

Stereoselective Synthesis of the ABC Ring System of Norzoanthamine

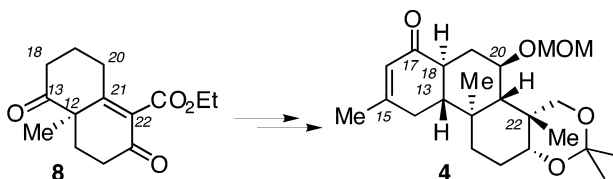
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ABSTRACT



An efficient synthesis of enone **4**, representing the ABC ring motif of norzoanthamine, is presented. The crucial C22 quaternary center was introduced via a stereoselective methylation of enone **8**. The trans-anti-trans relative configuration of the ABC framework of **4** was installed via a sequence of reactions that included a hydroboration and a modified Robinson annulation.

The zoanthamine alkaloids constitute a distinctive family of marine metabolites that have been isolated during the last 20 years from colonial zoanthids of the genus *Zoanthus* sp.¹ These natural products are characterized by a densely functionalized and stereochemically rich framework, as exemplified by the structures of zoanthamine (**1**),² norzoanthamine (**2**),³ and zoanthamide (**3**)⁴ (Figure 1), as well as by a wide spectrum of interesting biological activities.⁵ For example, compounds **1** and **3** were shown to inhibit phorbol myristate acetate (PMA)-induced inflammation in mouse ear,^{4,6} while **2** reportedly inhibits the growth of P-388 murine leukemia cells with an IC₅₀ value of 24 μg/mL.^{3b} More

significantly, norzoanthamine (**2**) represents a promising candidate for an antiosteoporotic drug due to its IL-6 inhibitory profile.^{1,7}

The combination of such challenging molecular architectures and potent biological profiles has spurred the development of novel synthetic strategies that rest primarily on Diels–Alder cycloaddition reactions.⁸ Nevertheless, despite such an effort none of these natural products has yet

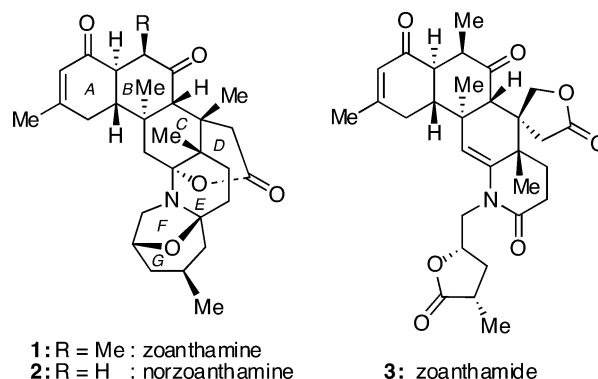


Figure 1. Selected structures of the zoanthamine alkaloids.

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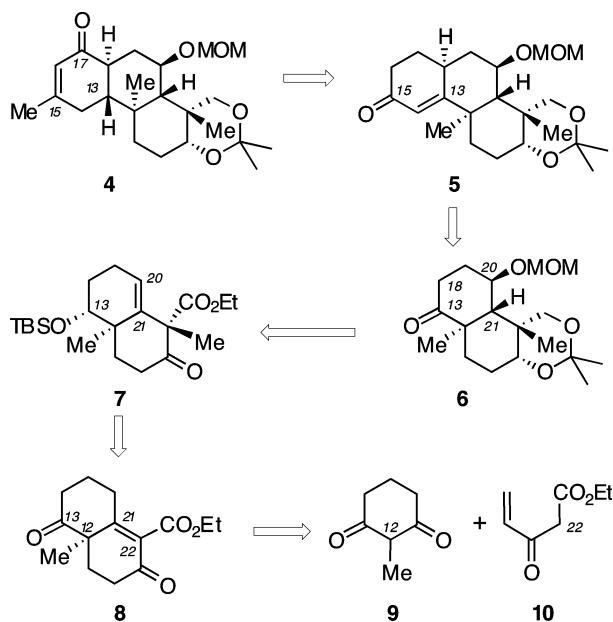


Figure 2. Retrosynthetic analysis of fragment **4**.

succumbed to a total synthesis.⁹ Herein we report a new synthetic strategy for these natural products. Our approach provides an efficient and stereoselective entry into the tricyclic ABC ring system of these complex alkaloids (represented as **4**, Figure 2) and paves the way toward their total synthesis.

