Literature Report 9

Enantioselective Synthesis of (-)-Acutumine and (-)-10-Hydroxyacutuminine

Reporter: Xiang Li
Checker: Gao-Wei Wang
Date: 2022-05-16

Li, F. Tartakoff, S. S. Castle, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 6674
Grünenfelder, D. C. Navarro, R. Wang, H. Fastuca, N. J. **Reisman, S. E.** *Angew. Chem. Int. Ed.* **2022**, *61*, e202117480

CV of Prof. Sarah E. Reisman

Research Interests:

- Natural Product Synthesis
- Synthetic Methods Development

Education:

- **1997-2001** B.S., Connecticut College, New London, CT
- **2001-2006** Ph.D., Yale University, New Haven, CT
- **2006-2008** Postdoc., Harvard University, Cambridge, MA
- **2008-2014** Assistant Professor, California Institute of Technology, Pasadena, CA
- **2014-Present** Professor, California Institute of Technology, Pasadena, CA

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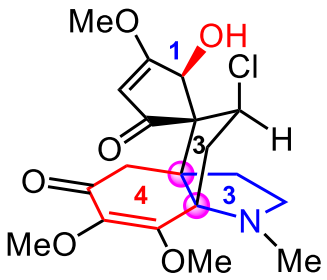
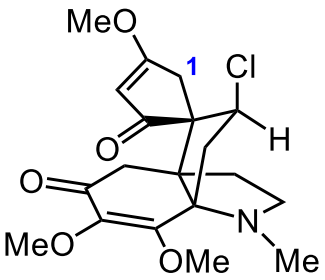
Introduction

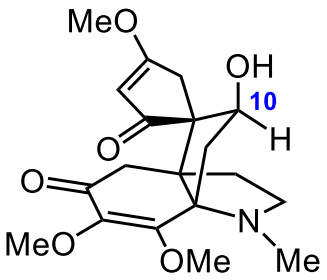


(-)-Acutumine (1)

***JACS* 2009**



(-)-Acutuminine (2)



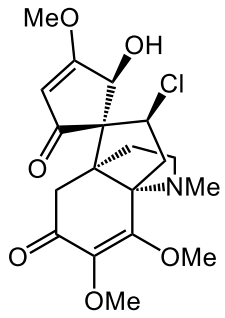
(-)-10-Hydroxyacutuminine (3)

***ACIE* 2022**

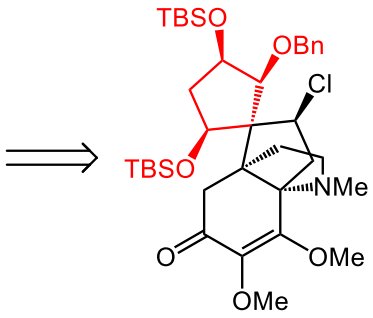
Sinomenium Acutum

- The spirocyclic alkaloid (-)-acutumine was **first isolated** from the Chinese moonseed plant, possesses **selective T-cell cytotoxicity** and **antiamnesic** properties.
- These alkaloids contain densely functionalized **[4.3.3]propellane** cores with a **spirofused cyclopentenone** and vicinal **quaternary centers**.

Retrosynthetic Analysis



(-)-Acutumine (1)
JACS 2009



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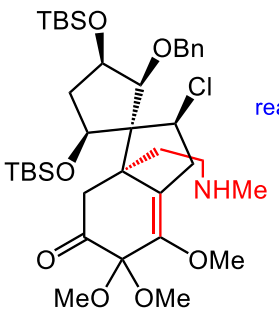

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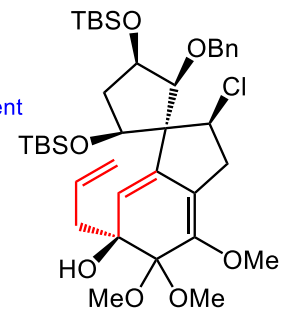
Cope-rearrangement



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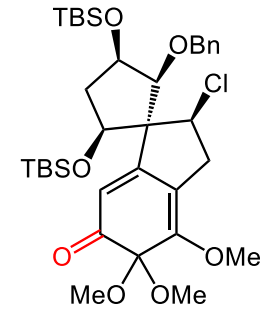

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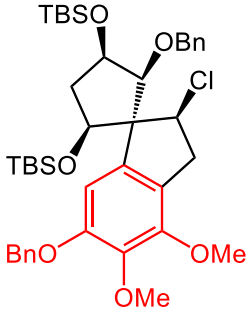
radical-polar crossover reaction



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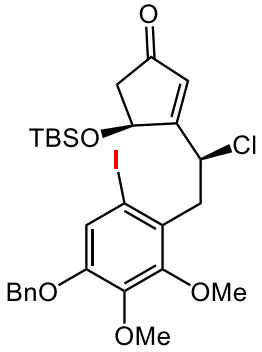

