Total Synthesis of (–)-Nakadomarin A

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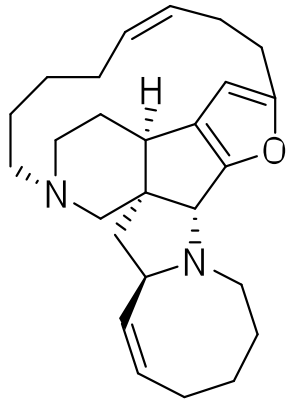


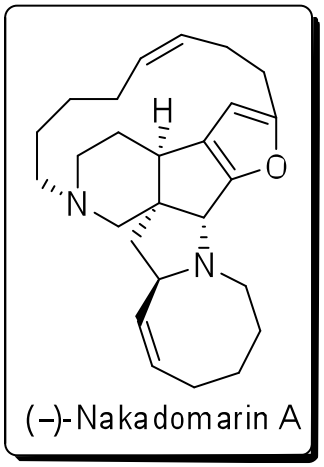
Marie-Céline Frantz

Wipf Group - Current Literature

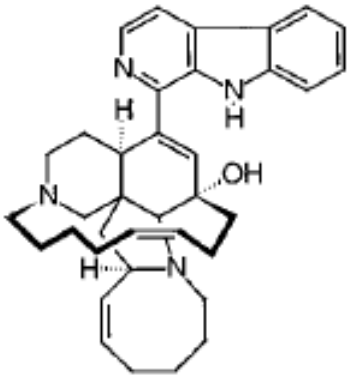
November 14, 2009

Nakadomarin A

- Isolated from the sponge *Amphimedon* sp. off the coast of the Kerama Islands, Okinawa, in 1997.
- Marine alkaloid of the manzamine family.
- Biological activity:
  - Cytotoxic activity against murine lymphoma L1210 cells (IC_{50} 1.3 *μ*g/mL)
  - Inhibition of cyclin dependent kinase 4 (IC_{50} 9.9 *μ*g/mL)
  - Antimicrobial activity against:
    - fungus *Trichophyton mentagrophytes* (MIC 23 *μ*g/mL)
    - Gram+ bacterium *Corynebacterium xerosis* (MIC 11 *μ*g/mL)
- Hexacyclic structure containing: - an 8/5/5/5/15/6 ring system (1 furan)
  - 4 stereogenic centers (1 quaternary)



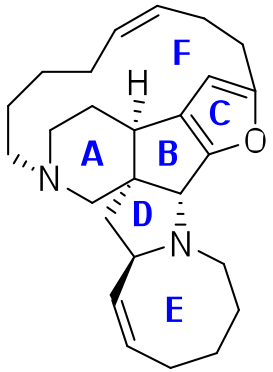
(–)-Nakadomarin A



Manzamine A

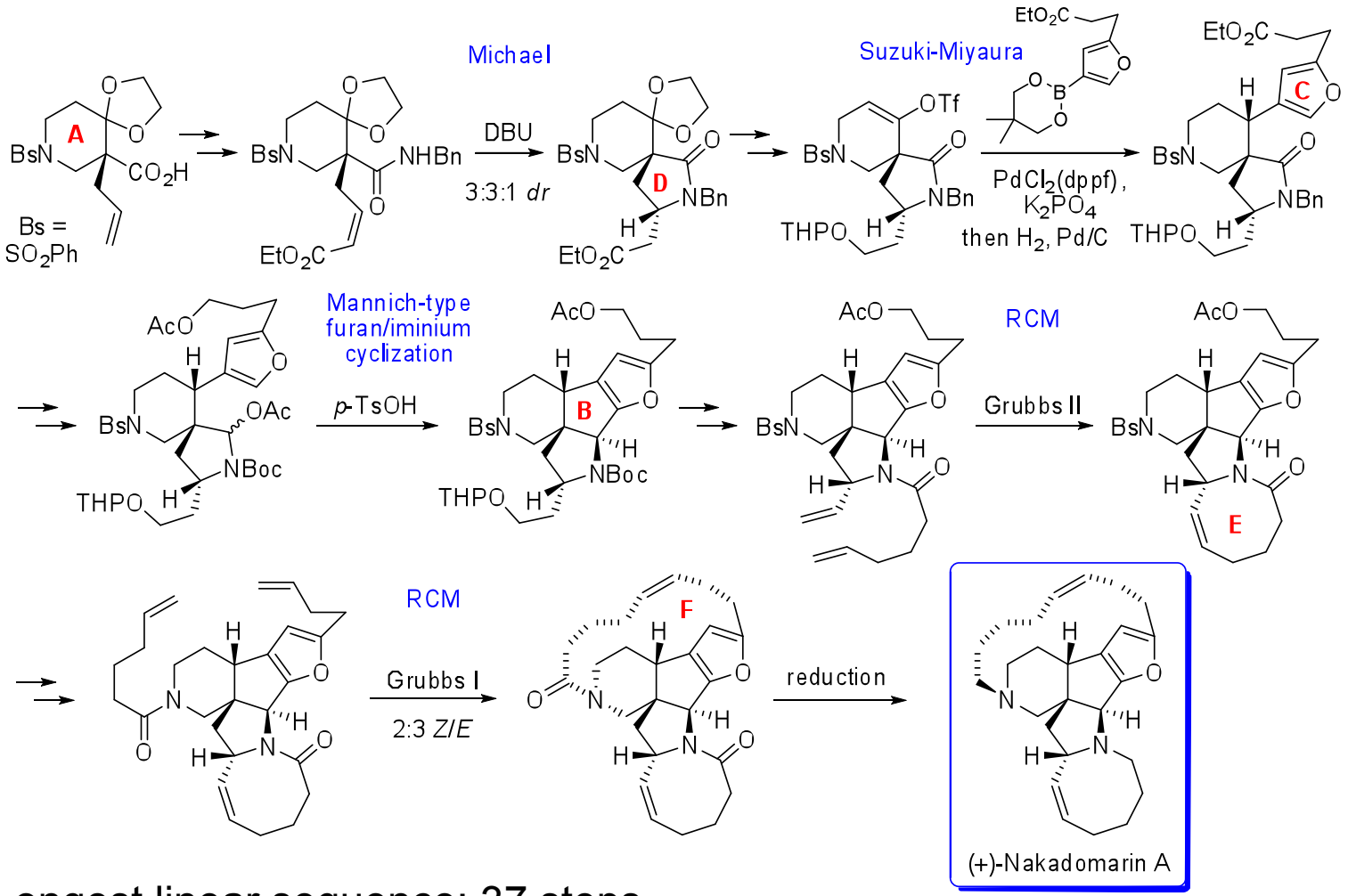
Kobayashi, J.; Watanabe, D.; Kawasaki, N.; Tsuda, M. *J. Org. Chem.* **1997**, *62*, 9236
Kobayashi, J.; Tsuda, M.; Ishibashi, M. *Pure Appl. Chem.* **1999**, *71*, 1123

