Literature Report V

Total Synthesis of Daphnillonin B

Reporter: Zheng Liu

Checker: Yu-Qing Bai

Zou, Y.-P.; Li, C.-C.* *et al. J. Am. Chem. Soc.* **2023**, *145,* 10998.

2023-09-04

CV of Prof. Chuang-Chuang Li

Background:

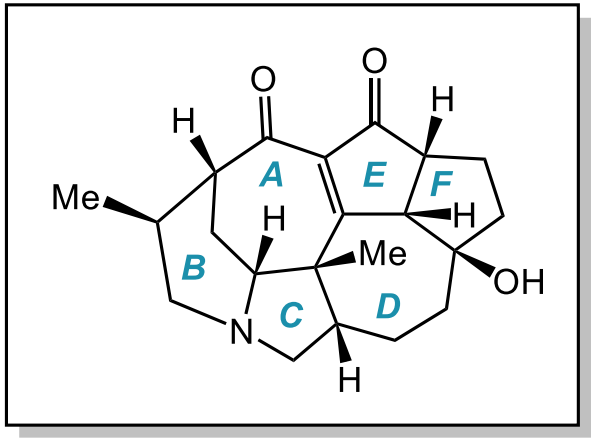
- **1997-2001** B.S., China Agricultural University
- **2001-2006** Ph.D., Peking University
- **2006-2008** Postdoc., Scripps Research Institute
- **2008-2013** Associate Professor, Shenzhen Graduate School, Peking University
- **2014-2017** Research Professor, SUSTech
- **2018-now** Professor, SUSTech

Research:

- Total Synthesis of Natural Products;
- Development of New Synthetic Methods.
- Medicinal Chemistry and Chemical Biology;

