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Formal Synthesis of (+)-Nakadomarin A

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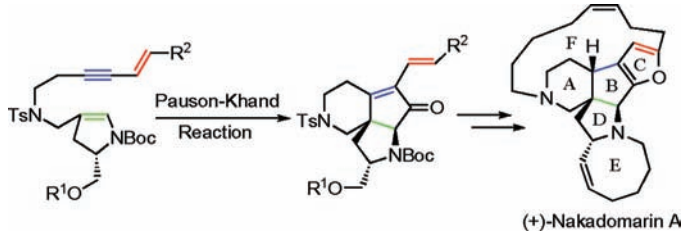
ABSTRACT



The formal synthesis of (+)-nakadomarin A was completed. The significant points of this synthesis are the highly stereoselective formation of the diazatricyclo[6.4.0.0^{1,5}]dodecane skeleton (A, B, and D rings) based on the Pauson−Khand reaction and novel furan ring (C ring) formation, using the vinyl residue of the Pauson−Khand product.

Nakadomarin A is a representative manzamine-related alkaloid that was isolated from the Okinawan marine sponge *Amphimedon sp.* (SS-264) by Kobayashi in 1997 (Figure 1).[1] Nakadomarin A exhibited a cytotoxicity against murine lymphoma L1210 cells (IC_{50} 1.3 μg/mL), inhibitory activity against cyclin dependent kinase 4 (IC_{50} 9.9 μg/mL), antimicrobial activity against a fungus (*Trichophyton mentagrophytes*, MIC 23 μg/mL), and a Gram-positive bacterium (*Corynebacterium xerosis*, MIC 11 μg/mL). This marine natural product has a unique fused-hexacyclic framework consisting of A through F rings (6−5−5−5−8−15 membered rings). Four total syntheses[2] of both the (−)- and (+)-nakadomarin A have so far been recorded besides several synthetic studies of nakadomarin A.[3] The first and second total syntheses of (+)-nakadomarin A (unnatural form) and (−)-nakadomarin A (natural form), respectively, were consecutively accomplished by Nishida in 2003[2a] and 2004.[2b] In addition, Kerr recently reported the total synthesis of (+)-nakadomarin A in 2007,[2c] and in the last year, the total synthesis of (−)-nakadomarin A was completed by Dixon.[2d]

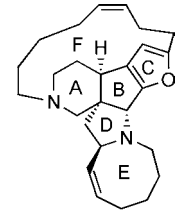


Figure 1. Structure of (−)-nakadomarin A.

We have recently been involved in the investigation of not only the stereoselective $Co_2(CO)_8$-mediated intramolecu-

(1) (a) Kobayashi, J.; Watanabe, D.; Kawasaki, N.; Tsuda, M. *J. Org. Chem.* **1997**, *62*, 9236–9239. (b) Kobayashi, J.; Tsuda, M.; Ishibashi, M. *Pure Appl. Chem.* **1991**, *71*, 1123–1126.

(2) (a) Nagata, T.; Nakagawa, M.; Nishida, A. *J. Am. Chem. Soc.* **2003**, *125*, 7484–7485. (b) Ono, K.; Nakagawa, M.; Nishida, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 2020–2023. (c) Young, I. S.; Kerr, M. A. *J. Am. Chem. Soc.* **2007**, *129*, 1465–1469. (d) Jakubec, P.; Cockfield, D. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 16632–16633.

(3) (a) Fürstner, A.; Guth, O.; Rumbo, A.; Seidel, G. *J. Am. Chem. Soc.* **1999**, *121*, 11108–11113. (b) Fürstner, A.; Guth, O.; Düffels, A.; Seidel, G.; Liebl, M.; Gabor, B.; Mynott, R. *Chem.—Eur. J.* **2001**, *7*, 4811–4820. (c) Nagata, T.; Nishida, A.; Nakagawa, M. *Tetrahedron Lett.* **2001**, *42*, 8345–8349. (d) Magnus, P.; Fielding, M. R.; Wells, C.; Lynch, V. *Tetrahedron Lett.* **2002**, *43*, 947–950. (e) Ahrendt, K. A.; Williams, R. M. *Org. Lett.* **2004**, *6*, 4539–4541. (f) Young, I. S.; Williams, J. L.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 953–955. (g) Nilson, M. G.; Funk, R. L. *Org. Lett.* **2006**, *8*, 3833–3836. (h) Deng, H.; Yang, X.; Tong, Z.; Li, Z.; Zhai, H. *Org. Lett.* **2008**, *10*, 1791–1793.

