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Synthetic Study of (−)-Norzoanthamine: Construction of the ABC Ring Moiety**

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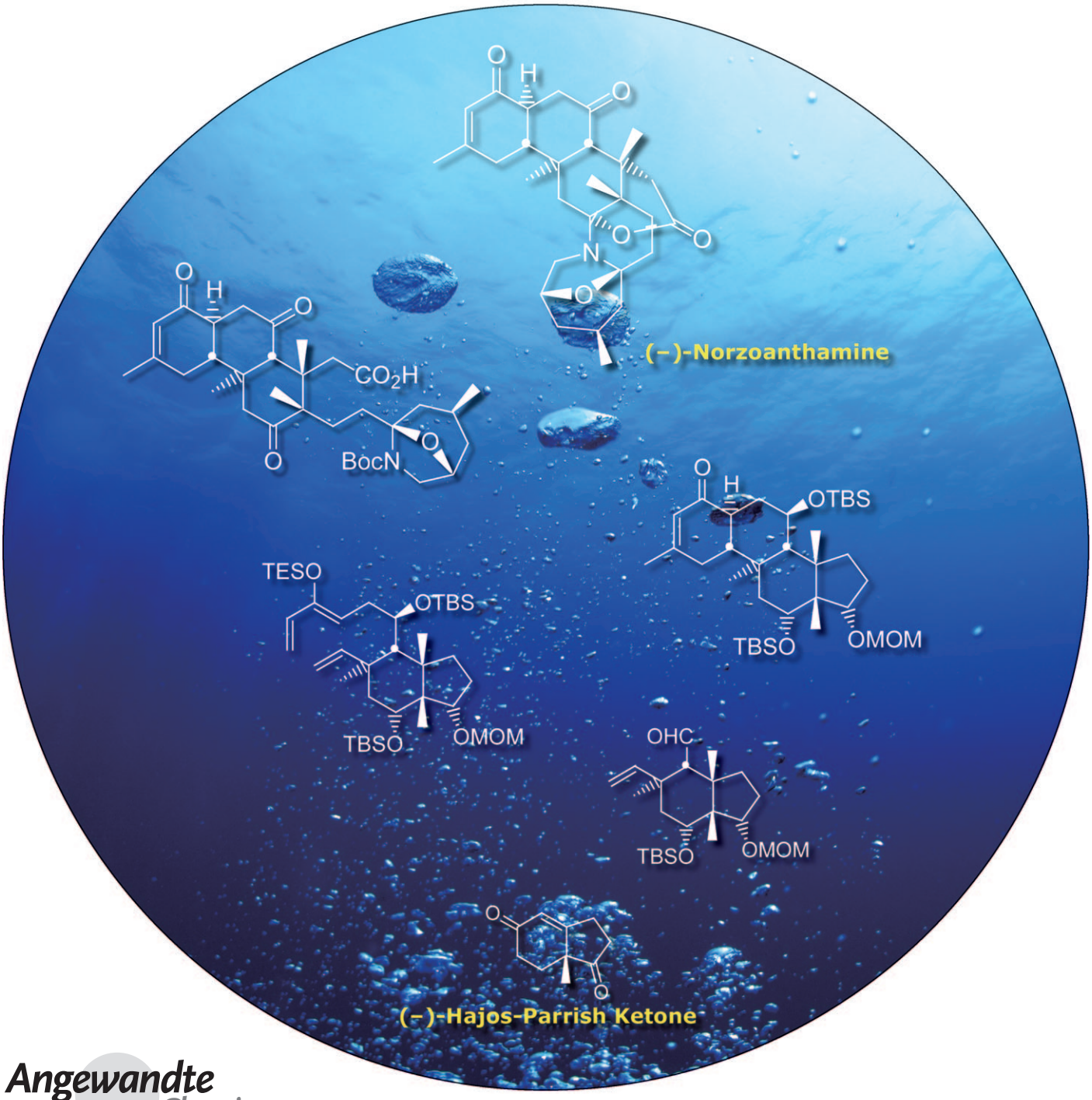
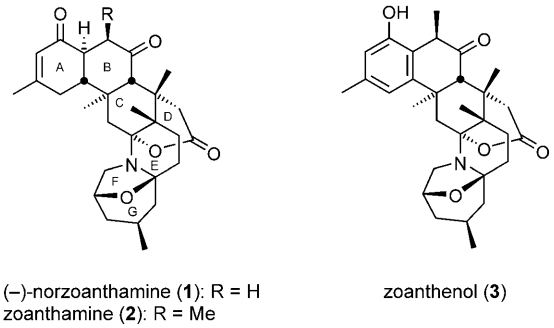
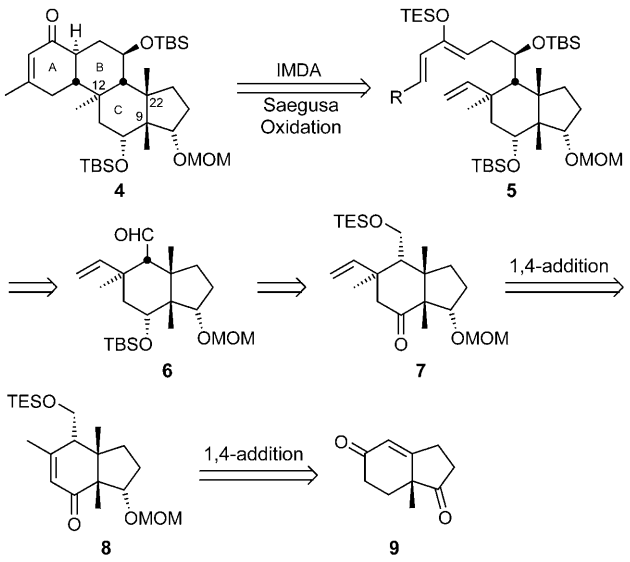