The retrosynthetic approach toward fragment **4** is shown in Figure 2. We envisioned that construction of the fully functionalized A ring of **4** could invoke conjugate reduction of enone **5** followed by functionalization of the C15 and C17 centers (zoanthamine numbering). Enone **5** could be formed from fragment **6**, representing the BC ring system, by implementing a Robinson annulation strategy.¹⁰ The trans decalin motif of **6** was projected to arise from hydroboration/

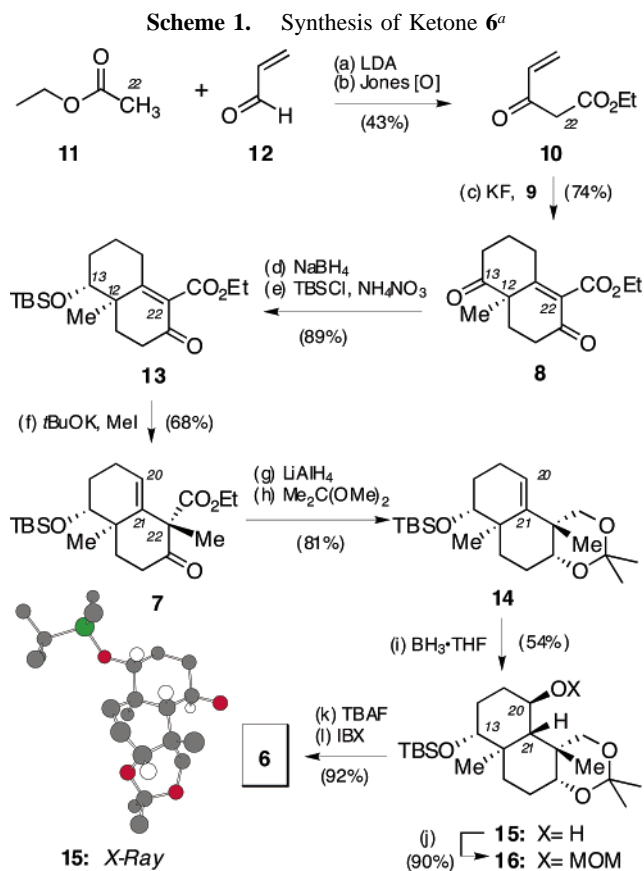
(5) For other alkaloids of the zoanthamine family, see: Rahman, A.-U.; Alvi, K. A.; Abbas, S. A.; Choudhary, M. I.; Clardy, J. *Tetrahedron Lett.* **1989**, *30*, 6825–6828. Daranas, A. H.; Fernández, J. J.; Gavin, J. A.; Norte, M. *Tetrahedron* **1998**, *54*, 7891–7896. Nakamura, H.; Kawase, Y.; Maruyama, K.; Murai, A. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 781–787. Venkateswarlu, Y.; Reddy, N. S.; Ramesh, P.; Reddy, P. S.; Jamil, K. *Heterocycl. Commun.* **1998**, *4*, 575–580.

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^a Reagents and conditions: (a) 1.1 equiv of LDA, 1.5 equiv of **12**, -78°C , 1 h, 72%; (b) Jones [O], $0-25^{\circ}\text{C}$, 2 h, 60%; (c) 1.1 equiv of **10**, 1 equiv of **9**, 2.2 equiv of KF, MeOH, 25°C , 24 h, 74%; (d) 0.25 equiv of NaBH₄, EtOH, 0.5 h, -78°C , 90%; (e) 1.5 equiv of TBSCl, 3.0 equiv of NH₄NO₃, DMF, 30 h, $0-25^{\circ}\text{C}$, 99%; (f) 1.1 equiv of *t*-BuOK, 5.0 equiv of CH₂I₂, benzene, $0-25^{\circ}\text{C}$, 12 h, 68%; (g) 2 equiv of LiAlH₄, THF, 0°C , 2 h 85%; (h) 3.0 equiv of 2,2-dimethoxypropane, 0.01 equiv of CSA, CH₂Cl₂, 0.5 h, $0-25^{\circ}\text{C}$, 95%; (i) 1.5 equiv of BH₃·THF, THF, 24 h, 0°C , 90% (3:2 in favor of **15**); (j) 3.0 equiv of MOMCl, 4.0 equiv of DIPEA, $0-25^{\circ}\text{C}$, 24 h, 90%; (k) 2.0 equiv of TBAF, THF, 48 h, 50°C , 95%; (l) 2.0 equiv of IBX, CH₂Cl₂/DMSO (10:1), 48 h, $0-25^{\circ}\text{C}$, 97%.

