Total Synthesis Hot Paper

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Asymmetric Total Synthesis of Norzoanthamine

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Abstract: *We report herein the asymmetric total synthesis of norzoanthamine using radical reactions as key steps for rapid access to the congested carbocyclic core, which is the major synthetic challenge for most zoanthamine alkaloids. (1) The Ueno–Stork radical cyclization was applied to construct the adjacent quaternary centers at the C-9 and C-22 positions; (2) a Co-catalyzed HAT radical reaction was successfully applied to construct the quaternary center at C-12 via Csp^3-Csp^2 bond formation; (3) a Mn-catalyzed HAT radical reaction was used to stereospecifically reduce the tetra-substituted olefin (C13=C18) and install the contiguous stereocenters in proximity to the quaternary center. A one-pot bio-inspired cyclization step was finally applied to forge the unstable bis-amino acetal skeleton. Our approach can precisely control the stereochemistry of seven vicinal stereocenters and effectively construct the highly congested heptacyclic skeleton.*

Natural products isolated from marine organisms have unique and diverse structures, and their biological activities differ from those of compounds derived from terrestrial plants, fungi, or microorganisms.[1] Zoanthamine alkaloids are a growing family of structurally unique and complex products with a wide range of biological activities (Figure 1).[2] Zoanthamine (**1**) was the first alkaloid of this family that was isolated from a Zoanthus species off the Visakhapatnam coast in India by Rao, Faulkner and co-workers in 1984.[3] Afterward, new discoveries began to spring up and resulted in a variety of structurally diverse members, such as zoanthenol (**4**), [4] zoanthenamine (**5**), [5] kuroshine A (**6**)[6] (Figure 1).[7] In 1995, Uemura and co-workers reported the isolation of norzoanthamine (**2**) from the same species collected off the Ayamaru coast of the Amami Islands south of Japan.[8] Biological studies showed that norzoanthamine (**2**) strongly mitigated the loss of bone mass and strength caused by ovariectomy in mice, suggesting its potential application as an anti-osteoporotic drug.[9] Structurally, the carbocyclic core of norzoanthamine (**2**) features a *trans-anti-trans*-fused perhydrophenanthrene A-B-C ring containing three quaternary chiral centers, which was common to most of these family members. Norzoanthamine (**2**) has attracted considerable attention from synthetic groups with different strategies.[10] In 2004, Miyashita and co-workers reported the first impressive synthesis of norzoanthamine (**2**) over 41 steps in 3.5 % overall yield,[11] through an intramolecular Diels–Alder reaction to construct the congested A-B-C ring bearing two quaternary centers and C-methylation reaction to establish the third quaternary center at C-9. In 2009, Kobayashi group reported the second total synthesis of norzoanthamine (**2**) over 47 steps, [12] featuring an intramolecular Diels–Alder reaction to prepare the A-B ring and copper-mediated Michael addition reaction to install the quaternary centers at C-12 and C-22.

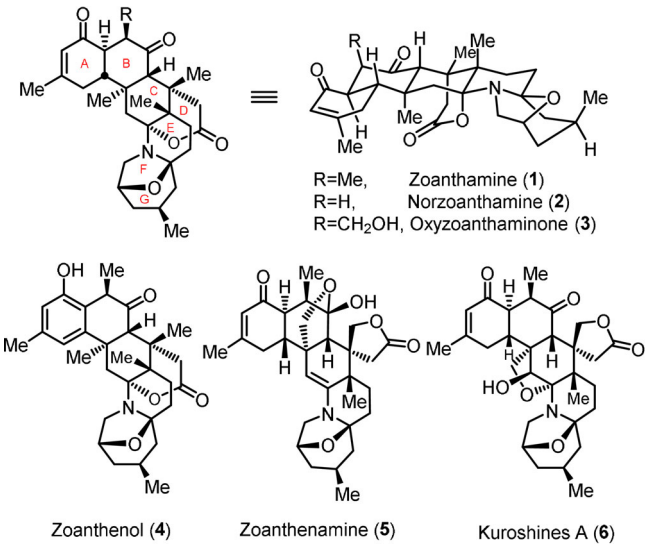

Figure 1. Structures of representatives of zoanthamine alkaloids.

