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Total Synthesis of (–)-Nakadomarin A

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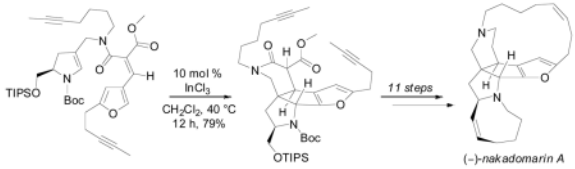
Abstract



A concise diastereoselective total synthesis of (–)-nakadomarin A has been completed in 21 steps from D-pyroglutamic acid. Key steps include an enecarbamate Michael addition/furan-*N*-acyliminium ion cascade cyclization to provide the tetracyclic core, and ring-closing alkyne and alkene metatheses to construct the 15- and 8-membered azacycles, respectively.

The manzamines are a class of architecturally fascinating, biologically active marine alkaloids.[1] Perhaps the most structurally intriguing member is nakadomarin A (**1**), isolated by Kobayashi[2a] from an Okinawan sponge *Amphimedon* sp. Its structure consists of an unprecedented 6/5/5/5/8/15 hexacyclic ring system and is the only manzamine alkaloid that embodies a furan ring. A biosynthetic pathway from ircinal A has been proposed by Kobayashi[2b] (Scheme 1).

This limited availability, coupled with an inspiring structure have made nakadomarin A the target of a number of synthetic groups.[3] Nishida and co-workers have reported pioneering, though lengthy, total syntheses of both **1**[4a] and *ent*-**1**[4b] (36 and 38 steps, respectively). Young and Kerr completed the total synthesis of *ent*-**1**[5] in 29 steps from D–mannitol. Most recently, the Dixon group reported the shortest synthesis of **1** to date, requiring only 16 total steps.[6] A strategy common to each of these syntheses is the utilization of ring-closing alkene metathesis to construct the 15-membered macrocycle. While attractive in its efficiency, this approach yielded a mixture of configurational isomers in each case, often favoring the undesired *E*-isomer.[7]

We recently reported our strategy for the rapid construction of the tetracyclic core of nakadomarin A.[3h] In the key step, enecarbamate **2** underwent a stereoselective intramolecular Lewis acid-catalyzed Michael addition, and the resulting *N*-acyliminium ion[8] **3** was trapped with the proximate furan to provide tetracycle **4** (Scheme 2). Based on the success of the model system study, we directed our efforts toward the preparation of a tetracycle analogous to **4** that would be fully functionalized for the completion of the total synthesis. Our retrosynthetic analysis is outlined in Scheme 3. Based on precedents from the previous total syntheses, ring-closing metathesis (RCM) could provide the eight- and fifteen-membered azacycles. We hoped to circumvent the *E*/*Z* selectivity problem in the

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Supporting Information Available: Spectroscopic data and experimental details for the preparation of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

construction of the macrocycle by utilizing a ring-closing alkyne metathesis (RCAM)[9]/semi-hydrogenation strategy to deliver the *Z*-cycloalkene as a single configurational isomer. The viability of this strategy was documented by Fürstner and co-workers in their synthesis of the macrocyclic perimeter of nakadomarin A.[3b] The key cyclization of enecarbamate **7** to the tetracycle **5** should follow the conjectured pathway in our model system. In this case, it was hoped that the Lewis acid-activated conjugated double bond would approach the enecarbamate from the face away from the bulky TIPS group[10] through an *anti* conformer to provide the *N*-acyliminium ion **6** that would subsequently undergo closure with the now more electron rich furan substituent to deliver lactam **5**. The key cyclization substrate **7** could be obtained as the thermodynamic product of Knoevenagel condensation of furaldehyde **8** with β– amido ester **9** (vida infra).

The preparation of amide **9** proceeded in a straightforward fashion (Scheme 4). Enecarbamate **11** was prepared from optically pure imide **10**[11] using the one-pot method recently reported by Yu.[12] Vilsmeier- Haack formylation of enecarbamate **11** followed by reductive amination of the resultant vinylogous imide **12** with 5-heptynylamine provided the corresponding secondary amine. *N*-acylation with methyl malonyl chloride gave amide **9**.

