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Total Synthesis of (−)-Nakadomarin A

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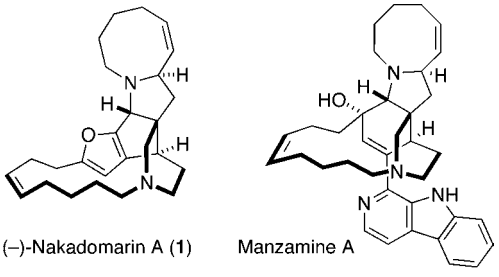
Supporting Information

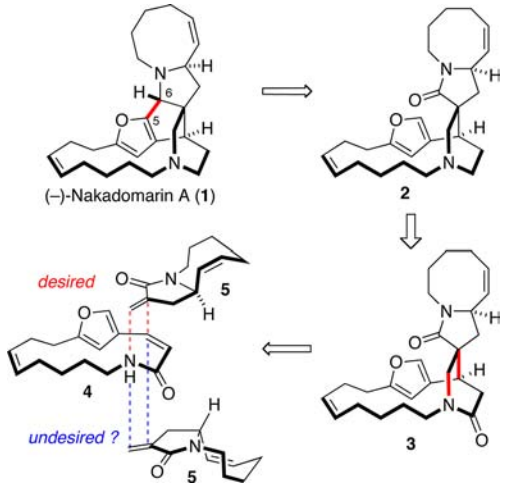
ABSTRACT: The convergent synthesis of the polycyclic alkaloid (−)-nakadomarin A (**1**) is reported. The synthesis plan identified macrocyclic lactam **4** as one of the important synthons (eight steps). The other synthon (five steps) was bicyclo[6.3.0] lactam **5** containing a single stereocenter that controlled all of the subsequent stereochemistry during the assembly process. A silyl triflate-promoted cascade of **4** and **5** was used to assemble the bulk of the alkaloid skeleton with the exception of the C5−C6 bond. The nakadomarin synthesis was then completed in one additional step.

(−)-Nakadomarin A (**1**) is an alkaloid that was isolated in 1997 from the marine sponge *Amphimedon* sp. found off the coast of the Kerama Islands, Okinawa.[1] Biological evaluation of **1** has revealed a wide range of potential therapeutic attributes, including cytotoxic, antimicrobial, and antibacterial activities. While this alkaloid belongs to the manzamine family,[2] it is architecturally distinct. Both its advertised biological properties and structural complexity have highlighted nakadomarin A as an attractive target for synthesis and subsequent drug development research. Accordingly, a number of syntheses and projected routes to this target have been reported.[3] Herein we report a new approach to the synthesis of this structure.



Previous approaches to **1** have relied upon the construction of the 15-membered-ring synthon as a late-stage event. In the present approach, we introduce the 15-membered macrocycle early in the synthesis for reasons to be described. The synthesis plan (Scheme 1) anticipated that nakadomarin A (**1**) might be obtained from bislactam **3** through selective reduction of the six-membered lactam moiety followed by intramolecular alkylation of the iminium ion derived from **2** to form the final C5−C6 bond. We reasoned that **3** could be accessed through a Lewis acid-promoted double conjugate addition of macrocyclic lactam **4** and lactam **5**. This transformation could also be viewed as a formal [4 + 2] cycloaddition. A significant drawback of this plan lay in the lack of an obvious π-facial bias in the reaction of **4** with **5**, which could lead to an undesired diastereomeric adduct.

Scheme 1. Synthesis Plan for (−)-Nakadomarin A



The decision to proceed with the plan illustrated in Scheme 1 was fortified by the potential interplay of competing C−O transition-state dipole effects that might favor an anti orientation of the dipoles in the formation of **3**. If successful, the stereocenter incorporated into bicyclic lactam **5** could be the singular chiral element in this transformation and might be expected to control the stereochemical outcome of the whole process.

