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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 D-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 ircinal is a common intermediate in the biosynthesis of both nakadomarin A[2] and the manzamines,[3] although the route to nakadomarin A is much less obvious. Nakadomarin A contains a range of potentially useful bioactivities (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.

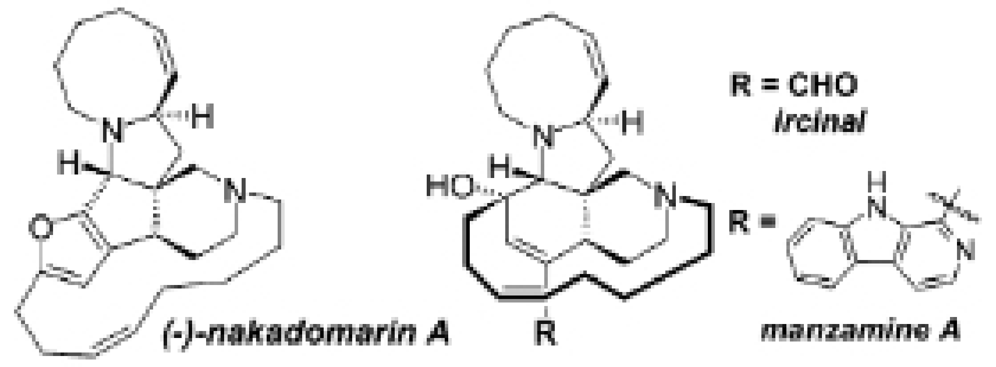

Figure 1. Nakadomarin A and related manzamines.

In 2003, we reported that nitrones **1** react with cyclopropanediesters **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*).[6a] The initial publication was followed by an improved protocol in which the nitrone is generated in situ from a hydroxylamine and aldehyde.[6b] 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 aminoalcohol **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.

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(1) Total syntheses of ircinal A and related manzamines: (a) Winkler, J. D.; Axten, J. M. *J. Am. Chem. Soc.* **1998**, *120*, 6425. (b) Martin, S. F.; Humphrey, J. M.; Ali, A.; Hillier, M. C. *J. Am. Chem. Soc.* **1999**, *121*, 866. For a comprehensive review on the manzamine alkaloids: Hu, J.-F.; Hamann, M. T.; Hill, R.; Kelly, M. *Alkaloids* **2003**, *60*, 207.

(2) (a) Kobayashi, J.; Watanabe, D.; Kawasaki, N.; Tsuda, M. *J. Org. Chem.* **1997**, *62*, 9236. (b) Kobayashi, J.; Tsuda, M.; Ishibashi, M. *Pure Appl. Chem.* **1999**, *71*, 1123.

(3) Kondo, K.; Shigemori, H.; Kikuchi, Y.; Ishibashi, M.; Sasaki, T.; Kobayashi, J. *J. Org. Chem.* **1992**, *57*, 2480.

(4) (a) Nilson, M. G.; Funk, R. L. *Org. Lett.* **2006**, *8*, 3833. (b) Ahrendt, K. A.; Williams, R. M. *Org. Lett.* **2004**, *6*, 4539. (c) Leclerc, E.; Tius, M. A. *Org. Lett.* **2003**, *5*, 1171. (d) Magnus, P.; Fielding, M. R.; Wells, C.; Lynch, V. *Tetrahedron Lett.* **2002**, *43*, 947. (e) Fürstner, A.; Guth, O.; Duffels, A.; Seidel, G.; Liebl, M.; Gabor, G.; Mynott, R. *Chem.-Eur. J.* **2001**, *7*, 4811. (f) Nagata, T.; Nishida, A.; Nakagawa, M. *Tetrahedron Lett.* **2001**, *42*, 8345. (g) Fürstner, A.; Guth, O.; Rumbo, A.; Seidel, G. *J. Am. Chem. Soc.* **1999**, *121*, 11108.

(5) (a) Nagata, T.; Nakagawa, M.; Nishida, A. *J. Am. Chem. Soc.* **2003**, *125*, 7484. (b) Ono, K.; Nakagawa, M.; Nishida, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 2020.

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(7) Young, I. S.; Williams, J. L.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 953.

