ACCOUNTS
of chemical research

Total Synthesis of Zoanthamine Alkaloids

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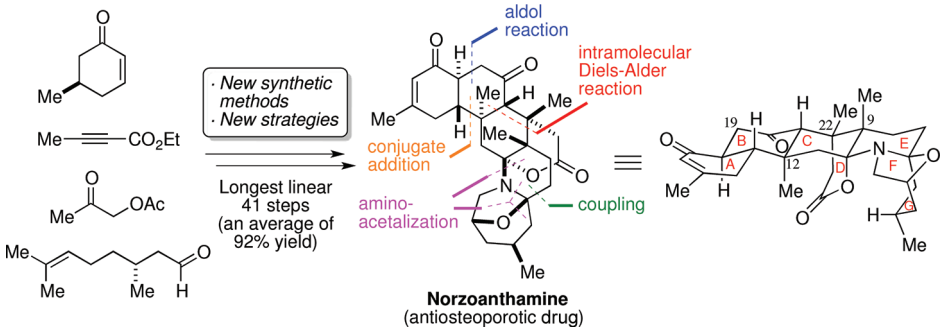
RECEIVED ON OCTOBER 19, 2011

CONSPECTUS



Zoanthamine alkaloids, isolated from organisms in the *Zoanthus* genus, constitute a distinctive family of marine metabolites. These molecules exhibit a broad spectrum of unique biological properties. For example, norzoanthamine inhibits interleukin-6, the key mediator of bone resorption in osteoporosis, providing a promising drug candidate for a disease that affects more than 10 million people over age 50 in the United States. In addition, these natural products are characterized by a densely functionalized heptacyclic framework, as exemplified by the structures of zoanthamine, norzoanthamine, and zoanthenol, which makes them extremely attractive targets for chemical synthesis. Prior to our first total synthesis of norzoanthamine in 2004, the densely functionalized and complex stereostructures of the zoanthamine alkaloids had impeded synthetic studies of these molecules. In this Account, we describe our synthetic approach toward the total synthesis of zoanthamine alkaloids, focusing on how we overcame various synthetic challenges.

At the beginning of our synthetic studies, we aimed to develop an efficient route that was flexible enough to provide access to several members of the family while allowing the synthesis of various analogues for biological testing. Our first project was the total synthesis of norzoanthamine, and we established an efficient synthetic route based on a novel strategy involving the following key features. First, we used a sequential three-component coupling reactions and subsequent photosensitized oxidation of a furan moiety to synthesize the precursor for the key intramolecular Diels–Alder reaction. Second, the key intramolecular Diels–Alder reaction constructed the ABC-ring carbon framework bearing two adjacent quaternary asymmetric carbon atoms at the C12 and C22 positions in a single stereoselective step. Third, we installed the third quaternary asymmetric carbon center at the C9 position by an intramolecular acylation of a keto alcohol followed by successive O-methylation and C-methylation reactions with complete stereoselectivity. Through the exploitation of a deuterium kinetic isoptope effect, we then efficiently synthesized the alkyne segment. Next, a coupling reaction between the alkyne segment and the amino alcohol segment and several subsequent synthetic transformations afforded the bis-aminoacetalization precursor. Finally, bis-aminoacetalization reactions carried out in one-pot constructed the DEFG-ring system and culminated in the total synthesis of norzoanthamine. Our synthetic route to norzoanthamine also allowed access to other zoanthamine alkaloids from a common synthetic intermediate, by way of stereoselective introduction of the C19 methyl group for zoanthamine, and isoaromatization for construction of the aromatic A-ring in zoanthenol. The chemistry described here not only allowed us to overcome formidable synthetic challenges but also opened a completely chemical avenue to naturally occurring zoanthamine alkaloids and their synthetic derivatives.

Introduction

Tremendous progress in the life sciences and in the development of medicines and medical supplies during the twentieth century, as well as growing interest in human health, has greatly contributed to the remarkable increase in the average human life span. Although such progress is of

Published on the Web 02/16/2012 www.pubs.acs.org/accounts
10.1021/ar200267a

course gratifying, the aging of the world population has a number of serious medical problems, including a steep increase in the incidence of osteoporosis. Osteoporosis is a chronic debilitating disease of multifactorial etiology that particularly affects the old.[1] Osteoporosis is caused by an imbalance between bone formation and bone resorption processes in the microarchitecture and is associated with a number factors, such as postmenopausal dysfunction in women, chronic dietary shortages of calcium and vitamin D, and hyperthyroidism. Osteoporosis results in fragile bones and therefore increases the risk of fractures, which seriously impairs the daily life of patients. Currently, approximately 10−12 million people over the age of 50 suffer from osteoporosis in the United States,[2] and the number of clinical osteoporotic fractures around the world in 2000 was estimated to be approximately 9.0 million.[2] Osteoporosis-related fractures in the elderly not only require long recuperation periods and incur high clinical costs but also are related to other significant sources of morbidity and mortality. Therefore, osteoporosis is one of the most important clinical issues in the world today.

Three types of bone resorption inhibitors, estrogen and selective estrogen receptor modulators, calcitonin, and bisphosphonates, are used to treat or prevent osteoporosis. However, their use has been clinically limited owing to serious side effects including concurrent comorbidities and inadequate long-term compliance.[1,3] Thus, the development of new types of antiosteoporotic drugs without side effects is urgently needed.