The synthesis of macrocyclic lactam **4** was accomplished in eight steps on a multigram scale (Scheme 2). Commercially available 3-furfural (**6**) was iodinated in 52% yield using the literature procedure.[4] Aldehyde **7** was protected as its dimethyl acetal and directly submitted to Heck coupling with allyl alcohol to afford **8** (69% over two steps).[5] Subsequent Wittig olefination with phosphonium salt **9**[6] followed by acidic isolation incorporated the cis olefin while removing the acetal, affording aldehyde **10** in 89% yield. A Horner−Wadsworth−Emmons *Z*-olefination reaction with **11** provided methyl ester **12** in 90% yield (*Z*/*E* >20:1). This ester was then hydrolyzed, and removal of the Boc protecting group followed by cyclization of the product using HBTU gave **4** in 74% yield. The product was recrystallized from MeOH (mp 125−126 °C) and characterized by X-ray analysis.

The synthesis of bicyclic lactam **5** (Scheme 3) featured the use of the Ellman chiral *tert*-butylsulfinamide[7] methodology. Acrolein was condensed with (*R*)-(+)-2-methyl-2-propanesulfinamide mediated by Ti(O*i*Pr)$_4$ to provide a 97% yield of chiral imine **13**,[8] which was subjected to Zn-mediated allylation

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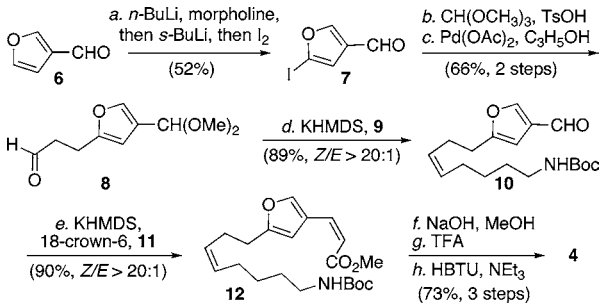
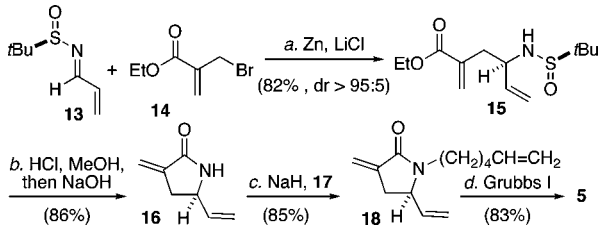
Scheme 2. Synthesis of Macrocyclic Lactam 4[a]



[a]Reagents and conditions: (a) *n*-BuLi, morpholine, THF, −78 °C, then *s*-BuLi, then I_2; (b) $CH(OMe)_3$, $TsOH·H_2O$, 3 Å molecular sieves (MS); (c) $Pd(OAc)_2$, allyl alcohol, $NaHCO_3$, DMF, 50 °C; (d) KHMDS, $BocNH(CH_2)_5PPh_3I$ (**9**), −78 to 0 °C, then HCl; (e) $CH_3O_2CCH_2P(O)(OCH_2CF_3)_2$ (**11**), 18-crown-6, KHMDS, THF, −78 °C; (f) NaOH, MeOH, H_2O, rt; (g) TFA, DCM, 0 °C to rt; (h) *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (HBTU), NEt_3, CH_3CN, 50 °C.

Scheme 3. Synthesis of Bicyclic Lactam 5[a]



[a]Reagents and conditions: (a) Zn, LiCl, DMF, H_2O (1 equiv); (b) HCl, MeOH, then NaOH; (c) NaH, **17**, DMF; (d) Grubbs I (3 × 0.5 mol %), DCM (0.002 M).