Contents

Introduction



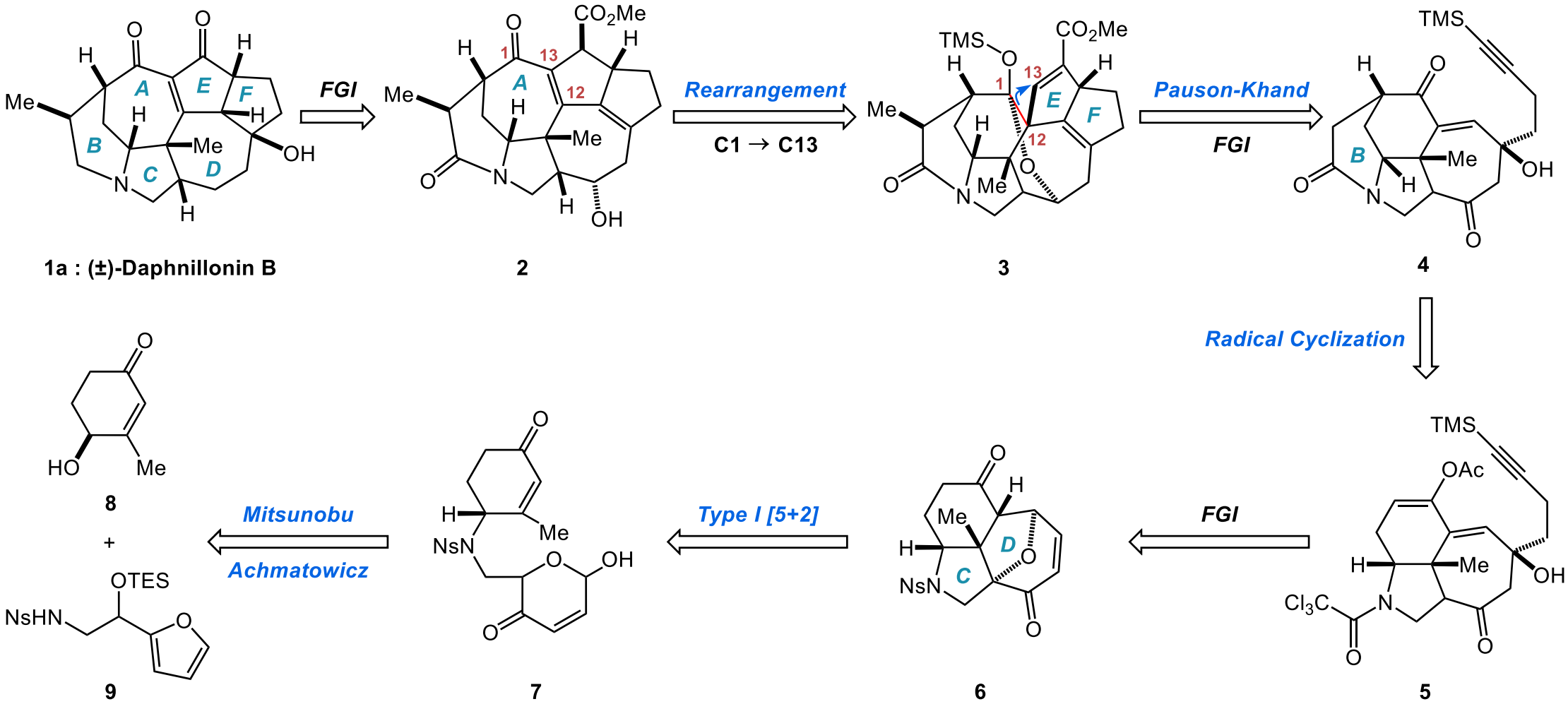
(−)-Daphnillonin B

Daphniphyllum longeracemosa

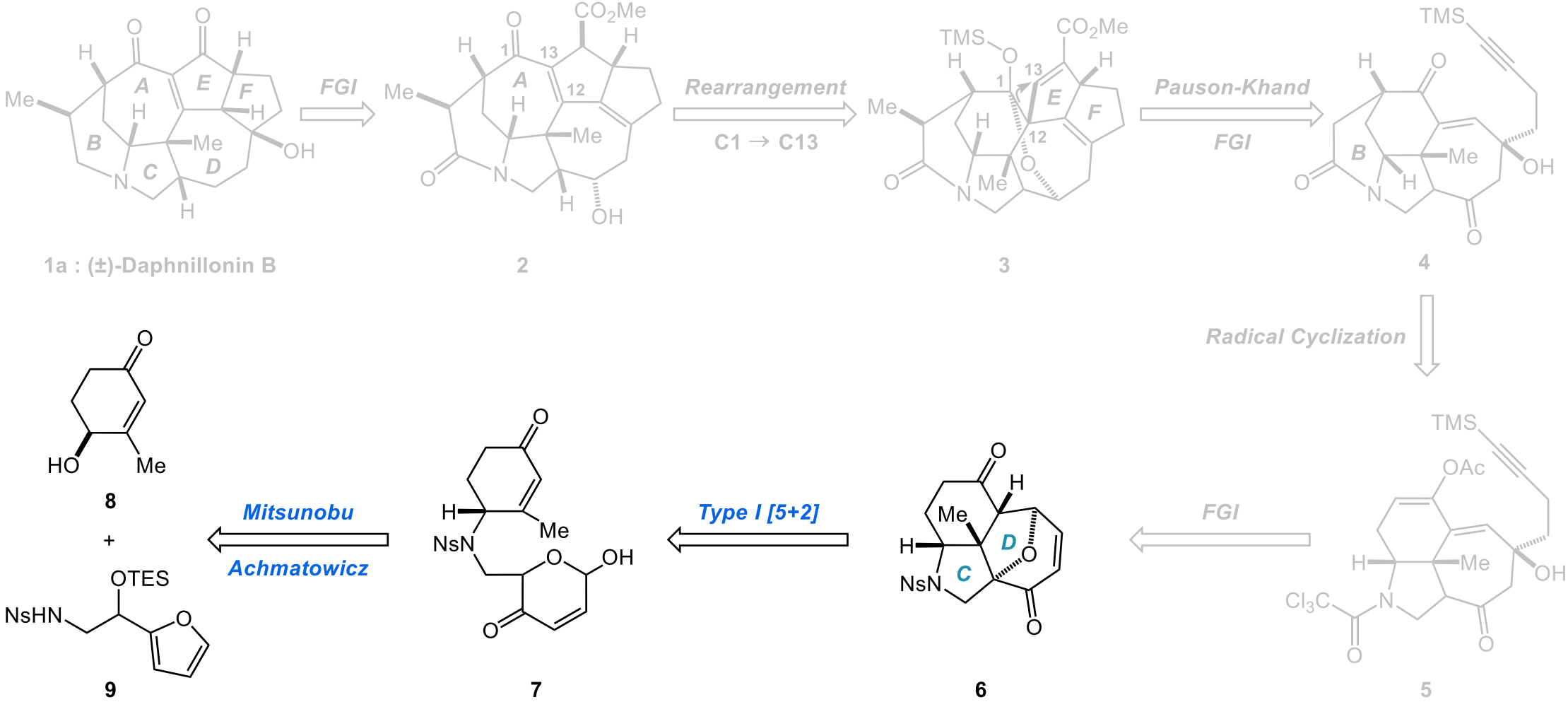
- It was isolated from *Daphniphyllum longeracemosa* and characterized in 2020;
- It contains a [7-6-5-7-5-5] A/B/C/D/E/F hexacyclic core with a bridged azabicyclo [4.3.1] A/B rings.

Zhang, D.-D., Yue, J.-M.* *et al. J. Org. Chem.* **2020**, *85,* 3742.

