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A Concise Asymmetric Synthesis of the ADE Fragment of Nakadomarin A

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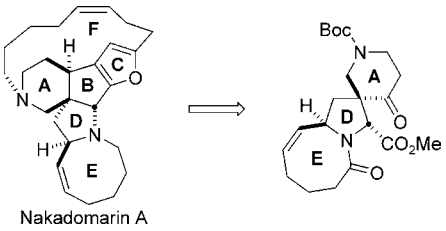
ABSTRACT



The ADE fragment of nakadomarin A has been synthesized in nine linear steps from commercial material. The key transformation is an asymmetric azomethine ylide [1,3]-dipolar cycloaddition to establish the AD-spirocyclic system containing three of the four stereocenters of the natural product.

During their search for biogenetic precursors of the manzamine alkaloids, Kobayashi and co-workers isolated nakadomarin A (**1**, Figure 1) from the sponge *Amphimedon* sp. (SS-264) in 1997 off the Okinawan coast.[1] Nakadomarin A is the only example of a manzamine alkaloid containing a furan ring, and its structure consists of an unprecedented hexacyclic 6/5/5/5/8/15 ring system. A biogenetic pathway to nakadomarin A from ircinal A (**2**, Figure 1) has been proposed by Kobayashi.[1] Ircinal A is also reported to be the direct biosynthetic precursor of the potent cytotoxic agent manzamine A (**3**, Figure 1).[2,3]

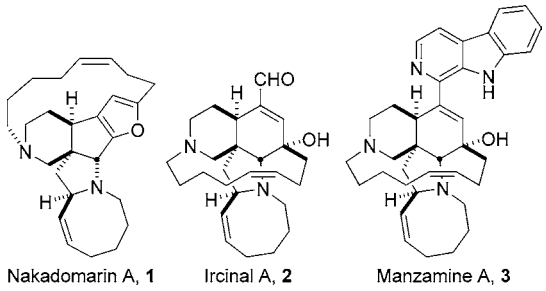


Figure 1. Nakadomarin A and related manzamine alkaloids.

Nakadomarin A exhibits a broad range of biological activities, including cytotoxicity against murine lymphoma L1210 cells (IC_{50} 1.3 μg/mL), inhibitory activity against cyclin dependent kinase 4 (IC_{50} 9.9 μg/mL), antimicrobial activity against the fungal strain *Trichophyton mentagrophytes* (MIC 23 μg/mL), and antibacterial activity against the Gram-positive bacterium *Corynebacterium xerosis* (MIC 11 μg/mL).[1] However, the limited availability of naturally occurring nakadomarin (6.0 mg, 0.0018% isolated yield) has precluded extensive investigations of its biological activity.

Recently, several research groups have undertaken efforts toward the total synthesis of the manzamine alkaloids including nakadomarin.[4] In 2003, Nishida and co-workers

(1) (a) Kobayashi, J.; Watanabe, D.; Kawasaki, N.; Tsuda, M. *J. Org. Chem.* **1997**, *62*, 9236. (b) Kobayashi, J.; Tsuda, M.; Ishibashi, M. *Pure Appl. Chem.* **1999**, *71*, 1123.

(2) Kondo, K.; Shigemori, H.; Kikuchi, Y.; Ishibashi, M.; Sasaki, T.; Kobayashi, J. *J. Org. Chem.* **1992**, *57*, 2480.

(3) For a review of the manzamine alkaloids, see: (a) Hu, J.-F.; Hamann, M. T.; Hill, R.; Kelly, M. In *The Alkaloids, Chemistry and Biology*; Cordell, G. A., Ed.; Elsevier: San Diego, 2003; Vol. 60, pp 207−285. (b) Magnier, E.; Langlois, Y. *Tetrahedron* **1998**, *54*, 6201. (c) Tsuda, M.; Kobayashi, J. *Heterocycles* **1997**, *46*, 765 and references therein.