following literature precedent.[9] A mixture of **13** and ethyl 2-(bromomethyl)acrylate (**14**)[10] was treated with Zn powder and LiCl in *N*,*N*-dimethylformamide (DMF) to give the desired chiral amine **15**. In early experiments, the use of excess **14** afforded an N-alkylation byproduct. This reaction was circumvented by the addition of 1 equiv of water to the reaction mixture to induce protonation of the Zn(II) amide intermediate. After reaction optimization, **15** was obtained in high yield. The sulfinamide was deprotected under the usual acidic conditions, and α-methylene-γ-lactam **16** was obtained in 86% yield upon exposure to NaOH. Lactam **16** was then N-alkylated with 1-iodo-5-hexene (**17**)[11] to give **18**, which was then subjected to ring-closing metathesis to afford **5** in 83% yield.[3e]

With fragments **4** and **5** in hand, we investigated the cascade reaction/cycloaddition, which could be initiated by any number of Lewis acids (Scheme 4). Initial studies were directed to conditions that would facilitate activation of **4** and induce conjugate addition to **5**. With these constraints in mind, we selected *tert*-butyldimethylsilyl triflate (TBSOTf) as a promoter.[12] A 1:1 mixture of **4** and **5** was treated with TBSOTf under a variety of conditions. After a number of attempts, the optimized formation of the polycyclic product **3** was observed. It was found that slow addition of **5** to a solution of **4** activated by TBSOTf in the presence of iPr_2NEt successfully afforded **3** in 79% yield with 9:1 dr (Scheme 4). Optimal results were obtained with 2.0 equiv of freshly distilled TBSOTf and 1.8 equiv of iPr_2NEt [0.3 M in 1,2-dichloroethane (DCE)]. Attempts to catalyze the reaction with TfOH alone failed, suggesting that the reaction is silyl-catalyzed. The major diastereoisomer **3** was recrystallized, and its structure was determined by X-ray crystallography (Figure 1).

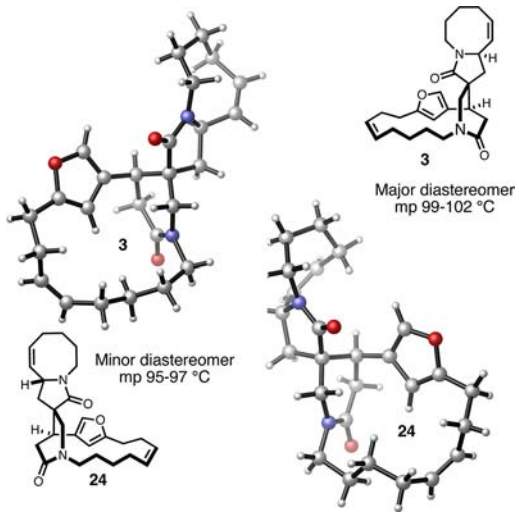


Figure 1. X-ray structures of lactams **3** and **24** (Scheme 4).

Efforts were then directed toward the selective reduction of the six-membered lactam in **3**. Unfortunately, the use of conventional reducing agents (diisobutylaluminum hydride or $LiAlH_4$) resulted in either complete reduction of the five-membered lactam moiety or a mixture of partial reduction products. Selective reduction of the six-membered lactam was achieved through regioselective alkylation of **3** with Me_3OBF_4 followed by $NaBH_4$ reduction of the activated amide intermediate **21** (Scheme 4). Semireduction product **2** was recrystallized, and its structure was confirmed by X-ray analysis. It is significant that the use of the slightly more hindered Meerwein salt (Et_3OBF_4) resulted in significantly reduced reduction selectivity. This implies that steric effects could play some role in the discrimination between the two competing amide carbonyl alkylation events; nevertheless, there appears to be little precedent for these observations. To complete the synthesis, treatment of lactam **2** using modified conditions similar to those reported by Dixon and co-workers[3h] (Tf_2O and 2,6-di-*tert*-butyl-4-methylpyridine) facilitated the rapid formation of intermediate **22**, which was trapped by the furan to afford intermediate **23**. Subsequent reduction using $NaBH_3CN$ afforded (−)-nakadomarin A (**1**) in 52% yield from **3**.

The transformation of bislactam **3** to **1** was then refined to a one-pot procedure. Upon treatment of **3** with Tf_2O and 2,6-di-*tert*-butyl-4-methylpyridine followed by the addition of sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al), both the iminium ion and the six-membered lactam moiety were reduced, affording **1** in 69% yield.

