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A Scalable Total Synthesis of (−)-Nakadomarin A

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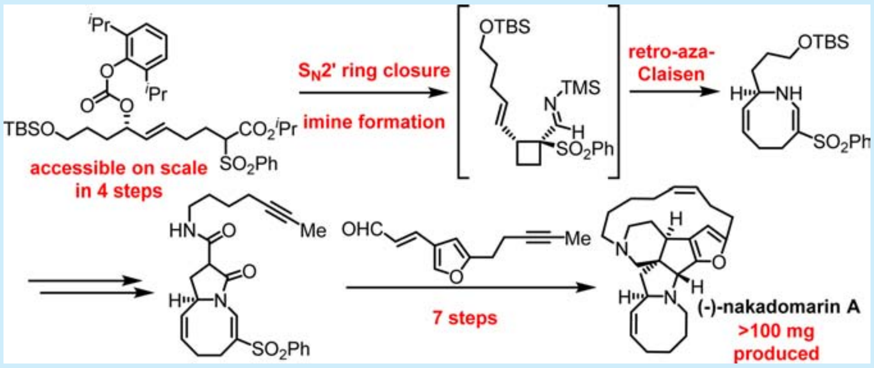
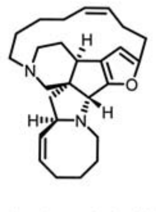
Ⓢ *Supporting Information*

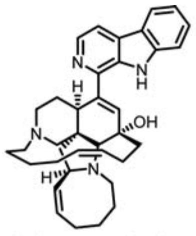


ABSTRACT: The convergent total synthesis of the manzamine alkaloid (−)-nakadomarin A (**1**) is described. The retrosynthetic analysis recognized spirocycle **3**, assembled via an organocatalyst-promoted Michael addition/cyclization between bicyclic lactam **4** and furan aldehyde **5**, both accessible from achiral starting materials and on a multigram scale. Lactam **4** is assembled through an S_N2'/reduction/Staudinger/retro-aza-Claisen sequence on scale. After spirocyclization, the synthesis of nakadomarin is completed in only six steps.

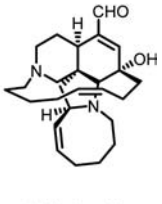
Isolated from the marine sponge *Amphimedon* sp. in 1997 by Kobayashi and co-workers,[1] the manzamine alkaloid (−)-nakadomarin A (**1**) has demonstrated a wide range of biological properties.[2−4] These include cytotoxic activity against murine lymphoma L1210 cells (IC_{50} = 1.3 μg/mL), inhibition of cyclin-dependent kinase 4 (IC_{50} = 9.9 μg/mL; associated with tumorigenesis of a variety of cancers), and antimicrobial activity against the Gram-positive bacterium *Corynebacterium xerosis* (MIC = 11 μg/mL) and the fungus *Trichophyton mentagrophytes* (MIC = 23 μg/mL).[1,5] In addition to biological activity, an architecturally unique framework has garnered much attention for nakadomarin A in the synthetic community, consequently resulting in a number of total syntheses[6−17] and synthetic approaches.[18−30] A preponderant number of strategies have entailed either creating a tricyclic core encompassing rings A, B, and D or constructing a DE fragment and appending A then C. One of the two most recent efforts by Evans and coworkers[12] features a novel strategy and is extraordinarily brief, creating ring A by combining a macrocyclic CF fragment with a chiral DE fragment. However, no synthesis to date has begun with racemic/achiral starting materials to produce the enantioenriched target, and thus, these methods require the use of chiral pool building blocks or resolution, which can limit the scalability and throughput of the synthetic route (versus, for example, chiral organocatalysis). Herein we describe an original and efficient approach toward (−)-nakadomarin A (**1**) utilizing achiral or racemic starting materials while minimizing the use of protecting groups.



(-)-nakadomarin A (**1**)



(+)-manzamine A



(+)-ircinal A

We envisioned (−)-nakadomarin A (**1**) as arising retrosynthetically from metathesis and partial hydrogenation of diyne **2** (Scheme 1), from which we anticipated that ring B could be readily accessed via Friedel−Crafts-type ring closure of spirocycle **3** (owing to the electrophilic character of the vinylogous sulfimidinium ion; vide infra). We believed that this spirocycle could be assembled by an organocatalyst-promoted Michael addition/spirocyclization cascade between bicyclic lactam **4** (10 steps from achiral and racemic starting materials) and unsaturated β-furyl aldehyde **5** (five steps).

