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Recent developments in the synthesis of zoanthamine alkaloids

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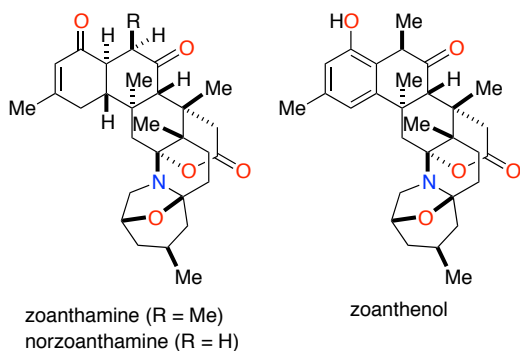
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Graphical abstract



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Abstract

This review provides a compilation of the most recent synthetic approaches and total syntheses of zoanthamine alkaloids, which are structurally unique heptacyclic marine natural products that display a range of interesting biological activities. This review is focused on synthetic methodologies for the construction of the three adjacent quaternary asymmetric carbon atoms on the cyclohexane ring (C-ring) of these compounds. The literature covered in this review dates from 2008 to the end of 2013.

Introduction

Zoanthamine alkaloids, which are isolated from species belonging to the genus *Zoanthus*, are a class of heptacyclic marine alkaloids that display distinctive biological and pharmacological properties.¹ For example, norzoanthamine (**1**) (Figure 1) was found to exhibit significant suppression of bone weight decrease and weakening in ovariectomized mice, and was consequently considered as a promising anti-osteoporotic drug candidate.² Zoanthamine (**2**) was first isolated in 1984 as the first reported member of this class of alkaloid, and has been reported to exhibit potent inhibitory activity towards phorbol myristate-induced inflammation.³ Zoanthenol (**3**) is another alkaloid belonging to this structural class and exhibits potent anti-platelet activity towards human platelet aggregation.⁴ With the exception of the methyl group at the C19 position and the oxidation level of the A-ring, these alkaloids (**1–3**) feature a densely functionalized and topologically unique heptacyclic framework (Figure 1).

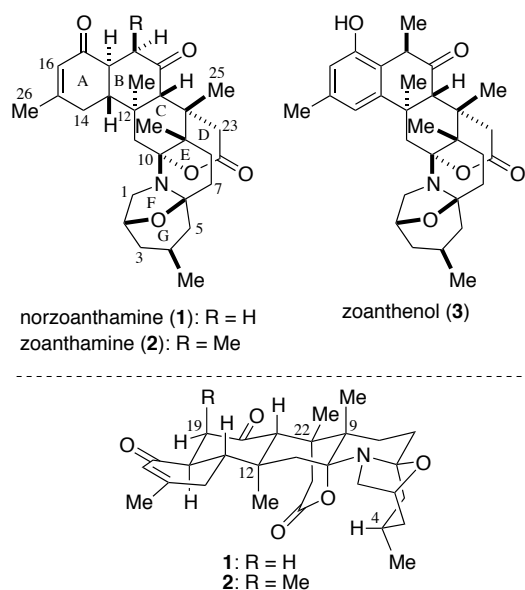


Figure 1. Structures of zoanthamine alkaloids.

The combination of their distinct biological properties and novel chemical structures have made this family of alkaloids extremely attractive targets for chemical synthesis, and a number of different research groups have been actively involved in the development of synthetic strategies directed towards the construction of zoanthamine alkaloids over the last two decades.¹ From a synthetic perspective, the greatest challenge associated with the synthesis of these alkaloids is the development of an

efficient and stereocontrolled method for the construction of the three adjacent quaternary carbon atoms at the C9, C12, and C22 positions of the C-ring, where the carbons at the C9 and C22 positions share a vicinal relationship.⁵ In 2004, twenty years after the isolation of the first reported zoanthamine alkaloid zoanthamine (**2**), Miyashita et al.^{6,7} achieved the first synthesis of norzoanthamine.

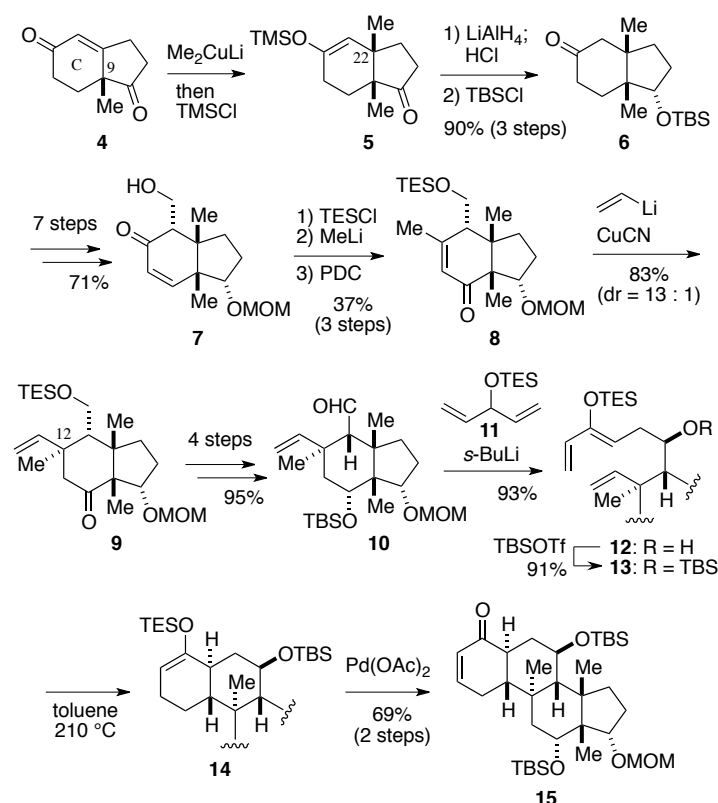
The chemistry of zoanthamine alkaloids was previously reviewed in early 2008 by Stoltz et al.¹ For this reason, the current review will focus primarily on recent synthetic studies associated with the total synthesis of zoanthamine alkaloids, and will cover reports from the literature from 2008 up until the end of 2013. The main focus of the current review will be on the development of methodologies directed towards the construction of quaternary asymmetric carbon atoms on the C-ring. This review begins with the second total synthesis of (–)-norzoanthamine, which was achieved by the Kobayashi group, followed by the first total syntheses of (+)-zoanthamine and (+)-zoanthenol, which were reported by the Miyashita group. The review then continues in chronological order, describing contributions from the Hirama, Stoltz, Theodorakis, Yang, and Yamashita groups.