Cascade diastereoselection. An attempt to identify the plausible origins of the stereochemical control in the reaction cascade used to merge fragments **4** and **5** was undertaken. While the single stereocenter embedded in **5** provides one of the stereochemical control elements, it was possible that characterization of the minor product diastereomer might reveal other transition-state control elements. Our preconceived idea of the structure of the other possible cascade diastereomer is shown in Scheme 1. After a scale-up of the transformation to give **3** (9:1 dr), we were able to isolate from the product mixture the minor lactam diastereomer **24** (mp 95−97 °C). Its X-ray structure is also

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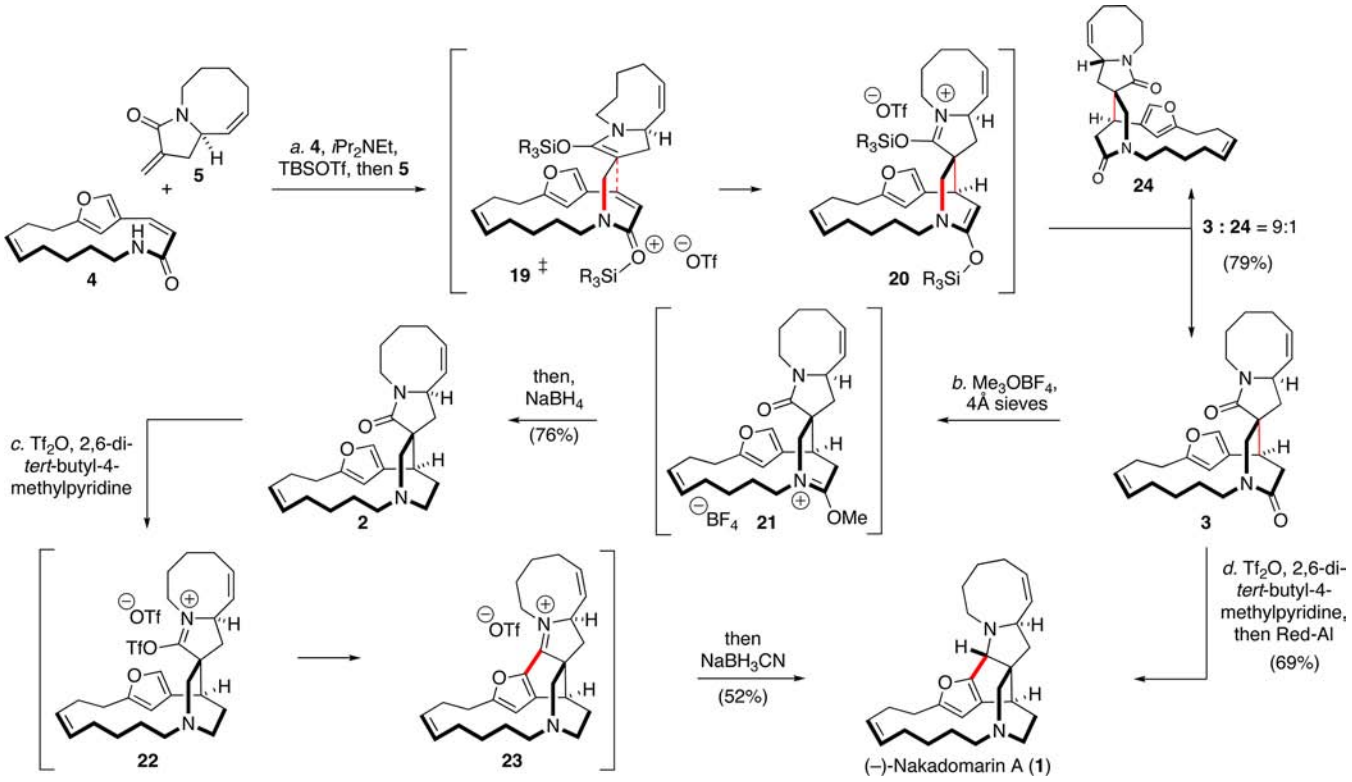
Scheme 4. The Cascade Reaction[a]



