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Total synthesis of (−)-nakadomarin A†

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A highly diastereoselective bifunctional organocatalyst controlled Michael addition, a nitro-Mannich/lactamization cascade, a furan *N*-acyliminium cyclisation, a sequential alkyne RCM/*syn*-reduction and an alkene RCM has allowed a 19 step, highly stereoselective synthesis of (−)-nakadomarin A.

(−)-Nakadomarin A is a marine alkaloid of the manzamine family first isolated by Kobayashi and co-workers in 1997 from the Haplosclerid sponge Amphimedon sp., collected off the coast of the Kerama Islands, Okinawa. This hexacyclic alkaloid contains an 8/5/5/5/15/6 ring system incorporating four stereogenic centres, including one quaternary carbon. Cytotoxic activity against murine lymphoma L1210 cells (IC_{50} = 1.3 μg mL^{-1}), inhibition of cyclin dependent kinase 4 (IC_{50} = 9.9 μg mL^{-1}) and antimicrobial activity against the fungus *Trichophyton mentagrophytes* (MIC = 23 μg mL^{-1}) and the gram-positive bacterium *Corynebacterium xerosis* (MIC = 11 μg mL^{-1}) have all been exhibited by this molecule in biological screens.[1,2]

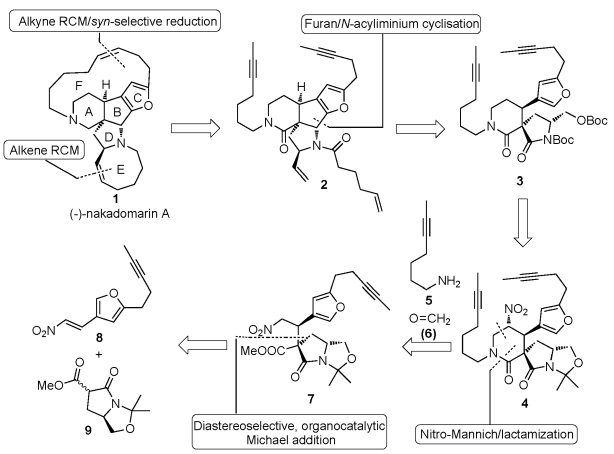
The biological activity and intriguing structural complexity has resulted in significant interest from the synthesis community. To date there have been nine papers describing the construction of the tetracyclic core,[3] five total syntheses[4–8] and two formal syntheses.[9,10] With the exception of a recent synthesis by Funk,[8] all of the other total synthesis papers, including the one from our group, used alkene ring closing metathesis (RCM) to construct the 15-membered ring and *E*/*Z* isomeric mixtures were obtained.

With the general failure of the routes to deliver high *Z*-selectivity in the alkene RCM we recognized that a solution was to employ an alkyne RCM combined with a concomitant *syn*-selective hydrogenation.[11,12] Herein we wish to report a new highly *Z*-selective route to (−)-nakadomarin A employing an alkyne RCM as a key macrocyclic ring-forming step.

Our retrosynthetic plan (Scheme 1) pivoted on the stereoselective synthesis of late stage tetracyclic intermediate **2** which would be suitably poised for a sequential alkyne RCM to construct the 15-membered ring and an alkene RCM to construct the 8-membered ring. We envisaged this product would be accessible from the nitro ester **7** through our documented nitro-Mannich/lactamization cascade chemistry[7] and a subsequent stereoselective intramolecular furanyl *N*-acyliminium cyclisation. Nitro ester **7** would be formed from a diastereoselective Michael addition of pronucleophile **9** with nitro olefin **8** controlled by a bifunctional organocatalyst.

Pronucleophile **9** was constructed on multigram scale through a two step protocol starting from pyroglutamol (see ESI†).[13] Nitro olefin **8** was synthesized from dimethyl (2-oxopropyl)-phosphonate in a route analogous to that previously reported (see ESI†).[7]

Pivotal to the success of our synthesis was the stereoselective construction of the C–C bond linking the quaternary stereocentre to the tertiary stereocentre bearing the functionalized furan heterocycle. Preliminary investigations (Scheme 2) into the levels of diastereocontrol that could be achieved using a nitro olefin Michael addition reaction were carried out using **9** and model nitro olefin **10**. Treatment of **9** and **10** with achiral base 1,4-diazabicyclo[2.2.2.]octane (DABCO) **15** in toluene led to the formation of two of the possible four diastereoisomers,



Scheme 1 Retrosynthetic analysis of (−)-nakadomarin A.