As part of their extensive search for new antiosteoporotic substances derived from marine organisms, Uemura and co-workers isolated a new compound, norzoanthamine (**1**, Figure 1), from a colonial zoanthid *Zoanthus* species collected near Amami Island in Japan in 1995.[4] This structurally unique heptacyclic alkaloid strongly inhibits the production of interleukin-6, the key mediator of bone resorption in osteoporosis. Moreover, norzoanthamine hydrochloride (**1**·HCl) significantly suppresses the loss of bone mass and strength when administered orally to ovariectomized mice, an animal model for postmenopausal osteoporosis.[5] Although the mechanism by which **1** acts *in vitro* has not been clarified in detail, pharmacological tests on ovariectomized mice demonstrated that the mechanism differs from that of estrogen. Therefore, **1** exhibits no side effects caused by estrogen.

Thus, **1** has been studied with keen interest, particularly in relation to the development of new antiosteoporotic drugs,[4−6] and it is considered to be a promising drug candidate. However, because of the limited quantity of **1**

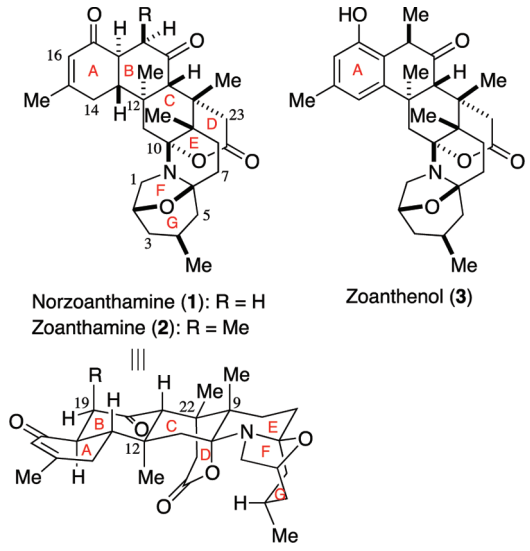


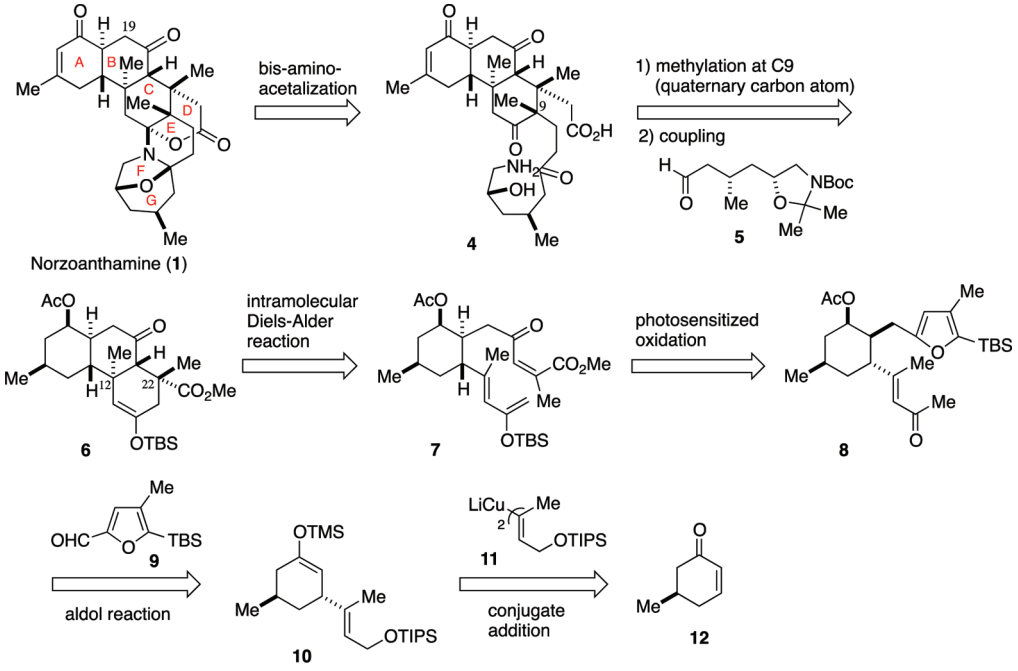
FIGURE 1. Structures of zoanthamine alkaloids.

found in nature (5 kg of dry *Zoanthus* species yields only 21 mg, or 4.2×10^{-4}%),[4] an efficient chemical synthesis of **1** is required for further biological and pharmacological studies.

Other members of this family of alkaloids also show various biological activities. For example, zoanthamine (**2**), the first member to be isolated (by Rao and Faulkner in 1984),[7] is a potent inhibitor of phorbol myristate-induced inflammation and has powerful analgesic effects,[7] and zoanthenol (**3**), isolated by Norte and co-workers in 1999,[8] shows potent antiplatelet activity in humans.[9]

Norzoanthamine (**1**), zoanthamine (**2**), and zoanthenol (**3**) have a common heptacyclic core, differing only in the substituent at the C19 position (methyl or hydrogen) and the oxidation state of the A-ring (Figure 1). As mentioned above, because of their distinctive biological and pharmacological properties, these alkaloids have attracted much attention from researchers in a wide variety of sciences, including medicinal chemistry, pharmacology, and natural products chemistry. In addition, their novel stereochemically complex chemical structures make this family of alkaloids extremely attractive targets for synthetic organic chemists. Indeed, several research groups have carried out extensive synthetic studies, which Stoltz and co-workers recently summarized in their excellent review.[6] However, because of the densely functionalized complex stereostructures of the zoanthamine alkaloids, no total synthesis had been achieved until we synthesized **1** in 2004.[10,11] We began our synthetic studies of norzoanthamine in 1999, aiming at developing an efficient route that was flexible enough to provide access to several members of the zoanthamine family while allowing the synthesis of various analogues for biological testing.

