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# Studies directed toward the synthesis of nakadomarin A

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ABSTRACT

The application of a Pummerer-initiated tandem reaction cascade leads to the highly stereoselective formation of the tetracyclic core of nakadomarin A.



Nakadomarin A **1** (Fig. 1) was first isolated from the Okinawan marine sponge *Amphimedon* sp. by Kobayashi in 1997.[1] The structure of **1** was elucidated spectroscopically and consists of an unprecedented hexacyclic ring system (8/5/5/5/15/6). Kobayashi has proposed an interesting biogenetic transformation for the conversion of ircinal A **2**, the precursor to manzamine A **3**,[2] to nakadomarin A **1**, underscoring the striking structural similarities among this compound class.[3]

Nakadomarin A **1** demonstrates a range of promising biological activities including cytotoxic activity against murine lymphoma L1210 cells ($IC_{50}$ 1.3 μg/mL), inhibitory activity against cyclin dependent kinase 4 ($IC_{50}$ 9.9 μg/mL), anti-microbial activity against a fungus (*Trichophyton mentagrophytes*, MIC 23 μg/mL), and a Gram-positive bacterium (*Cornebacterium xerosis*, MIC 11 μg/mL). However, its limited availability from natural sources ($1.8 \times 10^{-3}$% of sponge wet weight) has prevented a complete study of its biological activity. The structural complexity of nakadomarin A coupled with its intriguing and as yet not fully explored biological activity led to considerable effort directed toward the synthesis of **1**, culminating in a series of elegant total syntheses.[4] We describe herein a conceptually novel approach to the synthesis of manzamine core based on a Pummerer-initiated tandem reaction cascade.[5]

We envisioned that the ABCDE pentacyclic core **4** of nakadomarin A **1** could be obtained by global reduction of bislactam sulfide **5**, which we envisioned as the product of a Pummerer-initiated

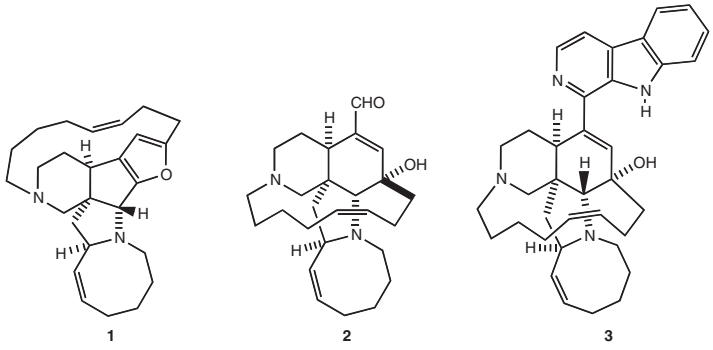


**Figure 1.** Nakadomarin A **1**, ircinal A **2**, and manzamine A **3**.

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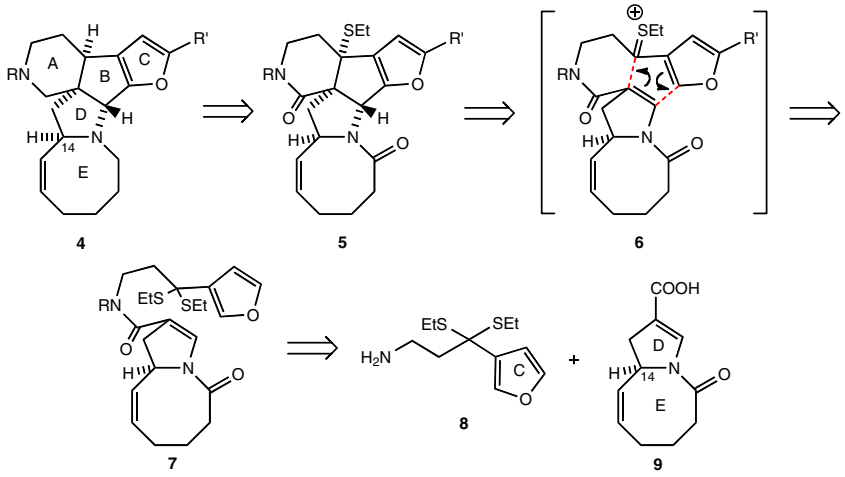
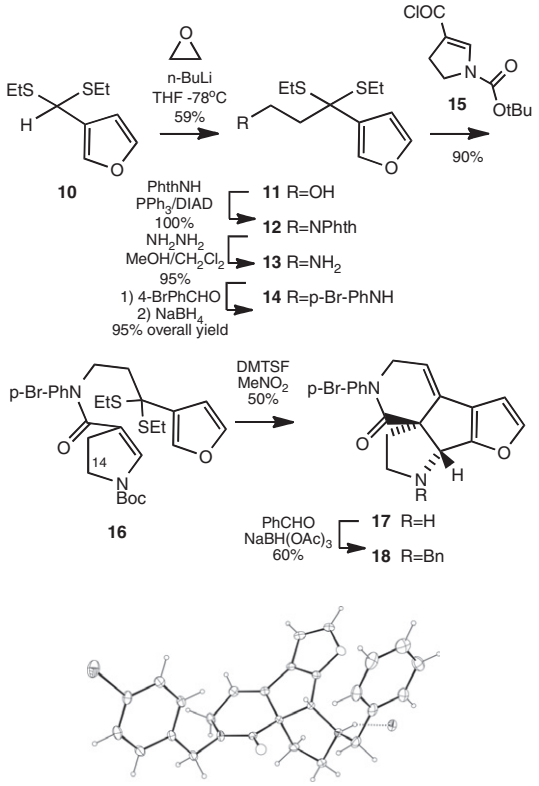


