Total Synthesis of (–)-Nakadomarin A

J. Stephen Clark* and Chao Xu

Abstract: *A highly efficient 12-step synthesis of the marine alkaloid (−)-nakadomarin A has been accomplished. The key advanced intermediate, tetracyclic ketone* ***13****, was constructed in just seven steps using a sequence that includes an asymmetric Pauson-Khand reaction, an Overman rearrangement reaction, a ring-closing metathesis reaction and an amination reaction. Late introduction of the furan (ring C) during the synthesis of (−)-nakadomarin A means that the tetracyclic ketone* ***13*** *has the potential to serve as an advanced intermediate for the synthesis of related marine alkaloids.*

(−)-Nakadomarin A (**1**) was first isolated from a sponge of *Amphimedon sp.* by Kobayashi and co-workers in 1997 and was found to possess a unique hexacyclic structure featuring fused 5-, 6-, 8- and 15-membered rings (Figure 1).[1] This alkaloid exhibits cytotoxicity against murine lymphoma L1210 cells, antimicrobial activity and inhibitory activity against cyclin-dependent kinase 4.[2] The intriguing structure of nakadomarin A (**1**) combined with its significant biological activity and limited availability make it a very attractive target for total synthesis, a fact that is reflected by the many studies that have been devoted to its synthesis.[3] To date, seven enantioselective total syntheses have been reported.[4] Following the original pioneering syntheses of nakadomarin A completed by the groups of Nishida[4a,b] and Kerr,[4c] impressive and innovative syntheses have been reported by the groups of Dixon[4d,g–i] and Evans,[4j] which set the benchmark with respect to efficiency.

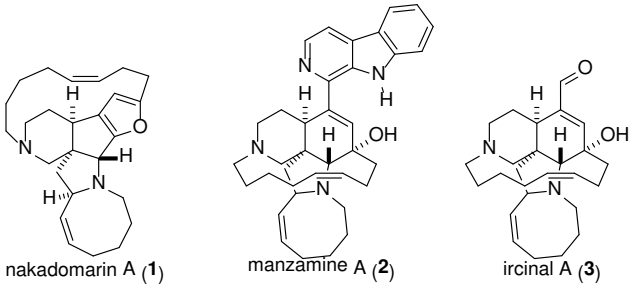
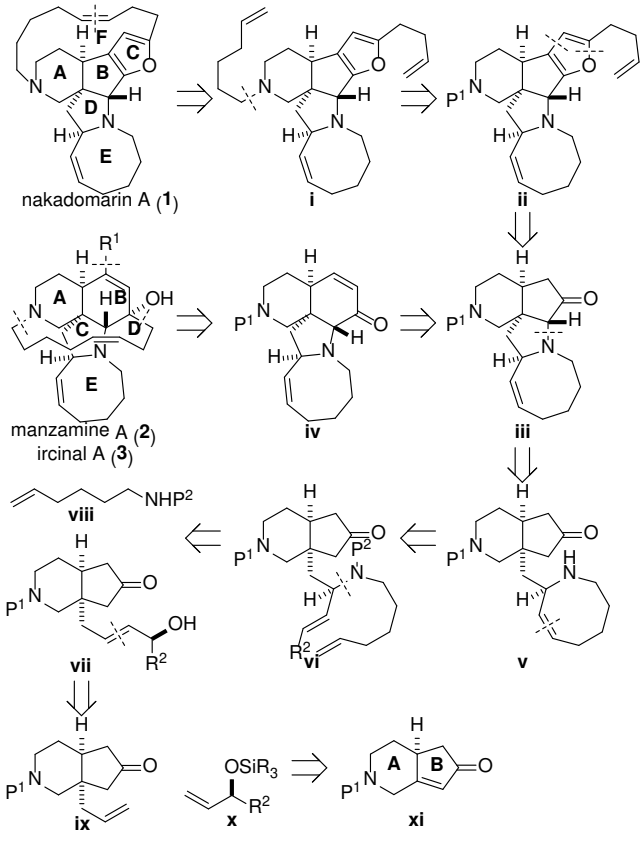


Figure 1. Selected members of the manzamine family of marine alkaloids.