SCHEME 1. Retrosynthetic Analysis of Norzoanthamine (**1**)



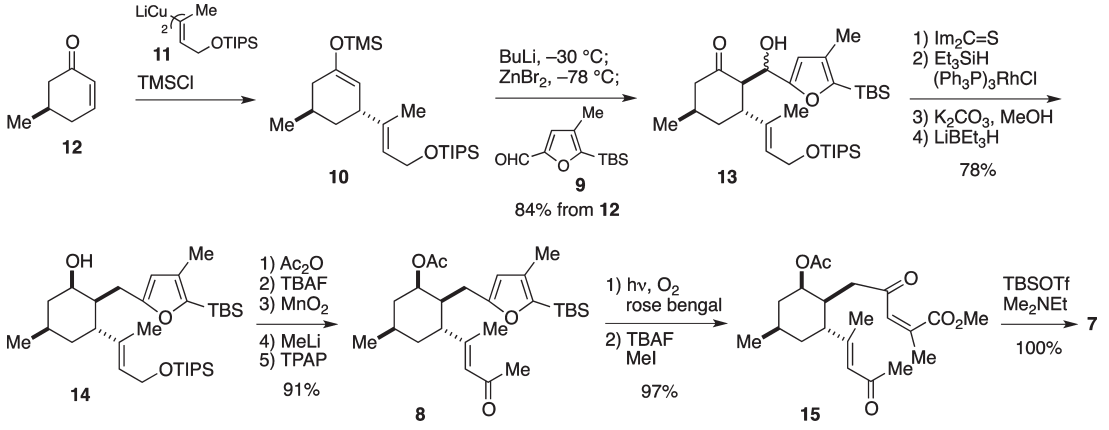
We went on to achieve the first total syntheses of **2**[11] and **3**[12] in 2009. In this Account, we describe our approach toward the total syntheses of these alkaloids, focusing on how we overcame various synthetic challenges.

Synthetic Challenges Posed by the Zoanthamine Alkaloids. The synthetic challenges posed by zoanthamine alkaloids **1**–**3** are as follows: (1) development of an efficient synthetic methodology for the ABC-ring carbon framework, which consists of a *trans-anti-trans*-fused perhydrophenanthrene skeleton, (2) construction of the stereochemically dense C-ring, which bears three adjacent quaternary asymmetric carbon atoms, at the C9, C12, and C22 positions, (3) stereoselective synthesis of the two novel amino acetal structures, including a bridged δ-lactone (D-ring) and a spiro tetrahydropyran ring (G-ring), and (4) development of a synthetic method for the unique aromatic A-ring of **3**.

To overcome these challenges, we employed tactics tailor-made for the structural features and stereochemical complexity of the zoanthamine alkaloids while keeping in mind our ongoing goal of developing new synthetic methodologies applicable to the synthesis of other complex natural products.

Synthetic Strategy for Norzoanthamine. We embarked first on synthetic studies of norzoanthamine (**1**). Our synthetic strategy is shown in Scheme 1. The DEFG-ring system, including the distinctive bis-amino acetal structures, was to be constructed from keto acid **4**, which bears an amino alcohol side chain, by bis-aminoacetalization at the last stage of the synthesis. Keto acid **4** was to be derived from tricyclic compound **6** via construction of the C9 quaternary stereogenic center and subsequent coupling with amino alcohol segment **5**. To construct the ABC-ring carbon framework of **6** stereoselectively, we designed a synthetic route involving an intramolecular Diels–Alder (IMDA) reaction[13] of triene **7**, taking our preliminary studies of the ABC-ring carbon framework into consideration.[14] Note that the key IMDA reaction of **7** involves the construction of two sterically congested quaternary asymmetric carbon atoms, at the C12 and C22 positions, and therefore the energy of the LUMO of the dienophile must be as low as possible. To lower the LUMO, we installed two electron-withdrawing groups on the dienophile moiety of **7** and we also installed a silyl enol ether on the diene moiety to increase the HOMO of the diene. If the key IMDA reaction occurred via the *exo*-transition state, as was the case for our model compound,[14] the ABC-ring carbon framework of **6** with the two quaternary asymmetric carbon atoms would be constructed in one step. The crucial diene **7** would be derived from chiral cyclohexenone **12**[15] via a sequential three-component coupling reactions involving a conjugate addition of cuprate **11**, followed by an aldol reaction of the resulting silyl enol ether **10** with silylated furaldehyde **9**, which is the latent dienophile component. The real dienophile moiety would be generated via photosensitized oxidation of the furan ring,

SCHEME 2. Synthesis of Triene **7** by Means of Sequential Three-Component Coupling Reactions



