Natural Products Synthesis

Asymmetric Total Synthesis of (−)-Nakadomarin A**

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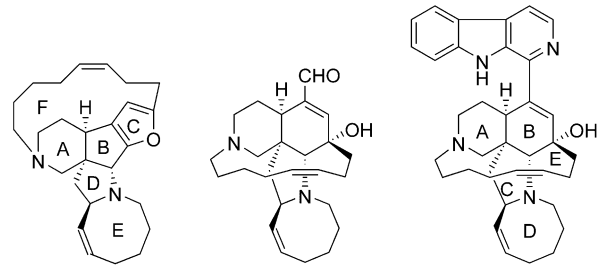
Nakadomarin A (**1**) was isolated in 1997 by Kobayashi and co-workers from the marine sponge *Amphimedon* sp., collected off the Kerama Islands, Okinawa,[1] and is considered to be a type of manzamine alkaloid.[2] However, the structure of **1** is different from those of other manzamines and consists of a unique hexacyclic system that includes a furan ring. Biological assays have indicated that it is cytotoxic against murine lymphoma L1210 cells, inhibits CDK4, and shows antimicrobial activity. This unique structure and biological activity prompted us and others to develop a total synthesis of **1**.[3] In 2001, we established a method for constructing the central ring system which involved a cyclization between an acyliminium cation and a furan ring.[4b] This procedure was successfully applied in our first asymmetric total synthesis of (+)-**1**, the non-natural enantiomer.[4a] Our total synthesis established the structure of **1**, including its absolute stereochemistry, as proposed by spectroscopic studies and biogenetic correlation.[1] In our synthesis, an enantiomerically pure intermediate was efficiently



(–)-Nakadomarin A (**1**) Ircinal A (**2**) Manzamine A (**3**)

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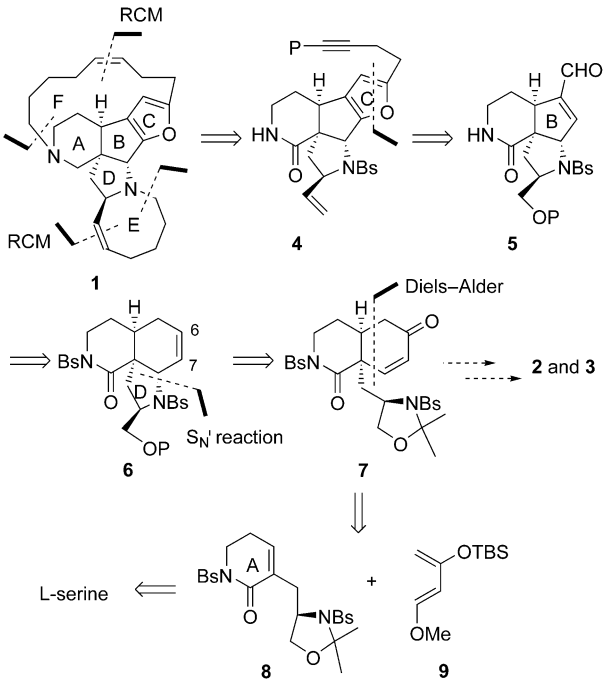
obtained by resolution of the key carboxylic acid as a cinchoninium salt. However, the preparation of the opposite, natural enantiomer was inefficient at that stage, and led us to develop another synthetic route to natural **1**. We report herein the first total synthesis of the natural enantiomer (−)-nakadomarin A (**1**).

We have also been studying the asymmetric total synthesis of ircinal A (**2**), which is a synthetic and biogenetic intermediate for manzamine A (**3**), via the key intermediate **7**.[5] As all the stereocenters of **1** are the same as those of **2** and **3**, we planned a new synthetic route involving the key intermediate **7** (Scheme 1). Retrosynthetic analysis showed that