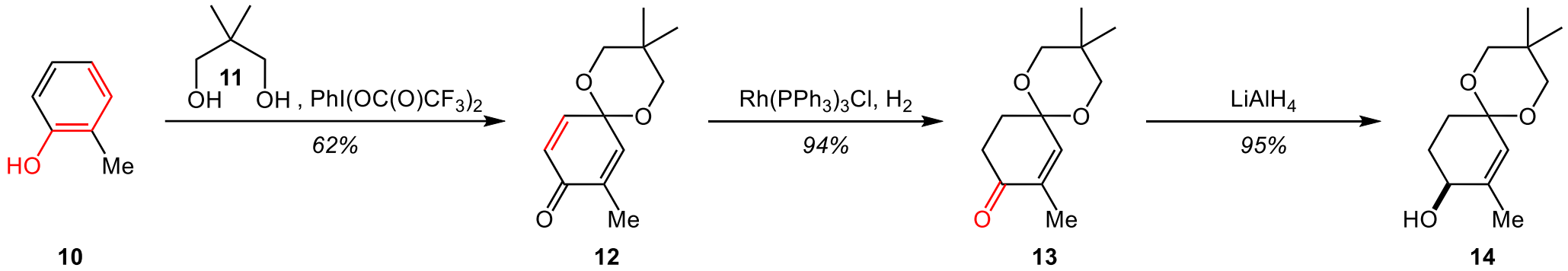
Retrosynthetic Analysis



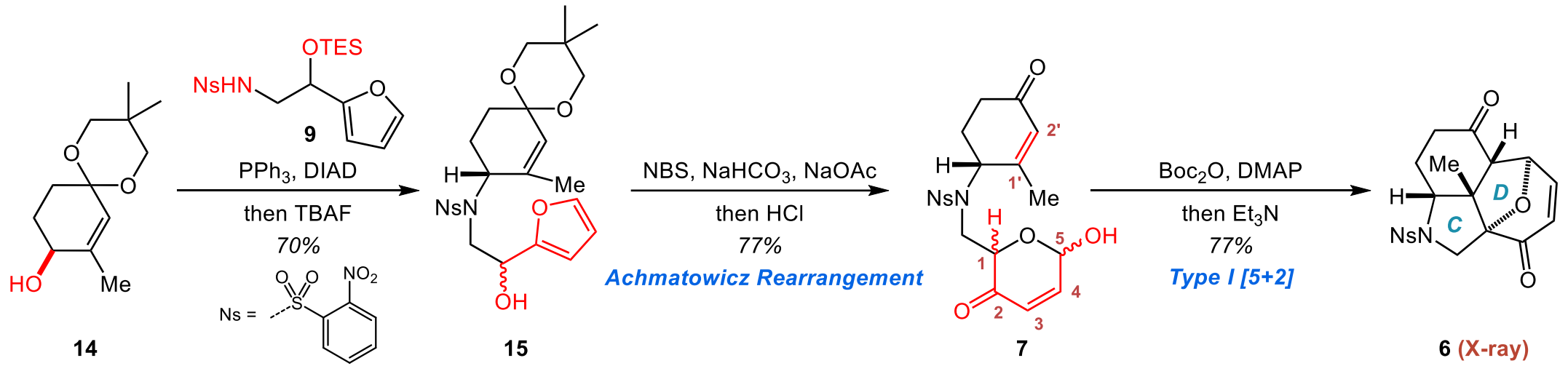
Retrosynthetic Analysis

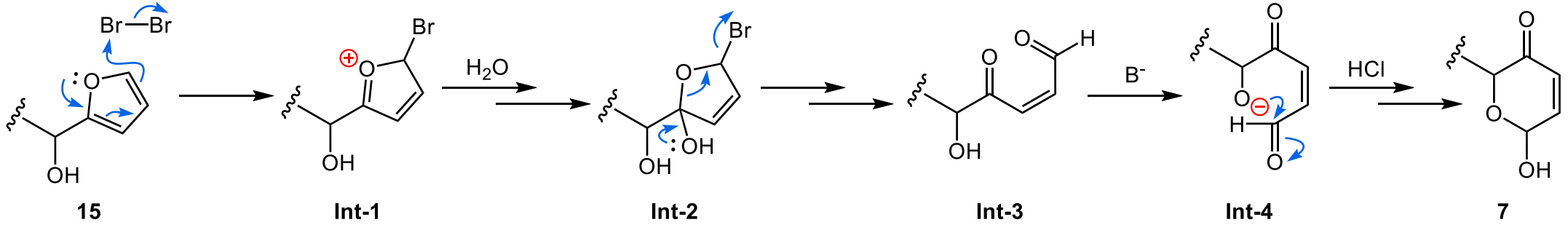