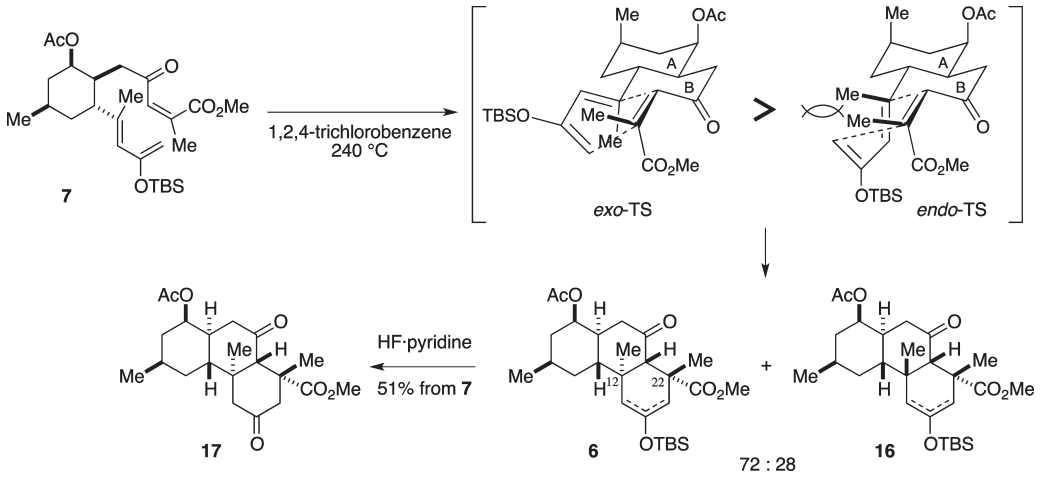
and the diene chromophore would be constructed by enolate formation of the methyl ketone moiety followed by silylation (**8** → **7**).

We envisioned the total synthesis of zoanthamine (**2**) via stereoselective introduction of a methyl group at the C19 position of an appropriate synthetic intermediate in the synthesis of norzoanthamine (**1**), and the synthesis of zoanthenol (**3**) would be achieved via oxidative aromatization of the A-ring in **2**.

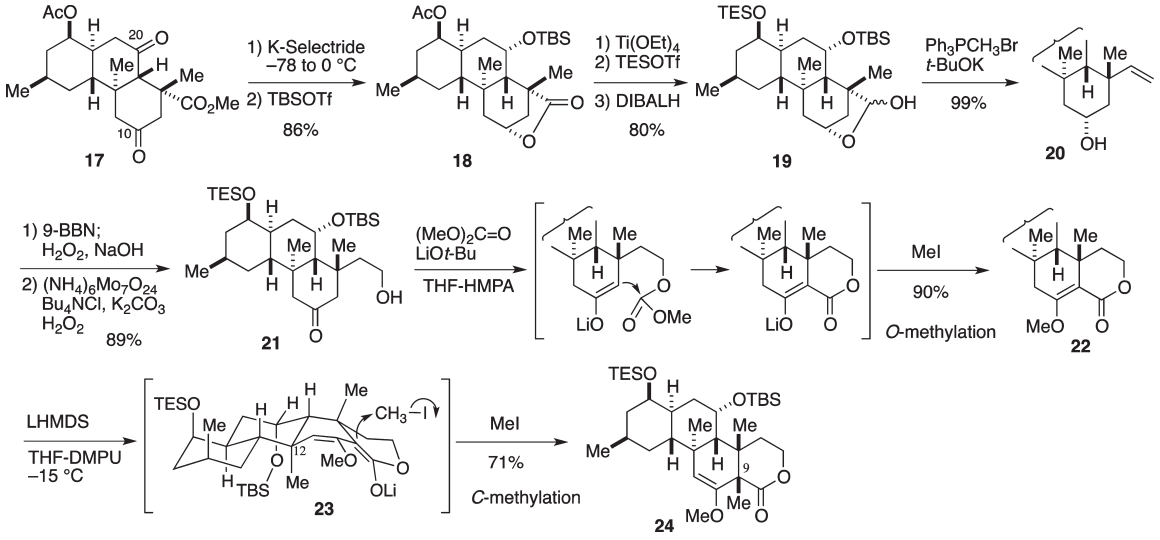
Synthesis of the IMDA Precursor via Sequential Three-Component Coupling Reactions. Our first objective was the stereoselective synthesis of the crucial IMDA precursor, triene **7**, via sequential three-component coupling reactions (Scheme 2). Conjugate addition of vinylcuprate **11**[11] to (*R*)-5-methyl-2-cyclohexenone (**12**)[15] in the presence of trimethylsilyl chloride[16] (TMSCl) followed by aldol reaction of the resulting silyl enol ether **10** with furaldehyde **9**[11] by means of the zinc enolate furnished the desired aldols **13** as a mixture of diastereomers. As we expected, the conjugate addition of **11** to **12** occurred exclusively from the opposite side of the secondary methyl group on the cyclohexene ring. After dehydration of aldols **13** by a Chugaev elimination, the resulting enones were subjected to a hydrosilylation reaction using Et_3SiH and $(Ph_3P)_3RhCl$ (the Wilkinson catalyst). Subsequent treatment of the silyl enol ether with K_2CO_3 in MeOH, followed by reduction of the resulting ketone, produced trisubstituted cyclohexanol derivative **14** with the desired stereochemistry. β-Alcohol **14** was converted to methyl ketone **8** by a routine five-step reaction sequence. The crucial photosensitized oxidation of the furan ring of **8** was performed according to the Katsumura protocol[17] and gave a (*Z*)-γ-keto unsaturated silyl ester. Because the silyl ester was unstable and tended to cyclize to a butenolide hemiacetal, the crude product was immediately converted to stable methyl ester **15**. In this way, the dienophile moiety with a (*Z*)-γ-keto α,β-unsaturated ester structure was efficiently constructed in a highly stereoselective manner by means of photosensitized oxidation of the furan ring and subsequent transesterification. The requisite triene **7** was synthesized by treatment of **15** with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) and Me_2NEt. Thus, key precursor **7** bearing the doubly activated dienophile moiety was synthesized via sequential three-component coupling reactions and subsequent photosensitized oxidation of the furan ring of **8** as the key steps.