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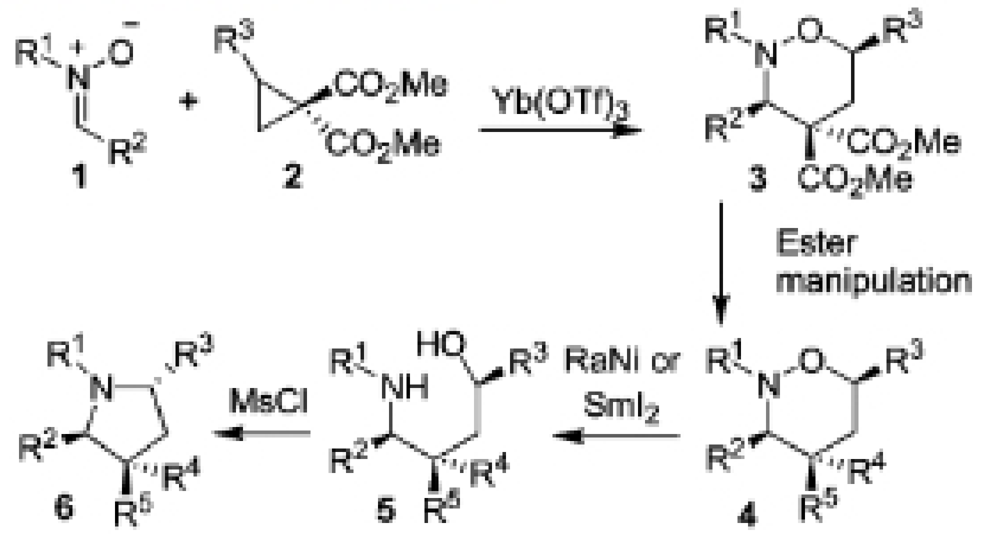
