ORGANIC LETTERS

2008
Vol. 10, No. 9
1791−1793

Expedient Synthesis of the Tetracyclic Core of *ent*-Nakadomarin A

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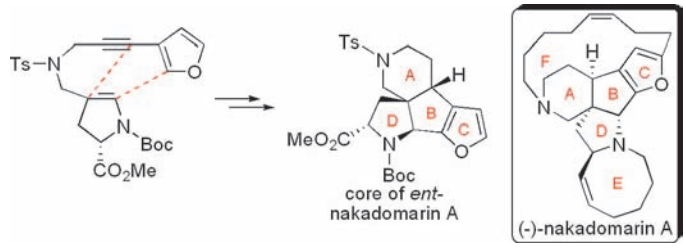
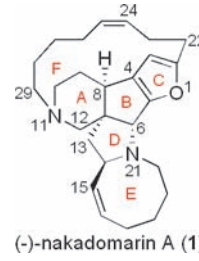
Received March 13, 2008

ABSTRACT



An efficient eight-step assembly of the tetracyclic core (ABCD rings) of *ent*-(+)-nakadomarin A, a bioactive hexacyclic marine alkaloid, has been realized with Sonogashira coupling, platinum(II)-promoted cascade cyclizations, and saturation of a challenging carbon−carbon double bond through a hydroboration/oxidation/xanthate formation/Barton−McCombie deoxygenation sequence as key transformations.

Marine natural products, perpetually manufactured by the oceans, have received immense popularity owing to their diverse and distinct structures and important physiological activities. (−)-Nakadomarin A (**1**), native to sea sponge *Amphimedon* sp. (SS-264) collected off the Kerama Islands, Okinawa, was first isolated and characterized through extensive NMR analyses by Kobayashi and co-workers a decade ago.[1] This manzamine-related marine alkaloid with remarkable architectural intricacy and intrinsic beauty features an unprecedented 8/5/5/5/15/6 hexacyclic framework that comprises four densely imbedded carbon-based stereocenters (including a quaternary one, i.e., C-7) and especially a furan moiety. (−)-Nakadomarin A was cytotoxic against murine lymphoma L1210 cells and displayed antimicrobial and CDK4-inhibitory activities.[2] The impressive structural features and valuable pharmacological profiles prompted global scientists to develop efficient and economical chemical syntheses based upon rational synthetic designs, which would in turn fuel further biological screening. Hitherto, several laboratories have communicated their synthetic studies,[3] culminating in three total syntheses of **1** and/or *ent*-**1**.[4]



(-)-nakadomarin A (**1**)

An original asymmetric synthesis project for nakadomarin A was launched in 2003. The hexacyclic skeleton of this

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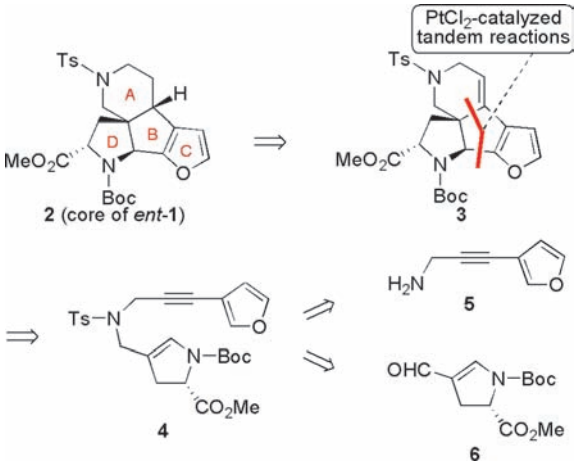
(2) Kobayashi, J.; Tsuda, M.; Ishibashi, M. *Pure Appl. Chem.* **1999**, *71*, 1123.
(3) (a) Furstner, A.; Guth, O.; Rumbo, A.; Seidel, G. *J. Am. Chem. Soc.* **1999**, *121*, 11108. (b) Furstner, A.; Guth, O.; Duffels, A.; Seidel, G.; Liebl, M.; Gabor, B.; Mynott, R. *Chem. Eur. J.* **2001**, *7*, 4811. (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**, *8*, 953. (h) Nilson, M. G.; Funk, R. L. *Org. Lett.* **2006**, *8*, 3833.

