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Different Modes of Cyclization in Zoanthamine Alkaloid System, Bisaminal versus Spiroketal Formation

Takahiro Nakajima, Daisuke Yamashita, Kaname Suzuki, Atsuo Nakazaki, Takahiro Suzuki, and Susumu Kobayashi*

Faculty of Pharmaceutical Sciences, Tokyo University of Science (RIKADAI), 2641 Yamazaki, Noda-shi, Chiba 278-8510, Japan

kobayash@rs.noda.tus.ac.jp

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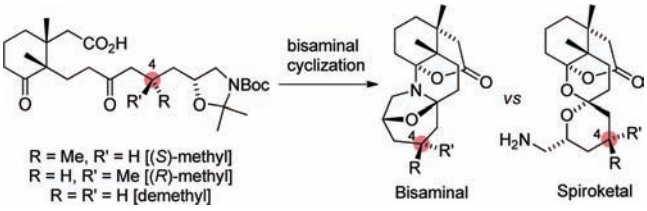
ABSTRACT



Bisaminal cyclization in the zoanthamine alkaloid system was strongly affected by the stereochemistry of the C4 methyl. While cyclization of the (4*S*)-methyl precursor gave only a bisaminal compound, cyclization of the (4*R*)-methyl isomer produced both spiroketal and bisaminal products.

Zoanthamine alkaloids are attractive target molecules from a synthetic point of view because of their structural complexity and potent biological activity (Figure 1).[1] Indeed, extensive synthetic studies have been carried out toward the synthesis of norzoanthamine (**1**), zoanthamine (**2**), and zoanthenol (**3**) over the past few years.[2] The total synthesis of norzoanthamine was accomplished by Miyashita/Tanino and our group.[3,4a,4b] One of the most challenging problems in the synthesis of zoanthamine alkaloids is the formation of the pentacyclic core (CDEFG ring), which possesses eight chiral centers including three quaternary carbons and two aminal moieties. In 1998, we reported the first entry for the construction of the fully functionalized pentacyclic bisaminal core (Scheme 1).[5a–c]

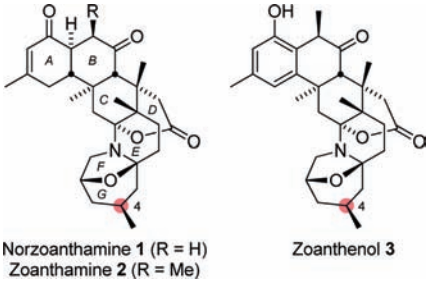


Figure 1. Zoanthamine alkaloids.

Namely, treatment of aminohydroxy diketocarboxylic acid **4a** with 2 N HCl in THF produced monoaminal **5**, and subsequent hydrogenolysis of the Cbz group resulted in simultaneous aminal formation to afford bisaminal **6**.[5a,b] We also developed a one-step transformation of Boc-protected precursor **4b** to specifically generate pentacyclic

(1) (a) Fukuzawa, S.; Hayashi, Y.; Uemura, D.; Nagatsu, A.; Yamada, K.; Ijuin, Y. *Heterocycl. Commun.* **1995**, *1*, 207–214. (b) Kuramoto, M.; Hayashi, K.; Fujitani, Y.; Yamaguchi, K.; Tsuji, T.; Yamada, K.; Ijuin, Y.; Uemura, D. *Tetrahedron Lett.* **1997**, *38*, 5683–5686. (c) Kuramoto, M.; Hayashi, K.; Yamaguchi, K.; Yada, M.; Tsuji, T.; Uemura, D. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 771–779.

(2) For a review, see: Behenna, D. C.; Stockdill, J. L.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 2365–2386.

(3) Miyashita, M.; Sasaki, M.; Hattori, I.; Sakai, M.; Tanino, K. *Science* **2004**, *305*, 495–499.

(4) (a) Murata, Y.; Yamashita, D.; Kitahara, K.; Minasako, Y.; Nakazaki, A.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 1400–1403. (b) Yamashita, D.; Murata, Y.; Hikage, N.; Takao, K.-i.; Nakazaki, A.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 1404–1406.

(5) (a) Hikage, N.; Furukawa, H.; Takao, K.-i.; Kobayashi, S. *Tetrahedron Lett.* **1998**, *39*, 6237–6240. (b) Hikage, N.; Furukawa, H.; Takao, K.-i.; Kobayashi, S. *Tetrahedron Lett.* **1998**, *39*, 6241–6244. (c) Hikage, N.; Furukawa, H.; Takao, K.-i.; Kobayashi, S. *Chem. Pharm. Bull.* **2000**, *48*, 1370–1372.

