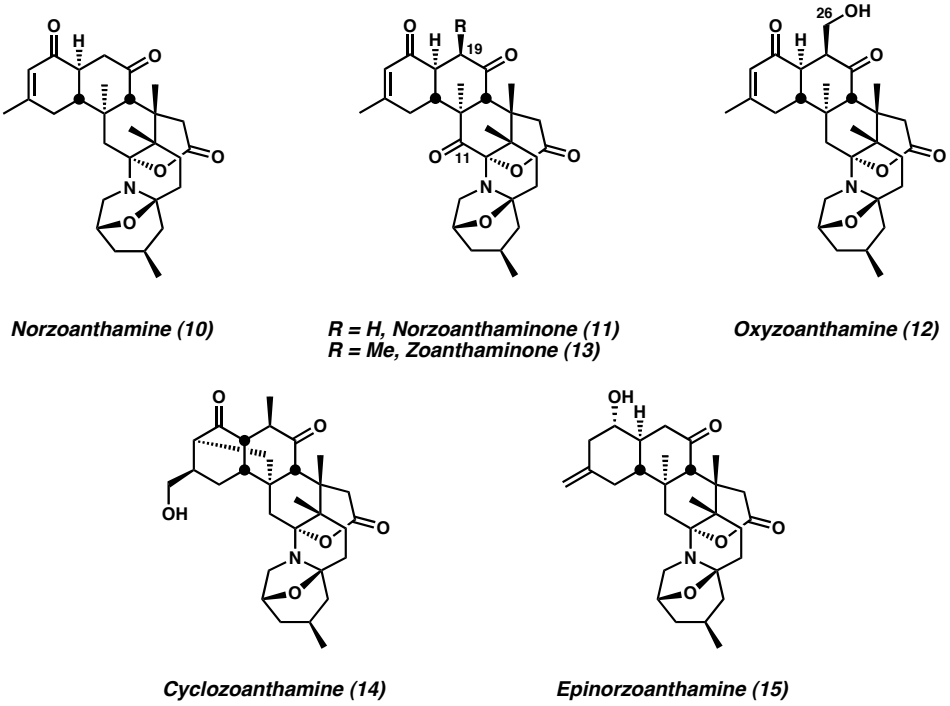


Figure 1.2.2 Zoanthamine natural products isolated by Uemura and Clardy.

In 1996, Norte and coworkers isolated a number of zoanthamine alkaloids with interesting oxidation patterns from zoanthids in the Canary Islands (Figure 1.2.3). Epioxyzoanthamine (**16**) is unique in its C(19) stereochemistry, which was determined by comparison with NMR data for oxyzoanthamine (**12**).[17] 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. Finally, zoanthenol (**21**) has a unique oxidized aromatic A ring, which removes the C(13) and C(18) stereocenters. As a

result of the structural change, extensive HMBC and ROESY correlation experiments were performed to confirm its structure and relative stereochemistry.[18]

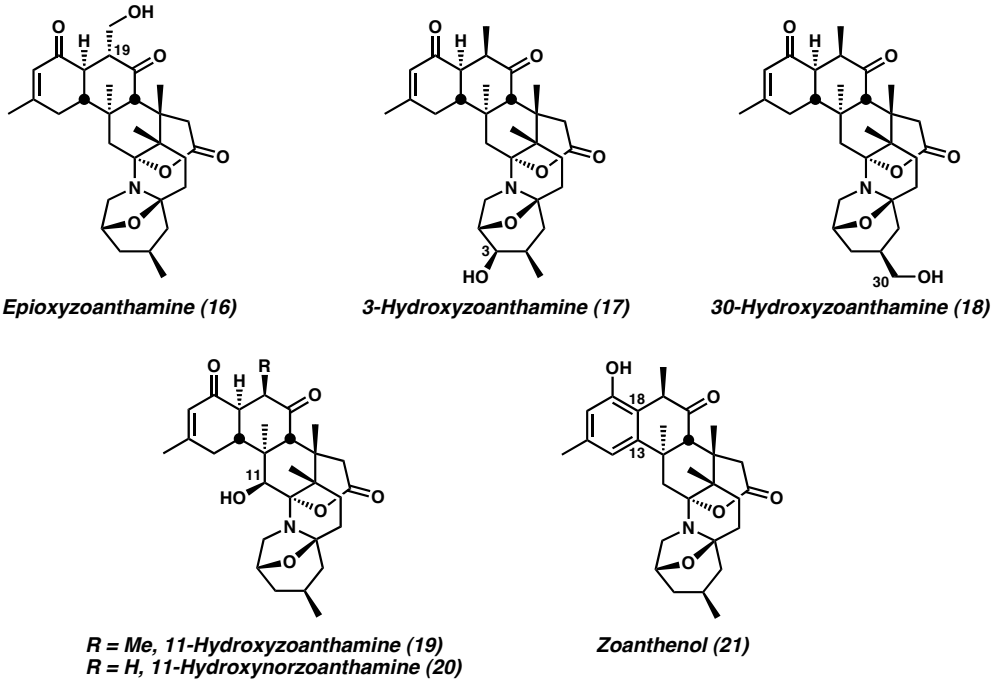
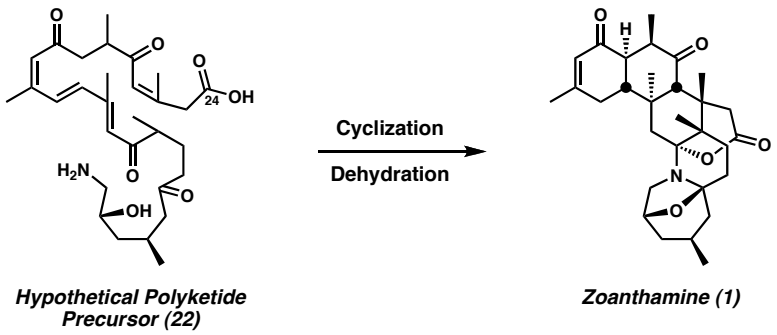


Figure 1.2.3 Zoanthamine natural products isolated by Norte.

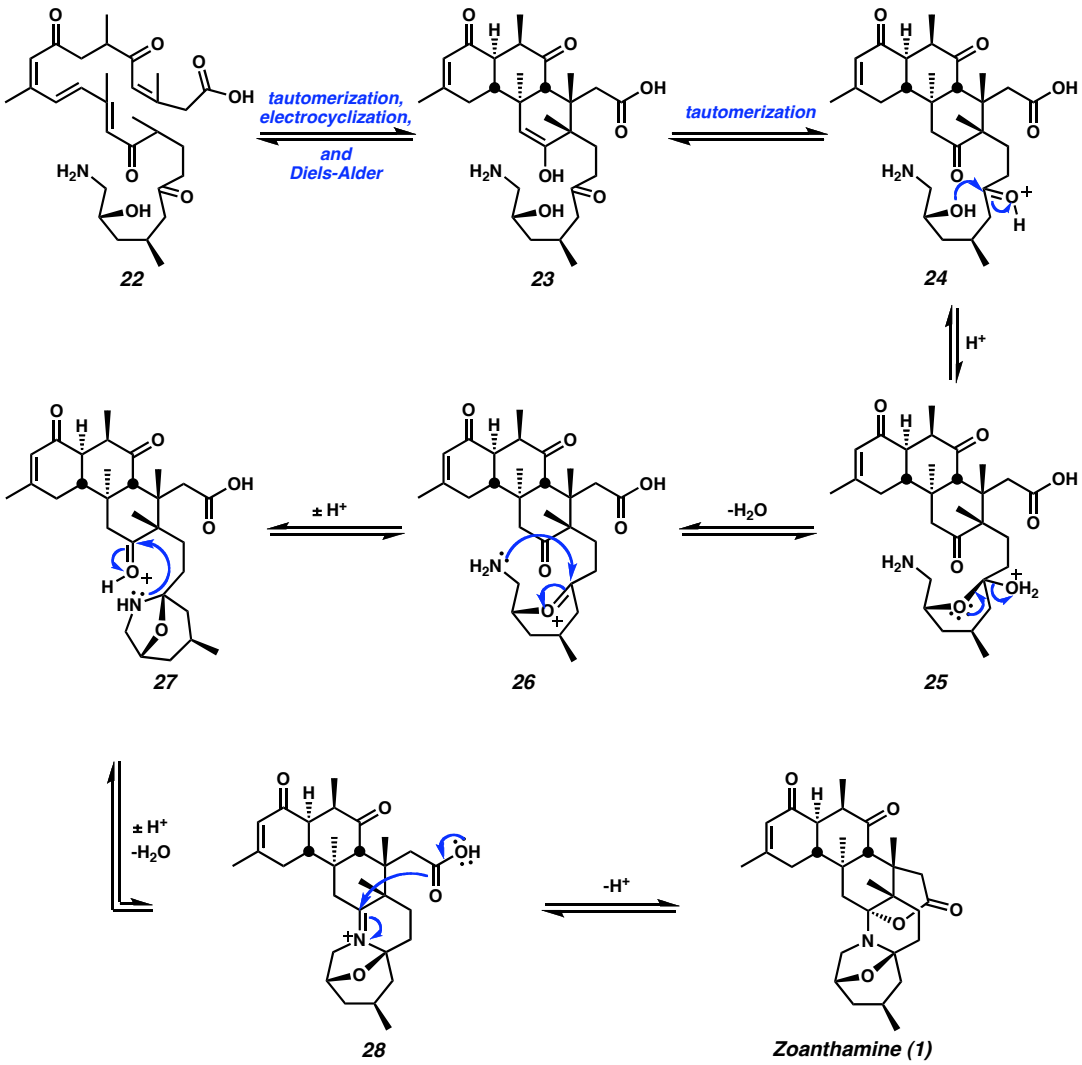
1.2.2 Biosynthesis of the Zoanthamine Natural Products

Despite their history of more than 20 years, relatively little is known about the biosynthesis of the zoanthamine natural products. Rao and coworkers noted in 1985 that elements of the 30-carbon zoanthamine skeleton suggest a triterpene origin, however they were unable to identify normal head-to-tail linkages to account for the zoanthamine skeleton.[4] More recently, Uemura has proposed that the zoanthamines may arise from polyketide precursor **22** (Scheme 1.2.1)[15,19] beginning at C(24) with a glycine unit,[5] but he does not further describe the pathway. 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 1.2.2).



Scheme 1.2.1 Hypothetical polyketide precursor.

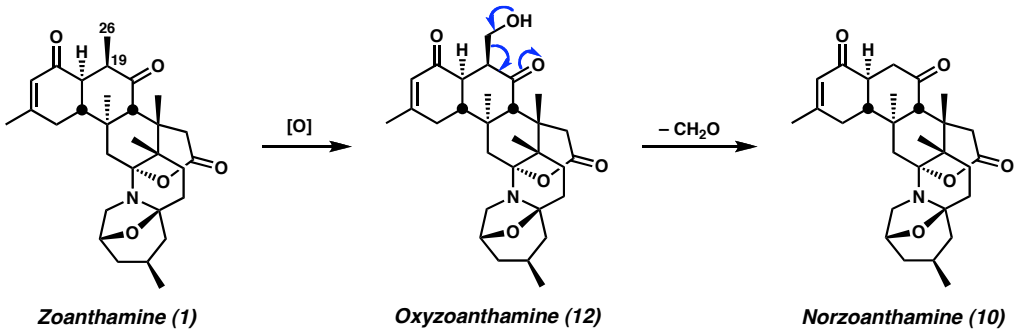
The conversion of **22** to **1** begins with tautomerization, electrocyclization, and Diels-Alder steps to form intermediate **23**. Tautomerization and carbonyl activation of **23** yield **24**, which undergoes 6-*exo* alcohol attack and protonation to form intermediate **25**. Oxocarbenium formation with loss of water gives **26**. Subsequent amine attack and proton transfer leads to intermediate **27**. Iminium formation provides **28**, then carboxylic acid attack and 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 this chapter.