Kobayashi's total synthesis of (–)-norzoanthamine (2009)

Kobayashi et al.⁸ reported the second total synthesis of (–)-norzoanthamine (**1**) in 2009. In contrast to the first total synthesis reported by the Miyashita group, Kobayashi's group employed a unique strategy involving the early-stage synthesis of the C-ring bearing three quaternary asymmetric carbon atoms, which was followed by the consecutive construction of the AB- and DEFG-ring systems. The initial phase of Kobayashi's synthesis focused on the stereoselective construction of the quaternary carbon atoms of the C-ring and the *trans*-decalin motif of the AB-ring (Scheme 1).^{8a} The synthesis began with the conjugate addition of Me₂CuLi to the readily available (–)-Hajos–Parrish ketone **4**,⁹ which already contained one of the three methyl groups of the C-ring (i.e., C9). The stereospecific formation of the methylation product **5** bearing the vicinal quaternary carbon atoms at C9 and C22 was consistent with attack of the reagent to the more accessible β-face of the bicyclic enone **4** to give **5**, which was converted to the hydroxy ketone **7** in nine further steps. Silylation of the primary alcohol in **7** followed by the 1,2-addition of methyl lithium to the enone and subsequent oxidative transposition of the resulting tertiary alcohol with PDC resulted in the

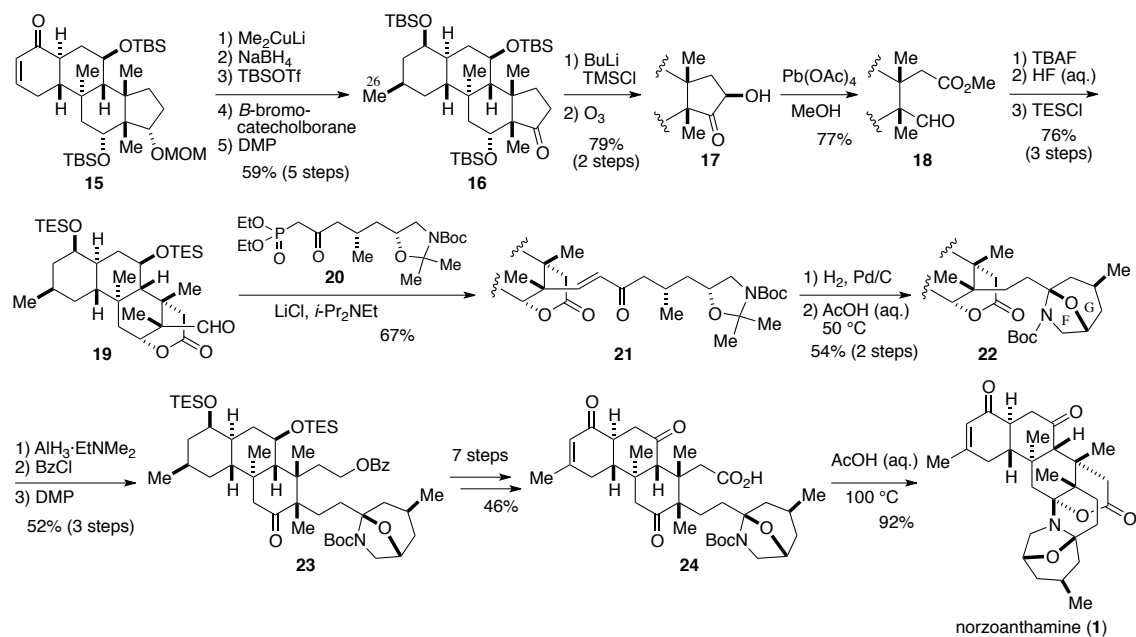
formation of enone **8**. The reaction of **8** with vinyl cyanocuprate gave the third quaternary carbon center at C12, and resulted in the formation of ketone **9** bearing the three requisite quaternary carbon atoms on the C-ring. This conjugate addition reaction occurred from the convex face of the *cis*-fused ring system and effectively highlights the synthetic utility of the conjugate addition reaction of organocuprates for constructing adjacent quaternary carbon atoms.

The next task in this synthesis involved the construction of the AB-ring system, which was achieved via an intramolecular Diels–Alder (IMDA) reaction. The diene moiety for the IMDA reaction was introduced by the addition of the allyl lithium species generated from siloxy diene **11** to aldehyde **10**, which afforded triene **13** after the silylation of the resulting alcohol. Subsequent heating **13** to 210 °C allowed for the IMDA reaction to proceed through the desired *exo*-transition state to give silyl enol ether **14** with the correct stereochemistry. Compound **14** was then converted to enone **15** using an Ito–Saegusa oxidation reaction.



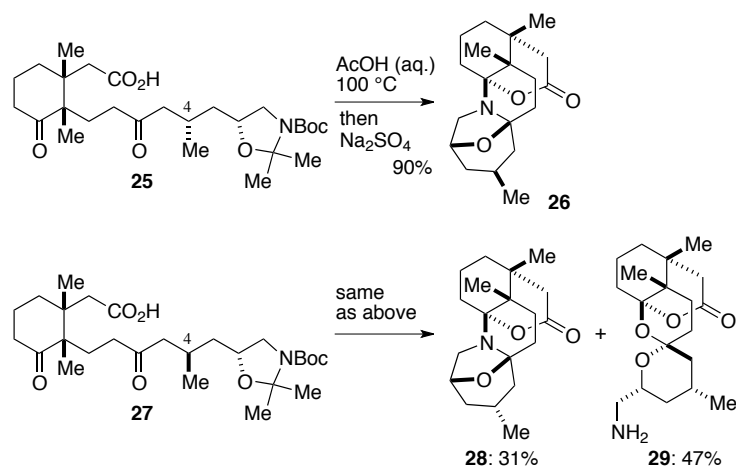
Scheme 1. Kobayashi's elaboration of the Hajos-Parrish ketone to give an advanced intermediate for the synthesis of norzoanthamine.

The total synthesis of norzoanthamine was achieved through the coupling of the ABC-ring system to the nitrogen-containing ketophosphonate **20** and subsequent bis-aminoacetalization to allow for the formation of the DEFG-ring system (Scheme 2).^{8b} The α,β -unsaturated cyclohexenone moiety in the A-ring was initially masked as a cyclohexanol derivative following the introduction of the C26-methyl group to **15**, with the cyclopentanone derivative **16** being formed in five steps. The ketone in **16** was converted to the corresponding silyl enol ether, which was subjected to an ozonolysis reaction¹⁰ to give hydroxy ketone **17**. Subsequent oxidative cleavage of the hydroxy ketone using $\text{Pb}(\text{OAc})_4$ afforded the formyl ester **18**. Compound **18** was then converted to the formyl lactone **19** in three steps because the sterically congested aldehyde in **18** exhibited low reactivity towards the coupling reaction with **20**. The Horner-Wadsworth-Emmons reaction of **19** with **20** was achieved under the Masamune–Roush conditions¹¹ to give enone **21**, which contained the entire carbon skeleton of norzoanthamine. Hydrogenation of the double bond in **21** followed by treatment with aqueous AcOH furnished the monoaminoacetal **22** (i.e., FG-ring formation), which was subsequently elaborated to triketone **24** in ten steps. Finally, using the conditions developed from their model studies towards the formation of the bisaminoacetal ring system (i.e., DEFG-ring system),¹² an aqueous solution of **24** in AcOH was heated to 100 °C to complete the total synthesis of (–)-norzoanthamine (**1**) (overall 47 steps from **4**). It is noteworthy that the cyclopentanone moiety of the (–)-Hajos–Parrish ketone **4** played an important role throughout the entire total synthesis in terms of the chemo- and stereoselectivity of the transformations, even though the ring was not incorporated into **1** in its original form.