Zoanthamines are members of a marine alkaloid family of compounds that display potent biological activities. In particular, (−)-norzoanthamine (**1**) is considered to be a promising anti-osteoporotic drug candidate because it suppresses the loss of bone weight and strength in ovariectomized mouse model (Scheme 1).[1] In addition to the significant biological activity, zoanthamines have attracted a great deal of attention from a synthetic point of view owing to their complex and unique heptacyclic structure. Indeed, a number of research groups, including ourselves, have been investigating synthetic routes to the zoanthamine family of compounds.[2–4] So far, only the research group of Miyashita has succeeded in the total synthesis of (−)-norzoanthamine.[4]



Scheme 1. Selected zoanthamine alkaloids.



Scheme 2. Retrosynthetic analysis. MOM = methoxymethyl, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl.

The characteristic structural features of (−)-norzoanthamine are: 1) a bisaminal skeleton in the CDEFG ring moiety, 2) a *trans*-decalin motif in the AB rings, and 3) a stereochemically dense C ring. As the bisaminal skeleton has been reported to be rather unstable,[1b,c] we reasoned that total synthesis could be achieved by forming this moiety at a late stage of the synthesis. In this regard, we initially developed the formation of the bisaminal skeleton. Indeed, we have already reported an excellent methodology by demonstrating a tandem cyclization to give a simplified model of zoanthamines.[3] With this methodology established, we embarked on the total synthesis of (−)-norzoanthamine. Herein we focus on the construction of the ABC ring system by demonstrating the synthesis of **4** from the enantiopure (−)-Hajos–Parrish ketone **9** (Scheme 2),[5] and the following paper describes the completion of the total synthesis of (−)-norzoanthamine.[6]

As mentioned earlier, construction of the ABC ring system is one of the major obstacles to the total synthesis of (−)-norzoanthamine. Consequently, most of the previous investigations have mainly focused on this moiety. The most challenging synthetic problem is the synthesis of the stereochemically dense C ring, which possesses three asymmetric quaternary carbon centers (C9, C12, and C22). Contrary to the impressive total synthesis by Miyashita and co-workers,[4] our basic strategy involves an initial formation of the C ring moiety with appropriate substituents that would be necessary for the construction of the AB and DEFG ring moieties. The key intermediate **6** might be derived from ketone **7**, and the quaternary chiral center at C12 could be constructed by a 1,4-addition of vinyl cuprate reagent to enone **8**. The methyl group at C22 could be introduced in a *syn* fashion by 1,4-addition to the (−)-Hajos–Parrish ketone **9**, in which one of the three quaternary methyl groups of the C ring is already installed. Although there is no precedent concerning the 1,4-addition to **9**, we expected it to proceed by analogy to the Wieland–Miescher ketone reaction.[7] We envisaged that the AB ring moiety could be constructed in the desired *trans* fashion by an intramolecular Diels–Alder reaction (IMDA).[8] Furthermore, the requisite diene unit could be introduced by the addition of a pentadienyl anion species onto the aldehyde **6**.[9] The cyclopentanol moiety in **6** might serve as a handle for annelating the DEFG ring system after oxidative cleavage.

