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Catalytic Asymmetric Synthesis of Pentacyclic Core of (–)-Nakadomarin A *via* Oxazolidine as an Iminium Cation Equivalent**

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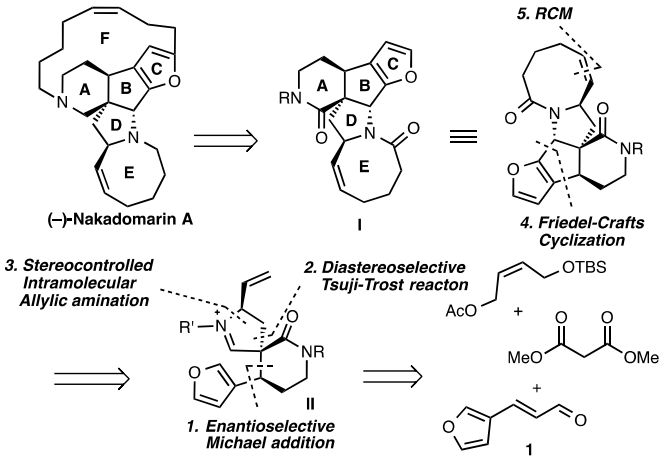
A facile and catalytic asymmetric synthesis of the pentacyclic core of (–)-nakadomarin A, containing all the stereogenic centers of the natural product, was achieved. The key intermediate involves oxazolidine moiety as an iminium cation equivalent. An efficient method for the removal of *N*-hydroxyethyl group is also described.

Introduction

(–)-Nakadomarin A was isolated from the marine sponge *Amphimedon* sp. collected off the coast of the Kerama Islands, Okinawa, by Kobayashi *et al.*[1] It consists of a highly fused nitrogen-containing hexacyclic ring system containing a 15-membered ring, an eight-membered ring and a furan ring, as well as four stereogenic centers including three adjacent chiral centers. It exhibits strong cytotoxicities, antimicrobial activities and inhibition of CDK4. These structural and biological features have attracted much attention from the synthetic community for more than a decade, and a number of elegant total syntheses,[2] formal total syntheses[3] and synthetic approaches[4] for (–)-nakadomarin A have been reported in the literature. However, most of the previous approaches employed chiral proline derivatives as starting materials or chiral auxiliaries to construct the stereocenters. No catalytic enantioselective synthesis has yet been reported, although it would be highly desirable for the development of practical and scalable syntheses. We envisioned that these four chiral centers, including an all-carbon quaternary center, could be constructed using a catalysis-based approach. To demonstrate this working hypothesis, we planned to synthesize the pentacyclic core of (–)-nakadomarin A (ABCDE rings, **I**) as a model target (Scheme 1), since 15-membered ring (F ring) formation *via* ring-closing metathesis (RCM) reactions is well established.[2] Herein, we report a novel catalyst-based approach for the synthesis of the pentacyclic core of (–)-nakadomarin A, with full enantiocontrol, through enantioselective Michael reaction of dimethyl malonate with α,β-unsaturated aldehyde **1**, subsequent diastereoselective Tsuji–Trost reaction and stereocontrolled allylic amination. In addition, during the course of Friedel–Crafts cyclization of the unstable iminium intermediate **II**, we found a stable but reactive iminium cation equivalent, which is also described in detail.