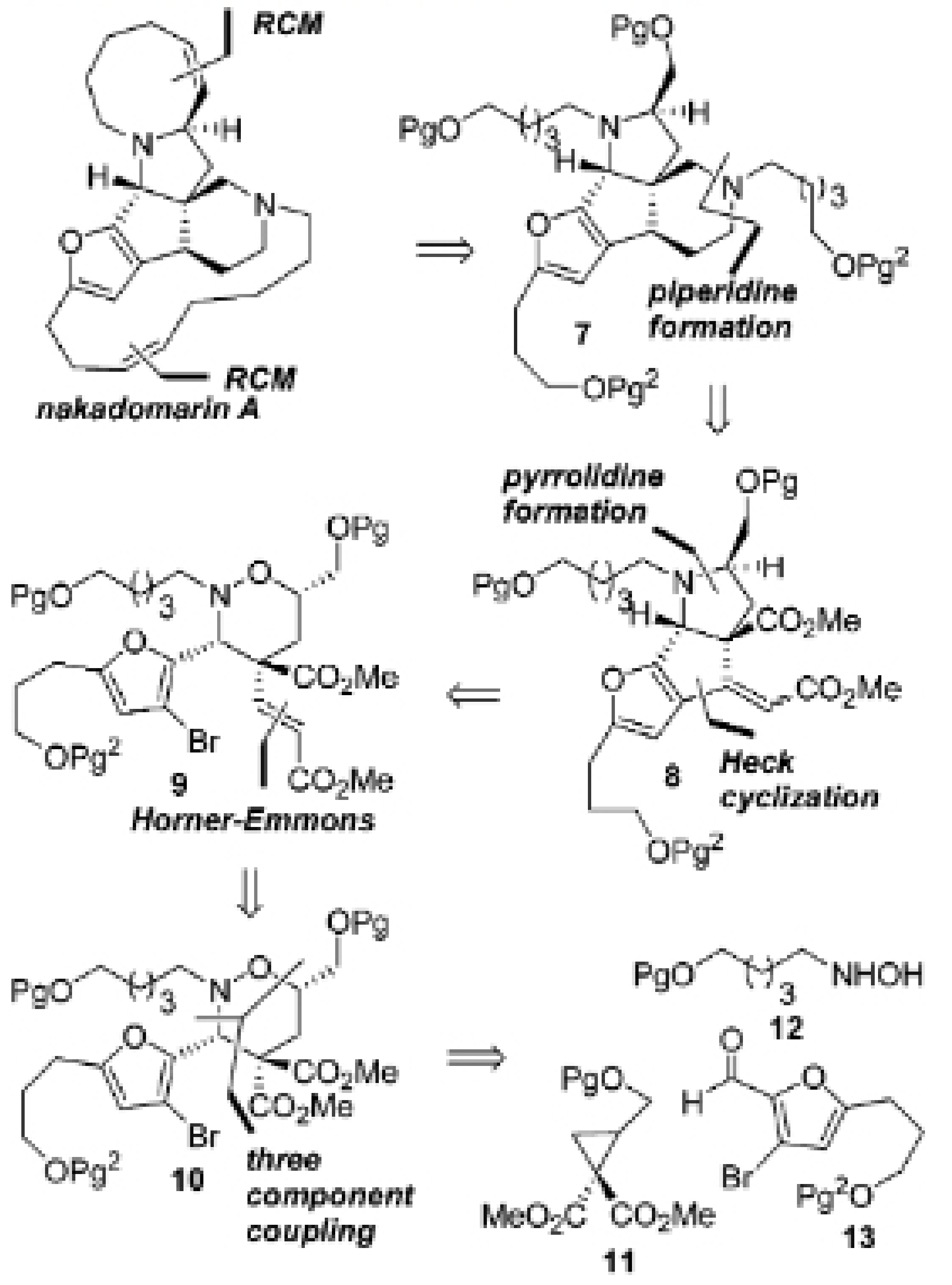
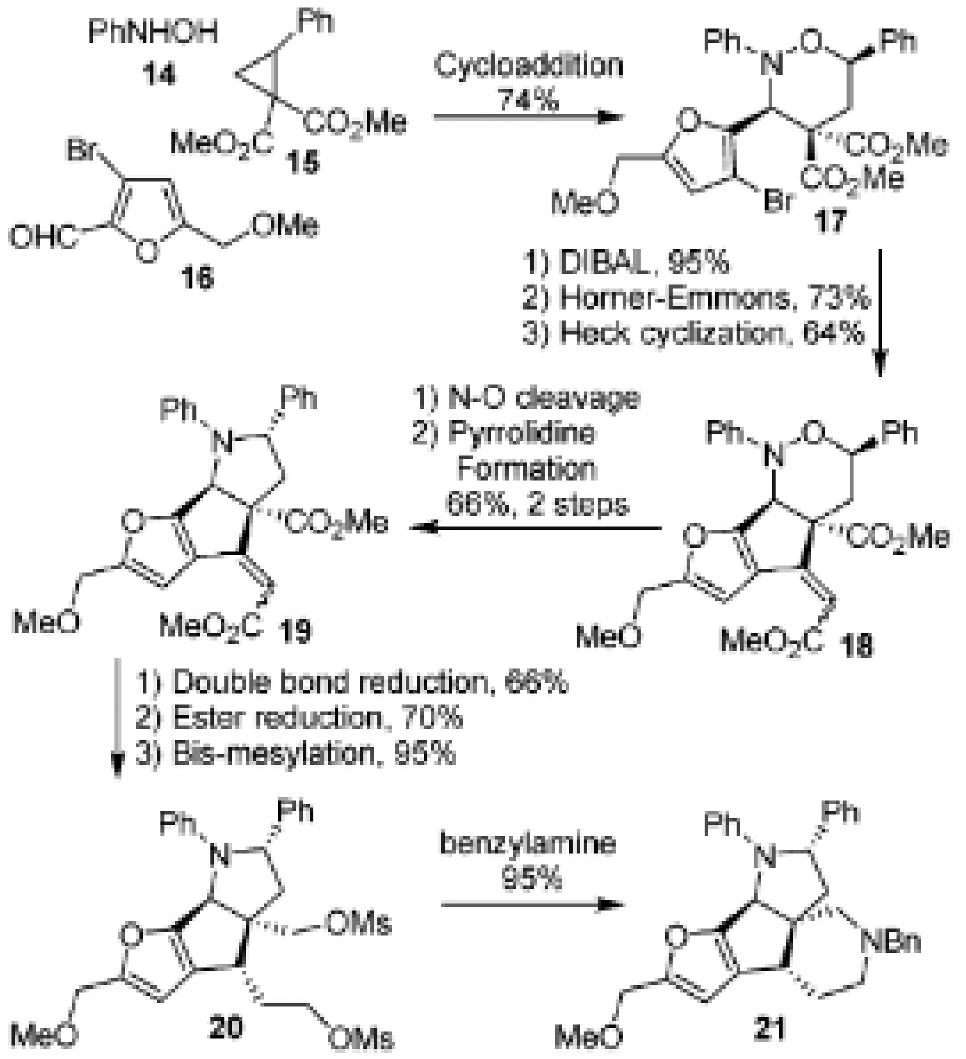
Scheme 1. Pyrrolidine Synthesis



