Total Synthesis of (+)-Nakadomarin A
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Abstract: The total synthesis of (+)-nakadomarin A is described. A three-component cycloaddition of a hydroxylamine, aldehyde, and cyclopropane to form a highly functionalized tetrahydro-1,2-oxazine serves as the foundation for this synthesis. The resulting oxazine is formed as a single diastereomer with the absolute configuration being dictated by the chirality of the cyclopropane. Other key steps include: desymmetrization of a malonate by reduction, Heck cyclization and pyrrolidine formation, and ring-closing metathesis to form both cycloalkenes. Overall, the synthesis required 23 linear steps from the cyclopropane, which in turn is available (six steps) in optically pure form from commercially available α-mannitol.

Introduction

The manzamines represent one of the most architecturally beautiful classes of alkaloids and have presented the synthetic chemist with a formidable challenge.1 Nakadomarin A (Figure 1), isolated by Kobayashi from an Okinawan sea sponge in 1997,2 is unique, as it is the only known member of the manzamine family to contain a furan ring. Kobayashi has postulated that iricinal is a common intermediate in the biosynthesis of both nakadomarin A2 and the manzamines,3 although the route to nakadomarin A is much less obvious. Nakadomarin A contains a range of potentially useful biological activities (anticancer, antifungal, and antibacterial), but the limited availability of natural material (6 mg isolated from 1 kg of wet sponge) has prohibited further screening.2

In addition to the potentially useful biological activities, nakadomarin A appeals to us as synthetic chemists due to its unique and demanding structure. The tetracyclic core consists of an angularly fused 6/5/5/5 ring system (containing three different heterocycles) and is flanked with fused 8-membered and bridging 15-membered rings. The tetracyclic core contains 4 stereogenic carbons including an all-carbon stereocenter. The intrigue of nakadomarin A has not gone unnoticed in the synthetic community, and several model studies have been reported.4 Only recently has Nishida reported syntheses of both the unnatural and the natural enantiomers.5 Herein, we present a concise and efficient asymmetric synthesis of nakadomarin A.

In 2003, we reported that nitrones 1 react with cyclopropanediester 2 under the influence of Yb(OTf)3 to form highly functionalized tetrahydro-1,2-oxazines 3, as single regioisomers and diastereomers (dr > 15:1 3,6-cis).6(a) The initial publication was followed by an improved protocol in which the nitrene is generated in situ from a hydroxylamine and aldehyde.6(b) This three-component procedure greatly increased the substrate scope of this methodology and allowed for the incorporation of a wide variety of substituents. Because of the limited number of natural products that contain the oxazine motif (phyllantidine and the FR900482 family being the most well-known examples), a methodology to convert the oxazine ring to a more prevalent heterocycle was developed.7 Through reductive cleavage of the nitrogen—oxygen bond of 4 and treatment of the resulting aminolcohol 5 with MsCl, pyrrolidines 6 bearing a 2,5-trans relationship were produced (Scheme 1).7 Examination of the natural product literature revealed that nakadomarin A contains the exact substitution pattern (2,5-trans relationship and quaternary center) present in the pyrrolidines generated by this methodology.

Figure 1. Nakadomarin A and related manzamines.


A retrosynthesis of nakadomarin A is shown in Scheme 2. Clearly (as illustrated by Nishida),\(^5\) the most expedient method for the formation of both the 8- and the 15-membered cyclic alkenes is via ring-closing metathesis (RCM). While the formation of the macrocycle by this method results in the formation of a greater amount of the unnatural trans-alkene, the sheer step economy afforded by RCM makes this method superior nonetheless. Our plan then was not to improve on the formation of the cyclic alkenes, but to showcase an extremely efficient and rapid synthesis of a tetracyclic core suitable for elaboration to the target. Our initial disconnection leads to 7, the tetracyclic core bearing the four requisite vinyl (or latent vinyl) groups. Excision of the nitrogen leads to a compound such as 8, which could arise from 9 by our pyrrolidine synthesis (reductive N–O bond cleavage and ring closure) and a Heck-type ring cyclization. The Heck substrate would arise from the oxazine 10, which is derived from the three-component coupling of a 1,1-cyclopropanediester 11, hydroxylamine 12, and furfural 13. The chirality of 11 (used in homochiral form) would establish the stereogenicity of the natural product.

