ORGANIC LETTERS

2010
Vol. 12, No. 21
4912−4915

Total Synthesis of (−)-Nakadomarin A

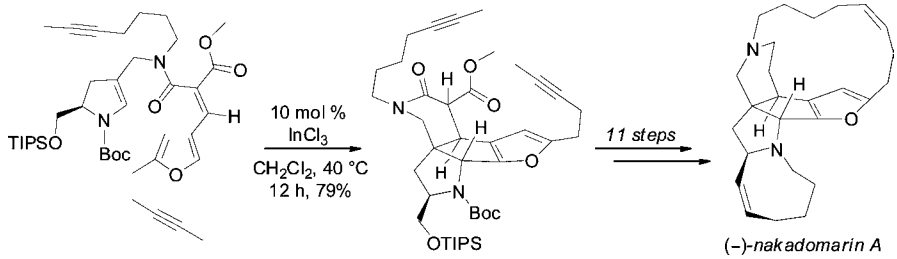
Mark G. Nilson and Raymond L. Funk*

Department of Chemistry, Pennsylvania State University, University Park, Pennsylvania 16802, United States

rlf@chem.psu.edu

Received August 31, 2010

ABSTRACT

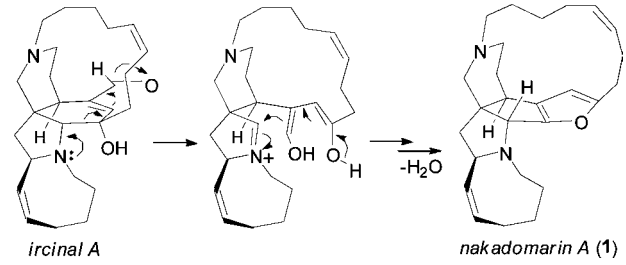


A concise diastereoselective total synthesis of (−)-nakadomarin A has been completed in 21 steps from D-pyroglutamic acid. Key steps include an enecarbamate Michael addition/furan-*N*-acyliminium ion cascade cyclization to provide the tetracyclic core and ring-closing alkyne and alkene metatheses to construct the fifteen- and eight-membered azacycles, respectively.

The manzamines are a class of architecturally fascinating, biologically active marine alkaloids.[1] Perhaps the most structurally intriguing member is nakadomarin A (**1**), isolated by Kobayashi[2a] from an Okinawan sponge *Amphimedon* sp. Its structure consists of an unprecedented 6/5/5/5/8/15 hexacyclic ring system and is the only manzamine alkaloid that embodies a furan ring. A biosynthetic pathway from ircinal A has been proposed by Kobayashi[2b] (Scheme 1).

This limited availability, coupled with an inspiring structure, have made nakadomarin A the target of a number of synthetic groups.[3] Nishida and co-workers have reported pioneering, though lengthy, total syntheses of both **1**[4a] and *ent*-**1**[4b] (36 and 38 steps, respectively). Young and Kerr completed the total synthesis of *ent*-**1**[5] in 29 steps from D-mannitol. Most recently, the Dixon group reported the shortest synthesis of **1** to date, requiring only 16 total steps.[6] A strategy common to each of these syntheses is the utilization of ring-closing alkene metathesis to construct the fifteen-membered macrocycle. While attractive in its ef-

Scheme 1. Proposed Biosynthesis of Nakadomarin A



(1) Nishida, A.; Nagata, T.; Nakadawa, M. *Top. Heterocycl. Chem* **2006**, *5*, 255, and references therein.

(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) (a) Fürstner, A.; Guth, O.; Rumbo, A.; Seidel, G. *J. Am. Chem. Soc.* **1999**, *121*, 11108. (b) Fürstner, A.; Guth, O.; Duffels, A.; Seidel, G.; Liebl, M.; Gabor, B.; Mynott, R. *Chem.—Eur. J.* **2001**, *7*, 4811. (c) Nagata, T.; Nishida, A.; Nakagawa, M. *Tetrahedron Lett.* **2001**, *42*, 8345. (d) Magnus, P.; Fielding, M. R.; Wells, C.; Lynch, V. *Tetrahedron Lett.* **2002**, *43*, 947. (e) Leclerc, E.; Tius, M. A. *Org. Lett.* **2003**, *5*, 1171. (f) Ahrendt, K. A.; Williams, R. M. *Org. Lett.* **2004**, *6*, 4539. (g) Young, I. S.; Williams, J. L.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 953. (h) Nilson, M. G.; Funk, R. L. *Org. Lett.* **2006**, *8*, 3833. (i) Deng, H.; Yang, X.; Tong, Z.; Li, Z.; Zhai, H. *Org. Lett.* **2008**, *10*, 1791. (j) Inagaki, F.; Kinebuchi, M.; Miyakoshi, N.; Mukai, C. *Org. Lett.* **2010**, *12*, 1800.

