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Synthetic approach towards nakadomarin A: efficient synthesis of the central tetracyclic core

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Abstract—An efficient synthesis of the tetracyclic core of nakadomarin A was accomplished starting from methyl 4-oxo-3-piperidinecarboxylate. The key steps were intramolecular cyclization of furan to *N*-acyliminium ions to construct the strained central cyclopentene ring. © 2001 Elsevier Science Ltd. All rights reserved.

Nakadomarin A was first isolated from the Okinawan marine sponge *Amphimedon* sp. by Kobayashi in 1997,[1] and was found to be biogenetically closely related to manzamine alkaloids, such as manzamine A and ircinal A (Fig. 1). Its structure was elucidated spectroscopically and consists of an unprecedented hexacyclic ring system (8/5/5/5/15/6) that includes a furan ring. An interesting biogenetic transformation of ircinal A to nakadomarin A has been proposed.[1] Although some biological activities of nakadomarin A, such as cytotoxicity against murine lymphoma L1210 cells, inhibitory activity against Cdk4, and anti-microbial activity, have been reported,[1] its limited availability (1.8×10^{-3}%, wet weight) has prevented a complete survey of its biological activity. In connection with our ongoing project on the total synthesis of manzamine alkaloids,[2] we were interested in nakadomarin A because of its unique structure and began a synthetic study. We report here an efficient synthesis of the ABCD ring system of nakadomarin A.[3,4]

Recent advances in ring-closing metathesis (RCM)[5] have facilitated access to unsaturated carbocycles or heterocycles with medium-sized to large rings. Considering both RCM and a cyclization methodology at the late stage of synthesis for constructing the 15-membered ring, we assumed that the ABCD tetracyclic core was a key synthetic intermediate for nakadomarin A (Scheme 1). Synthesis of this ABCD ring system could be retrosynthetically simplified to a spiro-γ-lactam with a substituted furan. We expected that the B ring could

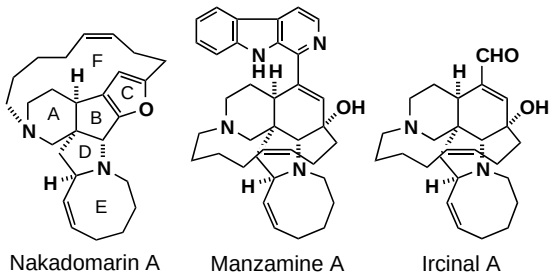

Figure 1.

be synthesized by cyclization of the furan ring to the iminium ion generated from the spiro-γ-lactam. The spiro-γ-lactam could be further simplified to methyl 4-oxo-3-piperidinecarboxylate hydrochloride.[6] One anticipated problem was generation of the iminium ion because of the poor reactivity of the carbonyl group due to steric hindrance.[7]

Methyl 4-oxo-3-piperidinecarboxylate hydrochloride **1** was first converted to allylated **2** in 77% yield in three steps (Scheme 2). Oxidative cleavage of the double bond of **2** gave **3**. Reductive cyclization of **3** to the desired spiro-γ-lactam **4** proceeded successfully when **3** was treated with 4-methoxybenzylamine followed by $NaBH_3CN$. Sequential deprotection of both methoxybenzyl and ketal groups with CAN and 70% $HClO_4$ gave γ-lactam **5**, which was acylated by Boc_2O to give **6**.

The keto group of **6** was converted to the enol triflate **7**. Suzuki–Miyaura coupling[8] of **7** with furan-3-boronic acid, prepared from 3-bromofuran, was performed under standard conditions using $Pd(PPh_3)_4$ to give coupling product **8** in 80% yield. For the critical

Keywords: nakadomarin A; manzamine alkaloid; furan; Suzuki–Miyaura coupling; *N*-acyliminium ion.

