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Toward the Synthesis of Norzoanthamine: Building Carbocyclic Core by a Transannular Michael Reaction Cascade

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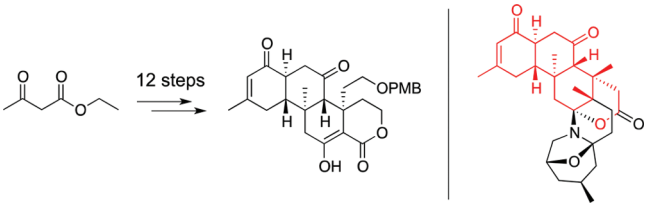
ABSTRACT



A 12-step synthesis of the ABC carbocyclic core of norzoanthamine is described. It features an organocatalytic asymmetric intramolecular aldolization to set the stereochemistry of the entire molecule, a fragment coupling by selective alkylation of a bis-enolate, and a transannular Michael reaction cascade for rapid and stereoselective synthesis of the polycyclic core.

Zoanthamine (**1**), norzoanthamine (**2**), zoanthenol (**3**), and 28-deoxyzoanthenamine (**4**) are representatives of a small group of marine alkaloids originally isolated from colonial zoanthids of the genus *Zoanthus* sp. (Figure 1).[1] These compounds show a range of interesting biological activities, such as cytotoxicity, inhibition of human platelet aggregation, and antibacterial and anti-inflammatory activities.[2] Norzoanthamine is arguably the most notable of this group due to its potent antiosteoporotic effect.[3] This property was characterized by suppression of the loss of bone weight and bone strength of ovariectomized mice,

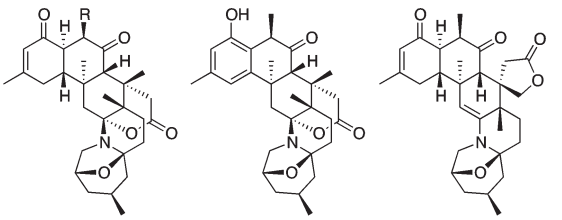


Figure 1. Examples of zoanthamines.

animal models that mimic postmenopausal osteoporosis.[4] When orally administered in the form of its HCl salt, norzoanthamine suppressed the loss of the trabecullar bone and induced thickening of the cortical bone of ovariectomized mice at a dosage of 2 mg/kg/day with no obvious side effects over a period of four weeks. While norzoanthamine appears to function through a mechanism that is different from that of estrogen in inhibiting osteoporosis,[3] its detailed mode-of-action remains unknown.

Most of the zoanthamine alkaloids feature a topologically complex heptacyclic molecular skeleton that is densely functionalized and stereochemically complex. For example, among the ten stereocenters of norzoanthamine (**2**), five are

(1) For an excellent review, see: Behenna, D. C.; Stockdill, J. L.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 2365–2386.

(2) For some references, see: (a) Rao, C. B.; Anjaneyulu, A. S. R.; Sarma, N. S.; Venkatateswarlu, Y.; Rosser, R. M.; Faulkner, D. J. *J. Org. Chem.* **1985**, *50*, 3757–3760. (b) Fukuzawa, S.; Hayashi, Y.; Uemura, D.; Nagatsu, A.; Yamada, K.; Ijuin, Y. *Heterocycl. Commun.* **1995**, *1*, 207–214. (c) Venkateswarlu, Y.; Reddy, N. S.; Ramesh, P.; Reddy, P. S.; Jamil, K. *Heterocycl. Commun.* **1998**, *4*, 575–580. (d) Villar, R. M.; Gil-Longo, J.; Daranas, A. H.; Souto, M. L.; Fernandez, J. J.; Peixinho, S.; Barral, M. A.; Santafe, G.; Rodriguez, J.; Jimenez, C. *Bioorg. Med. Chem. Lett.* **2003**, *11*, 2301–2306.

(3) (a) Fukuzawa, S.; Hayashi, Y.; Uemura, D.; Nagatsu, A.; YamadaK.; Ijuin, Y. *Heterocycl. Commun.* **1995**, *1*, 207–214. (b) Kuramoto, M.; Hayashi, Y.; Fujitani, K.; Yamaguchi, K.; Tsuji, T.; Yamada, K.; Ijuin, Y.; Uemura, D. *Tetrahedron Lett.* **1997**, *38*, 5683–5686. (c) Kuramoto, M.; Hayashi, K.; Fujitani, Y.; Yada, M.; Tsuji, T.; Uemura, D. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 771–779. (d) Yamaguchi, K.; Yada, M.; Tsuji, T.; Kuramoto, M.; Uemura, D. *Biol. Pharm. Bull.* **1999**, *22*, 920–924.