Scheme 1.2.2 Potential mechanism for cyclization of polyketide precursor **22**.

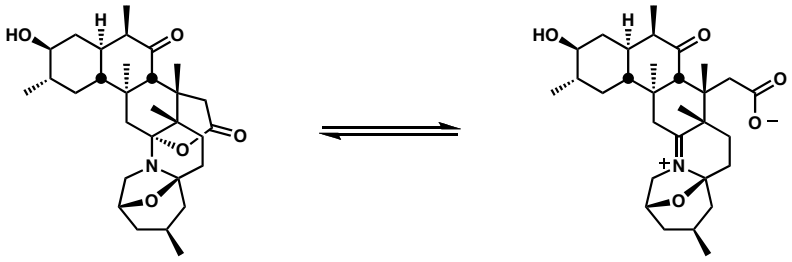
In addition to his polyketide proposal for zoanthamine, Uemura addresses the potential origin of the norzoanthamine-type alkaloids, which do not possess a methyl group at C(19). The isolation of oxyzoanthamine (**12**) prompted Uemura to propose an oxidative mechanism for the demethylation of zoanthamine (Scheme 1.2.3). Direct oxidation of zoanthamine at C(26) to the intermediate oxyzoanthamine, which is poised to undergo a retro-aldol reaction, formally releases formaldehyde and norzoanthamine (**10**).[14] It is unclear why Uemura does not propose substitution of an acetate unit for the relevant propionate unit proposed in Scheme 1.2.1. Such a modification would allow

quicker access to the zoanthamines lacking C(26), such as norzoanthamine (**10**), while direct oxidation of C(26) itself could still explain oxyzoanthamine (**12**).



Scheme 1.2.3 Proposed biosynthesis of norzoanthamine.

Another factor complicating the understanding of zoanthamine alkaloid biosynthesis 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*.[20] Although such symbiotic strains are difficult to culture in isolation, Nakamura and coworkers have been able to produce quantities of *Symbiodinium sp*. free of zoanthids.[5] While the algae produced different distributions of metabolites depending on the media used, significant experimentation with culture conditions allowed Nakamura's group to isolate a new C_{30} alkaloid they named zooxanthellamine (**29**). Zooxanthellamine exists as a mixture of lactone and zwitterionic iminium forms (Scheme 1.2.4). Its structure and relative configuration were established by extensive NMR studies. Zooxanthellamine has the same sense of absolute configuration as the zoanthamine alkaloids, as demonstrated by NMR comparison of its MTPA esters.[5]



Zooxanthellamine (29)

Scheme 1.2.4 Structure of zooxanthellamine.

The remarkable similarity between zooxanthellamine and zoanthamine has called into question the role of the zoanthids in producing the zoanthamine natural products.[21,22] 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 alkaloids' structures could be determined by factors in the marine environment or by the host zoanthid species. Alternatively, different species of algae may be involved in the production of different zoanthamines.

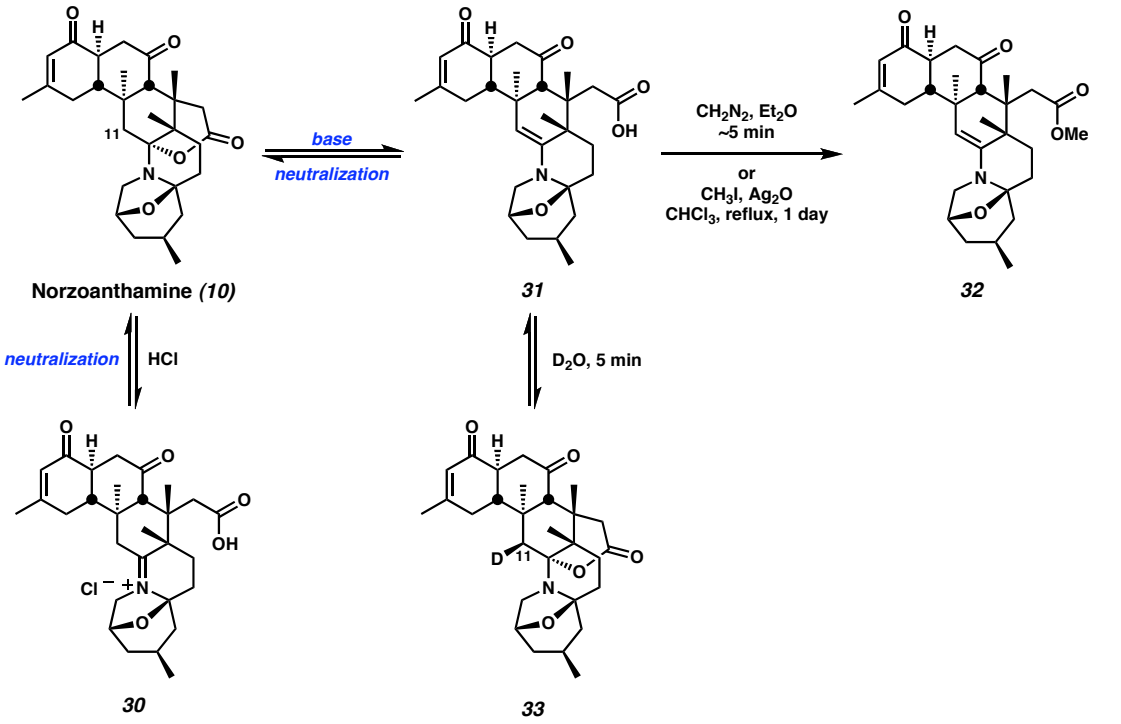
To date, there has been only one published attempt at a study directed toward the elucidation of the biogenesis of the zoanthamines. Norte and coworkers conducted a feeding study, during which labelled sodium acetate, glycine, and glucose were fed to small colonies of *Zoanthus* sp.[8] Although levels of incorporation of the labelled atoms were higher than 10% for all cases, the incorporation appeared to be random, leaving the question of the zoanthamines' biosynthesis 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, biosynthetic proposals cannot be either soundly supported or rationally refuted.

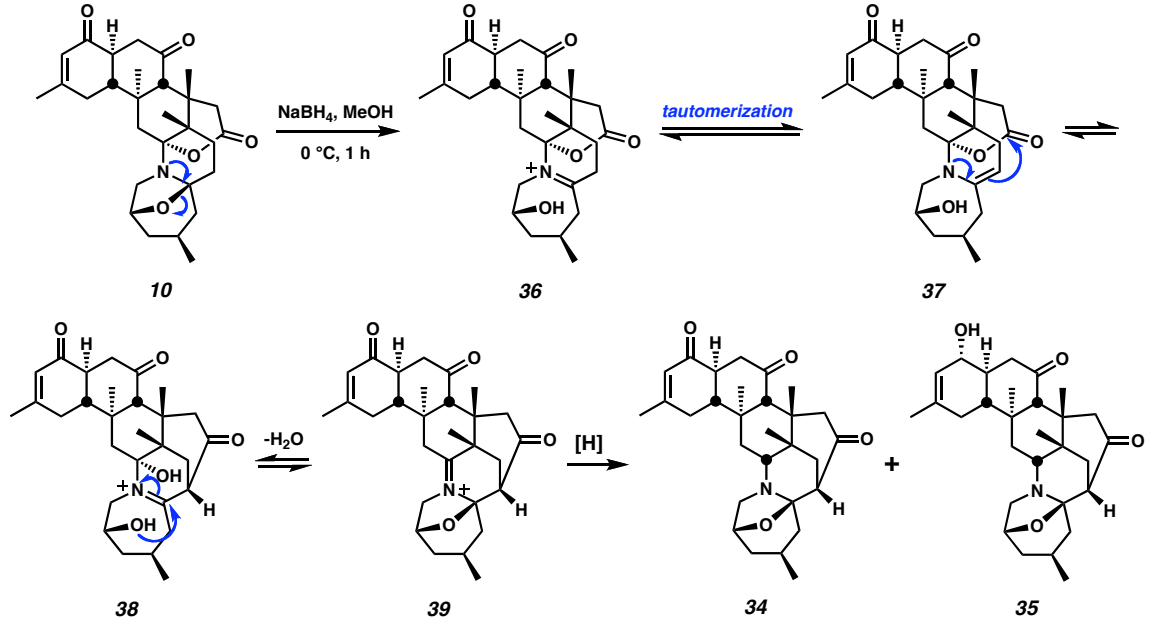
1.2.3 Reactivity Studies of Norzoanthamine

Following its isolation, norzoanthamine was subjected to a number of reaction conditions to aid in the formation of hypotheses about its mechanism of action for various biological activities. Fluxion between lactone and iminium isomers, similar to the equilibration observed with zooxanthellamine (Scheme 1.2.4), has been demonstrated in several zoanthamine natural products (Scheme 1.2.5). Norzoanthamine forms iminium 30 under acidic conditions and reverts upon neutralization.[19] Under neutral to basic conditions, elimination occurs to form enamine **31**. The equilibrium between norzoanthamine and enamine **31** was demonstrated by the conversion of norzoanthamine to methyl ester **32** in minutes upon exposure to diazomethane.[19] Furthermore, NMR spectra of norzoanthamine in D_2O show specific and complete deuterium incorporation at the 11β position to give deuteride **33** in minutes.[17,18] Similar rates of deuterium incorporation were observed with zoanthenol, 3-hydroxy-norzoanthamine, and 30-hydroxnorzoanthamine. In contrast, the 11β-hydroxy-zoanthamines did not show significant deuterium incorporation, suggesting that the elimination to an enamine is inaccessible.[18] This fluxional behavior in aqueous media at physiologically relevant pH 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 with sodium borohydride generates two anomalous products, enone **34** and allylic alcohol **35** (Scheme 1.2.6).[15,19] The formation of these products may be explained by 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 keto-iminium **38**. Dehydration generates iminium **39**, which undergoes reduction to give enone **34**. Further reduction affords allylic alcohol **35**.



Scheme 1.2.5 Equilibria between lactone and enamine isomers of norzoanthamine.



Scheme 1.2.6 Anomalous reduction of norzoanthamine.

1.3 Biological Activities of Zoanthamine Alkaloids

1.3.1 Anti-Osteoporotic Activity

Perhaps the best-studied and most well known biological activity of the zoanthamine alkaloids is the anti-osteoporotic effect first reported by Uemura in 1996.[23] Osteoporosis is a loss of bone mineral density that often results when osteoclasts reabsorb bone tissue at a rate faster than it is regenerated.[24] Norzoanthamine and its hydrochloride salt have been shown in vivo to prevent the symptoms of osteoporosis in ovariectomized mice, a pharmaceutical model for postmenopausal osteoporosis.[23] Ovariectomized mice, inherently deficient in estrogen, quickly lose bone mass and strength. However, at doses of 0.4 and 2.0 mg/kg/d (five days a week for 4 weeks, p.o.) of norzoanthamine hydrochloride, these mice retained femur weight at statistically higher rates than the untreated ovariectomized mice. With doses from 0.016–0.4 mg/kg/d of norzoanthamine hydrochloride, the femurs of ovariectomized mice maintained strength, measured by failure load at nearly comparable levels to nonovariectomized control mice. Finally, mice treated with norzoanthamine hydrochloride possessed cortical bone that is significantly thicker than that found in the control animals.[25]

In analogy to estrogen replacement therapy in postmenopausal women, treatment with 17β-estradiol rescues ovariectomized mice from the effects of osteoporosis. However, treatment with norzoanthamine hydrochloride 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.[25]

The origin of norzoanthamine's anti-osteoporotic effect 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. Estrogen thus derives its anti-osteoporotic properties from the inhibition of IL-6 production.[26] Norzoanthamine and

its hydrochloride salt (**24**) suppress the excretion of IL-6 from preosteoblastic cells at respective concentrations of 13 and 4.6 μg/mL in vitro.[27] However, in vitro studies with norzoanthamine hydrochloride showed no effect on osteoclast formation. Also, suppression of IL-6 secretion has not yet been demonstrated in vivo.[25] These last two points, along with the lack of uterine weight gain in ovariectomized mice, suggest that the zoanthamine alkaloids may act by a mechanism distinct from estrogen therapies.[28] Thus, they may offer treatments for post-menopausal osteoporosis that induce fewer side effects.

