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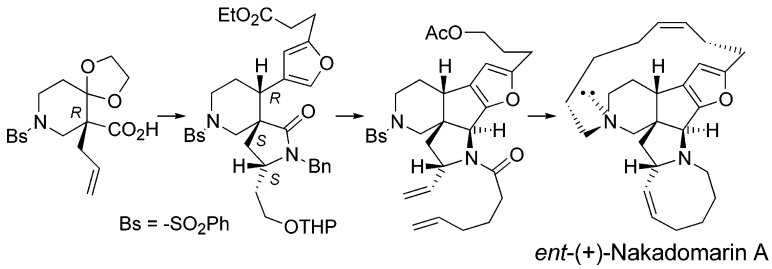

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The First Total Synthesis of Nakadomarin A

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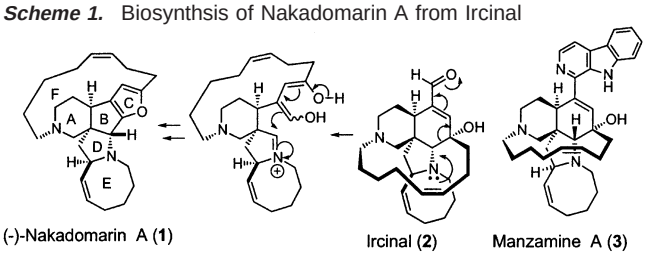
Nakadomarin A (**1**) was first isolated from a marine sponge collected at Okinawa by Kobayashi and co-workers.[1] Its structure was elucidated by exhaustive NMR study and shown to have a unique hexacyclic skeleton. Nakadomarin A was thought to be a member of the manzamine family,[2] and an interesting 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**.

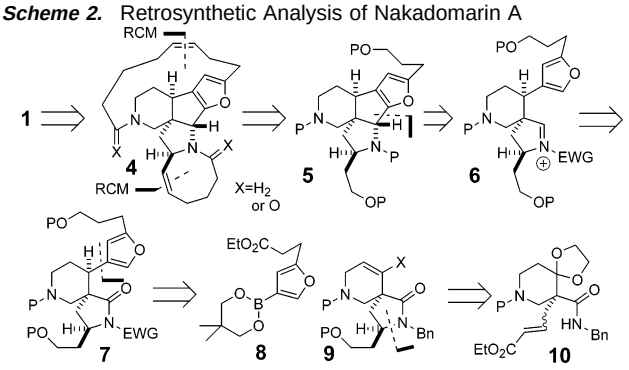
Condensation of (*R*)-(−)-**11**[5,10] with benzylamine, followed by catalytic dihydroxylation and oxidative cleavage of the 1,2-diol, gave aldehyde **12**, which was immediately converted to α,β-unsaturated ester **13** by Wittig olefination. Intramolecular Michael addition[11] of **13** upon treatment 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 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**, $[\alpha]^{20}_D$

Scheme 1. Biosynthsis of Nakadomarin A from Ircinal



Scheme 2. Retrosynthetic Analysis of Nakadomarin A



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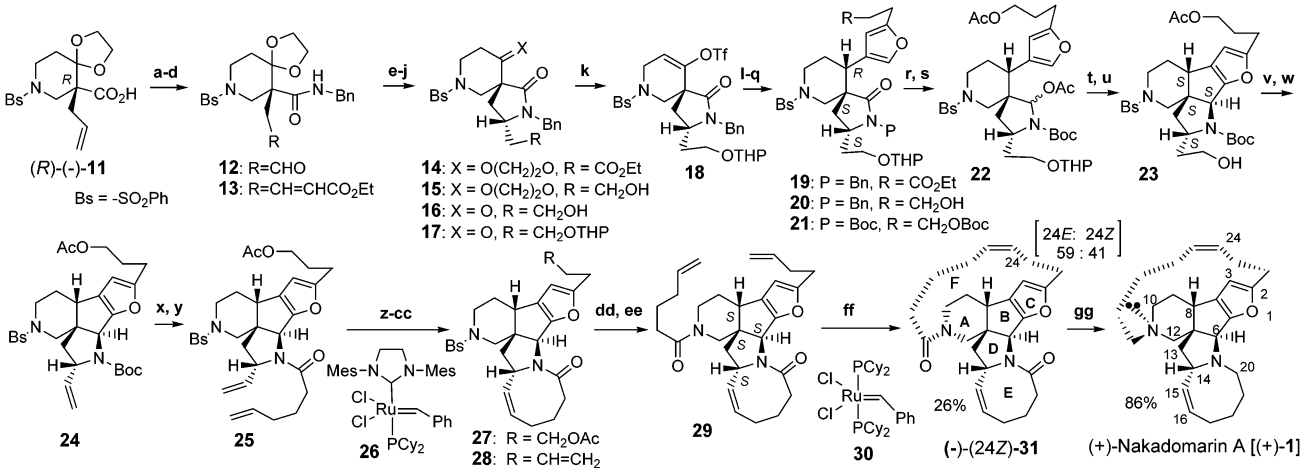
Scheme 3 [a]



[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.

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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.

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