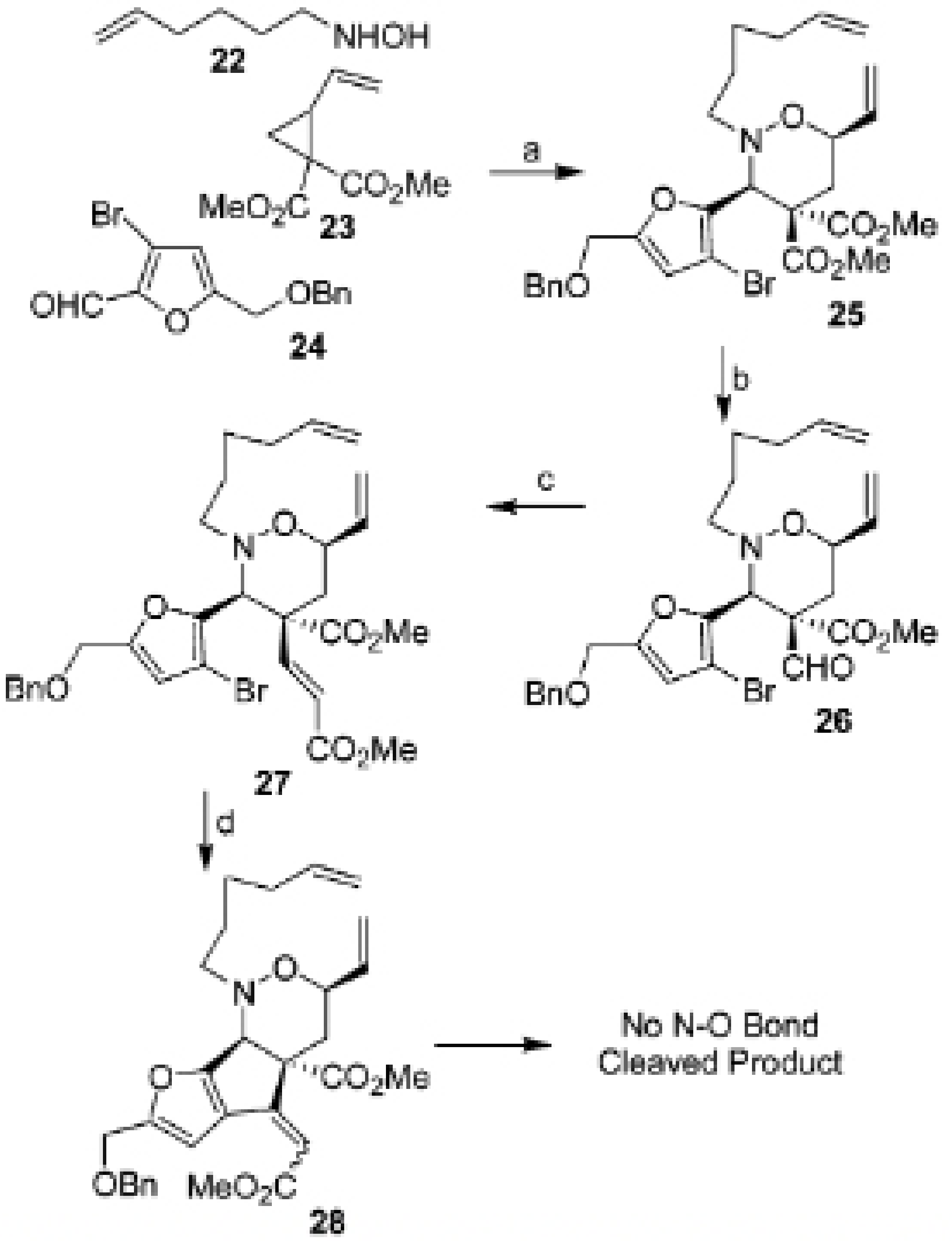
Scheme 2. Retrosynthesis of Nakadomarin A