The need to find nonestrogen osteoporosis therapies has spurred considerable effort to define a structure activity relationship (SAR) for norzoanthamine's anti-osteoporotic effects. Via semi-synthesis, Uemura and coworkers produced and tested a number of norzoanthamine derivatives (Figure 1.3.1).[19,27] 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.[29] The studies revealed that the removal of the olefin (ketone **41** and diol **42)** caused some loss in activity. Furthermore, disruption of the lactone/hemiaminal functionality (carboxylic acid **43** and ester **32**) resulted in a significant drop in activity as well.[19]

More recently, Hirama and coworkers 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 (Figure 1.3.2).[30] In their assays, the zoanthamine hydrochloride salts **30** and **44** showed the greatest inhibition of MH-60 cell growth with IC_{50} values of 13 and 26 μM, respectively. A mimic of zoanthenol's "northern" carbocyclic region **45** and a mimic of the zoanthamine "southern" heterocyclic region **46** both showed very poor activity. However, iminium **47**, demonstrated activity approaching that of the zoanthamine hydrochlorides. This result provides further support for two trends: (a) the hydrochloride salt form of a zoanthamine-related

molecule is typically a more active inhibitor of IL-6 production than the natural product, and (b) the heterocyclic portion of the molecule likely is important in the pharmacophore for IL-6 inhibition.

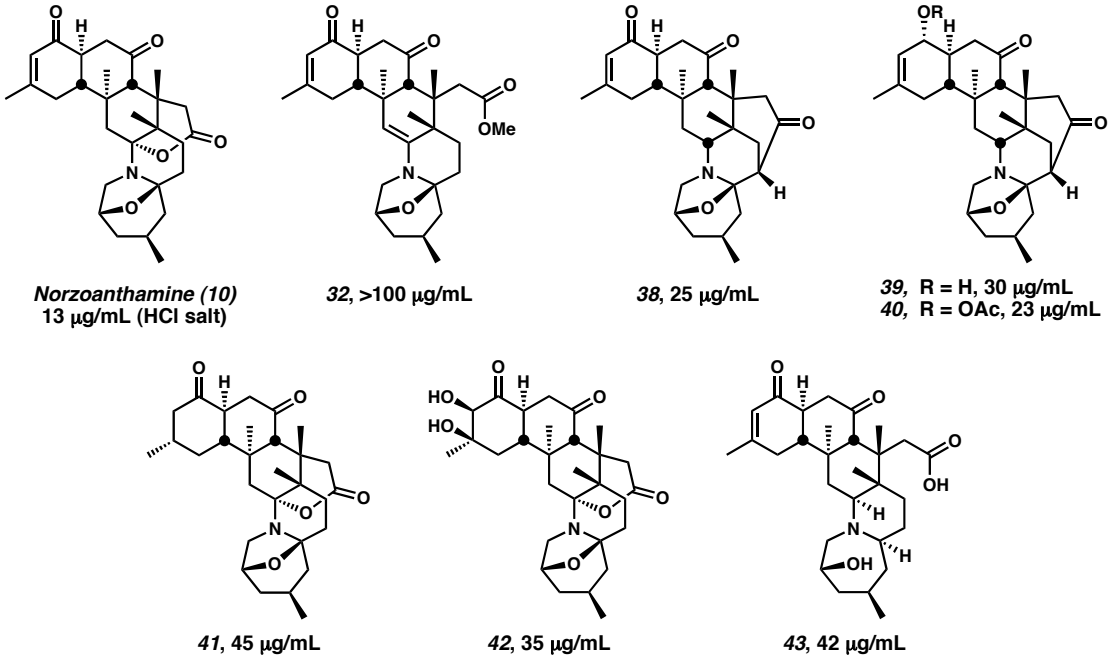


Figure 1.3.1 IC_{50} values for the inhibition of IL-6 production in Uemura's SAR study.

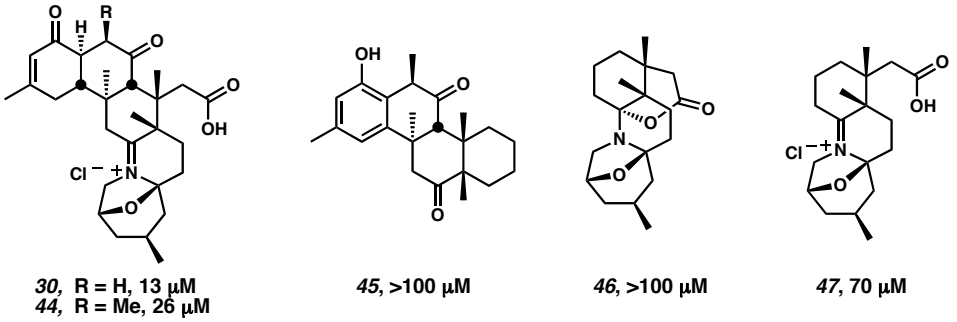


Figure 1.3.2 IC_{50} values for the inhibition of IL-6 dependent cell growth.

1.3.2 Miscellaneous Biological Activities

A variety of other biological activities have been reported for molecules in the zoanthamine family. As previously mentioned, zoanthamine (**1**), zoanthenamine (**6**), and zoanthenamide (**7**) were found to be inhibitors of PMA-induced inflammation in

mouse ear.[4,12] Uemura and coworkers reported that norzoanthamine (**10**), norzoanthaminone (**11**), oxyzoanthamine (**12**), cyclozoanthamine (**14**), and epinorzoanthamine (**15**) display significant cytotoxicity against P388 murine leukemia cells (Table 1.3.1).[14] The most potent cytotoxicity was displayed by norzoanthaminone.

Cytotoxicity

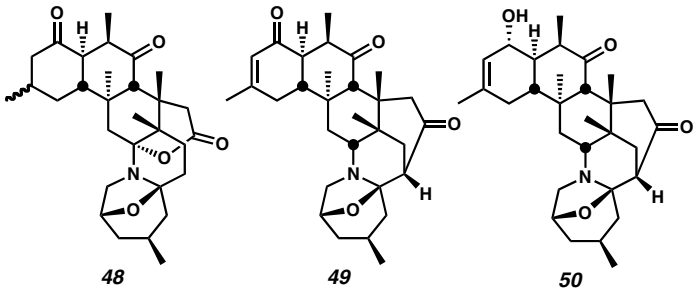
Compound	IC_{50} (μg/mL) for Inhibition of P388 Murine Leukemia Cells
Norzoanthamine *(10)*	24.0
Norzoanthaminone *(11)*	1.0
Oxyzoanthamine *(12)*	7.0
Cyclozoanthamine *(14)*	24.0
Epinorzoanthamine *(15)*	2.6

Table 1.3.1 Cytotoxicity of the zoanthamine alkaloids.

The antibacterial properties of zoanthamine and several of its reduced derivatives have also been investigated.[31] In disk susceptibility experiments, the zoanthamine alkaloids showed activity against both Gram negative and Gram positive bacteria (Table 1.3.2).

Antibacterial Activity

Compound	Inhibition Zone (diameter in mm)			
	Gram Negative		Gram Positive	
	S. typhimurium	*E. coli*	*B. sphaericus*	*S. aureus*
Zoanthamine *(1)*	6	6	8	7
48	12	6	8	10
49	7	6	8	10
50	6	7	7	9



48 *49* *50*

Table 1.3.2 Summary of antibacterial activities.

More recently, the effect of zoanthamine alkaloids on human platelet aggregation has been investigated.[32] 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 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. Formation of a thrombus due to abnormal platelet aggregation can lead to obstruction of a vein or artery, causing a cardiovascular event.[33] Several antithrombotic agents are already in use as cardiovascular disease treatments; however, their efficacy is limited by weak antithrombotic effects at the administered dosage and/or deleterious side effects such as the inhibition of haemostasis, leading to significant abnormal bleeding.[34] Experimental and clinical evidence indicate that a selective collagen receptor antagonist will result in only a very small change in haemostasis, meaning a safer, yet still potent drug.[34]

1.4 Synthetic Approaches Toward the Zoanthamine Natural Products

1.4.1 General Remarks

The intriguing diversity of biological activities and the densely functionalized structures of the zoanthamine alkaloids have inspired a host of synthetic chemistry 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 due to its stereochemical density. For example, the C ring contains three quaternary stereocenters in vicinal and nonvicinal relationships. In addition to the difficulty of synthesizing quaternary centers, their steric bulk also renders even routine transformations on nearby functionality troublesome.

Other researchers have focused on the synthesis of the heterocyclic DEFG rings. The DEFG ring system presents the challenge of forming the heterocycles with the correct hemiaminal connectivity and stereochemistry.

1.4.2 Miyashita's Synthesis of Norzoanthamine

Twenty years after the isolation of the first zoanthamine alkaloids, Miyashita and coworkers reported the first and, as yet, only completed total synthesis of a zoanthamine alkaloid with their synthesis of norzoanthamine.[35] The general synthetic plan is illustrated in Figure 1.4.1. This impressive 41-step effort included several creative solutions to problems that arose during the execution of the synthesis. Their Diels-Alder strategy for the construction of the ABC ring system of norzoanthamine was disclosed in 2002 (Scheme 1.4.1).[36]

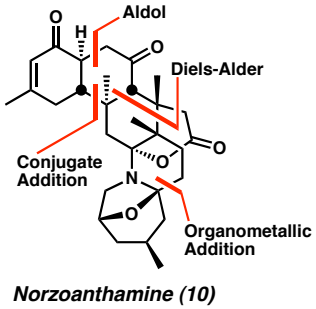
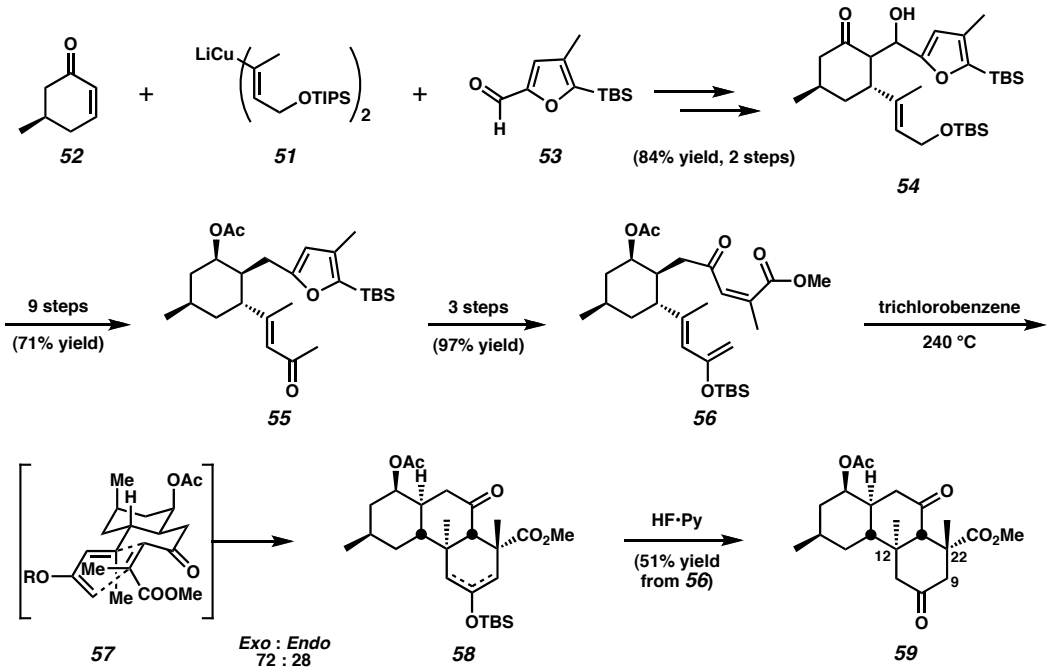


Figure 1.4.1 Miyashita's retrosynthetic analysis of norzoanthamine.

