

Synthetic Studies of Norzoanthamine. Preparation of the Diene-yne-diene Precursor of an ABC-ring Fragment

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The diene-yne-diene precursor of the ABC-ring fragment of norzoanthamine, a bioactive alkaloid from the colonial zoanthid *Zoanthus* sp., was prepared.

Norzoanthamine (**1**)¹ is a zoanthamine-type alkaloid² that was identified in the colonial zoanthid *Zoanthus* sp. in 1995. Zoanthamines have interesting biological activities.^{1–3} In particular norzoanthamine hydrochloride suppresses the decreases in bone weight and strength in ovariectomized mice without serious side effects.^{1c,4} Thus, norzoanthamine (**1**) is a good candidate for a potential anti-osteoporotic drug. Most zoanthamines have a complicated heptacyclic ring system with three contiguous quaternary centers in the C ring and an amino acetal. Moreover, since they are regarded as terpenoids based on their molecular formulas, zoanthamines are thought to have a polyketide-type biogenetic pathway (**3** → **2**).^{1b,1c} The biological activities, structural features and biogenesis of norzoanthamine have attracted the attention of synthetic chemists.⁵ However, only one total synthesis of norzoanthamine (**1**) has been reported by Miyashita and co-workers in 2004.⁵ⁿ We report here the preparation of the diene-yne-diene precursor of the ABC-ring fragment of norzoanthamine (**1**).

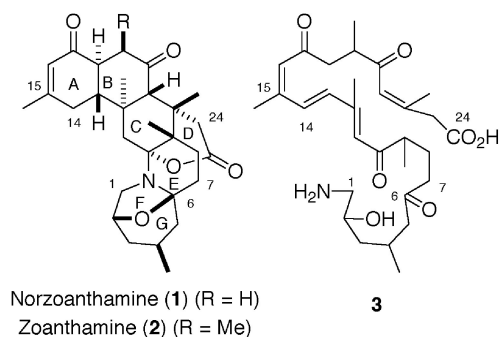
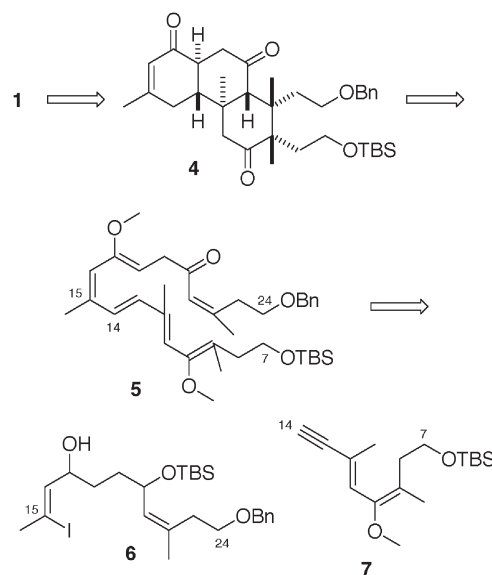


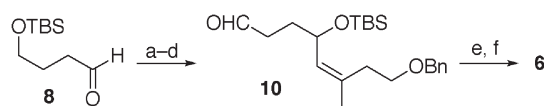
Figure 1.

Our strategy is shown in Scheme 1. Although some groups used the Diels–Alder reaction to produce an ABC-ring fragment,^{5a,5c,5m,5n} there is no strategy that involves a linear-carbon-chain intermediate. Therefore, we expected that the polyene fragment **5** or its derivatives might undergo sequential cyclizations⁶ to produce the ABC-ring fragment **4**. The polyene precursor would be prepared by the Pd-catalyzed coupling reaction between vinyl iodide **6** (C15–C24 fragment) and diene-yne **7** (C7–C14 fragment).

The synthesis of vinyl iodide **6** began with aldehyde **8**⁷ (Scheme 2). Vinyl iodide **9**⁸ was treated with *n*-BuLi, and the resulting lithiated **9** was added to **8** to give the allyl alcohol in 75% yield. Subsequent protection of the hydroxyl group of allyl alco-



Scheme 1. Retrosynthesis of norzoanthamine (**1**).