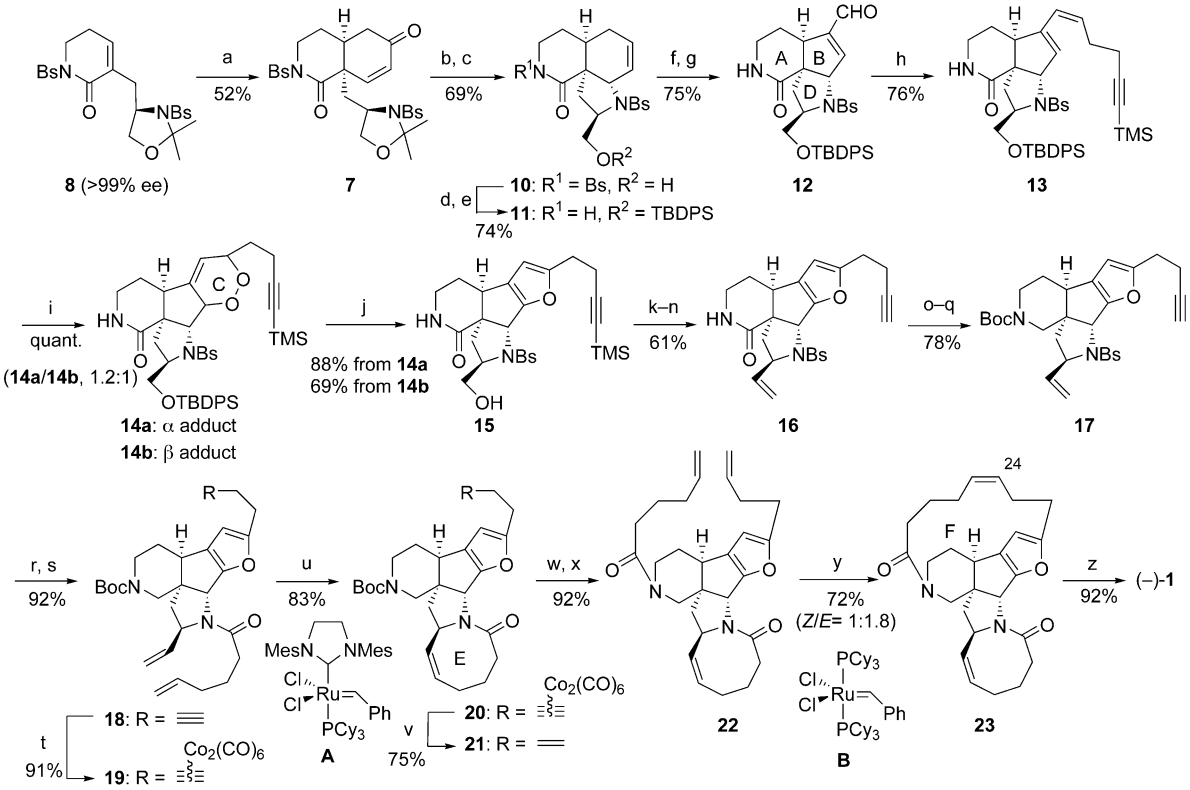
Scheme 1. Retrosynthetic analysis of (−)-nakadomarin A (**1**). TBS = *tert*-butyldimethylsilyl, Bs = benzenesulfonyl.

both the 15- and 8-membered azacycles could be obtained by ring-closing metathesis (RCM).[6] The furan ring could be constructed from unsaturated aldehyde **5**, which in turn could be available from a precursor such as **6**. We envisaged that the tricyclic intermediate **6**, which has a C6–C7 double bond, could be obtained by a stereoselective S_N' reaction from the key intermediate **7**.

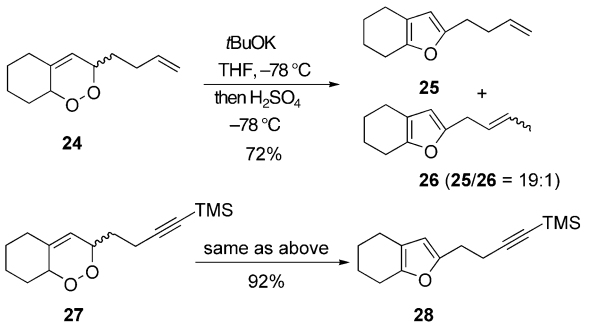
Highly functionalized hydroisoquinoline **7** was obtained by a Diels–Alder reaction between siloxydiene **9** and chiral dienophile **8**, which was prepared from L-serine in 47% yield (10 steps) by a slightly modified version of our previously published method.[7] Luche reduction of enone **7** gave allyl alcohols as a mixture of diastereomers (2:1), which were subjected to a key S_N' cyclization (Scheme 2). Treatment of the allyl alcohols with HCl (6N) at reflux in benzene gave tricyclic intermediate **10** in 70% yield by deprotection of the acetonide group followed by chemo- and stereoselective S_N' cyclization. The stereochemistry of **10** was unambiguously determined by X-ray crystallographic analysis.[8] After the primary alcohol was protected as a TBDPS ether, the *N*-benzenesulfonyl group in ring A was selectively removed with sodium anthracenide to give **11**, which was then converted into unsaturated aldehyde **12** by contraction of ring B. The six-membered ring B was cleaved by ozonolysis to give an unstable bisaldehyde, which was recyclized to a five-membered ring by aldol condensation with *N*-methylanilinium trifluoroacetate.[9] Wittig reaction of aldehyde **12** selectively gave *Z* olefin **13**, which was quantitatively converted into endoperoxides **14** as a mixture of two diastereomers (**14a**/**14b** = 1.2:1) by singlet oxygen. The reaction of each diastereomer of **14** with potassium *tert*-butoxide followed by treatment with a strong acid resulted in dehydration and deprotection of the TBDPS group, and gave the furan **15** in high yield.[10] The use of a TMS-protected alkyne in the side chain was essential as partial isomerization of the terminal double bond was observed under these conditions in a model study (Scheme 3).[11] The preparation of **15** corresponded to the stereoselective construction of a chiral ABCD-ring system, the central core of (−)-**1**.