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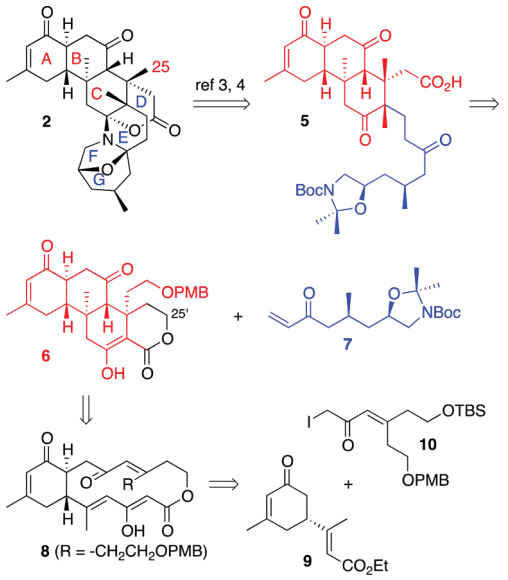
concentrated on the six-membered C-ring and three of them are all-carbon quaternary centers. The complex molecular structure and intriguing bioactivities make zoanthamines exciting but challenging synthetic targets. Twenty years after isolation of the first zoanthamine alkaloid (i.e., **1**) by the research groups of Rau and Faulkner,[5] Miyashita and co-workers completed the first synthesis of norzoanthamine in 2004 and subsequently converted it to zoanthamine and zoanthenol.[6] A second synthesis of norzoanathamine was reported by Kobayashi and co-workers in 2009.[7] These successes were preluded by preliminary studies from these two research groups and others.[8] Early investigations by the groups of Williams and Kobayashi showed that the topologically complex bis-hemiaminal DEFG ring system can be formed spontaneously from acyclic amino alcohols under acidic reaction conditions.[9] This polycyclization process (i.e., **5** to **2**, Scheme 1) was later adapted by both Miyashita and Kobayashi in their syntheses of norzoanthamine. The relative ease of formation of the DEFG ring system highlights the challenge associated with synthesizing the highly functionalized and stereochemically complex ABC carbocyclic core. Indeed, many of these early synthetic routes assembled the ABC carbocycle by intramolecular Diels–Alder reactions and subsequent functional group manipulations.[6,7] Development of efficient synthetic approaches to the ABC carbocyclic core has been and continues to be the focus of synthetic studies that aim at zoanthamine alkaloids.[10]

We embarked on developing an efficient synthetic route to norzoanthamine and its simplified analogs that would enable further biomedical investigation of this potent anti-osteoporotic compound. Our convergent synthetic design involved coupling of the tetracyclic β-ketoester **6** and the C1–C8 fragment **7** (or its equivalent) to form **5** (Scheme 1).[7] The tetracyclic β-ketoester **6** contains five contiguous stereocenters including two all-carbon quaternary ones.

Scheme 1. Synthetic Design



With the exception that its extra C25′ has to be later removed to complete the formation of Me-25, this tetracyclic compound is a faithful representation of the ABC carbocyclic core of norzoanthamine. It was envisioned to be the product of a transannular Michael reaction cascade of macrocyclic lactone **8**,[11] which could be synthesized from cyclohexenone **9** and α-iodoketone **10**. Herein we report a 12-step synthetic approach to the carbocyclic core of norzoanthamine (i.e., **6**) based on this synthetic design.

Our synthesis commenced with the enantioselective preparation of cyclohexenone **9** in 5 steps from ethyl acetoacetate (Scheme 2). A modification of Snider's original procedure was used to prepare the bis-allyl β-ketoester **11** by the one-pot double allylation reaction.[12] The trisubstituted enoate **12** was obtained in 87% yield by treatment of **11** with triflic anhydride in a biphasic aq LiOH-hexanes system to form a (*Z*)-enol triflate intermediate,[13] followed by $Fe(acac)_3$-catalyzed methylation with MeMgBr.[14] Only the (*E*)-enoate was