Nakadomarin A synthesis



- Methodologies targeting the core of nakadomarin A
  - Fürstner (Max Planck) **1999**: alkyne RCM/semireduction (CF rings)
  - Fürstner (Max Planck) **2001**: olefin RCM (ADE rings)
  - Magnus (Univ. Texas) **2002**: Pauson-Khand (ABC rings)
  - Tius (Univ. Hawaii) **2003**: Nazarov (BC rings)
  - Williams (Colorado State Univ.) **2004**: azomethine ylide [1,3]-dipolar cycloaddition (ADE rings)
  - Kerr (Univ. West. Ontario) **2005**: nitrone/cyclopropane cycloaddition (ABCD rings)
  - Funk (Penn. State Univ.) **2006**: Michael/*N*-acyliminium ion cyclization (ABCD rings)
  - Zhai (Shangai Institute) **2008**: Sonogashira, Pt(II)-cat. cyclizations, Barton-McComble (ABCD rings)
- 2 total syntheses of the antipode (+)-Nakadomarin A
  - Nishida (Chiba Univ.) **2003**: 37 steps (longest linear sequence)
  - Kerr (Univ. West. Ontario) **2007**: 29 steps (longest linear sequence)
- 1 total synthesis of (–)-Nakadomarin A
  - Nishida (Chiba Univ.) **2004**: 36 steps (longest linear sequence)

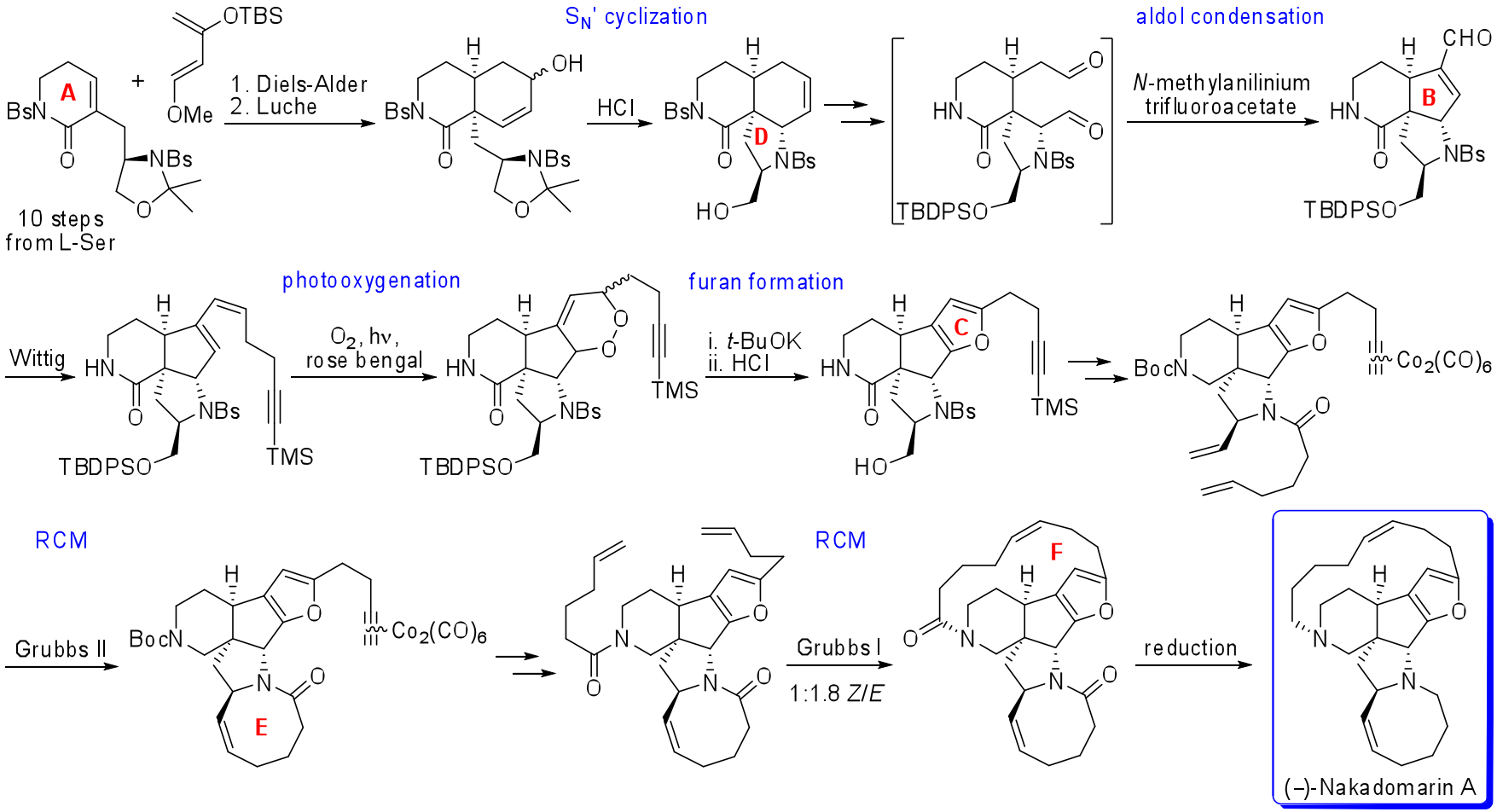
Nishida synthesis of (+)-Nakadomarin A (2003)