[a]Reagents and conditions: (a) **4**, TBSOTf, *i*Pr$_2$NEt, DCE, rt, then **5**, DCE, 14 h; (b) Me$_3$OBF$_4$, 4 Å MS, DCM, rt, 2 h, then NaBH$_4$, MeOH, 0 °C to rt; (c) Tf$_2$O, 2,6-di-*tert*-butyl-4-methylpyridine, DCM, rt, 30 min, then NaBH$_3$CN, MeOH, rt; (d) Tf$_2$O, 2,6-di-*tert*-butyl-4-methylpyridine, DCM, rt, 2 h, then Red-Al, −78 to 60 °C, 3 h.

provided in Figure 1. *Compound* **24** *was unexpectedly derived from the addition of the achiral unsaturated lactam* **4** *to the more congested concave face of the bicyclic lactam* **5**.

Kinetic selectivity and product stability. The computed energies (B3LYP/6-31G*) of the four possible silicon-alkylated product diastereomers **25**−**28TMS** are provided in Figure 2. The

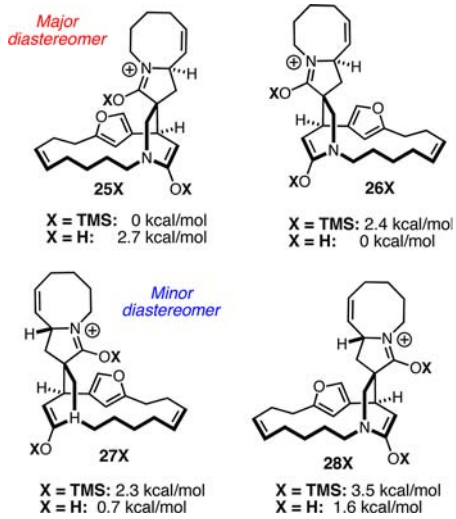


Figure 2. Computed energies (B3LYP/6-31G*) of silylated vs protonated products.

centrosymmetric trimethylsilyl moiety was used in place of the analogous TBS analogue to simplify the computations. As with any compromise, the relative energies of **25**−**28TMS** might under-represent the actual energy differences between **26TBS** and **27TBS**, as the TBS moiety is more sterically demanding than its TMS counterpart. Nevertheless, the energies of these structures substantiate that the most stable silylated structure is **25TMS**, an observation that is consistent with the structure of the major kinetic product diastereomer **3**. It is also evident that **27TMS** is lower in energy than **26TMS**, the minor diastereomer incorrectly projected in Scheme 1. It is evident that both of the isolated product diastereomers (**3** and **24**) have their respective C═O dipoles disposed in an anti orientation, as predicted by the computations.

Calculations for the protonated product diastereomers **25**−**28H** were also performed for comparison to probe the potential steric effects of the silicon substituent. The stability order of **25**−**28H** is quite different than that of **25**−**28TMS**. In this set of structures, **26H** is the most stable diastereomer. Hence, for structures **25**−**28H**, the computed product energies suggest that C−O dipole effects alone are not a major factor in determining the diastereomer stability and possibly the kinetic selectivities. We thus conclude that the structure of the reaction promoter (TMSOTf or TBSOTf) seems play a role in the observed reaction diastereoselectivity. It also appears that this reaction, first reported by Ihara,[12] could well be a concerted rather than stepwise transformation.

In conclusion, we have reported a convergent synthesis of (−)-nakadomarin A (**1**) from commercially available 3-furfural. The double Michael/cycloaddition reaction facilitates the rapid construction of the target skeleton, while the stereochemical outcome is dictated by the single stereocenter embedded in bicyclic lactam **5**.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic, crystallographic, and computational data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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