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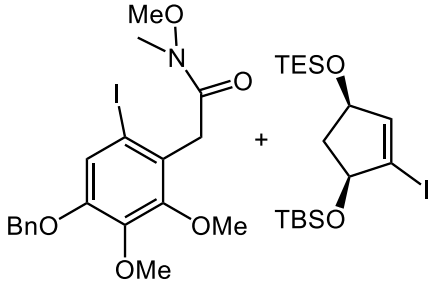
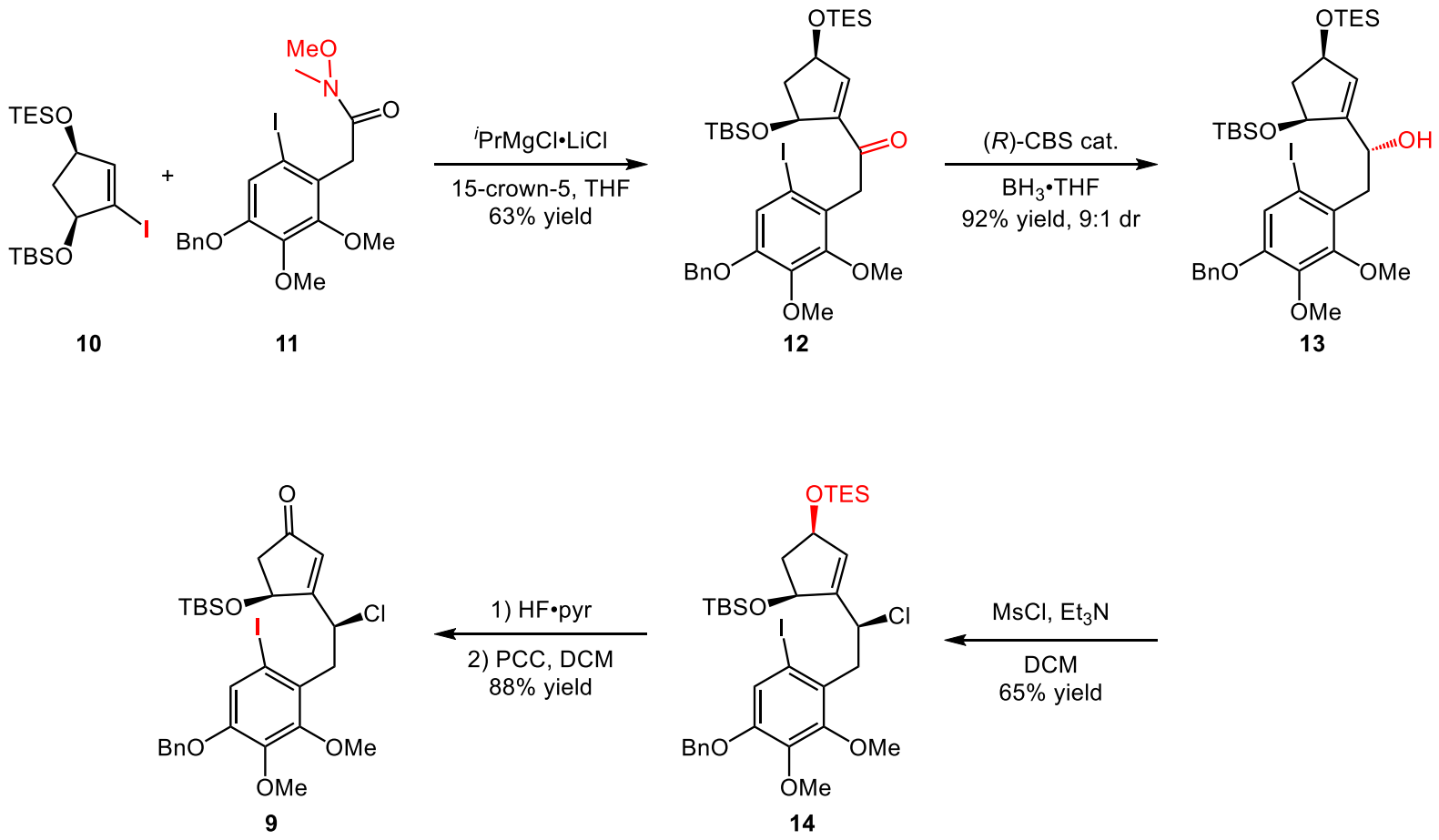
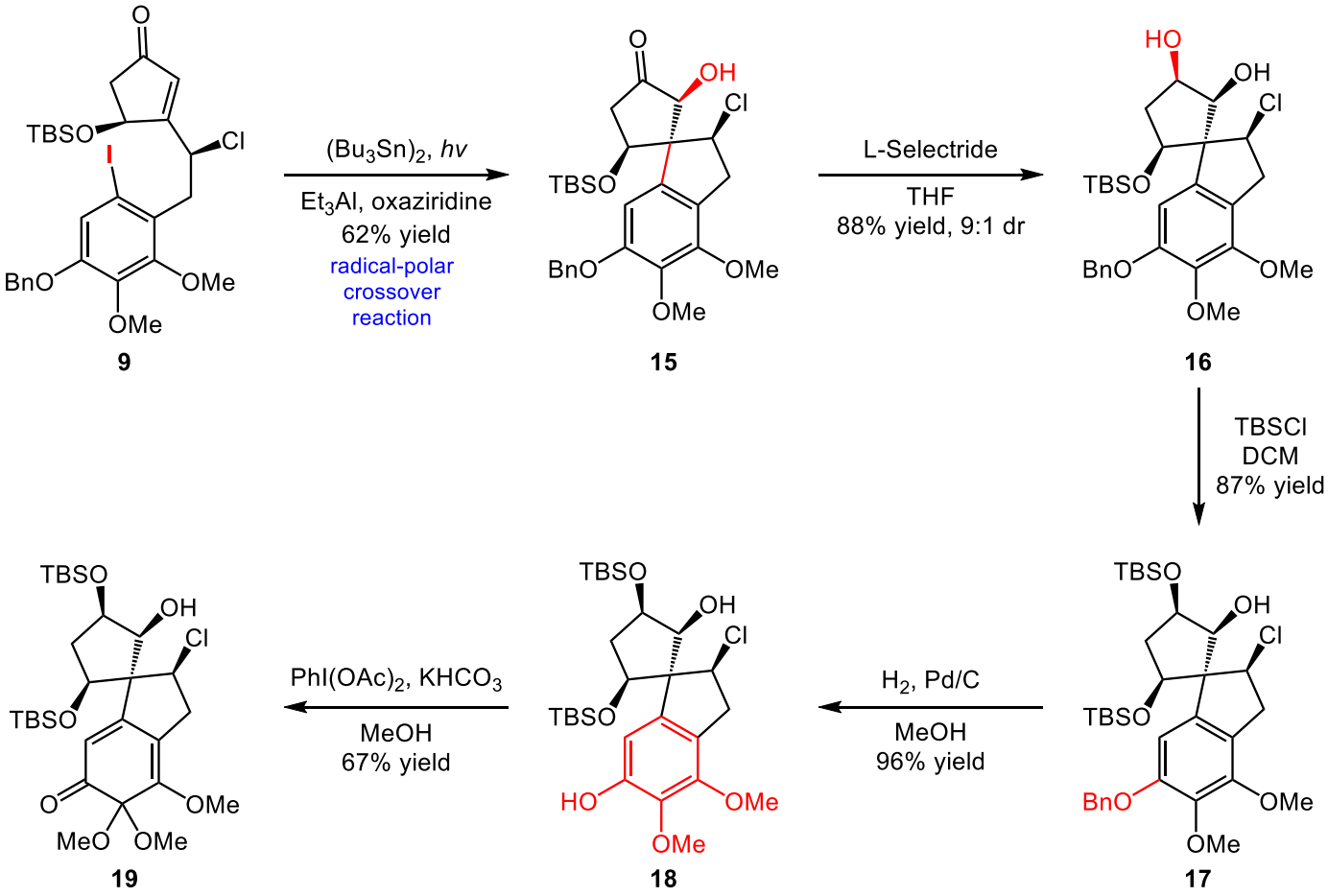