Synthesis of Compound 14

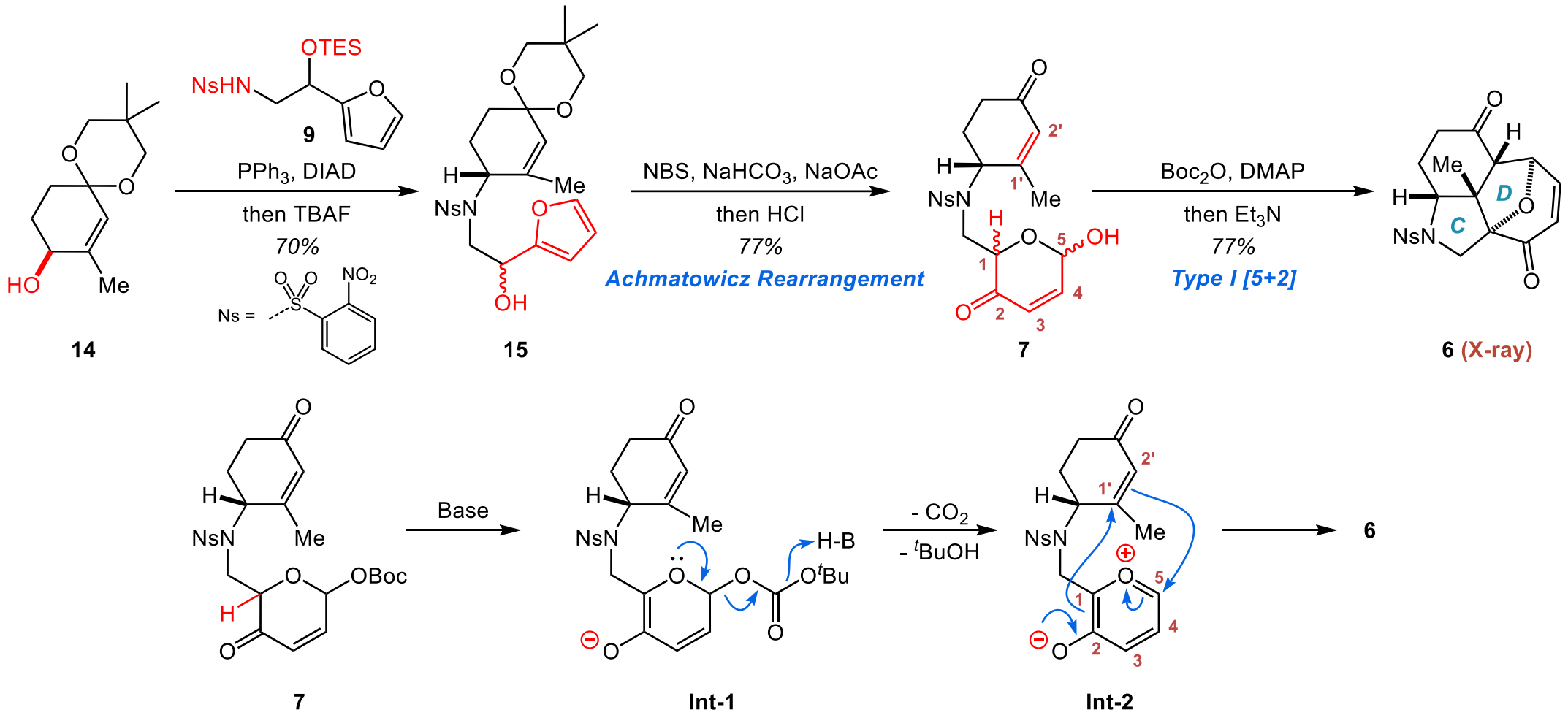


Synthesis of Compound 6





Synthesis of Compound 6



