

# Concise Total Synthesis of Lundurines A-C Enable by Gold Catalysis and a Homodienyl Retro-Ene/Ene Isomerization

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Echavarren, A. M. *et al.*  
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# Introduction

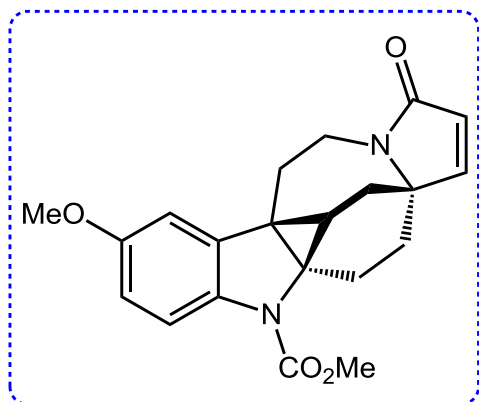
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Prof. Antonio M. Echavarren

## Education:

- 1982** **Ph.D.** at the *Universidad Autónoma de Madrid (UAM)*
- 1982–1984** **Postdoctoral Position** in Boston College
- 1984–1986** **Assistant Professor** at the *Universidad Autónoma de Madrid*
- 1986–1988** **NATO-fellow** in Colorado State University
- 1988–1992** **Junior Research Fellowship** at the Institute of Organic Chemistry of the CSIC (Spanish Research Council)
- 1992–** **Professor** at the *Universidad Autónoma de Madrid* and CSIC
- 2004–** **Group Leader** at the Institute of Chemical Research of Catalonia (ICIQ) in Tarragona