Key Intramolecular Diels–Alder Reaction: Stereoselective Construction of Two Adjacent Quaternary Carbon Centers. The next step was the IMDA reaction,[13] the key to the synthesis (Scheme 3), and we investigated this particular reaction thoroughly so as to optimize the conditions. We were pleased to find that the IMDA reaction of triene **7** occurred with high efficiency upon dropwise addition of a solution of **7** in 1,2,4-trichlorobenzene into the same solvent heated at 240 °C; the reaction produced a 72:28 mixture of *exo*-adduct **6** and *endo*-adduct **16**. When the adducts were treated with HF·pyridine, the major product **17** was readily obtained by recrystallization. We assumed beforehand that the IMDA reaction of **7** would occur via the chair conformation on the B-ring, and if that was the case, two transition states (TS) were feasible, an *exo*-TS and an *endo*-TS (Scheme 3). We expected the *exo*-TS to be preferable to the *endo*-TS, because we estimated that the steric repulsion between the 1,3-diaxial methyl groups in the *endo*-TS would be larger than that between the axial methyl group and the ester group in the *exo*-TS (the *A*-value of Me is 1.7 kcal/mol, whereas that of CO_2Me is 1.2 kcal/mol).[18] As we expected, the IMDA reaction occurred predominantly via the *exo*-TS and efficiently afforded the ABC-ring carbon framework

SCHEME 3. Key Intramolecular Diels–Alder Reaction of **7** and Plausible Transition States



SCHEME 4. Construction of the C9 Quaternary Carbon Center

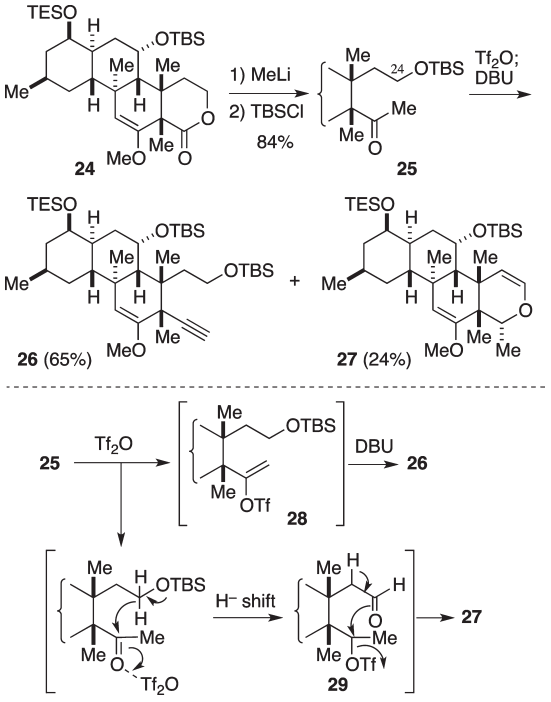


bearing two quaternary asymmetric carbon centers, at the C12 and C22 positions.

Construction of the C9 Quaternary Asymmetric Carbon Atom. We next focused on the construction of another quaternary asymmetric carbon center, at the C9 position (Scheme 4). Because Diels–Alder adduct **17** possesses four carbonyl groups, distinguishing them was essential for further transformations. To this end, treatment of **17** with K-Selectride at −78 to 0 °C afforded hydroxy lactone high stereoselectively: the C10 ketone was regioselectively reduced at −78 °C to form keto lactone *in situ*, and when the reaction temperature was raised to 0 °C, the C20 ketone was reduced from the β-side exclusively. After protection of the secondary alcohol as a TBS ether, the acetate group in **18** was replaced with a triethylsilyl (TES) group. Subsequent reduction of the lactone furnished lactol **19**, which was further transformed into keto alcohol **21** in three steps, including one-carbon homologation of **19** with a Wittig reagent.

With keto alcohol **21** in hand, we focused on the stereoselective construction of the quaternary asymmetric carbon center at the C9 position (Scheme 4). The key conversion was realized as follows. Upon treatment of **21** with dimethyl carbonate and LiO*t*-Bu in THF and hexamethylphosphoramide (HMPA), formation of the carbonate and subsequent intramolecular acylation proceeded smoothly to generate the lithium enolate of the β-keto lactone, which reacted with MeI to give methyl enol ether **22** as a single product. Although O-methylation occurred exclusively, this unexpected outcome was lucky, because the more reactive ketone moiety of the β-keto lactone could be selectively protected as a methyl enol ether. Further treatment of **22** with lithium hexamethyldisilazide (LHMDS) in THF and

SCHEME 5. Synthesis of Alkyne **26** and the Mechanism of Formation of Unexpected Vinyl Ether **27**

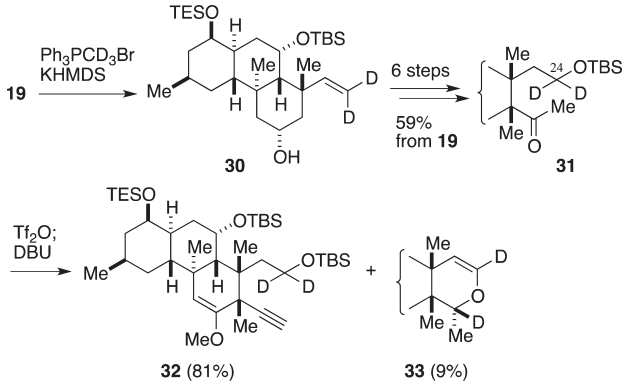


1,3-dimethyl-3,4,5,6,-tetrahydro-2(1*H*)-pyrimidinone (DMPU), followed by an addition of MeI, produced target compound **24** as a single stereoisomer in 71% yield. The second methylation reaction occurred exclusively from the β-side of the lactone enolate, probably via conformation **23**, so as to avoid steric hindrance between the C12 angular methyl group and methyl iodide. Thus, the quaternary asymmetric carbon center at the C9 position was constructed by the intramolecular acylation of keto alcohol **21** followed by successive O-methylation and C-methylation reactions in a highly stereoselective manner.