Our first task was a stereoselective construction of the asymmetric quaternary carbon center at C22 (Scheme 3). Treatment of the (−)-Hajos–Parrish ketone **9** (>99% *ee*) with Gilman reagent, and subsequent trapping of the enolate in situ by the addition of TMSCl and Et_3N, provided the silyl enol ether as a single diastereomer. The 1,4-addition occurred from the less hindered β face in a stereoselective manner. β-Selective reduction of the remaining carbonyl group with $LiAlH_4$, then quenching with aqueous HCl, and subsequent protection as the TBS ether, afforded ketone **10** in 90% overall yield from **9**. The relative stereochemistry was determined by NOE experiments.[10] Regioselective forma-

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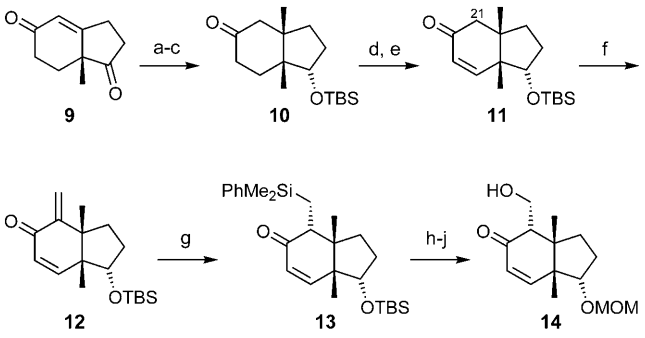
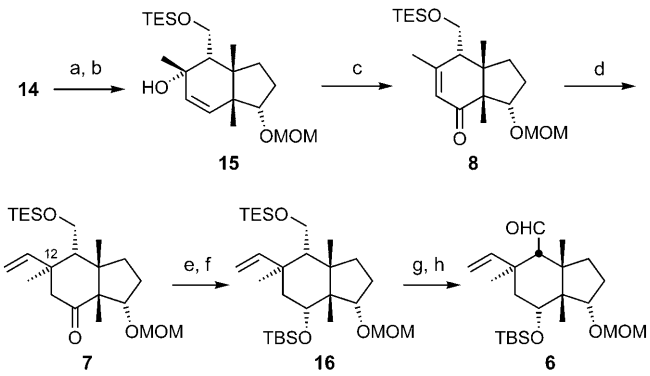


Scheme 3. Synthesis of primary alcohol **14**. Reagents and conditions: a) Me_2CuLi, Et_2O, −78→0 °C; then NEt_3, TMSCl, 0 °C; b) $LiAlH_4$, THF, −78 °C; then aq. HCl (1 N); c) TBSCl, imidazole, DMAP, DMF, RT, 90% (over 3 steps); d) TMSOTf, NEt_3, CH_2Cl_2, 0 °C; e) cat. $Pd(OAc)_2$, O_2, DMSO, 60 °C, 92% (over 2 steps); f) LDA, paraformaldehyde, THF, DMF, −78 °C→RT, 87%; g) $PhMe_2SiLi$, CuCN, THF, −78 °C; then SiO_2, RT, 95%; h) $HBF_4{\cdot}OEt_2$, CH_2Cl_2, 0 °C; i) MOMCl, iPr_2NEt, DMAP, DCE, 60 °C; j) aq. H_2O_2, $NaHCO_3$, KF, THF, MeOH, 0 °C→RT, 93% (over 3 steps). DCE = 1,2-dichloroethane, DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide, LDA = lithium diisopropylamide, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.