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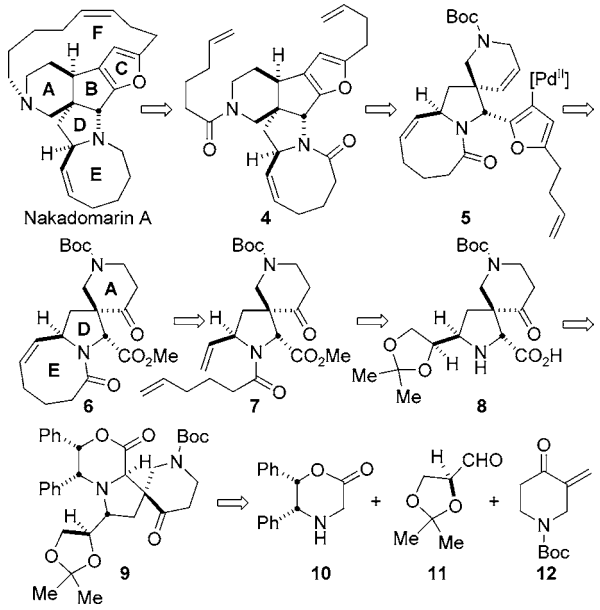
reported the first synthesis of *ent*-(+)-nakadomarin A.[4a] Shortly afterward, the Nishida group published the synthesis of the naturally occurring enantiomer.[4b] However, these total syntheses required 38 and 36 linear steps, respectively, from commercially available materials. Thus, a concise, scaleable synthesis of (−)-nakadomarin A remains a worthy objective that would yield additional material for biological studies. Furthermore, a synthesis amenable to the preparation of analogues would allow structure−activity information to be obtained.

Our retrosynthetic analysis of nakadomarin A is outlined in Scheme 1. A late-stage construction of the macrocyclic

Scheme 1. Retrosynthetic Analysis of Nakadomarin A



F-ring was envisioned to occur through ring-closing metathesis of pentacyclic compound **4**. Construction of the ABCDE core was anticipated to be accessible through an intramolecular Heck reaction of the furylorganopalladium intermediate **5**. The key ADE precursor **6** was thus predicted from ring-closing metathesis of spirocyclic diene **7**. This species was targeted via amino acid **8**, which we envisioned would be assembled by a stereoselective three-component [1,3]-dipolar cycloaddition reaction of **10**, **11**, and **12** followed by removal of the chiral template.

The [1,3]-dipolar cycloaddition of azomethine ylides is one of the most powerful methods for the formation of substituted pyrrolidine rings.[5] While catalytic enantioselective variants have recently been reported,[6] these methods all yield 2,5-*cis*-substituted pyrrolidines as a result of the *syn*-orientation of substituents in the metallo-stabilized azomethine ylides (Figure 2, **13**). However, azomethine ylides

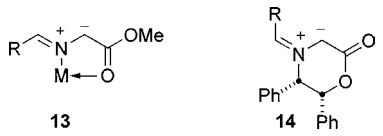
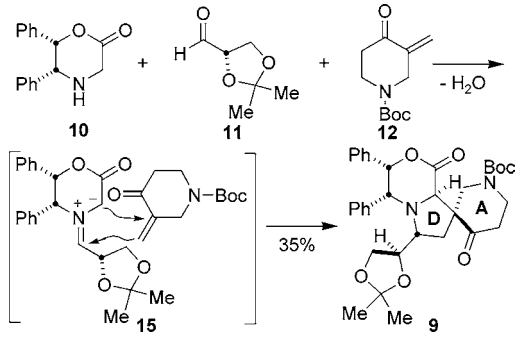


Figure 2. *Syn*-oriented metallo-stabilized azomethine ylide **13** and *anti*-oriented azomethine ylide **14** (M = transition metal).

derived from the diphenyl morpholinone template **10** afford 2,5-*trans*-substituted pyrrolidines due to the preferential *anti*-orientation of substituents with the use of bulky aldehydes (Figure 2, **14**).[7]

In this event, we observed the formation of the 2,5-*trans*-cycloadduct **9** as a single diastereomer from the three-component condensation reaction of **10**−**12** (35% yield based on compound **10**, Scheme 2). The intermediate *E*-azomethine

Scheme 2. Azomethine Ylide [1,3]-Dipolar Cycloaddition



ylide **15** undergoes cycloaddition with enone **12** in an *endo*-fashion from the stereoface opposite the phenyl moieties.