# Introduction



**(-)-Lundurine A**

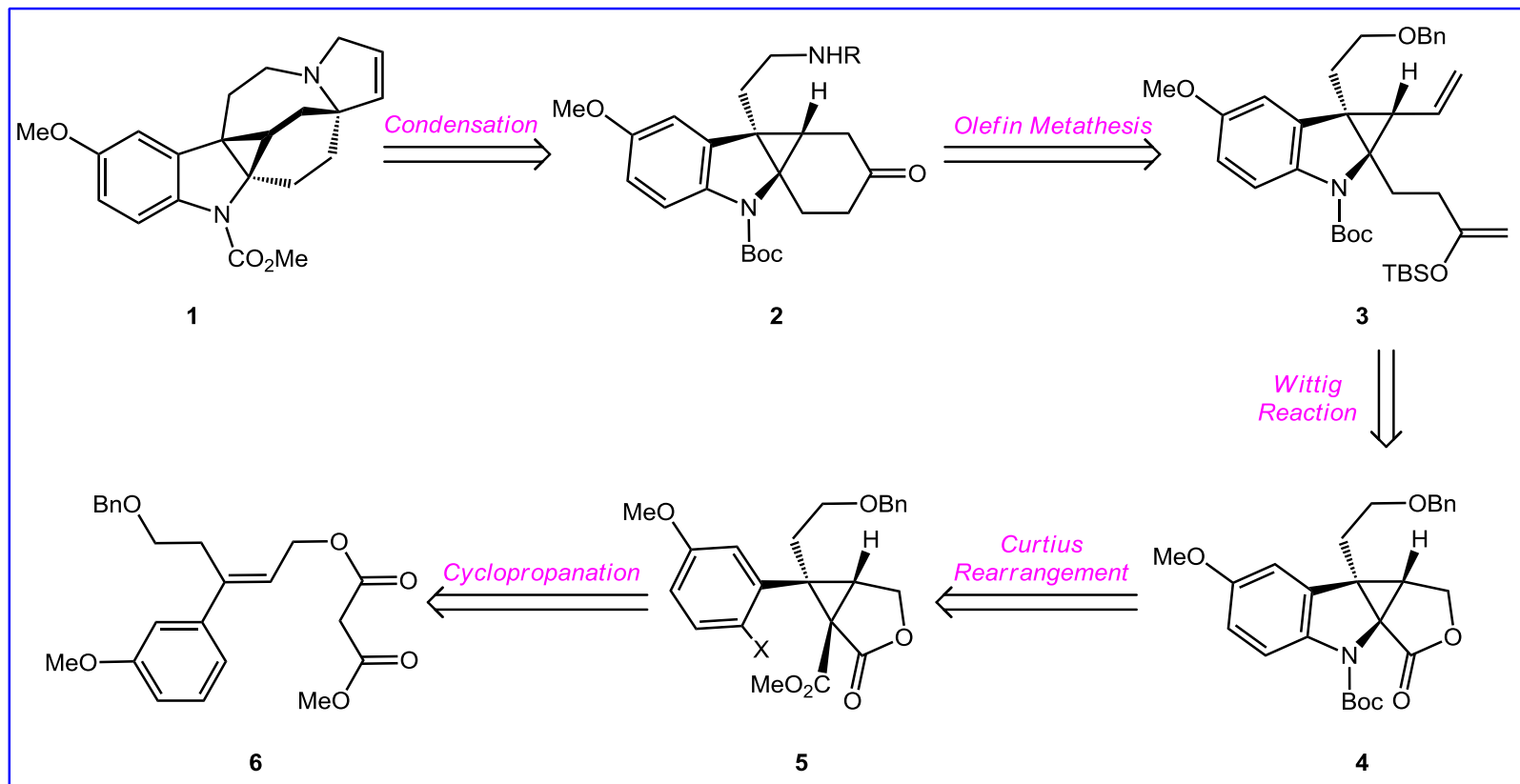


***Kopsia tenuis***  
(蕊木属植物)

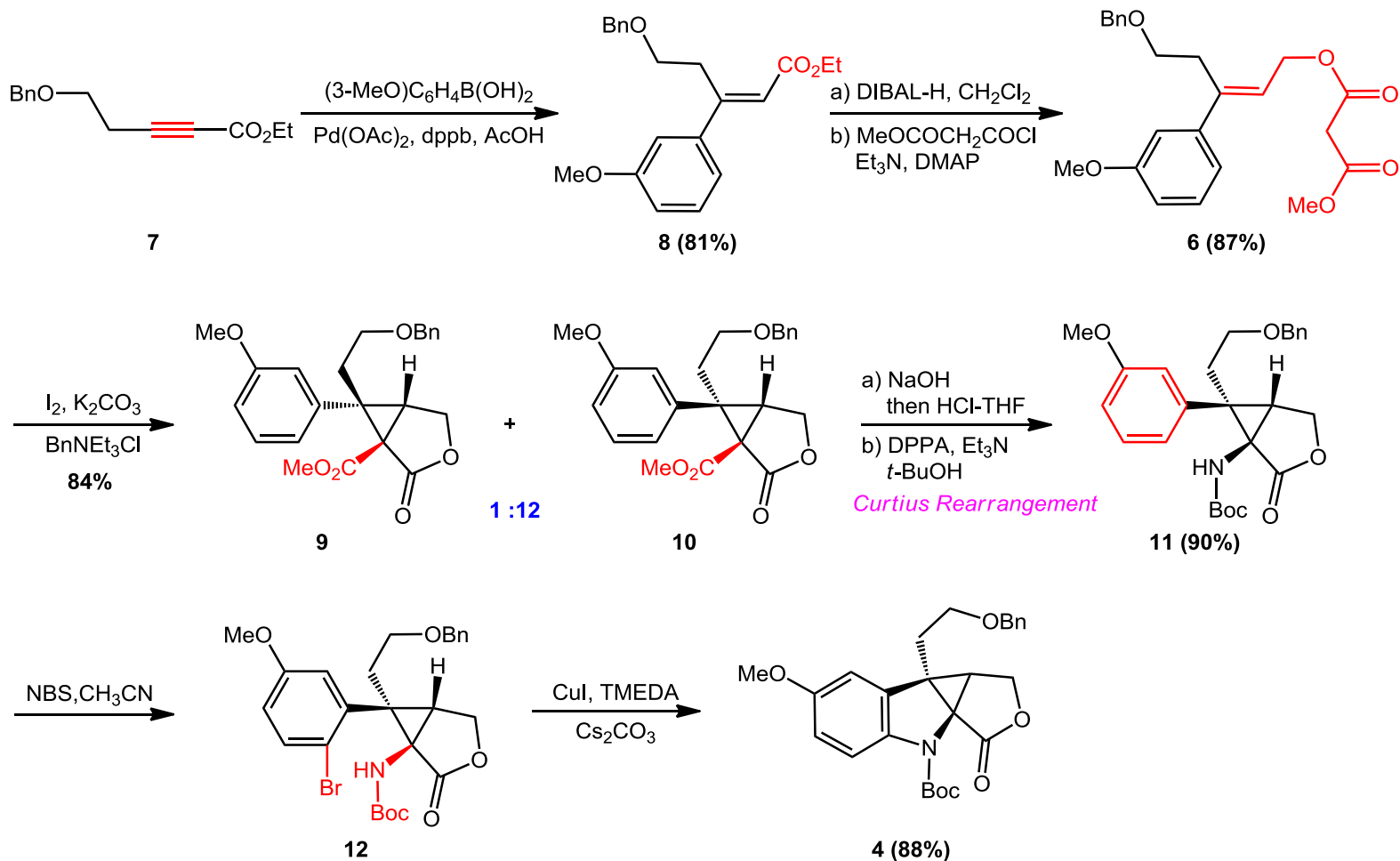
- Isolated from *Kopsia tenuis* in 1995
- Exhibit promising antitumor activity
- Four stereocenters, **hexacyclic** framework and **cyclopropane-fused indoline skeleton**