Scheme 4. Synthesis of aldehyde **6**. Reagents and conditions: a) TESCl, imidazole, DMAP, CH_2Cl_2, 0 °C, quant.; b) MeLi, THF, −78 °C, 96%; c) PDC, benzene, reflux, 39%; d) vinyl lithium, CuCN, Et_2O, −78→0 °C, 83% (d.r. 13:1); e) DIBAL-H, CH_2Cl_2, −78 °C; f) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, quant. (over 2 steps); g) PPTS, MeOH, RT; h) DMP, CH_2Cl_2, 0 °C, 95% (over 2 steps). DIBAL-H = diisobutylaluminum hydride, DMP = Dess–Martin periodinane, PDC = pyridinium dichromate, PPTS = pyridinium *p*-toluenesulfonate

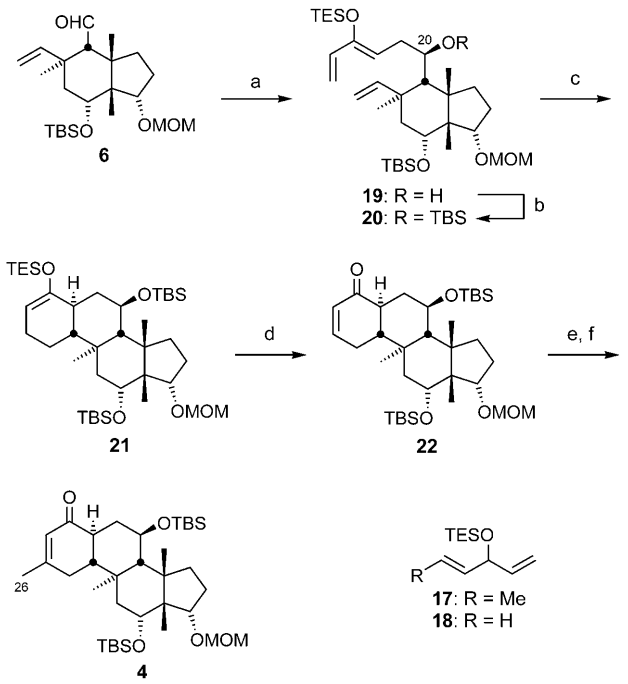
tion of silyl enol ether from **10** and subsequent Saegusa oxidation gave enone **11**.[11]

We next examined the introduction of a hydroxymethyl group at C21 of enone **11**. Initial attempts at the direct aldol reaction with paraformaldehyde did not stop at the aldol stage, but resulted in the formation of dehydrated *exo* olefin **12** in high yield. Other methods, such as the $Yb(OTf)_3$-mediated aldol reaction in aqueous solution,[12] were also unsuccessful owing to low yields as well as low stereoselectivities. We then considered an alternative route involving enone **12**. Exposure of enone **12** to $(PhMe_2Si)_2Cu(CN)Li_2$ and subsequent addition of silica gel led to γ-silyl ketone **13** as a single diastereomer. Highly diastereoselective protonation of the resulting enolate proceeded from the less hindered convex face to control the requisite *R* configuration at the C21 position. The configuration was determined by NOESY experiments that showed a correlation between the C21 hydrogen atom and the two angular methyl groups.[10] The phenyldimethylsilyl group in **13** was converted into a fluorodimethylsilyl group by treatment with $HBF_4{\cdot}OEt_2$. During this operation, concomitant deprotection of the silyl group afforded the secondary alcohol, which was protected as the MOM ether. Finally, oxidation with H_2O_2 gave the requisite hydroxymethylated enone **14**.[13] Although introduction of a hydroxymethyl group into **11** required five steps, **14** was obtained in a high overall yield (77%) with complete stereoselectivity.

Scheme 4 shows the final stage of the synthesis of the C ring. This most critical step secured the construction of the third quaternary carbon center at C12. Protection of the primary hydroxy group in enone **14** and subsequent 1,2-addition of the resulting enone afforded tertiary alcohol **15** in excellent yield as a single diastereomer. Oxidative rearrangement of **15** using PDC provided the desired enone **8** in 39% yield along with a substantial amount of the dehydrated diene, which might be attributed to steric hindrance at the concave face.

