

# Total Synthesis of (+)-Nakadomarin A

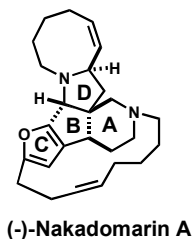
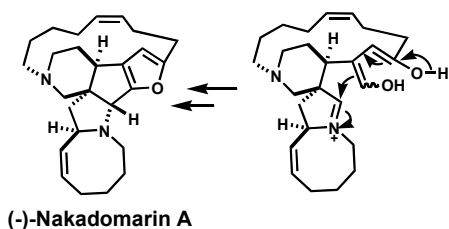
Ian S. Young and Michael A. Kerr\*

JACS, 2007, 129, 1465–1469

Presneted by: Sami Osman  
Feb. 19<sup>th</sup> 2007.

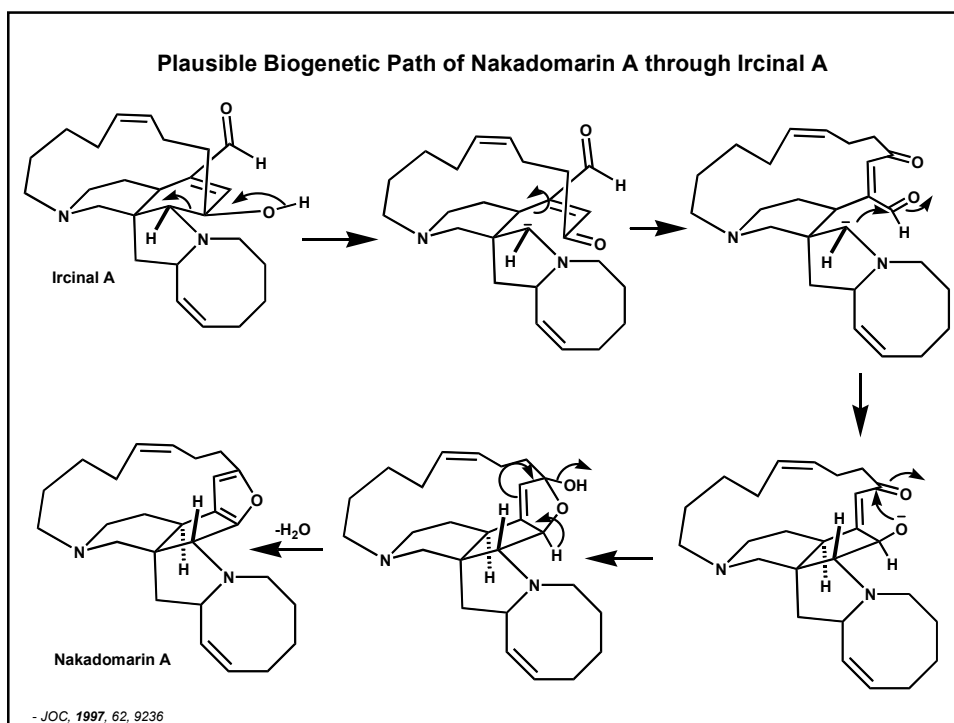
## Introduction

### Nishida's intramolecular Mannich-type cyclization

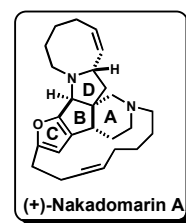
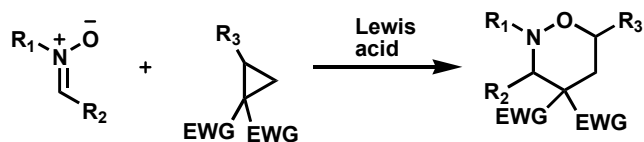


- ♪ Nakadomarin A isolated by Kobayashi from Okinawan sea sponge in 1997
- ♪ Reported biological activity include cytotoxicity, antimicrobial activities, and inhibitory activity against cyclin-dependent kinase A
- ♪ Limited availability slowed down further studies (6mg isolated from 1kg of wet sponge)
- ♪ Nishida recently reported first synthesis of *ent*-(+)-nakadomarin A.
  - ♪ Used a novel intramolecular Mannich-type cyclization of furan to iminium to construct strained ABCD core ring system
  - ♪ Used this route because of the proposed biogenetic pathway