(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**, *42*, 2020.

(5) Young, I. S.; Kerr, M. A. *J. Am. Chem. Soc.* **2007**, *129*, 1465.

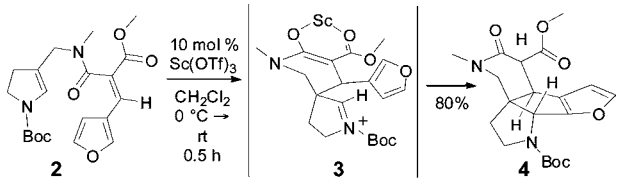
(6) Jakubec, P.; Cockfield, D. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 16632.

10.1021/ol102079z
Published on Web 10/08/2010

ficiency, this approach yielded a mixture of configurational isomers in each case, often favoring the undesired *E*-isomer.[7]

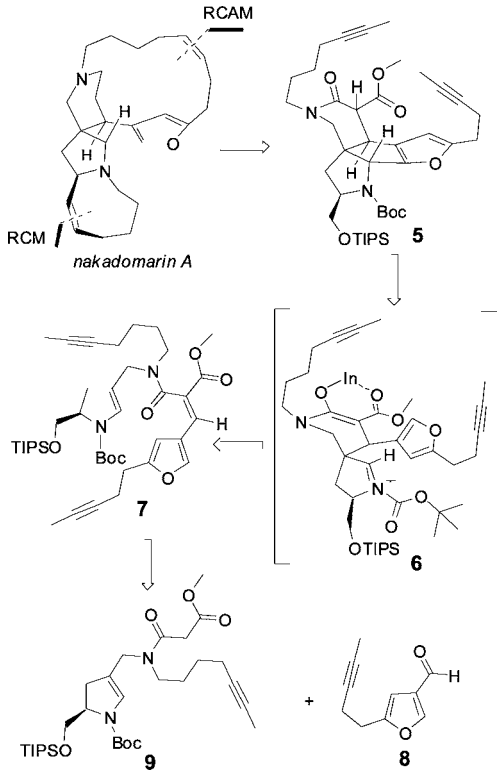
We recently reported our strategy for the rapid construction of the tetracyclic core of nakadomarin A.[3h] In the key step, enecarbamate **2** underwent a stereoselective intramolecular Lewis acid catalyzed Michael addition, and the resulting *N*-acyliminium ion[8] **3** was trapped with the proximate furan to provide tetracycle **4** (Scheme 2). On the basis of the success of the model system study,

Scheme 2. Model Study of the Construction of the Core of **1**



we directed our efforts toward the preparation of a tetracycle analogous to **4** that would be fully functionalized for the completion of the total synthesis. Our retrosynthetic analysis is outlined in Scheme 3. Based on precedents from the previous total syntheses,

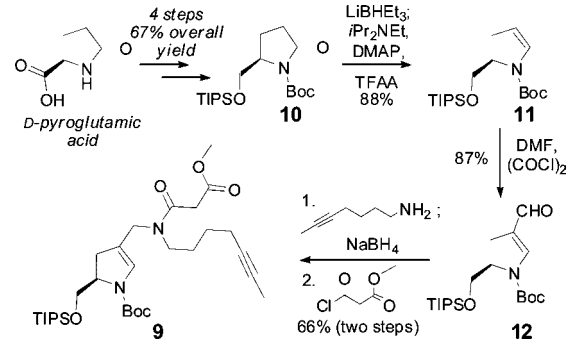
Scheme 3. Retrosynthetic Analysis of (−)-Nakadomarin A (**1**)