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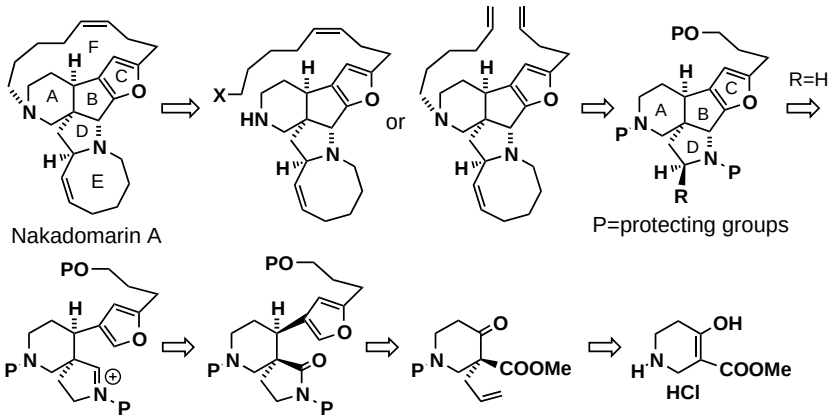
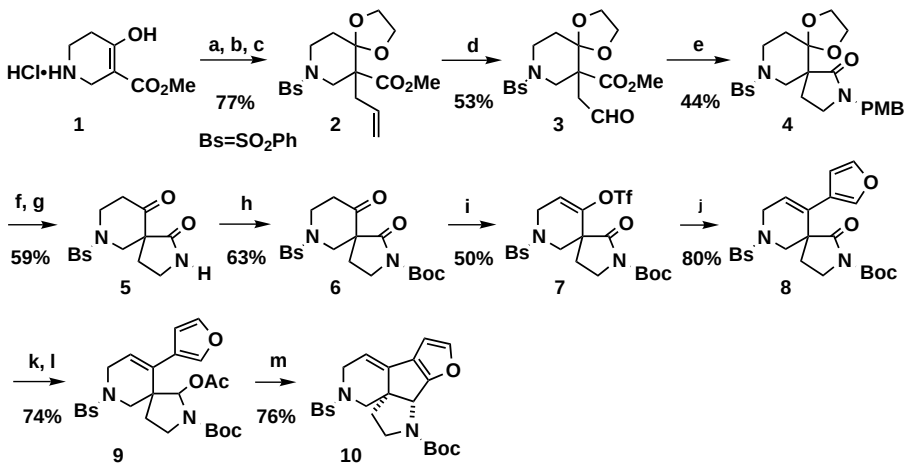


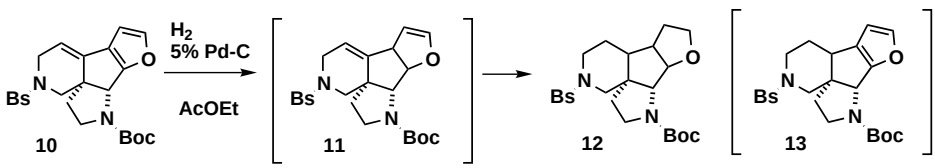
Scheme 1.



Scheme 2. *Reagents and conditions*: (a) $PhSO_2Cl$, $NaHCO_3$; (b) allyl bromide, K_2CO_3; (c) ethylene glycol, *p*TsOH; (d) OsO_4, $NaIO_4$, aq. THF; (e) PMB–NH_2, MeOH, AcOH, rt, 1 h, then $NaBH_3CN$, reflux, 2 h; (f) CAN, aq. MeCN, rt; (g) 70% $HClO_4$, CH_2Cl_2; (h) Boc_2O, Et_3N, DMAP; (i) $LiN(TMS)_2$, THF, −65°C, then $PhNTf_2$, 3°C; (j) furan-3-boronic acid, $Pd(PPh_3)_4$, LiCl, DME, aq. Na_2CO_3, 80°C, 3 h; (k) DIBAL, toluene, −65°C to rt; (l) Ac_2O, pyridine; (m) *p*TsOH, CH_2Cl_2.

intramolecular cyclization, the γ-lactam **8** was converted to acetoxypyrrolidine **9** by DIBAL reduction followed by acetylation. The presence of the Boc group is essential for selective and efficient reduction of **8**. No over-reduction was observed even when a large excess of DIBAL was used, probably due to stabilization of alkoxyaluminum intermediate of the hemiaminal by complex formation. Cyclization of **9** occurred regioselectively at the 2-position of the furan ring to give the tetracyclic key intermediate **10**[9] in 76% yield upon treatment with *p*-toluenesulfonic acid.[10] A molecular model suggested that *trans* cyclization was not possible.