The synthesis begins with addition of cuprate **51** to enantiopure enone **52**, followed by an aldol reaction with aldehyde **53** to provide ketone **54**. This efficient sequence set the absolute stereochemistry at C(13), from which the remaining stereocenters were derived. Following several functional group manipulations, furan **55** was photochemically oxidized using Katsumura conditions. Subsequent silyl enol ether formation provided Diels-Alder substrate **56**. Upon heating to 240 °C, the Diels-Alder reaction proceeded predominantly through the desired exo transition state **57** to a mixture of silyl enol ether isomers **58**. After silyl cleavage, diastereomerically pure

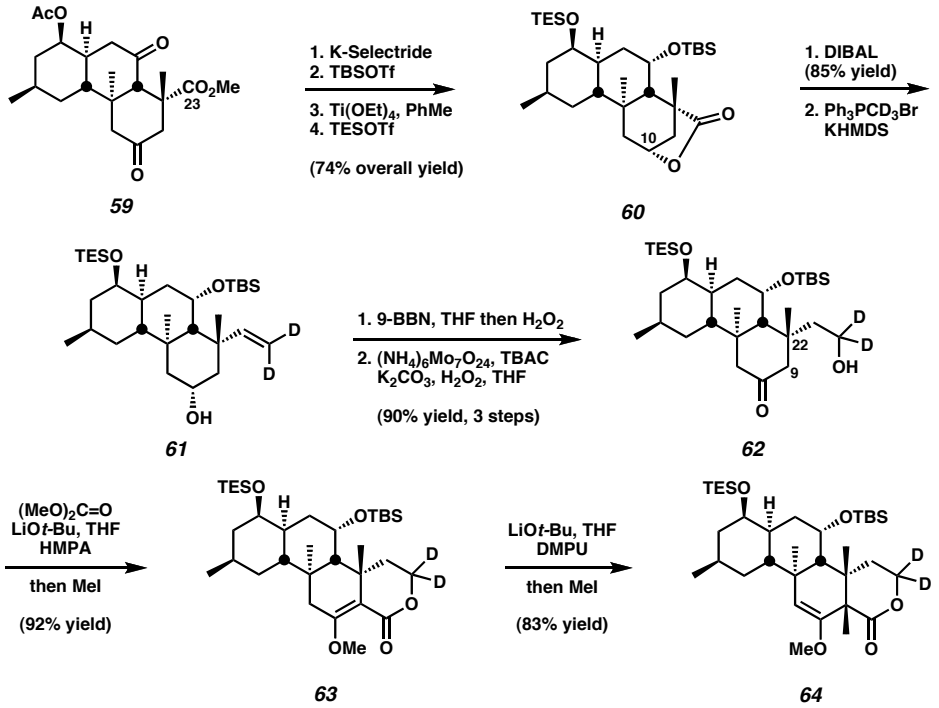
ketone **59** was isolated in 51% yield over the two steps. This Diels-Alder reaction sets both the C(12) and C(22) quaternary centers of norzoanthamine with the correct absolute stereochemistry.



Scheme 1.4.1 Miyashita's Diels-Alder construction of the ABC core.

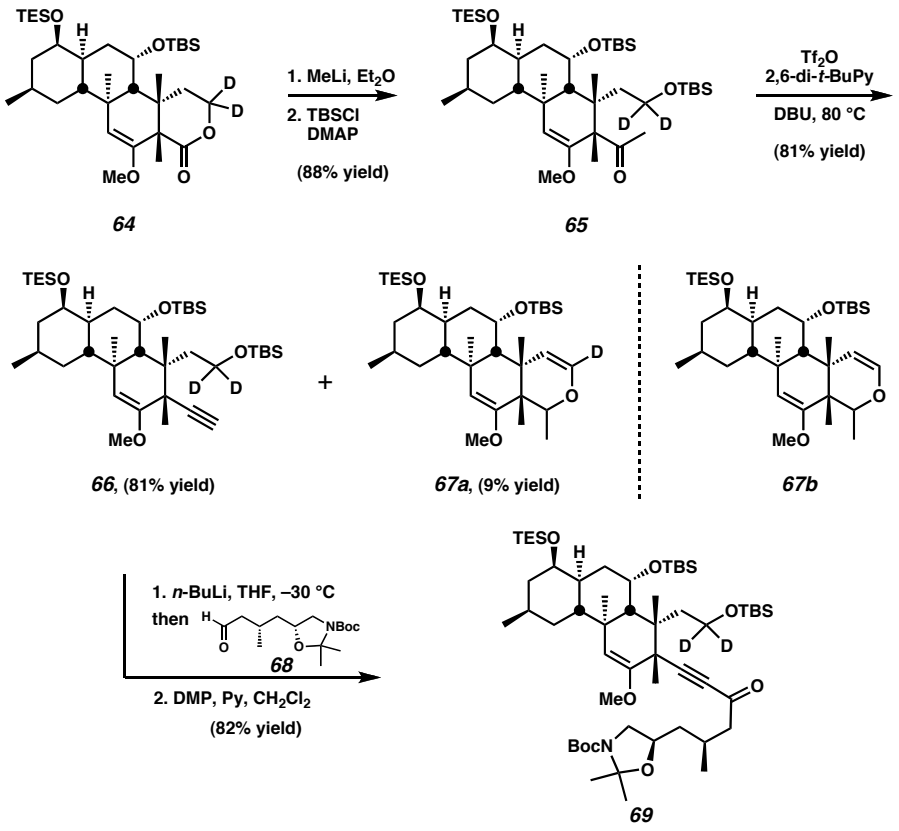
At this point, a number of functional group manipulations were undertaken to allow homologation at C(23) and installation of the final quaternary center at C(9) (Scheme 1.4.2). Diastereoselective reduction of both ketones in **59** was accomplished by K-selectride addition from the convex face, resulting in the desired lactone formation at the C(10) hydroxyl. Silylation with TBSOTf, acetate cleavage, and TES protection afforded protected lactone **60**. Reduction of the lactone to the lactol followed by Wittig reaction provided bis-deutero olefin **61**. Hydroboration and oxidation provided ketone **62**, which was poised for formation of the C(9) quaternary center. To that end, acylation of ketoalcohol **62** with dimethyl carbonate and lithium *tert*-butoxide proceeded regioselectively, presumably due to initial alcohol acylation and subsequent lactone formation 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.



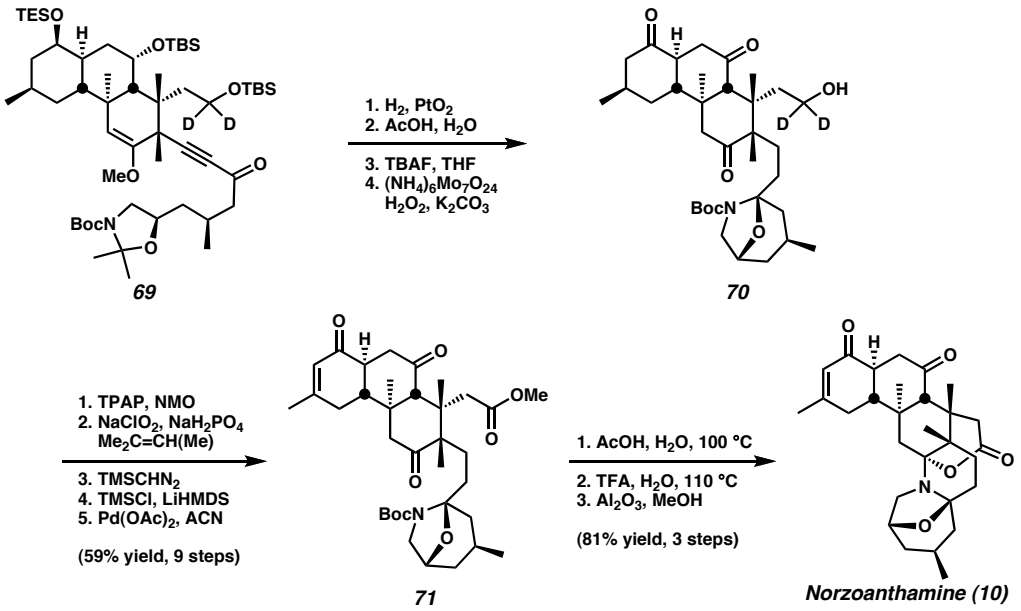
Scheme 1.4.2 Functionalization of the ABC core.

The synthesis of the southern portion of norzoanthamine began with conversion of the C(8) lactone to an alkyne followed by side chain addition (Scheme 1.4.3). Monoaddition of methyl lithium into lactone **64** then silyl protection provided methyl ketone **65**, which was converted to alkyne **66** by treatment with triflic anhydride and DBU. This conversion was accompanied by formation of a small amount of by-product **67a**. In the corresponding non-deuterated substrate, the by-product **67b** was formed in 30% yield, reducing the yield of the desired alkyne to 66%. The carbon skeleton of norzoanthamine 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 1.4.3 Attaching the southern side chain.

Completion of the target required a further twelve steps of deprotection, oxidation state adjustment, and dehydration (Scheme 1.4.4). From **69**, alkyne reduction, acidic enol ether cleavage and acetal removal, global desilylation, and secondary alcohol oxidation provided **70**. Sequential oxidation of the primary alcohol provided the carboxylic acid, which was esterified with TMS-diazomethane. Saegusa-Ito oxidation installed the A ring enone, yielding **71**. Treatment of **71** with hot aqueous acetic acid resulted in carbamate cleavage and iminium formation. Upon being subjected to aqueous TFA at 110 °C, the methyl ester added into the iminium ion, forming the TFA salt of norzoanthamine. The salt was treated with basic alumina in methanol to reveal the natural product. In addition to the impressive synthetic accomplishment, this synthesis also served to unambiguously confirm the absolute stereochemistry of norzoanthamine, which had previously been deduced from NMR experiments.



Scheme 1.4.4 The completion of norzoanthamine.

1.4.3 Tanner's Diels-Alder Approach to the Zoanthamine ABC Ring System

Tanner and coworkers also chose to assemble the ABC rings via a Diels-Alder approach (Figure 1.4.2). A Stille coupling was planned for the synthesis of the Diels-Alder precursor, and the synthesis would begin with perillyl alcohol (**72**), both enantiomers of which are available. The stereochemistry of all the remaining stereocenters would then be set by diastereoselective chemistry.