ring-closing metathesis (RCM) could provide the eight- and fifteen-membered azacycles. We hoped to circumvent the *E*/*Z* selectivity problem in the construction of the macrocycle by utilizing a ring-closing alkyne metathesis (RCAM)[9]/semihydrogenation strategy to deliver the *Z*-cycloalkene as a single configurational isomer. The viability of this strategy was documented by Fürstner and co-workers in their synthesis of the macrocyclic perimeter of nakadomarin A.[3b] The key cyclization of enecarbamate **7** to the tetracycle **5** should follow the conjectured pathway in our model system. In this case, it was hoped that the Lewis acid activated conjugated double bond would approach the enecarbamate from the face away from the bulky TIPS group[10] through an *anti* conformer to provide the *N*-acyliminium ion **6** that would subsequently undergo closure with the now more electron-rich furan substituent to deliver lactam **5**. The key cyclization substrate **7** could be obtained as the thermodynamic product of Knoevenagel condensation of furaldehyde **8** with β-amido ester **9** (vida infra).

The preparation of amide **9** proceeded in a straightforward fashion (Scheme 4). Enecarbamate **11** was prepared from

Scheme 4. Preparation of Amide **9**



optically pure imide **10**[11] using the one-pot method recently reported by Yu.[12] Vilsmeier−Haack formylation of enecarbamate **11** followed by reductive amination of the resultant vinylogous imide **12** with 5-heptynylamine provided the corresponding secondary amine. *N*-Acylation with methyl malonyl chloride gave amide **9**.

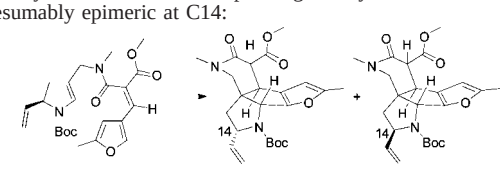
The preparation of furaldehyde **8** took advantage of Maldonado's methodology for the synthesis of 2,4-disubstituted furans from γ,γ'-diacetoxyenones.[13] Thus, metalation of dimethyl methyl phosphonate followed by treatment with methyl 4-hexynoate gave β-ketophosphonate **13** (Scheme 5).

(7) Nishida and Kerr obtained a 1:1.5 and 1:1.7 ratio of *Z*:*E* isomers, respectively. Dixon however obtained a favorable 1.7:1 *Z*:*E* ratio by including an excess of either enantiomer of camphorsulfonic acid in the metathesis reaction mixture.

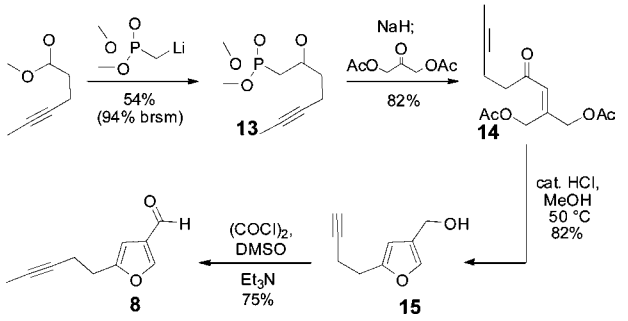
(8) For a review of *N*-acyliminium ion cyclizations, see: Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, T. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431.

(9) For reviews, see: (a) Zhang, W.; Moore, J. *Adv. Synth. Catal.* **2007**, *349*, 93. (b) Fürstner, A.; Davies, P. W. *Chem. Commun.* **2005**, *18*, 2307.

(10) A vinyl group was initially investigated, but its steric influence was found to be insufficient, as a 1:1 mixture of diastereomers was obtained from the cyclization to the corresponding tetracycle. These stereoisomers are presumably epimeric at C14:



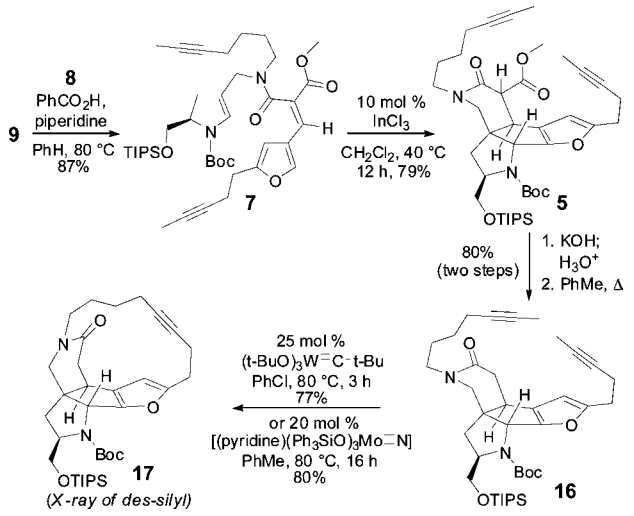
Scheme 5. Synthesis of Furaldehyde **8**



