J|A|C|S
COMMUNICATIONS

Published on Web 05/29/2003

The First Total Synthesis of Nakadomarin A

Toshiaki Nagata, Masako Nakagawa,† and Atsushi Nishida*

Graduate School of Pharmaceutical Sciences, Chiba University, 1-33 Yayoi-cho, Inage-ku, Chiba 263-8522, Japan

Received February 3, 2003; E-mail: nishida@p.chiba-u.ac.jp

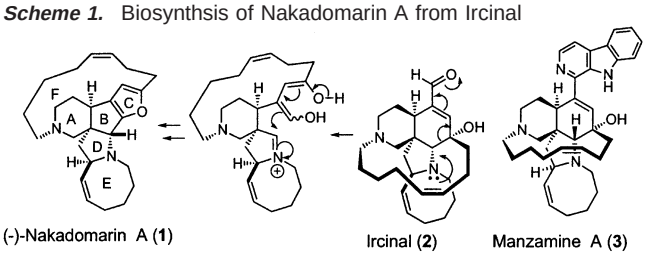
Nakadomarin A (**1**) was first isolated from a marine sponge collected at Okinawa by Kobayashi and co-workers.[1] Its structure was elucidated by exhaustive NMR study and shown to have a unique hexacyclic skeleton. Nakadomarin A was thought to be a member of the manzamine family,[2] and an interesting biogenetic pathway from ircinal A (**2**) was proposed (Scheme 1).[1,3] Although some biological activities of **1** have been reported, including cytotoxicity, antimicrobial activities, and inhibitory activity against cyclin-dependent kinase 4, its limited availability has prevented a complete survey of its biological activity.[1] Synthetic studies[4,5] of this molecule have been reported by Fürstner, Magnus, and us. However, no total synthesis of **1** has yet been reported. In connection with our synthetic study of manzamine alkaloids,[6] we started a total synthesis of **1** to confirm its structure, including its absolute stereochemistry, and to prepare enough natural nakadomarin A and its analogues for further biological testing.

A retrosynthetic analysis of nakadomarin A showed that both 15- and 8-membered azacycles could be obtained by ring-closing metathesis (RCM) (Scheme 2).[7] To construct strained ABCD core ring system **5**, a novel intramolecular Mannich-type cyclization of a furan to an iminium cation in **6** was attractive as a potential route in considering the proposed biogenetic pathway. The *N*-acyliminium ion **6**[8] could be obtained from spiro-γ-lactam **7**, which could be prepared by Suzuki−Miyaura coupling of **8**[9] and **9** followed by hydrogenation. Further retrosynthetic analysis of the key intermediate **9** led to unsaturated ester **10**.

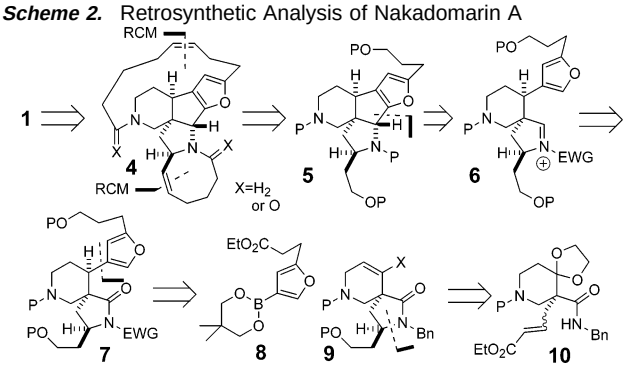
Condensation of (*R*)-(−)-**11**[5,10] with benzylamine, followed by catalytic dihydroxylation and oxidative cleavage of the 1,2-diol, gave aldehyde **12**, which was immediately converted to α,β-unsaturated ester **13** by Wittig olefination. Intramolecular Michael addition[11] of **13** upon treatment with DBU in EtOH gave the desired spirolactam as a major product (3.3:1) in an inseparable mixture of the diastereomers. The mixture was then hydrolyzed to acids to remove less polar impurities, including phosphine oxide, and re-esterified to give **14**. Reduction of **14** gave the separable alcohol **15** in 54% yield [eight steps from (*R*)-**11**]. Deprotection of the ketal group with 70% $HClO_4$ gave keto alcohol **16**. Its primary alcohol was selectively protected as THP ether to prevent intermolecular acetal formation. The ketone **17** was converted to the enol triflate **18**. Due to steric hindrance of the *N*-benzyl group, Suzuki−Miyaura coupling of **18** with furan-3-boronic ester **8**[9] proceeded under strong basic conditions[12] using $PdCl_2$(dppf) to give the coupling product in 95% yield. Stereoselective hydrogenation[13] occurred from the β-side (vide infra) to give **19** (5.7:1), as expected from a previous model study.[5]

