Alkaloid Synthesis

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Concise Synthesis of (−)-Nakadomarin A**

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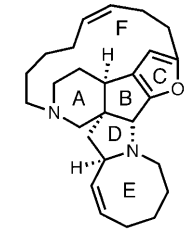
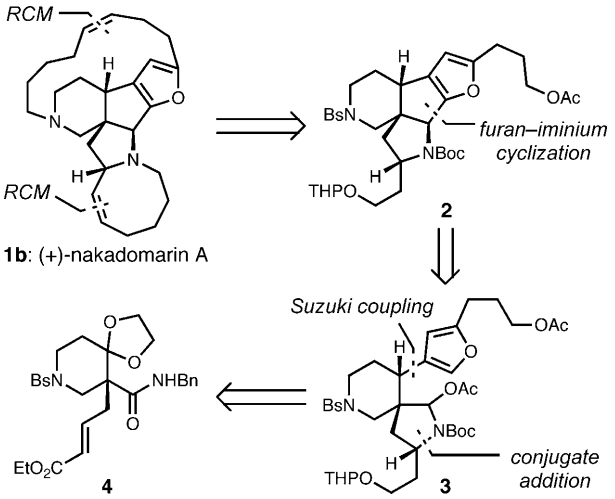
alkaloids · organocatalysis · ring-closing metathesis · synthesis design · three-component coupling

The chemical synthesis of complex alkaloids is an ideal forum for the development of strategy and the evaluation of methodology in organic chemistry. The limitations that functional groups impose on established methodology are often revealed by the presence of nitrogen atoms, and the complications that they often cause during planned strategic operations add significantly to the challenge of alkaloid synthesis. In meeting the challenge posed by complex alkaloid targets, different research groups frequently develop substantially different approaches. The fascinating group of alkaloids of the manzamine family has certainly been inspiring in this regard; for example, nakadomarin A (**1a**),[1] with its unique hexacyclic architecture, has been the subject of four unique syntheses.



1a: (−)-nakadomarin A

Credit should be awarded to the pioneering groups who complete the first synthesis of a complex molecule; those that follow have the duty and challenge of developing substantially more concise and instructive routes aided by the information disclosed by their predecessors. With respect to nakadomarin A, the pioneering efforts of the Nishida group, who published the first synthesis of the unnatural enantiomer (Scheme 1),[2] followed by the disclosure of a different strategy for the natural enantiomer (not shown),[3] must be acknowledged. Certainly, they developed the use of ring-closing metathesis (RCM) for closure of the E and F rings (see **1b**) and documented the feasibility of furan–iminium ion cyclizations to complete the B ring (**3**→**2**). The synthesis of *ent*-nakadomarin A by the Kerr group (Scheme 2) made use of their innovative cycloaddition methodology for the generation of highly substituted pyrrolidines (**9** + **10** + **11**→**8**→**7**), and ultimately yielded the alkaloid in a sequence that was more concise than those of their predecessors.[4] In addition to these completed syntheses, several approaches toward this popular target have been disclosed by other groups,[5] with



Scheme 1. Key steps in the Nishida synthesis of (+)-nakadomarin A. RCM = ring-closing metathesis, Bs = benzenesulfonyl, Bn = benzyl, Boc = *tert*-butoxycarbonyl, THP = tetrahydopyranyl.

those of the Funk[5f] and Zhai[5g] groups both being notable for the construction of the ABCD tetracycle by very short, stereocontrolled sequences; concise syntheses of nakadomarin A are surely being developed in these laboratories. In light of all the excellent previous work, the spectacular synthesis recently disclosed by Jakubec, Cockfield, and Dixon,[6] which no doubt benefited substantially from this prior art, raises the bar in terms of strategic elegance and step economy[7] for nakadomarin A.