10.1021/ol800579j CCC: $40.75
Published on Web 04/08/2008

marine alkaloid was considered as a strained tetracyclic core (ABCD rings) flanked with a fused eight-membered ring (E ring) and a bridged 15-membered ring (F ring). Both E and F rings should be accessible through ring-closing metathesis (RCM), as has been demonstrated by Nishida and Kerr, respectively. Our study was focused on the construction of tetracycle **2** (Scheme 1), a core structure of (+)-nakadomarin A (*ent*-**1**).

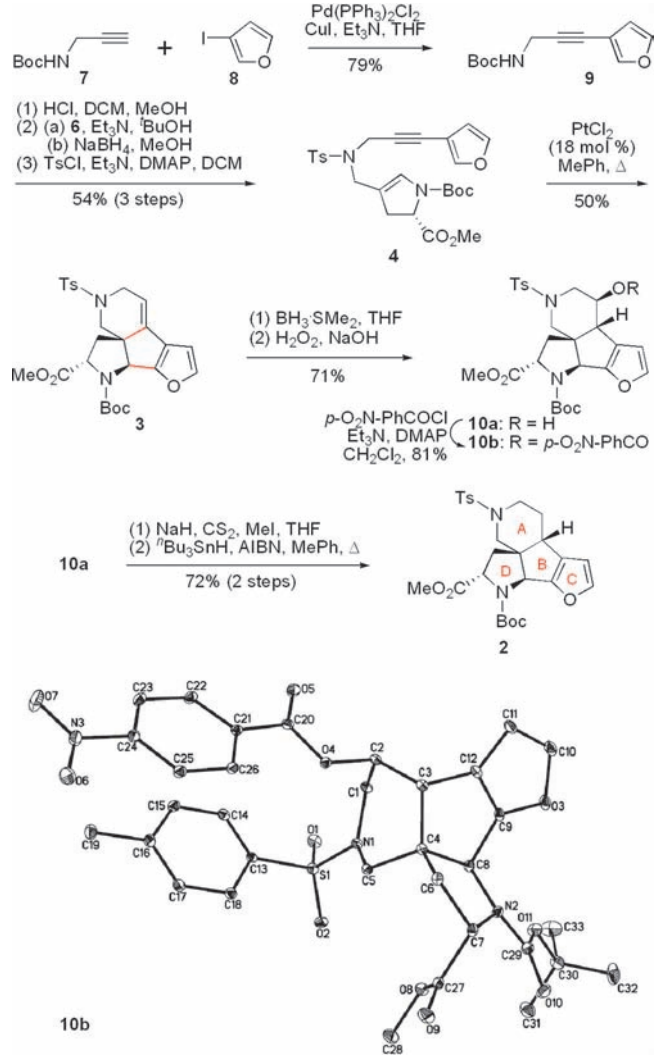
Scheme 1. Retrosynthetic Analysis of **2**



Tandem reactions[5] are advantageous in the total synthesis of structurally complex natural products owing to their intrinsic superb synthetic efficacies manifested by the formation of two or more rings within one operational step. Meanwhile, application of strongly electrophilic metal species, notably platinum(II)[6] and gold(I) and (III) salts,[7] has brought forth numerous efficient organic transformations including tandem reactions[8] and skeletal rearrangements.[9] In 2007, Dake and co-workers developed a novel platinum(II)-catalyzed cyclization method to generate quaternary carbon centers using enesulfonamides, enecarbamates, or enamides as nucleophiles.[10] We envisioned that this might serve as an alternative in the total synthesis of nakadomarin A to our initially adopted tandem Pummerer/*N*-acyliminium ion cyclization strategy. The retrosynthetic analysis (Scheme 1) shows that core **2** may be derived by saturation of the carbon−carbon double bond in **3**, which in turn may be accessible through the above-mentioned platinum(II)-promoted tandem reactions from substrate **4**, a reductive adduct of amine **5** and aldehyde **6**.

As delineated in Scheme 2, the synthesis of tetracycle **2** was commenced from $Pd(PPh_3)_2Cl_2$/CuI-catalyzed Sonogashira coupling of carbamate **7**[11] with 3-iodofuran (**8**) in degassed Et_3N/THF at room temperature, where **8** was generated in situ from 3-bromofuran following Negishi's procedure[12] (i.e., through halogen−lithium exchange followed by nucleophilic substitution with I_2 at −78 °C). Internal alkyne **9** was obtained as an orange solid (79%).

