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Enantioselective Synthesis of the ABC Ring Motif of Norzoanthamine Based on Asymmetric Robinson Annulation Reactions

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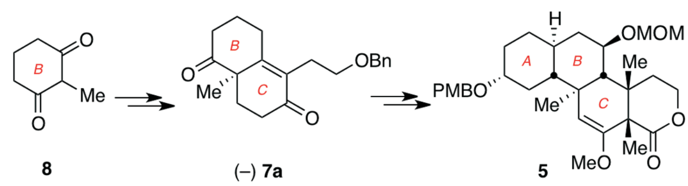
ABSTRACT



An enantioselective strategy for the synthesis of tetracyclic motif 5, representing the northern fragment of norzoanthamine, is presented. Key to the strategy is the use of two asymmetric Robinson annulation reactions that produce the tricyclic ABC ring system with excellent stereoselectivity. Further functionalization at the periphery of the C ring produces compound 5 containing six contiguous stereocenters of the natural product.

The zoanthamine alkaloids constitute a class of marine natural products that have been isolated from colonial zoanthids of the genus *Zoanthus sp.*[1] These compounds are structurally defined by a densely functionalized and stereochemically rich scaffold, as shown with the structures of zoanthamine (**1**),[2] norzoanthamine (**2**)[3] and zoanthamide (**3**)[4] (Figure 1).

In addition to their impressive chemical architecture, the zoanthamines also display an attractive spectrum of biological activities. For instance, several family members were found to inhibit thrombin-, collagen-, and arachidonic acid-induced inflammation of platelets[5] and exhibit potent cytotoxicity against a number of cancer cell lines.[4,6] In addition, **1** and **3** inhibit inflammation induced by myristate acetate in mouse ears,[4,6a] while **2**, the demethylated version of **1**, has been found to exhibit promising antiosteoporotic properties in vivo in ovariectomized mice.[1,7]

The combination of challenging structures and potent bioactivities has prompted the design of various synthetic approaches by several groups.[8,9] These efforts led to two total syntheses of norzoanthamine by the Miyashita[10] and

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Kobayashi[11] groups. More recently, Miyashita and coworkers also reported the total synthesis of zoanthenol via oxidation of norzoanthamine hydrochloride.[12]

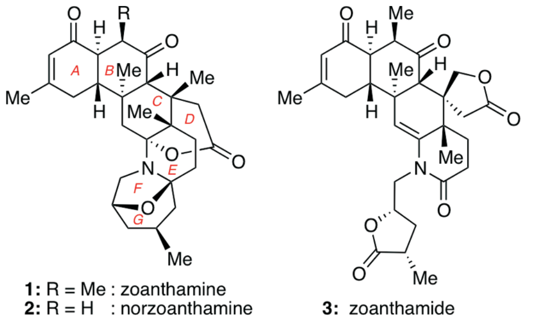

Figure 1. Structures of selected zoanthamine natural products.

Inspection of the polycyclic norzoanthamine framework suggests that this compound can be dissected in two main fragments: a rigid tricyclic ABC core and a bisaminal motif that forms the DEFG part. Arguably, the most significant challenges for the synthesis of **2** are the construction of the AB trans decalin system and the functionalization of the stereochemically rich C ring. In fact, both Miyashita and Kobayashi have shown that the synthesis of **2** could be achieved from condensation of compound **4** in which a partially folded C1–C8 side chain has been attached to a fully functionalized ABC motif (Figure 2). With this in mind, we focused our efforts on the development of an enantioselective synthesis of the ABC ring fragment, represented here by structure **5**. In the retrosynthetic direction, **5** can derive from **6** after functionalization at the periphery of the C ring and stereocontrolled installation of the C9 methyl group. Construction of the carbon backbone of **6** could be accomplished with two Robinson annulation reactions that would form rings A and C. Along these lines, reaction between **8** and **9a** promoted by a chiral reagent would produce bicyclic motif **7a** enantioselectively.[13] It should be noted that in a previous study we attempted the synthesis of the ABC ring fragment of **1** using bicyclic motif **7b** that was readily available from condensation of **8** with **9b**.[14] However, implementation of this strategy to an enantioselective synthesis of **7b** proved to be lengthy and inefficient.[15]