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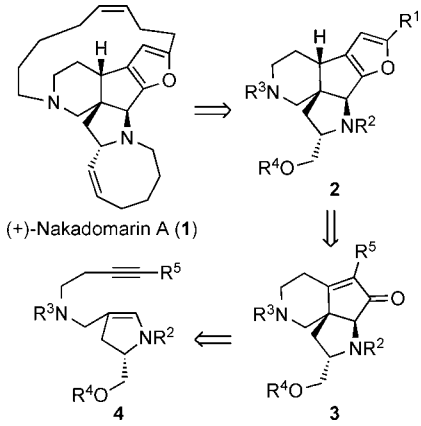
lar Pauson−Khand reaction (PKR) of enynes leading to the construction of bicyclo[*m*.3.0] skeletons ($m = 3, 4$),[4] but also the Rh(I)-catalyzed intramolecular Pauson−Khand type reaction of allene−alkyne substrates[5] and bis(allene)s[6] which successfully provided the larger-sized bicyclo[*m*.3.0] frameworks ($m = 4, 5, 6$). Thus, the Pauson−Khand (type) reactions unambiguously emerged as a powerful tool for constructing bicyclo[*m*.3.0] structures ($m = 3-6$). We now report the novel synthesis of (+)-nakadomarin A by taking advantage of the carbonylative [2+2+1] cycloaddition of the enyne derivative, which provides the central tricyclic framework (rings A, B, and D) in one operation. Our simple retrosynthetic analysis of (+)-nakadomarin A (**1**) is depicted in Scheme 1. The primary target molecule would be assumed

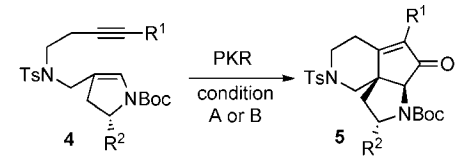
Scheme 1. Retrosynthesis of (+)-Nakadomarin A



to be the 6−5−5−5 tetracyclic compound **2**, because the compounds similar to **2** have already been transformed into (+)-nakadomarin A[2a,c] by the two ring-closing olefin metatheses. The key synthetic intermediate, a tetracyclic compound **2**, might be assembled from the carbonylative [2+2+1] cycloaddition product **3** via the furan ring formation by taking advantage of the proper carbon tether (R^5) at the position α to the carbonyl functionality of **3**. Therefore, our tactical feature involves the PKR of the enyne derivative **4** as the most significant step in the synthesis of (+)-nakadomarin A (**1**).

Prior to examining the PKR of **4** with suitable substituents, we initially investigated the ring-closing reaction using a simpler enyne derivative **4b**, which has a 2-benzyloxyethyl group at the triple bond terminus (Table 1, entry 2). Although

Table 1. Pauson−Khand Reaction of **4**



condition A: $Co_2(CO)_8$, ^{n}BuSMe, DCE, N_2, 80 °C
B: (i) $Co_2(CO)_8$, Et_2O, (ii) toluene, CO, 110 °C

entry	substrate	R^1	R^2	condition	product	yield (%)
1[a]	**4a**	H	H	A	**5a**	69
2	**4b**			A	**5b**	-
3	**4c**			B	**5c**	52

[a] This result was reported by Magnus. See ref 3d.