Scheme 1. Synthetic strategy for the pentacyclic core I of (–)-nakadomarin A

Results and discussion

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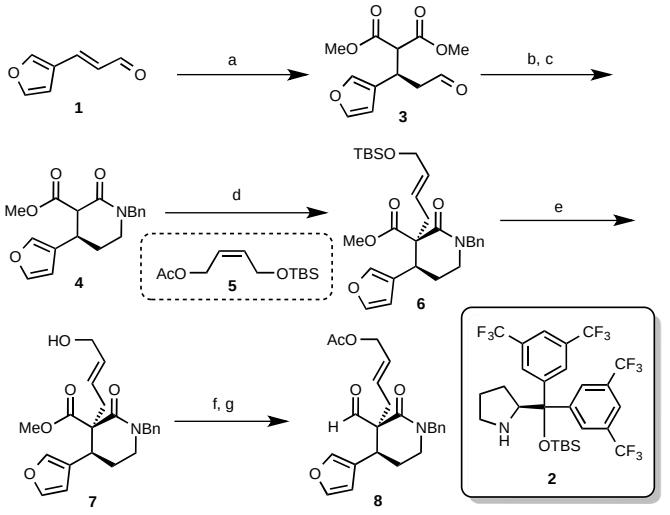
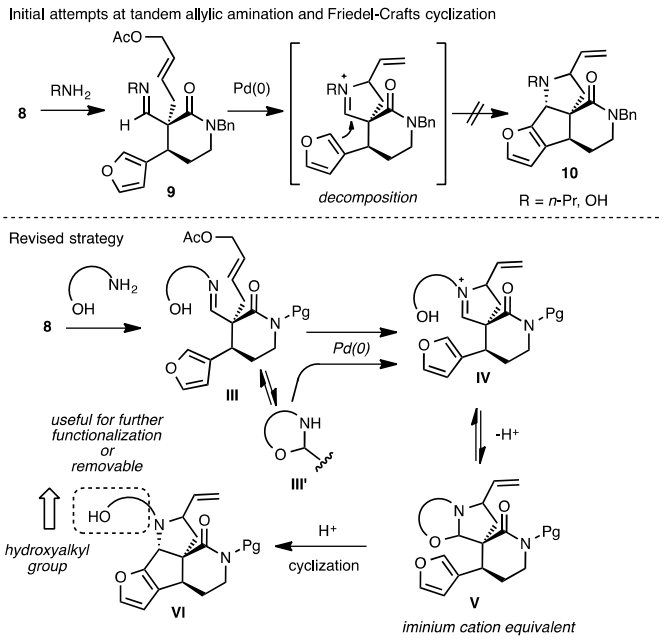
We first investigated the enantioselective Michael reaction of dimethyl malonate with **1** using a series of organocatalysts, and found that the Hayashi–Jørgensen catalyst **2**[5] showed the best catalytic activity; only 2 mol % of **2** furnished the corresponding adduct **3** in excellent enantioselectivity and high yield (Scheme 2). Reductive amination of the product **3**[6] with benzylamine facilitated a cyclization to afford lactam **4**, which was subjected to the Tsuji–Trost reaction conditions to construct the all-carbon quaternary center. To our delight, Pd(0)-catalyzed reaction of **4** with allylic acetate **5** in the presence of NaH proceeded in a highly stereoselective manner to furnish the silyl ether **6** in good yield, probably because of the steric hindrance of the furan ring. After deprotection of the TBS group of **6**, DIBAL reduction of the ester **7** and the subsequent acetylation furnished the aldehyde **8** in 90% yield over two steps.



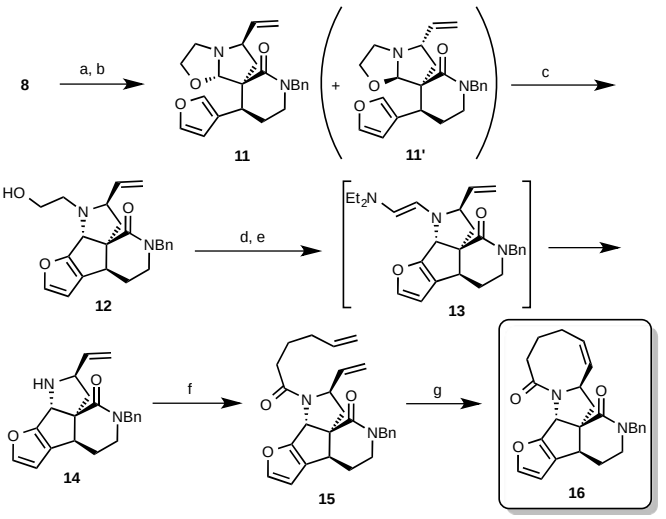
Scheme 2. Reagents and conditions: (a) dimethyl malonate, **2** (2 mol %), AcOH, H_2O, 45 °C, 24 h, 78 %, 97 %ee; (b) $BnNH_2$, MS 4Å, CH_2Cl_2; (c) $NaBH_4$, MeOH; (d) **5**, NaH, $Pd(PPh_3)_4$, THF; (e) DOWEX 50WX8, MeOH, 48% over 4 steps; (f) DIBALH, CH_2Cl_2, –78 °C; (g) Ac_2O, NEt_3, DMAP, CH_2Cl_2, 90% over 2 steps.

With **8** in hand, efforts were focused toward the key transformation involving stereocontrolled allylic amination/intramolecular Friedel–Crafts cyclization (Scheme 3). Initially, we expected allylic amination of imine **9** to furnish tetracyclic core **10** in a single step *via* an iminium intermediate, but all attempts[7] afforded only complex mixtures, indicating that the reactive iminium cation intermediate was unstable under the reaction conditions and decomposed easily.