The preparation of furaldehyde **8** took advantage of Maldonado's methodology for the synthesis of 2,4- disubstituted furans from γ, γ′-diacetoxyenones.[13] Thus, metalation of dimethyl methyl phosphonate followed by treatment with methyl 4-hexynoate gave β–ketophosphonate **13** (Scheme 5). Horner-Wadsworth- Emmons reaction between phosphonate **13** and 1,3- diacetoxyacetone provided γ, γ ′-diacetoxyenone **14**. This enone underwent smooth, acid-catalyzed cyclization in methanol at 50 °C to furanmethanol **15** in 82% yield. Finally, Swern oxidation of alcohol **15** furnished the desired furaldehyde **8**.

Based on observations made during our model system study, we anticipated that Knoevenagel condensation between amide **9** and furaldehyde **8** would provide unsaturated amide **7**, possessing the requisite *E*-geometry for the cyclization to tetracycle **5**. This thermodynamic control has been previously observed in related systems[14] and can be rationalized by better overlap of the ester and adjacent double bond in *E*-amide **7**, in contrast to the carbonyls of the corresponding Z-amide, both of which would be twisted out of conjugation. Much to our delight, heating amide **9** and furaldehyde **8** in benzene in the presence of benzoic acid and piperidine delivered the *E*-configurational isomer **7** as the sole product in 87% yield (Scheme 6). Subjection of enecarbamate **7** to our standard cyclization conditions (10 mol % $Sc(OTf)_3$, CH_2Cl_2, rt) resulted in cyclization to the desired tetracycle. However, these reaction conditions also caused partial cleavage of the silyl ether, resulting in the isolation of a mixture of tetracyclic silyl ether **5** and the corresponding alcohol. This minor setback could be avoided altogether if $InCl_3$ was employed as the catalyst and the reaction was run at reflux, providing tetracycle **5** in 79% yield. Saponification of ester **5** followed by thermally-promoted decarboxylation gave the lactam **16**. The diyne functionality of lactam **16** was subjected to several different alkyne metathesis systems with varying levels of success. Grela's optimized conditions[15] of the Mortreux alkyne metathesis system[16] ($Mo(CO)_6$, 2- fluorophenol, 3-hexyne, 1,2-diphenoxyethane in chlorobenzene at 140 °C, 3 h) gave cycloalkyne **17** in 41% yield (54% brsm). The Schrock carbyne catalyst[17] in chlorobenzene (25 mol %, 80 °C, 3 h) proved more effective, allowing cyclization to **17** in 77% yield on a gram scale. It should be noted the air-stable molybdenum nitride complex [(pyridine)$(Ph_3SiO)_3Mo{\equiv}N$] recently developed by Fürstner[18a] gave comparable results with a slightly lower catalyst loading (20 mol %, toluene at 80 °C, 16 h, 80% yield). The *cis* double bond of 15- membered ring was then introduced by straightforward Lindlar reduction of cycloalkyne **17** and unaccompanied by the *E*-olefin stereoisomer (Scheme 7).

Synthetic efforts were then directed to the construction of the azocine ring and completion of the total synthesis (Scheme 7). Deprotection of the TIPS ether **17** furnished alcohol **18**. Oxidation of alcohol **18** with IBX in DMSO followed by Tebbe olefination (Wittig, Peterson and Nysted protocols were ineffective) proceeded uneventfully to yield vinyl pyrrolidine **19**. Deprotection of the Boc carbamate with TFA and *N*-acylation with 5-hexenoyl chloride gave alkene metathesis substrate **20**. Ring-closing metathesis of diene **20** to azocine **21** proved problematic. The best yield was obtained when diene **20** was treated with an equimolar amount of Grubbs 1st-generation catalyst in refluxing methylene chloride. Reduction of the resultant bis-lactam **21** with alane provided (–)-nakadomarin A in 58% overall yield from diene **20**. Spectral data (NMR, IR, MS) was identical to that of natural **1**. The optical rotation confirmed its absolute configuration ($[\alpha]_D = -72.7$ (*c* = 0.12, MeOH), lit.[4a] $[\alpha]_D = -73.0$ (*c* = 0.08, MeOH)).

In conclusion, we have completed a concise total synthesis of (–)-nakadomarin A in 21 steps from D– pyroglutamic acid. Our previously reported strategy for the rapid assembly of the tetracyclic core, which features a tandem enecarbamate Michael addition/furan-*N*-acyliminium ion cyclization, has now been modified to incorporate functionality for the completion of a completely diastereoselective total synthesis. Moreover, a sequential ring-closing alkyne metathesis/semi-hydrogenation strategy was utilized to obtain the 15-membered azacycle as a single configurational isomer. The flexibility of this route allows for the preparation of nakadomarin A structural analogs. Indeed, the cyclization of a pyrrole analogous to furan **2** was successful. These studies are currently underway and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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7. Nishida and Kerr obtained a 1:1.5 and 1:1.7 ratio of *Z:E* isomers, respectively. Dixon however obtained a favorable 1.7:1 *Z:E* ratio by including an excess of either enantiomer of camphorsulfonic acid in the metathesis reaction mixture.