11 **10**

Synthesis of 9



Synthesis of 19



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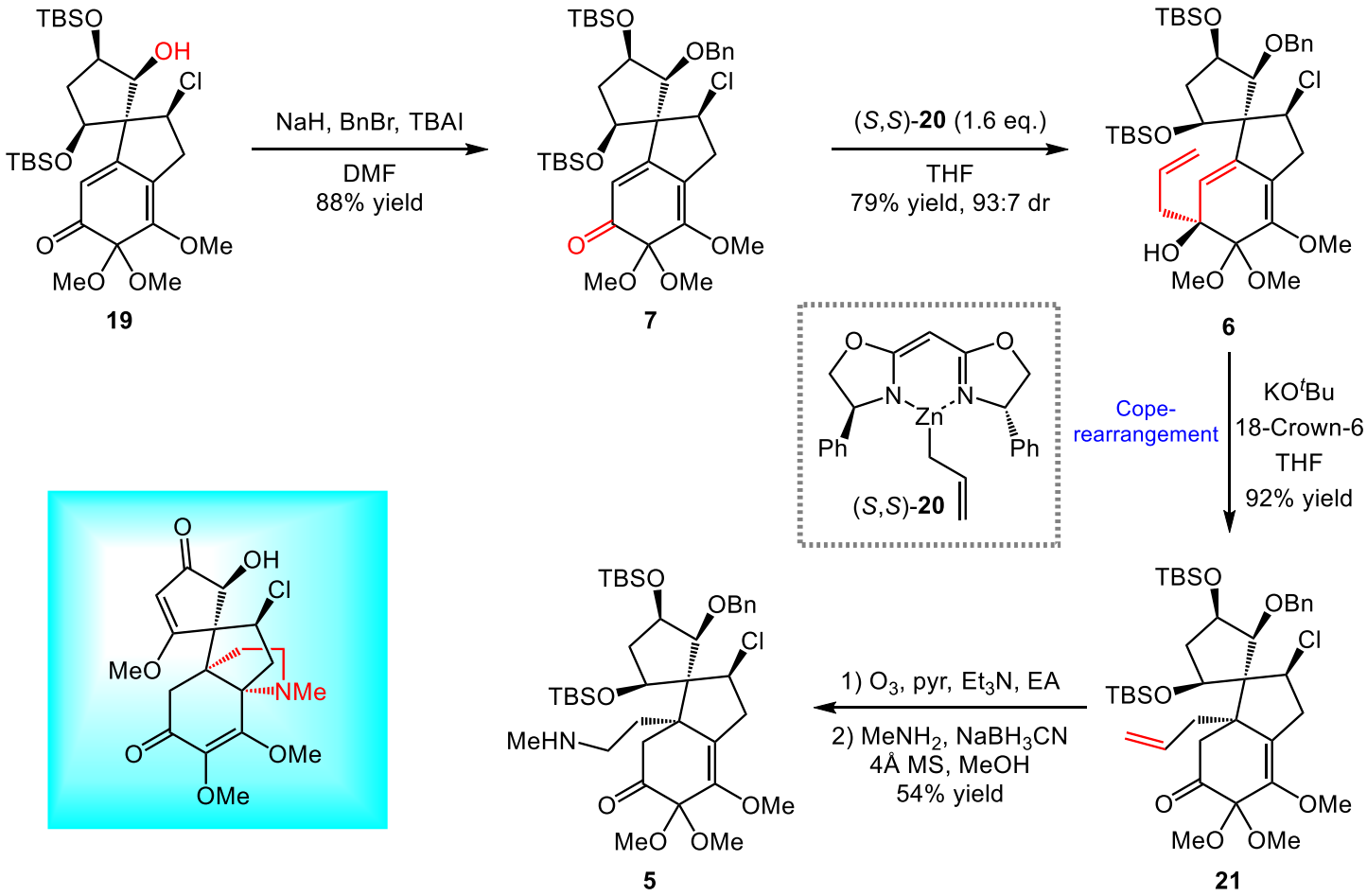
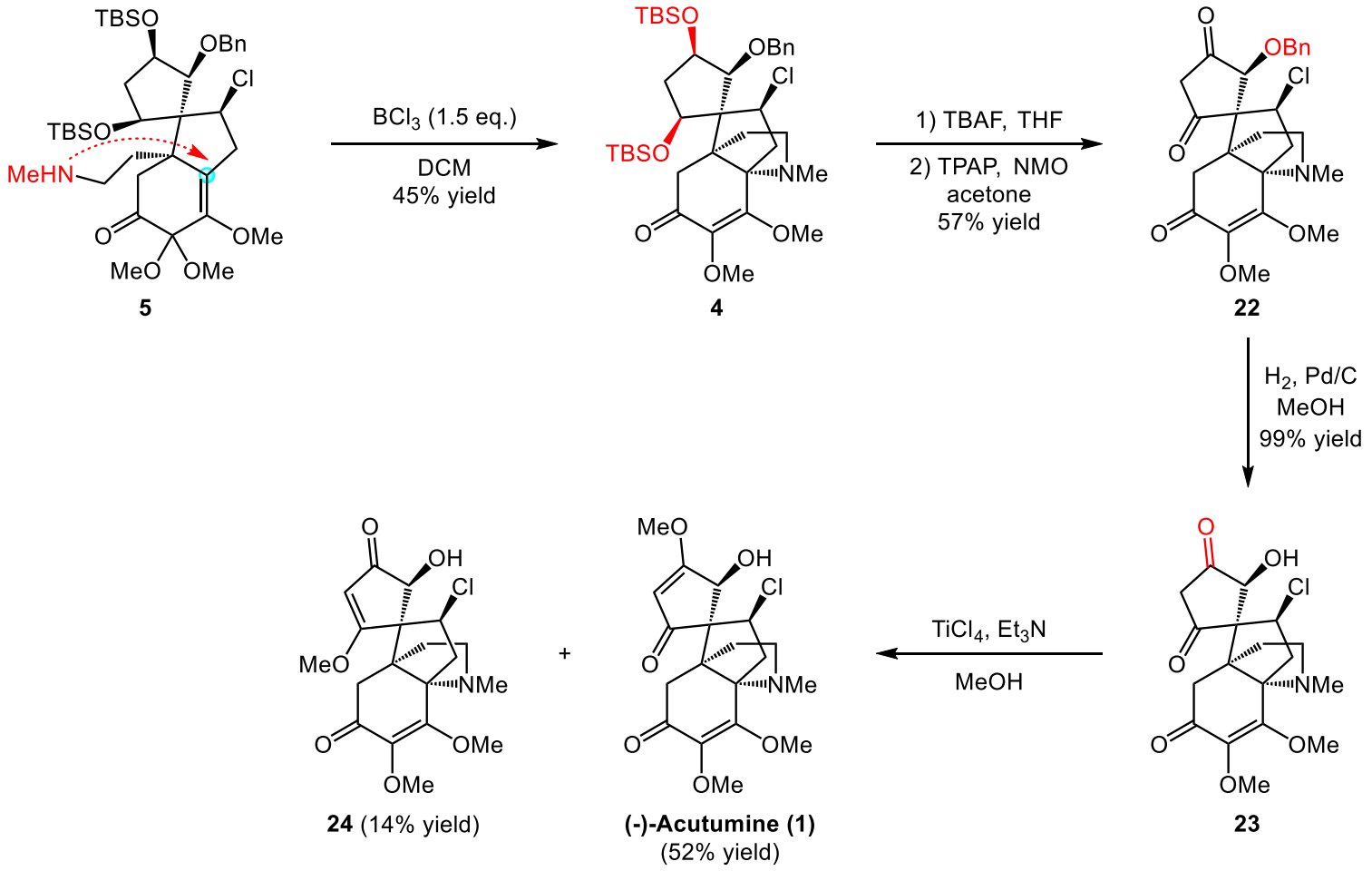
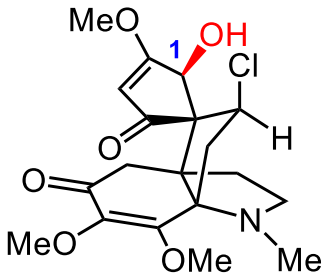


