

Total Synthesis of (–)-Nakadomarin A

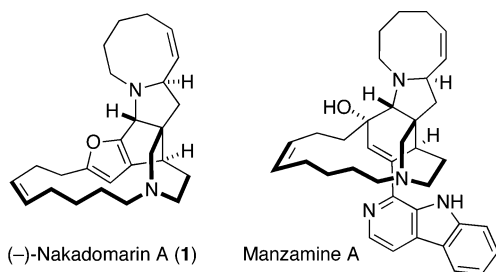
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S Supporting Information

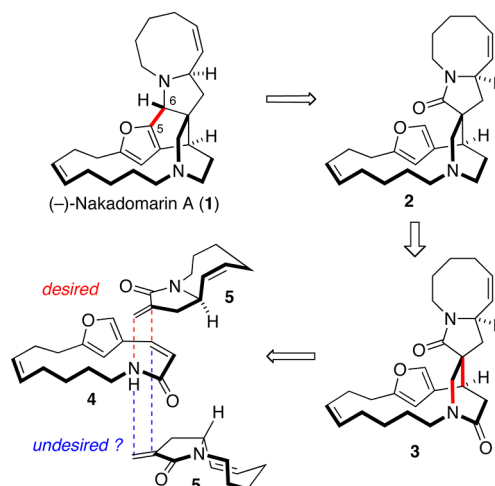
ABSTRACT: The convergent synthesis of the polycyclic alkaloid (–)-nakadomarin A (**1**) is reported. The synthesis plan identified macrocyclic lactam **4** as one of the important synthons (eight steps). The other synthon (five steps) was bicyclo[6.3.0] lactam **5** containing a single stereocenter that 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



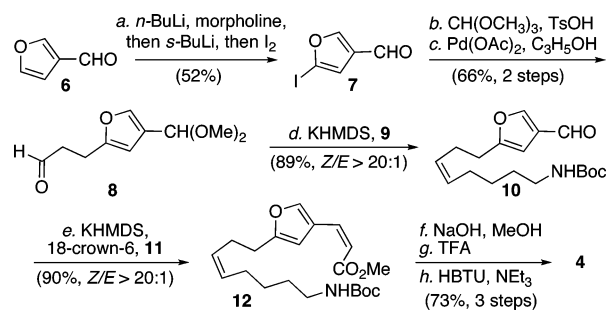
The decision to proceed with the plan illustrated in Scheme 1 was fortified by the potential interplay of competing C–O transition-state dipole effects that might favor an anti orientation of the dipoles in the formation of **3**. If successful, the stereocenter incorporated into bicyclic lactam **5** 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.

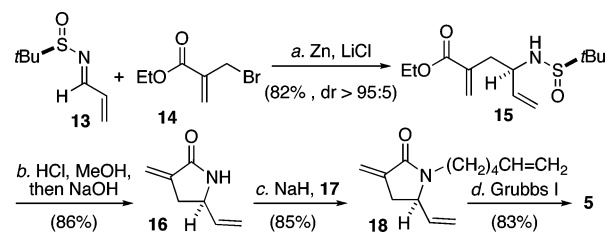
The synthesis of bicyclic lactam **5** (Scheme 3) featured the use of the Ellman chiral *tert*-butylsulfonamide⁷ methodology. Acrolein was condensed with (*R*)-(+)-2-methyl-2-propane-sulfonamide mediated by Ti(OiPr)₄ to provide a 97% yield of chiral imine **13**,⁸ which was subjected to Zn-mediated allylation

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Scheme 2. Synthesis of Macrocyclic Lactam **4**^a

^aReagents and conditions: (a) *n*-BuLi, morpholine, THF, $-78\text{ }^{\circ}\text{C}$, then *s*-BuLi, then I_2 ; (b) $\text{CH}(\text{OMe})_3$, TsOH, 3 \AA molecular sieves (MS); (c) $\text{Pd}(\text{OAc})_2$, allyl alcohol, NaHCO_3 , DMF, $50\text{ }^{\circ}\text{C}$; (d) KHMDS, $\text{BocNH}(\text{CH}_2)_5\text{PPh}_3\text{I}$ (**9**), -78 to $0\text{ }^{\circ}\text{C}$, then HCl; (e) $\text{CH}_3\text{O}_2\text{CCH}_2\text{P}(\text{O})(\text{OCH}_2\text{CF}_3)_2$ (**11**), 18-crown-6, KHMDS, THF, $-78\text{ }^{\circ}\text{C}$; (f) NaOH, MeOH, H_2O , rt; (g) TFA, DCM, $0\text{ }^{\circ}\text{C}$ to rt; (h) *N,N,N',N'*-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (HBTU), NEt_3 , CH_3CN , $50\text{ }^{\circ}\text{C}$.

Scheme 3. Synthesis of Bicyclic Lactam **5**^a

^aReagents and conditions: (a) Zn, LiCl, DMF, H_2O (1 equiv); (b) HCl, MeOH, then NaOH; (c) NaH, **17**, DMF; (d) Grubbs I ($3 \times 0.5\text{ mol \%}$), 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).