- JACS, 2003, 125, 7484-7485

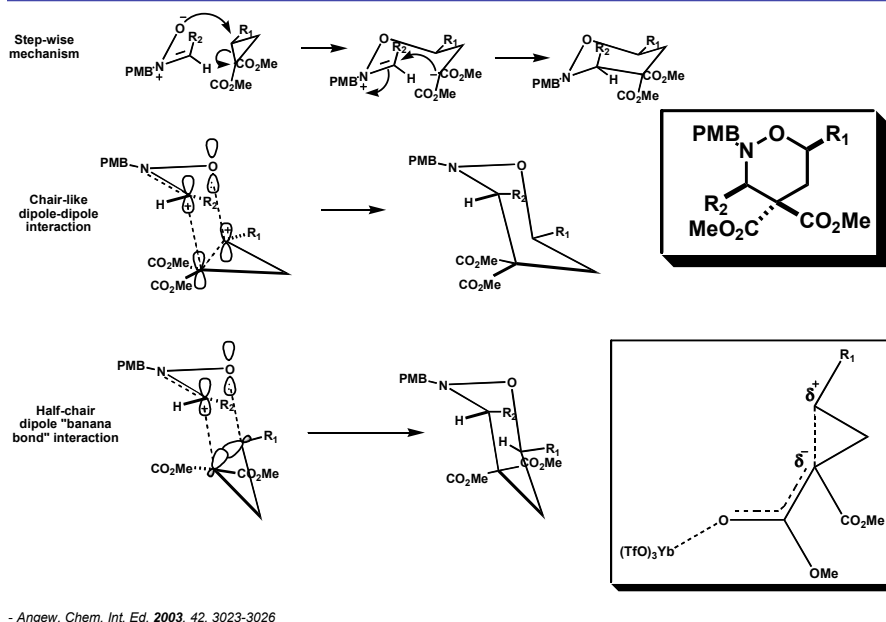


## Three Component Coupling

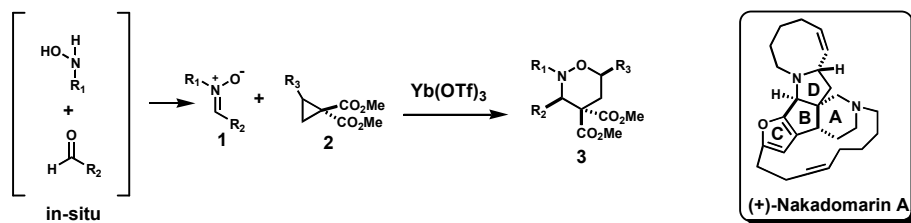


- ♪ Simple 1,1-cyclopropane diesters behave like  $\alpha,\beta$ -unsaturated carbonyl compounds
- ♪ React with nucleophiles could be considered homo-Michael addition
- ♪ Strained cyclopropane ring have significant  $\pi$  character
- ♪ Can be further weakened with lewis acid coordination on ester moiety
- ♪ Several lewis acids used ( $\text{BF}_3 \cdot \text{OEt}_2$ ,  $\text{Cu}(\text{OTf})_2$ ,  $\text{Sc}(\text{OTf})_3$ ,  $\text{TiCl}_4$ ,  $\text{SnCl}_4$ ,  $\text{AlCl}_3$ ,  $\text{Yb}(\text{OTf})_3$ )
- ♪  $\text{Yb}(\text{OTf})_3$  was superior over all others.