To construct the third quaternary carbon center at C12, 1,4-addition of enone **8** with vinyl cuprate was then performed. The reaction of **8** with the corresponding lithium cyanocuprate resulted in the formation of the desired ketone **7**, which bears the three requisite quaternary carbon centers on the C ring, in 83% yield with high diastereoselectivity (d.r. 13:1). As expected, this conjugate addition occurred from the more accessible convex face of the *cis*-fused ring system. Face selective reduction of the carbonyl group in ketone **7** and subsequent protection of the resulting hydroxy group as the TBS ether afforded **16** as a single diastereomer. After the selective cleavage of the primary TES group, the resulting alcohol was subjected to a Dess–Martin periodinane oxidation[14] to give aldehyde **6**—a key intermediate used for the preparation of the precursor of the intramolecular Diels–Alder reaction.

The synthesis of an appropriately functionalized ABC ring system was carried out by using an IMDA reaction as a key step (Scheme 5). To unite aldehyde **6** and the siloxy diene moiety, we utilized the nucleophilic addition of the allyl lithium generated from unsymmetrical siloxy diene **17**. It was hoped that this reaction would furnish the requisite precursor of the Diels–Alder reaction as employed by Oppolzer et al.[15] Unfortunately, all attempts at reactions involving the lithium species derived from **17** were unsuccessful and only gave a mixture of regioisomers. Based on these results, we decided to use allyl lithium generated from the symmetrical siloxy diene **18**. The missing methyl group at C26 could be introduced at a later stage of the synthesis. Treatment of aldehyde **6** with allyl lithium derived from **18** in THF at −78 °C afforded the desired hydroxy diene **19** in excellent yield as a single diastereomer. The hydroxy group at C20, which generates a chiral center by nucleophilic addition, eventually becomes a carbonyl carbon. However, we were aware that the stereochemistry of the hydroxy group would affect the Diels–Alder reaction. The



Scheme 5. Construction of the AB rings by an IMDA reaction. Reagents and conditions: a) **18**, *s*BuLi, THF, −78 °C, 93 %; b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 91 %; c) pyridine, toluene, 210 °C; d) cat. $Pd(OAc)_2$, DMSO, 70 °C, 69 % (over 2 steps); e) MeLi, $CuBr{\cdot}SMe_2$, TMSCl, HMPA, THF, −78 → −42 °C; f) $Pd(OAc)_2$, CH_3CN, 60 °C, 78 % (over 2 steps). HMPA = hexamethylphosphoramide.

R configuration as shown was determined after an IMDA reaction. After protection of **19** as the TBS ether, we were able to examine the crucial IMDA process. To our delight, the IMDA reaction of triene **20** proceeded at 210 °C in toluene, in the presence of a trace amount of pyridine as an acid scavenger, and gave the desired silyl enol ether **21**.[16] The silyl enol ether **21** was found to be relatively unstable, and was subsequently subjected to Saegusa oxidation under modified reaction conditions to obtain enone **22** in 69 % yield (over 2 steps) as a single diastereomer. The desired *trans*-decalin structure was confirmed by NOE and NOESY experiments,[10] which revealed that the key IMDA reaction might proceed through an exclusive *exo*-chair transition state, as anticipated. NMR experiments also lead to the determination of the *R* configuration at C20, inferring that the siloxy group at C20 occupies a favorable pseudoequatorial position in the transition state of the IMDA process. Finally, introduction of the methyl group at C26 by means of 1,4-addition and subsequent Saegusa oxidation afforded α,β-unsaturated ketone **4** bearing the appropriately functionalized ABC rings in good overall yield.

In conclusion, we have synthesized an ABC ring moiety of (−)-norzoanthamine. The present approach highlights the following important points: 1) all stereogenic centers in the C ring were constructed with complete stereoselectivity starting from the (−)-Hajos–Parrish ketone, (2) the intramolecular Diels–Alder reaction provided a requisite *trans*-decalin scaffold with complete diastereoselectivity. The cyclopentanol moiety in **4** might serve as a handle for annelating the DEFG ring in the total synthesis of (−)-norzoanthamine, which will be described in the following communication.

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