Exploitation of a Deuterium Kinetic Isotope Effect in the Synthesis of the Alkyne Segment. Consideration of a coupling reaction with amino alcohol segment **5** directed us to target the synthesis of the key alkyne segment **26** as a coupling partner (Scheme 5). Thus, alkyne **26** was derived from lactone **24** in three steps: addition of MeLi to lactone **24**, protection of the resulting primary alcohol with a TBS group to form **25**, and formation of an enol triflate by reaction with Tf_2O and subsequent elimination with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Although the desired product **26** was obtained in 65% overall yield from **24**, the final conversion was accompanied by the formation of unexpected vinyl ether **27** in 24% yield.

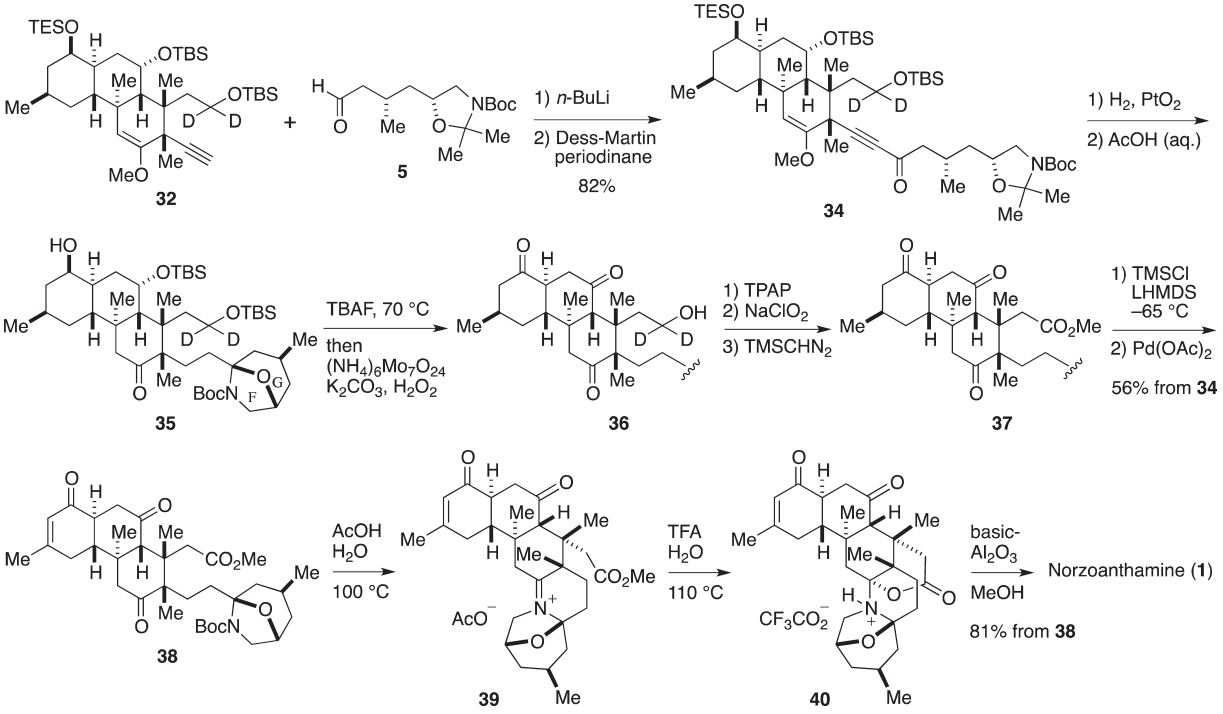
Formation of **27** was rationalized as follows (Scheme 5). Treatment of **25** with Tf_2O produced the corresponding enol triflate **28**, which was converted to alkyne **26** upon treatment with DBU. The enol triflate could also undergo a 1,5-hydride shift to the carbonyl group from the methylene adjacent to the TBS ether to generate **29** *in situ*, which could cyclize smoothly via an enolate to give vinyl ether **27**. This mechanistic analysis suggested that we could use a deuterium kinetic isotope effect[19] to suppress the problematic 1,5-hydride shift and, consequently, the formation of **27**. Fortunately, the carbon atom at the C24 position was to be oxidized to a carboxylic acid later in the synthesis (**36** → **37**), and the deuterium atoms would be removed at the oxidation step. Therefore, we synthesized deuterated methyl ketone **31** from lactol **19** using a commercially available deuterated Wittig reagent and a reaction sequence similar to that used for the synthesis of **25** (Scheme 6). When **31** was subjected to the alkynylation reaction, alkyne **32** was obtained in 81% yield, and the yield of byproduct **33** was reduced to 9%. Thus, we efficiently synthesized the requisite alkyne segment **32** by exploiting a deuterium kinetic isotope effect.