Longest linear sequence: 37 steps

Nagata, T.; Nakagawa, M.; Nishida, A. *J. Am. Chem. Soc.* **2003**, *125*, 7484

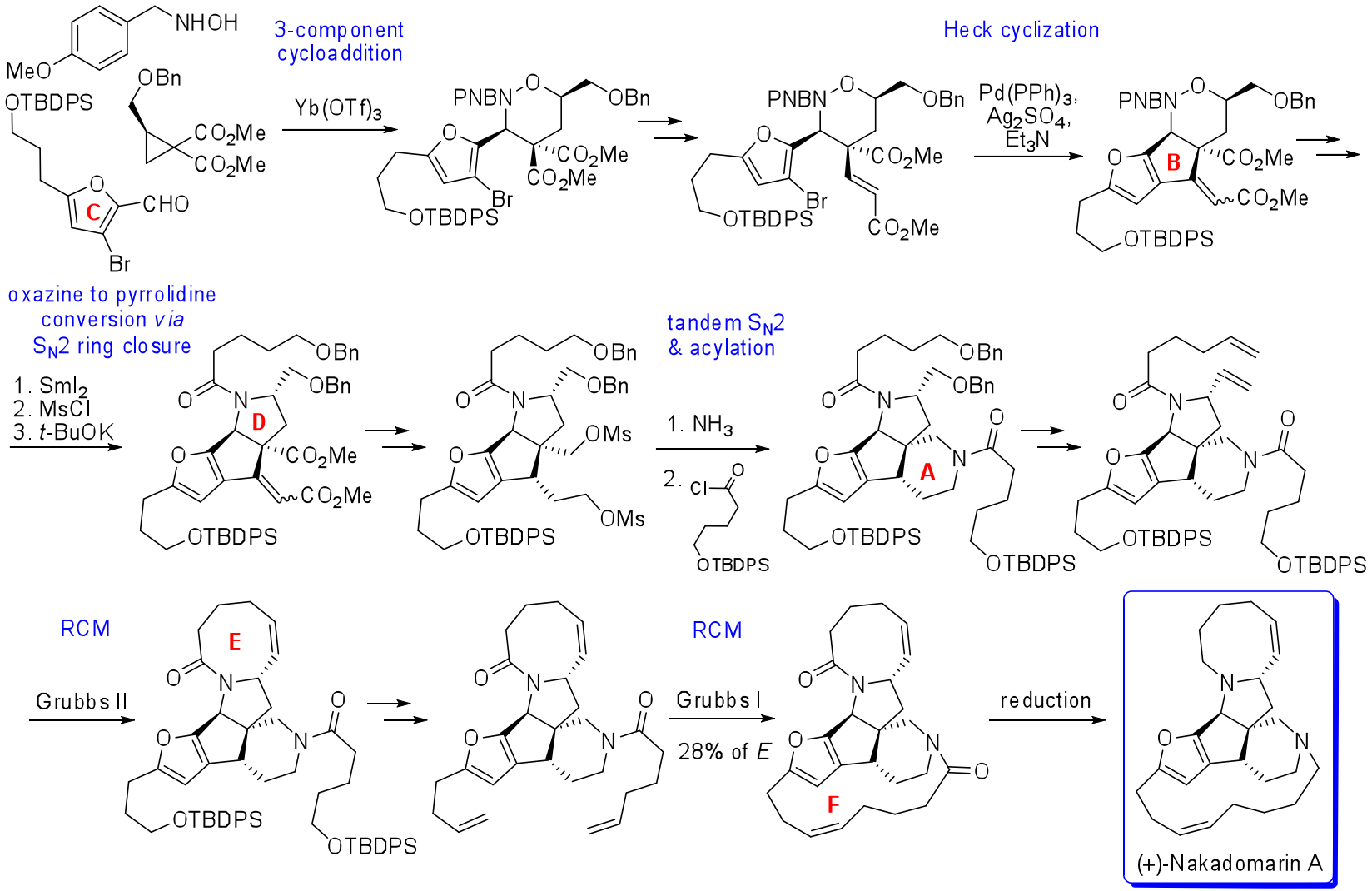
Nishida synthesis of (–)-Nakadomarin A (2004)



Longest linear sequence: 36 steps

Ono, K.; Nakagawa, M.; Nishida, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 2020

