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Total Synthesis of (−)-Nakadomarin A

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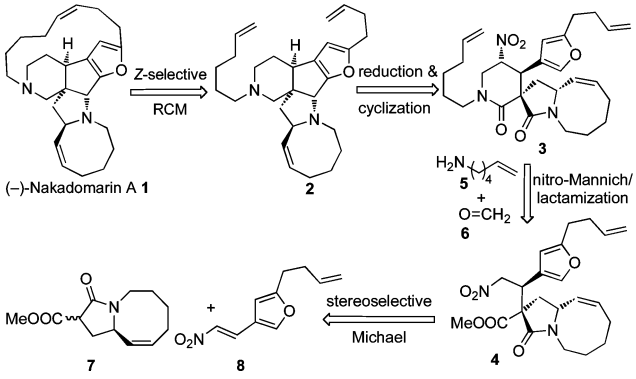
(−)-Nakadomarin A (**1**), a marine alkaloid of the manzamine family, was isolated from the sponge *Amphimedon* sp. off the coast of the Kerama Islands, Okinawa, in 1996. (−)-Nakadomarin A showed cytotoxic activity against murine lymphoma L1210 cells (IC_{50} = 1.3 μg/mL) and inhibition of cyclin dependent kinase 4 (IC_{50} = 9.9 μg/mL) and exhibited antimicrobial activity against the fungus *Trichophyton mentagrophytes* (MIC = 23 μg/mL) and the Gram-positive bacterium *Corynebacterium xerosis* (MIC = 11 μg/mL). This hexacyclic alkaloid contains an 8/5/5/5/15/6 ring system and four stereogenic centers, including one quaternary.[1,2]

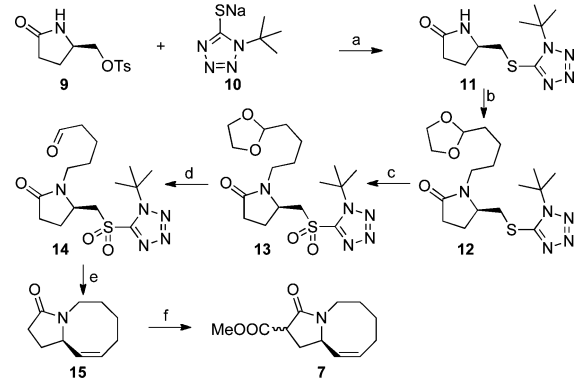
The challenging structure and impressive biological activities have made **1** an attractive target compound for the synthetic community. Numerous reports of methodologies targeting the core of nakadomarin A have appeared.[3−10] To date, however, only one synthesis of this natural product [36 steps (longest linear sequence)][14] and two syntheses of its antipode, (+)-nakadomarin A (longest linear sequences 37 and 29 steps, respectively),[12,13] have been achieved from commercially available starting materials. From extraction and synthesis, both nature and chemist have delivered only 8.5 mg of **1**. We believed that we could slash the step count from the current average of 34[11−13] and produce significant quantities of the target molecule by incorporating multiple catalyst-controlled carbon−carbon bond-forming steps and cascade sequences into our planned route.

Scheme 1. Synthetic Plan for (−)-Nakadomarin A (**1**)



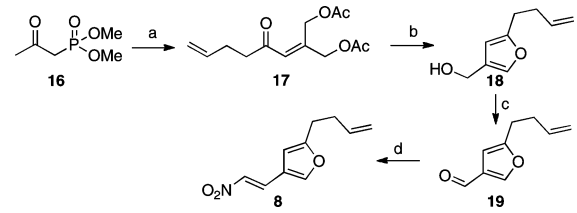
Our synthetic plan (Scheme 1) pivoted on the production of late-stage intermediate **3** on a multigram scale. Reduction of the nitro group and reductive manipulation of both carbonyl groups followed by a diastereoselective iminium ion cyclization would create diamine **2** poised for the final *Z*-selective olefin metathesis. We planned to construct intermediate **3** via a diastereoselective multicomponent nitro-Mannich/lactamization cascade of nitro ester **4** and the imine formed in situ from commercial amine **5** and formaldehyde **6**. As nitro ester **4** is the Michael adduct of 8,5-bicyclic pro-nucleophile **7** with nitro olefin **8**, we envisaged its stereocontrolled production using bifunctional organocatalysis.