The Dixon synthesis (Scheme 3) differs from the previous routes by the early introduction of the azocine E ring into one of their two building blocks; the syntheses of Nishida and Kerr introduced this ring and the F macrocycle near the end of their syntheses by ring-closing metathesis, which necessitated significant functional group manipulation to generate two different dienes for selective ring closure. In the Dixon synthesis an intramolecular Julia–Kocienski olefination reaction proved the method of choice for converting pyroglutamate-derived lactam **12** into azabicyclo[6.3.0]undecanone **13**, which is produced in six steps from commercially available materials. The topology of the bicycle is wisely leveraged to control the stereochemistry at C7, with recruitment of chiral urea catalyst **15a** for stereocontrol at C8 in the critical convergent conjugate addition to nitroalkene electrophile **14** (four steps from commercially available materials). This key union is an impressive application of the methodology

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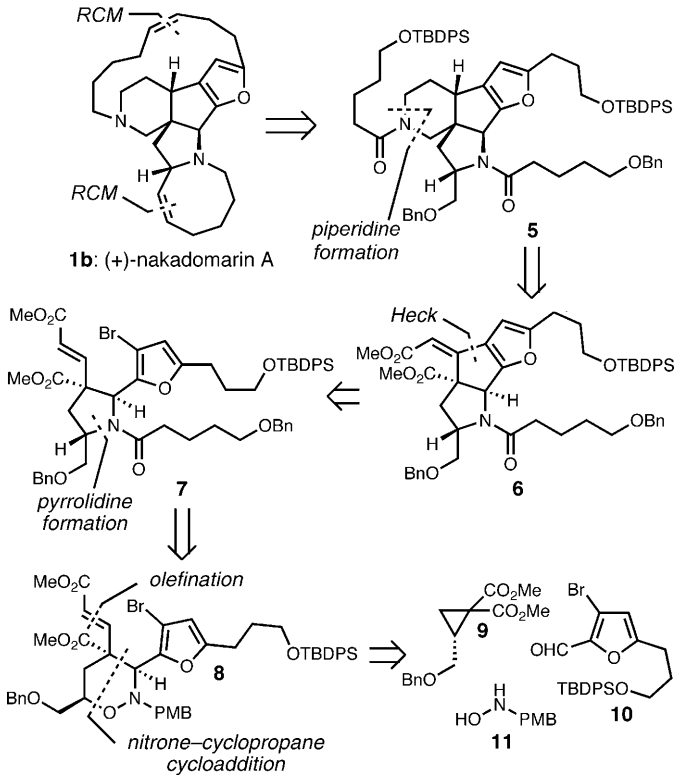
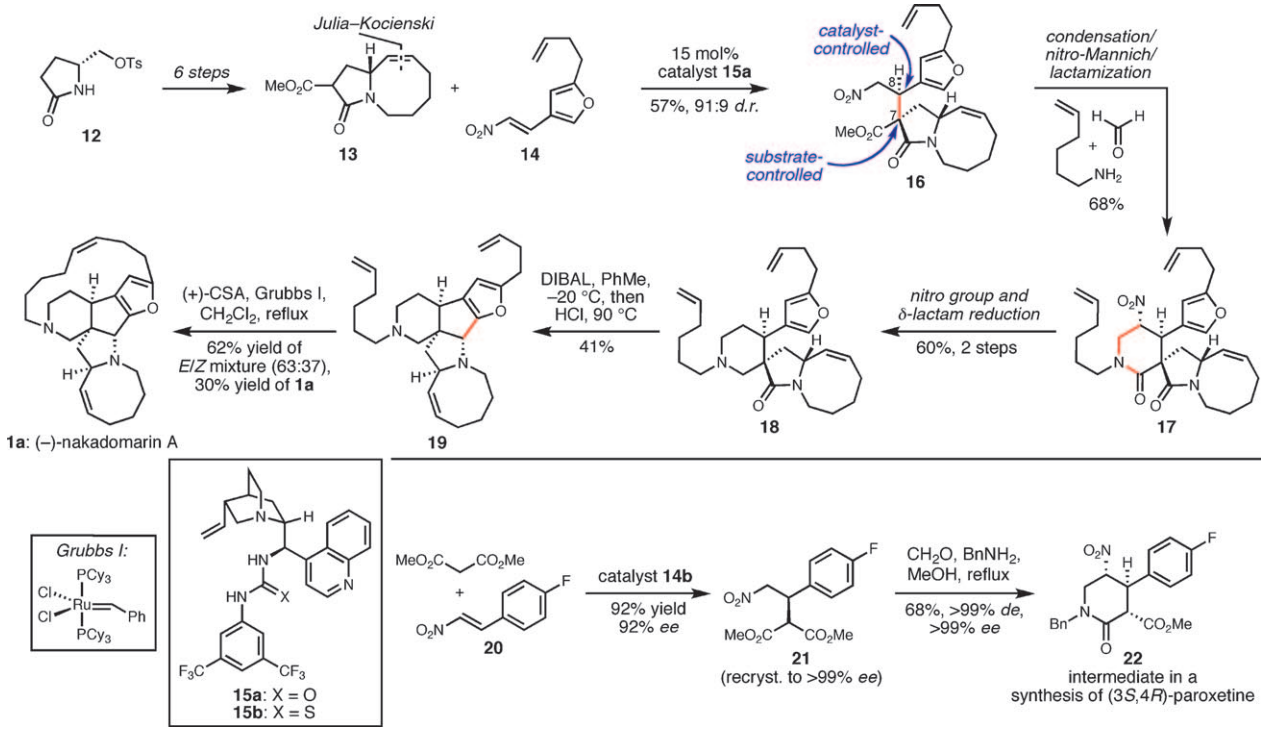