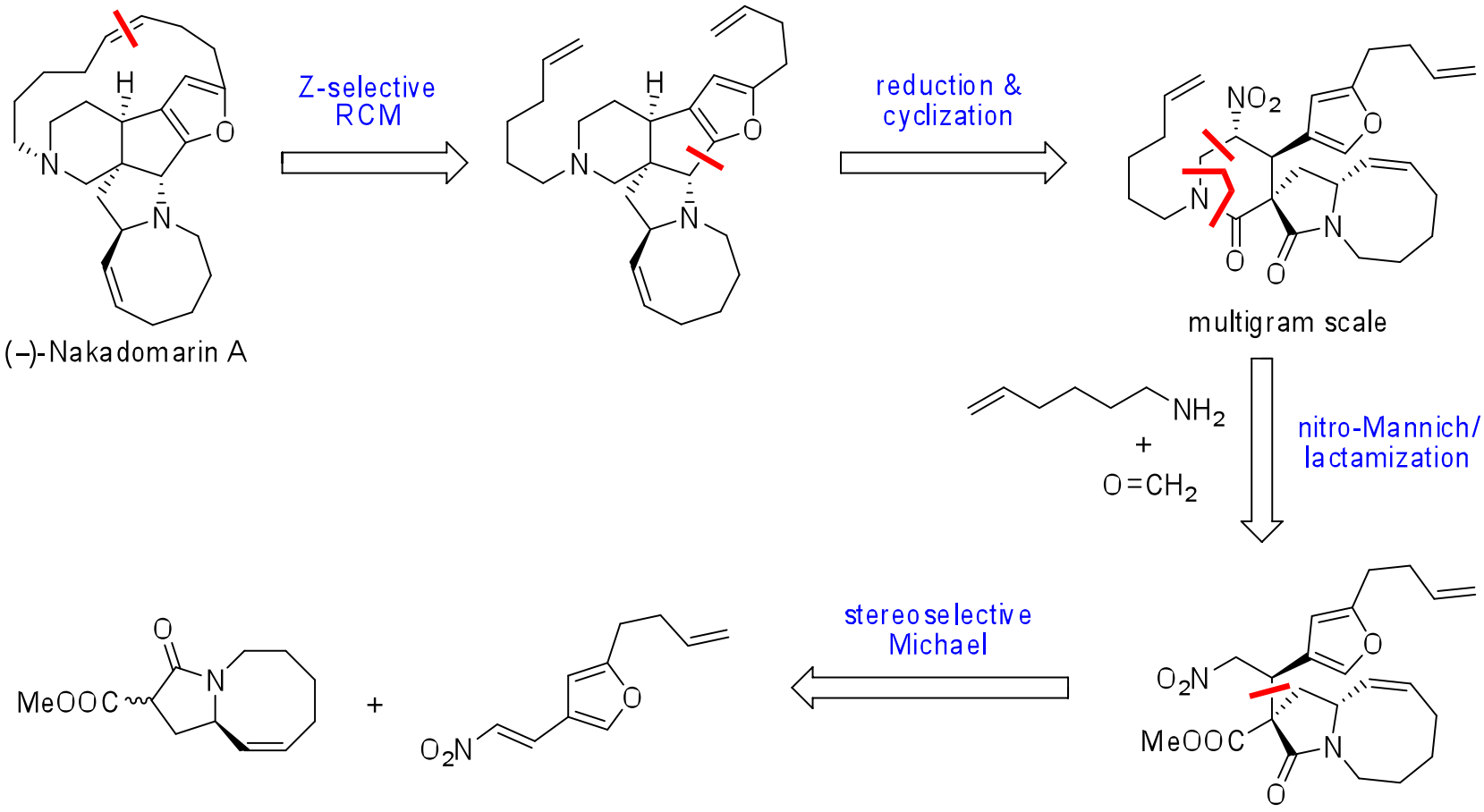
Kerr synthesis of (+)-Nakadomarin A (2007)