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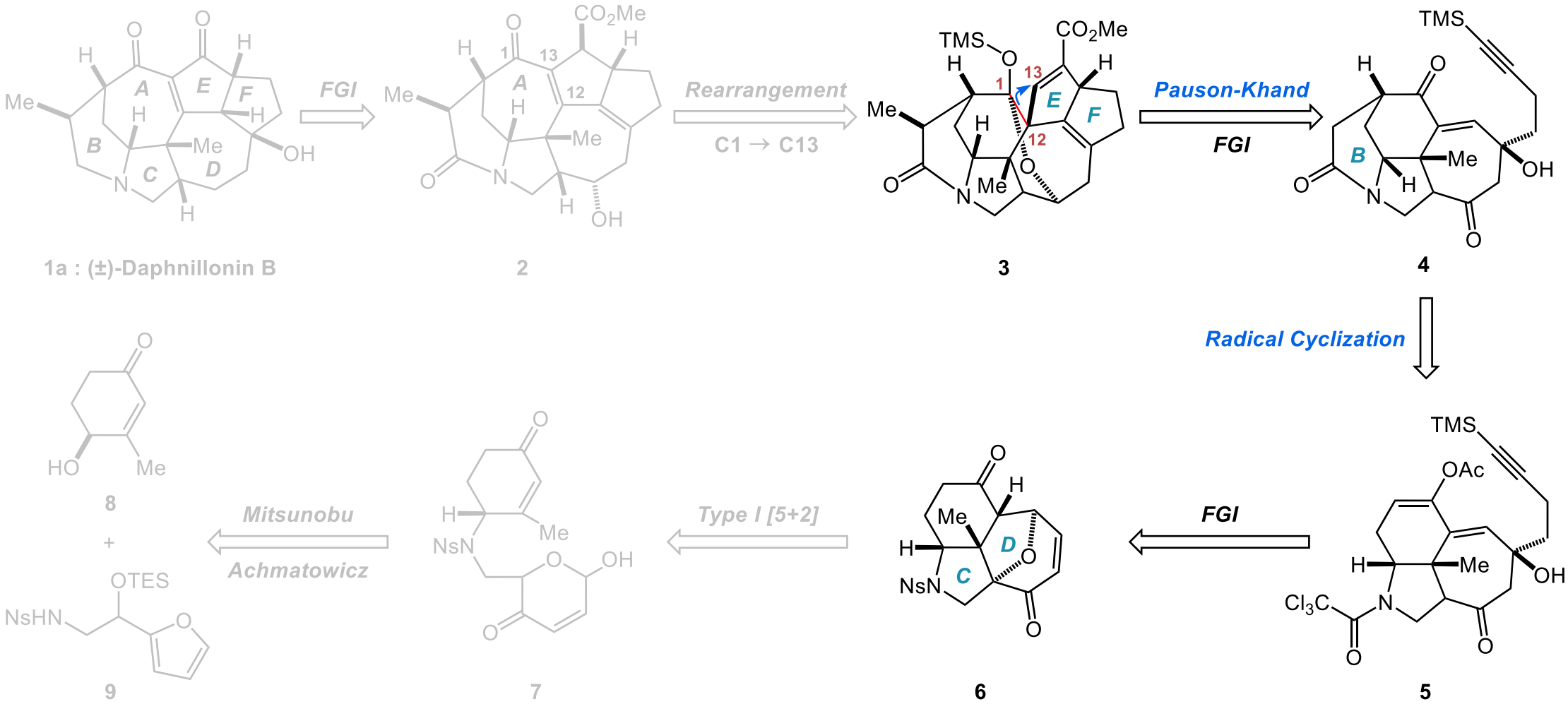
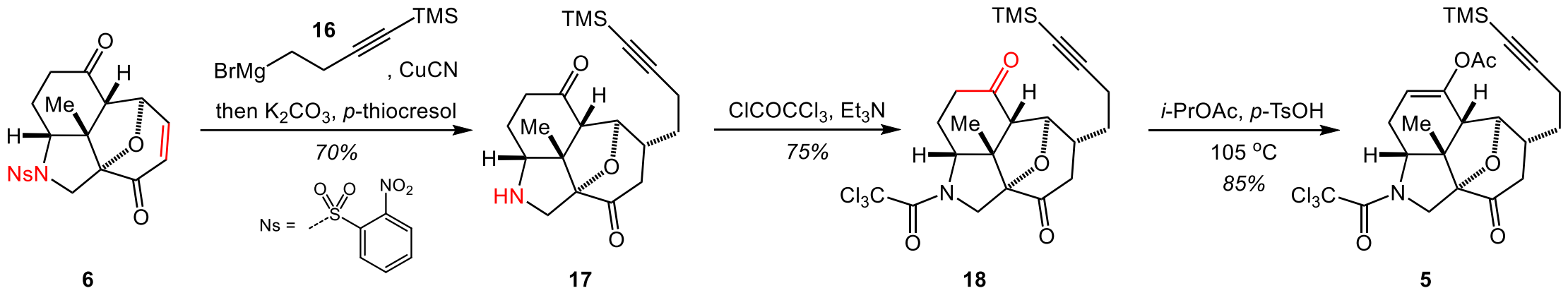
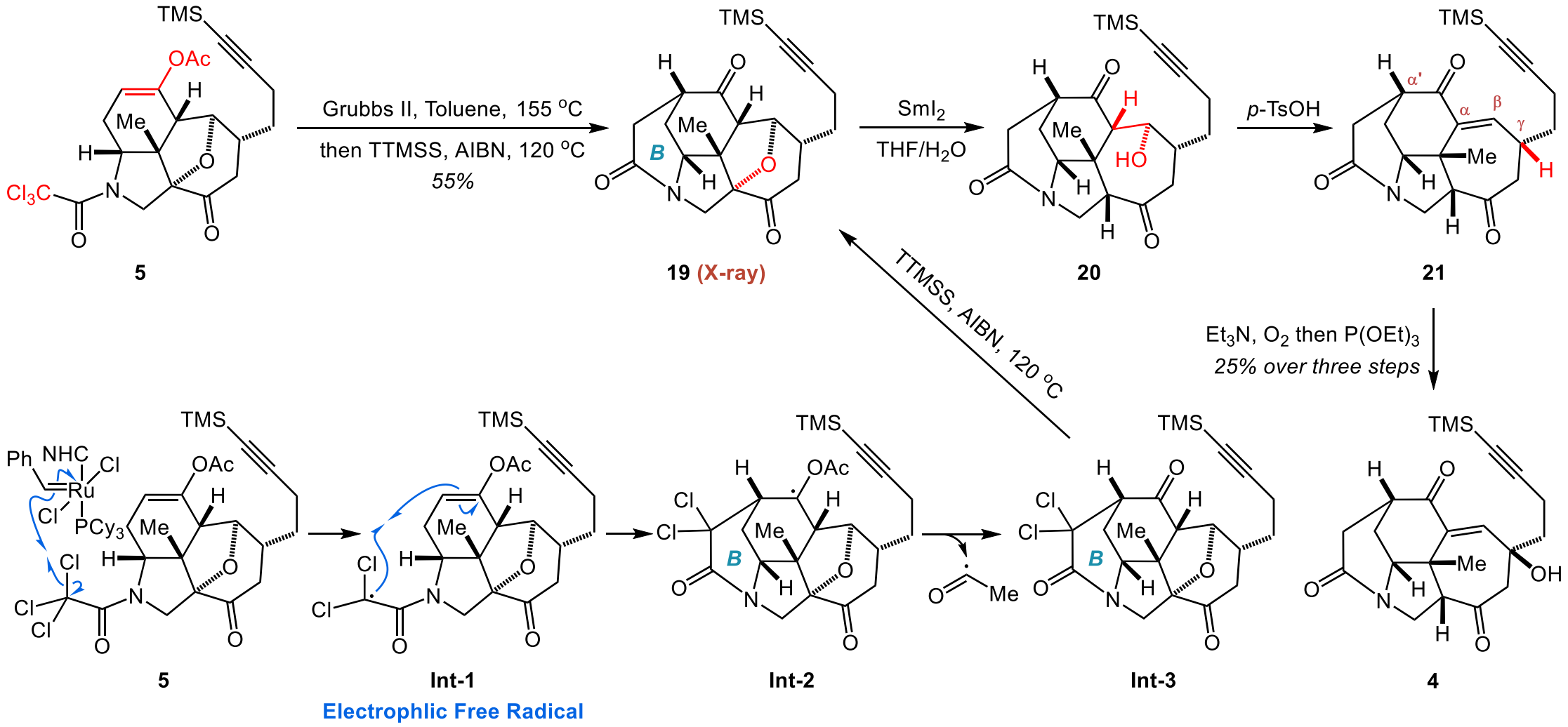