4b was exposed to various Pauson−Khand conditions, unexpectedly, no desired ring-closed products could be obtained. This observation is in sharp contrast to the result reported by Magnus,[3d] in which the intramolecular PKR of the much simpler enyne analogue **4a** (without a substituent at the triple bond terminus) produced the carbonylative [2+2+1] cycloaddition product **5a** in 69% yield (entry 1). We tentatively assumed that if a suitable π-electron donating component, such as an olefin, is present at the proper position to the alkyne−$Co_2(CO)_6$ complex moiety, it might anchimerically not only assist in the liberation of CO from the cobalt atom, but also accelerate the coordination of an internal olefin counterpart with the cobalt atom thus ending up with a favorable result.[7] Thus, an additional substrate **4c** having a vinyl group at the triple bond terminus was prepared. Compound **4c** was then treated with $Co_2(CO)_8$ to afford the corresponding $Co_2(CO)_6$ complex, which was subsequently exposed to several Pauson−Khand conditions, and we found that the most standard condition, namely heating in toluene at 110 °C under a CO atmosphere, effected the ring-closing step to produce the desired product **5c** in 52% yield (entry 3).

With the fact that the introduction of the vinyl group to the triple bond terminus provided the favorable result in the PKR of the alkyne−dihydropyrrole substrate in mind, the synthesis of (+)-nakadomarin A was initiated according to the protocol shown in Scheme 2. By taking the construction of both the furan and 15-membered rings at the latter stages into account, the homopropargyl amine **7** possessing a pentenyl residue at the triple bond terminus was prepared as follows. The Sonogashira coupling of the known vinylio-

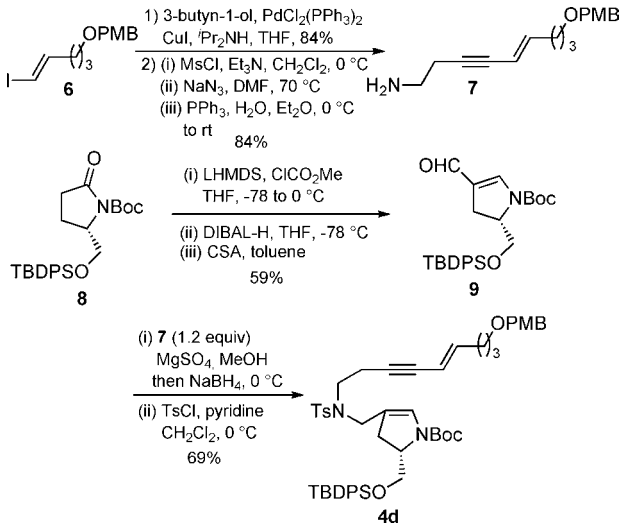
(4) (a) Mukai, C.; Kobayashi, M.; Kim, I. J.; Hanaoka, M. *Tetrahedron* **2002**, *58*, 5225–5230. (b) Nomura, I.; Mukai, C. *Org. Lett.* **2002**, *4*, 4301–4304. (c) Nomura, I.; Mukai, C. *J. Org. Chem.* **2004**, *69*, 1803–1812. (d) Kozaka, T.; Miyakoshi, N.; Mukai, C. *J. Org. Chem.* **2007**, *72*, 10147–10154.

(5) (a) Mukai, C.; Nomura, I.; Yamanishi, K.; Hanaoka, M. *Org. Lett.* **2002**, *4*, 1755–1758. (b) Mukai, C.; Nomura, I.; Kitagaki, S. *J. Org. Chem.* **2003**, *68*, 1376–1385. (c) Mukai, C.; Inagaki, F.; Yoshida, T.; Kitagaki, S. *Tetrahedron Lett.* **2004**, *45*, 4117–4121. (d) Mukai, C.; Inagaki, F.; Yoshida, T.; Yoshitani, K.; Hara, Y.; Kitagaki, S. *J. Org. Chem.* **2005**, *70*, 7159–7171. (e) Mukai, C.; Hirose, T.; Teramoto, S.; Kitagaki, S. *Tetrahedron* **2005**, *61*, 10983–10994. (f) Inagaki, F.; Kawamura, T.; Mukai, C. *Tetrahedron* **2007**, *63*, 5154–5160.