Synthetic challenges posed by norzoanthamine (**2**) include: 1) a topographically intricate heptacyclic skeleton bearing the *trans-anti-trans*-fused perhydrophenanthrene A-B-C ring, the bridged δ-lactone D ring, and the bis-amino acetal E-F-G ring (Scheme 1); 2) ten stereocenters, among them seven contiguous stereogenic centers located on the B and C rings, which also include three quaternary centers at the C-9, C-12, and C-22 positions; 3) densely functionalized and highly oxidized skeleton with two ketones, one lactone and bis-amino acetal. Thus, the key for the synthesis is the preparation of the densely substituted B-C ring and the rigid bis-amino acetal scaffold. Here we report a modular total synthesis of densely functionalized norzoanthamine (**2**) based on a new ring-forming strategy as a flexible and efficient synthetic route toward other members of zoanthamine alkaloids.

Inspired by the significant advances of radical chemistry,[13–16] we envisioned that the *trans-anti-trans*-fused perhydro-phenanthrene A-B-C ring and the quaternary centers at

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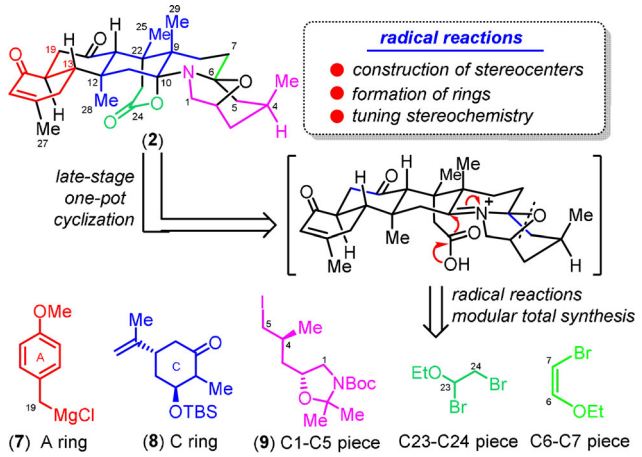
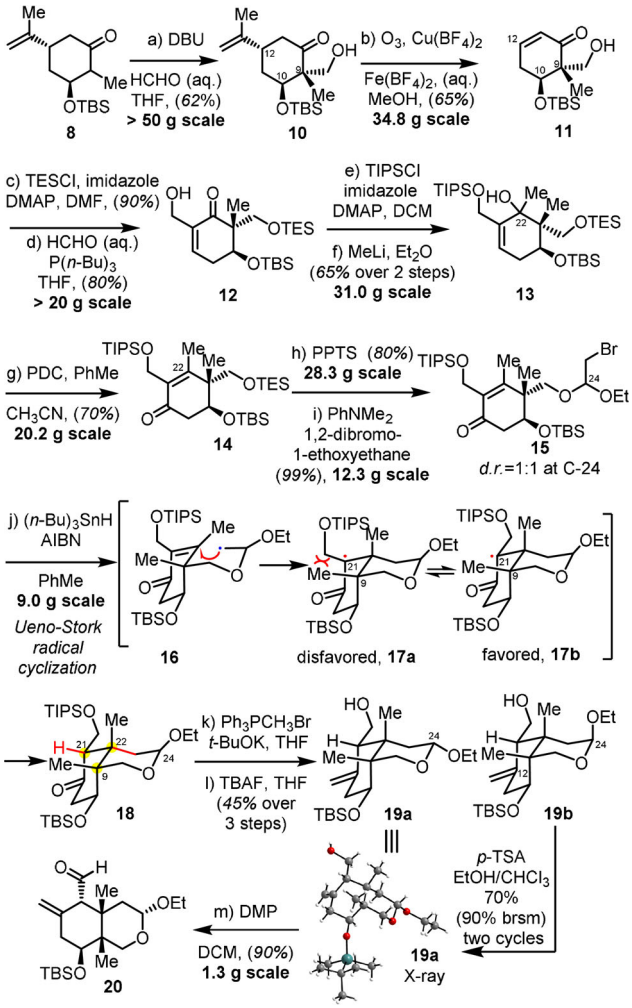


Scheme 1. Retrosynthetic analysis of norzoanthamine.

the C-9, C-12, and C-22 positions could be stereoselectively constructed via the radical processes (Scheme 1). Barbier-type reactions were used to couple the easily prepared fragments **7** (A ring), **8** (C ring) and short carbon pieces, such as C1-C5 piece **9**. Finally, based on the proposed biosynthetic pathway,[2b,17,18] a bio-inspired bis-aminoacetalization was applied to prepare the sensitive bis-aminal skeleton.