Nakadomarin A is classified as a member of the manzamine family of alkaloids, even though it is architecturally distinct from the other members because it possesses a furan and a contracted B-ring. Kobayashi and co-workers proposed a direct biosynthetic route from iricinal A to nakadomarin A,[1] which suggests that a common synthetic approach to both compounds might be possible. In all previous syntheses of nakadomarin A, a furan-containing starting material has been used or the furan has been constructed very early in the route.[4] We wanted to design a synthesis in which an advanced intermediate could also be used to synthesize many of the other manzamine alkaloids. Such a strategy would preclude the use of a functionalized furan as the starting material and would require construction of the C-ring relatively late in our synthesis.

Our strategy for the synthesis of nakadomarin A (**1**) and the other manzamine alkaloids evolved from the retrosynthetic analysis shown in Scheme 1. Disconnection through the alkene of ring F leads to the triene **i**. Replacement of the *N*-alkyl group with a protecting group in ring A gives the diene **ii** and disconnection of ring C reveals the key tetracyclic ketone **iii**. In the cases of manzamine A (**2**) and ircinal A (**3**), disconnection of the D-ring alkene and removal of the B-ring substituent (R^1) leads to the enone **iv**; subsequent retrosynthetic contraction of ring B delivers the ketone **iii**. Thus, retrosynthetic analyses for all three natural products converge on the tetracyclic ketone **iii** as an intermediate. It should be noted that the forward sequence of reactions, in which the ketone **iii** is converted into the enone **iv**, is in essence the reverse of the proposed biosynthetic process by which ircinal A is converted into nakadomarin A.[1]



Scheme 1. Retrosynthetic analysis of nakadomarin A (**1**), manzamine A (**2**) and ircinal A (**3**) via the tetracyclic ketone **iii**.

Disconnection of the C-N bond in ring D that links rings B and E in nakadomarin A leads to tricyclic amino ketone **v** and implies an unusual electrophilic amination reaction in the

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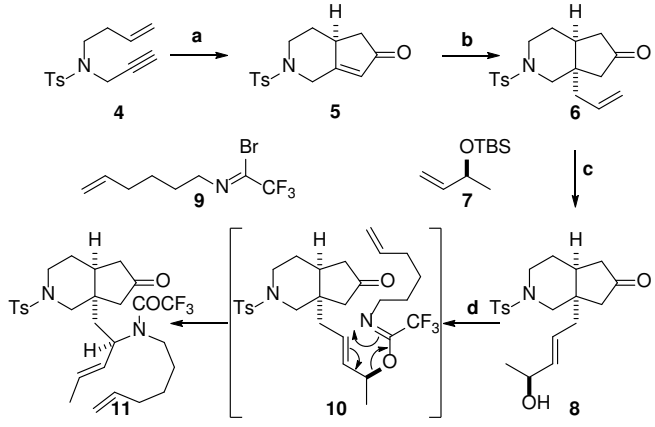
forward direction. Cleavage through the alkene in ring E furnishes the diene **vi** and further disconnection gives the allylic alcohol **vii** and the protected ω-amino alkene **viii**. Scission of the alkene in the allylic alcohol **vii** affords the ketone **ix** and the protected allylic alcohol **x**. Removal of the allyl chain then reveals the bicyclic enone **xi** as an early synthetic intermediate.[5]

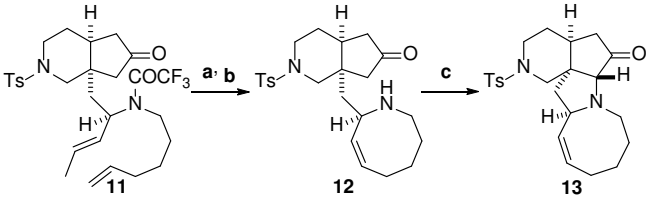
Our synthesis of (–)-nakadomarin A (**1**) commenced from the known enyne **4**,[6] which was prepared by alkylation of commercially available *N*-tosyl propargylamine with 4-bromobut-1-ene (Scheme 2).[5] The enyne **4** was converted into the fused bicyclic enone **5** in good yield and with excellent ee using the asymmetric cobalt-catalysed Pauson-Khand reaction developed by Hiroi and co-workers.[7] Reaction of the enone **5** with the organocopper reagent generated from allylmagnesium chloride and copper(I) iodide resulted in a highly diastereoselective conjugate addition reaction and established the quaternary stereogenic centre at the AB ring junction. The resulting terminal alkene **6** was functionalised by cross-metathesis with the silyl-protected allylic alcohol **7** to give the allylic alcohol **8** in high yield after desilylation during acidic work-up.