Synthesis of 1

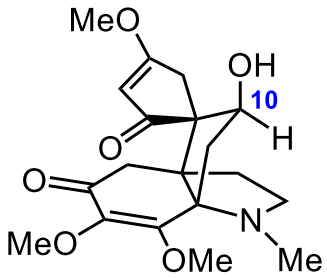


Synthesis of (-)-10-Hydroxyacutuminine



(-)-Acutumine (1)

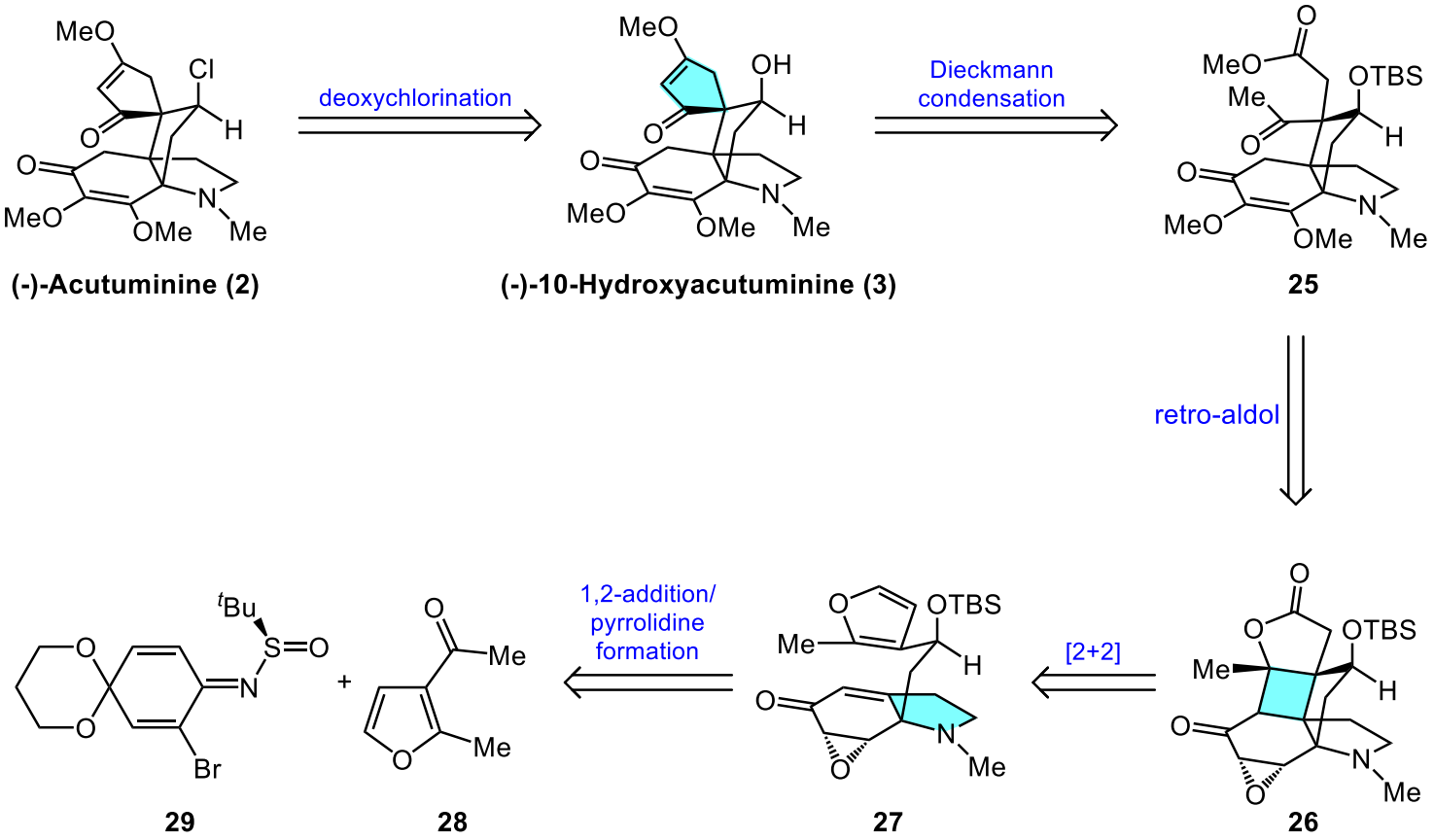
***JACS* 2009**



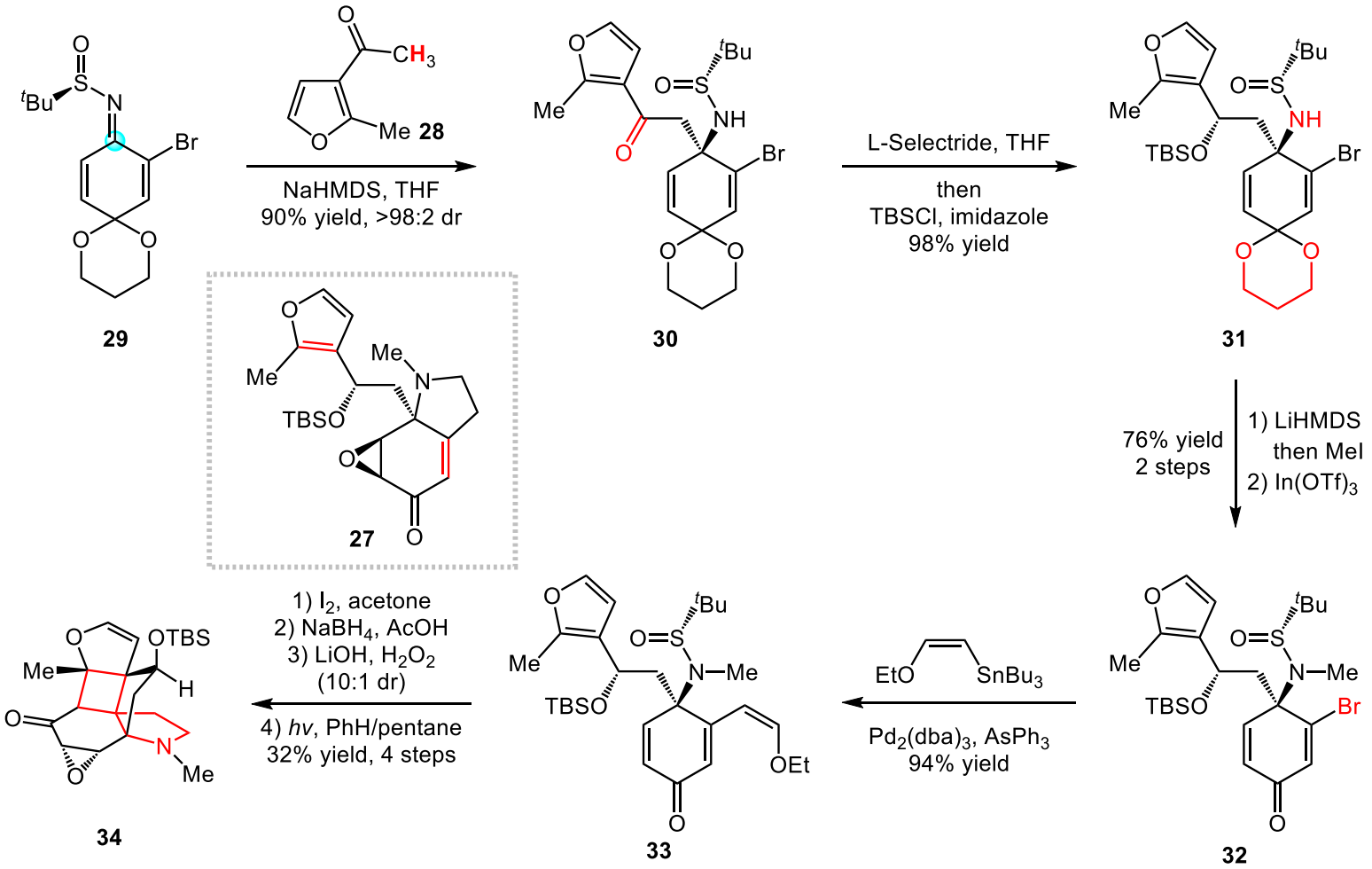
(-)-10-Hydroxyacutuminine (3)