The C ring (fragment **20**), which contains four contiguous stereocenters and two quaternary centers at C-9 and C-22 (Scheme 2), was first prepared using the known enantioenriched ketone **8** (d.r. = 10:1 at C-9) to build the required stereocenters.

Ketone **8** was easily synthesized from (*S*)-(+)-carvone[19] on a large scale (> 50 gram, Supporting Information). A hydroxymethyl group was then introduced at the C-9 position through a base-mediated aldol reaction, leading to the formation of compound **10**. Due to the bulky *tert*-butyldimethylsilyl ether group (-OTBS) at C-10, the stereochemistry of this transformation was well-controlled, and the C-9 quaternary center selectively formed as a single diastereomer. In addition, the bulky -OTBS group was critical for controlling the stereochemistry of the subsequent radical process. The isopropenyl group at C-12 of **10** was then removed through a generation of methoxy hydroperoxyl acetal and fragmentation process mediated by soluble $Cu(BF_4)_2$ and $Fe(BF_4)_2$ salts,[20] affording enone **11** in 65% yield on decagram scale. Afterward, the primary hydroxyl group of **11** was protected as a triethylsilyl ether group (-OTES), and a second hydroxymethyl group was introduced via a Baylis–Hillman reaction to give compound **12** in 72% yield over two steps. After the protection of the hydroxyl group of **12** as a triisopropylsilyl ether (-OTIPS) and the nucleophilic addition of methyllithium to the carbonyl group, the tertiary alcohol **13** was obtained as a mixture of two diastereomers (d.r. = 1:1 at C-22) and used for the subsequent oxidative allylic transposition. Pyridinium chlorochromate (PCC) was first used as the oxidant, but it led to the decomposition of the acid-sensitive analogue **13**. Therefore, the milder oxidant pyridinium dichromate (PDC) was applied at 65 °C and afforded the desired penta-substituted cyclohexanone **14** in 70% yield on decagram scale.[21] The TES group was then selectively



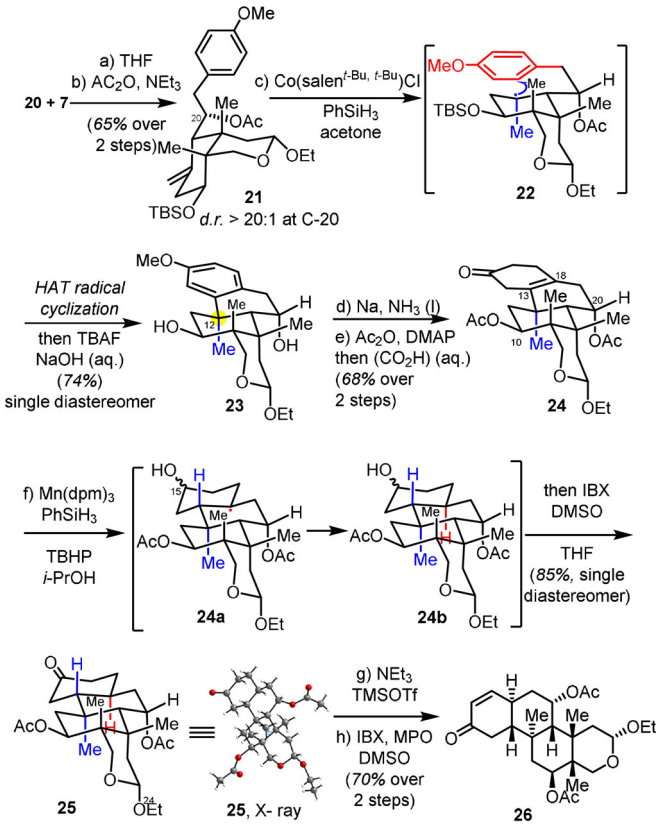
Scheme 2. Construction of C ring (fragment **20**). DBU = 1,8-diazabicyclo [5.4.0]undec-7-ene, DMAP = 4-(dimethylamino)pyridine, TESCl = chlorotriethylsilane, TIPSCl = triisopropylsilyl chloride, TBAF = tetrabutylammonium fluoride, THF = tetrahydrofuran, *p*-TSA = *p*-toluenesulfonic acid, DCM = dichloromethane.

removed with pyridinium *p*-toluenesulfonate (PPTS), and the resulting primary alcohol reacted with 1,2-dibromo-1-ethoxyethane under basic conditions to give bromoacetal **15** (d.r. = 1:1 at C-24) in 79% yield over 2 steps.