We first expected that the stereoselective hydrogenation of **10** would easily occur to give **13** (Scheme 3). Reduction from the α-side of **10** was expected according to a previous result with a related unsaturated spiro-lactam.[7] When **10** was hydrogenated under standard conditions, however, only **12**, an over-reduced product, was obtained in 80% yield.[11] To determine the presence of the desired **13**, the reduction was stopped before all of the starting material was consumed. A ^1H NMR study of the product mixture revealed the presence of **11** instead of **13**. These results showed that the reduction of **10** occurred first at the tetra-substituted double bond in the furan ring. This high reactivity of the

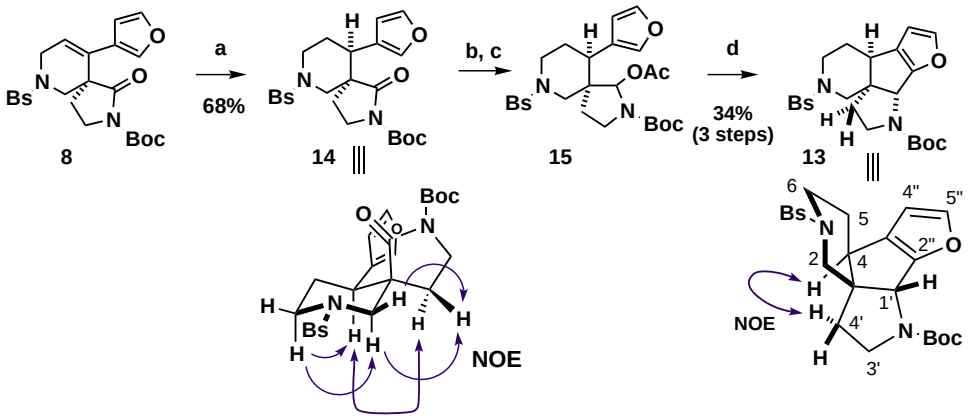


Scheme 3.

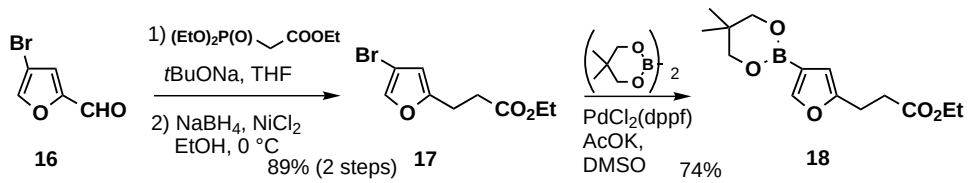
double bond in the furan ring can be explained by the strained character of **10**. Therefore, the hydrogenation of **8** was investigated next (Scheme 4). As expected, hydrogenation of **8** proceeded smoothly without reduction of the furan ring to give **14** in 68% yield as a single diastereomer. In a careful NMR study of **14**,[12] observation of nuclear Overhauser effects (NOE) between the axial methine proton and a proton of the methylene in γ-lactam suggested that reduction occurred from the α-side of **8**. Compound **14** was converted to **15** as above, which was subjected to the cyclization reaction under acidic conditions to give the desired tetracyclic framework of nakadomarin A **13**[13] in 34% yield from **14**. The *cis* relationship of the AB rings was confirmed by an NOE study.

The remaining task was elongation of the side chains to construct the 15-membered ring F. The required boronic ester of substituted furan was prepared as shown in Scheme 5. Wadsworth–Emmons–Horner reaction of 4-bromo-2-furaldehyde followed by careful reduction of the double bond using $NaBH_4$ in the presence of $NiCl_2$ gave **17** in 89% yield.[14] Compound **17** was then converted to **18** by the Pd-catalyzed reaction[15] with diborane.

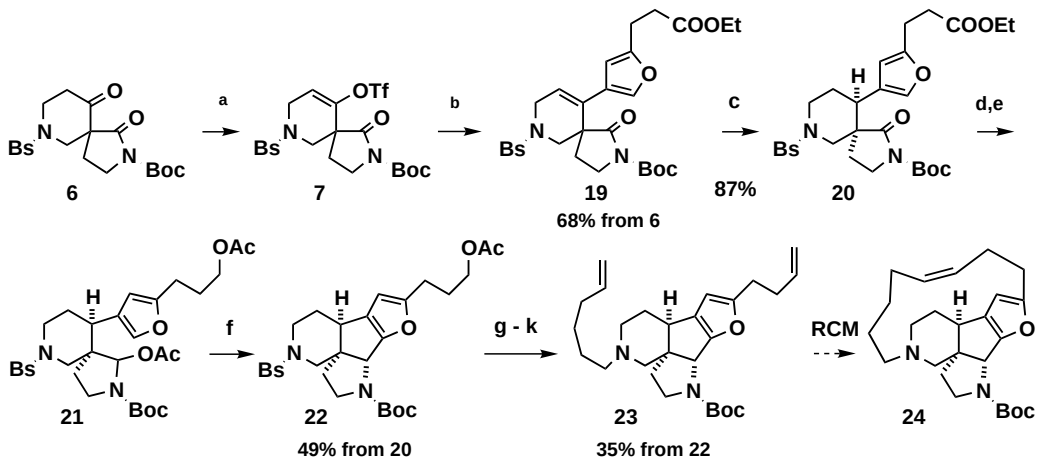
Suzuki–Miyaura coupling of **18** with the enol triflate **7**, which was obtained from **6**, gave highly substituted spirolactam **19** in fairly good yield (Scheme 6). Hydrogenation of the double bond followed by reduction of the lactam carbonyl and acetylation gave **21**. The