Our synthesis of (−)-nakadomarin A (**1**) commenced with the preparation of bicyclic lactam **4** (Scheme 2) via an initial Roush-modified[31] Horner−Wadsworth−Emmons (HWE) olefination of aldehyde **6** with phosphonate **7** in 90% yield. (*R*)-CBS-catalyzed reduction[32] of the resultant enone **8** provided the expected (*S*)-allylic alcohol, which was subsequently subjected to acylation with chloroformate **9** to provide allylic

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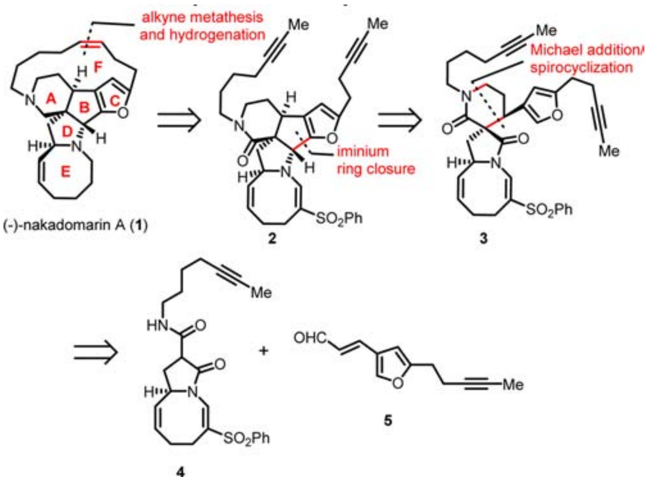
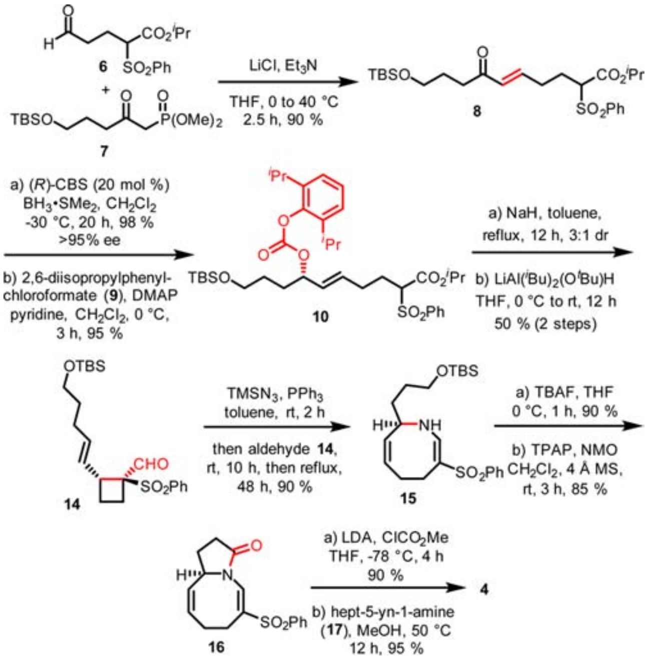
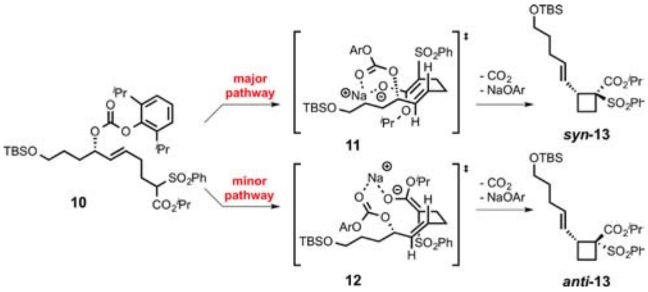
Scheme 1. Retrosynthetic Analysis for 1