For the subsequent synthesis of **18**, Ueno-Stork radical cyclization[22] was investigated. In particular, the two diastereomers of **15** were refluxed with $(n\text{-Bu})_3$SnH and azobisisobutyronitrile (AIBN) in toluene, generating the corresponding bicyclic product **18**. This process allowed precise control of the two new stereocenters at C-21 and C-22, providing the stereochemistry required for this natural product family. We reason that the radical intermediate **16** undergoes 6-*exo* cyclization through a chair-like transition state, and that the conformation of the acetal group at C-24 does not affect the stereochemistry of C–C bond formation. Due to a severe 1,3-diaxial strain between the methyl group at C-9 and the bulky -CH_2OTIPS group at C-21 in disfavored intermediate **17a**, the radical termination step would proceed through the favored radical intermediate **17b**, leading to the desired cyclized product **18**. The carbonyl group at C-12 of **18** was converted to

a methylene group via a Wittig reaction and the TIPS protecting group on the primary hydroxyl group was selectively removed to furnish alcohol **19a** and its epimer **19b** (**19a**:**19b** = 1:1.5) in 45% yield over three steps. The absolute configuration of the diastereomer containing an α-OEt group at C-24 (**19a**) was determined by X-ray diffraction analysis.[23] In order to facilitate the following transformations and structure determination, **19b** was converted into **19a** under acidic conditions in 70% yield over two cycles. The primary alcohol **19a** was finally oxidized with Dess–Martin periodinane (DMP) to give the desired aldehyde **20** (C ring) with four contiguous stereocenters in 90% yield.

With aldehyde **20** in hand, we next set out to install the third quaternary carbon center at C-12 position (Scheme 3). Compound **21** was prepared from aldehyde **20** through a two-step sequence, involving a nucleophilic addition (d.r. > 20:1 at C-20) of Grignard reagent **7** and the following acetylation with Ac_2O in 65% yield over two steps. Inspired by Co-catalyzed HAT reaction previously reported by Shenvi and co-workers,[14a–g] **21** was first treated with catalytic Co(salen$^{t\text{-Bu},t\text{-Bu}}$)Cl in the presence of $PhSiH_3$ in anhydrous acetone to furnish the desired tetracyclic core, which further underwent one-pot TBS deprotection to provide desired **23** in 74% yield on gram scale. Dearomatization of **23** via Birch reduction afforded a crude diene, which was converted into ketone **24** through the acetyl protection of the hydroxyl