We have previously published a synthesis of the tetracyclic core, which employed as its central feature a three-component coupling between hydroxylamine 14, aldehyde 16, and cyclopropanediester 15. This is summarized in Scheme 3.\(^7\) The core structure 21, however, was a model study used to determine the relative configuration of the four stereocenters produced by our route, and not a viable synthetic intermediate for advancement to the natural product.

**Results and Discussion**

On the basis of the success of the model system, we naively tried to incorporate the terminal alkenes required for forming the azocine by metathesis directly via the three-component
coupling. This strategy was attempted with trepidation as it was
unknown if a method to reduce the enolate double bond in the
presence of the terminal alkenes could be found. Cycloaddition
of alkylhydroxylamine 22, furfural 24,8 and cyclopropane 238
yielded cycloadduct 25 in 82% yield. Similar to the model
compound, selective DIBAL reduction to 26 (95%) followed
by Horner–Emmons olefination produced Heck cyclization substrate 27 in 80% yield. Heck closure between the bromofuran and
the enone in the presence of a silver ion9 proceeded without incident and gave 28 in 85% yield. The stage was set for N–O
bond cleavage and cyclization to the pyrrolidine. Treatment of
28 under a variety of conditions known to reduce the nitrogen–
oxygen bond led either to no reaction, or, if forcing conditions
were used, to complete destruction of the molecule (Scheme
4). It was suspected that the terminal alkenes of 28 might be
responsible for the expensive decomposition. To circumvent this
problem (and negate the selectivity issue of the enolate double
bond reduction), an analogue of 28 was prepared that contained
benzyl-protected alcohols as latent vinyl groups. Unfortunately,
a similar outcome was realized upon attempted N–O bond
 cleavage of the modified substrate. This result is not without
precedence, as in the development of pyrrolidine cyclization
methodology it was observed that oxazines containing an alkyl
substituent on both the nitrogen and the 6-position was
difficult to cleave.7 It was at this time that we re-evaluated our synthetic
strategy, and it was reasoned that introducing an electron-
withdrawing substituent (such as an amide) on the nitrogen of
the oxazine should facilitate N–O bond cleavage.

It was not possible to directly introduce an amide onto the
oxazine through the cycloaddition, so a hydroxylamine that
would allow for nitrogen deprotection and acylation at a later
step would serve as a suitable surrogate (Scheme 5). p-
Methoxybenzylhydroxylamine 29 was chosen for this task, and
cycloaddition of 29, furfural 31, and cyclopropane (R)-30 (ee
> 97%) furnished adduct 32 in 87% yield (ee > 97%). Similar
to the approach used in Scheme 4, monoreduction with DIBAL
(87%), Horner–Emmons olefination (93%), and Heck cyclization
produced 35 in 82% yield. The product 35 was a single
geometrical isomer about the enolate double bond; however,
the identity was never determined. This ultimately turned out to
be inconsequential because the olefinic moiety would undergo
subsequent reduction. Oxidative removal of the p-methoxybenzyl
group on the oxazine nitrogen gave 36 (56%), which was
acylated with an appropriate acid chloride10 to give amide 37
(89% yield). The deprotection of 35 proceeded in lower than
anticipated yield due to significant over-oxidation of the product
to the imine.

It was now time to test the amide hypothesis and attempt to
convert the oxazine to a pyrrolidine via our previously described
methodology. Evidence of the effect of the amide on N–O bond
scission was quickly realized, as cleavage was facilitated with
SmI211 in less than 30 min at 0 °C. It is interesting to note that
the SmI2 reduction had the unexpected consequence of isomer-

8 The syntheses of furfural 24 and cyclopropane 23 are readily available via
adoption of literature methods. Details are in the Supporting Information.
izing the enoate moiety, producing 38 as a 5:1 mixture of double bond isomers in favor of the non-isomerized. This ratio was influenced by the number of equivalents of Sml₂ added. Each isomer of 38 was carried through independently and combined upon formation of the common product 40. Selective O-mesylation of 38 and treatment of the unstable mesylate with base gave, as expected, the trans-2,5-pyrrolidine 39 (65% combined yield for both isomers, over three steps) by virtue of the S₈2 ring closure.