Longest linear sequence: 29 steps

Young, I. S.; Kerr, M. A. *J. Am. Chem. Soc.* **2007**, *129*, 1465

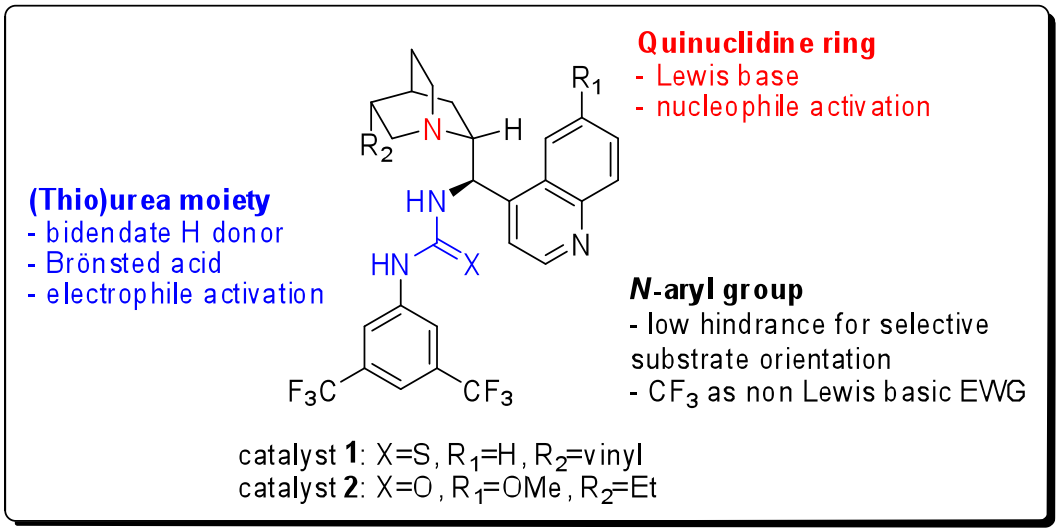
Title paper: Retrosynthesis



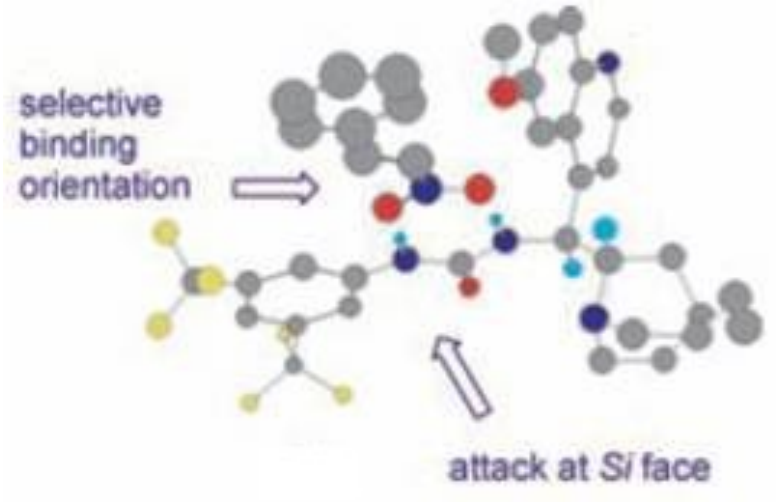
Jakubec, P.; Cockfield, D. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, ASAP

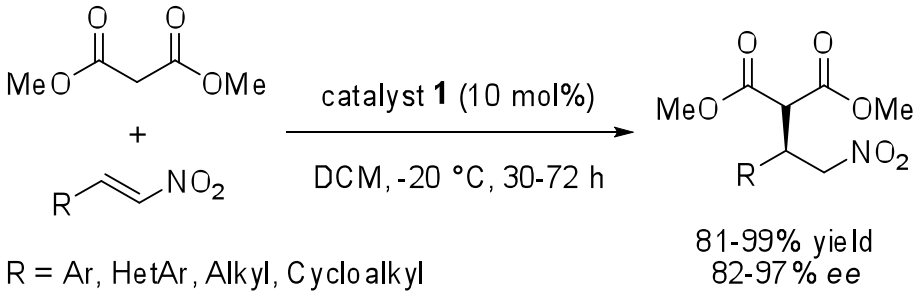
Enantioselective Michael addition

Cinchona alkaloid derivatives:
Bifunctional organocatalysts for the asymmetric addition of malonate to nitroalkenes



Proposed pretransition state assembly:
binding of nitro-alkene to catalyst **2**



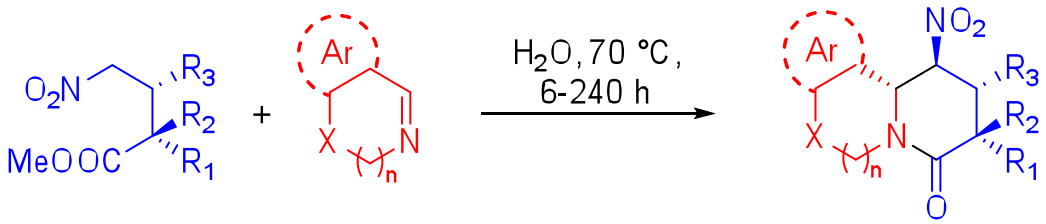


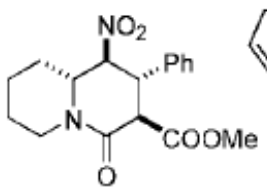
Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481

McCooey, S. H.; Connon, S. J. *Angew. Chem. Int. Ed.* **2005**, *44*, 6367

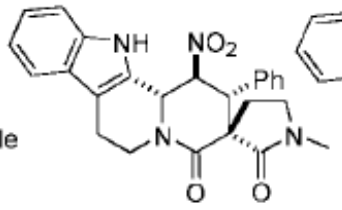
3-Component nitro-Mannich/lactamization cascade

Nitro-Mannich/lactamization cascade of γ-nitro esters with cyclic imines

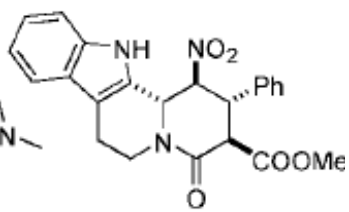




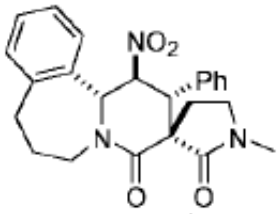
(±)-**1b**, 58%, dr 98:2 (97:3)[a]



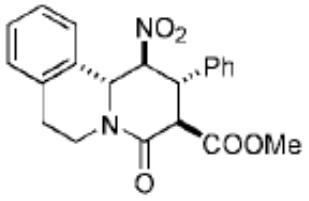
(±)-**1c**, 91%, dr >99:1 (>99:1)[a]



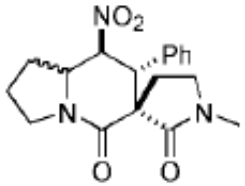
(±)-**1d**, 73%, dr 97:3 (94:6)[a]



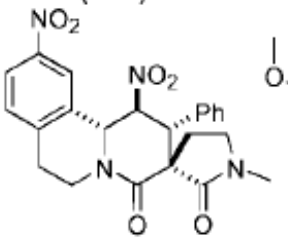
(±)-**1h**, 60%[b], dr >99:1 (>99:1)[a]



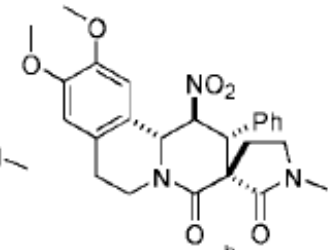
(±)-**1i**, 75%, dr 98:2 (98:2)[a]



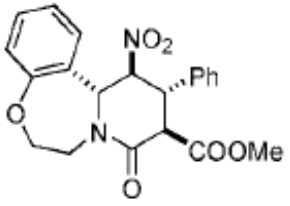
(±)-**1j**, 64%, dr 66:34 (64:34)[a]