ACIE 2022

Retrosynthetic Analysis

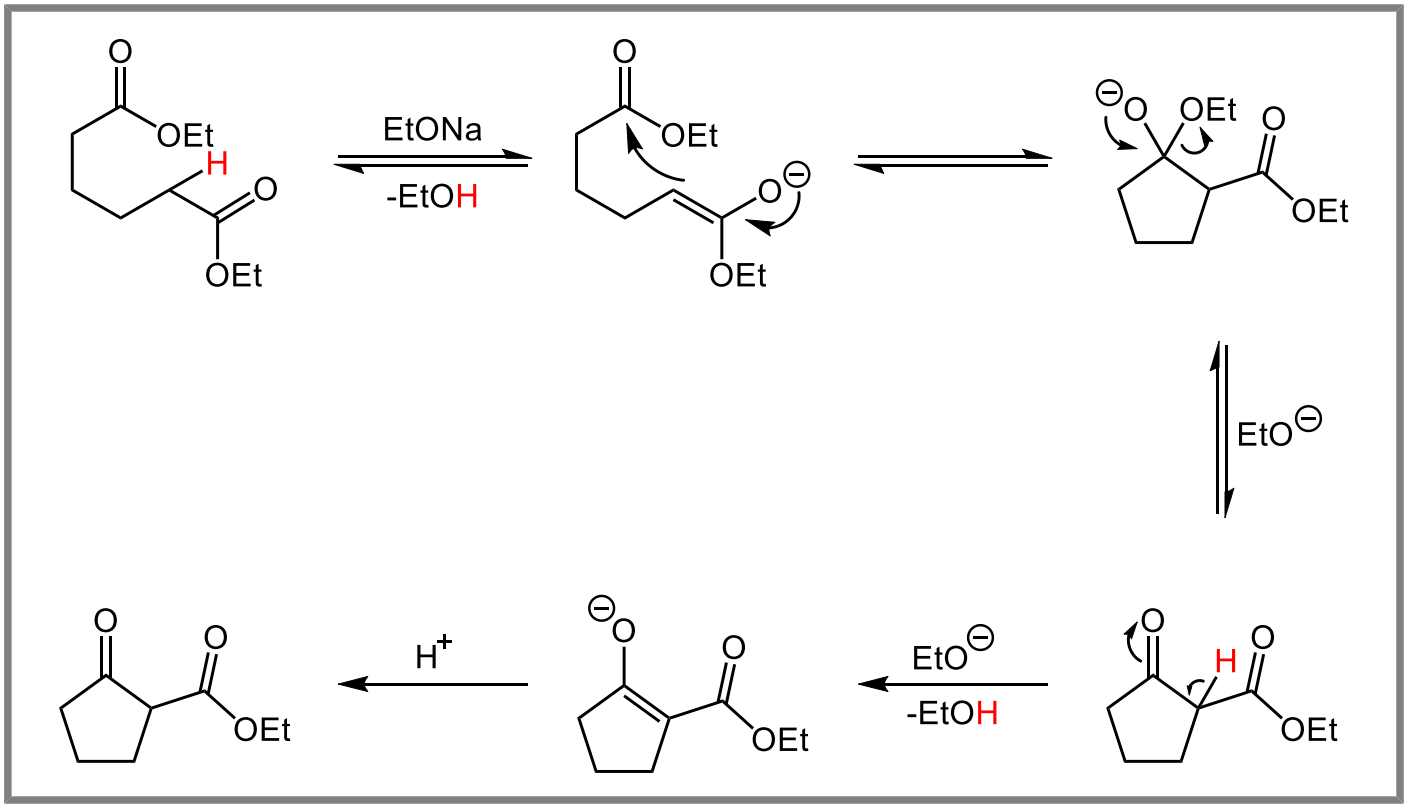


Synthesis of 34

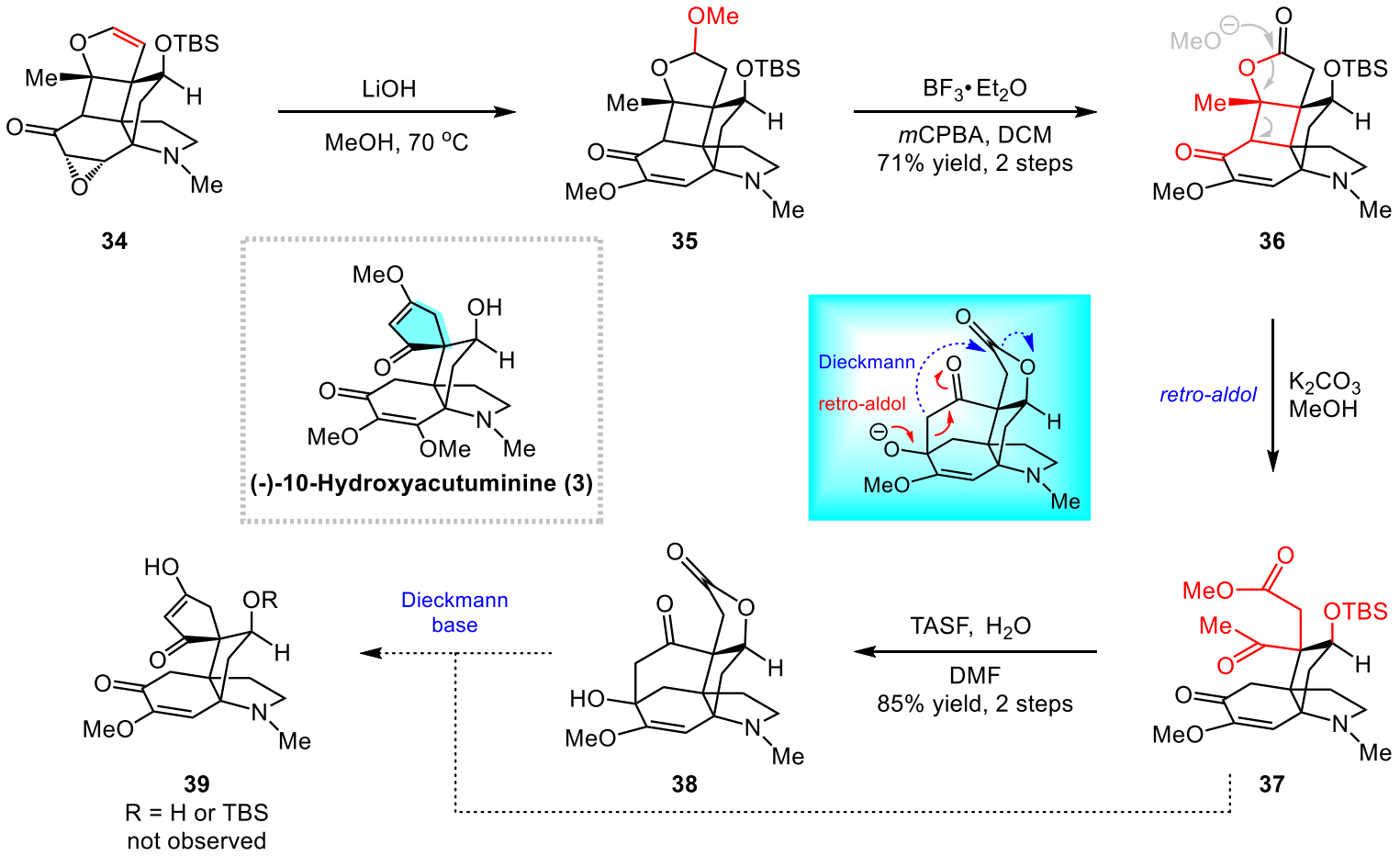


Dieckmann Condensation

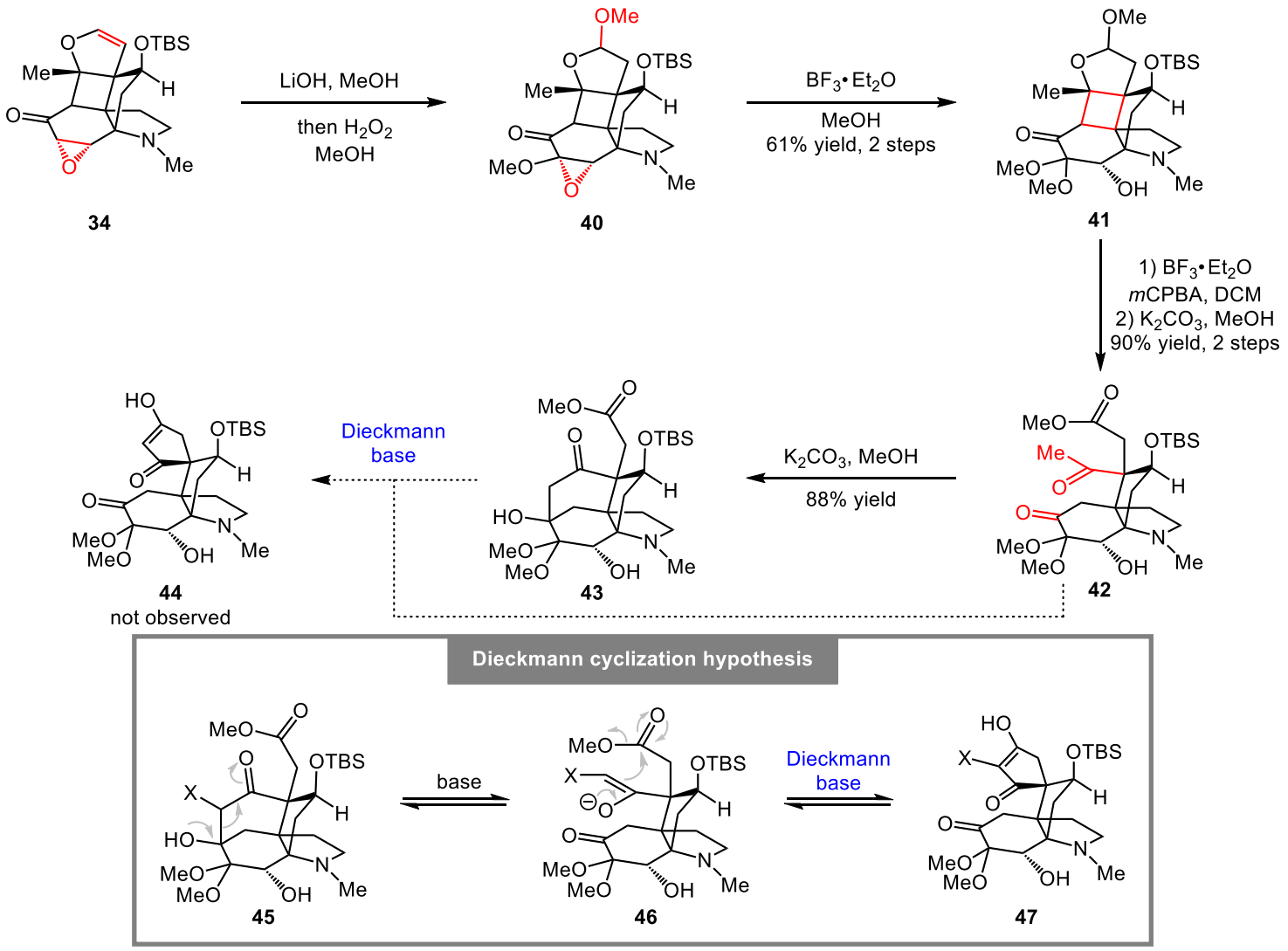
Dieckmann缩合是二酯在碱作用下发生分子内缩合生成*β*-酮酯的反应。



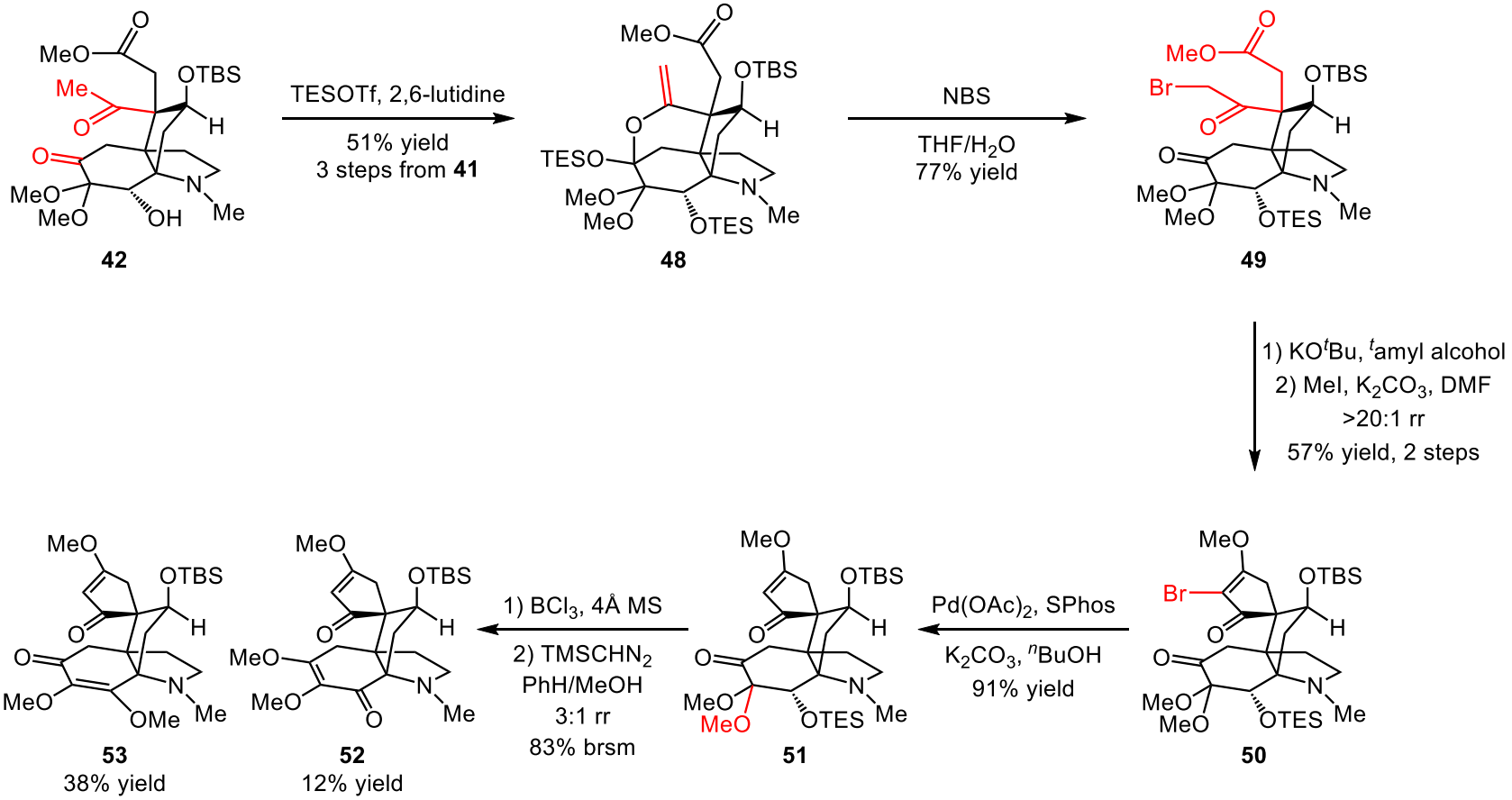
Synthesis of 39



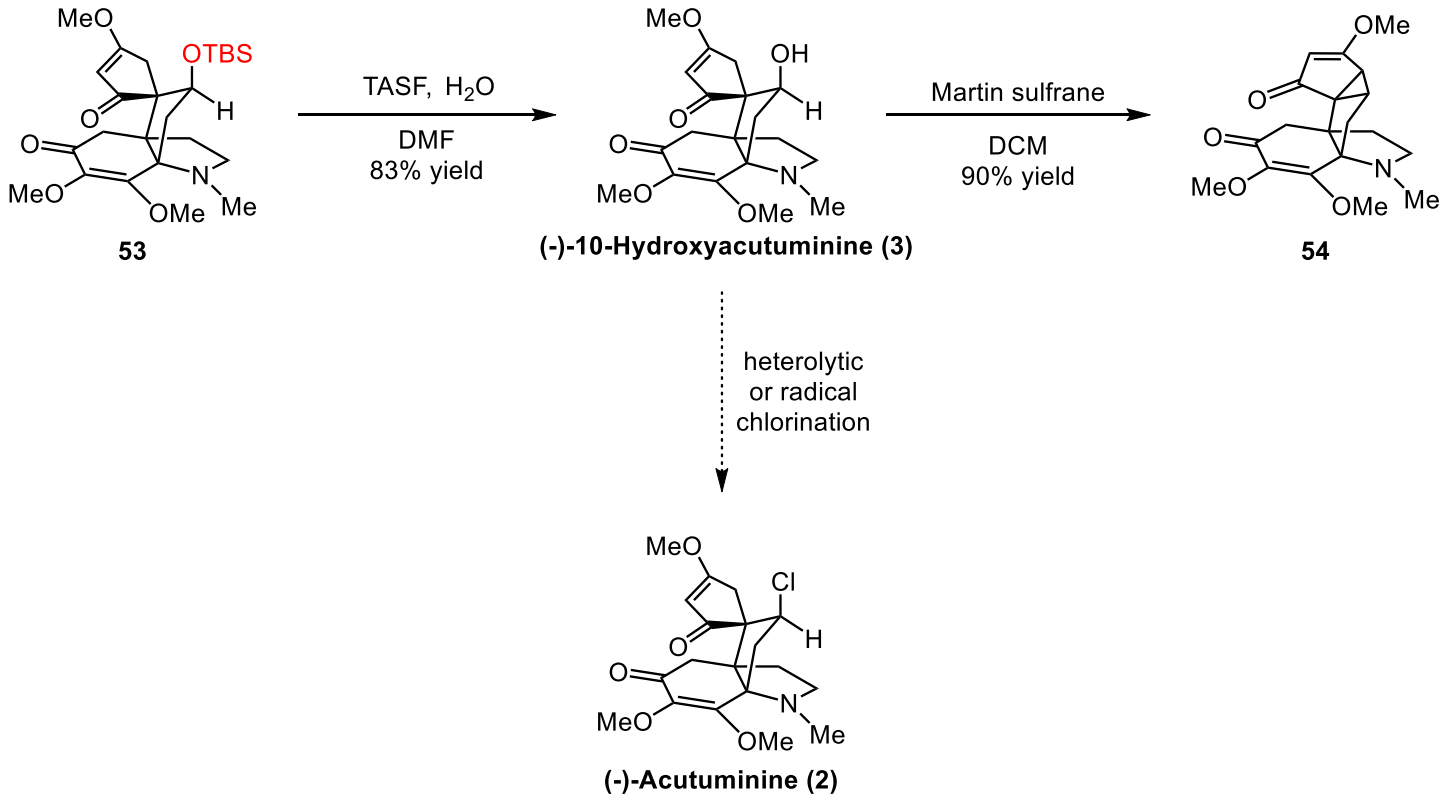
Synthesis of 44



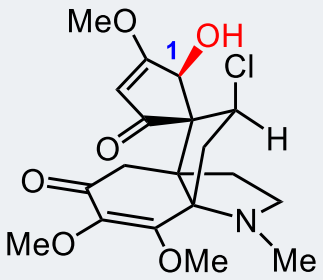
Synthesis of 53



Synthesis of 3

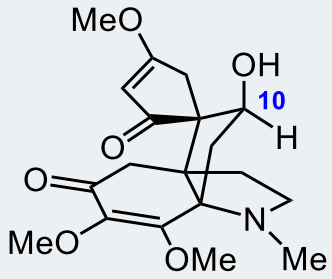


Summary



(-)-Acutumine (1)

- 17 steps, 0.46% total yield
- Radical-polar crossover reaction
- A reagent-controlled diastereoselective ketone allylation
- Oxy-Cope rearrangement to form quaternary stereocenter



(-)-10-Hydroxyacutuminine (3)

- 24 steps, 0.79% total yield
- Photochemical [2+2] cycloaddition
- A retro-aldol/Dieckmann sequence to build the requisite spirocyclic cyclopentenone

The First Paragraph

写作思路

化合物的来源和结构特征

↓

指出化合物的重要性

↓

合成化合物的方法

The First Paragraph