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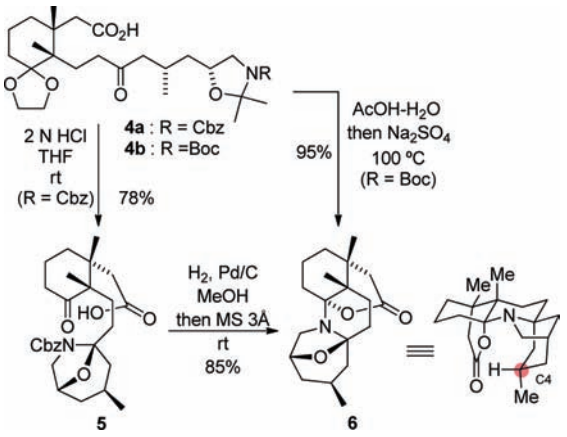
Scheme 1. Construction of Pentacyclic Bisaminal Core

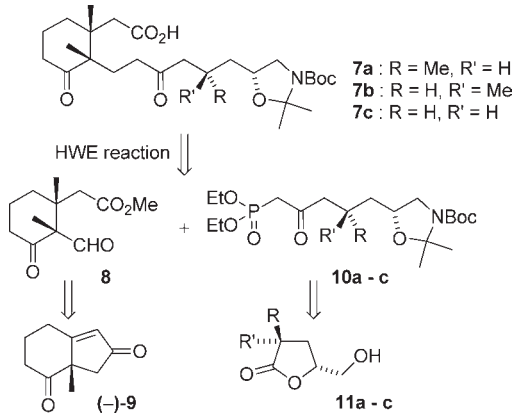


bisaminal **6** by heating in aqueous acetic acid.[5c] This methodology proved to be applicable to the final step in the total synthesis of zoanthamine alkaloids.[3,4a,5,6]

Although the formation of pentacyclic bisaminal **6** is the result of a thermodynamically favored process, we became interested in the factors that lead to selective bisaminal formation from among the many other possible cyclization products. All naturally occurring zoanthamine alkaloids possess a (4*S*)-methyl group. We reasoned that the stereochemistry of the C4-methyl might affect the mode of cyclization.

Herein, we report the effect of the stereochemistry of the C4 methyl group in terms of the cyclization with three precursors; (4*S*)- and (4*R*)-methyl isomers and a demethyl derivative.

Scheme 2. Synthetic Strategy for Cyclization Precursors **7a**–**c**



Our strategy for the preparation of three precursors **7a**–**c** is outlined in Scheme 2. The cyclization precursors could be obtained by Horner–Wadsworth–Emmons (HWE) reaction of aldehyde **8** and corresponding ketophosphonates **10a**–**c** (prepared from lactones **11a**–**c**).[7,8] Aldehyde **8** could be prepared from the bicyclic enone (−)-**9**[9] by introducing a methyl group followed by the regioselective cleavage of the cyclopentanone ring (Scheme 3).

Treatment of enone (−)-**9** with Gilman reagent and subsequent in situ trapping of the enolate by addition of TESCl and HMPA provided the silyl enol ether as a single diastereomer. Reduction of the remaining carbonylgroup with $LiAlH_4$, followed by desilylation with TBAF afforded ketone **12** in 92% overall yield from (−)-**9**. After protection of the resulting hydroxyl group as BOM ether, a regioselective silyl enol etherification of cyclopentanone **13** was examined. Selective deprotonation using a strong base, such as LDA, proved unsuccessful.

However, we were delighted to find that treatment of **13** with TBSOTf and NEt_3 in CH_2Cl_2 at −78 °C led to the isolation of desired silyl enol ether **14** in 96% yield. We next attempted an oxidative cleavage of silyl enol ether **14**.

Direct cleavage (ozone) or Rubottom-type oxidation of **14** (*m*-CPBA, DMDO, PIDA, Davis oxaziridine, or MoOPH) was unsuccessful because of the low yields.[10–12] Treatment of **14** with OsO_4 and NMO in acetone gave α-hydroxy ketone **15**, albeit in moderate yield.[13] Hydroxy ketone **15** was then successfully converted to *β*-keto aldehyde **8**, which can serve as a common intermediate for the preparation of cyclization precursors **7a**–**c**.