Scheme 4. *Reagents and conditions*: (a) H_2, 10% Pd-C; (b) DIBAL, toluene, −65°C to rt; (c) Ac_2O, pyridine; (d) *p*TsOH, CH_2Cl_2.



Scheme 5.



Scheme 6. *Reagents and conditions*: (a) $LiN(TMS)_2$, THF, −65°C, then $PhNTf_2$, 3°C; (b) **18**, $Pd(PPh_3)_4$, LiCl, DME, aq. Na_2CO_3, 80°C, 7 h; (c) H_2, 10% Pd-C; (d) DIBAL, toluene, −65°C to rt; (e) Ac_2O, pyridine; (f) *p*TsOH, CH_2Cl_2; (g) 1N NaOH, rt, MeOH; (h) Dess–Martin oxd. rt, CH_2Cl_2; (i) $Ph_3P{=}CH_2$, THF–toluene; (j) Na, anthracene, DME, −65°C; (k) $TsO(CH_2)_4CH{=}CH_2$, iPr$_2$NEt, THF.

cyclization of **21** under the above optimal reaction conditions proceeded smoothly to give **22** in 49% yield from **20**. The acetoxypropyl side chain at the furan ring was then converted to a 3-butenyl group by conventional transformations. The phenylsulfonyl group on the A ring was then deprotected by sodium anthracenide and the resulting secondary amine was alkylated with hexenyl tosylate to give **23**,[16] which is a good substrate for testing the RCM reaction to prepare the F ring in nakadomarin A. The results of the RCM reaction of **23** and further transformations for the total synthesis of nakadomarin A will be reported in due course.