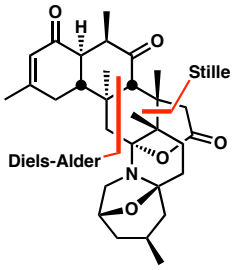
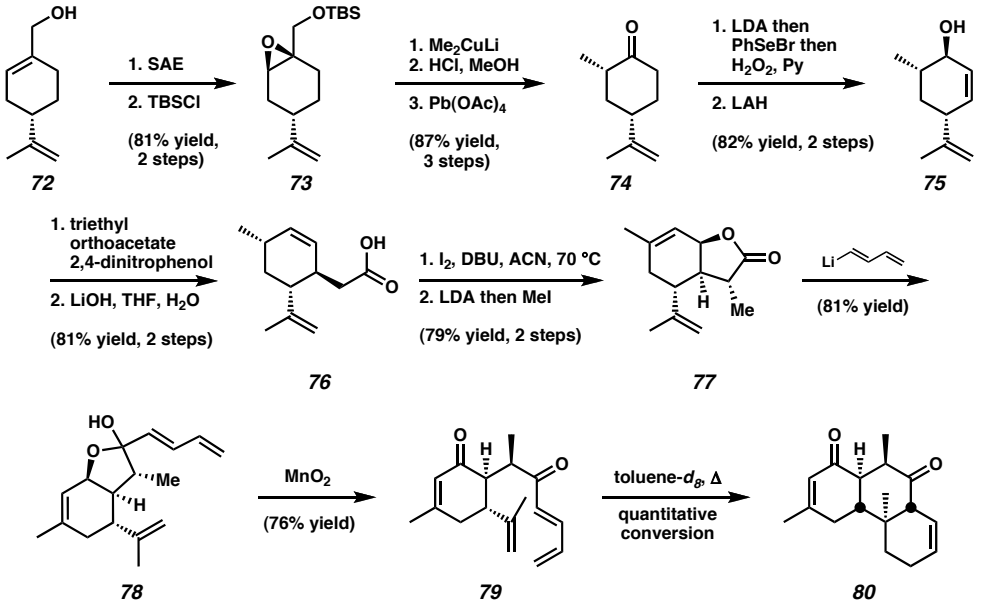


Figure 1.4.2 Tanner's retrosynthetic analysis of zoanthamine.

Tanner's synthesis began with Sharpless asymmetric epoxidation of known perillyl alcohol (**72**) followed by silylation to provide epoxide **73** (Scheme 1.4.5).[37] The C(15)

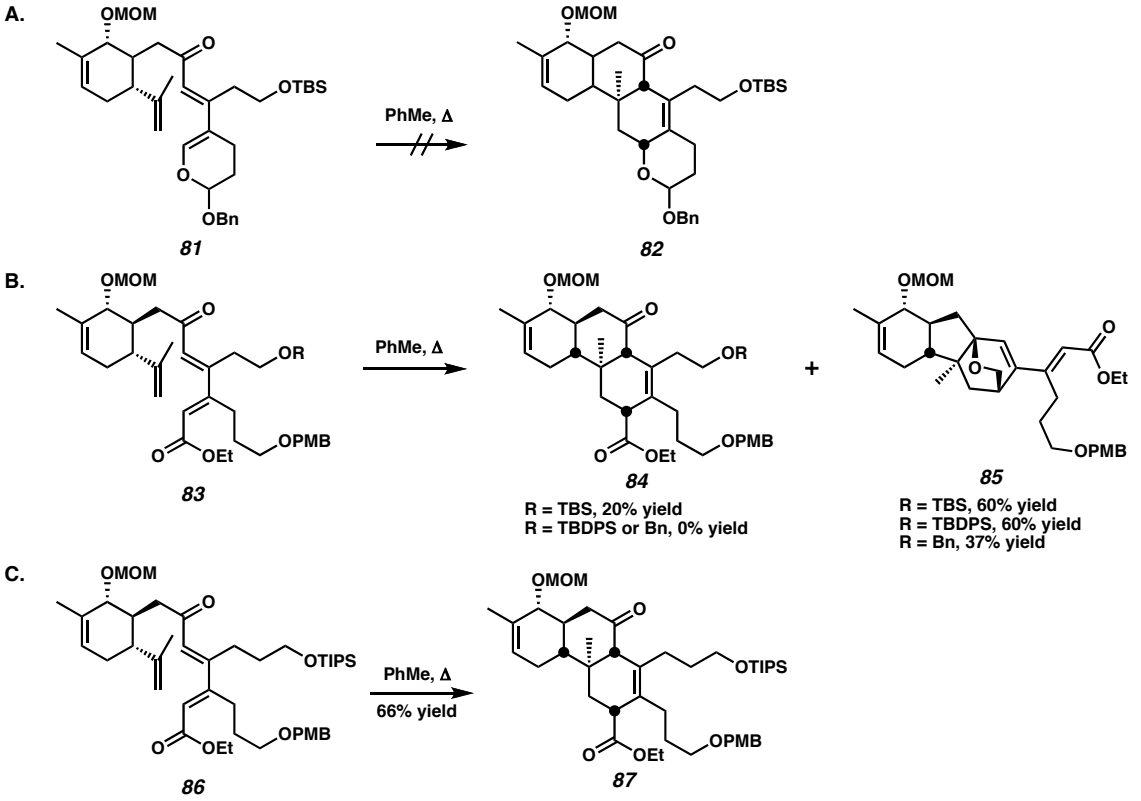
methyl group was installed by diastereoselective addition of Gilman's reagent into the epoxide. Removal of the silyl group and subsequent treatment with lead tetraacetate led to desired methyl ketone **74**. Trapping of the kinetic enolate with PhSeBr and peroxide oxidation allowed for enone installation, and subsequent LAH reduction led to allylic alcohol **75** as a single diastereomer. Alkylation with Claisen rearrangement was affected using triethyl orthoacetate and catalytic 2,4-dinitrophenol. This was followed by saponification with LiOH to form **76**. Iodolactonization occurred to give a mixture of 5- and 6-membered iodolactones that equilibrated upon heating. With DBU in the reaction mixture, the thermodynamically favored product was irreversibly trapped by elimination of HI. Diastereoselective alkylation of this enol lactone with MeI provided **77**, which was subjected to lithiobutadiene yielding hemiacetal **78**. Manganese dioxide oxidation provided Diels-Alder precursor **79**, and heating this intermediate in d_8-toluene provided quantitative conversion of **79** to tricycle **80**.



Scheme 1.4.5 Tanner's approach to a model ABC ring system.

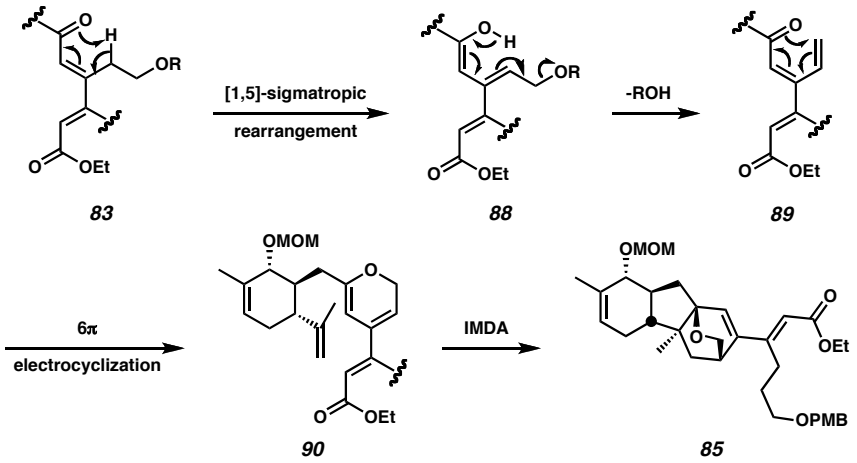
Encouraged by the success of this model Diels-Alder cycloaddition, the Tanner group set out to synthesize a more functionalized precursor. In order to more readily probe the

limitations of the reaction, a number of model substrates were synthesized from (–)-carvone. The first model substrate (**81**, Scheme 1.4.6) led to a disappointing, but critical, discovery. Upon heating in toluene for several days, no reaction was observed. It was determined that the extra electron density in the diene was rendering the desired inverse-electron demand Diels-Alder cycloaddition ineffective. Thus, DA substrate **83** (R = TBS) was synthesized. Upon heating, two products were observed: desired DA adduct **84** and an unusual side product **85**. Upon varying the nature of the protecting group (R), **85** was the sole product observed. However, a one-carbon homologation of the chain at C(22) (**86**) was sufficient to avoid the formation of the side-product, providing a 66% yield of **87** with the correct stereochemistry for the synthesis of zoanthamine.



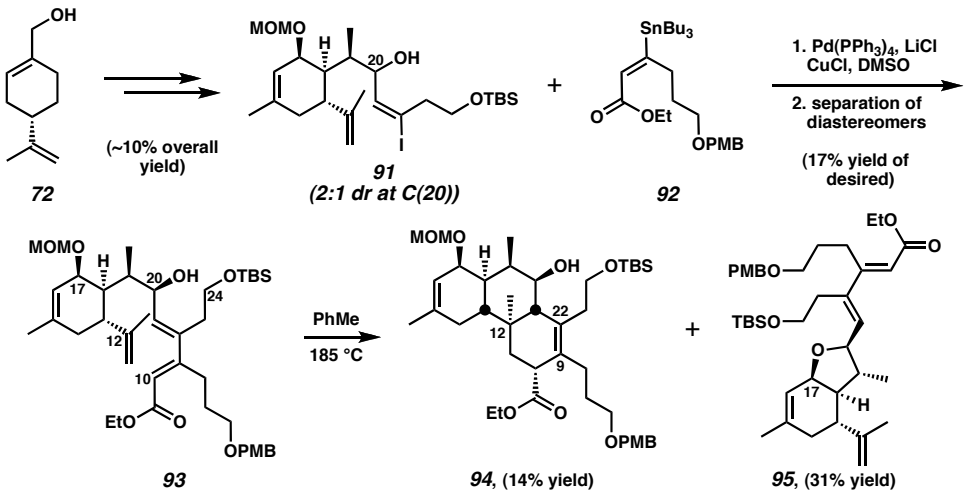
Scheme 1.4.6 Model cyclizations of compounds derived from (–)-carvone.

This final modification confirmed the mechanistic hypothesis illustrated in Scheme 1.4.7. From the DA substrate (**83**), a 1,5-sigmatropic rearrangement leads to extended enol **88**. Loss of ROH (R = TBS, TBDPS, Bn) then gave terminal olefin **89**. A 6π electrocyclization provided pyran **90**, which then underwent intramolecular Diels-Alder reaction to form the side product **85**.



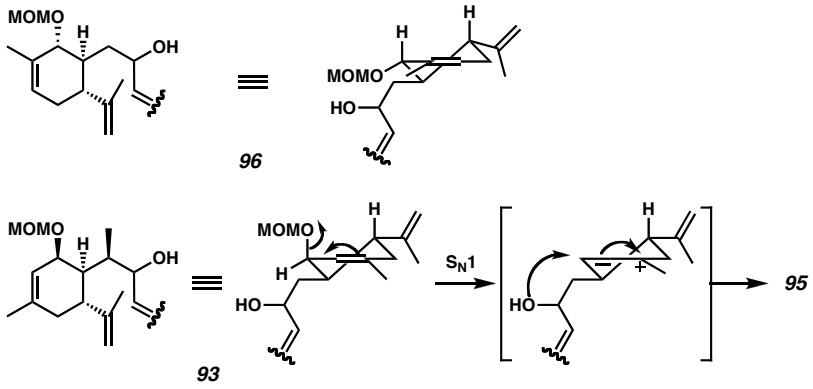
Scheme 1.4.7 Mechanism for formation of undesired products.

Armed with this information, perillyl alcohol was converted to vinyl iodide **91** (Scheme 1.4.8).[38] Stille coupling with stannane **92** proved difficult and required special conditions reported by Corey to afford reasonable yields of the Diels-Alder substrate **93**.[39-41] 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.