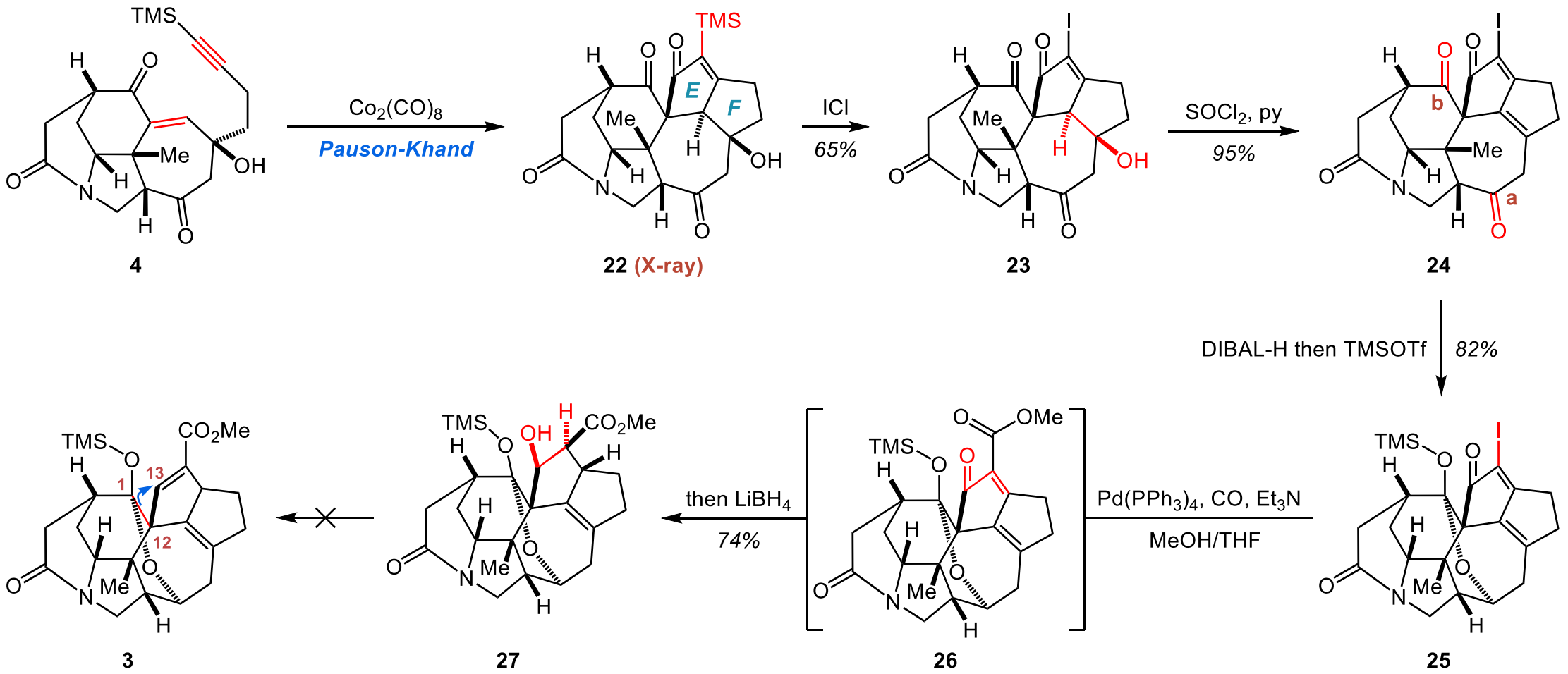
Synthesis of Compound 5



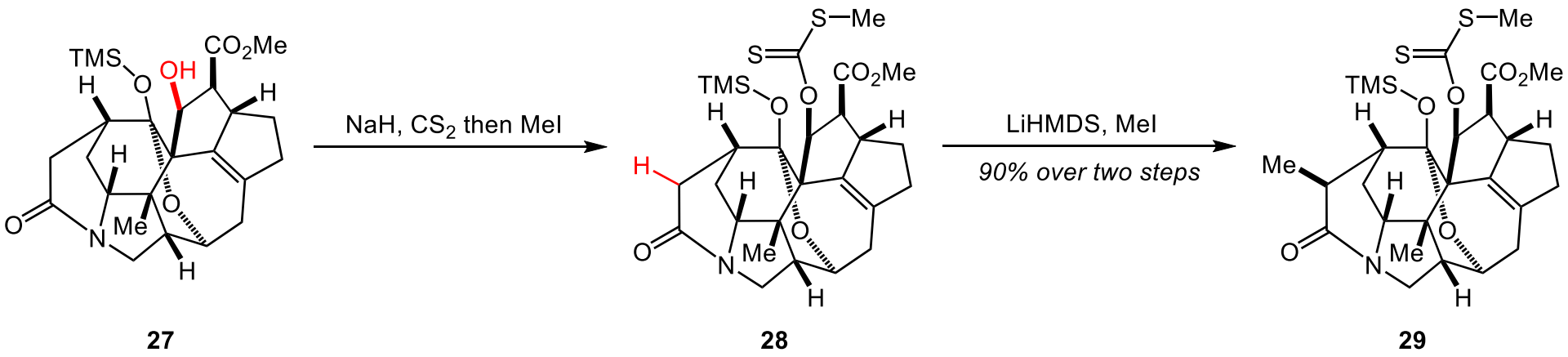