Next, we focused on the formation of 8- and 15-membered rings by sequential RCM. Dess–Martin oxidation of alcohol **15** gave the corresponding aldehyde, which was converted into olefin **16** by Peterson olefination followed by deprotection of the TMS group. After protection of the amine with a Boc group, the carbonyl function of **16** was reduced to give **17** by sequential reduction with DIBAH and $Et_3SiH/BF_3{\cdot}Et_2O$.[12] Deprotection of the benzenesulfonyl group of **17** followed by *N*-acylation gave dienyne **18**, a precursor for RCM to synthesize the azocine ring. A problem that arose at this stage was the high reactivity of the terminal alkyne under RCM conditions. When alkyne **18** was exposed to second-generation Grubbs catalyst **A**, no cyclization product was obtained. Based on our previous report,[13] the terminal alkyne of **18** was protected as a dicobalt hexacarbonyl complex, which was then treated with catalyst **A**, and a facile RCM gave azocine lactam **20** in 83% yield. After direct conversion of the dicobalt hexacarbonyl complex into olefin **21**[14] by reductive decomplexation,[15] deprotection of the Boc group of **21** followed by *N*-acylation gave **22**, a precursor for the second RCM. When **22** was exposed to the first-generation Grubbs catalyst **B**, ring F was formed to give a mixture of geometrical isomers, from which (*Z*)-**23** was isolated in 26% yield. Finally, reduction of bislactam (*Z*)-**23** with Red-Al resulted in the first asymmetric total synthesis of (−)-nakadomarin A (**1**). All spectral data for synthetic (−)-**1** (NMR, IR, MS) closely matched those published for the *ent*-(+)-**1**, whose NMR spectrum was identical to that of natural (−)-nakadomarin A in the presence of HCl.[4a] The optical rotation of synthetic (−)-**1** confirmed its absolute configuration ($[\alpha]_D^{23} = -73.0$ ($c = 0.08$, MeOH); natural (−)-**1**: $[\alpha]_D^{20} = -16$ ($c = 0.12$, MeOH)[1]).

In conclusion, we completed the first asymmetric total synthesis of (−)-nakadomarin A (**1**) from optically active hydroisoquinoline **7**. Further optimization of the synthetic procedures and a biological evaluation of synthetic analogues are now in progress and will be reported elsewhere.



Scheme 2. Asymmetric total synthesis of (−)-**1**. a) **9** (3.0 equiv) neat, 180 °C, 1 h; then TFA, CH_2Cl_2, room temperature, 52 % (diastereomer 35 %); b) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, CH_2Cl_2/MeOH, −78 °C, 98 % (d.r. = 2:1); c) HCl (6 N), benzene, reflux, 1 h, 70 %; d) TBDPSCl, imidazole; e) Na/anthracene, DME, −65 °C, 74 % (two steps); f) O_3, CH_2Cl_2, −78 °C; then Me_2S, room temperature; g) *N*-methylanilinium trifluoroacetate, THF, reflux, 75 % (two steps); h) $IPh_3PCH_2CH_2CH_2CCTMS$, NaH, THF, −78 °C → RT, 76 %; i) O_2, halogen lamp, Rose Bengal, CH_2Cl_2/MeOH, 0 °C, quant. (**14a**/**14b** = 1.2:1); j) *t*BuOK, THF, −78 °C; then HCl (6 N), room temperature, 88 % (from **14a**), *t*BuOK, THF, −30 °C, then HCl (6 N), room temperature, 69 % (from **14b**); k) Dess–Martin oxidation, 90 %; l) $TMSCH_2MgCl$, Et_2O, room temperature, 83 % (d.r. = 2:1); m) $BF_3 \cdot Et_2O$, CH_2Cl_2, room temperature; n) K_2CO_3, MeOH, 81 % (two steps); o) Boc_2O, DMAP, Et_3N, CH_2Cl_2, 93 %; p) DIBAH, toluene, −78 °C; q) Et_3SiH, $BF_3 \cdot Et_2O$, CH_2Cl_2, −78 °C, 84 % (two steps); r) Na/naphthalene, DME, −65 °C; s) 5-hexenoyl chloride, Et_3N, CH_2Cl_2, 92 % (two steps); t) $Co_2(CO)_8$, CH_2Cl_2, 91 %; u) Grubbs catalyst **A** (25 mol %), CH_2Cl_2 (to 1.0 mM) reflux, 1.5 h, 83 %; v) nBu_3SnH, benzene, 65 °C, 75 %; w) TFA, CH_2Cl_2; x) 5-hexenoyl chloride, Et_3N, CH_2Cl_2, 92 % (two steps); y) Grubbs catalyst **B** (20 mol %), CH_2Cl_2 (to 0.5 mM), reflux, 24 h, *Z* isomer 26 %, *E* isomer 46 %; z) Red-Al, toluene, reflux, 92 %. TFA = trifluoroacetic acid, TBDPS = *tert*-butyldiphenylsilyl, DME = 1,2-dimethoxyethane, TMS = trimethylsilyl, Boc = *tert*-butoxycarbonyl, DMAP = 4-dimethylaminopyridine, DIBAH = diisobutylaluminum hydride, Red-Al = sodium bis(2-methoxyethoxy)aluminum hydride, Mes = mesityl = 2,4,6-$Me_3C_6H_2$, Cy = cyclohexyl.