The stereochemistry of cycloadduct **9** was confirmed by the ^{1}H NMR NOE enhancements indicated in Figure 3.[8]

The cycloaddition precursors **10**−**12** are readily obtained from commercially available materials. Morpholinone **10**[9] and aldehyde **11**[10] were prepared in one step as described in

(4) Nakadomarin: (a) Nagata, T.; Nakagawa, M.; Nishida, A. *J. Am. Chem. Soc.* **2003**, *125*, 7484. (b) Ono, K.; Nakagawa, M.; Nishida, A. *Angew. Chem., Int. Ed.* **2004**, *42*, 2020. (c) Fürstner, A.; Guth, O.; Duffels, A.; Seidel, G.; Liebl, M.; Gabor, B.; Mynott, R. *Chem. Eur. J.* **2001**, *7*, 4811. (d) Magnus, P.; Fielding, M. R.; Wells, C.; Lynch, V. *Tetrahedron Lett.* **2002**, *43*, 947. (e) Leclerc, E.; Tius, M. A. *Org. Lett.* **2003**, *5*, 1171. Manzamine A: (f) Winkler, J. D.; Axten, J. M. *J. Am. Chem. Soc.* **1998**, *120*, 6425. (g) Martin, S. F.; Humphrey, J. M.; Hillier, M. C. *J. Am. Chem. Soc.* **1999**, *121*, 866. (h) See ref 3a for a list of over 75 references on synthetic efforts toward the manzamine alkaloids.

(5) For reviews of azomethine ylide [1,3]-dipolar cycloaddition reactions, see: (a) *Synthetic Applications of Dipolar Cycloaddition Chemistry towards Heterocyclic and Natural Products*; Padwa, A., Pearson, W., Ed.; Wiley-VCH: Weinheim, 2002. (b) Gothelf, K. I. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863. (c) Wade, P. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, p 1111 and references therein.

(6) (a) Gothelf, A. S.; Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4236. (b) Longmire, J. M.; Wang, B.; Zhang, X. *J. Am Chem. Soc.* **2002**, *124*, 13400. (c) Chen, C.; Li, X.; Schreiber, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 10174.

(7) (a) Williams, R. M.; Zhai, W.; Aldous, D.; Aldous, S. *J. Org. Chem.* **1992**, *57*, 6527. (b) Sebahar, P. R.; Williams, R. M. *J. Am. Chem. Soc.* **2000**, *122*, 5666. (c) Sebahar, P. R.; Williams, R. M. *Heterocycles* **2002**, *58*, 563.

(8) See the Supporting Information for spectral data.

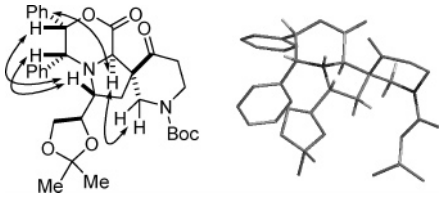
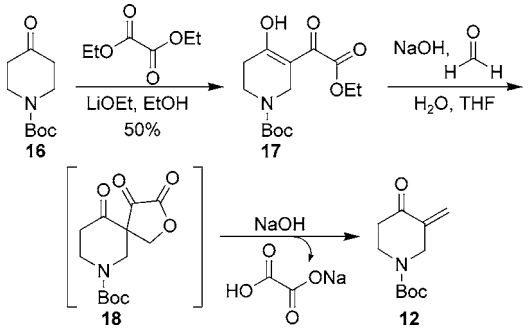


Figure 3. Observed ^{1}H NMR NOE's and molecular mechanics model of cycloadduct **9**.