Synthesis of Compound 4



Synthesis of Compound 27

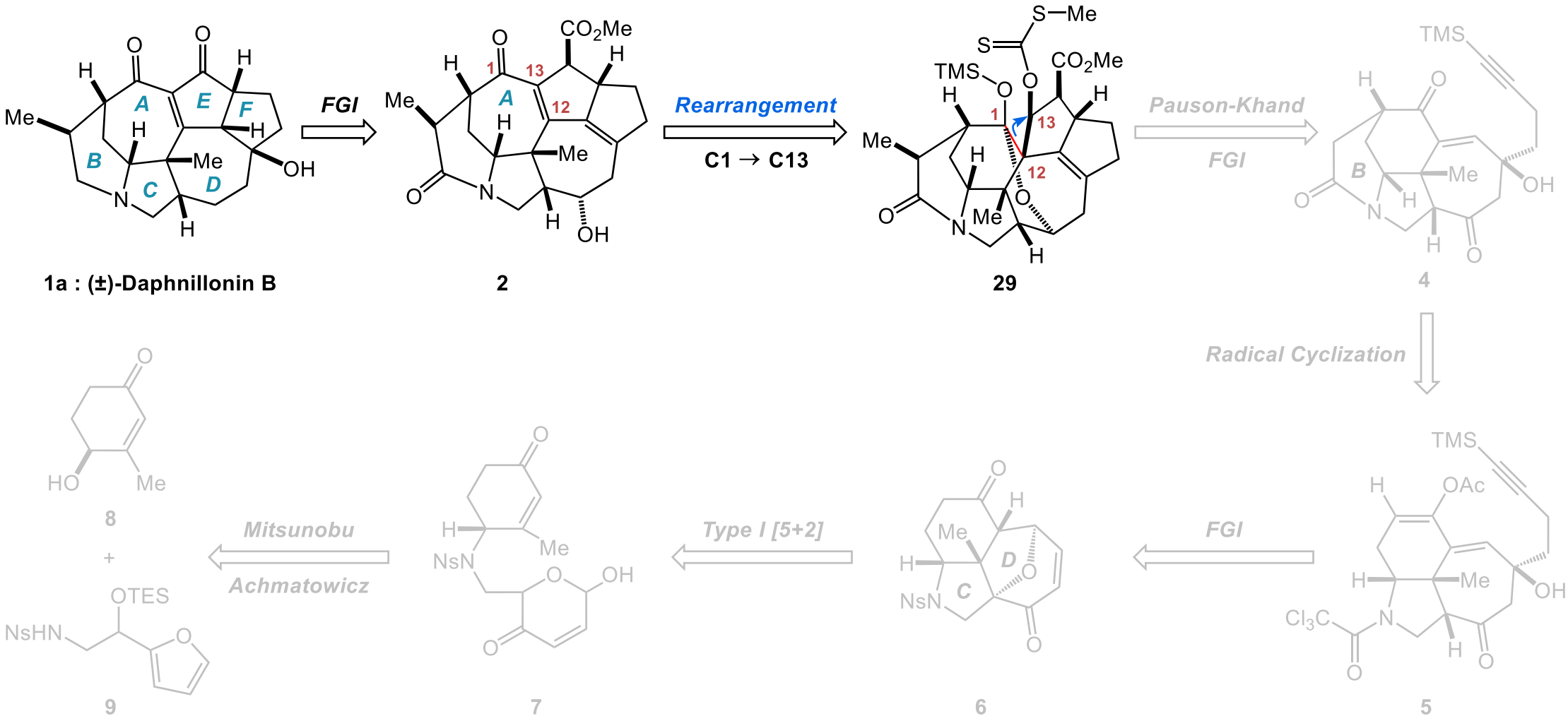


Synthesis of Compound 29