Scheme 2. Synthesis of the functionalised AB ring system using a Pauson-Khand reaction and subsequent installation of functionality using an Overman rearrangement reaction. a) $Co_2(CO)_8$, (*R*)-BINAP, CO, then NMO, PhMe, 65 °C, 72% (97% ee); b) CH_2CHCH_2MgCl, CuI, LiCl, TMSCl, THF, –10 °C, 91%; c) **7**, Hoveyda-Grubbs II catalyst (3 mol %), CH_2Cl_2, reflux, then 1M HCl, 85%; d) NaHMDS, **9**, THF, –30 °C then K_2CO_3, PhMe, reflux, 73%.

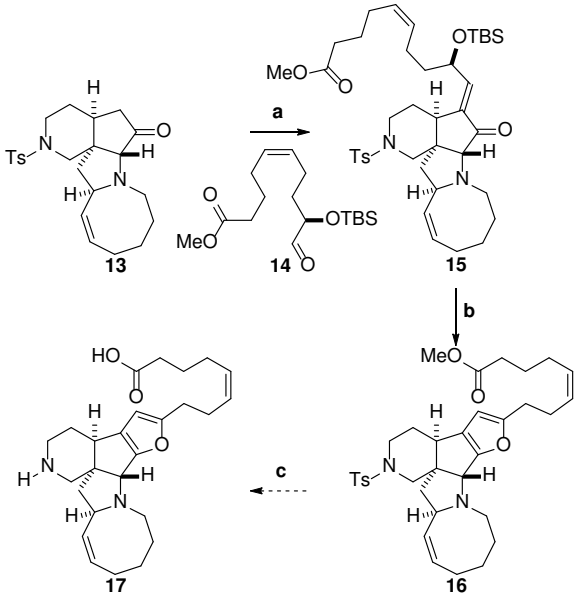
The stage was now set for introduction of the allylic amine using an Overman rearrangement reaction.[8,9] A solution of the alcohol **8** in THF was deprotonated and the resulting alkoxide was treated with the imidoyl bromide **9** at –30 °C.[10] After complete formation of the trifluoroacetimidate **10**, potassium carbonate was added and the mixture was diluted with toluene, then heated at reflux for two days. The one-pot imidate formation and [3,3]-sigmatropic rearrangement reaction afforded the trifluoroacetamide **11** as a single diastereomer in 73% yield.

Construction of ring E was accomplished by use of a ring-closing metathesis reaction (RCM). Treatment of the diene **11** with the Grubbs second-generation catalyst (15 mol %) delivered the azocine in 81% yield (Scheme 3). Subsequent base-mediated cleavage of the trifluoroacetamide afforded the tricyclic amine **12** and closure of ring D was performed by treatment of this compound with pyrrolidone hydrotribromide and DMAP. This reaction delivered the crystalline ketone **13** in excellent yield, the structure of which was confirmed by X-ray crystallography.[11] A related procedure has been used by Kreis and Carreira during their synthesis of the alkaloid natural product dendrobine and there is an earlier literature precedent for this reaction from the Rabe and Kindler synthesis of quinine.[12] In our case, it is not clear whether C–N bond formation occurs by attack of an enol on an *N*-bromoamine or results from displacement of bromide from the ±-bromoketone by the E-ring amine.



Scheme 3. Sequential construction of rings E and D. a) Grubbs II catalyst (15 mol %), CH_2Cl_2, reflux, 81%; b) 10% K_2CO_3 aq., MeOH, rt, 88%; c) pyrrolidone hydrotribromide, DMAP, THF, rt, 90%.