Acknowledgements

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6. (a) The starting material, methyl 4-oxo-3-piperidinecarboxylate, **1** is commercially available and can also be easily prepared in large scale from simple reagents: Baty, J. D.; Jones, G.; Moore, C. *J. Chem. Soc. (C)* **1967**, 2645–2647; (b) All of the compounds shown in this paper are racemic. However, an asymmetric allylation of **1** has been reported: Shilay, V.; Alyev, A.; Grishina, G. *Bull. Soc. Chim. Belg.* **1992**, *101*, 751–752.
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9. For **10**: According to ^{1}H NMR, compound **10** was observed as a 1:1 mixture of amide rotamers. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.53 (9H, s), 1.85–2.15 (1H, m), 2.25–2.55 (1H, m), 2.67 (1H, d, $J=10.8$ Hz), 3.34 (1H, brd, $J=16.8$ Hz), 3.58 (2H, brt, $J=10.8$ Hz), 3.98 (1H, d, $J=10.8$ Hz), 4.25 (1H, dd, $J=16.8$, 3.1 Hz), 4.69 (0.5H, brs), 4.83 (0.5H, brs), 5.43 (1H, t, $J=3.1$ Hz), 6.30 (1H, brs), 7.38 (1H, brs), 7.52–7.62 (3H, m), 7.82 (2H, d, $J=7.0$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.8, 34.0, 34.8, 44.9, 45.9, 46.5, 48.9, 59.1, 60.3, 61.7, 80.6, 105.3, 109.7, 126.4, 127.8, 129.6, 133.3, 135.1, 136.9, 148.7, 149.0, 154.6, 155.3, 162.5; IR (neat, cm^{-1}) ν 1697, 1394, 1360, 1167, 1146, 1101; LRMS (EI) 442 (M^+).
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11. For **12**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.45 (9H, brs), 1.40–1.95 (9H, m), 2.2–2.60 (2H, m), 3.02–3.06 (1H, m), 3.41–3.51 (2H, m), 3.64–3.70 (2H, m), 3.95–4.09 (2H, m), 7.52–7.63 (3H, m), 7.62–7.75 (2H, m); IR (neat, cm^{-1}) ν 1693, 1402, 1365, 1167, 578; LRMS (EI) 448 (M^+); HRMS (EI) calcd for $C_{23}H_{32}N_2O_5S$ 448.2032; found 448.2055.
12. For **14**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.50 (9H, s, Boc), 1.57–1.71 (2H, m, Hβ-4′, Hα-5), 1.92–2.03 (1H, m, Hα-4′), 2.45 (1H, dd, $J=12.1$, 3.9 Hz, Hα-4), 2.51 (1H, ABq, $J=12.4$ Hz, Hα-2), 2.55–2.64 (1H, m, Hα-6), 2.70–2.85 (1H, m, Hβ-5), 3.17–3.25 (1H, m, Hα-3′), 3.41–3.67 (1H, m, Hβ-3′), 3.74 (1H, dd, $J=11.6$, 1.5 Hz, Hβ-6), 3.96 (1H, ABq, $J=12.4$, 1.5 Hz, Hβ-2), 6.31 (1H, d, $J=1.9$ Hz, H-4″), 7.28 (1H, brd, $J=1.4$ Hz, H-2″), 7.32 (1H, brd, $J=1.6$ Hz, H-5″), 7.54–7.61 (3H, m, Bs), 7.88 (2H, dd, $J=8.0$, 1.7 Hz, Bs); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.2 (C5), 28.5 (*t*Bu), 28.9 (C4′), 40.5 (C4), 42.8 (C3′), 46.3 (C6), 47.9 (C3), 52.1 (C2), 83.2 (*t*Bu), 110.9 (C4″), 124.2 (C3″), 128.4 (Bs), 129.4 (Bs), 133.2 (Bs), 137.2 (Bs), 140.7 (C2″), 143.5 (C5″), 150.4 (C=O), 173.1 (C1′); IR (KBr, cm^{-1}) ν 1755, 1712, 1323, 1155; HRMS (FAB) calcd for $C_{23}H_{28}N_2OSNa$ 483.1566 (M+Na$^+$); found 483.1596.
13. For **13**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.53 (9H, s, Boc), 1.57–1.64 (1H, m, Hβ–5), 1.87–1.92 (2H, m, Hα,β-4′), 2.01–2.08 (1H, m, Hα-5), 2.76 (1H, brt, $J=6.3$ Hz, Hα-4), 3.06–3.25 (2H, m, Hα,β-6), 3.08 (1H, ABq, $J=12.4$ Hz, Hα-2), 3.26–3.75 (2H, m, H-3′), 3.34 (1H, ABq, $J=12.4$ Hz, Hβ-2), 4.65 (1H, s, Hβ-1′), 6.14 (1H, d, $J=1.8$ Hz, H-4″), 7.33 (1H, brs, H-5″), 7.50–7.63 (3H, m. Bs), 7.77 (2H, dd, $J=8.4$, 1.5 Hz, Bs); ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.6 (C5), 28.8 (*t*Bu), 36.3 (C4″), 39.1 (C4), 42.8 (C6), 45.3 (C3′), 50.0 (C2), 61.2 (C3), 62.5 (C1′), 80.5 (*t*Bu), 107.3 (C4″), 127.7 (Bs), 128.9 (C3″), 129.6 (Bs), 133.1 (Bs), 137.8 (Bs), 147.7 (C5″), 154.8 (C=O), 157.3 (C2″); IR (neat, cm^{-1}) ν 1693, 1398, 1167, 737; HRMS (FAB) calcd for $C_{23}H_{28}N_2O_5SNa$ 467.1617 (M+Na$^+$); found 467.1629.
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16. For **23**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20–1.60 (5H, m), 1.53 (9H, s), 1.69–1.78 (1H, m), 1.99–2.09 (4H, m), 2.14–2.19 (1H, m), 2.17 (1H, ABq, $J=11.9$ Hz), 2.30–2.42 (4H, m), 2.45–2.55 (1H, m), 2.59 (1H, t, $J=7.5$ Hz), 2.68 (2H, t, $J=7.1$ Hz), 2.79 (1H, ABq, $J=11.9$ Hz), 3.47–3.53 (2H, m), 4.66 (1H, brs), 4.92–5.08 (4H, m), 5.75–5.89 (2H, m), 5.81 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.3, 26.8, 28.5 (overlapped peaks), 30.6, 32.1, 33.6, 36.1, 38.0, 45.5, 51.9, 58.6, 59.6, 60.4, 62.5, 79.5, 102.7, 114.5, 115.1, 130.9, 137.6, 138.8, 154.9, 155.7, 159.7; IR (neat, cm^{-1}) ν 1697, 1394, 1173; HRMS (FAB) calcd for $C_{27}H_{41}N_2O_3$ 441.3117 (MH^+); found 441.3121.