# Total Synthesis of (+/-)-Lundurine B

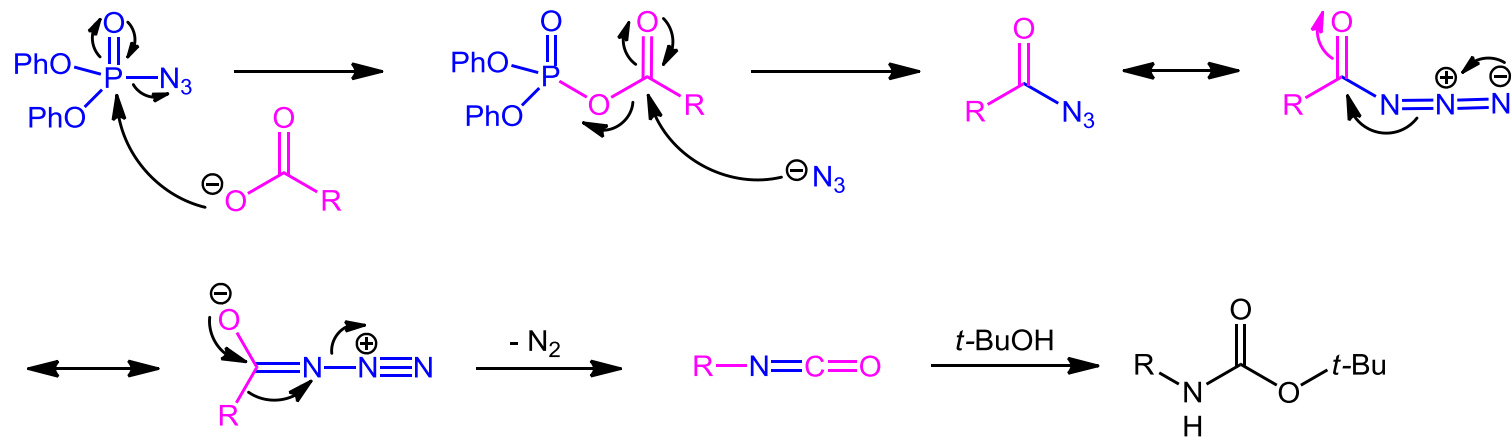
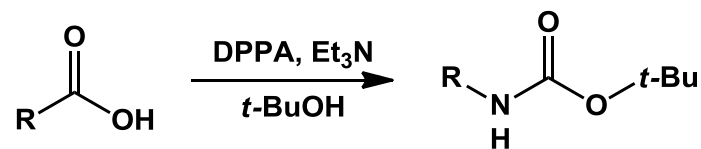
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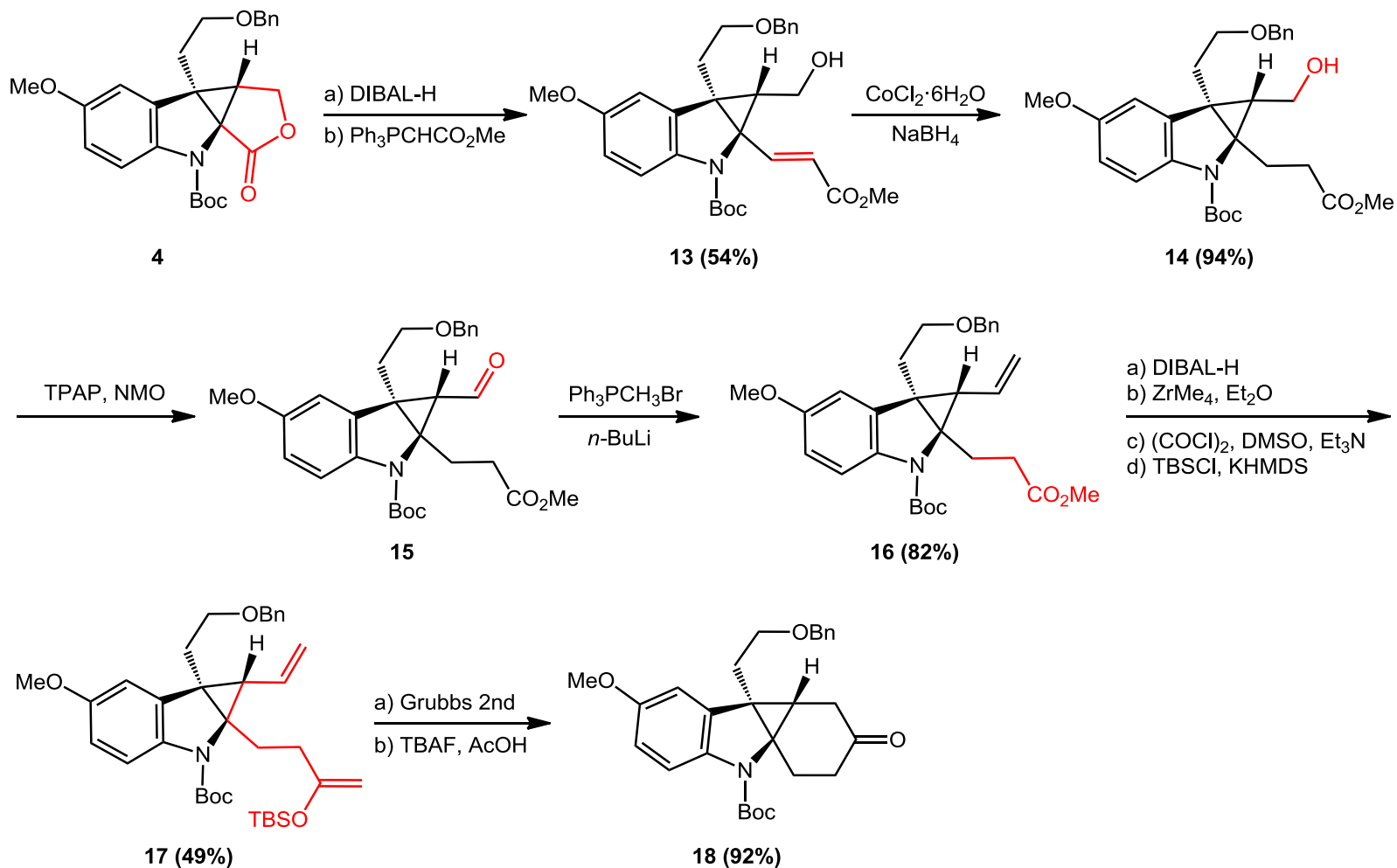
# Total Synthesis of (+/-)-Lundurine B