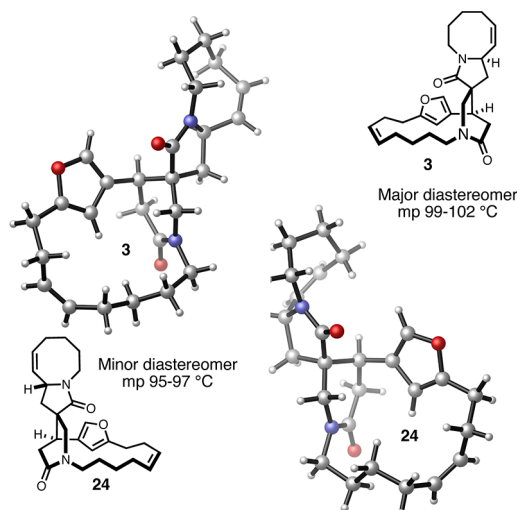
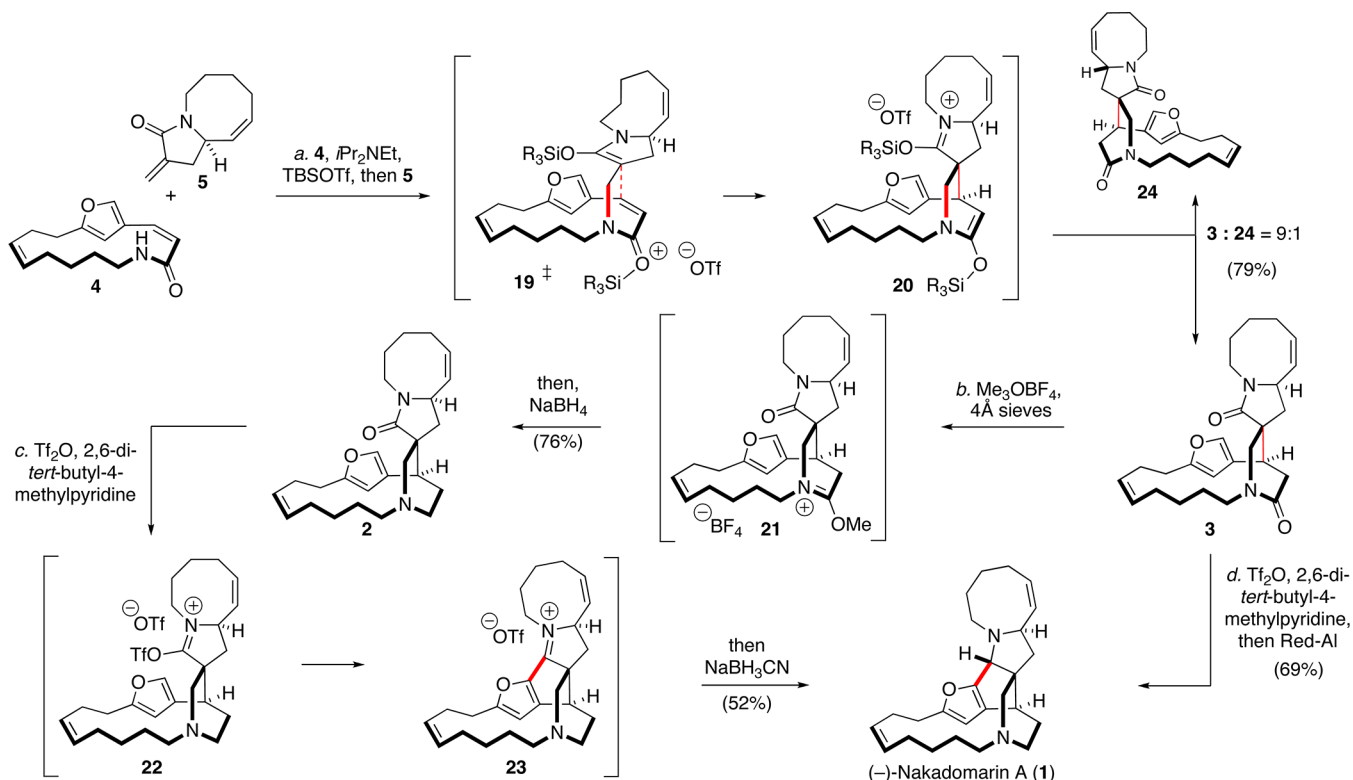


Figure 1. X-ray structures of lactams **3** and **24** (Scheme 4).

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

Scheme 4. The Cascade Reaction^a

^aReagents and conditions: (a) 4, TBSOTf, $i\text{Pr}_2\text{NEt}$, DCE, rt, then 5, DCE, 14 h; (b) Me_3OBF_4 , 4 Å MS, DCM, rt, 2 h, then NaBH_4 , MeOH, 0 °C to rt; (c) Tf_2O , 2,6-di-*tert*-butyl-4-methylpyridine, DCM, rt, 30 min, then NaBH_3CN , MeOH, rt; (d) Tf_2O , 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

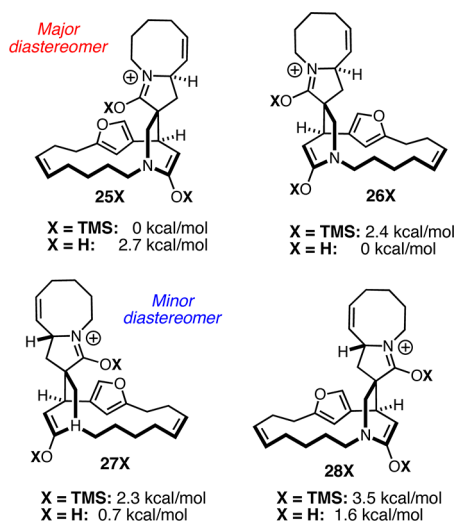


Figure 2. Computed energies (B3LYP/6-31G*) of silylated vs protonated products.

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**.

■ 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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