Scheme 2. The completion of Kobayashi's total synthesis of (–)-norzoanthamine.

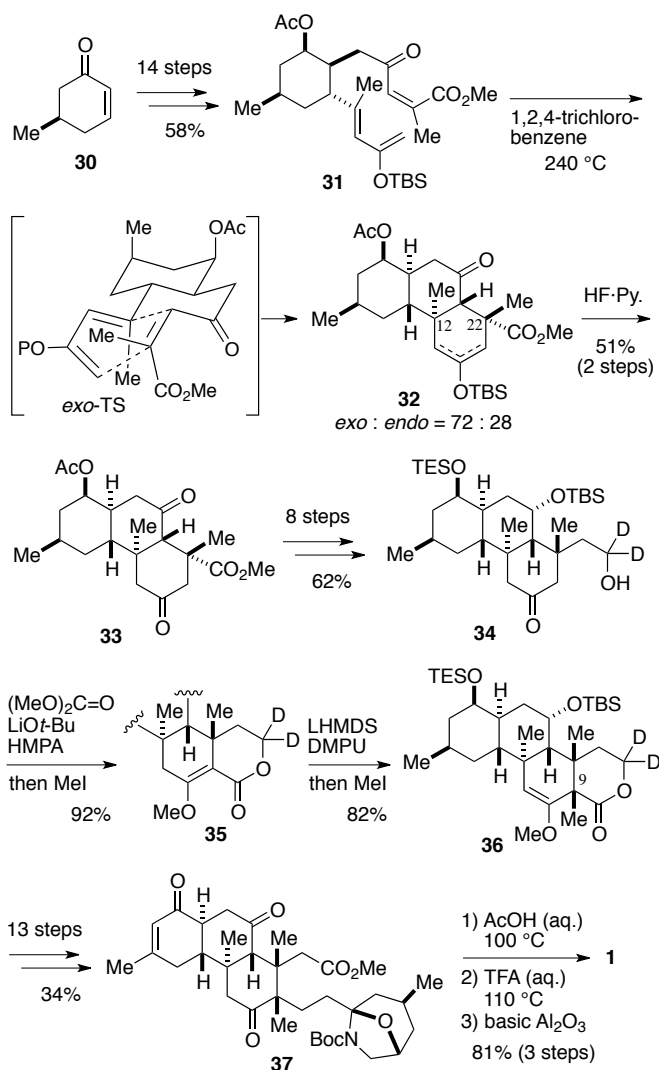
One of the most challenging aspects of the total synthesis of zoanthamine alkaloids is achieving the stereoselective formation of the bisaminoacetal ring system (i.e., DEFG-ring system) ahead all of the other possible cyclization products. In connection with their total synthesis of norzoanthamine⁸ and their previous efforts towards the synthesis of the CDEFG-ring system of norzoanthamine,¹² Kobayashi et al.¹³ reported that the stereochemistry at the C4 position had a pronounced impact on the mode of cyclization (Scheme 3). Namely, the cyclization of the *4S*-methyl precursor **25** gave bisaminoacetal **26** as the sole product, whereas the corresponding *4R*-isomer **27** produced a mixture of bisaminoacetal **28** and spiroketal **29**.



Scheme 3. Comparison of cyclization mode reported by Kobayashi.

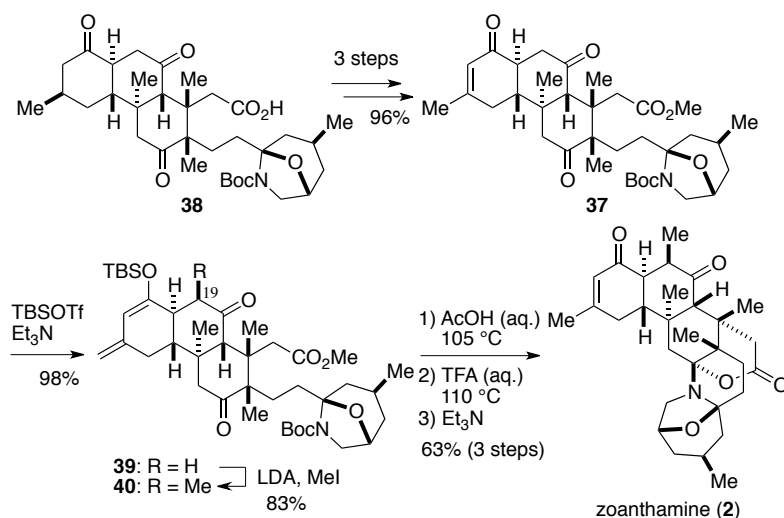
Miyashita's total synthesis of (+)-zoanthamine (2009)

Prior to entering into a discussion of the total synthesis of zoanthamine, it is important to provide a brief outline of the first total synthesis of (–)-norzoanthamine (**1**), which was reported by the Miyashita group in 2004 (Scheme 4).^{6,7,14} This particular total synthesis is highlighted by (1) the construction of the ABC-ring framework bearing two adjacent quaternary asymmetric carbon atoms at the C12 and C22 positions using an IMDA reaction, which proceeded through the *exo*-transition state (**31**→**32**); (2) installation of the C9 quaternary asymmetric carbon atom by the intramolecular acylation of a keto alcohol followed by successive *O*-methylation and *C*-methylation reactions with complete stereoselectivity (**34**→**35**→**36**); and (3) Brønsted acid-induced bisaminoacetalization (i.e., DEFG-ring formation, **37**→**1**). The total synthesis of **1** was completed in 41 steps from chiral enone **30**. This efficient synthetic route provided access not only to norzoanthamine, but also to zoanthamine and zoanthenol from the late-stage common synthetic intermediate **38** (*vide infra*).



Scheme 4. Outline of the Miyashita's first total synthesis of (–)-norzoanthamine.

The total synthesis of (+)-zoanthamine (**2**) was accomplished from synthetic intermediate **37**, which was originally prepared for the total synthesis of norzoanthamine (**1**) in 2009 (Scheme 5).¹⁴ The A-ring enone moiety of **37**, which was prepared from carboxylic acid **38**, was selectively protected as a TBS dienol ether, and the resulting ether **39** was subjected to a C19-methylation reaction with LDA and MeI to give the methylation product **40** as a single diastereomer. Compound **40** was then elaborated to (+)-**2** according to a three-step bisaminoacetalization sequence, which was similar to that used for the conversion of **37** to **1** (overall 43 steps from **30**).