# Curtius Rearrangement

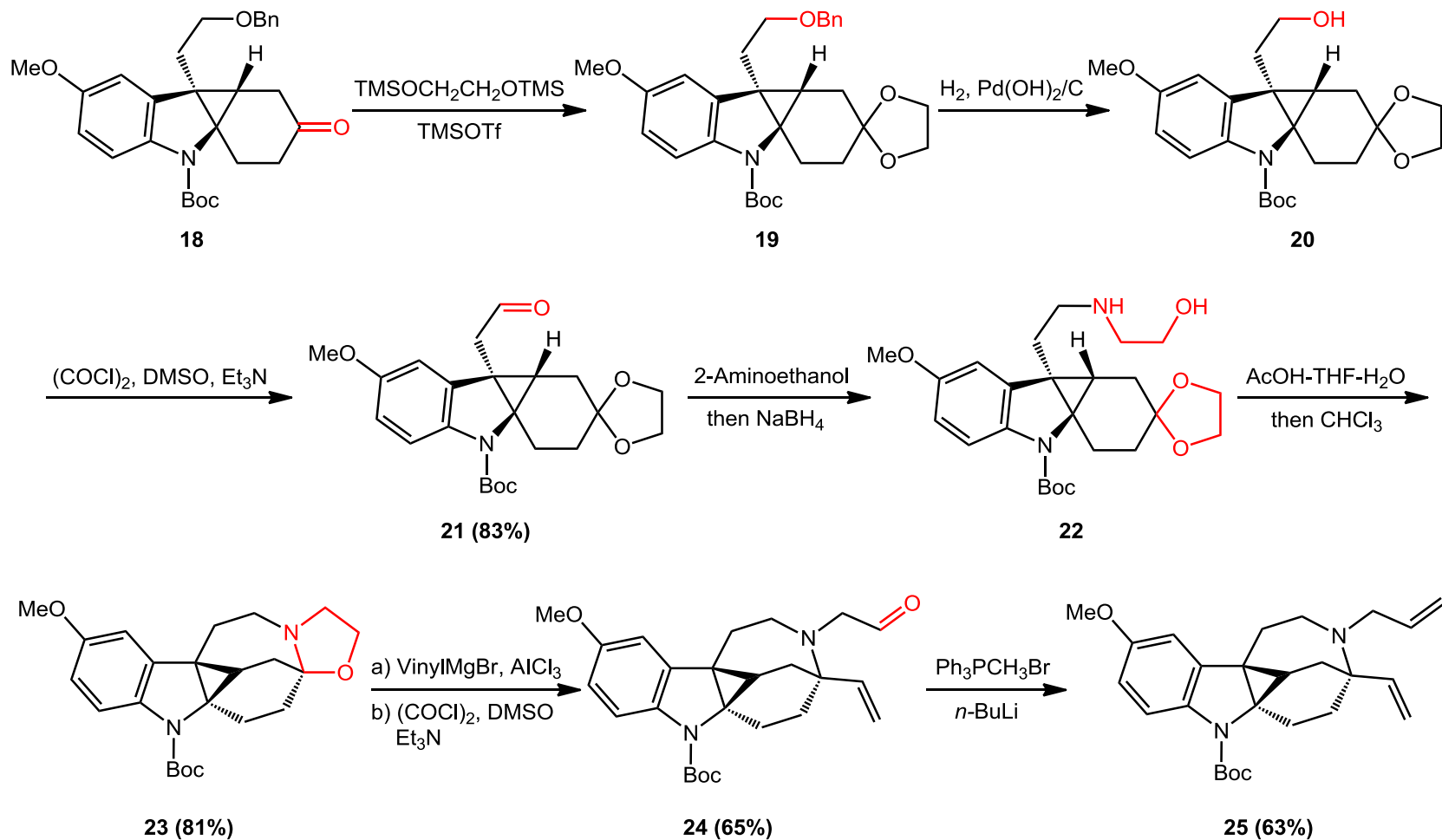


# Total Synthesis of (+/-)-Lundurine B

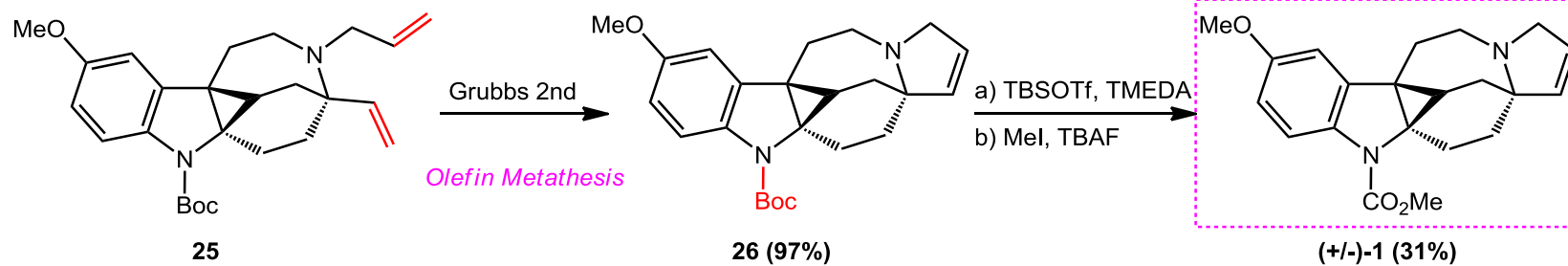




# Total Synthesis of (+/-)-Lundurine B