**Scheme 1.** Retrosynthetic analysis for the synthesis of the pentacyclic core **4** of nakadomarin A.

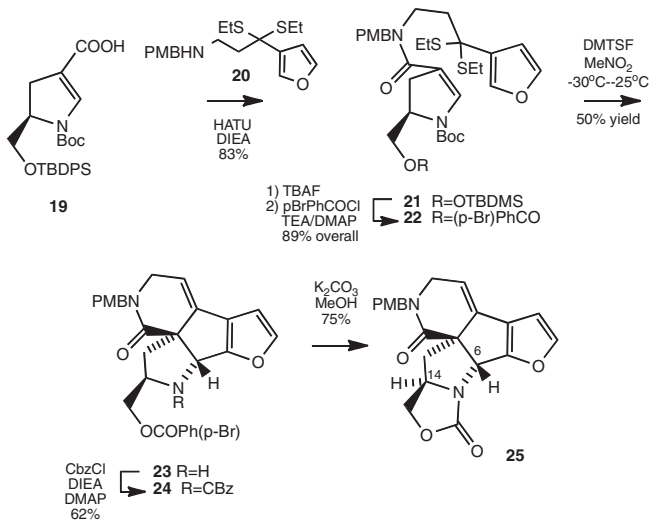
tandem reaction cascade of **7** via the intermediacy of thionium ion **6** (Scheme 1). We note that the elegant studies of Martin,[2b] Mukai,[4g] and Zhai[6] suggest that the C-14 stereocenter would lead to the desired diastereoselectivity in the cascade cyclization reaction via approach of the thionium ion **6** from the α-face of the pyrroline D-ring to give **5**. We anticipated that the requisite cyclization substrate **7** could be prepared via coupling of **8** and **9**.

To examine the feasibility of the key cascade sequence, we examined the reaction in the simpler model system **16**,[7] lacking the C-14 stereocenter, as outlined in Scheme 2. Metalation of **10**,[8] based on the work of Das, and the reaction of the derived anion with ethylene oxide delivered alcohol **11**, which on Mitsunobu reaction with phthalimide afforded **12**. Deprotection of **12** with hydrazine and reductive alkylation with *p*-bromobenzaldehyde gave secondary amine **14**, which was coupled with acid chloride **15**[2b] to give the cascade cyclization substrate **16**. Exposure of **16** to dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF)[9] led to the exclusive formation of the desired tetracycle **17**, the structure of which was unambiguously confirmed via X-ray crystallographic analysis of the hydrochloride salt of the derived tertiary amine **18**, as shown in Scheme 2.[10]

The extension of these results to a substrate containing the C-14 stereocenter is outlined in Scheme 3. Reaction of the known acid **19**[2b] with the *p*-methoxybenzyl amine **20** (obtained from **13** by reductive alkylation) gave amide **21**. While the reaction of **21** with DMTSF resulted in extensive decomposition of the starting material without the formation of the desired product, we were delighted to find that exposure of the corresponding benzoate **22** to DMTSF led to the formation of the desired cyclization product **23** in 50% yield, which was fully characterized as the corresponding Cbz analog **24**.[11] The stereoselective formation of **23** is consistent with the addition of the thionium ion from the α-face of the pyrroline ring, as noted in related systems by Zhai[6] and Martin.[2b] Further support for this stereochemical assignment, albeit indirect, was obtained by cyclization of **24** to the cyclic urethane **25**, which revealed no NOE between the two methines (C-6 and C-14 using