Scheme 2. Preparation of Bicyclic Lactam 4



Scheme 3. Transition States for S_N2' Cyclization

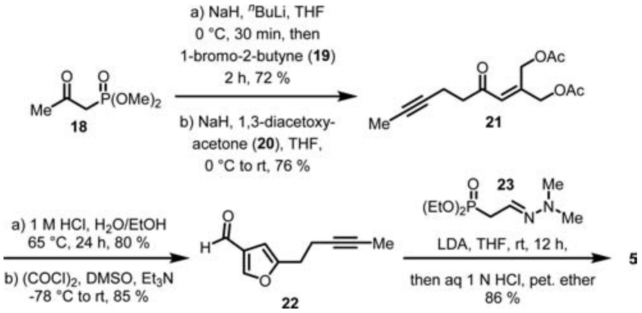


carbonate **10** in high yield and enantiomeric excess (93%, >95% ee) over two steps. Using methodology previously developed in our laboratories,[33−37] azocine **15** was assembled from allylic carbonate **10** via an S_N2'/reduction/Staudinger/retro-aza-Claisen sequence. Allylic carbonate **10** was deprotonated to give the more stable *Z* sodium enolate, which can exist as two rotamers about the adjacent single bond in the counterion-templated transition states **11** and **12** (Scheme 3).[35] It has been postulated that the phenylsulfonyl group should prefer the *syn* transition state **11**, as it leads to a reduction in steric interactions with the adjacent olefinic side chain compared with **12**.[35] This is consistent with observed 3:1 diastereoselectivity favoring the desired major diastereomer, *syn*-**13**. During the formation of cyclobutane *syn*-**13** and its diastereomer, the diisopropylphenoxycarbonyloxy group is displaced, ultimately degrading to CO_2 and diisopropylphenolate. The use of phenyl choroformate, however, results in diminished yields because of regeneration of the (*S*)-allylic alcohol via deacylation of **10**. The purified cyclobutane *syn*-**13** was then directly reduced to aldehyde **14** with LDBBA[38] (50% over two steps). Aldehyde **14** was immediately subjected to Staudinger imine formation using preformed TMS phosphanimine to minimize the formation of the oxocine via retro-Claisen rearrangement. The resulting imine underwent thermal retro-aza-Claisen rearrangement, and azocine **15** was thus obtained in 90% yield from **14** and from allylic carbonate **10** with excellent overall efficiency.

With azocine **15** in hand, cleavage of the primary silyl ether followed by oxidation of the resulting alcohol using TPAP/NMO,[39] subsequent ring closure, and further in situ oxidation provided bicyclic lactam **16** in 77% overall yield. Carboxylation followed by amidation with alkynyl amine **17** gave lactam **4** in high yield. The foregoing sequence is one of two reported routes that does not employ ring-closing metathesis to construct the five/eight-membered D/E rings of (−)-nakadomarin A and has been executed reproducibly on multigram scale.

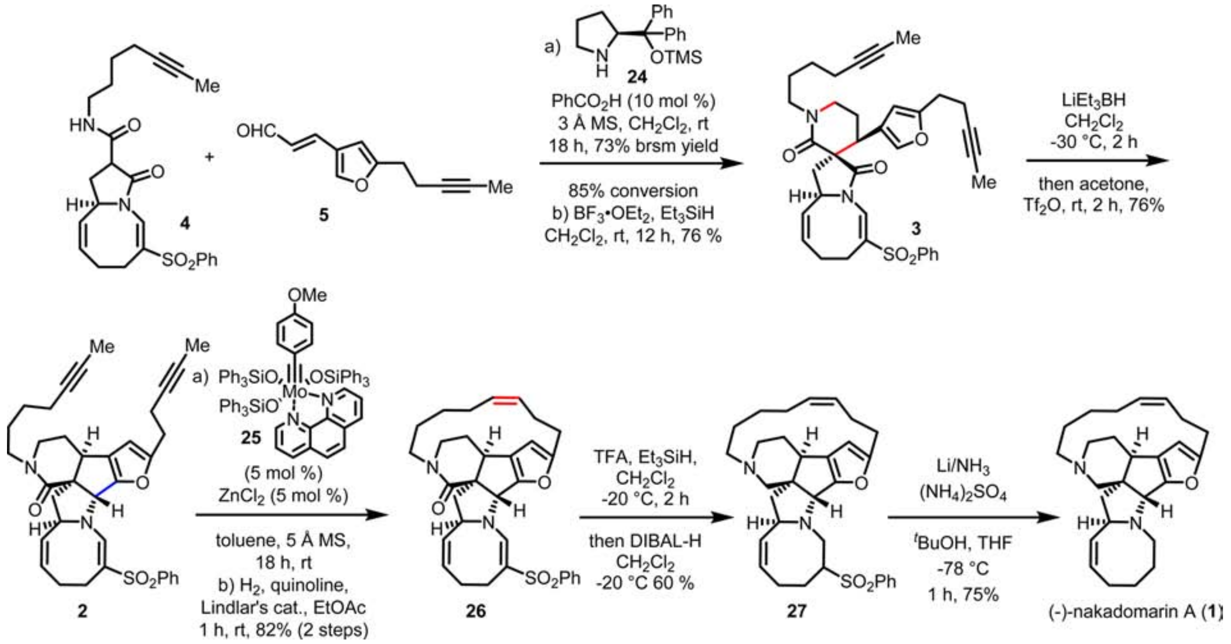
By means of procedures adapted from those reported by Dixon[14] and Funk,[16] the synthesis of *β*-furyl aldehyde **5** commenced with propargylation of the dianion of phosphonate **18** with 1-bromo-2-butyne (**19**) (Scheme 4). Subsequent HWE olefination with 1,3-diacetoxyacetone (**20**) provided enone **21** (55% over two steps). Acid-catalyzed cyclization in ethanol followed by Swern oxidation provided furyl aldehyde **22** (68% over two steps). HWE reaction with iminophosphonate **23** followed by biphasic hydrolysis (HCl/petroleum ether) provided *β*-furyl aldehyde **5** in high yield (86%).