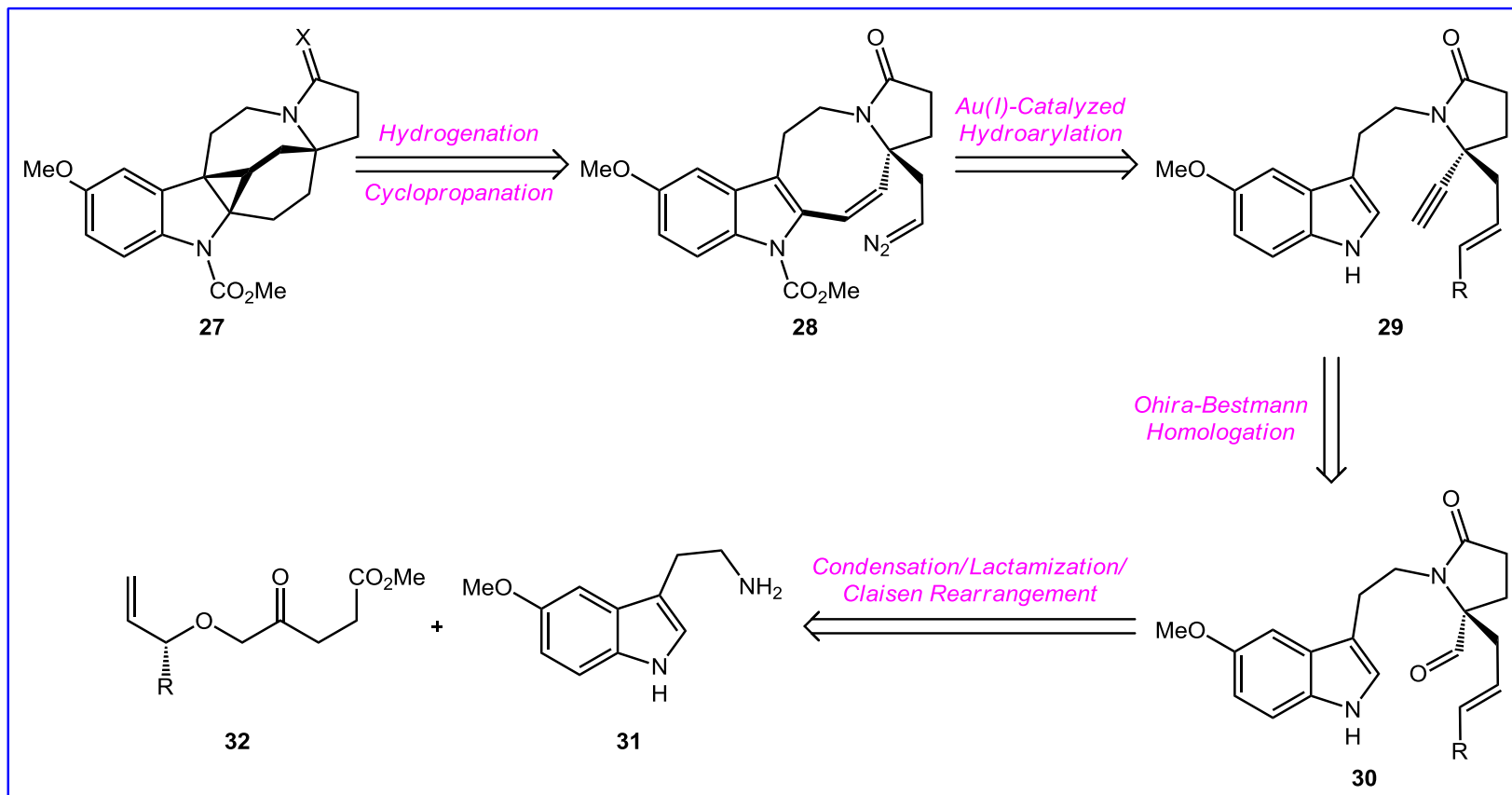


# Total Synthesis of (+/-)-Lundurine B

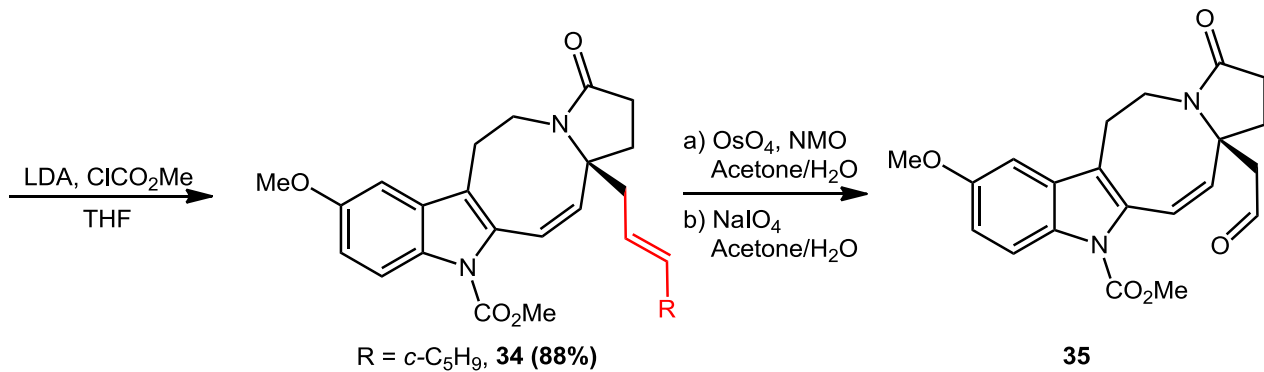
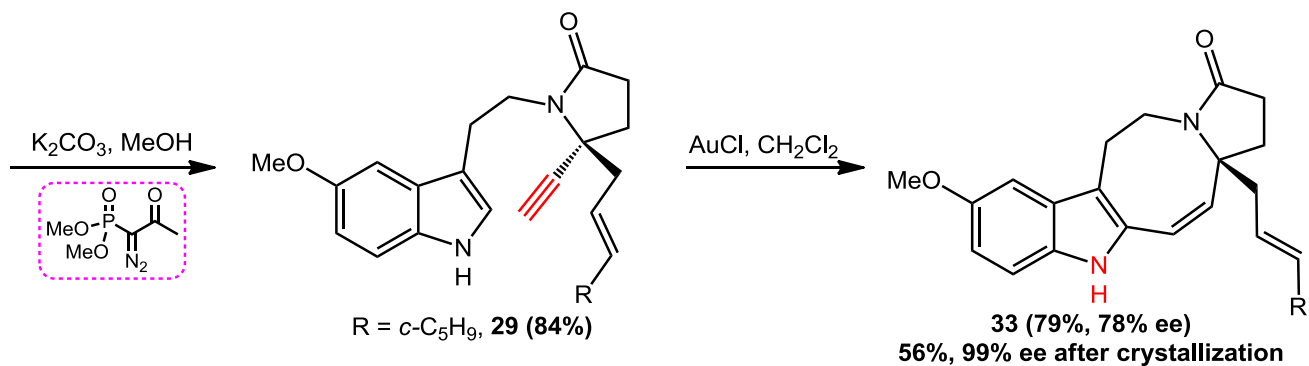
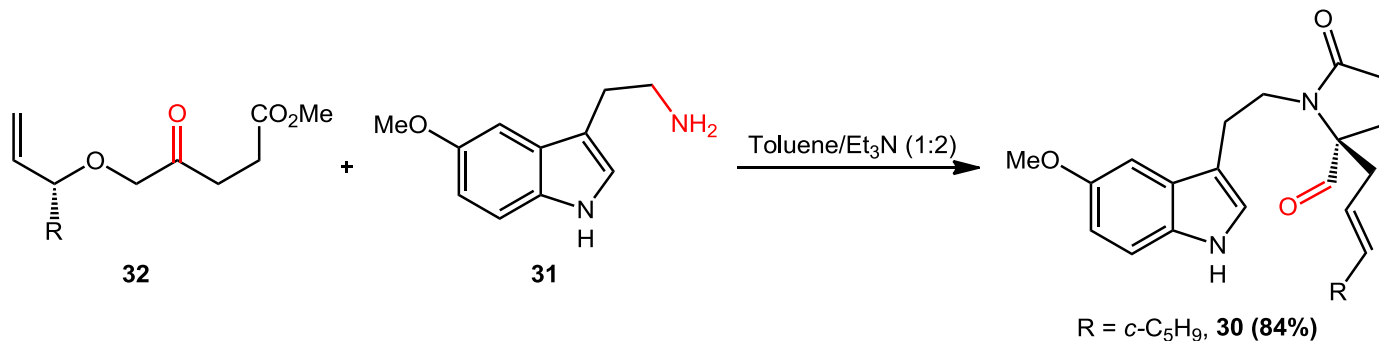