8. For a review of N-acyliminium ion cyclizations, see: Maryanoff BE, Zhang HC, Cohen JH, Turchi TJ, Maryanoff CA. Chem Rev. 2004; 104:1431. [PubMed: 15008627]
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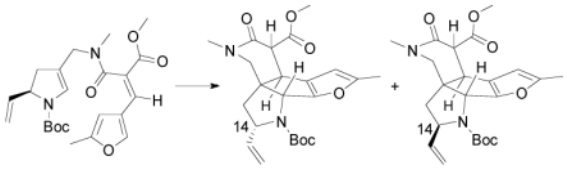
10. A vinyl group was initially investigated, but its steric influence was found to be insufficient, as a 1:1 mixture of diastereomers was obtained from the cyclization to the corresponding tetracycle. These stereoisomers are presumably epimeric at C14:



11. Prepared in four steps from D-pyroglutamic acid in 67% overall yield. For details, see Supporting Information.
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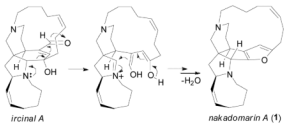
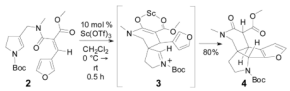
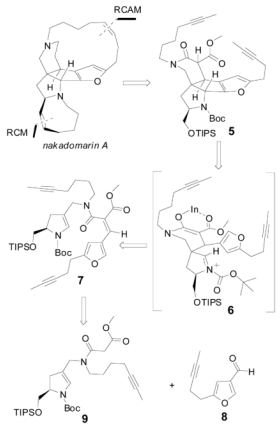


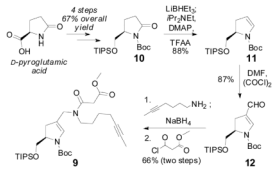
Scheme 1.
Proposed biosynthesis of nakadomarin A.



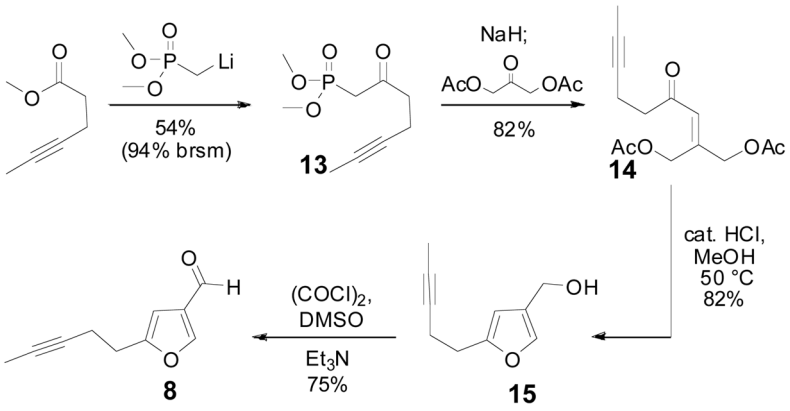
Scheme 2.
Model study of the construction of the core of **1**.