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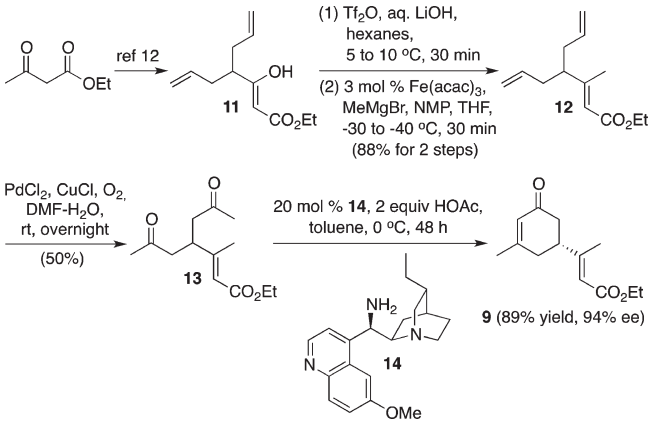
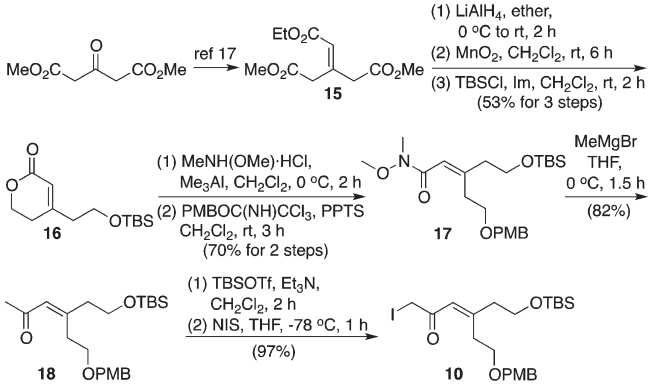
Scheme 2. Enantioselective Synthesis of Cyclohexenone **9**



formed in this two-step procedure. Simultaneous oxidation of both of the terminal alkenes of **12** by the Wacker oxidation gave the symmetrical 2,6-heptanediketone **13** in 50% yield.[15] A highly enantiomerically enriched cyclohexenone **9** (94% ee, determined by HPLC using chiral stationary phase, see Supporting Information) was obtained in 89% yield by the asymmetric intramolecular aldolization of **13** catalyzed by the quinidine-derived primary amine **14**.[16] The catalyst could be recovered by column chromatography and reused without affecting its activity and the enantioselectivity of the reaction.

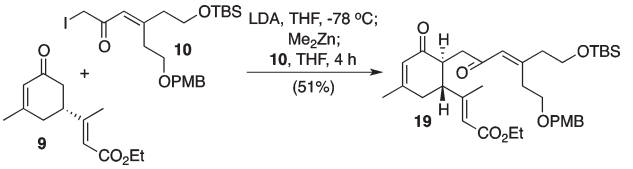
Scheme 3. Synthesis of Iodoketone **10**



The synthesis of α-iodoketone **10** started with the Wittig olefination of dimethyl-1,3-acetonedicarboxylate (Scheme 3).[17] Global reduction of the triester **15** followed by selective allylic oxidation of the resulting triol with MnO_2 generated an α,β-unsaturated-γ-lactone intermediate, in which the free hydroxyl group was protected with TBSCl to give **16**. Aminolysis of **16** by MeNH(OMe)·HCl−Me_3Al and protection of the resulting primary hydroxyl group as its PMB ether gave **17** in high yield.[18] The methyl ketone **18** was obtained in 82% yield by reaction of the Weinreb amide **17** with MeMgBr. For α-halogenation, the methyl ketone was enolized (TBSOTf, Et_3N) to form a silyl enol ether intermediate which was subjected to halogenation with NIS to give the stereochemically defined α-iodoketone **10**.[19]

With both **9** and **10** in hand, efforts were made to unite the two fragments and synthesize macrocyclic lactone **8**. Fragment coupling by enolization of **9** with LDA at −78 °C and alkylation with α-iodoketone **10** in the presence of Me_2Zn gave **19** in 51% yield (Scheme 4). However, all attempts to convert **19** to macrocyclic lactone **8** were either unsuccessful or occurred with low efficiency.

Scheme 4. Coupling of **9** and **10**



To improve the overall efficiency, we sought to functionalize **9** prior to its coupling with α-iodoketone **10** so that the number of transformations necessary to arrive at macrocycle **8** would be minimized. The functionalization of **9** started from reduction/oxidation to give aldehyde **20** in 58% yield (Scheme 5). This was followed by the Roskamp reaction with $SnCl_2$ and ethyl diazoacetate to give β-ketoester **21**.[20] After extensive experimentation, it was found that regioselective alkylation of **21** could be achieved by deprotonation with 2.1 equiv of LDA at −78 °C in a solvent of THF-HMPA followed by treatment with α-iodoketone **10** to give the desired coupling product **23** in 53% yield. Presumably, deprotonation of **21** with excess of LDA led to formation of bis-enolate **22**, which regioselectively reacted with **10** at the more nucleophilic endocyclic enolate. This reaction represents a rare example of regioselective alkylation of bis-enolates even though similar regioselective alkylations of dianions of β-ketoesters have been well-known. Further functionalization of **23** by desilylation and macrolactonization led to macrocyclic lactone **8**. A buffered condition (HF-TBAF-Py) was necessary for optimal yield of desilylation of **23** while macrocyclization required refluxing a dilute solution of **24** in toluene.[21,22] A reactive acylketene (**25**) was presumably formed under the reaction condition, and this transient intermediate underwent an intramolecular acylation reaction to give the macrocyclic lactone **8**.