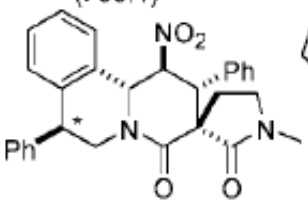
(±)-**1e**, 73%, dr >99:1 (>99:1)[a]



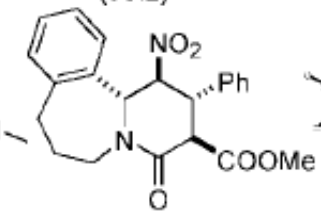
(±)-**1f**, 74%[b], dr 94:6 (95:5)[a]



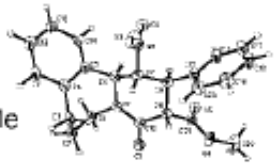
(±)-**1g**, 71%, dr >99:1 (>99:1)[a]



(±)-**1k**, 85%, dr 85:15 (85:15)[a]



(±)-**1l**, 63%, dr >99:1 (98:2)[a]



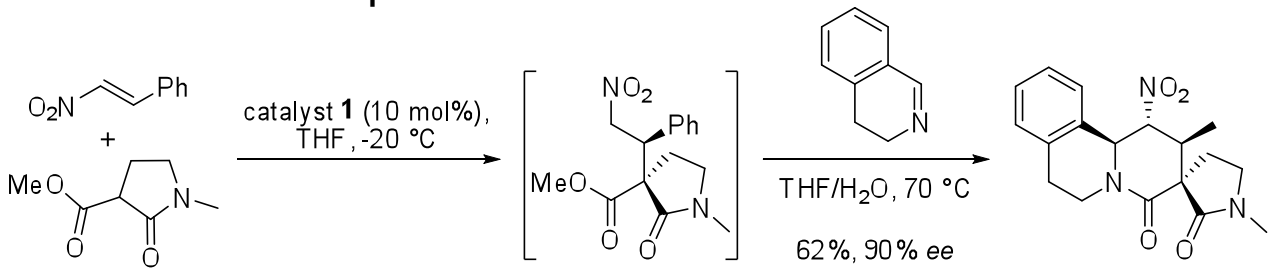
X-ray of (±)-**1l**

[a]dr in crude product. [b]1:1 H_2O:MeOH mixture used as a solvent.

Jakubec, P.; Halliwell, M.; Dixon, D. J. *Org. Lett.* **2008**, *10*, 4267

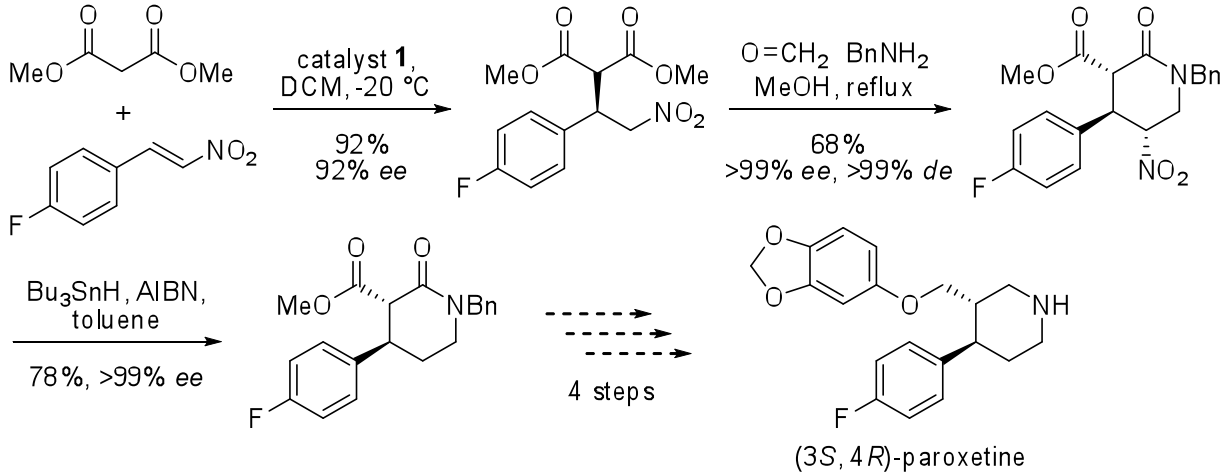
Applications of Michael/nitro-Mannich/lactamization sequence

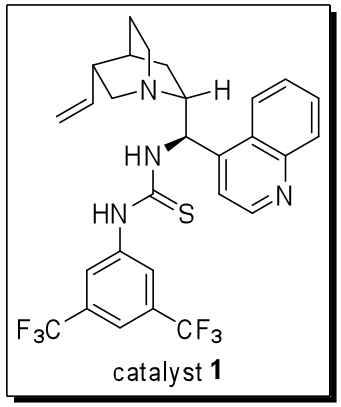
Enantio- and diastereoselective, one-pot, 3-component Michael/nitro-Mannich/ lactamization sequence