We next attempted HWE reaction of **8** with ketophosphonate **10c** (Scheme 4). Under normal conditions,[14] the yield of **17c** was very low because of the predominant deformylation affording **19** through intermediate **18**. After extensive experiments, we found that the addition of HMPA[15] or DMPU dramatically improved the yield of **17c**. This remarkable effect might be attributed to a facile elimination of diethyl phosphate from intermediate **18** in aprotic polar solvents. Other enones, **17a** and **17b**, were also prepared in good yield. Enones (**17a**–**c**) were subjected to a catalytic hydrogenation followed by alkaline hydrolysis to obtain cyclization precursors **7a**–**c**.

With three cyclization precursors in hand, we next examined a tandem cyclization under different acidic conditions. The conditions we examined were as follows: (Conditions A) AcOH–H_2O at 60 °C for 6 h, then

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(7) **11a** and **11b** can be prepared from lactones **11c**, by methylation and epimerization.

(8) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863–927.

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(13) McCormick, J. P.; Witold, T.; Johnson, M. W. *Tetrahedron Lett.* **1981**, *22*, 607–610.

(14) KHMDS/THF (trace), *n*-BuLi/THF (trace), LiCl, *i*-Pr_2NEt/CH_3CN (13%), and NaH/THF (18%).

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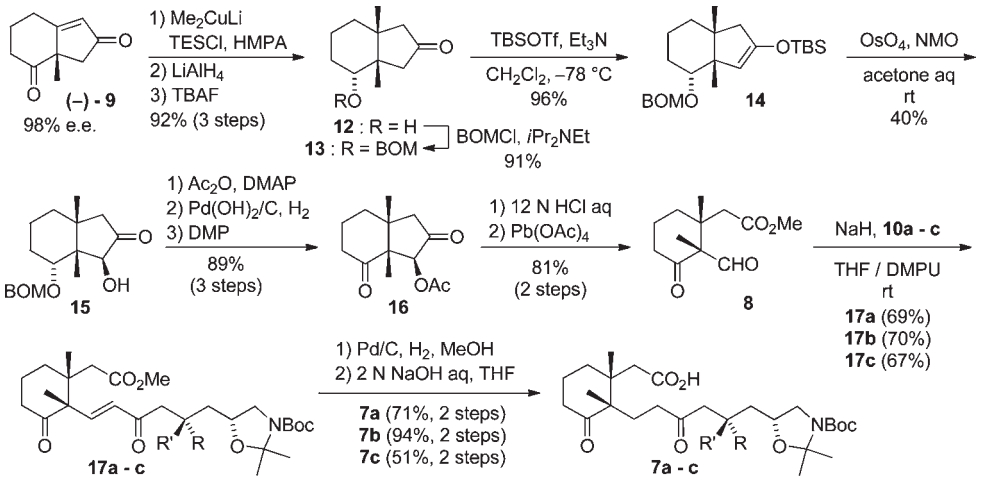
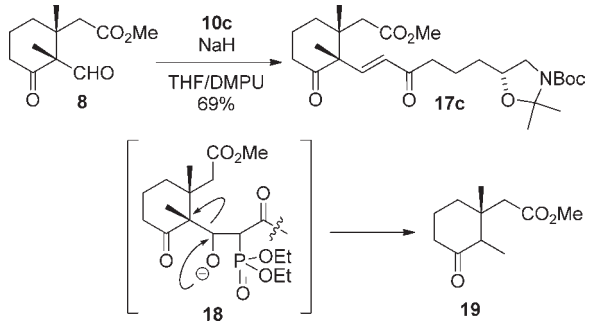
Scheme 3. Synthesis of Cyclization Precursors **7a**–**c**



Scheme 4. HWE Reaction of Ketoaldehyde **8**



Na_2SO_4, at rt for 20 h; (conditions B) 2 N HCl aq at rt for 4 h; (conditions C) AcOH–H_2O at 100 °C for 9 h, then Na_2SO_4 at rt for 3 h; (conditions D) AcOH–H_2O at 100 °C for 24 h, then Na_2SO_4 at rt for 12 h. The results are summarized in Table 1. When cyclization precursors (**7a**–**c**) were subjected to conditions A and B, monoaminals (**20a**–**c**) and spiroketals (**21a**–**c**) were subsequently isolated. It should be noted that the ratio of monoaminal/spiroketal was highly dependent on the stereochemistry of C4-methyl. In the case of (4*S*)-methyl derivative **7a**, monoaminal **20a** was isolated as a major isomer. By contrast, spiroketal **21b** was a major product for (4*R*)-methyl derivative **7b**. The results of demethyl derivative **7c** were intermediate between those of **7a** and **7b**. Because the *N*-Boc group remain protected under these conditions, monoaminals **20a**–**c** did not undergo bisaminal formation.