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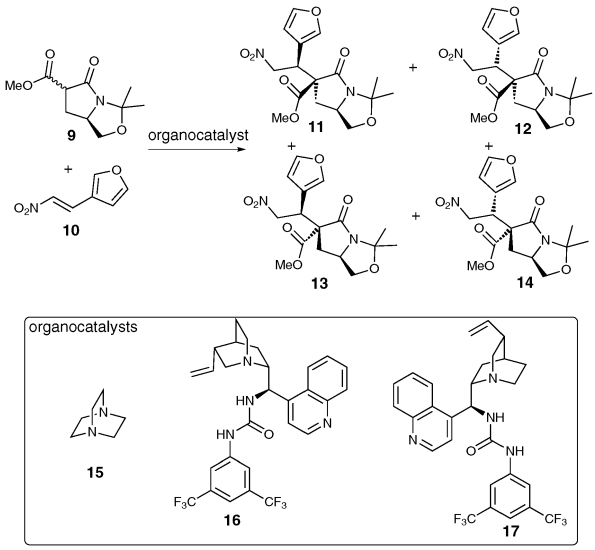


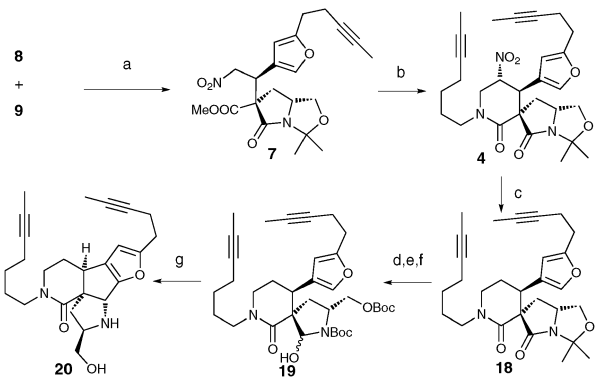
Scheme 2 Preliminary nitro olefin Michael addition studies. (a) Catalyst **15** (10 mol%), toluene, 30 °C, 7 days, 4.3 : 1 : 0 : 0 crude dr, 38% yield (mixture of diastereoisomers); (b) Catalyst **16** (10 mol%), toluene, 30 °C, 48 h, 15 : 1 : 0 : 0 crude dr, 80% yield (single diastereoisomer **11**); (c) Catalyst **17** (10 mol%), toluene, 30 °C, 5 days, 4 : 12 : 1 : 1 crude dr, 61% yield [mixture of diastereoisomers (6 : 19 : 1 : 1 dr)].

11 and **12**, in a 4.3 : 1 ratio respectively. The relative stereochemistries of the major diastereoisomer **11** and the minor diastereoisomer **12** were unambiguously determined by single crystal X-ray analysis (see ESI†). Epimeric at the newly formed tertiary stereocentre these diastereoisomers resulted from exclusive addition to the convex face of the enolized bicyclic pronucleophile, however, facial selectivity on addition to the nitro olefin was only poorly imparted by the chiral pronucleophile. To improve diastereoselection, bifunctional organocatalysts introduced by our group and others were investigated.[14] Pleasingly using cinchonine derived urea **16** as catalyst at 10 mol% a significantly improved diastereoselectivity was observed; after 48 h **11** and **12** were formed in a ratio of 15 : 1 and the isolated yield of pure **11** after flash column chromatography *and* a recrystallization was 80%.

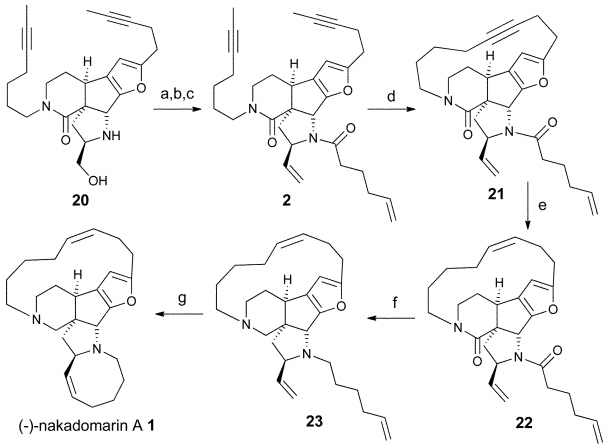
Interestingly use of pseudoenantiomeric cinchonidine derived urea **17** resulted in a reduced reaction rate (5 days), as well as a poor and reversed diastereoselection (**11** : **12** : **13** : **14**, 4 : 12 : 1 : 1 dr). These data confirm that bifunctional organocatalyst stereocontrol dominates the inherent substrate stereocontrol and that pronucleophile **9** and cinchonine derived organocatalyst **16** are matched for the production of **11**, whereas **17** and **9** are mismatched.