SCHEME 6. Exploitation of a Deuterium Kinetic Isotope Effect in the Synthesis of Alkyne Segment **32**



Total Synthesis of Norzoanthamine. With **32** in hand, we then needed to couple it with amino alcohol segment **5**,[11] install a double bond into the A-ring, and perform the crucial bis-aminoacetalization to form the DEFG-ring system (Scheme 7). The coupling of **32** and **5** with BuLi, followed by oxidation of the adducts afforded alkynyl ketone **34**. Hydrogenation of the triple bond in **34** and subsequent treatment of the crude product with aqueous AcOH furnished amino acetal **35**. Four concomitant transformations were involved in the last reaction: removal of the acetonide, removal of the TES group, intramolecular aminoacetalization leading to formation of the FG-ring, and hydrolysis of the methyl enol ether. After removal of the two TBS groups in **35** with tetraammonium fluoride (TBAF), oxidation of the

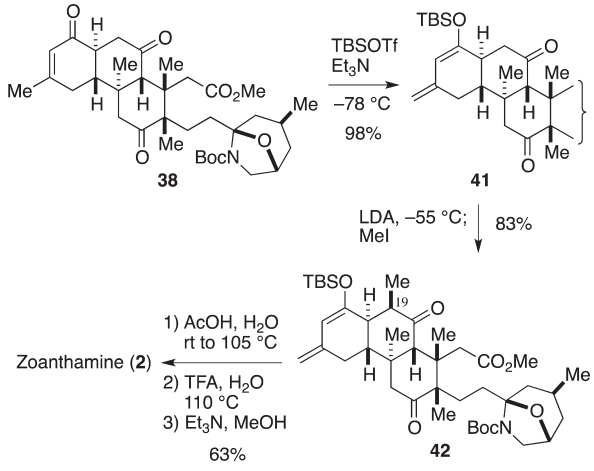
SCHEME 7. Total Synthesis of Norzoanthamine (**1**)



resulting triol with ammonium molybdate and H_2O_2 (Trost oxidation)[20] allowed chemoselective oxidation of the two sterically congested secondary hydroxyl groups, leading to keto alcohol **36**. We found that the combination of TBAF-mediated desilylation and subsequent Trost oxidation[20] in a one-pot operation was a powerful tool for the conversion of a silyl ether of a secondary alcohol to the corresponding ketone. Keto alcohol **36** was further transformed into keto ester **37** by a three-step reaction sequence during which the deuterium atoms were removed.

A double bond was introduced regioselectively into the A-ring of **37** by the Ito–Saegusa method[21] to give the desired enone **38**. The final critical bis-aminoacetalization, that is, the construction of the DEFG-ring system culminating in the total synthesis of norzoanthamine (**1**), was achieved by initial treatment of **38** with aqueous AcOH at 100 °C, followed by treatment of the resulting iminium salt **39** with aqueous trifluoroacetic acid (TFA) at 110 °C, to produce the ammonium salts of norzoanthamine **40**. Finally, desalination of the ammonium salts with basic alumina furnished **1** in 81% yield (three steps).[10,11] The synthetic compound was identical in all respects to naturally occurring norzoanthamine. Thus, the absolute structure of norzoanthamine was rigorously verified by the present total synthesis. The total yield of synthetic norzoanthamine was 3.5% over 41 steps, (92% average yield per step) starting from

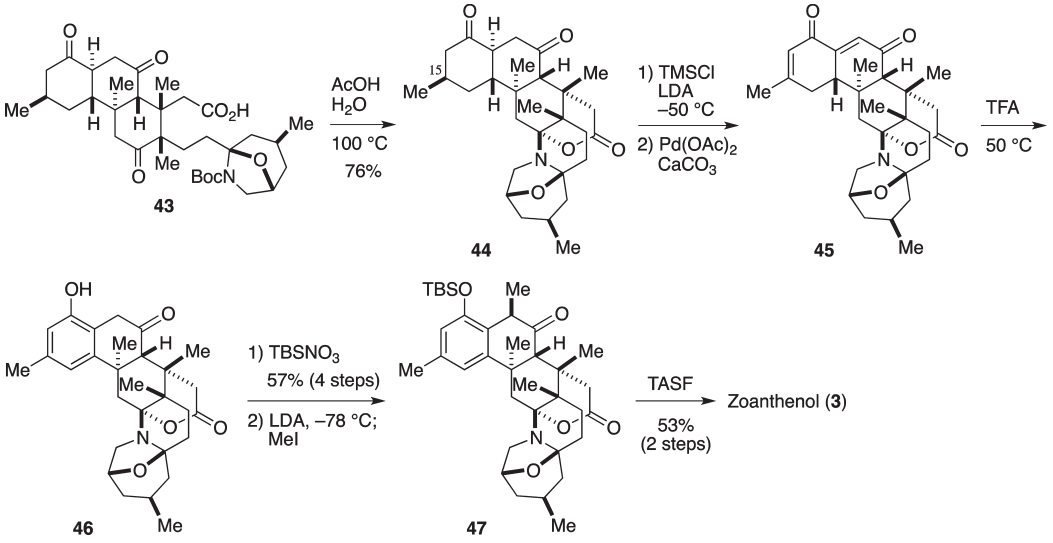
SCHEME 8. Total Synthesis of Zoanthamine (**2**)



(*R*)-5-methyl-2-cyclohexenone (**12**). Five years after our synthesis, Kobayashi and co-workers reported the second total synthesis of norzoanthamine.[22]

Total Synthesis of Zoanthamine. The achievement of the total synthesis of **1** prompted us to pursue the total synthesis of zoanthamine (**2**). The only synthetic challenge for the latter was the stereoselective introduction of the methyl group at the C19 position, and we considered two synthetic routes: synthesis from norzoanthamine by stereoselective introduction of the C19 methyl group and the use of an appropriate synthetic intermediate from the total