Horner−Wadsworth−Emmons reaction between phosphonate **13** and 1,3-diacetoxyacetone provided γ,γ'-diacetoxyenone **14**. This enone underwent smooth, acid-catalyzed cyclization in methanol at 50 °C to furanmethanol **15** in 82% yield. Finally, Swern oxidation of alcohol **15** furnished the desired furaldehyde **8**.

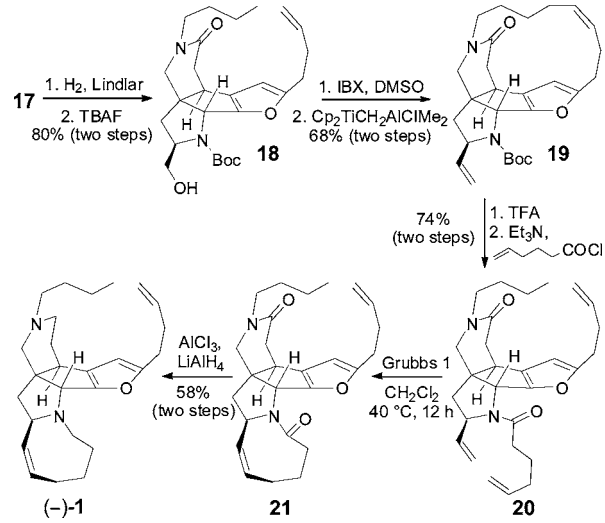
On the basis of observations made during our model system study, we anticipated that Knoevenagel condensation between amide **9** and furaldehyde **8** would provide unsaturated amide **7**, possessing the requisite *E*-geometry for the cyclization to tetracycle **5**. This thermodynamic control has been previously observed in related systems[14] and can be rationalized by better overlap of the ester and adjacent double bond in *E*-amide **7**, in contrast to the carbonyls of the corresponding Z-amide, both of which would be twisted out of conjugation. Much to our delight, heating amide **9** and furaldehyde **8** in benzene in the presence of benzoic acid and piperidine delivered the *E*-configurational isomer **7** as the sole product in 87% yield (Scheme 6). Subjection of enecarbamate **7** to our standard

Scheme 6. Construction of the Pentacyclic Core of **1**



cyclization conditions (10 mol % $Sc(OTf)_3$, CH_2Cl_2, rt) resulted in cyclization to the desired tetracycle. However, these reaction conditions also caused partial cleavage of the silyl ether, resulting in the isolation of a mixture of tetracyclic silyl ether **5** and the corresponding alcohol. This minor setback could be avoided altogether if $InCl_3$ was employed as the catalyst and the reaction was run at reflux, providing tetracycle **5** in 79% yield. Saponification of ester **5** followed by thermally promoted decarboxylation gave the lactam **16**. The diyne functionality of lactam **16** was subjected to several different alkyne metathesis systems with varying levels of success. Grela's optimized conditions[15] of the Mortreux alkyne metathesis system[16] ($Mo(CO)_6$, 2-fluorophenol, 3-hexyne, 1,2-diphenoxyethane in chlorobenzene at 140 °C, 3 h) gave cycloalkyne **17** in 41% yield (54% brsm). The Schrock carbyne catalyst[17] in chlorobenzene (25 mol %, 80 °C, 3 h) proved more effective, allowing cyclization to **17** in 77% yield on a gram scale. It should be noted the air-stable molybdenum nitride complex [(pyridine)$(Ph_3SiO)_3Mo{\equiv}N$] recently developed by Fürstner[18a] gave comparable results with a slightly lower catalyst loading (20 mol %, toluene at 80 °C, 16 h, 80% yield). The *cis* double bond of the fifteen-membered ring was then introduced by straightforward Lindlar reduction of cycloalkyne **17** and was unaccompanied by the *E*-olefin stereoisomer (Scheme 7).