Scheme 1.4.8 Tanner's approach to the functionalized ABC ring system.

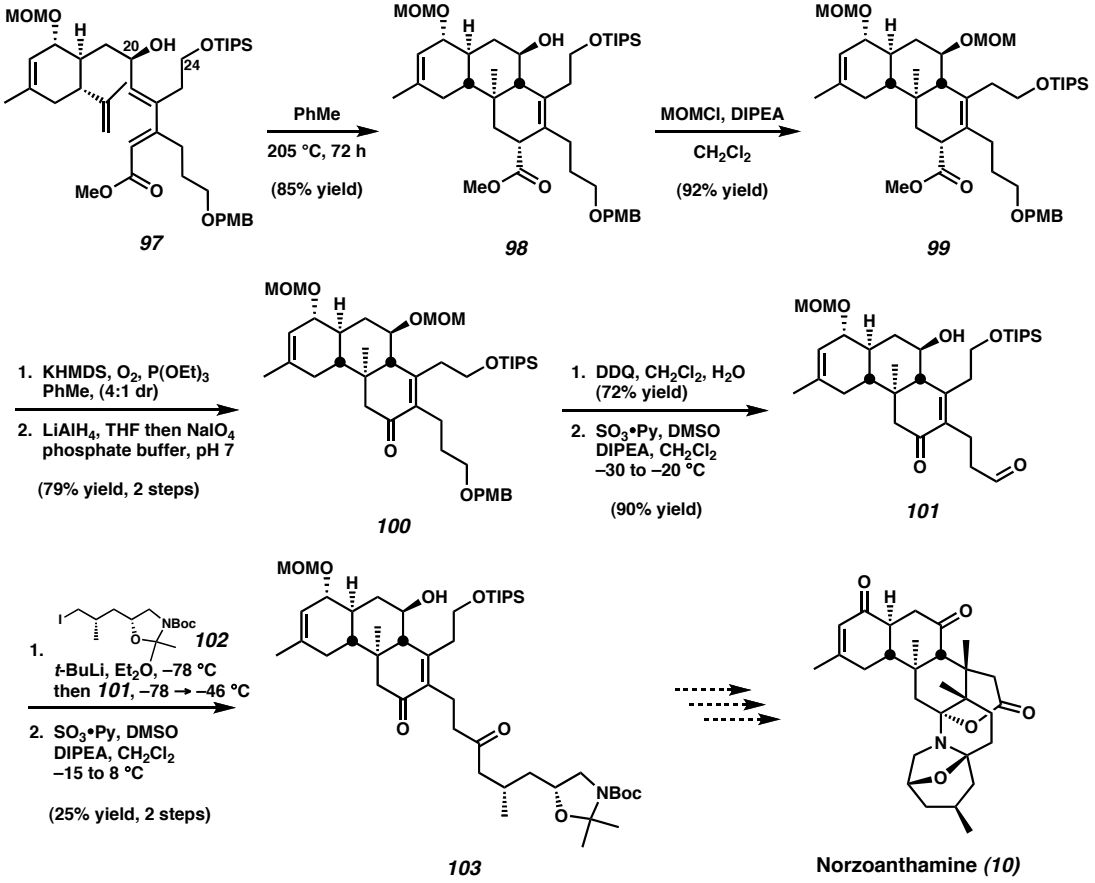
Upon examining the differences between this perillyl alcohol-derived substrate and the corresponding carvone-derived substrate (reaction not shown), Tanner and coworkers noted that the allylic MOM-protected alcohol was arranged in a pseudo-axial orientation in DA precursor **93**, whereas the model substrate (**96**) possesses a pseudo-equatorial MOM ether (Scheme 1.4.9). It is believed that this difference allows for S_N1-type displacement and cyclization to form tetrahydrofuran **95**.



Scheme 1.4.9 Mechanism for formation of by-product **95**.

Based on this rationale, a new Diels-Alder substrate (**97**) was synthesized and cyclized by treatment with toluene at 205 °C (Scheme 1.4.10).[42] Gratifyingly, the Diels-Alder proceeded smoothly through an exo transition state to provide tricycle **98** in 85% yield. Protection of the C(20) alcohol as the MOM-ether (**99**) was followed by an

oxidative cleavage sequence to afford enone **100**. Subsequent PMB-ether removal and oxidation provided aldehyde **101**. At this point, side chain **102** was treated with *t*-butyl lithium, aldehyde **101** was added, and the resulting alcohol was oxidized to afford advanced intermediate **103**.



Scheme 1.4.10 Diels-Alder cyclization and cycloadduct advancement.

While this Diels-Alder strategy nicely established the quaternary center at C(12), it will require the formation of the difficult vicinal C(9) and C(22) quaternary centers at a late stage in the synthesis. The Tanner 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 C(24) and cyclization of the side chain to form the DEFG rings remain to complete the total synthesis of norzoanthamine.

1.4.4 Uemura's Approach to the Norzoanthamine ABC Ring System

Recently, Uemura and coworkers have reported a synthetic strategy based on their biosynthetic hypothesis, which purports that the zoanthamine alkaloids arise from a linear polyketide skeleton, which then undergoes numerous pericyclic cyclizations.[43] To support this hypothesis, they endeavored to synthesize and cyclize polyene **104** en route to the natural product (Figure 1.4.3).

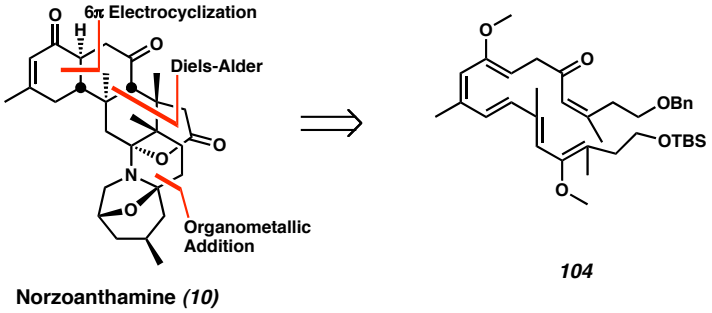
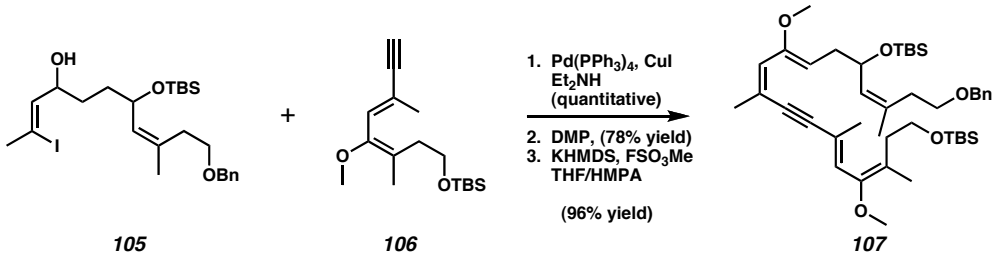


Figure 1.4.3 Uemura's retrosynthetic analysis of norzoanthamine.

Vinyl iodide **105** and alkyne **106** were efficiently assembled then united by Sonogashira coupling.[44] Conversion to enyne **107** was completed by oxidation and methylation (Scheme 1.4.11). 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**.



Scheme 1.4.11 Uemura's approach to norzoanthamine.

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

Williams and coworkers have explored approaches to the synthesis of both the carbocyclic AB rings and the heterocyclic EFG rings of norzoanthamine and zoanthenol.

Their Diels-Alder strategy constructs the AB rings, which will be followed by appending the C ring (Figure 1.4.4).[45] The EFG ring system is formed by conjugate addition of an enamine into a functionalized linear enone then cyclization to form the stereochemistry and connectivity observed in the natural products.

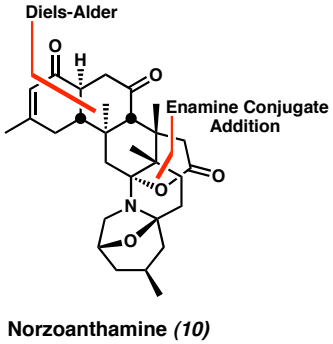
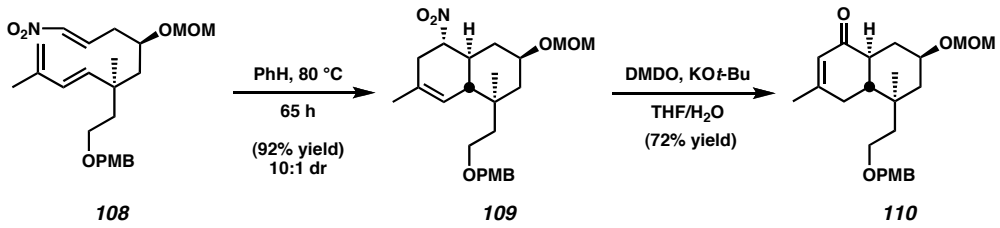


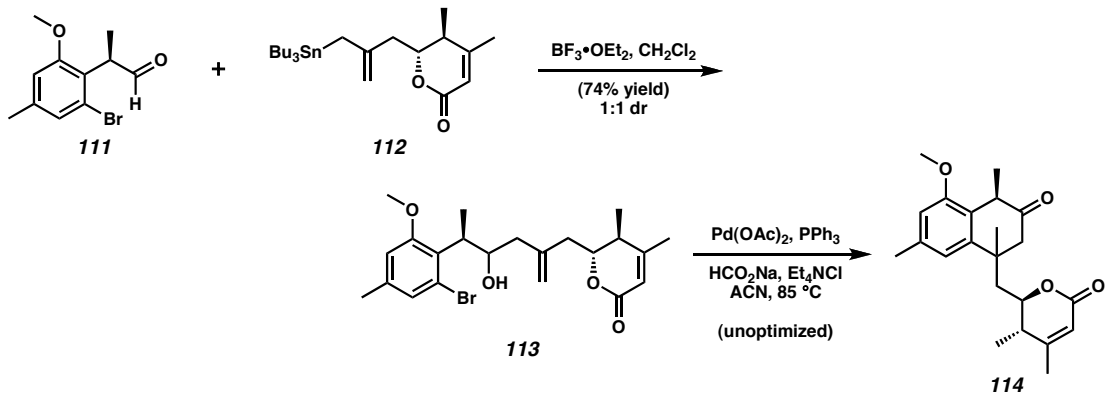
Figure 1.4.4 Williams's retrosynthetic analysis of norzoanthamine.

In the key Diels-Alder reaction, nitro-alkene **108** underwent reaction in benzene at reflux via an endo transition state to afford decalin **109** in good yield and 10:1 dr (Scheme 1.4.12). A Nef reaction[46] converted the nitro moiety to the desired ketone and facilitated olefin migration. The product enone (**110**) has the necessary stereochemistry and functionality to begin C ring annulation.



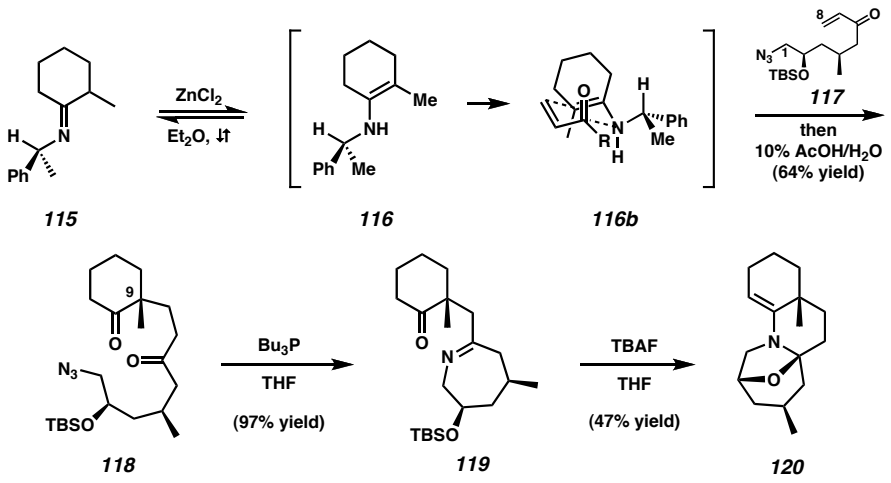
Scheme 1.4.12 Williams's early efforts toward the norzoanthamine AB rings.

