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Stereoselective Synthesis of the ABC Ring System of Norzoanthamine

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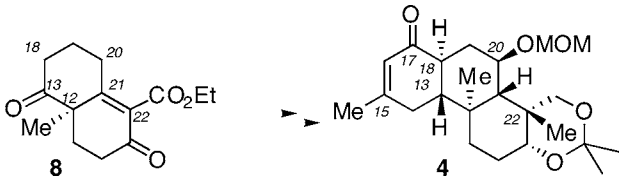
ABSTRACT



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 IC_{50} 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

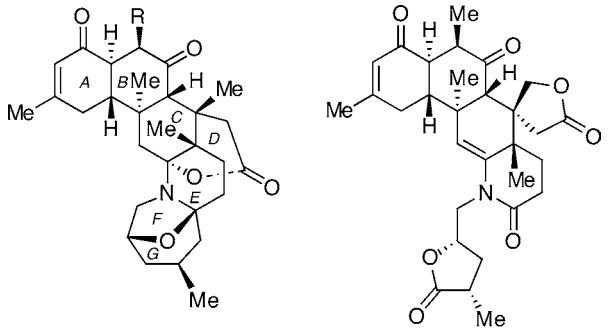


Figure 1. Selected structures of the zoanthamine alkaloids.

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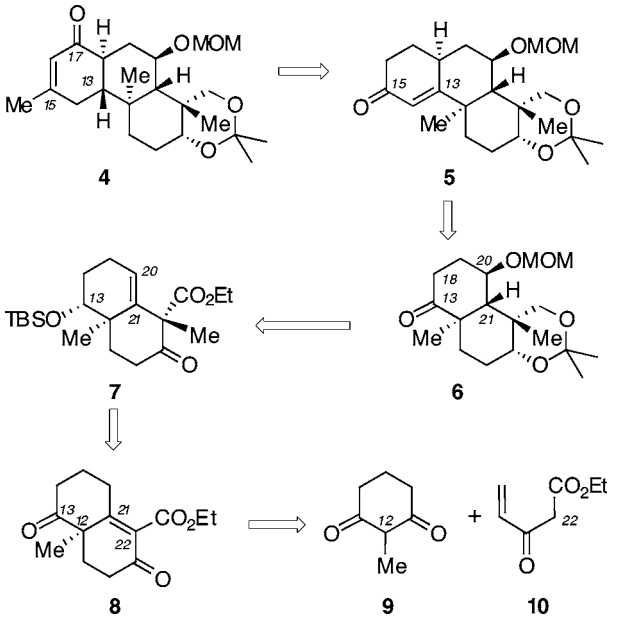
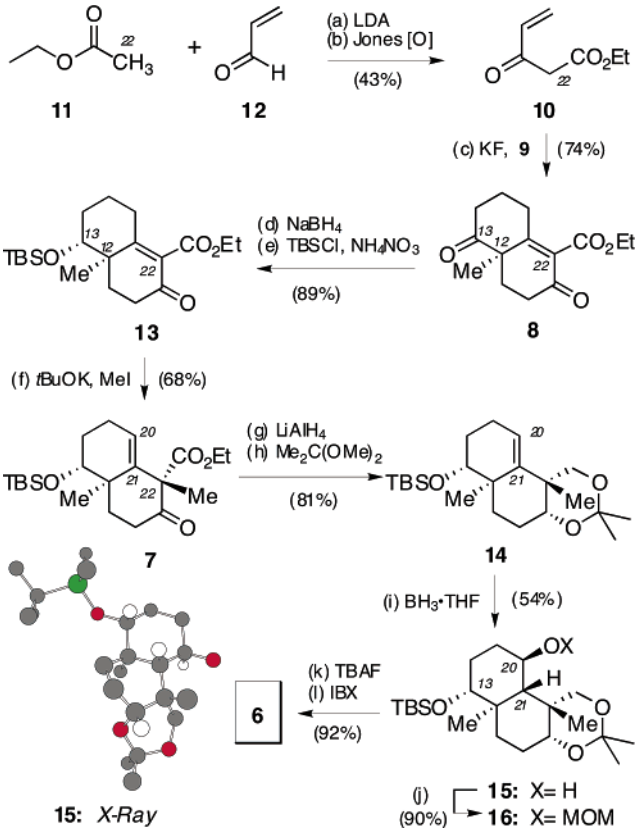


Figure 2. Retrosynthetic analysis of fragment **4**.