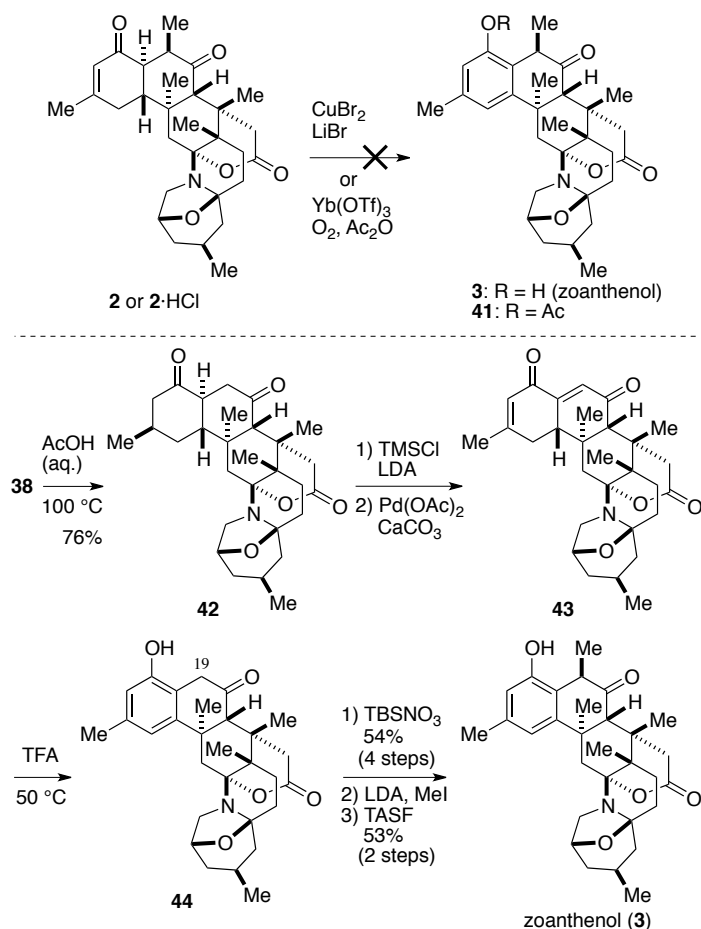


Scheme 5. Miyashita's total synthesis of (+)-zoanthamine.

Miyashita's total synthesis of (+)-zoanthanol (2009)

In the same year, Miyashita et al.¹⁵ also reported the first total synthesis of (+)-zoanthanol (**3**), which has a unique aromatic ring system (Scheme 6). Given that the only structural difference between **3** and zoanthamine (**2**) is the oxidation level of the A-ring, Miyashita's group initially investigated the oxidative aromatization of **2** and its·HCl salt. Unfortunately, however, all of their attempts at an oxidative aromatization (i.e., Putti protocol with $\text{CuBr}_2\text{--LiBr}$ ¹⁶ and a novel oxidation with $\text{Yb}(\text{OTf})_3\text{--Ac}_2\text{O--O}_2$ ¹⁵) failed, leading to the decomposition of the substrates. At this point, the group turned their attention to the fact that Brønsted acids were effective for the formation of aminoacetals (cf. **37**→**1** and **40**→**2**), whereas Lewis acids such as CuBr_2 and $\text{Yb}(\text{OTf})_3$ led to the decomposition of the substrates because of the instability of the aminoacetal moiety. For this reason, a new synthetic methodology was designed for the construction of aromatic rings involving an Ito–Saegusa reaction followed by the Brønsted acid-mediated isoaromatization¹⁷ of the resulting bis-enone moiety (**42**→**43**→**44**). This new synthetic route allowed for the total synthesis of **3**. The keto acid **38** was initially converted to dihydronorzoanthamine (**42**), which was converted to bis-enone **43** by means of a regioselective bis-silyl enol ether formation followed by an Ito–Saegusa reaction. Subsequent treatment of **43** with trifluoroacetic acid (TFA) facilitated the desired aromatization reaction to give norzoanthanol (**44**). Three further steps, including the installation of the methyl group at the C19 position, allowed for the successful conversion of **44** into (+)-zoanthanol (**3**) (overall 42 steps

from **30**).

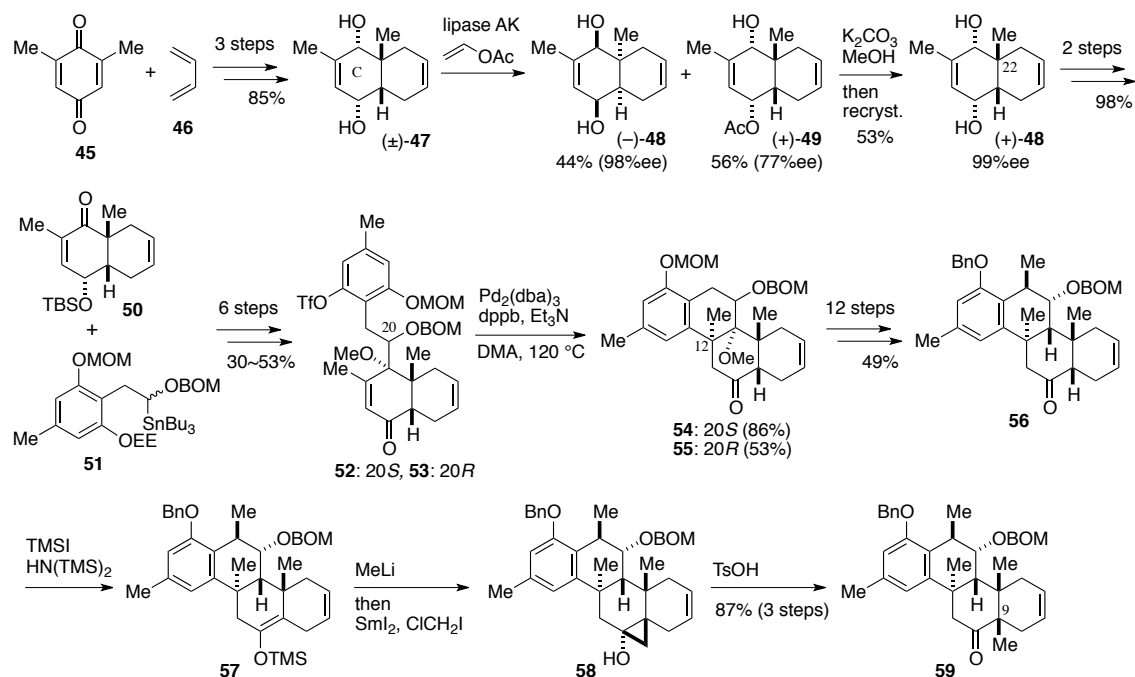


Scheme 6. Miyashita's total synthesis of (+)-zoanthenol from the late-stage synthetic intermediate of norzoanthamine.