Cyclization precursors (**7a**–**c**) were next heated in aqueous AcOH (conditions C and D). The *N*-Boc group was cleaved in AcOH–H_2O at 100 °C as we already developed, and initially formed monoaminals were transformed to the corresponding bisaminals **6a**–**c** in moderate to high yields depending on the substrates. Thus, bisaminal **6a** was obtained in high yield from (4*S*)-methyl isomer **7a** after 9 h (entry 7). In contrast, (4*R*)-methyl isomer **7b** was transformed to bisaminal **6b** very slowly (entries 8 and 11), and spiroketal **22b** remained even after 24 h. Structures of these products were fully established by ^{1}H NMR, ^{13}C NMR, and HRMS spectra (Figure 2).

These results are best explained in a qualitative manner as follows: Formation of monoaminal **20a**, rather than spiroketal **21a**, can be understood by considering the axial orientation of C4-methyl in spiroketal **21a**. In a similar manner, monoaminal **20b** seems to be thermodynamically less favorable by the nonbonding interaction caused by axial C4-Me. The C4-methyl group occupies an equatorial position in spiroketal **21b**, and **21b** does not undergo a facile recyclization to bisaminal **6b** through monoaminal. In the case of C4-demethyl derivative, both monoaminal **20c** and spiroketal **21c** do not suffer from nonbonding interactions. Therefore, spiroketal **21c** was readily transformed to the thermodynamically favorable bisaminal **6c** via monoaminal **20c** under conditions C.

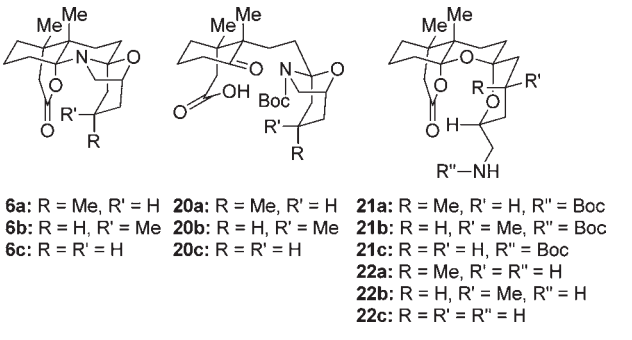
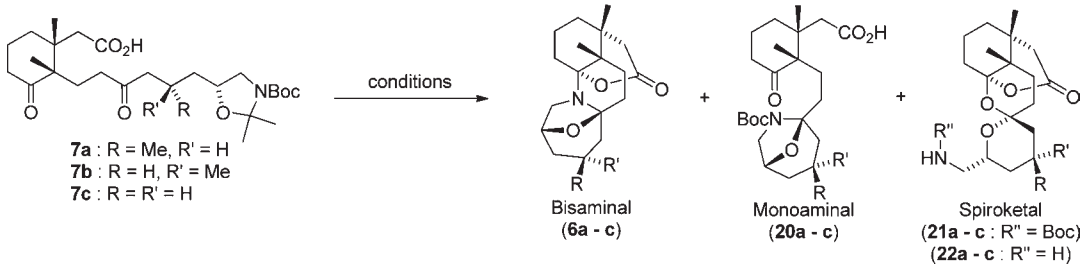


Figure 2. Structure of bisaminal, monoaminal, and spiroketal.

Table 1. Cyclization of **7a**–**c**



			yield (%)			
entry	condition[a]	precursor	bisaminal **6**	monoaminal **20**	spiroketal **21**	spiroketal **22**
1	A	**7a**		58	14	
2	A	**7b**		10	51	
3	A	**7c**		48	19	
4	B	**7a**		77		
5	B	**7b**		32	44	
6	B	**7c**		33	35	
7	C	**7a**	90			
8	C	**7b**	31			47
9	C	**7c**	65			
10	D	**7a**	95			
11	D	**7b**	62			27
12	D	**7c**	74			

[a] Conditions A: AcOH–H_2O at 60 °C for 6 h, then Na_2SO_4 at rt for 24 h. Conditions B: 2 N HCl aq at rt for 4 h. Conditions C: AcOH–H_2O at 100 °C for 9 h, then Na_2SO_4 at rt for 3 h. Conditions D: AcOH–H_2O at 100 °C for 24 h, then Na_2SO_4 at rt for 12 h.

In conclusion, we reveal that the mode of cyclization is dependent on the stereochemistry at the C4 methyl in zoanthamine alkaloids.

In addition, we also developed a straightforward and efficient route to cyclization precursor **7** from ketoaldehyde **8** by the Horner–Wadsworth–Emmons reaction in the presence of DMPU. A synthetic study of zoanthamine using the present methodology is currently underway.

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Supporting Information Available. Detailed experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.