Scheme 3. Synthesis of a Nakadomarin A Core Model



Scheme 4. Inability To Cleave the N−O Bond[a]



[a] Reaction conditions: (a) 15% Yb(OTf)$_3$, 4A MS, room temperature, 82%; (b) DIBAL, CH$_2$Cl$_2$, −78 °C, 95%; (c) (MeO)$_2$P(O)CH$_2$CO$_2$Me, *t*-BuOK, THF, room temperature, 80%; (d) Pd(PPh$_3$)$_4$, Ag$_2$SO$_4$, NEt$_3$, DMF, reflux, 85%.

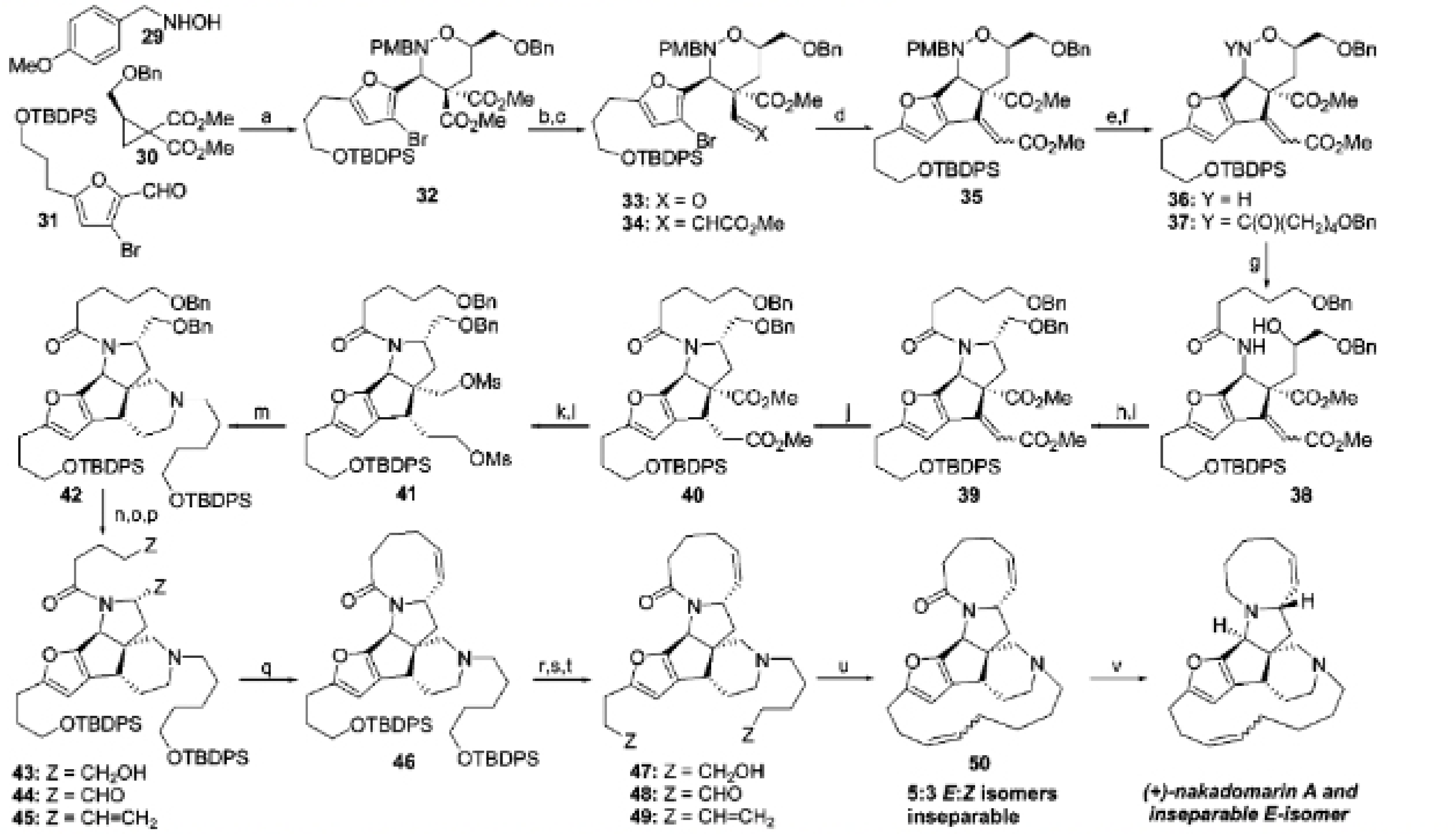
A retrosynthesis of nakadomarin A is shown in Scheme 2. Clearly (as illustrated by Nishida),[5] the most expedient method for the formation of both the 8- and the 15-membered cyclic alkenes is via ring-closing metathesis (RCM). While the formation of the macrocycle by this method results in the formation 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