To overcome these difficulties, our attention was next focused on introducing an intramolecular iminium cation stabilizer as shown in Scheme 3. We expected that imine **III** bearing an intramolecular nucleophilic moiety, such as a hydroxyl group, would prevent the decomposition of iminium cation intermediate **IV** after the Pd-catalyzed intramolecular allylic amination. The oxazolidine derivative **V** would be isolated as an iminium cation equivalent, and its intramolecular Friedel–Crafts cyclization would proceed under acidic conditions to afford the desired tetracyclic core **VI**, again with all four stereogenic centers. We also envisaged that the generated hydroxyalkyl moiety of **VI** could be utilized for further carbon–carbon bond formations or removed as a protecting group to afford the free secondary amine for further transformations.



Scheme 3. Preliminary attempts and revised strategy for synthesis of tetracyclic core **VI**



Scheme 4. Reagents and conditions: (a) 2-aminopropanol, NaOAc, CH_2Cl_2; (b) $Pd(PPh_3)_4$, DBN, 1,4-dioxane, 60 °C, 80% over 2 steps; (c) TfOH (1.2 equiv.), CH_2Cl_2, 35 °C, 90%; (d) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, then NEt_3; (e) Et_2NH, EtOH, then 1N HCl aq., 70 °C; (f) 5-hexenoic acid, EDCI, DMAP, CH_2Cl_2, 83% over 3 steps; (g) Grubbs II, CH_2Cl_2 (1 mM), 50 °C, 90%.

Among various amino alcohols[8] investigated for the reaction with aldehyde **8** and the subsequent Pd(0)-catalyzed allylic amination, 2-aminoethanol was the best choice in terms of chemical yield and diastereoselectivity, affording the desired spirocycle **11** in 80% yield along with diastereomer **11'** (ca. 16%, determined by ^1H NMR), respectively. It is worth noting that **11** and **11'** both had the *anti* configuration,[9] probably because of the tight [3,3,0]-bicyclic scaffold. In contrast, a mixture of all four possible diastereomers was obtained when 3-aminopropanol was used instead of 2-aminoethanol, with poor selectivities (data not shown), indicating the importance of the tether length for the stereoselective intramolecular allylic amination. The

choice of base was also critical[10] for the selectivity; the use of Et_3N or inorganic bases such as NaH decreased the selectivity (**11**:**11'** ≈ 1:1) compared with 1,5-diazabicyclo[4.3.0]-5-nonene (DBN, **11:11'** = 4:1) and 1,8-diazabicyclo[5.4.0]-7-undecene (DBU, **11:11'** = 3:1). These bases would promote substitution *via* a σ-palladium complex rather than a π-complex,[11] to give the kinetically favored product **11**,[10] and/or simply work as a bulky ligand of Pd.[12] The choice of the Pd source, phosphine ligand[13] and solvent[14] was also important, and $Pd(PPh_3)_4$ in 1,4-dioxane was the best system in terms of both diastereoselectivity and chemical yield.

With **11** in hand, the intramolecular Friedel–Crafts cyclization was investigated, and we found that trifluoromethanesulfonic acid (TfOH) efficiently promoted the reaction, furnishing the tetracyclic core **12** in 90% yield, as expected. Several attempts at the elongation of the hydroxyethyl group of **12** resulted in failure, and therefore we decided to remove the *N*-hydroxyethyl moiety, although no reliable and general methods have yet been reported.[15] After various investigations, we achieved the removal by hydrolysis *via* 1,2-diaminoethylene intermediate **13**; Swern oxidation of the primary alcohol of **12** and subsequent 1,2-diaminoethylene formation with diethylamine, followed by hydrochloric acid-mediated hydrolysis resulted in the successful production of free amine **14**.[16] 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) mediated condensation of **14** and 5-hexenoic acid afforded the RCM precursor **15** in 83% yield (three steps starting from **12**). Gratifingly, RCM of amide **15** with Grubbs second-generation catalyst afforded pentacyclic bisamide[17] **16** in excellent yield.

Conclusions

In conclusion, we have achieved a catalytic asymmetric synthesis of the pentacyclic core of (–)-nakadomarin A. All four stereogenic centers were efficiently constructed by organocatalyzed enantioselective Michael reaction, diastereoselective Tsuji–Trost reaction, and Pd-catalyzed allylic amination, followed by intramolecular Friedel–Crafts cyclization *via* an oxazolidine as an iminium cation equivalent. In addition, we established an effective method for the cleavage of an *N*-hydroxyethyl group. This oxazolidine chemistry in combination with the established removal method could be applied to various bond-forming reactions to synthesize complex alkaloids. This cleavage method also has significant potential to be developed as a novel method to deprotect *N*-allyl and *N*-prenyl groups. This work is currently underway in our laboratory, and will be reported in due course.

Acknowledgements

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17 Both amide moieties can be reduced to the corresponding amines; see ref. 2.