Hirama's asymmetric synthesis of the ABC-ring framework of zoanthenol (2008)

In 2008, Hirama et al.¹⁸ reported the enantioselective synthesis of the fully functionalized ABC-ring of zoanthenol (**3**) using the Mizoroki–Heck/Simmons–Smith reaction strategy for the construction of the congested quaternary asymmetric carbon atoms (Scheme 7). Hirama's synthesis began with the enzymatic kinetic optical resolution of the racemic diol **47** containing a quaternary carbon atom that was prepared in three steps from *p*-quinone **45** and 1,3-butadiene (**46**) through a Diels–Alder reaction followed by a series of stereoselective reductions. The requisite enantiomerically pure diol (+)-**48** was obtained by the enzymatic acylation of (±)-**47** followed by sequential methanolysis and recrystallization of the resulting acetate (+)-**49** to allow for the formation of the C22 quaternary stereocenter. Compound (+)-**48** was then converted to

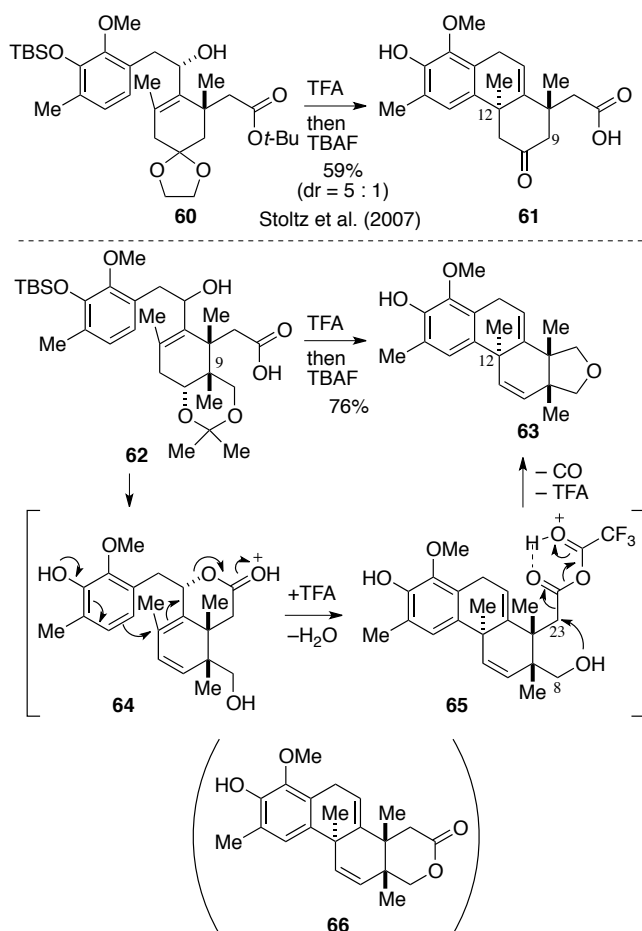
enone **50** in two steps, which was reacted with the lithium anion generated from stannane **51**. The subsequent adjustment of the oxidation state followed by a series of protecting group manipulations gave the aryl triflates **52** and **53** as separable isomers at the C20 position. Exposure of **52** and **53** to intramolecular Mizoroki–Heck conditions (i.e., $\text{Pd}_2(\text{dba})_3$, dppb, Et_3N)¹⁹ triggered a 6-*exo* cyclization reaction to afford the desired tetracyclic compounds **54** and **55**, respectively, with the C12 asymmetric quaternary carbon atom established. The 20*S*-isomer **52** gave much better results than the 20*R*-isomer **53** in this cyclization. In 12 additional steps, both **54** and **55** were elaborated to tetracyclic ketone **56**. The third C9 quaternary carbon center on the C-ring was constructed according to a three-step reaction sequence from ketone **56**. Thus, **56** was initially converted to the thermodynamically favored silyl enol ether **57**. The SmI_2 -mediated Simmons-Smith cyclopropanation of the lithium enolate generated from **57**, followed by the acid-catalyzed ring opening of the resulting cyclopropanol **58**, allowed for the regio- and stereoselective production of the fully functionalized ABC-ring **59** of zoanthenol (**3**).



Scheme 7. Hirma's asymmetric synthesis of the fully functionalized ABC-ring of zoanthenol.

Stoltz's decarbonylative cyclization in the synthesis of zoanthenol ABC-ring system (2009)

In 2009, the Stoltz et al.²⁰ reported an unusual S_N'-type cyclization reaction, where a desilylation, acetonide elimination, and CO extrusion occurred in one-pot as well as the desired 6-*endo* cyclization (Scheme 8). Prior to this publication in 2007, Stoltz's group described the development of a unique acid-mediated 6-*endo* S_N'-type cyclization for the construction of the carbocyclic core of zoanthanol, where the exposure of allyl alcohol **60** to TFA gave the tricyclic compound **61** and established the C12 quaternary asymmetric carbon atom.²¹ Unfortunately, the introduction of the C9 quaternary stereocenter to **61** was unsuccessful. Anticipating the formation of the tetracyclic lactone **66**, Stoltz's group moved on to explore the similar S_N'-type cyclization of carboxylic acid **62**, which already contained the C9-quaternary carbon atom. Unexpectedly, the treatment of **62** with TFA afforded the tetrahydrofuran-containing product **63** with the desired C12 stereochemistry. A mechanism for the formation of **63** has been proposed involving sequential lactonization, elimination of the acetonide, and protonation steps to afford intermediate **64**, which would undergo a 6-*endo* S_N'-type cyclization. Subsequent condensation of the resulting carboxylic acid with TFA would give the mixed anhydride **65**, and the resulting alcohol at the C8 position in **65** would then attack the C23 position to give **63**, which would be accompanied by the release of CO.

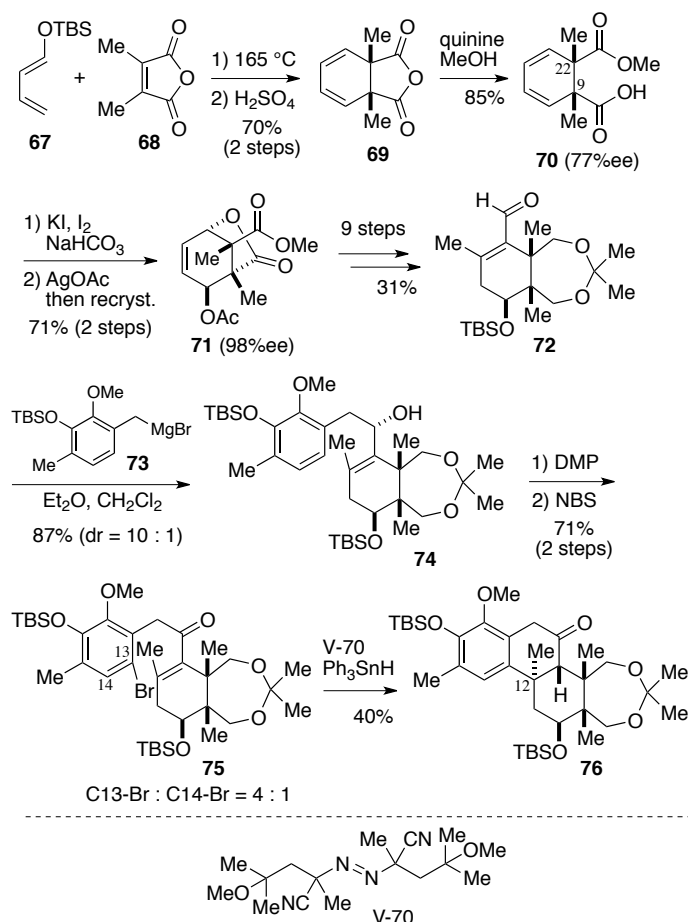


Scheme 8. Unexpected decarbonylative cyclization during the formation of the ABC-ring of zoanthanol by the Stoltz group.