Scheme 7. Completion of the Total Synthesis of **1**



Synthetic efforts were then directed to the construction of the azocine ring and completion of the total synthesis (Scheme 7). Deprotection of the TIPS ether **17** furnished

(11) Prepared in four steps from D-pyroglutamic acid in 67% overall yield. For details, see Supporting Information.

(12) Yu, J.; Truc, V.; Riebel, P.; Hierl, E.; Mudryk, B. *Tetrahedron Lett.* **2005**, *46*, 4011.

(13) Díaz-Cortés, R.; Silva, A. L.; Maldonado, L. A. *Tetrahedron Lett.* **1997**, *38*, 2207.

(14) (a) Brown, J. M.; Guiry, P. J.; Laing, J. C. P.; Hursthouse, M. B.; Malik, K. M. A. *Tetrahedron* **1995**, *51*, 7423. (b) Hamper, B. C.; Kolodziej, S. A.; Scates, A. M. *Tetrahedron Lett.* **1998**, *39*, 2047. (c) Tietze, L. F.; Schünke, C. *Eur. J. Org. Chem.* **1998**, 2089.

(15) Sashuk, V.; Ignatowska, J.; Grela, K. *J. Org. Chem.* **2004**, *69*, 7748.

(16) (a) Mortreux, A.; Blanchard, M. *J. Chem. Soc., Chem. Commun.* **1974**, 786. (b) Mortreux, A.; Dy, N.; Blanchard, M. *J. Mol. Catal.* **1975/1976**, *1*, 101.

alcohol **18**. Oxidation of alcohol **18** with IBX in DMSO followed by Tebbe olefination (Wittig, Peterson, and Nysted protocols were ineffective) proceeded uneventfully to yield vinyl pyrrolidine **19**. Deprotection of the Boc carbamate with TFA and *N*-acylation with 5-hexenoyl chloride gave alkene metathesis substrate **20**. Ring-closing metathesis of diene **20** to azocine **21** proved problematic. The best yield was obtained when diene **20** was treated with an equimolar amount of Grubbs first-generation catalyst in refluxing methylene chloride. Reduction of the resultant bis-lactam **21** with alane provided (−)-nakadomarin A in 58% overall yield from diene **20**. Spectral data (NMR, IR, MS) was identical to that of natural **1**. The optical rotation confirmed its absolute configuration ($[\alpha]_D = -72.7$ (*c* 0.12, MeOH), lit.[4a] $[\alpha]_D = -73.0$ (*c* 0.08, MeOH)).

In conclusion, we have completed a concise total synthesis of (−)-nakadomarin A in 21 steps from D-pyroglutamic acid. Our previously reported strategy for the rapid assembly of the tetracyclic core, which features a tandem enecarbamate Michael addition/furan-*N*-acyliminium ion cyclization, has now been modified to incorporate functionality for the completion of a completely diastereoselective total synthesis. Moreover, a sequential ring-closing alkyne metathesis/semihydrogenation strategy was utilized to obtain the fifteen-membered azacycle as a single configurational isomer. The flexibility of this route allows for the preparation of nakadomarin A structural analogues. Indeed, the cyclization of a pyrrole analogous to furan **2** was successful. These studies are currently underway and will be reported in due course.

Acknowledgment. We appreciate the financial support provided by the National Institutes of Health (GM28663).

Supporting Information Available: Spectroscopic data and experimental details for the preparation of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL102079Z

(17) (a) Schrock, R. R.; Clark, D. N.; Sancho, J.; Wengrovius, J. H.; Rocklage, S. M.; Pedersen, S. F. *Organometallics* **1982**, *1*, 1645. (b) Schrock, R. R. *Polyhedron* **1995**, *14*, 3177.

(18) (a) Bindl, M.; Stade, R.; Heilmann, E. K.; Picot, A.; Goddard, R.; Fürstner, A. *J. Am. Chem. Soc.* **2009**, *131*, 9468. Another catalyst has been recently reported but was not investigated, see: (b) Heppekausen, J.; Stade, R.; Goddard, R.; Fürstner, A. *J. Am. Chem. Soc.* **2010**, *132*, 11045.