Jakubec, P.; Halliwell, M.; Dixon, D. J. *Org. Lett.* **2008**, *10*, 4267

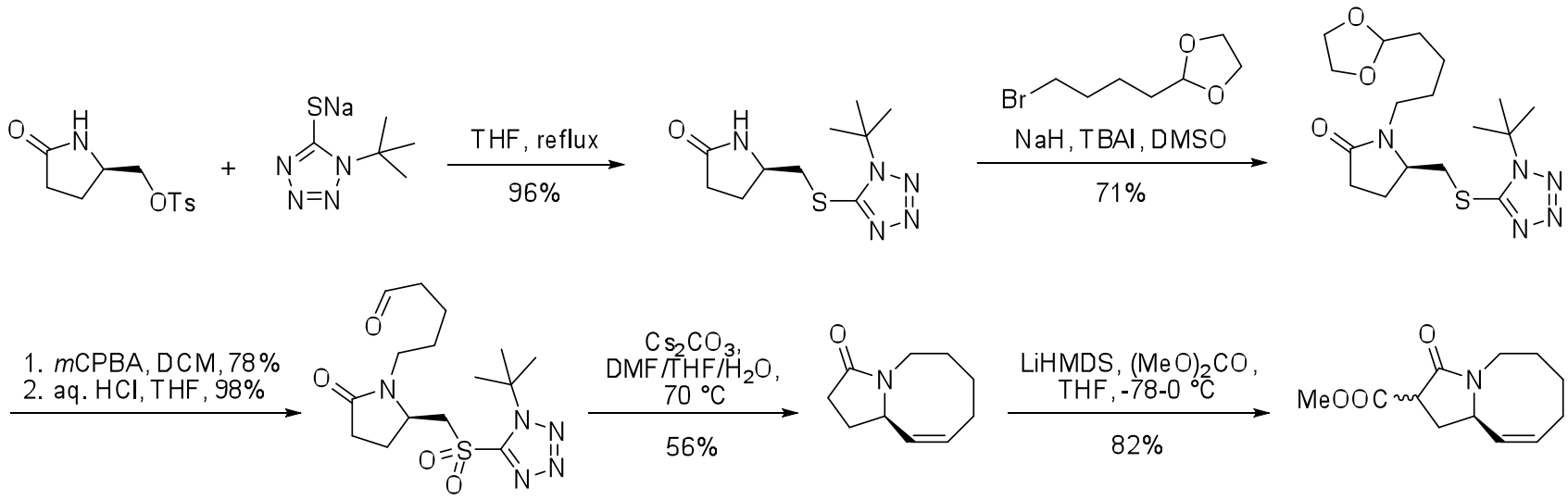
Formal synthesis of (3*S*,4*R*)-paroxetine





Hynes, P.; Stupple, P. A.; Dixon, D. J. *Org. Lett.* **2008**, *10*, 1389

Title paper: Synthesis of the Pro-Nucleophilic Fragment

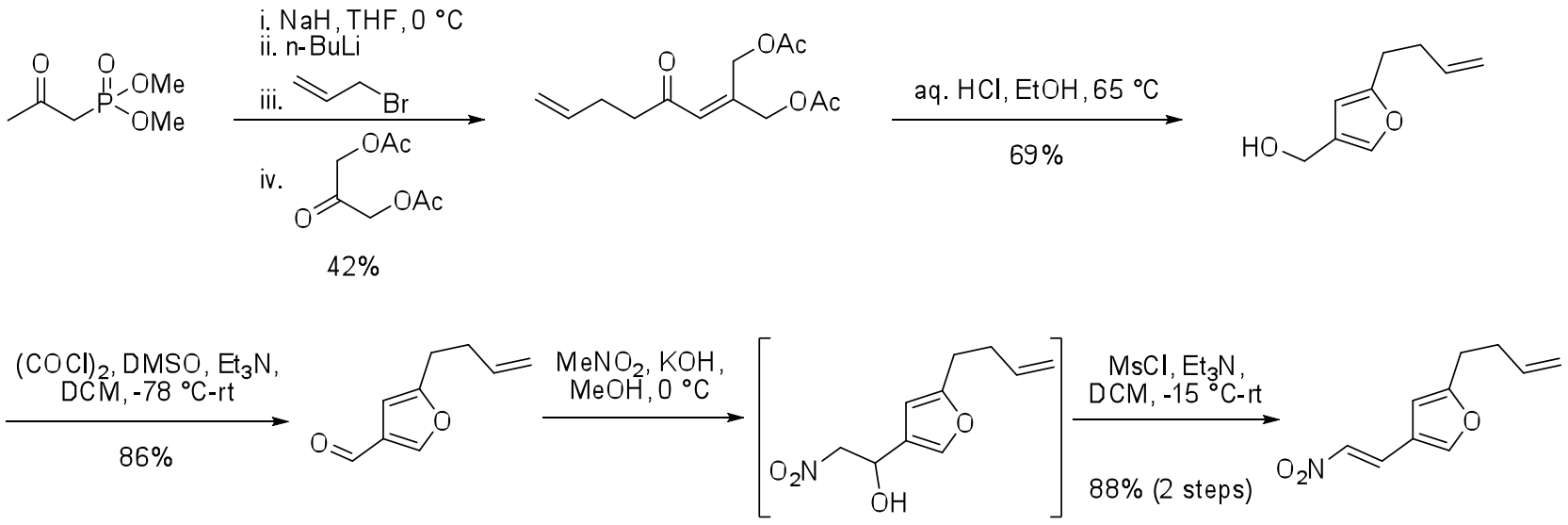


Intramolecular Julia-Kocienski olefination:

Unprecedented highly diastereoselective formation of a (*Z*)-alkene in an 8-membered ring