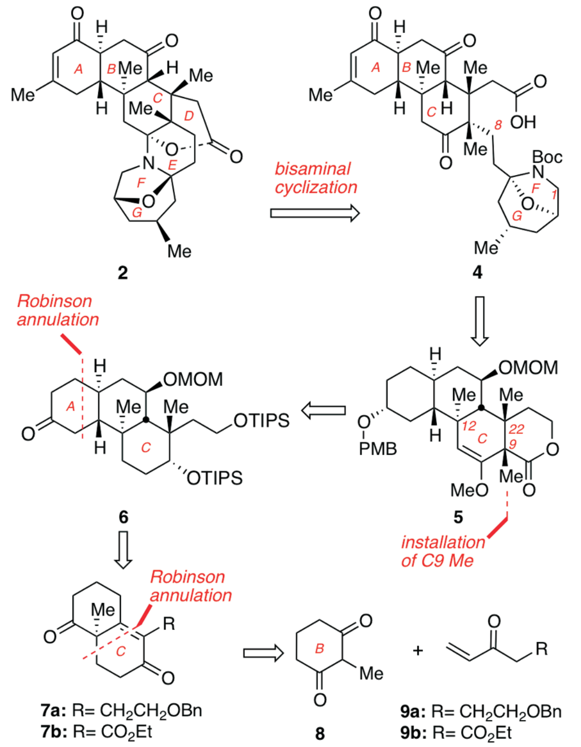

Figure 2. Retrosynthetic analysis of norzoanthamine (**2**).

The synthesis of the BC ring system of **2** is shown in Scheme 1. Compound **10**, the required precursor for the asymmetric Robinson annulation, was produced in high yield after Michael addition of 2-methyl-1,3-cyclohexadione (**8**) to enone **9a**. The latter was synthesized from butane-1,4-diol according to a reported protocol.[16] Treatment of **10** with D-Phe and R-CSA in DMF[17] gave the annulated product **7a**, containing the C12 quaternary center, in 75% yield. The enantioselectivity of this reaction was 85% ee as determined by the chiral shift agent Eu(hfc)$_3$.[18] The C13 carbonyl group of **7a** was selectively

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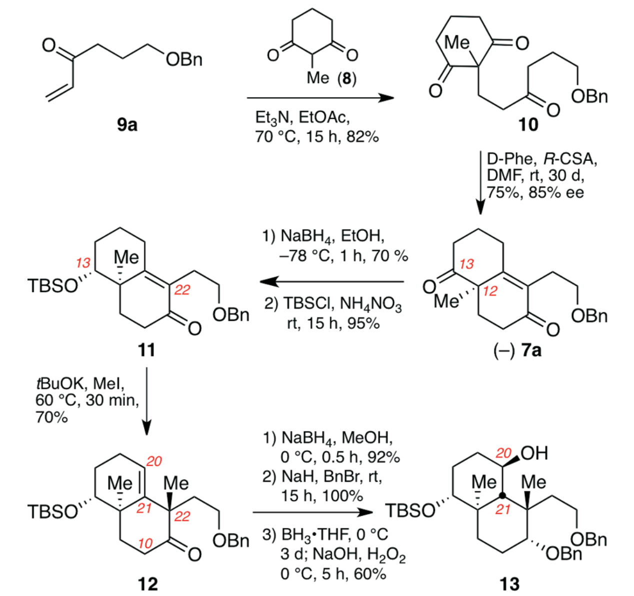
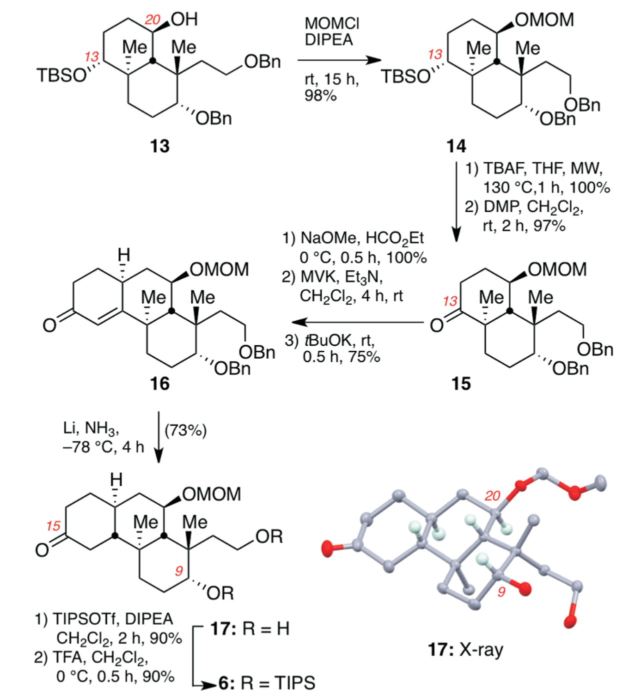
reduced with sodium borohydride, and the resulting alcohol was protected as a silyl ether to afford enone **11** (67% overall yield). The second quaternary center at C22 was then installed. Methylation of **11** with *t*-BuOK produced **12** as a single stereoisomer. Reduction of the carbonyl group of **12** gave an alcohol, which was protected as a benzyl ether. Stereoselective hydroboration of the C20–C21 alkene occurred at 0 °C over the course of 72 h to give alcohol **13** (55% yield over three steps).