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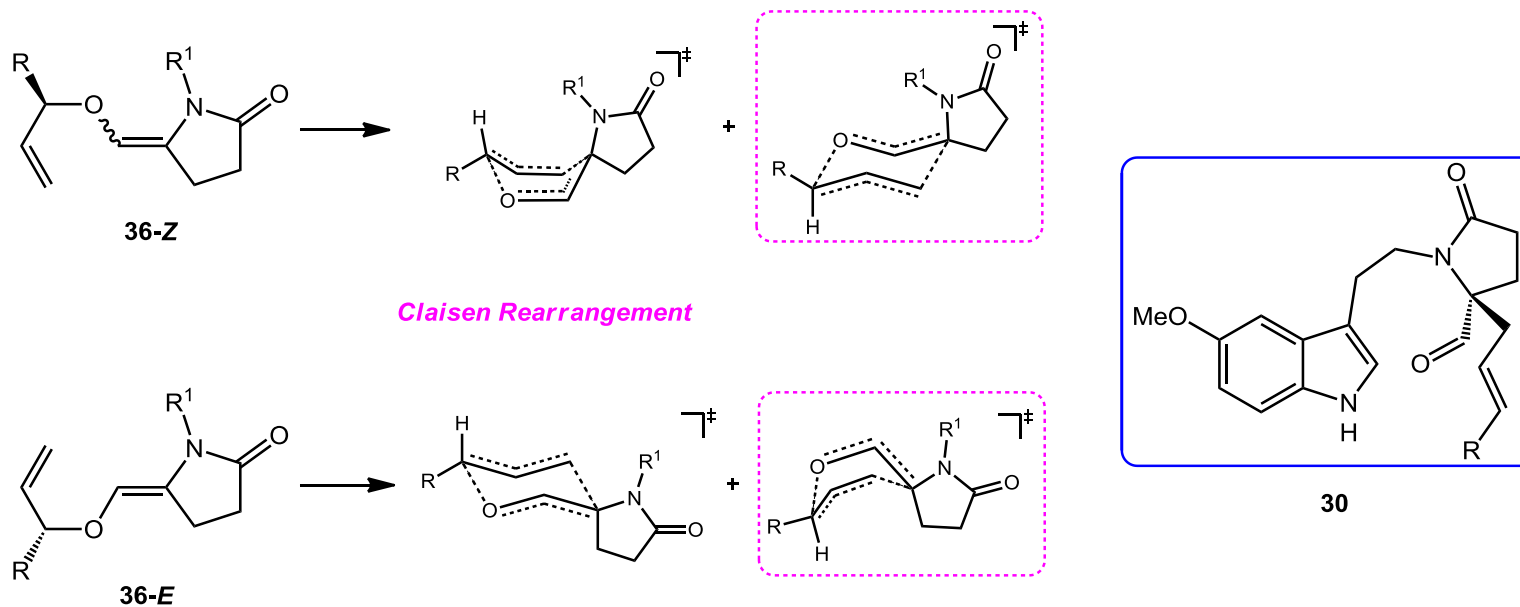
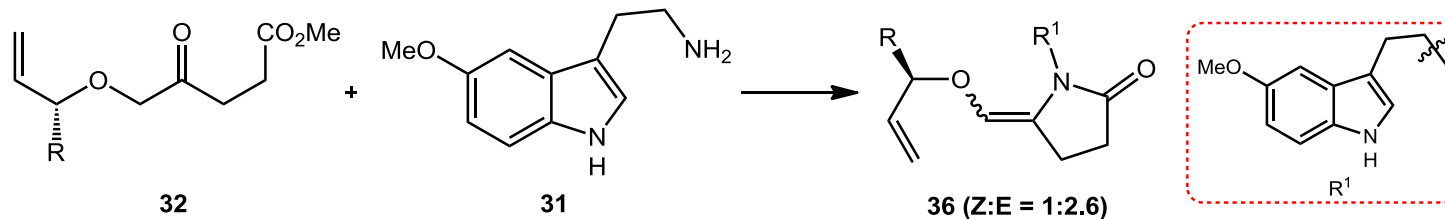
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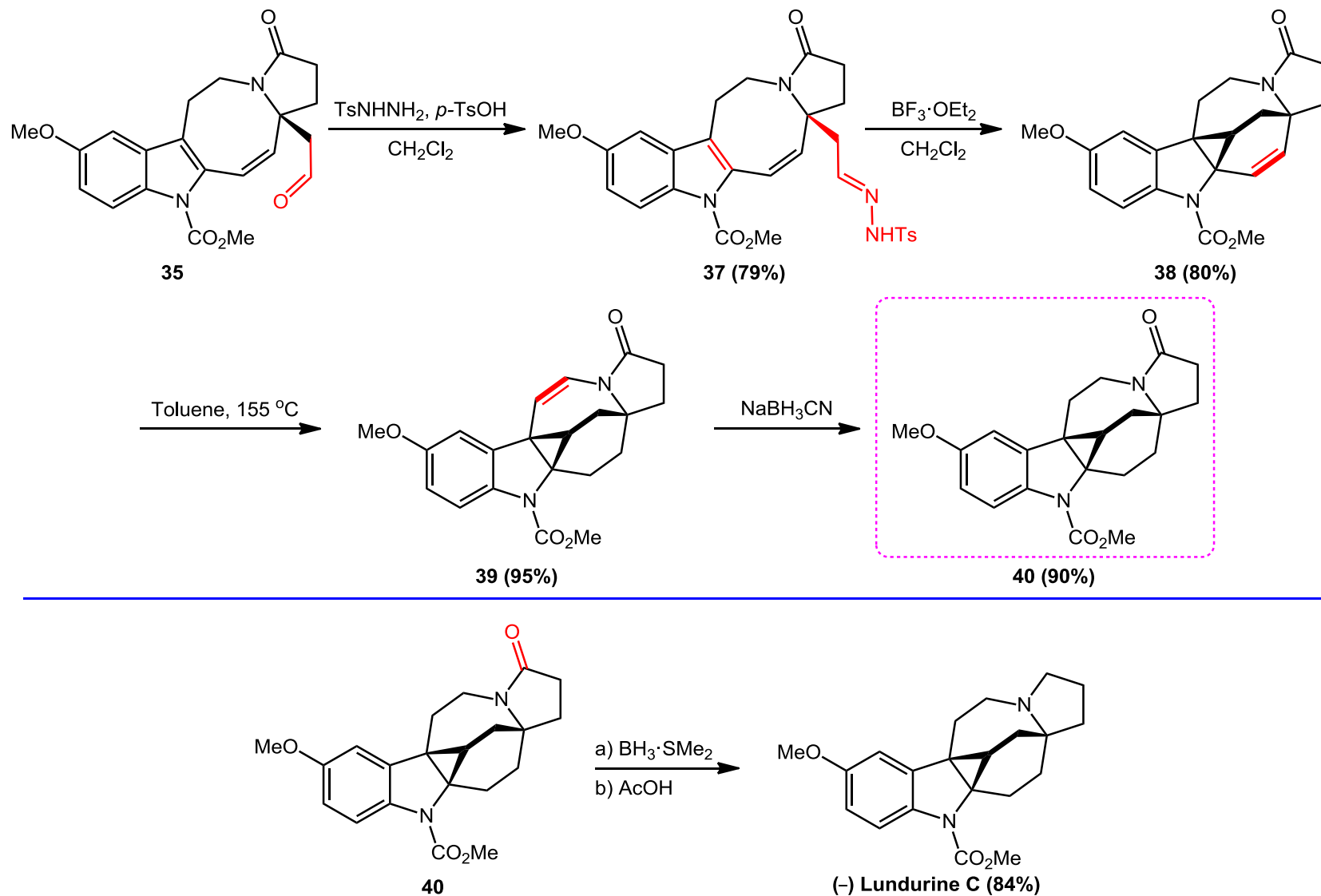
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