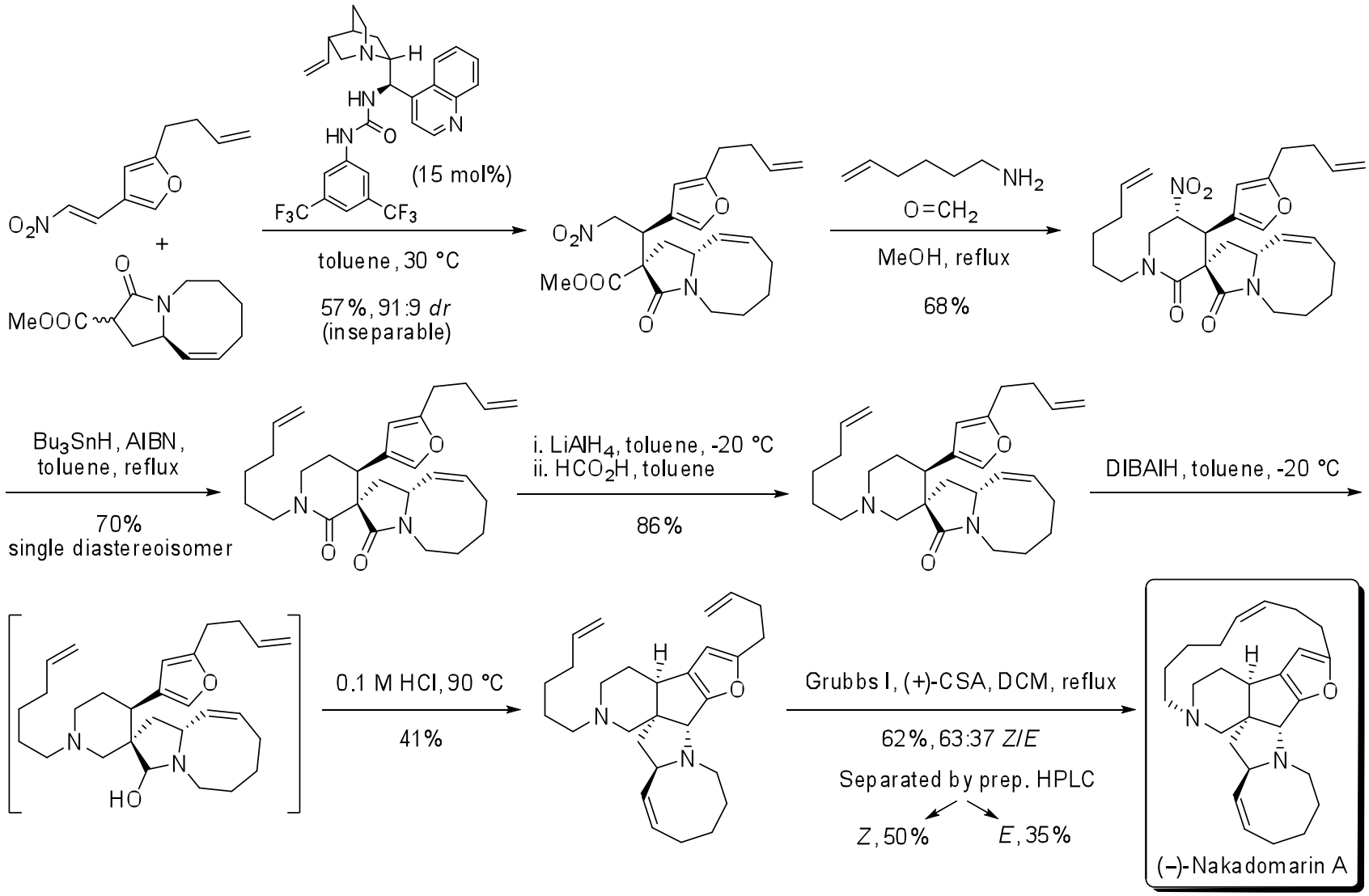
Jakubec, P.; Cockfield, D. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, ASAP

Title paper: Synthesis of the Electrophilic Fragment



Jakubec, P.; Cockfield, D. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, ASAP

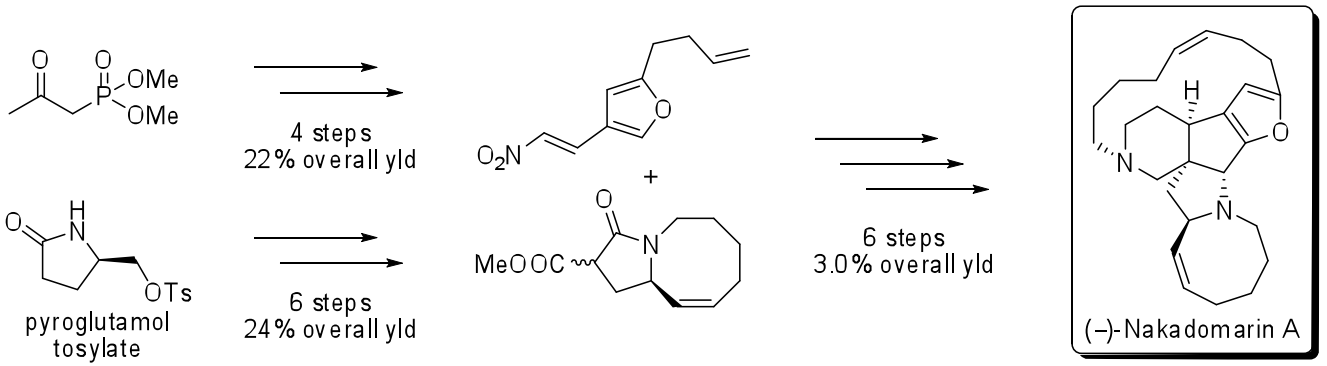
Title paper: End Play to (–)-Nakadomarin A



Jakubec, P.; Cockfield, D. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, ASAP

Conclusion and Perspectives

- Short and highly stereoselective total synthesis of (–)-Nakadomarin A
  - Longest linear sequence: 12 steps (from pyroglutamol tosylate), 16 steps in total
  - Previous total syntheses: average of 34 steps
  - Total of 100 mg of compound prepared (8.5 mg available so far from extraction and synthesis)



- Key steps
  - (*Z*)-selective intramolecular Julia-Kocienski olefination to form an 8-membered ring
  - Diastereoselective nitro-olelfin Michael addition with bifunctional cinchonine catalyst
  - Three-component nitro-Mannich/lactamization cascade
  - Diastereoselective Mannich-type furan/iminium ion cyclization
  - (*Z*)-selective RCM in the presence of protonated amines
- Perspectives: synthesis of natural product analogs