oxidation of alkene **7** which, in turn, suggested enone **8** as its synthetic precursor. The latter structure can be formed by annealing 2-methyl-1,3-cyclohexanedione (**9**) with Nazarov reagent (**10**).¹¹ Herein, we disclose the results of our studies based on such strategic bond disconnections.

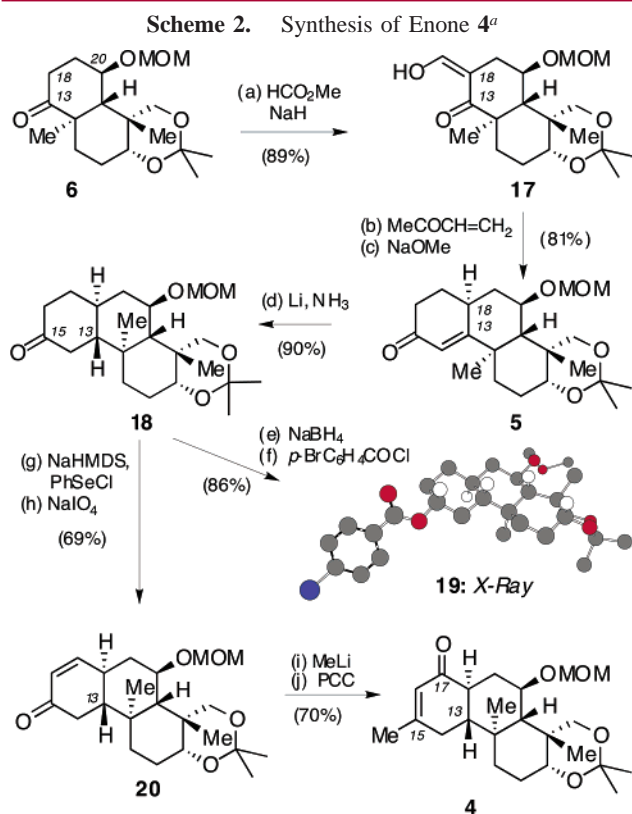
Our synthetic studies commenced with construction of enone **8**, which was formed by a KF-induced condensation of ketoester **10** with diketone **9** as previously described (Scheme 1).¹² Stereoselective reduction of the C13 carbonyl group of **8**¹³ and silylation of the resulting alcohol gave rise to enone **13** (two steps, 89% overall yield). When this silylation was performed in the presence of conventional bases, such as imidazole or pyridine, silyl ether **13** was

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contaminated with a disilylated adduct arising from concomitant reaction with the enone functionality. However, use of NH_4NO_3 in combination with TBSCl led to exclusive formation of **13**, which was isolated in 99% yield.¹⁴ Treatment of enone **13** with potassium *tert*-butoxide produced the extended enolate that upon reaction with methyl iodide formed compound **7** as a single isomer at the C22 center (zoanthamine numbering) (68% yield). The β -ketoester functionality of **7** was then reduced with LiAlH_4 ,¹⁵ and the resulting diol was converted to the corresponding acetonide **14** (two steps, 81% combined yield). Hydroxylation of the C20–C21 double bond ($\text{BH}_3\cdot\text{THF}/\text{H}_2\text{O}_2$) occurred predominantly from the more accessible β -face of **14** and afforded the desired *trans*-fused bicyclic motif of **15** together with its *cis* isomer (3:2 isomeric ratio in favor of **15**).¹⁶ Gratifyingly, the two isomers were easily separable by column chromatography and the relative stereochemistry of the major product **15** was unequivocally confirmed by X-ray analysis (Scheme 1; for clarity, only the hydrogens at chiral centers are shown).¹⁷ Treatment of **15** with MOMCl and DIPEA produced adduct **16** that after desilylation and oxidation gave rise to ketone **6** (three steps, 83% combined yield).