(6) Inagaki, F.; Narita, S.; Hasegawa, T.; Kitagaki, S.; Mukai, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 2007–2011.

(7) (a) Krafft, M. E.; Scott, I. L.; Romero, R. H.; Feibelmann, S.; Van Pelt, C. E. *J. Am. Chem. Soc.* **1993**, *115*, 7199–7207. (b) Wender, P. A.; Croatt, M. P.; Deschamps, N. M. *J. Am. Chem. Soc.* **2004**, *126*, 5948–5949. (c) Croatt, M. P.; Wender, P. A. *Eur. J. Org. Chem.* **2010**, 19–32. (d) Brusey, S. A.; Banide, E. V.; Dörrich, S.; O'Donohue, P.; Ortin, Y.; Müller-Bunz, H.; Long, C.; Evans, P.; McGlinchey, M. J. *Organometallics* **2009**, *28*, 6308–6319.

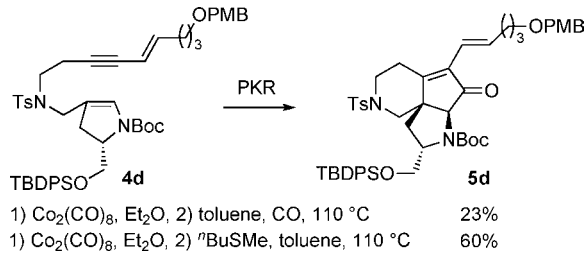
Scheme 2. Synthesis of Dienyne **4d**



dide **6**, prepared from 4-pentyn-1-ol according to the literature,[8] with 3-butyn-1-ol to furnish the homoallylic alcohol derivative in 84% yield, was subsequently converted to the primary amine derivative **7** in 84% yield by the standard methods. Meanwhile, preparation of another aldehyde fragment **9** commenced with the introduction of an ester group at the α position to the carbonyl functionality of the known (*R*)-**8**,[9] derived from L-pyroglutamic acid, to produce the ketoester derivative. Reduction of the resulting 1,3-dicarbonyl compound was followed by acid treatment to afford the aldehyde **9** in a 59% overall yield. The reductive amination of the aldehyde **9** with the primary amine **7** in the presence of $NaBH_4$ furnished the secondary amine derivative, which was subsequently converted into the corresponding tosyl amide **4d** in 69% yield (2 steps).

Our endeavor then focused on the stereoselective PKR of the dienyne **4d** having suitable substituents. According to a preliminary experiment, **4d** was exposed to specific conditions (treatment with $Co_2(CO)_8$ in Et_2O and heating in toluene at 110 °C under CO) to afford the desired tricyclic compound **5d** (Scheme 3). However, the yield was much lower (23%)

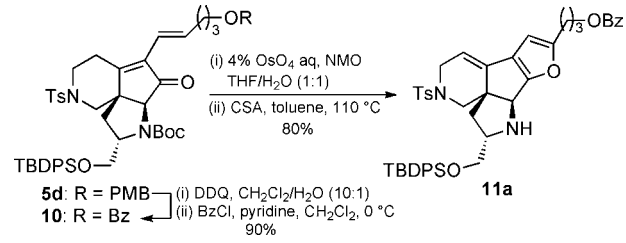
Scheme 3. Pauson−Khand Reaction of **4d**



compared to that of the preliminary experiment (52%). After screening several Pauson−Khand conditions again, we finally reached the condition that involves consecutive treatment of **4d** with $Co_2(CO)_8$ in Et_2O and heating of the resulting cobalt complex in toluene at 110 °C in the presence of ^{n}BuSMe[10] providing **5d** in 60% yield in a highly stereoselective manner.[11] The stereoselective formation of **5d** must be attributed to the preferential approach of the $Co_2(CO)_6$ complex to the olefin moiety of the dihydropyrrole ring from the opposite side of the siloxymethyl group in order to avoid any serious nonbonding interaction.