Applying the findings of the model system, pronucleophile **9** (2 eq.) was reacted with furanyl nitro olefin **8** in toluene at 30 °C in the presence of 10 mol% **16**. The reaction was complete after 52 h, was highly diastereoselective (dr 18 : 1 : 0 : 0) and the desired Michael adduct **7** was isolated as a single diastereomer in 81% yield [1.99 g of **7** (largest single batch)]. The good reactivity and high selectivity achieved in this key C–C bond forming transformation using pronucleophile **9** represents a significant improvement from our previously reported route to (−)-nakadomarin A.[7] With gram quantities of **7** in hand, treatment with hept-5-yn-1-amine **5** and formaldehyde (**6**) in refluxing methanol afforded nitro piperidin-2-one **4** as a single diastereomer in 52% yield.[15] Reductive removal of the nitro group occurred smoothly using tributyltin hydride and AIBN.[16] To construct the tetracyclic core *via* an *N*-acyliminium ion cyclisation, selective delivery of one hydride to **3** was required. This was readily achieved after a protecting group switch: acid catalyzed methanolysis of the isopropylidene protecting group of **18** allowed exhaustive Boc protection of NH and OH functionality. Treatment of this compound with Superhydride® at low temperature afforded **19**. Subjecting this substrate to neat formic acid for 15 h followed by an alkaline hydrolytic work-up afforded the tetracyclic core of (−)-nakadomarin A **20** as a single diastereoisomer (Scheme 3).[3b,4] Dissolution in formic acid facilitated the desired *N*-acyliminium ion formation/cyclisation and double Boc deprotection but also afforded hydrolysable formic acid derived side products.

Aware of the compatibility of alkyne ring closing metathesis with alkene functionality but the known incompatibility of some catalysts to amine functionality,[17] the most attractive alkyne RCM precursor was **2**. Transformation of **20** to **2** was readily achieved in three standard transformations; a selective hexenoylation of the pyrrolidine nitrogen atom was followed by an IBX oxidation and Wittig olefination (Scheme 4). With alkyne RCM precursor in hand a range of commercial and literature reported alkyne RCM catalysts were screened and in our hands the Schrock tungsten neopentylidyne catalyst[18] was by far the best producing the desired product in 69% yield when the reaction was performed at moderate dilution in chlorobenzene at 80 °C (largest scale: 36 mg of diyne **2**). The best stereo- and chemoselectivity in the alkyne hydrogenation was found using nickel boride in the presence of excess ethylenediamine.[19] Hydrogenation in the absence of ethylenediamine and when using Lindlar conditions rapidly resulted in a complex mixture of products attributed to reduction of the alkene functionalities in the molecule. To complete the total synthesis two steps remained; the alkene ring-closing metathesis to construct the 8-membered ring and the



Scheme 3 Synthesis of tetracyclic core **20**. Reaction conditions: (a) organocatalyst **16** (10 mol%), toluene, 30 °C, 52 h, 81%, single diastereoisomer; (b) hept-5-yn-1-amine **5**, CH_2=O (**6**), MeOH, reflux, 8 h, 52%; (c) AIBN, Bu_3SnH, mesitylene, 165 °C, 2.5 h, 65%; (d) PTSA, MeOH, reflux, 5 h, 87%; (e) di-*tert*-butyl dicarbonate, DMAP, Et_3N, CH_2Cl_2, rt, 15 h, 88%; (f) lithium triethylborohydride, THF, −78 °C, 2 h, 79%; (g) HCOOH, rt, 15 h, then LiOH, MeOH, 50 °C, 5 h, 86%.



Scheme 4 Synthesis of (−)-nakadomarin A **1**. Reaction conditions: (a) hex-5-enoyl chloride, Et_3N, CH_2Cl_2, −20 °C to rt, 3 h, 89%; (b) IBX, DMSO, rt, 24 h; (c) $MePPh_3Br$, KO^{t}Bu, THF/toluene, rt, 15 min, 74% (2 steps); (d) $[(CH_3)_3CO]_3W{\equiv}C{-}C(CH_3)_3$, chlorobenzene, 80 °C, 2 h, 69%; (e) H_2, $NaBH_4$, $Ni(OAc)_2{\cdot}4H_2O$, $NH_2CH_2CH_2NH_2$, EtOH, rt, 1.3 h, 87%; (f) DIBAL-H, toluene, 0 °C to rt, 6 h, 59%; (g) Grubbs' 1st generation catalyst, (+)-CSA, CH_2Cl_2, reflux, 8 h, 70%.

exhaustive amide/lactam functional group reduction to the diamine. Owing to difficulties in our hands closing the 8-membered ring directly on **22**, the amide and lactam functional groups were first reduced using an excess of DIBAL-H at 0 °C in toluene. Subsequent treatment of diamine **23** with Grubbs' first generation catalyst in the presence of (+)-CSA afforded (−)-nakadomarin A **1** in 70% yield (6.5 mg). The structure of synthetic (−)-nakadomarin A **1** was confirmed by comparison of the spectral data and specific rotation with those of the literature.[4–8]

In summary, a 19 step route (longest linear sequence) to (−)-nakadomarin A **1** employing an alkyne ring-closing metathesis to enable the stereoselective construction of the *Z*-configured alkene in the 15-membered ring has been achieved. Furthermore 'matched' catalyst and substrate control facilitated a highly diastereoselective nitro olefin Michael addition to fix two of the four stereogenic centres in one key step. While longer than our first reported route to (−)-nakadomarin A [12 steps (longest linear sequence)] significant improvements have been made. This second generation route compares favourably to all of the other total syntheses reported including the synthesis of Funk[8] [21 steps (longest linear sequence)] which also employed an alkyne ring closing metathesis step.

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