**Scheme 2.** Synthesis of the tetracyclic core **17**.



**Scheme 3.** Synthesis of tetracyclic model system **23**.

the numbering of the nakadomarin ring system) of the pyrrolidine ring of **25**.[12]

We have developed an alternative strategy to the elegant work of Zhai[6] on the use of the glutamate-derived stereochemistry to control the establishment of the key stereochemical relationships of the core structure of nakadomarin A. In both Zhai's work and the current study, a single stereocenter leads to the establishment of all of the key stereochemical relationships of the nakadomarin tetracyclic core. Further studies on the application of this strategy to the synthesis of biologically relevant systems are underway in our laboratories and our results will be reported in due course.

## Acknowledgments

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11. Characterization data for **24**: $[\alpha]_D^{24.1}$ +83.36, *c* 1.00 ($CDCl_3$); $^{1}H$ NMR (500 MHz, $CDCl_3$, 335 K) $\delta$ 7.87 (d, $J$ = 7.6 Hz, 2H), 7.57 (d, $J$ = 8.4 Hz, 2H), 7.47 (br s, 1H), 7.46–7.28 (m, 5H), 7.16 (d, $J$ = 8.4 Hz, 2H), 6.72 (d, $J$ = 8.2 Hz, 2H), 6.32 (d, $J$ = 1.6 Hz, 1H), 5.76 (s, 1H), 5.70 (d, $J$ = 5.0 Hz, 1H), 5.28 (d, $J$ = 2.4 Hz, 2H), 4.91 (d, $J$ = 13.5 Hz, 1H), 4.73 (dd, $J$ = 4.7, 10.5 Hz, 1H), 4.63 (t, $J$ = 9.4 Hz, 1H), 4.35 (br, 1H), 4.33 (d, $J$ = 14.3 Hz, 1H), 4.03 (d, $J$ = 17.3 Hz, 1H), 3.74 (dd, $J$ = 6.2, 17.4 Hz, 1H), 3.69 (s, 3H), 2.44 (d, $J$ = 13.7 Hz, 1H), 2.21 (dd, $J$ = 8.6, 13.7 Hz, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$, 335 K) $\delta$ 171.0, 165.3, 159.4, 148.9, 136.5, 131.7, 131.3, 129.5, 129.2, 128.4, 128.2, 127.9, 124.2, 114.4, 109.0, 105.0, 67.6, 64.5, 62.0, 58.3, 55.2, 50.0, 47.5, 38.1, 29.7; IR (neat) 2917, 2850, 2253, 1714, 1698, 1652, 1590, 1514, 1486, 1404, 1354, 1272, 1248, 1175, 1118, 1030 $cm^{-1}$; HRMS (ESI) $m/z$ calcd for $C_{36}H_{31}BrN_2NaO_7$ [$MNa^+$] 705.1212, obsd 705.1236.
12. Characterization data for **25**: $[\alpha]_D^{24.2}$ +122.85, *c* 1.00 ($CDCl_3$); $^{1}H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.49–7.45 (m, 1H), 7.18 (d, $J$ = 8.5 Hz, 2H), 6.88–6.81 (m, 2H), 6.35 (d, $J$ = 1.9 Hz, 1H), 5.94 (s, 1H), 5.72 (dd, $J$ = 2.0, 6.5 Hz, 1H), 4.61 (d, $J$ = 14.4 Hz, 1H), 4.54 (d, $J$ = 14.4 Hz, 1H), 4.48 (dd, $J$ = 7.4, 8.9 Hz, 1H), 4.17 (dd, $J$ = 2.3, 9.1 Hz, 1H), 4.01–3.93 (m, 2H), 3.79 (s, 3H), 3.75 (dd, $J$ = 6.5, 17.3 Hz, 1H), 2.36 (dd, $J$ = 7.1, 12.8 Hz, 1H), 2.00 (dd, $J$ = 9.1, 12.8 Hz, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 170.5, 159.4, 159.2, 159.1, 149.8, 136.5, 129.6, 128.9, 127.0, 114.2, 109.8, 105.5, 67.7, 66.9, 62.9, 58.0, 55.3, 49.4, 47.8, 44.0; IR (neat) 2969, 2925, 2856, 1750, 1646, 1611, 1510, 1398, 1375, 1248, 1222, 1178, 1029 $cm^{-1}$; HRMS (ESI) $m/z$ calcd for $C_{22}H_{21}N_2O_5$ [$MH^+$] 392.1372, obsd 392.1348.