Stoltz's radical cyclization approach to the ABC core of zoanthanol (2009)

During the same year, Stoltz et al.²² also disclosed an innovative strategy, where it was envisioned that the ABC-ring system of zoanthanol could be constructed by the radical-induced intramolecular conjugate addition of aryl bromide **75** (Scheme 9). Their synthesis commenced with the conversion of 2,3-dimethylmaleic anhydride (**68**) into *meso* anhydride **69** in two steps via the Diels–Alder reaction of **68** with siloxydiene **67** followed by the elimination of silanol. Treatment of **69** with quinine and methanol induced desymmetrization²³ to give the half-ester **70** in an enantio-enriched form (77%ee). This procedure therefore allowed for the vicinal quaternary asymmetric carbon atoms at C9 and C22 to be established in a single step. Iodolactonization of **70** proceeded with good regioselectivity, and subsequent treatment of the resulting iodolactone with AgOAc led to a *syn*-periplanar S_N2' displacement reaction involving

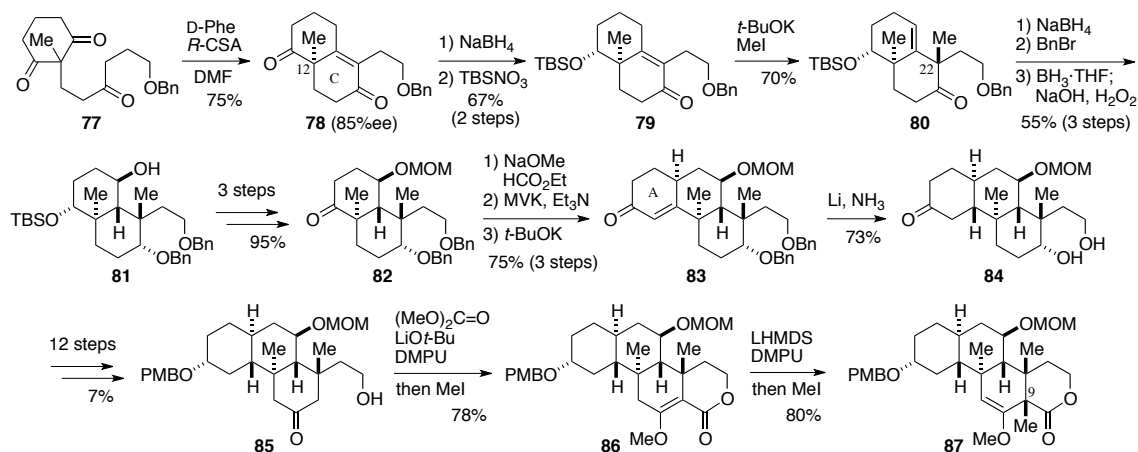
the acetate nucleophile to give acetoxy lactone **71**. The enantiopurity of **71** was enhanced to 98% by recrystallization. After a series of functional group manipulations over nine steps, the resulting aldehyde **72** was coupled with the A-ring Grignard reagent **73** to provide alcohol **74**. Dess-Martin oxidation followed by aromatic bromination with NBS afforded bromoarene **75** as a 4:1 mixture of regioisomers at the C13 and C14 positions, respectively. The key 6-*endo* radical cyclization was affected by the treatment of **75** with Ph₃SnH and V-70 (radical initiator) to provide the ABC core **76** as a single diastereomer, which established the C12 quaternary asymmetric carbon atom. This synthetic accomplishment demonstrates the viability of the radical-induced intramolecular conjugate addition²⁴ as an approach to the efficient assembly of the ABC-ring system of zoanthanol (**2**) (18 steps from **67** and **68**). Furthermore, the enantioselective desymmetrization of a bis-quaternary *meso* anhydride proved to be a promising method for providing rapid access to valuable chiral building blocks bearing vicinal quaternary centers.



Scheme 9. Stoltz's radical approach to the zoanthanol ABC core.

Theodorakis' asymmetric Robinson annulation approach to norzoanthamine ABC-ring motif (2011)

In 2011, the Theodorakis et al.²⁵ presented an approach for the construction of the ABC-ring motif of norzoanthamine that featured two asymmetric Robinson annulation reactions that allowed for the formation of the A and C-rings with excellent enantioselectivity (Scheme 10). Their efforts began with the first asymmetric Robinson annulation of the triketone **77**, which was readily prepared from 2-methyl-1,3-cyclohexanedione. According to the Hagiwara's procedure,²⁶ the treatment of **77** with D-Phe and R-CSA gave the annulation product **78** bearing the C12 quaternary asymmetric carbon atom with high enantioselectivity (85%ee). Reduction of **78** and subsequent silylation afforded the α,β -unsaturated enone **79**. The second quaternary asymmetric carbon center at the C22 position was established by the deconjugative methylation of **79** with *t*-BuOK and MeI, which gave ketone **80** as a single isomer. Following a series of functional group manipulations, the resulting *trans*-decalone derivative **82** was subjected to a three-step Robinson annulation sequence to give the tricyclic enone **83**. The *trans-anti-trans* perhydrophenanthrene system **84** was synthesized by a dissolving metal reduction of **83**, and subsequently converted to hydroxy ketone **85** in 12 steps. The last quaternary asymmetric carbon atom (C9) was constructed using Miyashita's methodology (cf. **34**→**35**→**36**).^{6,14} Thus, treatment of **85** with dimethylcarbonate, LiOt-Bu, and MeI yielded methyl enol ether **86**, which was treated with LHMDS and MeI to give the ABC-ring motif **87** of norzoanthamine (**1**).

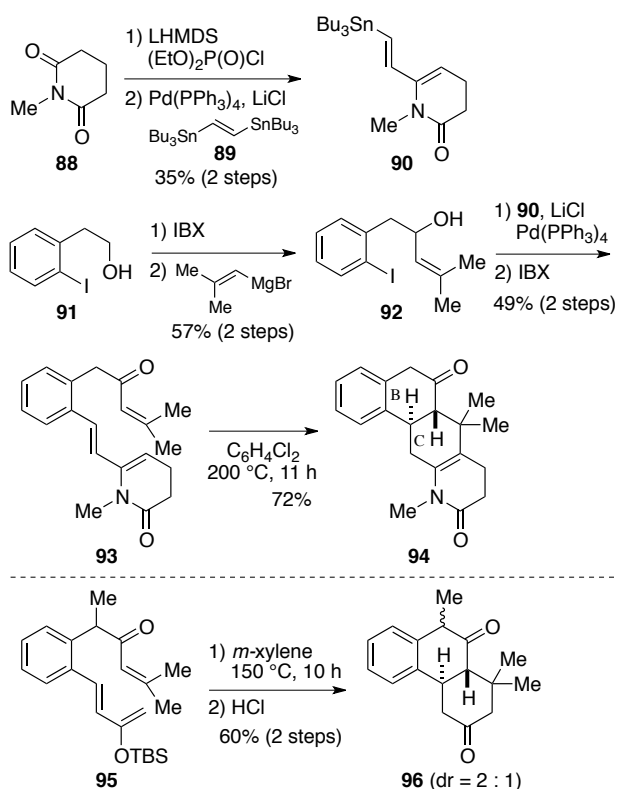


Scheme 10. Theodorakis' enantioselective synthesis of the ABC-ring motif of

norzoanthamine.