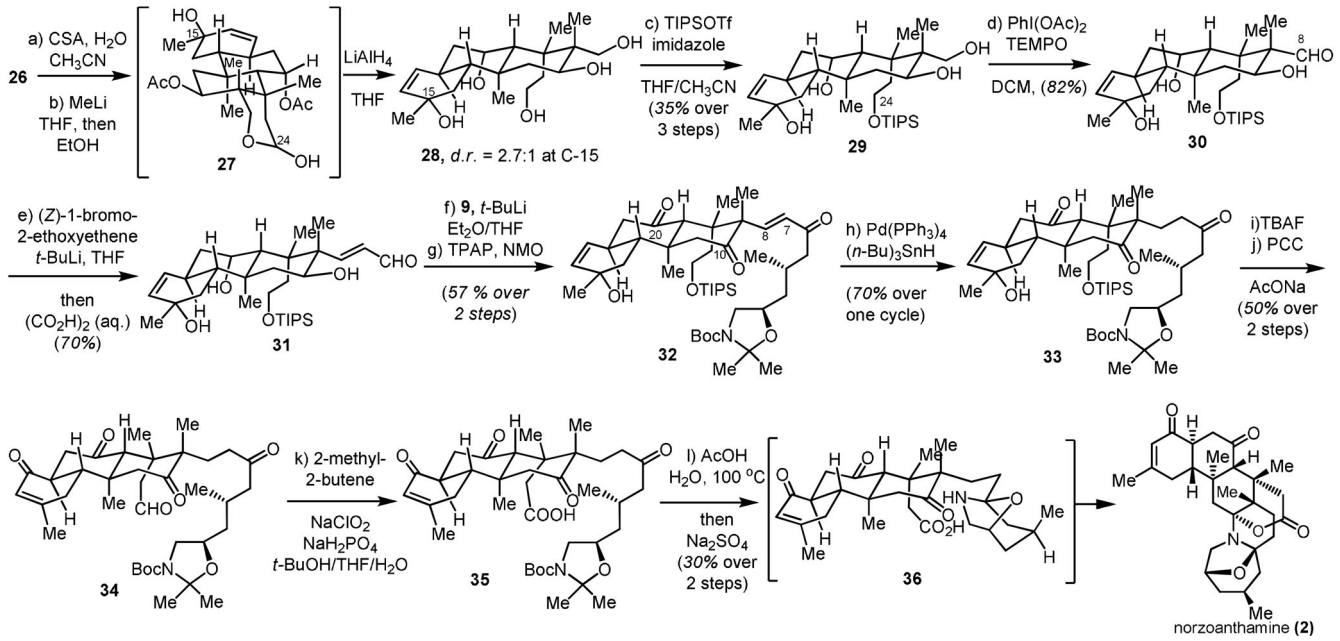


Scheme 3. Construction of A-B-C ring through the Co- and Mn-catalyzed HAT radical reactions. TBHP = *tert*-butyl hydroperoxide, DMSO = dimethyl sulfoxide, IBX = 2-iodoxybenzoic acid, TMSOTf = trimethylsilyl trifluoromethanesulfonate.

groups at C-10 and C-20 and the following acid-mediated hydrolysis of vinyl ether. The following synthetic challenge was diastereoselective reduction of tetra-substituted olefin (C13=C18) (Scheme 3). We postulated that *trans-anti-trans*-fused perhydrophenanthrene A-B-C ring was more thermodynamic stable comparing to other relative configurations. To test this hypothesis, the Mn-catalyzed HAT hydrogenation reaction[15] was explored using Shenvi's protocol.[15a] As expected, an *anti*-addition of hydrogen took place via the radical intermediate **24a**, affording the thermodynamically stable *trans*-decalin A-B ring with good diastereoselectivity, but low yield was obtained. After extensive optimizations, we found that excess of $PhSiH_3$ (> 4.0 equiv.) and *t*-butyl hydroperoxide (> 4.0 equiv.) must be used to make sure the complete conversion of **24**, accompanying with the reduction of the carbonyl group, which was subjected to subsequent one-pot oxidation with 2-iodoxybenzoic acid to yield the tetracyclic compounds **25** (single diastereomer) bearing the desired *trans-anti-trans*-fused perhydrophenanthrene A-B-C ring on gram scale in 85% yield. The absolute configuration of **25** was determined and confirmed by X-ray diffraction analysis.[23] Then, ketone **25** was treated with TMSOTf/NEt_3 affording silyl enol ether intermediate, which was subsequently oxidized using IBX/4-methoxypyridine N-oxide (MPO) to yield enone **26** in 70% yield over two steps.[24]

For the synthesis of the bis-aminal D-E-F-G ring, the C1-C5 fragment was prepared via a Co(salen)-catalyzed asymmetric nitroaldol reaction to add the chiral amino alcohol moiety with good diastereo- and enantioselectivity. Five additional transformations led to iodide **9**[10h] (see details in the Supporting Information).

With *trans-anti-trans*-fused perhydrophenanthrene A-B-C ring and six contiguous stereocenter forged effectively, our focus turned to oxidation state modification and side-chain installation (Scheme 4). After hydrolysis of the acetal group at C-24 with camphorsulfonic acid (CSA), a methyl group was introduced on C-15, giving the crude allylic alcohol **27**,[25] which was directly reduced with $LiAlH_4$ to remove the two acetal protecting groups and open the lactol ring. The obtained compound **28** was extremely polar due to the five free hydroxyl groups. In order to selectively treat these functional groups, we first explored the protection of the less hindered primary hydroxyl group at C-24. After extensive attempts, we found this primary alcohol could be selectively protected with TIPSOTf/imidazole to provide **29** (d.r. = 2.7:1 at C-15) in 35% yield over three steps. Next, the primary hydroxyl group at C-8 was selectively oxidized to aldehyde **30** in 82% yield using the (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) radical and $PhI(OAc)_2$ in dichloromethane.[26] In order to extend the carbon side chain, the freshly prepared anion intermediate of (*Z*)-1-bromo-2-ethoxyethene was nucleophilically added to **30**, followed by treatment under acidic conditions to give the unsaturated aldehyde **31**. The Li-I exchange in iodide **9** using *tert*-butyllithium induced the formation of the corresponding anion species, which successfully attacked the unsaturated aldehyde **31**, leading to the formation of allylic alcohol analogue. This allylic alcohol was subjected to Ley-Griffith oxidation to give triketone **32** in 57% yield over two steps. After testing various reduction