The efficient construction of the fused furan ring (C ring) was the next subject for our synthesis (Scheme 4). The

Scheme 4. Synthesis of Tetracyclic Compound **11a**



protecting group on the primary hydroxyl group of **5d** was first changed from the PMB group to the benzoyl group under the standard conditions to furnish **10**. On the basis of the literature precedent,[12] hydroxylation of the isolated double bond of the α-pentenyl-α,*β*-cyclopentenone framework of **10** was examined expecting the formation of the corresponding furan derivative, but no desired furan derivatives could be formed. Alternatively, successive treatment of **10** with OsO_4 and acid treatment (CSA in toluene at 110 °C) underwent efficient dihydroxylation and furan ring formation to give the tetracyclic furan derivative **11a** in 80% yield accompanied by loss of the Boc protecting group. Easy furan ring formation could be achieved, but **11a** has an undesired double bond on ring A.

Judging from the literature precedents,[3c,h] the selective reduction of the double bond of **11a** by direct hydrogenation seemed to be less hopeful due to the high reactivity of the strained furan ring. Indeed, only a trace amount of the desired **12a** was obtained when the NH compound was exposed to the hydrogenation conditions along with the production of fairly high amounts of the over-reduced products (Table 2,

(8) Mandal, A. K.; Schneekloth, J. S., Jr.; Crews, C. M. *Org. Lett.* **2005**, *7*, 3645–3648.

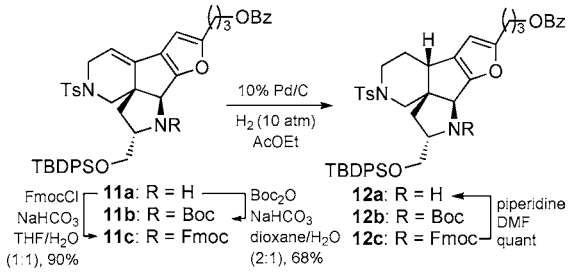
(9) (a) Zanardi, F.; Sartori, A.; Curti, C.; Battistini, L.; Rassu, G.; Nicastro, G.; Casiraghi, G. *J. Org. Chem.* **2007**, *72*, 1814–1817. (b) Shinada, T.; Hamada, M.; Kawasaki, M.; Ohfune, Y. *Heterocycles* **2005**, *66*, 511–525.

(10) Sugihara, T.; Yamada, M.; Yamaguchi, M.; Nishizawa, M. *Synlett* **1999**, 771–773.

(11) The stereochemistry of **5d** was determined based on a NOE experiment of the amine compound, which was derived from **5d** by removing of the Boc group.

(12) (a) Hou, X. L.; Cheung, H. Y.; Hon, T. Y.; Kwan, P. L.; Lo, T. H.; Tong, S. Y.; Wong, H. N. C. *Tetrahedron* **1998**, *54*, 1955–2020. (b) Maiti, S.; Sengupta, S.; Giri, C.; Achari, B.; Banerjee, A. K. *Tetrahedron Lett.* **2001**, *42*, 2389–2391. (c) Boto, A.; Hernández, D.; Hernández, R. *Org. Lett.* **2007**, *9*, 1721–1724.

Table 2. Stereo- and Regioselective Hydrogenation of **11**



entry	Substrate	R	time (h)	product	yield (%)
1	**11a**	H	24	**12a**	trace
2	**11b**	Boc	24	**12b**	32
3[a]	**11c**	Fmoc	6	**12c**	51

[a] 20% Pd/C was used.