## Three Component Coupling

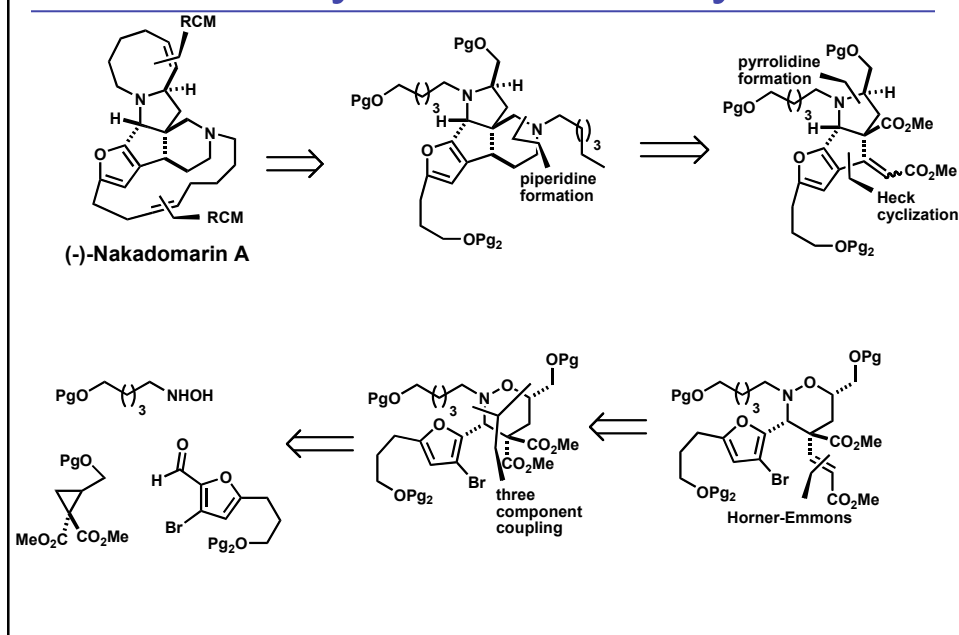


## Three Component Coupling

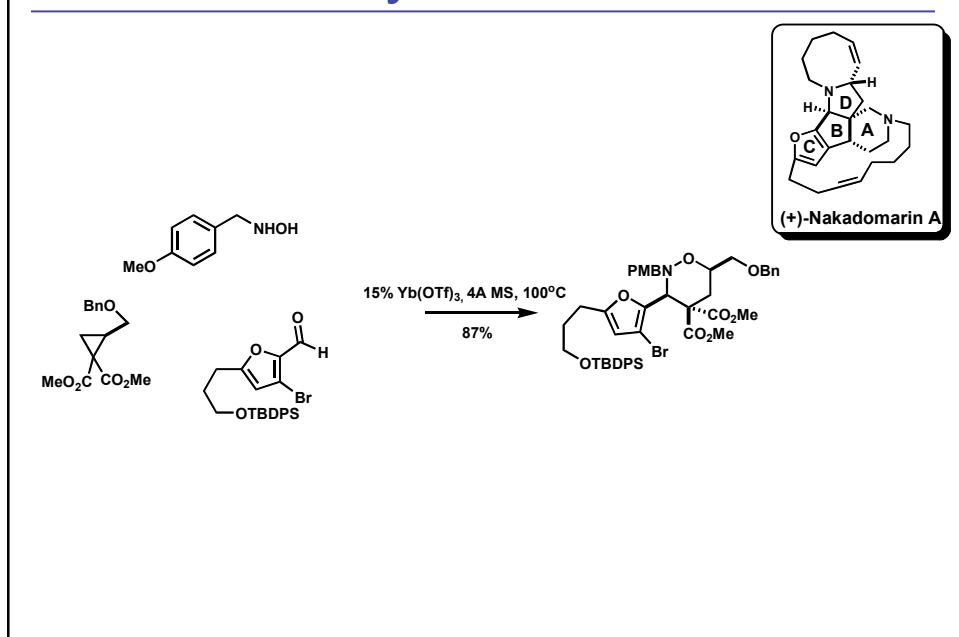


- ♪ Following this, developed an improved protocol for in-situ generation of nitrone from hydroxylamine and aldehyde
- ♪ Three component coupling increased methodology scope

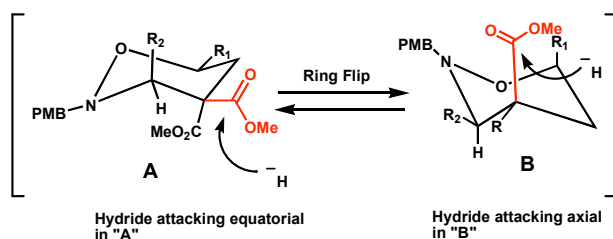
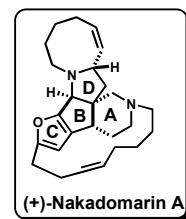
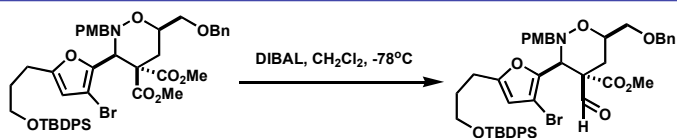
## Retrosynthesis Analysis