The conversion of ketone **6** to enone **4** is highlighted in Scheme 2. Our initial plan to alkylate the enolate of **6** with methyl vinyl ketone en route to a Robinson annulation sequence gave rise to a mixture of products, including isomers at the C18 center. This problem was circumvented by alkylating **6** with methyl formate to produce the β -keto-carbonyl adduct **17**, which underwent a smooth Michael addition in the presence of methyl vinyl ketone and triethylamine.¹⁸ Subsequent treatment with NaOMe led to a Robinson annulation with concomitant removal of the formyl group, thereby affording **5** as a single isomer at the C18 center (72% combined yield). Reduction of enone **5** with lithium in liquid ammonia gave rise to ketone **18** (90% yield). Unambiguous structural proof of compound **18** was obtained after derivatization to the corresponding *p*-bromobenzoate **19**, which upon recrystallization from methanol/water yielded



^a Reagents and conditions: (a) 2.0 equiv of NaH, HCO_2Me (excess), THF/PhMe (1:1), 0–25 °C, 24 h; (b) 1.5 equiv of $\text{MeCOCH}=\text{CH}_2$, 4.0 equiv of Et_3N , CH_2Cl_2 , 2 h; (c) 5.0 equiv of NaOMe, MeOH, 0–25 °C, 24 h, 72% (three steps); (d) 3.0 equiv of Li, liq NH_3 , EtOH, THF, –78 °C, 4 h, 90%; (e) 2.0 equiv of NaBH_4 , EtOH, 0 °C, 0.5 h, 95% (4:1); (f) 1.5 equiv of *p*- $\text{BrC}_6\text{H}_4\text{COCl}$, 2.5 equiv of Et_3N , DMAP (cat.), CH_2Cl_2 , 0–25 °C, 1 h, 90%; (g) 1.2 equiv of NaHMDS, 1.1 equiv of PhSeCl, –78 °C, 75%; (h) 2.0 equiv of NaIO_4 , $\text{H}_2\text{O}/\text{THF}$ (1:2), 25 °C, 92%; (i) 1.2 equiv of MeLi, Et_2O , 0 °C, 0.5 h, 90%; (j) 2 equiv of PCC, 3 Å MS, CH_2Cl_2 , 2 h, 0 °C, 78%.

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(16) The functionality at the C13 center was found to be crucial to the diastereomeric outcome of this hydroxylation reaction. For example, the *cis* decalin was obtained as a major product upon hydroxylating a substrate having a ketal functionality at the C13 center. See also: Gool, M. V.; Vandewalle, M. *Eur. J. Org. Chem.* **2000**, 3427–3431.

(17) CCDC-226516 (**15**) and CCDC-226517 (**19**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

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crystals suitable for X-ray analysis (Scheme 2; for clarity, only the hydrogens at chiral centers are shown).¹⁷ This study confirmed the desired *trans*-anti-*trans* stereorelation of the tricyclic motif of **19**.

Introduction of the desired functionalities on the A ring of **18** was accomplished by a NaHMDS-promoted phenylselenenylation followed by oxidation and elimination of the resulting selenide to produce enone **20** in 69% yield.¹⁹ The latter compound was treated with methyllithium and the resulting tertiary alcohol was subjected to a PCC-mediated oxidative rearrangement to produce enone **4** (two steps, 70% combined yield),²⁰ which represents a fully functionalized ABC tricyclic motif of norzoanthamine.

In summary, we present herein an efficient synthesis of the ABC ring framework **4** of norzoanthamine. The approach

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rests upon a stereocontrolled methylation of β -ketoester **13**, that establishes the critical C22 quaternary center. Other key steps include a stereoselective hydroxylation of alkene **14** and a modified Robinson annulation that set the desired relative stereochemistry of this scaffold.

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Supporting Information Available: Synthetic procedures and spectroscopic data, including ^1H and ^{13}C NMR spectra, for compounds **4–8** and **13–20**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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