The Williams group has recently published an interesting approach to the zoanthenol AB rings involving allylation of aldehyde **111** with stannane **112** (Scheme 1.4.13).[47] Upon treatment with BF_3 etherate, a 1:1 mixture of diastereomers of alcohol **113** was formed. Though the conditions remain unoptimized, the desired product of Pd insertion and intramolecular Heck coupling (**114**) has been isolated with good recovery of unreacted starting material.



Scheme 1.4.13 Williams's recent efforts toward the norzoanthamine AB rings.

In addition, the Williams group demonstrated an efficient strategy to append the C(1)–C(8) (EFG) fragment to the ABC ring system and stereospecifically establish the C(9) quaternary center.[48] When heated with zinc (II) chloride, chiral imine **115** generates a significant amount of enamine **116** at equilibrium (Scheme 1.4.14). The enamine undergoes conjugate addition into enone **117** from the β face over the smaller methyl group of the energy-minimized conformation depicted in **116b**.[49] Enone **117** was prepared in enantioenriched form using Evans chiral oxazolidinone chemistry.[50] Hydrolysis of the intermediate iminium affords diketone **118** with excellent diastereoselectivity (22:1). Staudinger reduction of azide **118** provides imine **119**. Treatment with TBAF cleaves the silyl ether. The resultant alcohol attacks the imine and condenses onto the ketone to give the EFG model enamine **120** after dehydration.



Scheme 1.4.14 Williams's synthesis of a model EFG ring system.

1.4.6 Theodorakis's Annulation Approach to the Norzoanthamine ABC Ring System

Theodorakis and coworkers propose a unique annulation strategy that begins with an intact B ring and sequentially appends the C and A rings (Figure 1.4.5).[51] The unifying theme of the Robinson annulation is applied for the synthesis of both rings.

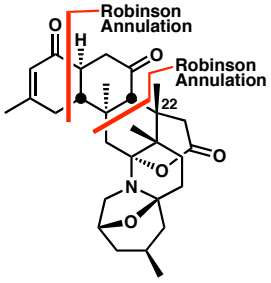
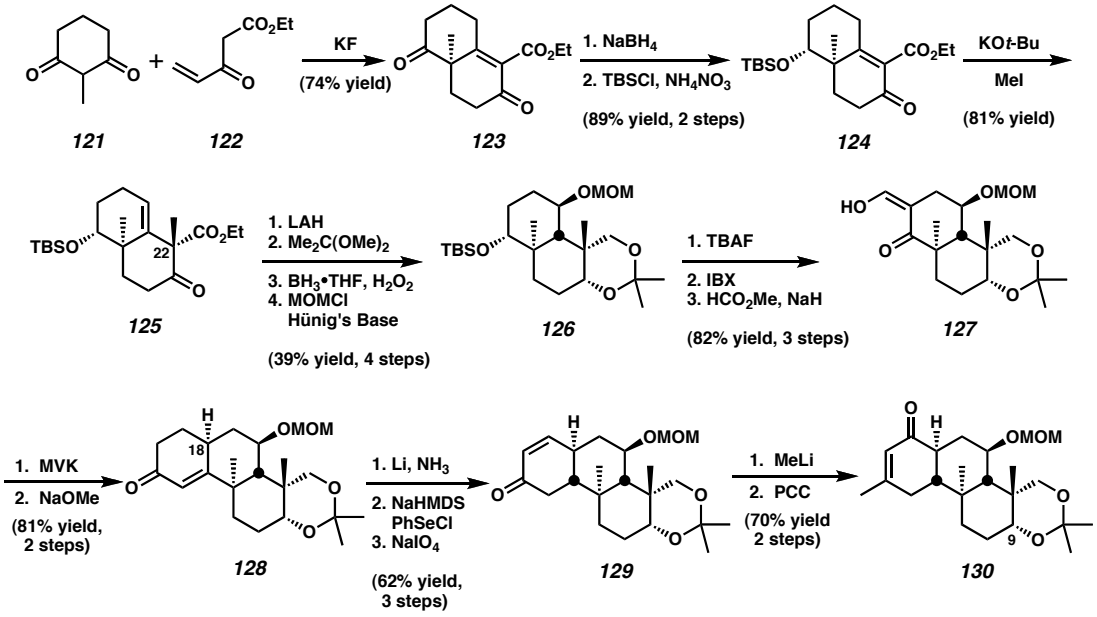


Figure 1.4.5 Theodorakis's retrosynthetic analysis of norzoanthamine.

The synthesis commences with condensation of meso-diketone **121** and ketoester **122** with potassium fluoride conditions to afford enone **123** (Scheme 1.4.15).[52] Sodium borohydride reduction and silylation provided **124**. Treatment of α,β-unsaturated ketoester **124** with potassium *tert*-butoxide and methyl iodide produced the quaternized ketoester **125** with complete diastereomeric control. Exhaustive reduction with LAH produced a diol, which was then protected as the acetonide. Hydroboration and

oxidation followed by MOM-ether formation provided **126**. Desilylation, oxidation, and alkylation with methyl formate provided hydroxyenone **127**. A two-step Robinson annulation[53] protocol gave enone **128** as a single isomer. Enone **128** was then reduced to the corresponding ketone, and olefin installation provided **129**. Methyl lithium addition and PCC oxidation afforded the transposed enone **130**, which contained all the functionality and stereochemistry in the AB rings.

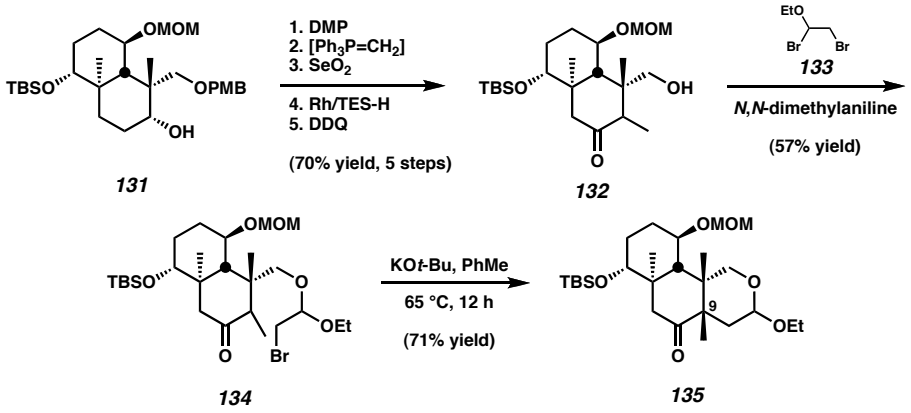


Scheme 1.4.15 Theodorakis's approach to the ABC ring system.

In a related study, Theodorakis demonstrated that the installation of the difficult C(9) quaternary center was possible from selectively protected alcohol **131** (Scheme 1.4.16).[54] Oxidation to the corresponding ketone and olefination, followed by allylic oxidation provided an exocyclic enone. Conjugate reduction and PMB ether cleavage then provided methyl ketone **132**. Acetal formation between Stork's dibromo-acetal reagent **133**[55] and the alcohol moiety of methyl 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. Additionally, the alkylation gave complete selectivity for the desired C(9) epimer of acetal **128**, as confirmed by X-ray structure determination.

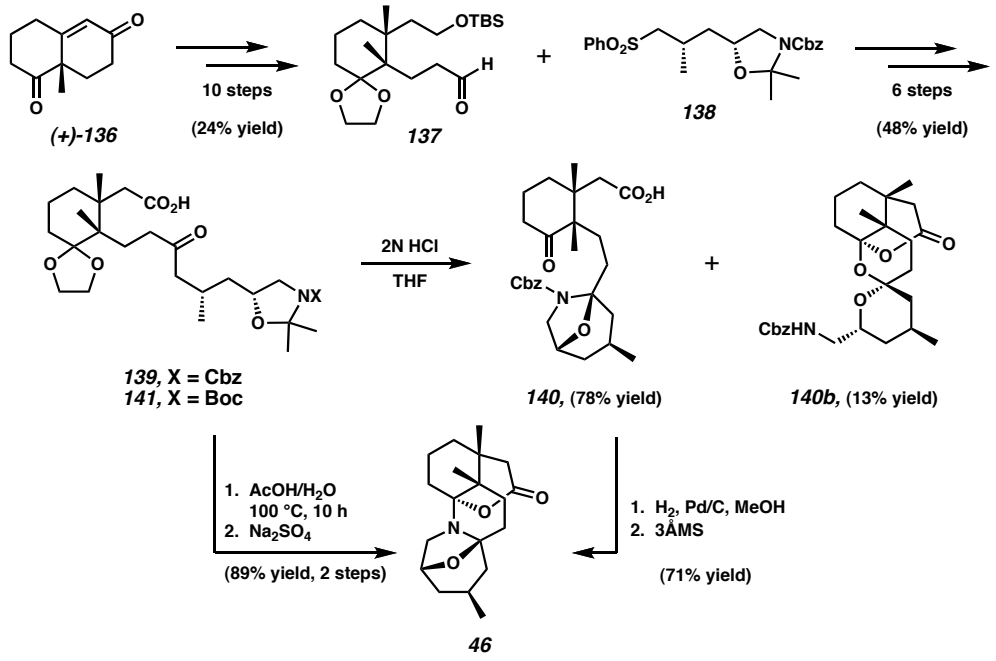
Taken in conjunction with Theodorakis's other work, this strategy solves the difficult problem of generating all three of the C ring quaternary centers and produces a norzoanthamine ABC ring system well poised for the completion of the total synthesis.



Scheme 1.4.16 Theodorakis's installation of the C(9) quaternary center.

1.4.7 Kobayashi's Synthesis of the Heterocyclic CDEFG Zoanthamine Ring System

In 1998, Kobayashi and coworkers disclosed an enantioselective route to the CDEFG ring system.[56] The Wieland-Miescher ketone (**136**)[57] served as the starting material to produce aldehyde **137** (Scheme 1.4.17). The coupling of the lithium salt of sulfone **138** to aldehyde **137** and oxidation state adjustment 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. Resubjection of this by-product to acidic conditions did not form an aminal-containing product. Tricyclic intermediate **140** was hydrogenolyzed and dehydrated to furnish pentacyclic hemiaminal **46**. A single-flask protocol for cyclization was subsequently investigated using Boc-protected substrate **141** in acidic conditions and gave an excellent yield of hemiaminal **46**.[58]



Scheme 1.4.17 Kobayashi's sulfone approach to the CDEFG ring system.

1.4.8 Hirama's Strategy for the Zoanthenol ABC Ring System

The strategy proposed by Hirama and coworkers is specifically geared toward the synthesis of zoanthenol's ABC ring system. The key Heck[59] disconnection of the C(12)–C(13) bond relies on the aromatic A ring unique to zoanthenol (Figure 1.4.6). Addition of a stannane into an enone was envisioned for the formation of the C(20)–C(21) bond.