Scheme 3. Model study of the construction of a fused furan ring.

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

[2] E. Magnier, Y. Langlois, *Tetrahedron* **1998**, *54*, 6201.

[3] a) E. Leclerc, M. A. Tius, *Org. Lett.* **2003**, *5*, 1171; b) P. Magnus, M. R. Fielding, C. Wells, V. Lynch, *Tetrahedron Lett.* **2002**, *43*, 947; c) A. Fürstner, O. Guth, A. Düffels, G. Seidel, M. Liebl, B. Gabor, R. Mynott, *Chem. Eur. J.* **2001**, *7*, 4811; d) A. Fürstner, O. Guth, A. Rumbo, G. Seidel, *J. Am. Chem. Soc.* **1999**, *121*, 11108.

[4] a) T. Nagata, M. Nakagawa, A. Nishida, *J. Am. Chem. Soc.* **2003**, *125*, 7484; b) T. Nagata, A. Nishida, M. Nakagawa, *Tetrahedron Lett.* **2001**, *42*, 8345.

[5] a) M. Nakagawa, *J. Heterocycl. Chem.* **2000**, *37*, 567; b) M. Nakagawa, Y. Torisawa, H. Uchida, A. Nishida, *J. Synth. Org. Chem. Jpn.* **1999**, *57*, 1004; c) H. Uchida, A. Nishida, M. Nakagawa, *Tetrahedron Lett.* **1999**, *40*, 113; d) Y. Torisawa, T. Soe, T. Katoh, Y. Motohashi, A. Nishida, T. Hino, M. Nakagawa, *Heterocycles* **1998**, *47*, 655.

[6] For recent reviews on ring-closing metathesis, see: a) T. M. Trnka, R. H. Grubbs, *Acc. Chem. Res.* **2001**, *34*, 18; b) A.

Fürstner, *Angew. Chem.* **2000**, *112*, 3140; *Angew. Chem. Int. Ed.* **2000**, *39*, 3012.
[7] M. Nakagawa, H. Uchida, K. Ono, Y. Kimura, M. Yamabe, T. Watanabe, R. Tsuji, M. Akiba, Y. Terada, D. Nagaki, S. Ban, N. Miyashita, T. Kano, C. Theeraladanon, K. Hatakeyama, M. Arisawa, A. Nishida, *Heterocycles* **2003**, *59*, 721. We have succeeded in the direct isomerization of the *exo* olefin, which was prepared by aldol reaction of *N*-benzenesulfonyl-2-piperidone and Garner aldehyde followed by dehydration, to *endo* olefin **8** under a hydrogen atmosphere in the presence of Pd/C without any racemization.
[8] See Supporting Information for complete experimental details and crystallographic, spectroscopic, and analytical data. CCDC-230159 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).
[9] J.-L. Gras, *Tetrahedron Lett.* **1978**, *19*, 2111.
[10] K. Kondo, M. Matsumoto, *Tetrahedron Lett.* **1976**, *17*, 4363.
[11] In a model study of the construction of a fused furan ring with terminal alkene **24** as the substrate, isomerization to an internal alkene was observed under strong acidic conditions. However, alkyne TMS-protected **27** was tolerated under the same conditions (Scheme 3).
[12] a) T. Hosaka, Y. Torisawa, M. Nakagawa, *Tetrahedron Lett.* **1997**, *38*, 3535; b) C. Pedregal, J. Ezquerra, A. Escribano, M. C. Carreño, J. L. G. Ruano, *Tetrahedron Lett.* **1994**, *35*, 2053.
[13] K. Ono, T. Nagata, M. Nakagawa, A. Nishida, *Synlett* **2003**, 1207.
[14] The enantiopurity (>99% *ee*) of **21** was confirmed by chiral HPLC analysis after conversion to a known *N*-Bs derivative[4a] of **21** (1) TFA 2) BsCl, $NaHCO_3$).
[15] S. Hosokawa, M. Isobe, *Tetrahedron Lett.* **1998**, *39*, 2609.