## Synthesis

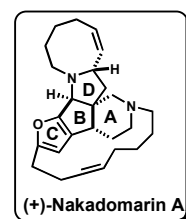
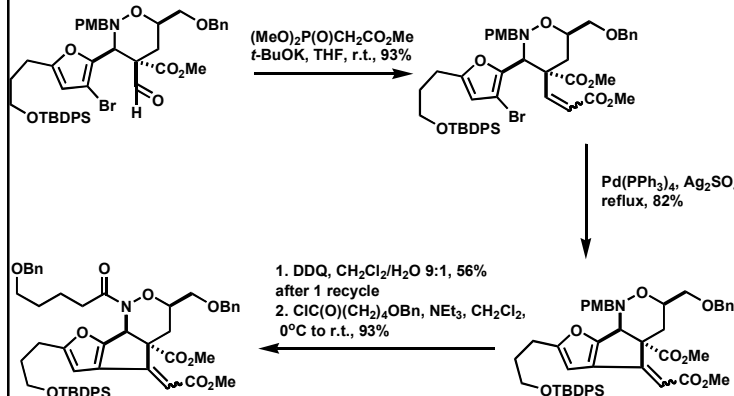


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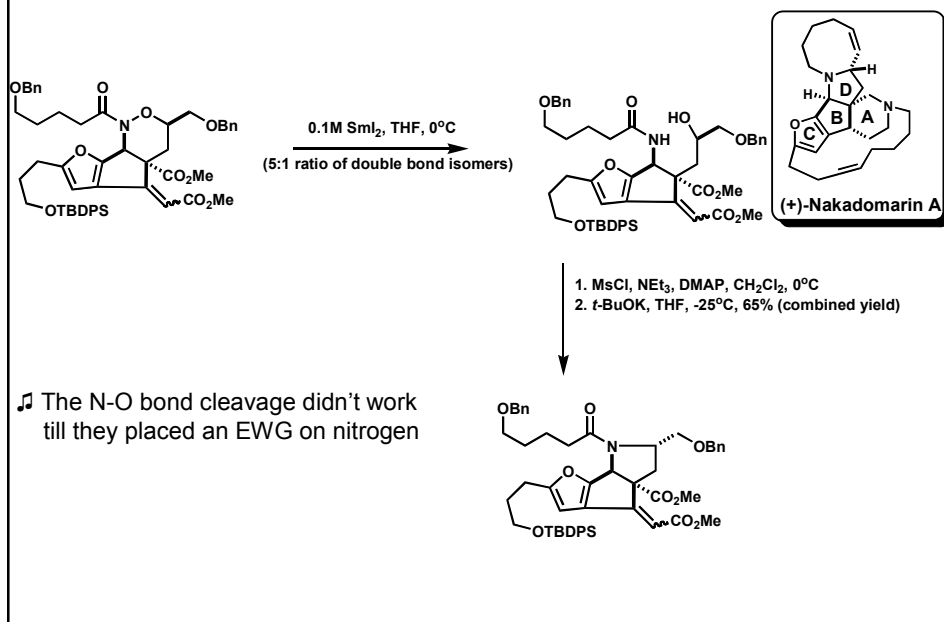


MAYBE STERICS??

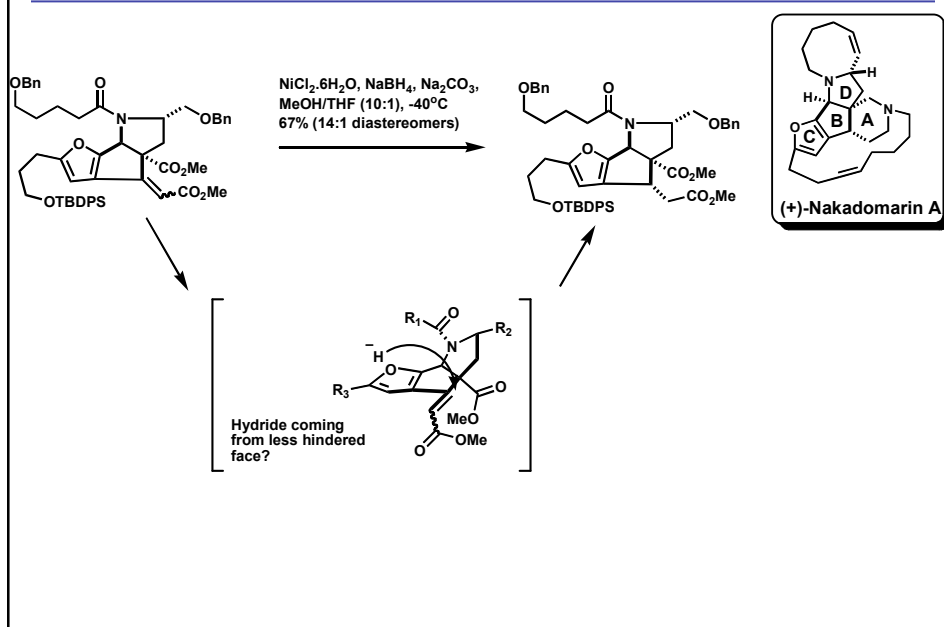
## Synthesis of Ring "B" & "D"