Scheme 1. Enantioselective Synthesis of Fragment **13**



With the fully functionalized BC ring system in hand, we shifted our attention to the stereoselective construction of the *trans*,*anti*,*trans*-fused perhydrophenanthrene skeleton of norzoanthamine (Scheme 2). Alcohol **13** was protected as the corresponding MOM ether in 98% yield. The C13 silyl ether of **14** was then deprotected using TBAF under microwave (MW) radiation at 130 °C for 1 h. It is worth noting that conventional heating in THF under reflux gave only a 50% conversion after 5 days. The resulting C13 alcohol was oxidized using Dess–Martin periodinane (DMP) to provide compound **15** in 97% yield over two steps. Our initial attempts to react **15** with methyl vinyl ketone (MVK) using a strong base led to a complex mixture of products. To circumvent this problem, we converted **15** to a β-keto aldehyde that underwent a smooth Michael addition with MVK and triethylamine.[19] The Robinson cyclization proceeded cleanly with *t*-BuOK to provide the tricyclic motif **16** in 75% yield over three steps. The final *trans,anti,trans*-decalin **17** was synthesized after stereoselective reduction of **16** using lithium–ammonia conditions. Under these reductive conditions, both benzyl ethers were cleaved, producing diol **17**. The chemical structure and stereochemistry of compound **17** were unambiguously confirmed via single-crystal X-ray analysis.[20]

Scheme 2. Stereoselective Synthesis of *trans*,*anti*,*trans*-Fused Perhydrophenanthrene Fragment **6**



Conversion of diol **17** to the corresponding di-TIPS ether **6** was achieved in two steps: (a) exhaustive silylation of both ketone and diol functionalities of **17** and (b) deprotection of the silyl enol ether using TFA (80% yield overall). This two-step strategy was necessary because the C15 ketone was shown to be more reactive over the C9 secondary alcohol.

The next task was the complete functionalization of the C ring including the installation of the last quaternary center at C9 (Scheme 3). To this end, the C15 carbonyl group of **6** was stereoselectively reduced at –78 °C,[21] and the resulting equatorial alcohol was protected as the *p*-methoxybenzyl ether. The two silyl ether groups were then removed using TBAF to provide diol **18** (42% yield over three steps). Selective TBDPS monoprotection of the primary alcohol followed by DMP oxidation of the C9 hydroxyl group afforded ketone **19** in excellent yield (82% yield over two steps).