With 39 in hand, the enoate double bond was reduced with nickel boride in a stereoselective fashion to yield 40 (67%), thus installing the last stereogenic center required for the synthesis of nakadomarin A. Unlike reduction of the model compound 19, which yielded a single diastereomer, great care had to be taken in controlling the reaction temperature to maintain the amount of the undesired diastereomer below 10%. Reduction of the carbomethoxy groups in 40 to the primary alcohols and derivatization with methanesulfonyl chloride gave bis mesylate 41 in 79% overall yield. A tandem S₈2 displacement with 5-tert-butyldiphenylsilyloxy-n-pentylamine was effective in forming the piperidine ring in 42 (74% yield). At this juncture, the core structure of nakadomarin A was secured replete with the required appendages for formation of the 8- and 15-membered rings. Bis debenzylation to the dial 43 (67%), oxidation to the dial 44, and double methylation gave diene 45 (55% yield overall). The formation of 46 containing the azocine ring present in the target was effected with Grubbs’ second generation metathesis catalyst in 75% yield. The only significant task remaining to secure the natural product was the formation of the 15-membered azacycle. To this end, we employed a finale similar to Nishida. Desilylation to 47, oxidation to 48, and methylation produced 49 (31% overall yield), which proved to be a worthy substrate for macrocyclization via ring-closing metathesis in the event, treatment of 49 with Grubbs’ first generation catalyst gave a 5:3 mixture of the trans- to desired cis-cycloalkene 50 in a combined 66% yield. This ratio parallels that observed by Nishida, for a similar bisamide substrate (51). These compounds were not separable by flash column, silver impregnated thin layer chromatography, or HPLC on standard or reverse phase columns. With much trepidation, we subjected the mixture 50 to Red-AL reduction with hopes that the final product could be separated from the E-alkene contaminant. Unfortunately, this was not the case, and nakadomarin A was produced with the inseparable E-isomer in 80% combined yield. Overall, the route yielded inseparable nakadomarin A in 28 linear steps from α-mannitol. For the total synthesis of nakadomarin A as a “geometrically pure” compound to be realized, one final revision to the synthetic scheme was necessary.

Comparison of substrate 49 and inseparable product 50 to those prepared by Nishida for the successful synthesis of Nakadomarin A presents one subtle but important difference. Nishida’s substrate 51 introduces an amide into the 15-membered macrocycle that likely decreases the flexibility of the metathesis product 52, allowing for separation of the E- and Z-isomers by standard silica flash column chromatography (Figure 2).

The additional amide was introduced through slight modification of the approach used in Scheme 5. The successful completion of the total synthesis of (+)-nakadomarin A is shown in Scheme 6. Contrary to treating bis-mesylate 41 with 5-tert-butyldiphenylsiloxo-n-pentylamine, 41 was subjected to ethanoic ammonia and the resulting secondary amine acylated with 5-tert-butyldiphenylsiloxo-n-pentanoyl chloride to produce bisamide 53. The reactions now required to reach nakadomarin A

Figure 2. Comparison of metathesis reactions.

![Scheme 6](image-url)
are essentially a reiteration of those used in Scheme 5. Bis-
debenzylation (71%), oxidation, and Wittig olefination (30–
45% yield for two steps) produced metathesis substrate 56. The
yields for the oxidation/methylenation sequence are lower for
54 than 43, and this is assumed to be a consequence of the
hindered rotation of the newly introduced amide restricting
access to the α-branched aldehyde. Azocine 57 was prepared
in 84% yield by treatment of diene 56 with Grubbs’ second
generation metathesis catalyst. Removal of the silyl groups,
oxidation to bis aldehyde 59 (70% 2 steps), and methylenation
produced 51 (Nishida’s penultimate intermediate), which could
not be efficiently separated from triphenylphosphine oxide. A
small sample was purified by preparative thin layer chroma-
tography, and the spectral data for 51 were identical to those
reported by Nishida, constituting a formal synthesis. Analogous
treatment of crude 51 with Grubbs’ first generation
catalyst gave the desired cis-cycloalkene 52 along with 28% of
the undesired trans isomer (two steps). Reduction of the amido
carbonyls with Red-Al gave ent-(+)-nakadomarin A (20%, three
steps) ([α]D = +60.7 (c = 0.27, MeOH), literature [α]D =
−73.0 (c = 0.08, MeOH)), which was consistent spectroscopi-
cally with the published data.

Conclusions

We have described a synthesis of nakadomarin A in a 22-
step sequence from the cycloaddition adduct (29 linear steps
overall from D-mannitol). This sequence is shorter than either
of the previously reported routes; however, the overall yield
reported by Nishida compares favorably with ours. The synthesis
illustrates the flexibility of the nitrone/cyclopropane cycload-
dition in preparing useful scaffolds for complex target synthesis.

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Supporting Information Available: Experimental procedures
and compound characterization data for all new compounds.
This material is available free of charge via the Internet at
http://pubs.acs.org.

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