Scheme 4. Preparation of *β*-Furyl Aldehyde 5



With the coupling partners **4** and **5** in hand, we sought to investigate the organocatalyst-promoted Michael/spirocyclization cascade with malonamide as a nucleophile to construct ring A (Scheme 5). It was found that under the optimized conditions, the Jørgensen−Hayashi catalyst **24** was the most effective among those examined (pyrrolidine as an achiral catalyst did not afford acceptable diastereoselectivity in an analogous system).[40−42] Catalytic benzoic acid was required to

Scheme 5. Spirocycle Formation and Completion of the Synthesis of (−)-Nakadomarin A



facilitate iminium formation, and the presence of 3 Å molecular sieves was required to sequester the H_2O generated in order to prevent retro-Paal−Knorr-type cleavage of furan **5**. The resulting adduct was obtained in good yield (73% yield, 85% conversion) with very good selectivity (92:8 dr) on at least a 0.5 g scale of amide **4**. The resulting cycloadduct with a chiral auxiliary incorporated (as confirmed by X-ray crystallographic analysis; see the Supporting Information) was treated with BF_3−OEt_2 and triethylsilane to cleave the auxiliary to provide **3**. Efforts to conduct the reaction employing catalytic **24** (in the absence of molecular sieves in order to release the catalyst via hydrolysis) resulted in hydrolytic decomposition (retro-Paal−Knorr) of furan **5**. Further investigation of the feasibility of a catalytic process is currently underway in our laboratories.

The pentacyclic core of (−)-nakadomarin A (ABCDE ring system) was then completed by a Friedel−Crafts-type closure to afford ring B, promoted by the formation of the tricyclic iminium ion via regioselective reduction of the more reactive vinylogous sulfimide carbonyl to the aminol borate with $LiEt_3BH$ and subsequent triflation. Under the optimized conditions, addition of acetone was required to quench any remaining hydride. Cyclization then occurred efficiently under milder conditions than for related transformations,[6−30] affording pentacyclic system **2** in a good yield (76%) due to the increased electrophilicity of the more electron-deficient vinylogous sulfimidinium ion.

In the presence of the alkyne metathesis catalyst **25**, developed by Fürstner,[43] diyne **2** was readily converted to the 15-membered-ring macrocycle **26** in 78% overall yield after hydrogenation of the resulting macrocyclic alkyne in the presence of Lindlar's catalyst. Interestingly, when the RCAM was performed on the azocine derivative of **2** bearing no vinyl sulfone group (a free tertiary amine), the major product obtained was the saturated acyclic dimer of the substrate.

Treatment of hexacyclic amine **26** with TFA/Et_3SiH followed by in situ treatment with DIBAL-H resulted in reduction of both the lactam and the vinylogous sulfonamide to afford sulfone **27** in 60% yield (unoptimized). When desulfonylation of this material was initially attempted with Li/NH_3/^{t}BuOH, (−)-nakadomarin A (**1**) was produced in low yield along with a major byproduct resulting from β-elimination (ring opening) of eight-membered azocine ring E. Fortunately, inclusion of $(NH_4)_2SO_4$[44] promoted protonation of the intermediate carbanion, resulting in clean desulfonylation without fragmentation to give **1** in 75% yield. Spectral data (IR, ^1H and ^{13}C NMR) of synthetic (−)-nakadomarin A ($[\alpha]_D^{25}$ = −72.6 (c = 0.26, CH_3OH)) were compared to those of synthetic (−)-nakadomarin A and found to be identical.

In conclusion, we report herein an efficient synthesis of (−)-nakadomarin A (**1**) from achiral and racemic starting materials. The synthesis is completed in 17 steps (longest linear) in 3% overall yield. This route has to date provided >100 mg of **1**. Current efforts in our laboratories toward a second-generation synthesis aimed at improving the overall selectivity, scalability, and efficiency of the synthetic route are well underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03137.

Experimental procedures and spectroscopic and crystallographic data (PDF)

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Notes

The authors declare no competing financial interest.

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