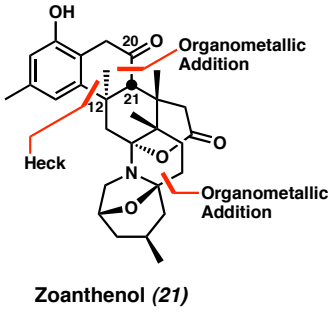
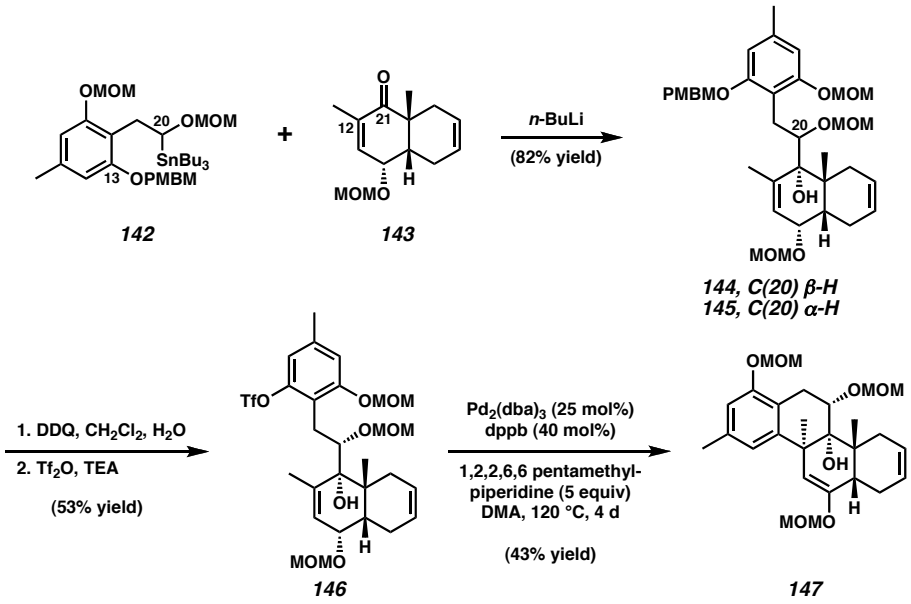


Figure 1.4.6 Hirama's retrosynthetic analysis of zoanthenol.

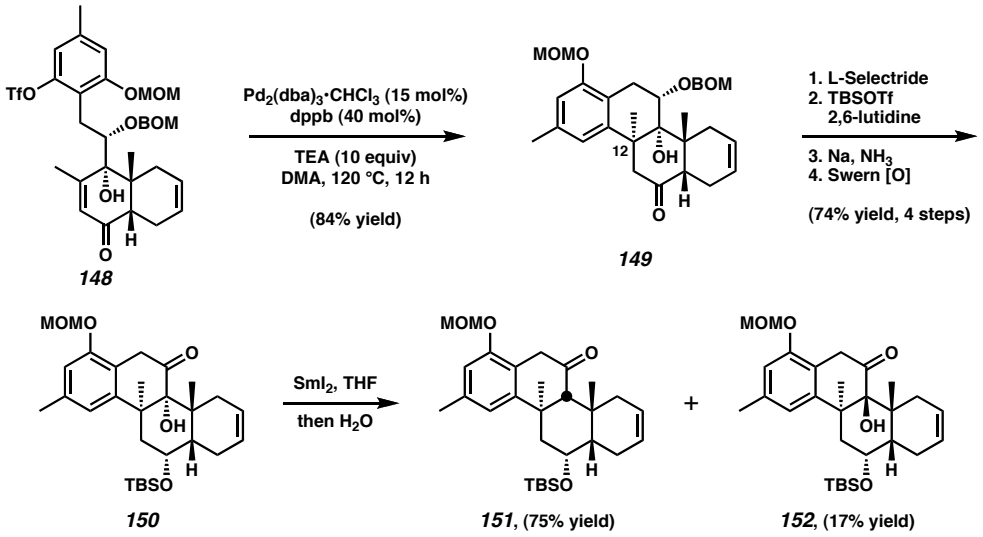
Transmetalation of stannane **142** and addition into enone **143**, derived from an asymmetric quinone Diels-Alder reaction,[60] afforded tertiary alcohols **144** and **145** as a mixture of diastereomers at C(20) (Scheme 1.4.18). PMB ether cleavage followed by

triflate formation 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.[61] Though the reaction did proceed with excellent diastereoselectivity, it had several drawbacks, including high palladium loading, long reaction times, and side products from simple reduction of the triflate substrate.



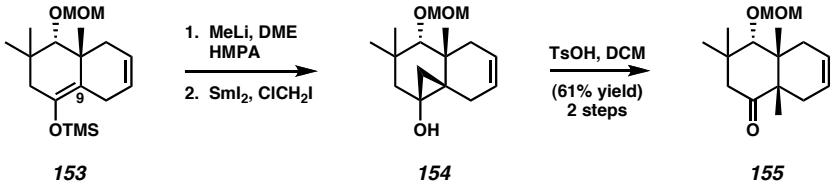
Scheme 1.4.18 Hirama's Heck strategy for the zoanthenol ABC ring system.

Heck substrate **146** was altered to increase the electrophilicity of the accepting olefin. As shown in Scheme 1.4.19, exposure of enone **148** to reductive Heck conditions produced ketone **149** in excellent yield. With the difficult C(12) stereocenter established, the C ring ketone was selectively reduced with L-Selectride, and the resulting alcohol was then silylated. The next goal was the reduction of the tertiary alcohol moiety of ketone **149**. BOM ether reduction 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**, produced in 17% yield.[62]



Scheme 1.4.19 Hirama's alternative assembly of the B ring.

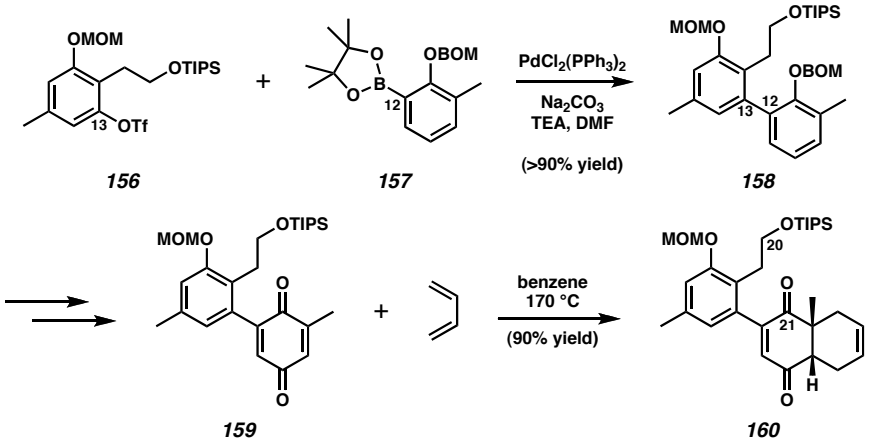
The largest challenge that remains in Hirama's synthesis is the establishment of the C(9) quaternary stereocenter. However, his group has already demonstrated a highly diastereoselective methylation of silyl enol ether **153** as a model of methylation at C(9) (Scheme 1.4.20).[63] The methylation was achieved by samarium(II) iodide-promoted cyclopropanation and acid-mediated ring opening to give methyl ketone **155** and its C(9) epimer with a favorable 3:1 dr.



Scheme 1.4.20 Hirama's installation of the C(9) methyl group.

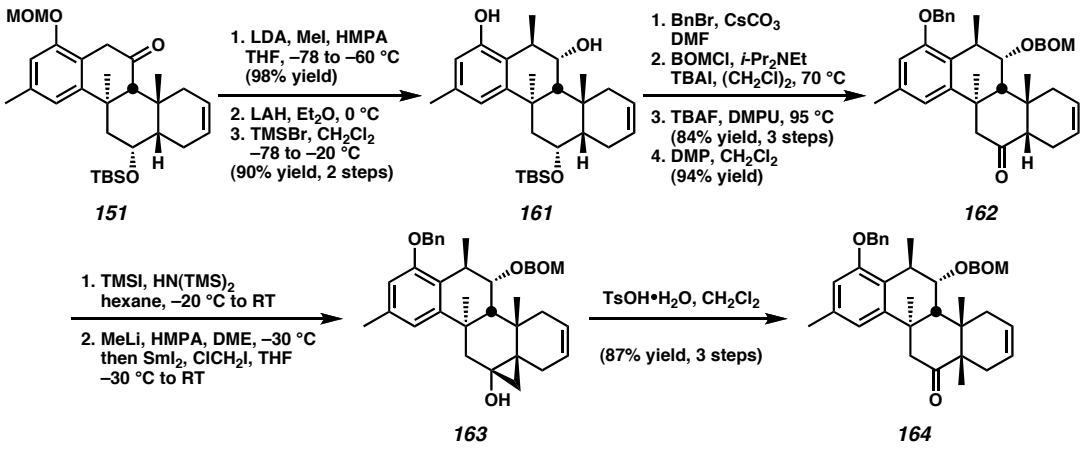
Hirama and coworkers have also disclosed an alternate strategy for the assembly of zoanthenol's ABC ring system. This approach reverses the order in which the B ring bonds are formed.[64] As depicted in Scheme 1.4.21, Suzuki coupling of aryl triflate **156** and borane **157** unite the A and C ring synthons via the C(12)–C(13) bond to yield biaryl **158**. BOM removal and oxidation provided quinone **159**, which was heated with butadiene to form **160**. Upon the elaboration of Diels-Alder adduct **161**, the final B ring

bond, C(20)–C(21), 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 the C(20) aldehyde.



Scheme 1.4.21 An alternate approach by Hirama.

Recently, Hirama and coworkers published the synthesis of the fully functionalized ABC rings of zoanthenol.[65] From intermediate ketone **151**, enolization and trapping with methyl iodide afforded the desired methylated B ring in excellent yield (Scheme 1.4.22). Subsequent ketone reduction and MOM ether cleavage provided phenol **161**. Benzylation and BOM ether formation were followed by desilylation and oxidation to form C ring ketone **162** in 79% yield over four steps. At this point, the quaternary methyl installation modeled above was executed. Ketone **162** was converted to the thermodynamic silyl enol ether, the lithium enolate was formed by treatment with methyl lithium, and the enolate was cyclopropanated under radical conditions yielding cyclopropyl alcohol **163**. Reformation of the ketone occurred with concomitant cyclopropane cleavage upon treatment with toluenesulfonic acid monohydrate to provide the fully functionalized tricyclic core of zoanthenol.



Scheme 1.4.22 Hirama's synthesis of the fully functionalized ABC core of zoanthenol.

1.5.1 Summary and Outlook

The zoanthamine alkaloids are a structurally unique family of natural products. Though they are isolated from soft coral of the order zoantharia, it may be that symbiotic algae play a large role in the biosynthesis of these secondary metabolites. 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. Anti-osteoporotic, antibiotic, anti-inflammatory, and cytotoxic biological activities have been observed in 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 of interesting structure or biological significance to succumb to total synthesis within one to two years of the isolation. By comparison, twenty years passed between the isolation of zoanthamine and Miyashita's total synthesis of norzoanthamine in 2004. Any successful synthesis of these alkaloids

requires expertise in both carbocyclic and heterocyclic chemistry. Construction of the carbocyclic ABC rings is hindered by the stereochemical density 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 utilizing 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 yet unanswered, interest in the zoanthamine alkaloids is likely to increase for the foreseeable future.

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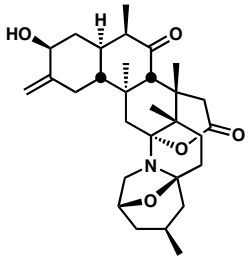
21. Also in this study, a molecule closely related to palytoxin, zooxanthellatoxin, was isolated. See ref 5 for details.
22. A similar natural product, lobozoanthamine, was recently isolated from soft corals of the genus *Lobophytum*:



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