The stage was now set for the crucial construction of ring B by cyclization to iminium cation. Before this crucial transformation, a protecting benzyl group on a nitrogen in ring D was converted to a Boc group, since carbamate protection is essential for the efficient reduction of lactams to cyclic aminals. First, an ester side chain in

Scheme 1. Biosynthsis of Nakadomarin A from Ircinal



Scheme 2. Retrosynthetic Analysis of Nakadomarin A

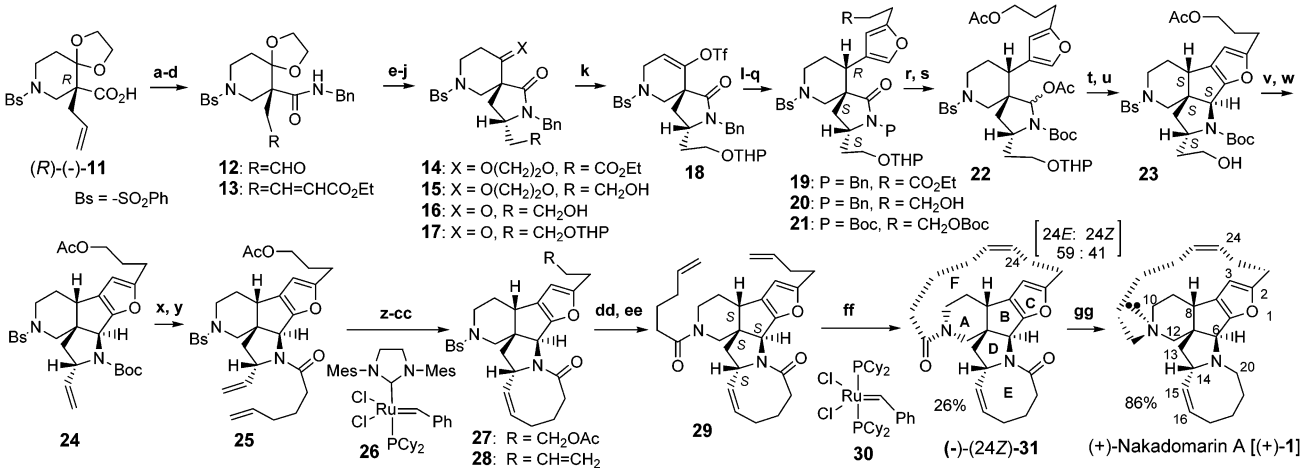


the furan ring was reduced with $LiBH_4$. The *N*-benzyl group in **20** was converted to a Boc group by deprotection−protection procedures to give **21**. Next, reduction of both Boc imide and carbonates with DIBALH, followed by treatment with Ac_2O/pyridine, gave the ester **22** as a 3:2 inseparable mixture of the two diastereomers in 62% yield (six steps from **19**). No over-reduction was observed even when a large excess of DIBALH was used. Treatment of **22** with *p*-TsOH, followed by deprotection of the THP ether, gave the desired tetracyclic product **23** in 87% yield as a single isomer. In the next phase of the synthesis, **23** was elaborated to set the stage for the formation of the 15- and 8-membered rings by sequential RCM reactions, where the sequence began with the parallel refunctionalization of the two protected primary alcohols. Selenation of **23** followed by oxidation of the selenide resulted in the formation of **24**. Deprotection of the Boc followed by *N*-acylation gave the diene **25** (54% from **23**). When **25** was exposed to the second-generation Grubbs catalyst **26**,[14] a facile RCM reaction ensued to furnish azocine lactam **27** in 70% yield. The same reaction using **30** afforded **27** in only 15% yield after 48 h with recovery of **25** (36%).[15] Hydrolytic removal of acetate followed by oxidation furnished an aldehyde that underwent a Wittig reaction under salt-free conditions to give **28** (53%, three steps), which was characterized by X-ray crystallography.[9] Reductive removal of the sulfonamide from **28** and *N*-acylation gave **29** (77%, two steps). When the diene **29** was exposed to the Grubbs ruthenium catalyst **30**,[16] the second RCM reaction occurred to give a mixture of geometrical isomers (Z/E = ca. 2:3 by NMR) from which (24*Z*)-**31** was isolated in 26% yield. Reduction of bislactam (24*Z*)-**31** with Red-Al resulted in the first total synthesis of (+)-nakadomarin A (free), **1**, $[\alpha]^{20}_D$