Scheme 2. Key steps in the Kerr synthesis of (+)-nakadomarin A. TBDPS = *tert*-butyldiphenylsilyl, PMB = *para*-methoxybenzyl.

developed by the Dixon group in a complex setting; they had previously disclosed the use of the closely related thiourea catalyst **15b** to promote the enantioselective conjugate addition of malonate esters to nitroalkenes (see **20**→**21**),[8] and had documented a single example of ester-substituted γ-lactams functioning as the nucleophilic component (not shown).[9]

Similarly, the clever three-component coupling that generates the A ring in a single operation (**16**→**17**) is also a procedure previously developed by this research group (see **21**→**22**).[9,10] The sequence of in situ formaldimine formation, nitro-Mannich addition, and terminal lactam formation is a non-obvious way to convert a γ-nitroester into a δ-lactam by introduction of a methylamino unit. In this case, the nitro group facilitates two key C–C bond-forming events, but its nitrogen atom is not included in the product lactam. The nitro group and the two carbonyls that facilitated such a rapid buildup of complexity were then reduced with excellent selectivity: reductive removal of the nitro group under radical conditions was preceded by a remarkably selective reduction by $LiAlH_4$ of the δ-lactam in the presence of the γ-lactam to afford **18**. The one-pot reaction consisting of partial reduction of the pyrrolidinone followed by furan–iminium ion cyclization completed the ABCDE pentacycle (**19**) of nakadomarin A.

In all previous syntheses, macrocyclization by means of ring-closing metathesis generated mixtures somewhat enriched in the undesired *E* isomer. The modest but significant change in the *Z*/*E* isomer ratio ostensibly caused by protic acid in the final macrocyclizing metathesis (63:37 *Z*/*E* with CSA, 40:60 *Z*/*E* without acid) is intriguing, and begs the



Scheme 3. The Dixon synthesis of (–)-nakadomarin A, and relevant prior methodology. Ts = tosyl, DIBAL = diisobutylaluminum hydride, (+)-CSA = (+)-camphorsulfonic acid, Cy = cyclohexyl.

question of whether protonation of amines might be a general approach for altering kinetic (or thermodynamic) product mixtures in the formation of azamacrocycles by metathesis. Fortunately, separation of the desired *Z* isomer from the minor *E* isomer was feasible by HPLC (in previous approaches, these isomers could never be separated at the amine oxidation state), affording pure (−)-nakadomarin A in approximately 30% yield. It is noteworthy that the alkenes required for this final ring closure were introduced directly; the common practice of using protected alcohols or aldehydes as alkene surrogates was avoided, as this naturally decreases step economy. The successful route proceeds in 12 linear steps from commercially available materials (16 total steps); this represents fewer than half the number of operations in previous syntheses, and enables access to substantial quantities of (−)-nakadomarin A.

The Dixon synthesis is characterized by an outstanding buildup of complexity in the course of few transformations, excellent use of the chiral pool, a beautiful example of combined substrate- and catalyst-controlled diastereoselectivity (double stereodifferentiation), and productive use of a three-component coupling for δ-lactam formation. Overall, this most effective synthesis of nakadomarin A seamlessly integrates the Dixon group's methodology with high-level strategic planning, and is one that should be read by all students of synthesis.

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