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Diastereoselective Synthesis of Pyrrolidines Using a Nitrone/Cyclopropane Cycloaddition: Synthesis of the Tetracyclic Core of Nakadomarin A

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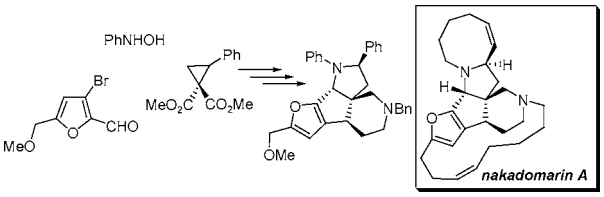
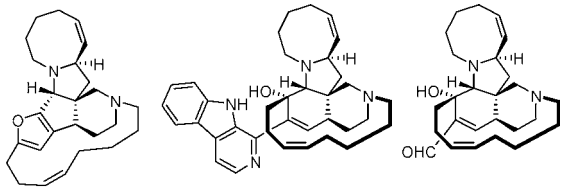
ABSTRACT



The synthesis of the tetracyclic core of nakadomarin A is described. The core contains all the heterocycles and the required stereocenters found in the natural product and provides a promising route to the target itself. The strategy utilizes a general, diastereoselective pyrrolidine synthesis that proceeds via a homo 3 + 2 dipolar cycloaddition. The scope of this methodology is also described.

The pyrrolidine ring is an enormously ubiquitous member of the community of naturally occurring alkaloids. From proline to the indolizidine and pyrrolizidine alkaloids to other classes of compounds, the natural products containing a pyrrolidine are too numerous to list.[1] Our interest in the pyrrolidine ring as a synthetic target stems from its position at the core of the natural product nakadomarin A, its biogenetic relatives, the manzamines, and the biogenetic parent ircinal.

Nakadomarin A was isolated by Kobayashi from an Okinawan sea sponge in 1997[2] and is the only manzamine alkaloid to contain a furan ring. While nakadomarin A contains a range of potentially useful bioactivities (anticancer, antifungal, and antibacterial), the paucity of natural material has made a full screening prohibitive.



Of interest to us as synthetic chemists is the challenging molecular structure, which consists of a compact, angularly fused 6/5/5/5 ring system (containing three different heterocycles) with fused 8-membered and bridging 15-membered rings. Others have also been intrigued by the synthetic challenge posed by nakadomarin A,[3] and Nishida has recently

(1) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435 and previous reports in this series.

(2) Kobayashi, J.; Watanabe, D.; Kawasaki, N.; Tsuda, M. *J. Org. Chem.* **1997**, *62*, 9236.

(3) (a) Ahrendt, K. A.; Williams, R. M. *Org. Lett.* **2004**, *6*, 4539. (b) Leclerc, E.; Tius, M. A. *Org. Lett.* **2003**, 5, 1171. (c) Magnus, P.; Fielding, M. R.; Wells, C.; Lynch, V. *Tetrahedron Lett.* **2002**, *43*, 947. (d) Fürstner, A.; Guth, O.; Duffels, A.; Seidel, G.; Liebl, M.; Gabor, G.; Mynott, R. *Chem. Eur. J.* **2001,** *7*, 4811. (e) Fürstner, A.; Guth, O.; Rumbo, A.; Seidel, G. *J. Am. Chem. Soc.* **1999**, *121*, 11108.

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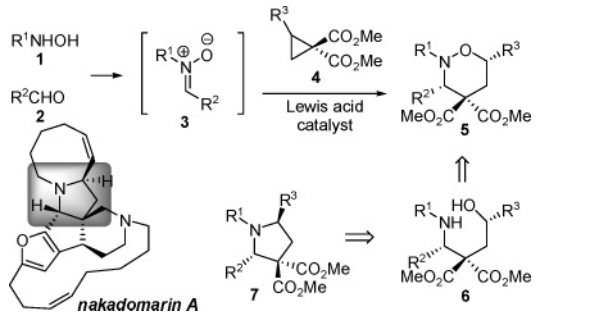
been successful in preparing both the unnatural and natural enantiomers.[4]

Recently, we reported a homo 3 + 2 dipolar cycloaddition of nitrones **3** with cyclopropanes **4**, a process resulting in high yields of tetrahydrooxazines **5** with excellent diastereoselectivity (Scheme 1).[5] The requisite nitrones can be formed