† Present address: Department of Chemistry, Faculty of Science, Kanagawa University, Hiratsuka, Kanagawa 259-1293, Japan.

10.1021/ja034464j CCC: $25.00

Scheme 3 [a]



[a] Conditions: (a) $BnNH_2$, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (WSC)·HCl, HOBt, DMF, 91%; (b) cat. OsO_4, NMO, aq THF, rt; (c) $NaIO_4$, CH_2Cl_2:H_2O (2:1), rt; (d) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, reflux; (e) DBU, EtOH; (f) 2 N NaOH, MeOH; (g) AcCl, EtOH, 54% (8 steps); (h) $LiBH_4$, MeOH, THF, 99%; (i) 70% $HClO_4$, CH_2Cl_2, rt, 91%; (j) DHP, cat. CSA, 91%; (k) i) $LiN(TMS)_2$, THF, −78 °C, ii) $PhNTf_2$, 87%; (l) **8**, $PdCl_2$(dppf), K_3PO_4, 80 °C, 3 h, 95%; (m) i) H_2, 10% Pd−C, MeOH, rt, 1.5 h, 71% (8α-H:8β-H = 1:5.7), ii) PPTS, EtOH, iii) separation of diastereomers, (iv) DHP, cat. CSA, 69%; (n) $LiBH_4$, MeOH, THF, 99%; (o) Li, liq. NH_3; (p) $PhSO_2Cl$, aq $NaHCO_3$, 80% (2 steps); (q) $(Boc)_2O$, Et_3N, cat. DMAP, 98%; (r) DIBALH, CH_2Cl_2, toluene; (s) Ac_2O, pyridine, 80% (2 steps); (t) *p*-TsOH, CH_2Cl_2; (u) 1 N HCl, THF, 87% (2 steps); (v) 2-nitrophenylselenocyanate, *n*-Bu_3P; (w) *m*CPBA, aq K_2HPO_4; (x) TFA, CH_2Cl_2; (y) 5-hexenoic acid, WSC·HCl, HOBt, 73% (4 steps); (z) **26** (20 mol %), CH_2Cl_2, 2 mM, 50 °C, 1.5 h; (aa) 2 N NaOH, MeOH, rt, 1.5 h, 64% (2 steps); (bb) Dess−Martin periodinane, 80%; (cc) $Ph_3P{=}CH_2$, 72%; (dd) Na, naphthalene; (ee) 5-hexenoic acid, WSC·HCl, HOBt, 77% (2 steps); (ff) **30** (15 mol %), CH_2Cl_2, 0.5 mM, 50 °C, 24 h, 26% (24*Z*), 44% (24*E*); (gg) Red-Al, toluene, reflux.

= +79.2 (*c* 0.12, MeOH), in 86% yield (Scheme 3). The same reduction of (24*E*)-**31** gave (+)-(24*E*)-nakadomarin A in 63% yield.

Although the ^{1}H NMR spectrum of synthetic (+)-nakadomarin A was similar to that of natural (−)-**1** reported by Kobayashi, the vinylic protons in the eight-membered ring and the methylene and methine protons connected to two tertiary amines of natural (−)-**1** were shifted downfield. Therefore, the ^{1}H NMR spectra of both natural and synthetic (+)-**1** were measured again in the presence of HCl under the same conditions by Professors Kobayashi and Tsuda. Those spectra clearly showed that these compounds were identical.[9] Furthermore, a careful comparison of the specific rotation [synthetic (+)-nakadomarin A (2HCl salt), **1**, $[\alpha]^{20}_D$ +45 (*c* 0.13, MeOH)] showed that the absolute configuration of all stereo centers in natural **1** [$[\alpha]^{20}_D$ −16 (*c* 0.12, MeOH)] could be assigned to be *R*.[17]

In summary, the first total synthesis of *ent*-(+)-nakadomarin A was completed from the readily available chiral **11**. The absolute configuration of natural **1** was assigned to be *R*. Finally, the procedure described here provides an access to structural analogues of nakadomarin A for further study, including biological evaluation.