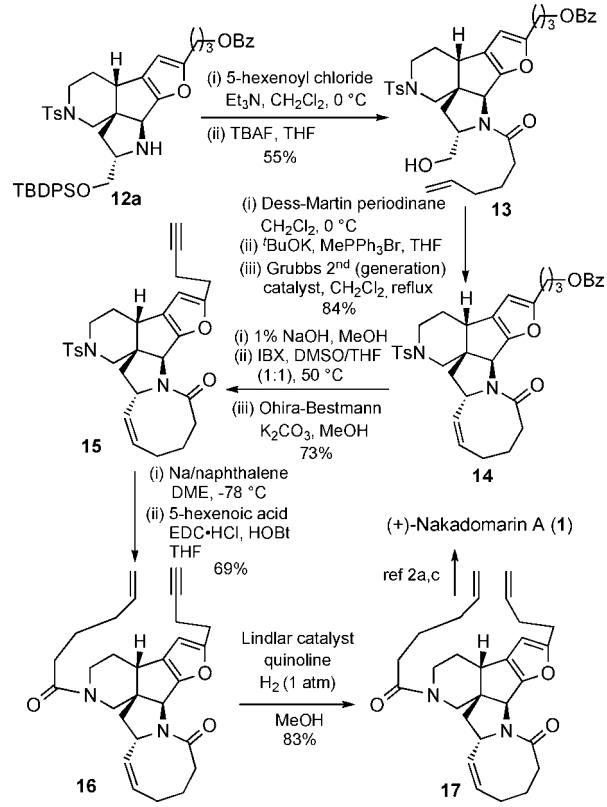
entry 1). Introduction of the Boc group on the secondary amine of **11b**, however, significantly improved the yield. In fact, the hydrogenation of **11b** proceeded under 10 atm of H_2 in the presence of 10% Pd/C in AcOEt to furnish the desired hydrogenated product **12b** in 32% yield (entry 2). Furthermore, compound **11c** with a bulkier Fmoc group on the secondary amine produced **12a** in 51% yield under similar conditions (20% Pd/C /10 atm of H_2/AcOEt, entry 3) by removing the protecting group.[13] Thus, the direct transformation of **11c** into **12a** was realized by a simple hydrogenation and deprotection.

The amine compound **12a** was acylated with 5-hexenoyl chloride to afford the amide, which was subsequently treated with TBAF to give **13** in 55% yield (Scheme 5). The formation of the 8-membered ring was performed by successive oxidation with Dess−Martin reagent, Wittig reaction, and ring-closing olefin metathesis with Grubbs second (generation) catalyst to furnish **14** in 84%. The remaining manipulation before completion of synthesis of the (+)-nakadamarin A is the construction of the 15-membered ring. Therefore, the introduction of both hexenyl and butenyl residues on rings A and C, respectively, was our next objective. The terminal alkyne derivative **15** was prepared in a 73% overall yield by the debenzoylation of **14**, oxidation, and treatment with Ohira−Bestmann reagent.[14] Removal of the Ts group of **15** proceeded upon exposure to sodium naphthalenide producing the secondary amine, which was condensed with 5-hexenoic acid to give **16** in 69% yield. Hydrogenation of **16** in the presence of the Lindlar catalyst provided **17** in 83% yield. The synthetic **17** was identical with the previously synthesized ones by comparison of their spectral data. Since Nishida[2a] and Kerr[2c] have already

(13) The stereochemistry of **12a** was confirmed by the NOESY experiment.

(14) (a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561–564. (b) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521–522.

Scheme 5. Formal Synthesis of (+)-Nakadomarin A



completed their total syntheses of (+)-nakadomarin A from **17**, the present synthesis of **17** amounts to the formal synthesis of (+)-nakadomarin A.

In summary, we have completed the formal synthesis of (+)-nakadomarin A from the commercially available L-pyroglutamic acid. The most significant feature of this synthesis involves (i) the PKR of an alkyne−dihydropyrrole derivative having a vinyl functionality at the triple bond terminus, which enabled us to stereoselectivley construct the desired 6−5−5 tricyclic ring system with suitable substituents, and (ii) novel furan ring formation and selective hydrogenation.

Acknowledgment. This work was supported in part by a Grant-in Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan, for which we are thankful.

Supporting Information Available: Preparation and characterization data for compounds **4d**, **5c**, **5d**, **7**, **9**, **10**, **11a**, **11c**, **12a**, **13**−**16**, and **17** and ^{1}H and ^{13}C NMR spectra for compounds **4d**, **5c**, **5d**, **7**, **9**, **10**, **11a**, **11c**, **12a**, **13**−**16**, and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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