Scheme 2. Synthesis of Pro-Nucleophile **7**[a]



[a] Reaction conditions: (a) THF, reflux, 12 h, 96%; (b) 2-(4-bromobutyl)-1,3-dioxolane, NaH, Bu_4NI (cat), DMSO, 12 h, RT, 71%; (c) MCPBA, CH_2Cl_2, 14 h, RT, 78%; (d) HCl, THF, 2 h, RT, 98%; (e) Cs_2CO_3, DMF, THF, H_2O, 70 °C, 10 h, 56%; (f) LHMDS, dimethylcarbonate, THF, −78 to 0 °C, 2.5 h, 82%.

Scheme 3. Synthesis of Electrophile **8**[a]



[a] Reaction conditions: (a) NaH, BuLi, THF, 0 °C, 1 h, allylbromide, then 2-oxopropane-1,3-diyl diacetate, THF, RT, 2 h, 42%; (b) HCl, EtOH, 24 h, 65 °C, 69%; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to RT, 0.5 h, 86%; (d) $MeNO_2$, KOH, EtOH, 0 °C, 2 h, then MsCl, Et_3N, −15 °C to RT, 15 min, 88%.

Fragment **7**, the 8,5-bicyclic pro-nucleophile, was constructed in six steps beginning with the tosylate of pyroglutamol **9** (Scheme 2). Nucleophilic substitution with sodium thiolate **10** afforded sulfide **11**. N-Alkylation with 2-(4-bromobutyl)-1,3-dioxolane followed by sulfide-to-sulfone oxidation and acetal deprotection generated **14**, the precursor to the intramolecular Julia−Kocienski olefination. At moderate dilution on a multigram scale, this was efficiently carried out without racemization using cesium carbonate as the base in wet THF/DMF. Addition of water was crucial for the high yield, diastereoselectivity, reproducibility, and enantiomeric purity of the 8,5-bicyclic product **15**. This is the first example of a highly diastereoselective formation of a *Z* alkene in an eight-membered ring via an intramolecular Julia−Kocienski reaction and the first example of such a process in complex natural product synthesis.[14] C-Acylation with dimethyl carbonate completed this practical multigram synthesis of pro-nucleophile **7**.

Fragment **8**, the furanyl nitro olefin, was constructed in four steps from ketophosphonate **16** on a multigram scale (Scheme 3). A one-pot sequential multistep allylation[15]/WHE reaction using allyl bromide

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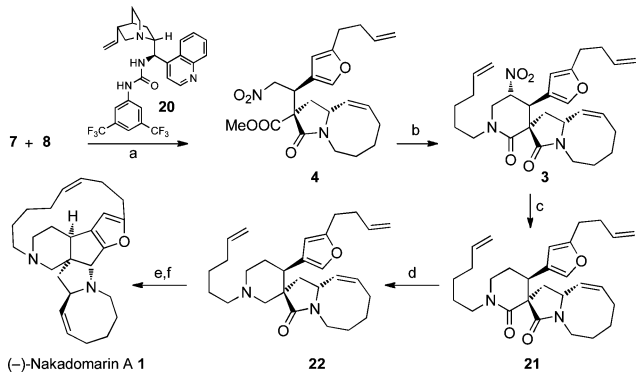
Scheme 4. Synthesis of (−)-Nakadomarin A (**1**)[a]



[a] Reaction conditions: (a) organocatalyst **20** (15 mol %), toluene, 30 °C, 8 days, 57%, 91:9 dr; (b) hex-5-enamine, CH_2═O, MeOH, reflux, 3 h, 68%; (c) AIBN, Bu_3SnH, toluene, reflux, 4 h, 70%; (d) $LiAlH_4$, toluene, −20 °C, 1 h, then HCOOH, RT, 14 h, 86%; (e) DIBAL, toluene, −20 °C, 1 h, then HCl, 90 °C, 24 h, 41% (yield of **2**); (f) Grubbs first-generation catalyst, (+)-CSA, CH_2Cl_2, reflux, 3.5 h, 62%, 63:37 *Z*/*E*.

and diacetyl dihydroxyacetone afforded enone **17**. An acid hydrolysis then afforded furanyl alcohol **18**,[16,17] which was subjected to Swern oxidation and Henry-type condensation to give the desired nitro olefin **8**.