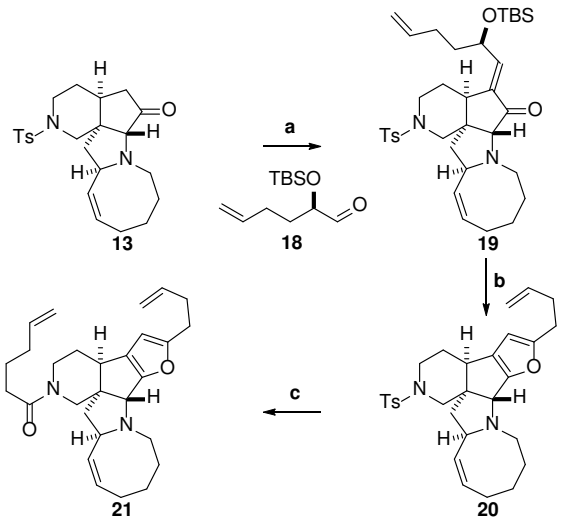
Construction of the ketone **13**, which corresponds to the complete tetracyclic ABDE core of nakadomarin A, meant that introduction of the remaining carbon framework required for construction of rings C and F could be explored (Scheme 4). Regioselective deprotonation of the ketone **13** with LDA, followed by aldol condensation of the lithium enolate with the aldehyde **14**[13] afforded the enone **15** in 46% yield.[14,15] Acid-mediated cleavage of the TBS protecting group with concomitant dehydrative cyclisation delivered the furan **16**.[16]



Scheme 4. Attempted synthesis of the diamino acid substrate required for macrolactamisation to form ring F. a) LDA, **14**, THF, –78 °C, 46%; b) TsOH, PhMe, rt, 95%; c) Na, naphthalene, DME, –78 °C then sat. LiOH aq., rt.

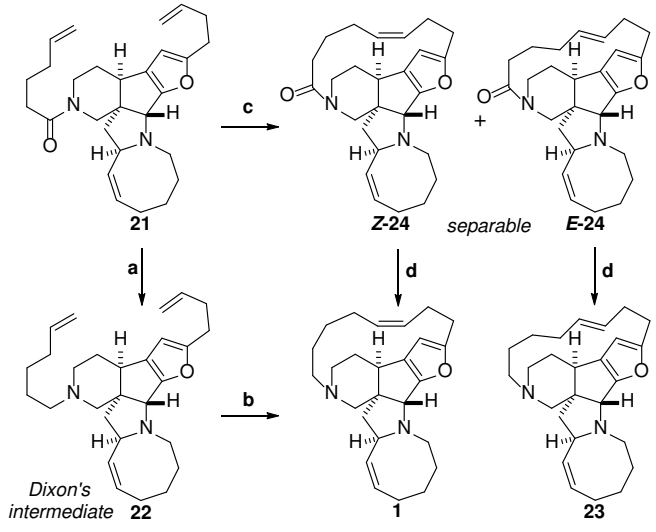
The next challenge was to remove the tosyl protecting group and cleave the methyl ester, thereby generating the amino acid required to close ring F by a macrolactamization reaction. A one-pot sulfonamide cleavage and saponification sequence was performed in which the *N*-tosyl amine **16** was treated with sodium naphthalenide and then lithium hydroxide solution was added to hydrolyse the ester. Unfortunately, the highly polar amino acid **17** was not isolated and so it was necessary to implement an alternative end-game strategy.

The aldehyde **18** was prepared[17] and then subjected to an aldol condensation reaction with the lithium enolate generated from the ketone **13** (Scheme 5). The aldol condensation reaction delivered the enone **19**[15] and this compound was then converted into the furan **20** in good yield by acid-mediated desilylation, cyclization and dehydration.[16] Subsequent one-pot cleavage of the sulfonamide and *N*-acylation with 5-hexenoyl chloride delivered the amide **21** as a mixture of rotamers.