Acknowledgment. This research was supported by a Grant-in-Aid for Scientific Research of Priority Areas (A) "Exploitation of Multi-Element Cyclic Molecules" from the Ministry of Education, Culture, Sports, Sciences, and Technology. Financial support from the Uehara Memorial Foundation is also gratefully acknowledged. We thank Professors J. Kobayashi and M. Tsuda (Hokkaido University) for their help in identifying natural **1** and synthetic *ent*-**1**. We also thank Dr. K. Yamaguchi for X-ray analysis and Ms. R. Hara for MS at the Analytical Center, Chiba University.

Supporting Information Available: Schemes for the preparation of **8** and *rac*-**11**; experimental procedures and characterization data for all new compounds reported in Scheme 3; copies of ^{1}H and ^{13}C NMR spectra for selected compounds (PDF). X-ray crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(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) Magnier, E.; Langlois, Y. *Tetrahedron* **1998**, *54*, 6201.
(3) Baldwin, J. E.; Whitehead, R. C. *Tetrahedron Lett.* **1992**, *33*, 2059.
(4) (a) Fürstner, A.; Guth, O.; Rumbo, A.; Seidel, G. *J. Am. Chem. Soc.* **1999**, *121*, 11108. (b) Fürstner, A.; Guth, O.; Düffels, A.; Seidel, G.; Liebl, M.; Gabor, B.; Richard, M. *Chem. Eur. J.* **2001**, *7*, 4811. (c) Magnus, P.; Fielding, M. R.; Wells, C.; Lynch, V. *Tetrahedron Lett.* **2002**, *43*, 947.
(5) Nagata, T.; Nishida, A.; Nakagawa, M. *Tetrahedron Lett.* **2001**, *42*, 8345.
(6) (a) Uchida, H.; Nishida, A.; Nakagawa, M. *Tetrahedron Lett.* **1999**, *40*, 113. (b) Nakagawa, M.; Torisawa, Y.; Uchida, H.; Nishida, A. *J. Synth. Org. Chem., Jpn.* **1999**, *57*, 1004. (c) Nakagawa, M. *J. Heterocycl. Chem.* **2000**, *37*, 567.
(7) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012.
(8) Winkler, J. D.; Axten, J. M. *J. Am. Chem. Soc.* **1998**, *120*, 6425.
(9) See the Supporting Information for complete experimental details and crystallographic, spectroscopic, and analytical data.
(10) The racemic acid **11**, which was prepared in >75% yield from commercially available methyl 4-oxopiperidinecarboxylate, was resolved to give the (*R*)-**11** in 99.6% ee using (+)-cinchonine. The absolute stereochemistry of (*R*)-**11** was determined by X-ray analysis of its cinchoninium salt.[9]
(11) Littel, R. D.; Masjedizadeh, M. R.; Wallquist, O.; McLoughlin, J. I. In *Organic Reactions*; Paquette, L. A., Ed.; Wiley: New York, 1995; p 315.
(12) (a) Miyaura, N.; Suzuki, *A. Chem. Rev.* **1995**, *95*, 2457. (b) Suzuki, A. *Pure Appl. Chem.* **1994**, *66*, 213.
(13) Brands, K. M. J.; DiMichele, L. M. *Tetrahedron Lett.* **1998**, *39*, 1677.
(14) Scholl, M.; Ding. S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.
(15) Humphrey, J. M.; Liao, Y.; Ali, A.; Rein, T.; Wong, Y.-L.; Chen, H.-J.; Courtney, A. K.; Martin, S. F. *J. Am. Chem. Soc.* **2002**, *124*, 8584.
(16) Grubbs, R. H.; Miller, S.; Fu, G. *Acc. Res.* **1995**, *28*, 446.
(17) The difference between these values is likely attributable to a difference in purity or partial racemization of **1** in its biosynthesis. Tsuda, M.; Inaba, K.; Kawasaki, N.; Honma, K.; Kobayashi, J. *Tetrahedron* **1996**, *52*, 2319.

JA034464J