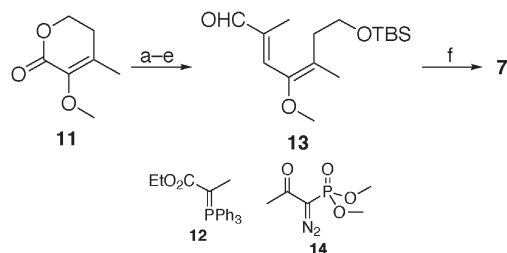


Scheme 2. Reagents and conditions: (a) **9**, *n*-BuLi, ether, -78°C , 75%; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2 , -78°C , quant.; (c) Al_2O_3 , hexane, rt, 97%; (d) PDC, MS4A, CH_2Cl_2 , rt, 82%; (e) 1-propynylmagnesium bromide, ether, -78°C , 94%; (f) Red-Al[®], ether, rt, then I_2 , ether/THF = 2/1, 0°C , 73%.

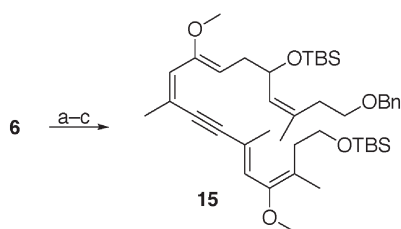
hol, selective desilylation and oxidation gave aldehyde **10**. Finally, addition of 1-propynylmagnesium bromide to **10**, (*Z*)-selective hydroalumination, and iodination produced vinyl iodide **6**.

The synthesis of diene-yne **7** began with methyl enol ether **11**.⁹ Reduction with DIBAL-H, followed by the Wittig reaction and protection of the resultant hydroxyl group, produced the ethyl ester (Scheme 3), which was reduced and oxidized to give aldehyde **13**. Finally, **13** was converted to diene-yne **7** in 69% yield by the Ohira–Bestmann procedure.

The synthesis of the diene-yne-diene fragment **15** began with the Sonogashira coupling reaction between vinyl iodide **6** and diene-yne **7**. This reaction produced the diene-yne-ene quantitatively, which was smoothly oxidized to the enone with Dess–Martin periodinane (DMP), although other oxidants gave complex mixtures (Scheme 4). Finally, (*Z*)-selective conversion of enone to the methyl enol ether with KHMDS and methyl fluoro-sulfonate in THF/HMPA produced the diene-yne-diene **15**¹⁰ in good yield. Diene-yne-diene **15** was very weak against acids,



Scheme 3. Reagents and conditions: (a) DIBAL-H, CH_2Cl_2 , -78°C ; (b) **12**, MeCN, reflux; (c) TBSCl, imidazole, DMF, rt, 49% (3 steps); (d) DIBAL-H, CH_2Cl_2 , -78°C , 82%; (e) MnO_2 , CH_2Cl_2 , rt, 91%; (f) **14**, K_2CO_3 , MeOH, rt, 69%.



Scheme 4. Reagents and conditions: (a) **7**, $\text{Pd}(\text{PPh}_3)_4$, CuI, Et_2NH , rt, quant.; (b) DMP, CH_2Cl_2 , rt, 78%; (c) KHMDS, FSO_3Me , THF/HMPA = 10/1, -78°C , 96%.

but could be isolated.

In conclusion, the diene-yne-diene precursor of an ABC-ring fragment of norzoanthamine (**1**) was prepared. Sequential cyclizations to give the ABC-ring fragment based on the biogenetic hypothesis are currently in progress in our laboratory.

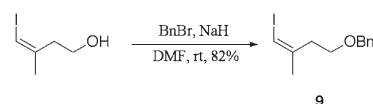
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- 9** was prepared by benzyl protection of the corresponding alcohol.



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- ^1H NMR (400 MHz, C_6D_6) of **15**: δ 7.35–7.08 (m, 5H), 6.71 (br s, 1H), 5.89 (br s, 1H), 5.47 (t, $J = 8.1$ Hz, 1H), 5.46 (t, $J = 8.1$ Hz, 1H), 4.64–4.62 (m, 1H), 4.36 (s, 2H), 3.62 (s, 3H), 3.56 (t, $J = 6.6$ Hz, 2H), 3.45–3.35 (m, 2H), 3.24 (s, 3H), 2.77–2.72 (m, 1H), 2.65–2.60 (m, 1H), 2.54–2.47 (m, 1H), 2.35–2.28 (m, 1H), 2.22 (s, 3H), 2.24–2.21 (m, 2H), 1.87 (s, 3H), 1.79 (s, 3H), 1.63 (s, 3H), 1.04 (s, 9H), 0.97 (s, 9H), 0.16 (s, 3H), 0.14 (s, 3H), 0.05 (s, 6H). The stereochemistry of **15** was determined by an NOE experiment.