The spirocyclic alkaloid (-)-acutumine was first isolated from the Chinese moonseed plant, a climbing shrub used in traditional folk medicine for its analgesic, anti-inflammatory, and anti-rheumatic properties. After its isolation in 1929, the structure of **1** evaded elucidation for nearly 40 years, until it was finally solved by single-crystal X-ray diffraction in 1967. In preliminary studies, (-)-**1** was shown to exhibit selective T-cell cytotoxicity and anti-amnesic activity, the latter which was investigated in a Morris mouse model and patented in 2003. Since the initial isolation of **1**, several additional acutumine alkaloids have been isolated, including (-)-dechloroacutumine and (-)-acutuminine. These alkaloids contain densely functionalized [4.3.3]propellane cores with a spirofused cyclopentenone and vicinal quaternary centers. In addition, **1** and **2** bear a neopentyl chloride, a rare structural feature for terrestrial natural products.

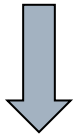
The First Paragraph

Due to their complex and unusual structures, there has been significant interest in the biosynthesis, biological activity, and de novo syntheses of the acutumine alkaloids. Two completed syntheses of **1** have been disclosed, the first from Castle and co-workers in 2009 and the second from Herzon and co-workers in 2013. In this communication, we report a synthetic approach to the acutumine alkaloids that leverages a [2+2] cycloaddition/retro-aldol sequence to build the propellane core and provides access to (-)-10-hydroxyacutuminine.

The Last Paragraph

写作思路

总结工作



指出合成路线中所用方法的特点

The Last Paragraph

In summary, an enantioselective synthesis of (-)-10-hydroxyacutuminine was completed in 24 steps from 2-bromo-4-methoxyphenol. Our approach featured an intramolecular, photochemical [2+2] cycloaddition to build the propellane core. Subsequent application of a retro-aldol/Dieckmann sequence afforded the requisite spirocyclic cyclopentenone found in natural products; use of α-bromoketone **29** proved crucial for the successful Dieckmann cyclization. Subsequent installation of the C7/C8 dimethoxy enone and TBS deprotection afforded (-)-10-hydroxyacutuminine. Although efforts to install the C10 neopentyl chloride were ultimately unsuccessful, **3** bears the complete carboskeleton and oxidation pattern of (-)-acutuminine. These studies highlight the strategic advantages and challenges of leveraging carbonyl chemistry to prepare densely functionalized natural products.

Representative Examples

1. These alkaloids contain densely functionalized [4.3.3]propellane cores with a spirofused cyclopentenone and vicinal quaternary centers. (螺桨烷，相邻的、附近的)

2. Due to their complex and unusual structures, there has been significant interest in the biosynthesis, biological activity, and de novo syntheses of the acutumine alkaloids. (从头合成，从新合成)

3. These studies highlight the strategic advantages and challenges of leveraging carbonyl chemistry to prepare densely functionalized natural products. (突出……策略优势和挑战)

Acknowledgement

Thanks for your attention