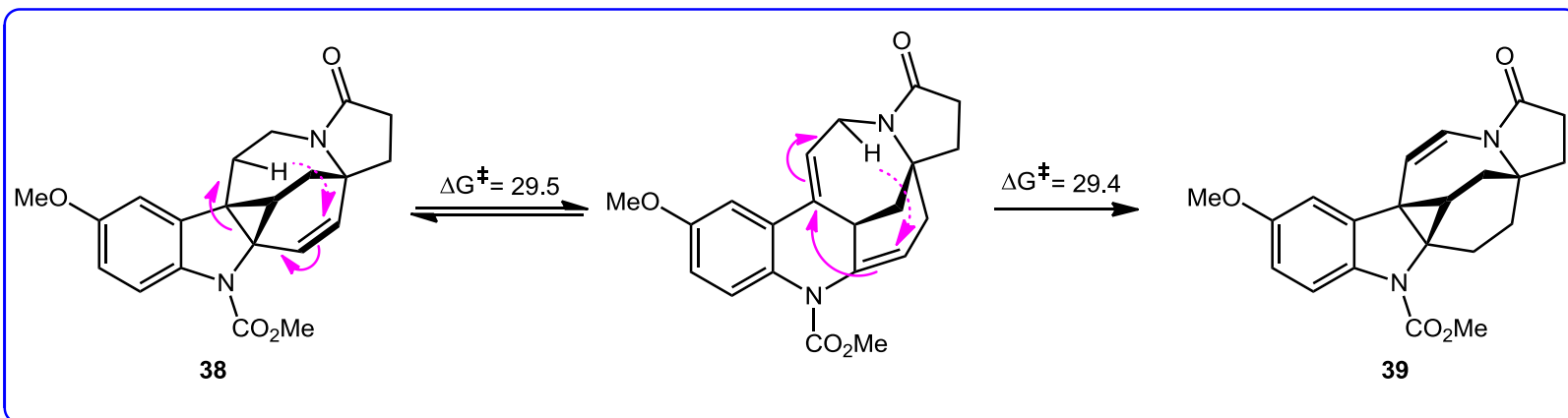
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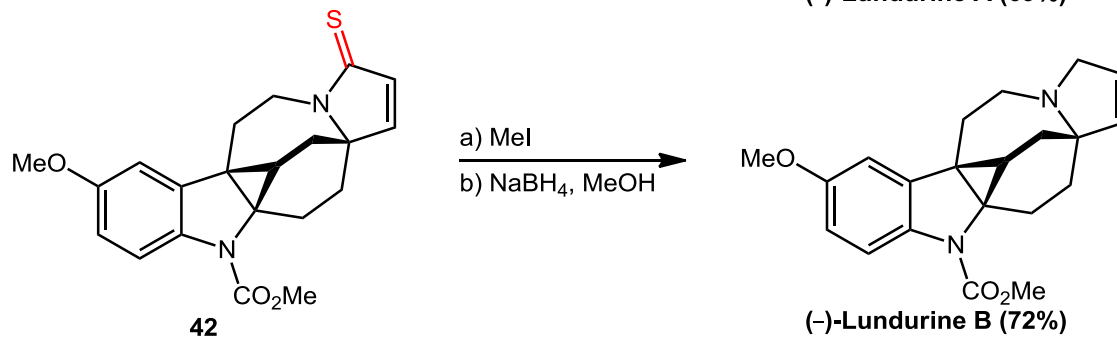
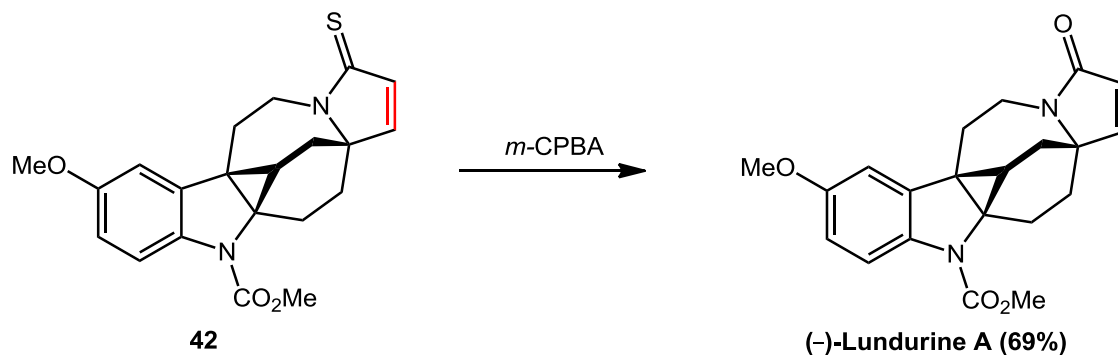
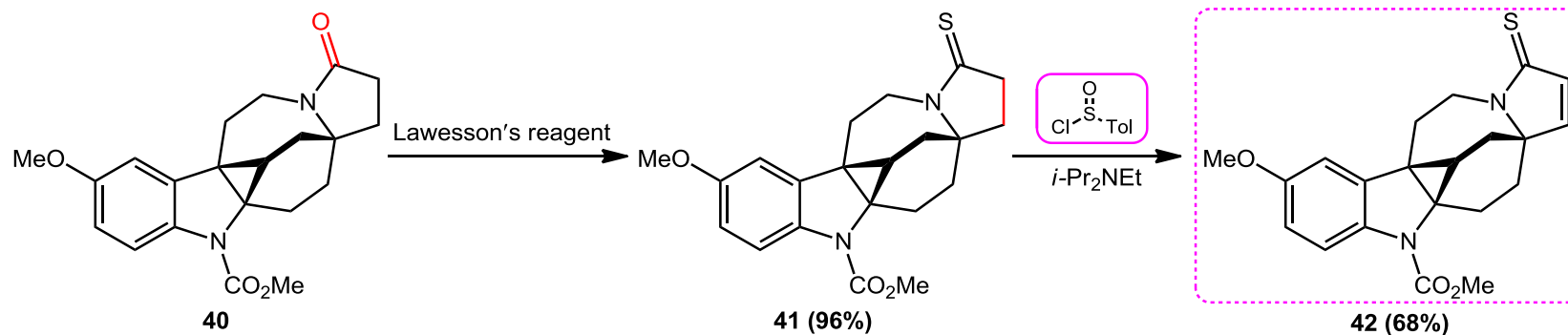
# Total Synthesis of (-)-Lundurines A-C