the literature. Enone **12** was synthesized as outlined in Scheme 3.[11] Acylation of *N*-Boc-piperidinone **16** with

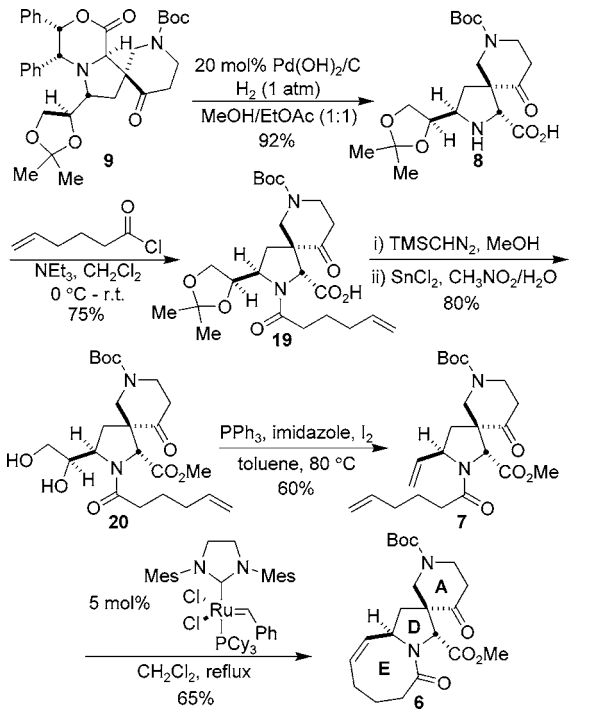
Scheme 3. Synthesis of Enone **12**



diethyloxalate in the presence of LiOEt provided **17**. Reaction of **17** with aqueous formaldehyde and NaOH generated diketolactone **18**, which rapidly decomposed in the presence of NaOH to yield the labile enone **12**.[12]

The dipolar cycloadduct **9** was further elaborated to the ADE intermediate of nakadomarin A as illustrated in Scheme 4. Removal of the chiral template was accomplished by hydrogenolysis with Pearlman's catalyst (92% yield). Pyrrolidine **8** was then *N*-acylated with 5-hexenoyl chloride (75% yield). Treatment of **19** with trimethylsilyl diazomethane followed by $SnCl_2$ yielded the diol **20** (80% yield, two steps), which was subsequently converted to the olefin **7** (60% yield).[13] Ring-closing metathesis of **7** with Grubbs' second-generation catalyst afforded the ADE intermediate **6** (65% yield).[14,15]

Scheme 4. Synthesis of the ADE Fragment of Nakadomarin A



In summary, the asymmetric synthesis of the ADE fragment of nakadomarin A has been accomplished in nine linear steps from commercially available materials. The key transformation is a highly diastereostereoselective azomethine ylide [1,3]-dipolar cycloaddition to set three of the four stereogenic centers of the natural product, including the AD-spirocenter. Efforts are currently underway to apply this approach to the total synthesis of nakadomarin A and congeners.

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

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(9) The *N*-BOC-protected diphenyl morpholinone and its antipode are commercially available from Aldrich Chemical Co. Removal of the Boc group is performed with HCl (Supporting Information).

(10) Aldehyde **11** is obtained by periodate cleavage of 1,2:5, 6-di-*O*-isopropylidene-D-mannitol: Earle, M. J.; Abdur-Rashid, A.; Priestley, N. D. *J. Org. Chem.* **1996**, *61*, 5697.

(11) Ksander, G. M.; McMurry, J. E.; Johnson, M. *J. Org. Chem.* **1977**, *42*, 1180.

(12) Due to its extreme instability, enone **12** was used in the dipolar cycloaddition reaction immediately after its preparation from **17**.

(13) Garegg, P. J.; Samuelsson, B. *Synthesis* **1979**, 469.

(14) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

(15) For a review of ring-closing metathesis applied to oxygen- and nitrogen-containing heterocycles, see: Deiters, A.; Martin. S. F. *Chem. Rev.* **2004**, *104*, 2199 and references therein.