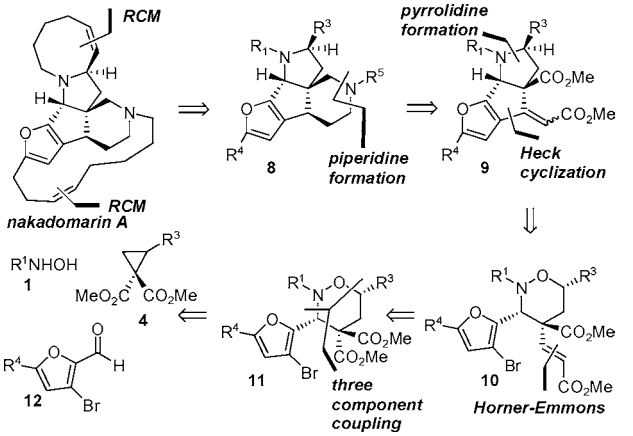
Scheme 1. Synthesis of Pyrrolidines via a Nitrone/Cyclopropane Cycloaddition



in situ from hydroxylamines **1** and aldehydes **2**, reducing the process to a simple three-component coupling.[6] It occurred to us (as it has to others[7]) that cleavage of the N−O bond, conversion of the resultant hydroxyl functionality to a leaving group, and subsequent ring closure would result in the formation of a pyrrolidine ring. In our case, since the tetrahydrooxazines are formed as the cis products, ring closure with inversion of stereochemistry would result in the preparation of 2,5-trans-substituted pyrrolidines. An analysis of the structure of nakadomarin A reveals a pyrrolidine as a central structural feature with the same trans stereochemistry. Moreover, the diester moiety present in the cycloadducts would allow access to the required quaternary center.

Our retrosynthesis of nakadomarin A is shown in Scheme 2. Like Nishida, we envision formation of the 8- and 15-

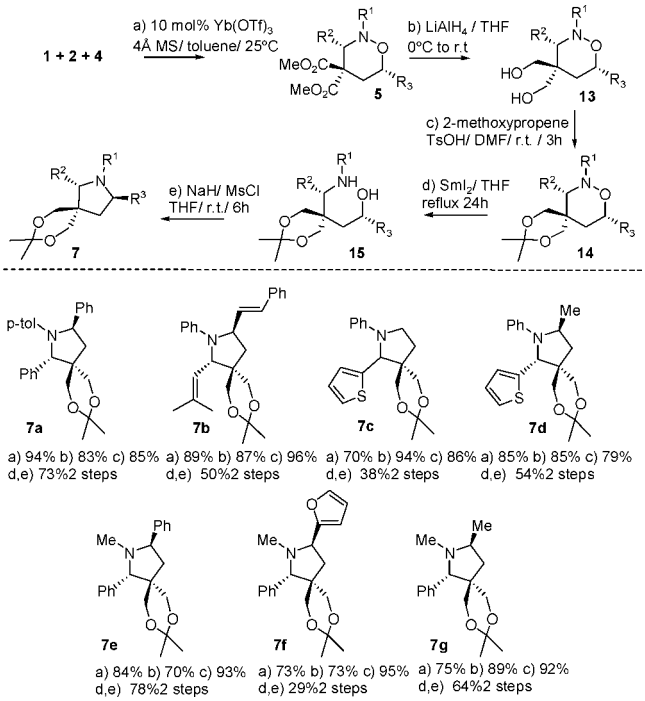
Scheme 2. Retrosynthesis of Nakadomarin A



membered rings to take place via ring-closing metathesis, giving **8** as a key intermediate. Excision of the nitrogen leads to a compound such as **9**, which could arise from **10** by the pyrrolidine synthesis outlined in Scheme 1 and a Heck-type ring closure. The Heck substrate would arise from the diester **11**, which is simply the product of a three-component coupling of a suitable hydroxylamine, furfural **12**, and 1,1-cyclopropanediester **4**.

To demonstrate the feasibility and generality of the proposed pyrrolidine synthesis, a variety of tetrahydrooxazines were prepared using our method (Scheme 3). Upon

Scheme 3. Diastereoselective Pyrrolidine Synthesis



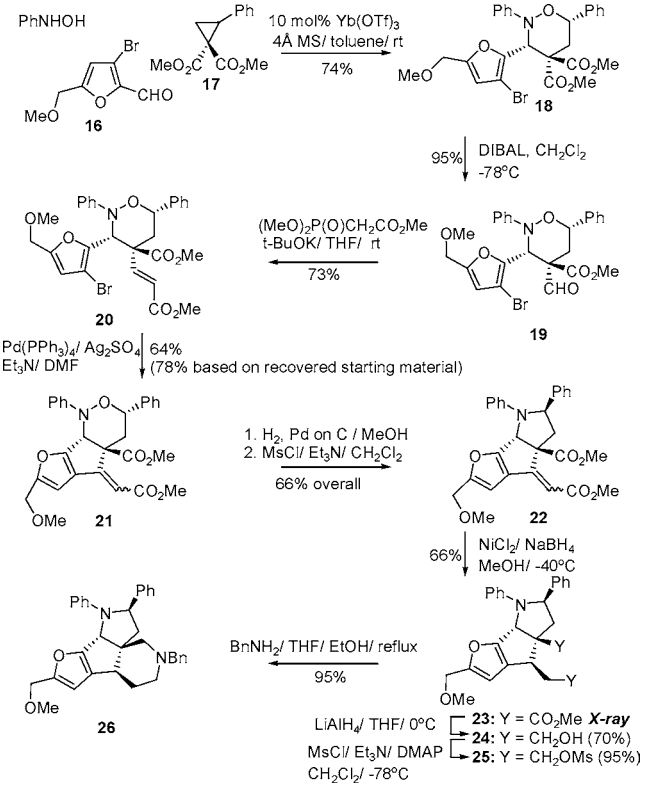
treatment of the N−O bond in **5** with a variety of typical reducing agents, we were met with disappointment. Hydrogenation conditions and the use of molybdenum hexacarbonyl,[8] activated zinc,[9] and samarium iodide[10] failed to produce the desired product. Raney nickel did indeed reduce the N−O bond in some cases, but the product amino alcohol underwent a retro-Mannich-type fragmentation as a result of the disposition of the amino group β to the diester moiety. The diester group in **5** was therefore reduced and the 1,3-diol **13** protected as an acetonide, providing a more suitable substrate **14** for our study. Treatment of **14** with either Raney