Scheme 2. Synthesis of **2** and X-ray Structure of **10b**



However, no coupling product was formed if 3-bromofuran was used instead of **8**. Carbamate **9** was converted into sulfonamide **4** in 54% overall yield after a three-step reaction sequence: (1) removal of the Boc group to form the HCl salt of **5**, (2) reductive amination with unsaturated aldehyde

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(12) Liu, F.; Negishi, E. *J. Org. Chem.* **1997**, *62*, 8591.

6[13] to afford a secondary amine, and (3) N-sulfonylation with TsCl. Here the reductive amination was conducted in a stepwise fashion. If MeOH was used in the imine formation step, the overall yield for the secondary amine dramatically dropped because acetalization of **6** took place prominently. Acetalization can be inhibited using CH_2Cl_2 as solvent, but imine formation was also shut off. As all of the enecarbamate, alkyne, and arene functionalities are arranged in appropriate positions in the same molecule, compound **4** is ready for the cascade reactions promoted by platinum(II) chloride. Indeed, treatment of **4** with $PtCl_2$ (18 mol %) in toluene at reflux effected the desired tandem reaction sequence in an apparently regiospecific (6-*endo* versus 5-*exo*) and stereospecific manner since spiro-fused tetracyclic heterocycle **3** was obtained exclusively. The starting material seemed to be susceptible to decomposition at the reaction temperature. Therefore, a syringe pump was used for addition of the substrate to secure a better yield (see experimental procedures in Supporting Information). In contrast, under Dake's conditions (i.e., reaction with $PtCl_2$ in toluene in a sealed tube heated at 110 °C) the reaction produced **3** in only 38% yield. The cascade sequence presumably consists of the following steps: (1) nucleophilic attack of enecarbamate on the $PtCl_2$-activated alkyne, (2) interception of the intermediate azacarbenium ion by the proximate furan moiety at the α-position, and (3) rearomatization of the dihydrofuranyl cation to furan and release of a proton leading to the desired product and regeneration of the platinum catalyst.

Compared to the target **2**, tetracycle **3** possesses extra unsaturation in the A ring, which needs to be hydrogenated or reduced to generate an additional stereogenic center at C-8 (a fused point between A and B rings). This seemingly simple task represented a major challenge to the synthetic strategy. Standard hydrogenation (H_2, Pd/C) of **3** was totally infeasible because the trisubstituted double bond was less reactive toward hydrogenation than the tetrasubstituted double bond in the furan moiety in such a constrained environment, similar to Nishida's findings during their synthetic studies on nakadomarin A.[3c] Other methods such as TFA/Et_3SiH or hydroboration followed by protonation (with HBr or HOAc) also were not successful. However, we were eventually delighted to discover that **3** could be converted to alcohol **10a** in moderate yield (71%) via stereoselective hydroboration (BH_3•SMe_2) followed by oxidation (H_2O_2, NaOH). Barton−McCombie alcohol deoxygenation[14] ($^nBu_3SnH$, AIBN, toluene, reflux) with precedent xanthate formation (NaH, CS_2, MeI, THF, room temperature) afforded the desired tetracyclic core structure **2** as a white solid (mp 78−80 °C; $[\alpha]^{22}_D$ −94.8 (*c* 1.15, $CHCl_3$)) in 72% yield over two steps from **10a**. In the meantime, alcohol **10a** was acylated (*p*-O_2N-PhCOCl, Et_3N, DMAP, CH_2Cl_2, room temperature, 2 h) to give ester **10b** as colorless crystals in good yield (81%). The structure of **10b** was unambiguously confirmed by X-ray crystallographic analysis.

In summary, we have accomplished the construction of the tetracyclic core (ABCD rings, see **2**) of *ent*-(+)-nakadomarin A in high efficiency (8 steps; 10.9% overall yield). Key transformations of the present synthesis involved (i) platinum(II)-promoted cascade reaction sequence, (ii) Sonogashira coupling of 3-iodofuran, and (iii) saturation of an otherwise difficult carbon−carbon double bond in A ring of **3** through a hydroboration/oxidation/xanthate formation/Barton−McCombie deoxygenation sequence. Development of other cyclization methods for assembly of the tetracyclic core and completion of the total synthesis of nakadomarin A are currently underway and will be disclosed in due course.

Acknowledgment. Financial support was provided by grants from NSFC (90713007; 20772141; 20625204; 20632030).

Supporting Information Available: Experimental procedures, analytical data, and copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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