Scheme 4. Total synthesis of norzoanthamine. CSA = camphorsulfonic acid, TIPSOTf = triisopropylsilyl trifluoromethanesulfonate, TEMPO = 2,2,6,6-tetramethylpiperidinyloxy, TPAP = tetrapropylammonium perruthenate, NMO = *N*-methylmorpholine-*N*-oxide.

conditions, such as Stryker's Reagent,[27] Raney Ni/EtOH,[28] $(Ph_3P)RhCl/Et_3SiH$,[29] MeCu/DIBAL-H,[30] we found that Pd^0-catalyzed 1,4-conjugate addition with tin hydride[31] was the effective method for chemoselective reduction of unsaturated double bonds in triketone **32**, furnishing ketone **33** in 70% yield.

To complete the total synthesis (Scheme 4), compound **33** first underwent the removal of the TIPS with TBAF, followed by one-pot PCC-mediated oxidation of primary alcohol and oxidative rearrangement of the tertiary allylic alcohol to yield aldehyde **34**, which harbors an enone group in the A ring. A Pinnick-Lindgren-Kraus oxidation was applied to convert the aldehyde group into a carboxylic acid **35**, the precursor of the final cyclization. Inspired by the hypothetical biosynthetic pathway[2b,17] and Kobayashi's studies,[10n,18] the crude carboxylic acid **35** was treated with heated aqueous acetic acid to remove the acetonide and Boc protecting groups. Then, the presence of anhydrous sodium sulfate realized the bis-aminoacetalization in one-pot to afford norzoanthamine (**2**), and this process further corroborated the biosynthetic hypothesis. The successful synthesis of **2** was confirmed by NMR spectroscopy and high-resolution mass spectrometry, all of which gave results consistent with those reported for the natural product.[8]

In summary, the concise asymmetric total synthesis of norzoanthamine, a marine alkaloid with significant biological activity, was achieved based on a modular strategy. Radical cyclization reactions were mainly used to form the challenging carbocyclic core, which was shared by most of zoanthamine alkaloids. The Ueno-Stork radical cyclization, was efficiently applied to construct the vicinal quaternary stereocenters at the C-9 and C-22 positions of norzoanthamine (**2**). The M-HAT radical reactions allowed rapid access to the *trans-anti-trans-fused* perhydrophenanthrene A-B-C ring decorated by three quaternary centers. A one-pot acid-induced cascade bis-aminoacetalization further corroborated the biosynthetic hypothesis. This convergent, 36-step longest linear sequence (LLS) from the commercially available material (*S*)-(+)-Carvone can precisely control the stereochemistry of seven adjacent stereocenters and effectively construct the highly congested heptacyclic skeleton. Therefore, we expect that this modular approach will provide a flexible and reliable solution for the chemical synthesis of naturally available zoanthamine alkaloids in adequate amounts for biological studies.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: metal-catalyzed HAT reaction · norzoanthamine · quaternary centers · radical reactions · total synthesis

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Communications

Total Synthesis

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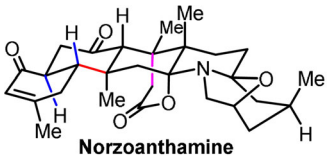
Asymmetric Total Synthesis of Norzoanthamine



- ***modular strategy***
- ***stereospecific radical reactions for core structure***
  - *Ueno-Stork reaction (quaternary centers)*
  - *Co-cat. HAT reaction* (C_{sp3}-C_{sp2} bond)
  - *Mn-cat. HAT reaction* (C_{sp3}-C_{sp3} bond)
- ***one-pot bio-inspired cyclization***

We report herein an asymmetric total synthesis of norzoanthamine, a complex marine zoanthamine alkaloid, via radical and bio-inspired cyclizations comprising the following key steps: 1) the Ueno–Stork radical cyclization; 2) a unique Co-catalyzed HAT radical reaction; 3) a Mn-catalyzed HAT radical reaction; and 4) a one-pot bio-inspired bis-amino-acetalization