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

Taiji Irifune,*[†] Tomohiro Ohashi,[†] Takao Ichino,[†] Emi Sakai,[†] Kiyotake Suenaga,[†,#] and Daisuke Uemura[†,††]
[†]*Department of Chemistry, Graduate School of Science, Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464-8602*
[††]*Institute for Advanced Research, Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464-8602*

(Received April 20, 2005; CL-050541)

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 alkaloid[2] 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**).

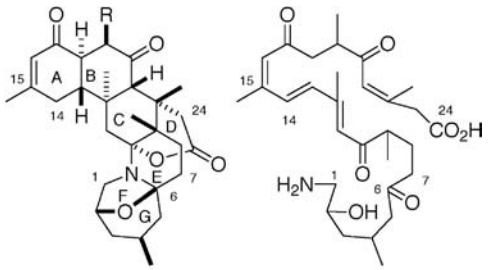
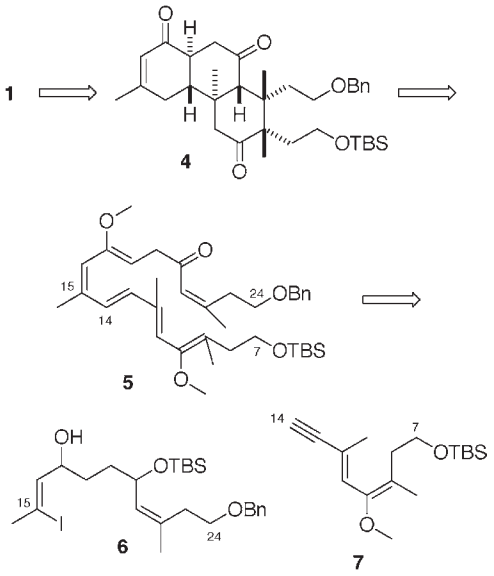


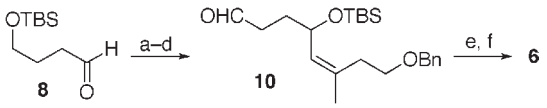
Figure 1.

Our strategy is shown in Scheme 1. Although some groups used the Diels–Alder reaction to produce an ABC-ring fragment,[5a,5e,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 cyclizations[6] 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 alcohol, selective desilylation and oxidation gave aldehyde **10**. Finally, addition of 1-propynylmagnesium bromide to **10**, (*Z*)-selective hydroalumination, and iodation produced vinyl iodide **6**.



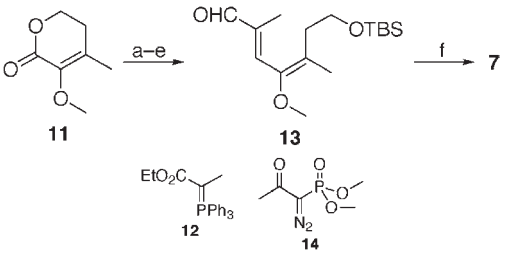
Scheme 1. Retrosynthesis of norzoanthamine (**1**).



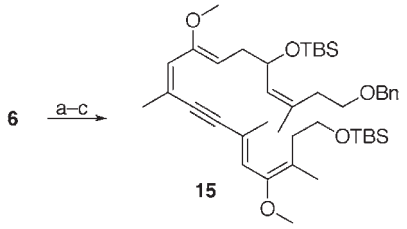
Scheme 2. Reagents and conditions: (a) **9**, *n*-BuLi, ether, −78 °C, 75%; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, quant.; (c) Al_2O_3, hexane, rt, 97%; (d) PDC, MS4A, CH_2Cl_2, rt, 82%; (e) 1-propynylmagnesium bromide, ether, −78 °C, 94%; (f) Red-Al®, ether, rt, then I_2, ether/THF = 2/1, 0 °C,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

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 fluorosulfonate 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**, $Pd(PPh_3)_4$, 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.

This work was supported in part by a Grant-in-Aid for Scientific Research, and the 21st century COE program (Establishment of COE on Materials Science) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

References and Notes

Present address: Department of Chemistry, University of Tsukuba.

1 a) S. Fukuzawa, Y. Hayashi, D. Uemura, A. Nagatsu, K. Yamada, and Y. Ijyuin, *Heterocycl. Commun.*, **1**, 207 (1995). b) M. Kuramoto, K. Hayashi, Y. Fujitani, K. Yamaguchi, T. Tsuji, K. Yamada, Y. Ijyuin, and D. Uemura, *Tetrahedron Lett.*, **38**, 5683 (1997). c) M. Kuramoto, K. Hayashi, K. Yamaguchi, M. Yada, T. Tsuji, and D. Uemura, *Bull. Chem. Soc. Jpn.*, **71**, 771 (1998).