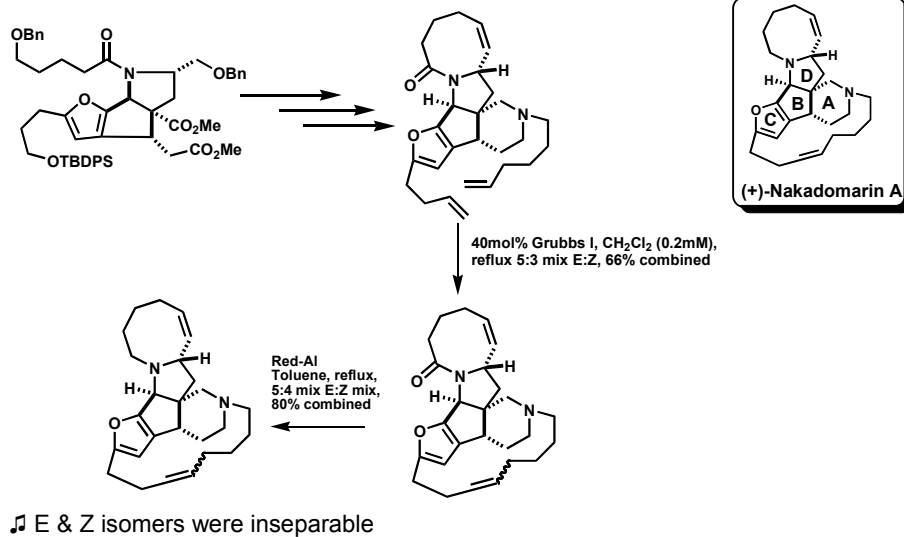
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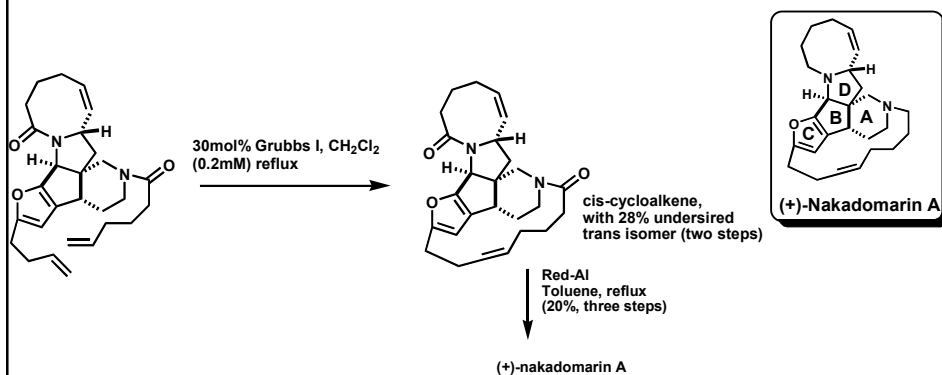
## Synthesis



## Final Stage of Synthesis



## Final Stage of Synthesis



- ♫ Used a similar intermediate as Nishada's for the final metathesis stage
- ♫ The introduced amide group decreases the flexibility of the metathesis product
- ♫ This allowed for separation of E and Z isomer.

## Summary

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- ♪ Synthesis of nakadomarin A was accomplished in 29 linear steps from D-mannitol
- ♪ Showcase of the three component coupling methodology flexibility
- ♪ Overall yield not as good though as Nishida's synthesis