Trial Michael addition reactions of **7** and **8** using stoichiometric LHMDS or KHMDS at low temperature led to inseparable diastereomeric mixtures (60:40 dr in both cases), whereas stoichiometric DABCO led to decomposition of the nitro olefin. That two of the possible four diastereoisomers were produced was attributed to a strong stereochemical bias toward the most accessible exo face of the enolate of the 8,5-bicyclic system. This implies that poor stereofacial control to the nitro olefin was responsible for the 60:40 mixture. Accordingly, a chiral catalyst known to impart high levels of enantiocontrol in nitro olefin Michael additions was sought. Pleasingly, use of bifunctional cinchona catalyst **20**[18−21] introduced by our group and others facilitated the diastereoselective Michael addition and the isolation of the desired material in good yield as a 10:1 mixture of diastereomers (Scheme 4). Subjection of **4** to a three-component nitro-Mannich/lactamization cascade under our previously reported conditions[21,22] facilitated the construction of **3** in 68% yield. Traceless reduction of the nitro group was achieved using a modification of the Ono procedure[23] and provided **21** as a single diastereoisomer. To exploit a furan/iminium ion cyclization to create the pentacyclic core, it was necessary to fully reduce the carbonyl of δ-lactam **21** and partially reduce that of the γ-lactam, which overall was a challenging task. Pleasingly, we found a remarkable reactivity difference between the lactams: a low-temperature $LiAlH_4$ reduction facilitated exclusive delivery to the carbonyl of the δ-lactam. When the reaction mixture was quenched with excess formic acid and allowed to warm to ambient temperature, amine **22** was isolated in 86% yield. Reports of the partial reduction of a pyrrolidin-2-one derivative to its aminol are rare.[24,25] The low reactivity of the carbonyl relative to the metalated aminol intermediates results either in over-reduction to the pyrrolidine or return of unreacted starting material.[26] After significant optimization, we achieved single hydride delivery with DIBAL in toluene at −20 °C. The resulting reaction mixture was then added to chilled HCl (0.1 M) and subsequently heated for 24 h. A highly stereoselective cyclization occurred, affording pentacycle **2**. This unprecedented reduction/iminium ion formation/diastereoselective C−C bond-forming cyclization cascade[27] is a powerful transformation that allowed us to circumvent more lengthy alternatives.

Our synthesis of (−)-nakadomarin A (**1**) was completed by a *Z*-selective olefin metathesis (63:37 *Z*/*E*), which was achieved using Grubbs first-generation catalyst in the presence of an excess of either (+)- or (−)-CSA. In the absence of CSA, good reactivity but an undesirable bias toward the *E* isomer (60:40 *E*/*Z*; in agreement with the three previous syntheses)[11−13] was witnessed. Protonation of amines during alkene ring-closing metathesis is a well-documented process.[28] However, to the best of our knowledge, this is the first example where an *E*/*Z* selectivity was reversed when protonated amines were used. Diastereomer separation was achieved using normal-phase semi-preparative HPLC. The spectroscopic data (^{1}H NMR, ^{13}C NMR), high-resolution mass spectrometric data, and specific rotation of our synthetic material were in excellent agreement with published data.[11−13]

In conclusion, we have developed a short and highly stereoselective synthesis of (−)-nakadomarin A (**1**) (longest linear sequence 12 steps from tosylate **12**, 16 steps in total). The significant quantities of **1** prepared by this route (101 mg total, largest batch 69 mg) will allow the future production of natural-product analogues. The results of these endeavors will be published in due course.

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Supporting Information Available: Experimental procedures and characterization data for **1** and all new compounds (**2**−**4**, **7**, **8**, **11**−**15**, **17**−**19**, **21**, and **22**). This material is available free of charge via the Internet at http://pubs.acs.org.

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