2 a) C. B. Rao, A. S. R. Anjaneyula, N. S. Sarma, Y. Venkateswarlu, R. M. Posser, D. J. Faulkner, M. H. M. Chen, and J. Clardy, *J. Am. Chem. Soc.*, **106**, 7983 (1984). b) C. B. Rao, A. S. R. Anjaneyula, N. S. Sarma, Y. Venkateswarlu, R. M. Posser, and D. J. Faulkner, *J. Org. Chem.*, **50**, 3757 (1985). c) C. B. Rao, D. V. Rao, V. S. N. Raju, B. W. Raju, B. W. Sullivan, and D. J. Faulkner, *Heterocycles*, **28**, 103 (1989). d) A.-U. Rahman, K. A. Alvi, S. A. Abbas, M. I. Choudhary, and J. Clardy, *Tetrahedron Lett.*, **30**, 6825 (1989). e) H. Nakamura, Y. Kawase, K. Maruyama, and A. Murai, *Bull. Chem. Soc. Jpn.*, **71**, 781 (1998). f) A. H. Daranas, J. J. Fernández, J. A. Gavín, and M. Norte, *Tetrahedron*, **54**, 7891 (1998). g) A. H. Daranas, J. J. Fernández, J. A. Gavín, and M. Norte, *Tetrahedron*, **55**, 5539 (1999).

3 a) R. M. Villar, J. Gil-Longo, A. H. Daranas, M. L. Souto, J. J. Fernández, S. Peixinho, M. A. Barral, G. Santafé, J. Rodríguez, and C. Jiménez, *Bioorg. Med. Chem.*, **11**, 2301 (2003). b) G. Hirai, H. Oguri, M. Hayashi, K. Koyama, Y. Koizumi, S. M. Moharram, and M. Hirama, *Bioorg. Med. Chem. Lett.*, **14**, 2647 (2004).

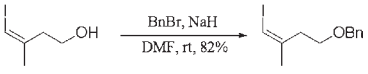
4 a) K. Yamaguchi, M. Yada, T. Tsuji, M. Kuramoto, and D. Uemura, *Biol. Pharm. Bull.*, **22**, 920 (1999). b) K. Yamada, M. Kuramoto, and D. Uemura, *Recent Res. Dev. Pure Appl. Chem.*, **3**, 245 (1999). c) M. Kuramoto, K. Yamaguchi, T. Tsuji, and D. Uemura, in "Drugs from the Sea," ed. by N. Fusetani, Karger, Basel (2000), p 98.

5 a) D. Tanner, P. G. Anderson, L. Tedenborg, and P. Somfai, *Tetrahedron*, **50**, 9135 (1994). b) D. Tanner, L. Tedenborg, and P. Somfai, *Acta Chem. Scand.*, **51**, 1217 (1997). c) T. E. Nielsen and D. Tanner, *J. Org. Chem.*, **67**, 6366 (2002). d) D. R. Williams and G. S. Cortez, *Tetrahedron Lett.*, **39**, 2675 (1998). e) D. R. Williams and T. A. Brugel, *Org. Lett.*, **2**, 1023 (2000). f) N. Higasa, H. Furukawa, K. Takao, and S. Kobayashi, *Tetrahedron Lett.*, **39**, 6237 (1998) g) N. Higasa, H. Furukawa, K. Takao, and S. Kobayashi, *Tetrahedron Lett.*, **39**, 6241 (1998). h) N. Higasa, H. Furukawa, K. Takao, and S. Kobayashi, *Chem. Pharm. Bull.*, **48**, 1370 (2000). i) G. Hirai, H. Oguri, and M. Hirama, *Chem. Lett.*, **1999**, 141. j) S. M. Moharram, G. Hirai, K. Koyama, H. Oguri, and M. Hirama, *Tetrahedron Lett.*, **41**, 6669 (2000). k) G. Hirai, H. Oguri, S. M. Moharram, K. Koyama, and M. Hirama, *Tetrahedron Lett.*, **42**, 5783 (2001). l) G. Hirai, Y. Koizumi, S. M. Moharram, H. Oguri, and M. Hirama, *Org. Lett.*, **4**, 1627 (2002). m) M. Sakai, M. Sasaki, K. Tanino, and M. Miyashita, *Tetrahedron Lett.*, **43**, 1705 (2002). n) M. Miyashita, M. Sasaki, I. Hattori, M. Sakai, and K. Tanino, *Science*, **305**, 495 (2004). o) S. Ghosh, F. Rivas, D. Fischer, M. A. Gonzalez, and E. A. Theodorakis, *Org. Lett.*, **6**, 941 (2004).

6 The cyclization of 2-methoxy-1,3,5-hexatriene to enone was reported. P. von Zezschwitz, F. Petry, and A. de Meijere, *Chem.—Eur. J.*, **7**, 4035 (2001).

7 P. C. Bulman-Page and P. C. Paquette, *Tetrahedron Lett.*, **24**, 3555 (1982).

8 **9** was prepared by benzyl protection of the corresponding alcohol.

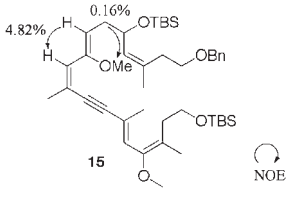


9

S. Ma and E. Negishi, *J. Org. Chem.*, **62**, 784 (1997).

9 M. Quimpère, L. Ruest, and P. Deslongchamps, *Synthesis*, **1992**, 132.

10 ^{1}H 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.



Published on the web (Advance View) July 5, 2005; DOI 10.1246/cl.2005.1058