Scheme 5. Synthesis of Nakadomarin A as a Mixture of Alkene Geometrical Isomers[a]



[a] (a) 15% Yb(OTf)$_3$, 4A MS, 100 °C, 87%; (b) DIBAL, CH_2Cl_2, −78 °C, 87%; (c) $(MeO)_2P(O)CH_2CO_2Me$, *t*-BuOK, THF, room temperature, 93%; (d) Pd(PPh$_3$)$_4$, Ag_2SO_4, NEt$_3$, DMF, reflux, 82%; (e) DDQ, CH_2Cl_2/H_2O 9:1, 56% after 1 recycle; (f) ClC(O)(CH$_2$)$_4$OBn, NEt$_3$, CH_2Cl_2, 0 °C → room temperature, 89%; (g) 0.1 M SmI$_2$, THF, 0 °C (5:1 ratio of double bond isomers); (h) MsCl, NEt$_3$, DMAP, CH_2Cl_2, 0 °C; (i) *t*-BuOK, THF, −25 °C, 65% combined yield (three steps); (j) NiCl$_2$·6H$_2$O, NaBH$_4$, Na$_2$CO$_3$, MeOH/THF (10:1), −40 °C, 67% (14:1 diastereomers); (k) LiAlH$_4$, THF, 0 °C; (l) MsCl, NEt$_3$, DMAP, CH_2Cl_2, −78 °C → room temperature, 79% (two steps), 14:1 diastereomers; (m) TBDPSO(CH$_2$)$_5$NH$_2$, EtOH/THF (10:1), reflux (74%); (n) BCl$_3$, CH_2Cl_2, −78 °C (67%); (o) IBX, DMSO, room temperature; (p) *t*-BuOK, MePPh$_3$I, THF, 0 °C, 55% (two steps); (q) 20 mol % Grubbs II, CH_2Cl_2 (0.7 mM), reflux, 75%; (r) TBAF, THF, room temperature; (s) Dess−Martin periodinane, CH_2Cl_2, 0 °C → room temperature; (t) *t*-BuOK, MePPh$_3$I, THF, 0 °C, 31% (three steps); (u) 40 mol % Grubbs I, CH_2Cl_2 (0.2 mM), reflux, 5:3 mix *E*:*Z*, 66% combined; (v) Red-Al, toluene, reflux, 5:4 mix *E*:*Z*, 80% combined.

coupling. This strategy was attempted with trepidation as it was unknown if a method to reduce the enoate double bond in the presence of the terminal alkenes could be found. Cycloaddition of alkylhydroxylamine **22**, furfural **24**,[8] and cyclopropane **23**[8] 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 enoate in the presence of a silver ion[9] 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 extensive decomposition. To circumvent this problem (and negate the selectivity issue of the enoate 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 were 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 enoate 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 chloride[10] 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 SmI$_2$[11] in less than 30 min at 0 °C. It is interesting to note that the SmI$_2$ reduction had the unexpected consequence of isomer-

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[8] The syntheses of furfural 24 and cyclopropane 23 are readily available via adoption of literature methods. Details are in the Supporting Information.

[9] Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4130.

[10] See the Supporting Information for preparation of this compound.