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/

Scheme 1. Synthesis of Ketone **6**[a]



[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 °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 $NaBH_4$, EtOH, 0.5 h, −78 °C, 90%; (e) 1.5 equiv of TBSCl, 3.0 equiv of NH_4NO_3, DMF, 30 h, 0−25 °C, 99%; (f) 1.1 equiv of *t*-BuOK, 5.0 equiv of CH_3I, benzene, 0−25 °C, 12 h, 68%; (g) 2 equiv of $LiAlH_4$, THF, 0 °C, 2 h 85%; (h) 3.0 equiv of 2,2-dimethoxypropane, 0.01 equiv of CSA, CH_2Cl_2, 0.5 h, 0−25 °C, 95%; (i) 1.5 equiv of BH_3·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 °C, 24 h, 90%; (k) 2.0 equiv of TBAF, THF, 48 h, 50 °C, 95%; (l) 2.0 equiv of IBX, CH_2Cl_2/DMSO (10:1), 48 h, 0−25 °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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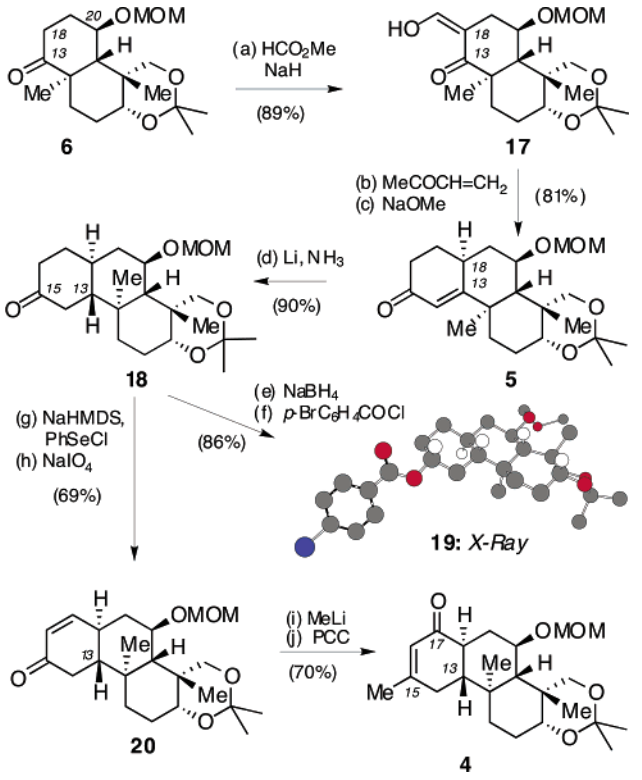
(10) For a general review in annulation chemistry, see: Jung, M. E. *Tetrahedron* **1976**, *32*, 3−31.

(11) Nazarov, I. N.; Zavyalov, S. I. *Zh. Obshch. Khim.* **1953**, *23*, 1703; Engl. Trans. **1953**, *23*, 1793−1794; *Chem. Abstr.* **1954**, *48*, 13667h. Zibuck, R.; Streiber, J. M. *Org. Synth.* **1993**, *71*, 236−241.

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 (BH_3·THF/H_2O_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-ketocarbonyl 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

Scheme 2. Synthesis of Enone **4**[a]



[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 $MeCOCH{=}CH_2$, 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*-BrC_6H_4COCl, 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 $NaIO_4$, H_2O/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%.

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 phenylselenylation 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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(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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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 ^{1}H 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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