Theodorakis' intramolecular Diels–Alder approach (2011)

In 2011, Theodorakis et al.²⁷ also reported the development of a synthetic strategy for the construction of the ABC-ring system based on an IMDA reaction (Scheme 11). Because the Diels–Alder reaction is an efficient transformation capable of generating high levels of structural and stereochemical complexity in a single operation, several groups have already explored the use of IMDA reactions as the key step in their synthetic studies towards the zoanthamine alkaloids.^{6,8a,14,28} Inspired by the proposed biosynthetic pathways of these alkaloids,^{2b} Theodorakis' group designed the alternative IMDA reaction of a 2-amino-1,3-diene for the formation of the zoanthenol ABC-ring model. In light of the potential instability of 2-amino-1,3-dienes towards hydrolysis, Theodorakis' group chose the more stable 2-amido-1,3-diene (cf. **93**) as the IMDA reaction precursor. Their synthesis commenced with the preparation of vinyl stannane **90**. *N*-Methylglutarimide (**88**) was treated with LHMDs and chlorodiethylphosphonate to form the vinyl phosphonate, which was coupled with bis-stannane **89** to give **90**. In contrast, aryl iodide **92** was prepared from alcohol **91** according to the conventional two-step reaction sequence. The Stille coupling of **92** with **90** followed by oxidation of the resulting alcohol gave 2-amido-1,3-diene **93**, which underwent the IMDA reaction via the *exo*-transition state when it was heated at 200 °C to afford tetracyclic compound **94** bearing a nitrogen atom as a single isomer. A comparison with the IMDA reaction of the 2-oxo-1,3-diene **95**, where the reaction proceeded at 150 °C, indicated that the 2-amido-1,3-diene **93** was a much less reactive precursor.

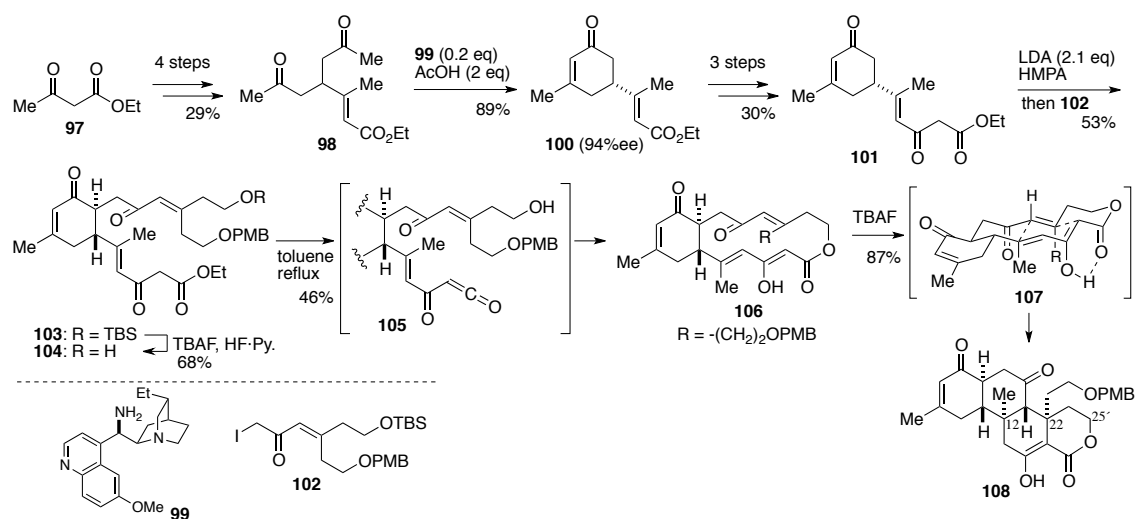


Scheme 11. Theodorakis' Diels-Alder approach to the ABC-ring motif of zoanthamine alkaloids.

Yang's approach to the ABC-ring of norzoanthamine using a transannular Michael reaction cascade (2011)

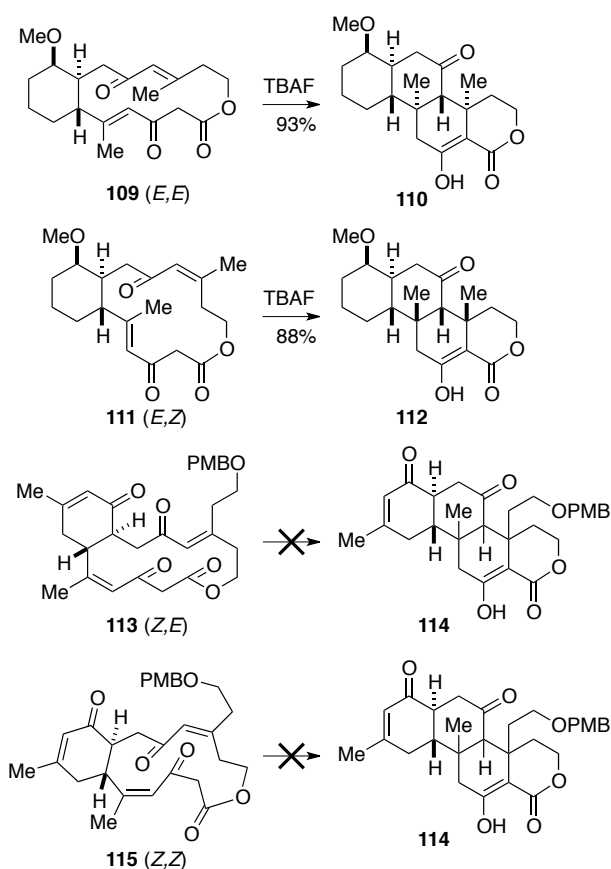
In 2011, the Yang group published an impressive approach to the ABC-ring of norzoanthamine involving the use of a transannular Michael reaction cascade²⁹ on the basis of macrocyclic stereocontrol³⁰ (Scheme 12).³¹ The synthesis commenced with the conversion of ethyl acetoacetate (**97**) to diketone **98** in four steps. Treatment of **98** with a catalytic amount of quinidine-based primary amine **99**³² and acetic acid allowed for the asymmetric intramolecular aldol cyclodehydration of **98** to proceed smoothly to give enone **100** with high enantiopurity (94%ee). Following the three-step homologation of the side chain in **100**, the resulting β -ketoester **101** was regioselectively alkylated with LDA and alkyl iodide **102** via the lithium bis-enolate to furnish enone **103**. Further functionalization of **103** by desilylation and macrocyclization led to the 14-membered macrocyclic lactone **106**, where the cyclization required **104** to be refluxed in toluene under high dilution condition. Yang's group proposed that this cyclization went through the reactive acyl ketene intermediate **105**. Exposure of β -ketolactone **106** to TBAF