Scheme 5. Synthesis of the final ring-closing metathesis precursor. a) LDA, **18**, THF, –78 °C, 50%; b) TsOH, PhMe, rt, 93%; c) Na, naphthalene, DME, –78 °C, then $CH_2CH(CH_2)_3COCl$, Et_3N, 90%.

Reduction of amide **21** with Red-Al delivered the diamine **22** in 81% yield (Scheme 6). The diamine **21** featured as the final intermediate in the synthesis of (–)-nakadomarin A published by Dixon and co-workers; spectroscopic and other data for our sample of triene **22** were identical to those reported previously.[4d] The triene **22** was then subjected to the RCM reaction under conditions described by Dixon and co-workers and a mixture of (−)-nakadomarin A (**1**) and its *E* isomer **23** was obtained in 38% yield.



Scheme 6. Completion of the synthesis of nakadomarin A. a) Red-Al, PhMe, reflux, 81%; b) Grubbs I catalyst (15 mol %), camphor sulfonic acid, CH_2Cl_2, reflux, 38% (**1** + **23**). c) Grubbs II catalyst (15 mol %), CH_2Cl_2, reflux, 80% (60:40 ***Z*-24**:***E*-24**); d) Red-Al, PhMe, reflux, **1** 89%, **23** 84%.

The modest yield for the final RCM reaction and that fact that nakadomarin A (**1**) could not be separated from the *E*-isomer **23** without recourse to HPLC prompted us investigate reversal of the final two steps in the synthesis (Scheme 6). Direct macrolactam formation by RCM of the amide **21** delivered a mixture of ***Z*-24** and ***E*-24** in high yield. To our delight, it was found to be possible to separate the alkene isomers using conventional chromatography on basic alumina and so pure samples of both isomeric lactams were obtained. Interestingly, *Z*-selectivity was achieved using the Grubbs second-generation catalyst (60:40, *Z*:*E*), whereas a reversal of selectivity (40:60, *Z*:*E*) was observed when the RCM reaction was performed using the Grubbs first-generation catalyst. The synthesis of (–)-nakadomarin A (**1**) was completed by reduction of the lactam ***Z*-24** using Red-Al in toluene at reflux. The spectroscopic data (^{1}H NMR and ^{13}C NMR), high-resolution mass spectrometric data, and specific rotation of our synthetic material were in excellent agreement with the published data for the natural product.[1,4]

In conclusion, we have developed a concise and stereoselective synthesis of (–)-nakadomarin A (**1**) from the simple acyclic enyne **4** (longest linear sequence 12 steps). The tetracyclic intermediate **13** was synthesized enantioselectively in just seven steps, with high efficiency and overall yield. The ketone **13** has the potential to serve as a common late-stage intermediate for the synthesis of other manzamine alkaloids, such as manzamine A (**2**) and ircinal A (**3**). The application of our synthetic strategy to the total synthesis other manzamine alkaloids will be reported in due course.

Acknowledgements

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Keywords: natural products • polycyclic alkaloids • Overman rearrangement • ring-closing metathesis

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[13] The aldehyde **14** was synthesised from commercially available *tert*-butyldimethylsilyl (*R*)-glycidylether. For further details see Supporting Information.

[14] The alcohol arising from the aldol reaction without dehydration was also obtained in 30% yield.

[15] The enones **15** and **19** were obtained with high stereoselectivity and the assignment of *E* configuration was based on the outcomes of dehydration reactions of closely related aldol products: K. C. Nicolaou, W. Tang, P. Dagneau, R. Faraoni, *Angew. Chem. Int. Ed.* **2005**, *44*, 3874–3879.

[16] The formation of the furans **16** and **20** from the *E*-configured enones **15** and **19** suggests that equilibration of the *E* and *Z* isomers occurs by reversible hydration of the enone.

[17] The aldehyde **18** was synthesised from (*R*)-1-(*tert*-butyldimethylsilyl-oxy)hex-5-en-2-ol that was prepared following a literature procedure: G. J. Florence, J. C. Morris, R. G. Murray, J. D. Osler, V. R. Reddy, T. K. Smith, *Org. Lett.* **2011**, *13*, 514–517. For further details, see Supporting Information.