(4) (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.
(5) Young, I. S.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3023.
(6) Young, I. S.; Kerr, M. A. *Org. Lett.* **2004**, *6*, 139.
(7) For examples, see: (a) Pulz, R.; Al-Harrasi, A.; Reissig, H.-U. *Org. Lett.* **2002**, *4*, 2353. (b) Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2000,** *122*, 4583.
(8) Cicchi, S.; Goti, A.; Brandi, A.; Guarna, A.; De Sarlo, F. *Tetrahedron Lett.* **1990**, *31*, 3351.
(9) Wuts, P. G. M.; Jung, Y.-W. *J. Org. Chem.* **1988**, *53*, 1957.
(10) (a) Keck, G. E.; McHardy, S. F.; Wagner, T. T. *Tetrahedron Lett.* **1995**, *36*, 7419. (b) Chiara, J. L.; Destabel, C.; Gallego, P.; Marco-Contelles, J. *J. Org. Chem.* **1996**, *61*, 359.

nickel or SmI_2 successfully cleaved the N−O bond, with SmI_2 being the method of choice. Generation of an alkoxide and quenching with methanesulfonyl chloride gave an amino mesylate that was not isolable but quickly cyclized to produce the desired pyrrolidine. A short series of pyrrolidines prepared using this method is shown in Scheme 3. The relative stereochemistry of the products was confirmed by X-ray analysis of a number of these compounds.

With an optimized procedure for conversion of the 1,2-tetrahydrooxazines to pyrrolidines in hand, we turned our attention to the task of applying this method to the synthesis of the core structure of nakadomarin A (Scheme 4). If our approach was to be successful for the synthesis of the natural product, we needed to address the issues of relative stereochemistry in a conclusive manner. We therefore chose phenylhydroxylamine and the phenyl cyclopropane diester **17** for our study since the cycloaddition product and subsequent compounds were more likely to yield crystals suitable for X-ray analysis. The synthesis of the natural product itself will require the use of a hydroxylamine and cyclopropane with substituents that may be elaborated to the eight-membered ring. We have shown that such cycloadditions work very well.

Scheme 4. Synthesis of the Tetracyclic Nakadomarin A Core



The synthesis of the nakadomarin A core commences with the three-component coupling of phenylhydroxylamine, furfural **16**,[11] and cyclopropane **17**[12] to produce the adduct **18** in 74% yield. Selective DIBAL reduction of the equatorial ester[13] to the aldehyde **19** and Horner−Emmons olefination produces enoate **20**, which undergoes smooth Heck cyclization to **21**. The presence of Ag_2SO_4 as an additive was essential for the success of the Heck reaction.[14] Cleavage of the N−O bond and recyclization to the pyrrolidine proceeds efficiently to give the tricyclic compound **22**. Interestingly, the best method for the N−O bond reduction in this instance was hydrogenation over a palladium catalyst. The increased strain in the tricycle **21** is suspected to be the source of the increased N−O bond lability. The last required stereocenter was set via reduction of the enoate double bond with nickel boride,[15] yielding saturated diester **23**. The stereochemistry was confirmed by X-ray analysis of **23**. At first glance, it seems that the hydride must be approaching from the concave face of **22**; however, the ring system is fairly flat, and approach is anti to the adjacent methyl ester to yield the desired isomer. Formation of the piperidine ring was straightforward via ester reduction to diol **24**, preparation of dimesylate **25**, and double displacement with benzylamine. Thus, a nakadomarin A tetracyclic core model was produced in 10 steps from the readily available furfural **16**.

In summary, we have reported a general and diastereoselective synthesis of pyrrolidines. This method should be generally useful for alkaloid synthesis, and we have illustrated this with a synthesis of the tetracyclic core of nakadomarin A. Our efforts toward the preparation of the natural product will be reported in due course.

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

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(11) Furfural **16** was prepared using a combination of methods: (a) Chiarello, J.; Joullie, M. M. *Tetrahedron* **1998**, *44*, 41. (b) Zaluski, M.-C.; Robba, M.; Bonhomme, M. *Bull. Soc. Chim. Fr.* **1970**, 1838.

(12) Landor, S. R.; Punja, N. *J. Chem. Soc. C* **1967**, *23*, 2495.

(13) We have seen this selectivity in selective hydrolysis as well, the origin of which is not obvious on the basis of analysis of models.

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