resulted in the formation of tetracyclic lactone **108** as a single diastereomer, and simultaneously establishing the C12 and C22 quaternary asymmetric carbon atoms. The stereochemical outcome of this reaction was attributed to the arrangement shown for the all-chair-like transition state **107**. In this way, the synthesis of the ABC-ring was completed in only 12 steps from **97**. What makes this approach particularly effective is the efficient and convergent synthesis of macrocycle **106**. Moving on towards the total synthesis of norzoanthamine (**1**), it would be necessary to remove the extra carbon atom (C25') in **108** to complete the formation of C25-Me.



Scheme 12. Yang's transannular Michael reaction cascade for the synthesis of the carbocyclic core of norzoanthamine.

In their following full paper, Yang et al.³³ described their systematic investigation of the transannular Michael reaction cascade of 14-membered macrocyclic 1,7-bis-eneones to give angular 6-6-6 tricyclic ring systems (Scheme 13). Treatment of the *E,E*-macrocyclic lactone **109** and the corresponding *E,Z*-isomer **111** with TBAF resulted in the transannular Michael reaction reactions to give the tetracyclic lactones **110** and **112**, respectively, as single isomers. It is noteworthy that this procedure allowed for the formation of two bonds, two rings, and three contiguous stereocenters in a single step. In contrast, the *Z,E*-macrocyclic lactone **113** and the corresponding *Z,Z*-isomer **115** did not undergo the cyclization reaction under similar conditions. These results indicated that the geometries of the double bonds in the cyclization precursors had a significantly impact on the reactivity of the materials as well as the stereochemical outcome of this cascade reaction.

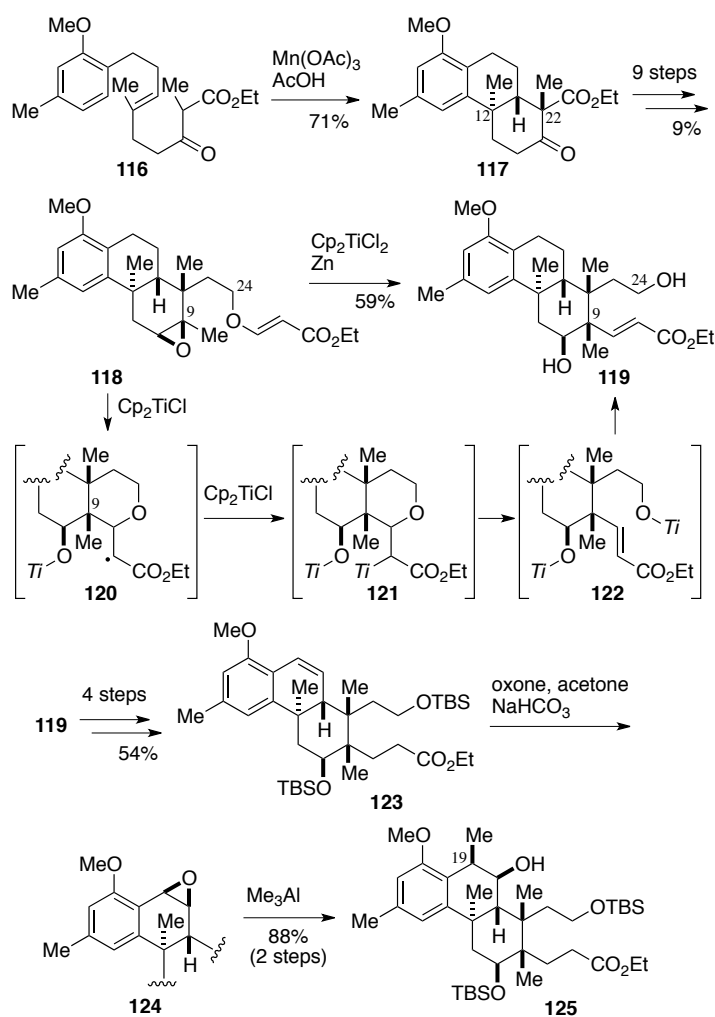


Scheme 13. Comparison of transannular Michael reaction cascades.

Yamashita's radical approach toward the zoanthenol ABC-ring (2013)

In 2013, Yamashita et al.³⁴ presented an interesting approach to the zoanthenol core featuring two sequential radical reactions (Scheme 14). Yamashita's synthesis began with the construction of the β -ketoester **116** from 7-methylcoumarin in six steps. According to Snider's procedure,³⁵ the key tricyclic ketone **117** was stereoselectively synthesized by a manganese-mediated oxidative tandem radical cyclization, which allowed for the simultaneous introduction of the quaternary carbon centers at C12 and C22. Compound **117** was then elaborated to β -alkoxy acrylate **118** according to a nine-step sequence. The last quaternary carbon center was constructed using a titanium-mediated radical-induced atom transfer reaction. Thus, the treatment of **118** with titanocene chloride, which was generated by the reaction of titanocene dichloride with zinc,³⁶ led to the formation of diol **119** as the sole reaction product, where the acryl ester in **118** was transferred from the C24 oxygen to the C9 carbon with an inversion in the configuration of C9. The authors speculated that this atom transfer

proceeded sequentially through the reaction intermediates **120**, **121**, and **122**. Compound **119** was subsequently converted to the styrene derivative **123** in four steps. Epoxidation of **123** followed by the stereospecific installation of the methyl group at C19 using Me_3Al , which occurred with retention of the configuration, gave the ABC-ring **125**. Asymmetric induction remains a challenge for the enantioselective total synthesis of zoanthenol (**3**).



Scheme 14. Yamashita's radical approach towards the ABC-ring of zoanthenol.

Conclusions

We have provided a summary of recent synthetic approaches towards the total synthesis of zoanthamine alkaloids, which are heptacyclic marine natural products with three adjacent quaternary carbon atoms. This review covers reports published in the literature from 2008 to the end of 2013. Innovative methodologies for assembling the

sterically congested quaternary asymmetric carbon atoms and the combination of creative synthetic strategies with classical synthetic technologies for the construction of heptacyclic frameworks have contributed greatly to recent advances in the total synthesis of these alkaloids. Despite these major advances, the development of a novel and reliable methodologies allowing for the direct assembly of vicinal quaternary asymmetric carbon atoms remains a significant challenge to the development of ideal total syntheses because only a limited number of these methodologies are currently available.^{5,37} The efficient synthetic routes described in this review will also allow for the development of a deeper understanding of the biological effects of zoanthamine alkaloids at the molecular level.³⁸

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