# Total Synthesis of (-)-Lundurines A-C

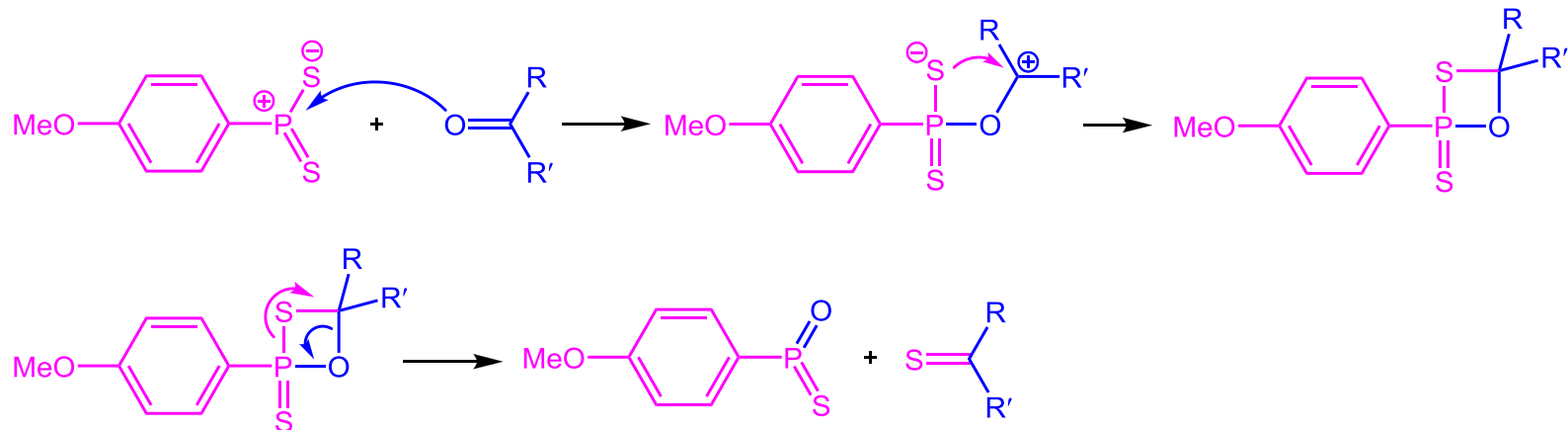
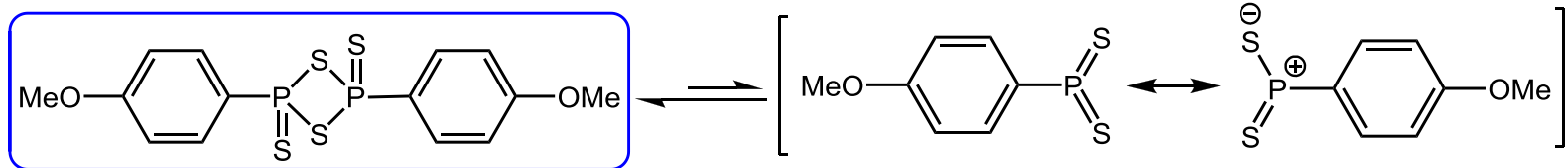


# Total Synthesis of (-)-Lundurines A-C



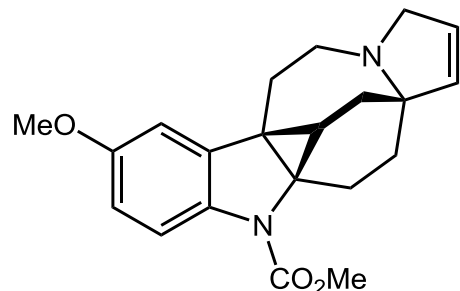


# Lawesson's reagent



# Summary

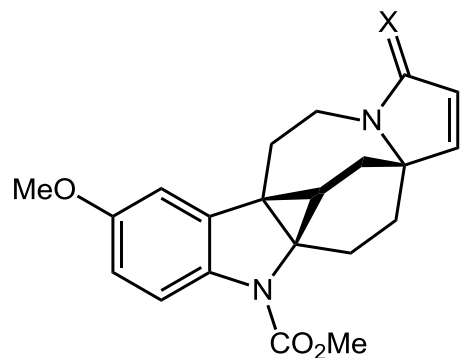
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- 29 steps, 2.4% overall yield
- Curtius rearrangement
- Olefin metathesis
- Copper-mediated cyclization

Nishida, A. *et al. Org. Lett.* **2014**, 16, 768.

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- 15 steps, 6.6% overall yield
- Claisen rearrangement
- Au(I)-catalyzed hydroarylation
- Homodienyl retro-ene/ene rearrangement

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Lundurines A, B, and C were isolated from *Kopsia tenuis*, a plant endemic to the north of Borneo, and show interesting cytotoxicity. **These alkaloids feature a unique indoline-fused polyhydropyrroloazocine and cyclopropyl moiety fused to the indoline.** Related alkaloids lacking the cyclopropane ring, such as lapidilectam, lapidilectines, grandilodines, and tenuisines, have also been isolated from plants of the *Kopsia* genus.

In conclusion, we have developed a unified approach toward the synthesis of lundurines A–C, including the first enantioselective total synthesis of lundurine C, taking advantage of a gold(I)-catalyzed *8-endo-dig* selective hydroheteroarylation to build the polyhydroazocine ring. Our synthesis of the lundurines is the shortest and most efficient to date and is perfectly suited to the preparation of analogues for biological evaluation as well as its extension to the synthesis of other *Kopsia* alkaloids.

Worthy of note is the implementation of a practical chirality transfer in a complex tandem transformation and the new intramolecular cyclopropanation of indoles by formation of a pyrazoline by formal [3+2] cycloaddition in the presence of a Lewis acid. Finally, as often encountered in total synthesis endeavors, serendipity also played a significant role in the discovery of a new transformation in which a double bond migrates by means of a homodienyl retro-ene/ene rearrangement, which streamlined the access to this family of alkaloids.