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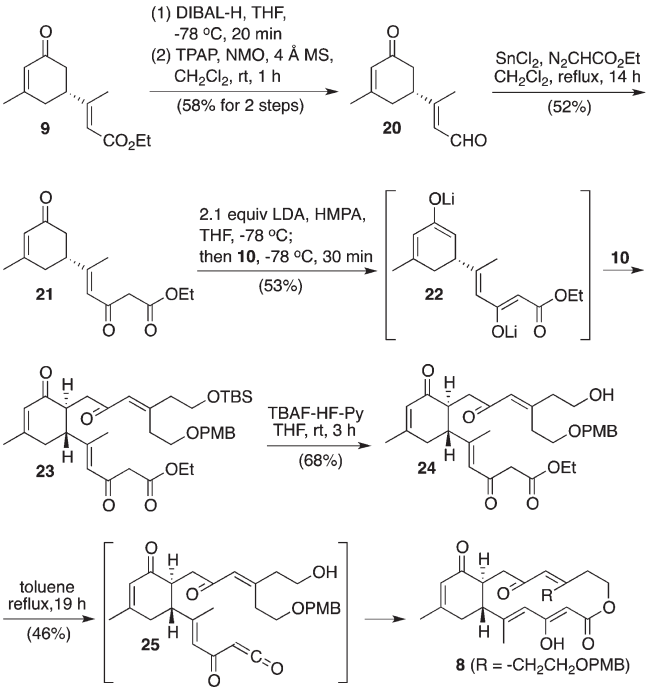
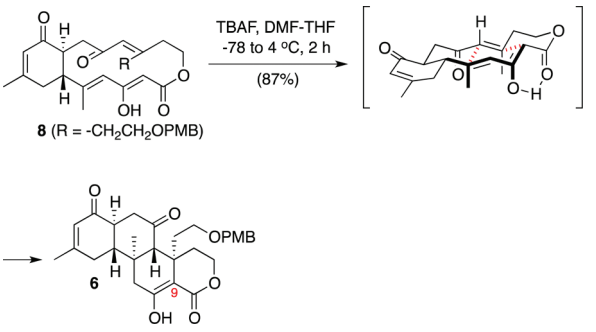
Scheme 5. Synthesis of Macrocyclic Lactone



Scheme 6. Transannular Michael Reaction Cascade of **8**



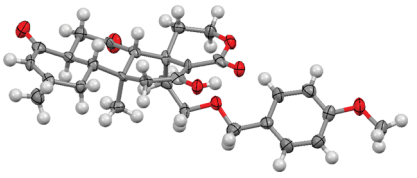


Figure 2. X-ray based ORTEP drawing of **6**. Spheres are drawn at the 65% probability level.

The transannular Michael reaction cascade was effected by treatment of **8** with TBAF in a solvent of DMF-THF at 4 °C for 2 h to give the tetracyclic **6** in 87% yield (Scheme 6). Two bonds, two rings, and three consecutive stereocenters (including two all-carbon quaternary ones) were simultaneously formed in this reaction. Only one diastereomeric product was isolated, highlighting the stereoselective nature of this transannular process. The stereochemistry of **6** was determined by NMR spectroscopy and verified by X-ray crystallography (Figure 2).[23] Formation of **6** is consistent with an all-chair-like transition state for the transannular Michael reactions. However, this does not rule out the possibility of a transannular Diels–Alder reaction pathway.[24] These two mechanistic possibilities cannot be distinguished because the highly informative stereochemical information of one of the initially formed chiral centers (C9) was lost to tautomerization.

In summary, we developed a short synthesis of the densely functionalized and stereochemically complex carbocyclic core of norzoanthamine, which contained five consecutive stereocenters including two all-carbon substituted quaternary ones. The synthesis proceeded in 12 linear steps from ethyl acetoacetate and dimethyl-1,3-acetonedicarboxylate. Most of the reactions were carried out at a gram or multigram scale.[25] Highlights include the organocatalytic asymmetric intramolecular aldolization to enantioselectively synthesize the cyclohexenone and set the stereochemistry of the entire carbocyclic core, strategic inclusion of a lactone (i.e., **16**) to exploit the hidden symmetry of fragment **10**, regioselective alkylation through the intermediacy of a bis-enolate, and a highly stereoselective transannular Michael reaction cascade. Completing the synthesis of norzoanthamine and exploring the scope and stereochemical outcome of the transannular Michael reaction cascade are the focus of our current research.

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Supporting Information Available. Experimental details and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) Crystallographic data for **6** have been deposited with the Cambridge Crystallographic Data Centre (CCDC 841829), and copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

(24) See the discussion in ref 11n.

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