Conversion of **19** to ketone **22** was accomplished via a sequence of five steps that included (a) triflation of the C9

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(20) CCDC-820554 (**17**) and CCDC-820555 (**5**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/const/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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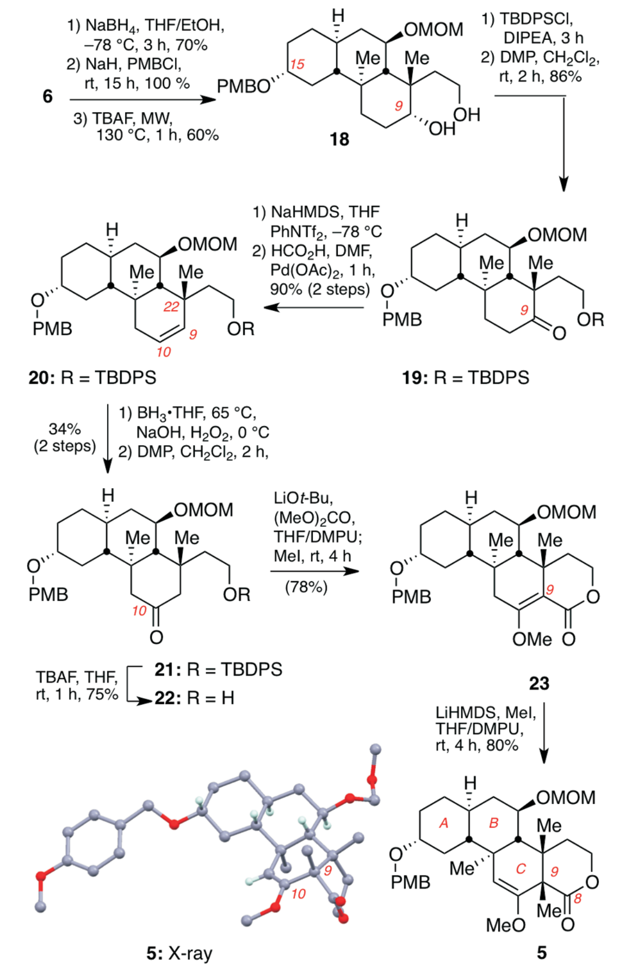
Scheme 3. Stereoselective Synthesis of the ABC Ring System **5**



ketone; (b) reduction of the resulting vinyl triflate using formic acid and palladium(II) acetate to give alkene **20**; (c) hydroboration/oxidation of the C9–C10 alkene; (d) oxidation of the resulting alcohol to ketone **21**; and (e) deprotection of the primary silyl ether (23% yield over five steps). We anticipated that, by virtue of steric hindrance, the C22 quaternary carbon center would lead to a regioselective hydroboration reaction in favor of the desired product (hydroxylation at C10). Indeed, this hydroxylation produced, after further oxidation, a 2:1 mixture of ketones **21** and **19** (34% and 17% yield, respectively). The undesired ketone **19** can be recycled to yield the desired product **21**. Treatment of **22** with *t*-BuOLi as base, dimethyl carbonate, and iodomethane yielded methyl enol ether **23** that, upon alkylation with LiHMDS and iodomethane, formed the desired compound **5** (two steps, 62% yield).[10a] The absolute stereochemistry of **5** was confirmed by single-crystal X-ray analysis.[20]

In conclusion, we have described an enantioselective approach to the fully functionalized ABC ring system of norzoanthamine, represented by compound **5**. Key to the strategy is a double Robinson annulation reaction that installs the C and A rings of this motif. The initial Robinson annulation (formation of the BC ring) proceeds with excellent enantioselectivity, setting the desired stereochemistry at the C12 quaternary group. A sequence of stereoselective transformations was then developed to install the five remaining stereocenters. The C8 lactone functionality could serve as an attachment point for the remaining side chain of norzoanthamine.

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Supporting Information Available. Experimental procedures, characterization data, and copies of the ^{1}H and ^{13}C NMR of all new compounds, as well as X-ray data of compounds **5** and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.