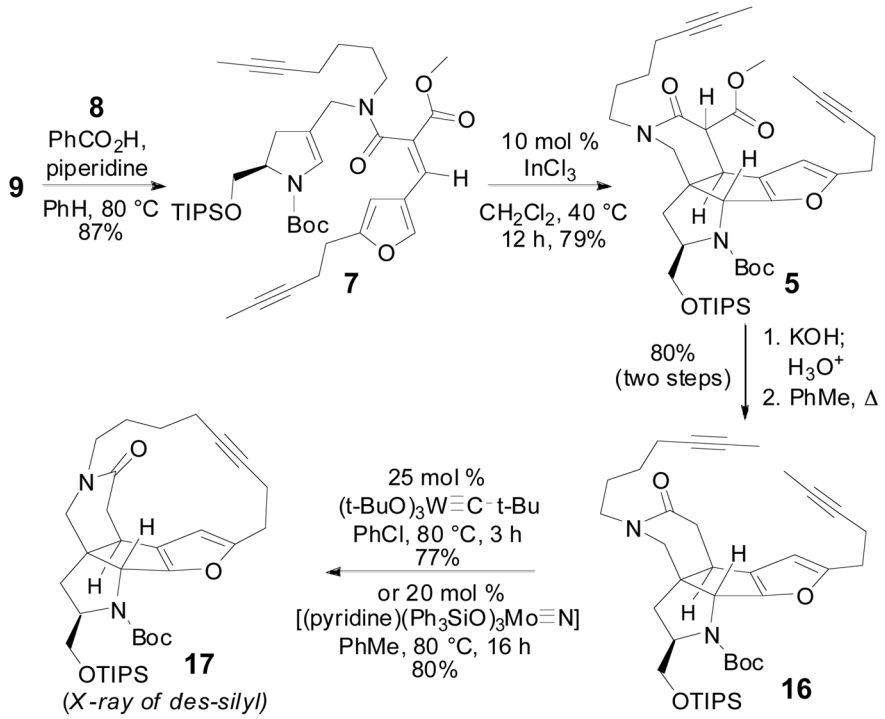
Scheme 3.
Retrosynthetic analysis of (–)-nakadomarin A (**1**).



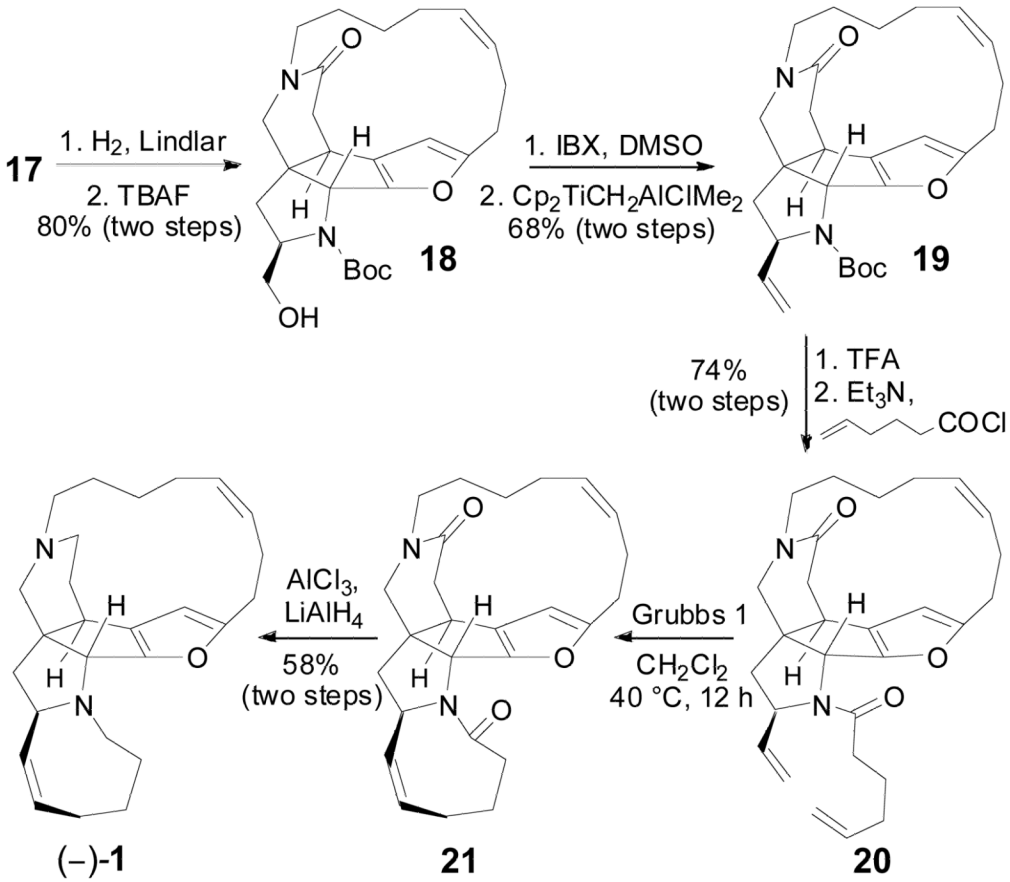
Scheme 4.
Preparation of amide **9**.



Scheme 5.
Synthesis of furaldehyde **8**.



Scheme 6.
Construction of the pentacyclic core of **1**.



Scheme 7.
Completion of the total synthesis of **1**.