SCHEME 9. Total Synthesis of Zoanthenol (**3**) by Means of Isoaromatization



synthesis of **1**. We first investigated the former route and soon found that **1** and its protected derivatives were extremely labile under various methylation conditions, particularly, the basic conditions required for the generation of enolate anions. Therefore, we abandoned the first route and explored the second. After going down many dead-end trails, we finally synthesized **2** from precursor **38** (Scheme 8). Initially, the enone moiety in the A-ring of **38** was selectively protected as a diene TBS ether (**41**). The diene ether was then subjected to the key methylation reaction with lithium diisopropylamide (LDA) and MeI: treatment of **41** with LDA in THF at −55 °C followed by addition of MeI afforded methylation product **42** as a single stereoisomer. Product **42** was converted to **2** by the bis-aminoacetalization reaction sequence: (1) aqueous AcOH at 105 °C, (2) aqueous TFA at 110 °C, and (3) desalination by Et_3N in MeOH.[11] The total yield of synthetic zoanthamine was 2.2% over 43 steps (91% average yield per step) starting from **12**.

Total Synthesis of Zoanthenol Based on an Isoaromatization Strategy. Having achieved efficient total syntheses of **1** and **2**, we next focused on the synthesis of zoanthenol (**3**), which is unique among the zoanthamine alkaloids in having an aromatic ring. Because the only structural difference between **3** and **2** is the oxidation pattern of the A-ring, we thought that **3** could be directly synthesized by oxidative aromatization of zoanthamine. Using the tetracyclic enone (ABC-ring system) as a model substrate, we arrived at two potentially efficient protocols for the transformation: the Pucci protocol with $CuBr_2$ and LiBr[23] and a novel oxidation with Ac_2O and $Yb(OTf)_3$ under an oxygen atmosphere.[12b] Unfortunately, all attempts at oxidative aromatization of **2**, **2**·HCl, and a late-stage synthetic intermediate containing an FG-ring amino acetal moiety by both protocols failed totally, resulting in decomposition or the formation of unidentified degradation products, presumably owing to lability of the amino acetal moieties under the reaction conditions. Therefore, an alternative method to construct the aromatic ring was required for the total synthesis of **3**.

At this stage, we turned our attention to the aminoacetalization step in the total synthesis of **1**, which involved (1) removal of the Boc group and subsequent formation of an iminium ion by treatment with aqueous AcOH (**38** → **39**), (2) hydrolysis of the methyl ester by treatment with aqueous TFA, and (3) lactonization (**39** → **40**). In these reactions, the use of Brønsted acids did not appreciably affect either the amino acetal moiety or the ABC-ring system. Therefore, we designed a new synthetic methodology for constructing the aromatic ring by a combination of the Ito–Saegusa reaction and subsequent Brønsted acid–mediated isoaromatization[24] of the resulting bis-enone moiety (**44** → **45** → **46**). This new synthetic route permitted the total synthesis of **3** as follows (Scheme 9). First, keto acid **43** was converted to dihydronorzoanthamine (**44**) by treatment with aqueous AcOH at 100 °C. Bis-enone **45**, the crucial precursor for the key aromatization, was synthesized from **44** by means of the Ito–Saegusa reaction,[21] which involved regioselective formation of a bis-silyl enol ether on the AB-ring followed by oxidation with $Pd(OAc)_2$ and $CaCO_3$. Upon treatment of **45** with TFA at 50 °C, the desired aromatization occurred to produce **46** (norzoanthenol). After protection of the phenolic alcohol in **46** as a TBS ether, the methyl group at the C19 position was introduced stereoselectively by treatment of the TBS ether

with LDA at −78 °C, followed by addition of MeI. Finally, desilylation of the TBS ether of **47** furnished **3**.[12] The total yield of synthetic zoanthenol was 1.1% over 42 steps (90% average yield per step) starting from **12**.

We also developed an efficient synthetic route to **3** from commercially available norzoanthamine hydrochloride (**1**·HCl).[12] Hydrogenation of **1**·HCl afforded (15*S*)-15,16-dihydronorzoanthamine,[4b] the C15-epimer of **44**, which was transformed into aromatic compound **46** by a three-step reaction sequence, similar to that used to convert **44** to **46**.

Conclusions

We achieved the first total syntheses of norzoanthamine (**1**), zoanthamine (**2**), and zoanthenol (**3**) from a common intermediate (**43**), and we rigorously verified their absolute structures by these syntheses. The synthetic challenges included (1) sequential three-component coupling reactions, followed by photosensitized oxidation of the furan derivative, for the synthesis of the IMDA precursor, (2) the key IMDA reaction for the stereoselective construction of the ABC-ring system bearing two quaternary stereogenic centers, (3) synthesis of the alkyne segment facilitated by a deuterium kinetic isotope effect, (4) sequential bis-aminoacetalization for construction of the DEFG-ring system, and (5) isoaromatization for construction of the aromatic ring of **3**. Our synthetic strategies and methodologies are flexible enough to allow for the synthesis of various analogues for biological testing. The chemistry described here not only offers a solution to formidable synthetic problems but also opens a complete chemical avenue to naturally occurring zoanthamine alkaloids and their synthetic derivatives.

We are grateful to all the co-workers who were involved in these projects; their names are listed in the references. We thank professors Daisuke Uemura (Nagoya University) and Kazuo Tachibana (The University of Tokyo) for providing us with natural norzoanthamine and zoanthamine, respectively. Financial support from the Ministry of Education, Culture, Sports, Science, and Technology, Japan (MEXT) is gratefully acknowledged.

BIOGRAPHICAL INFORMATION

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FOOTNOTES

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