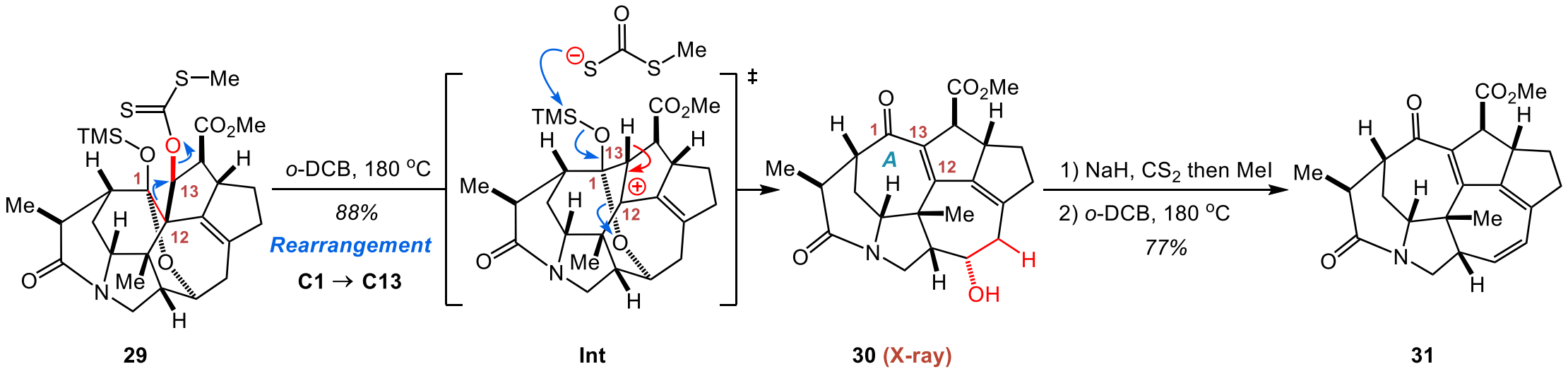


27 **28** **29**

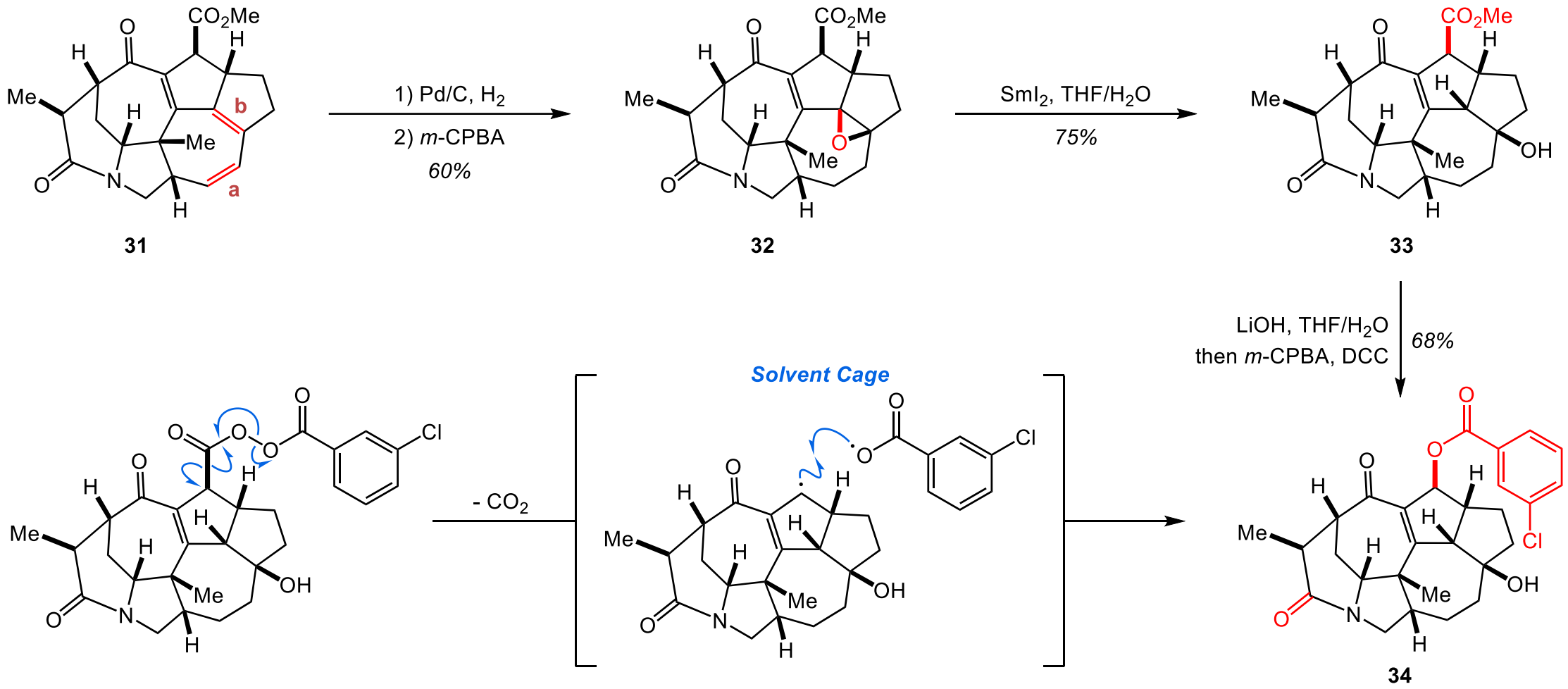
Retrosynthetic Analysis



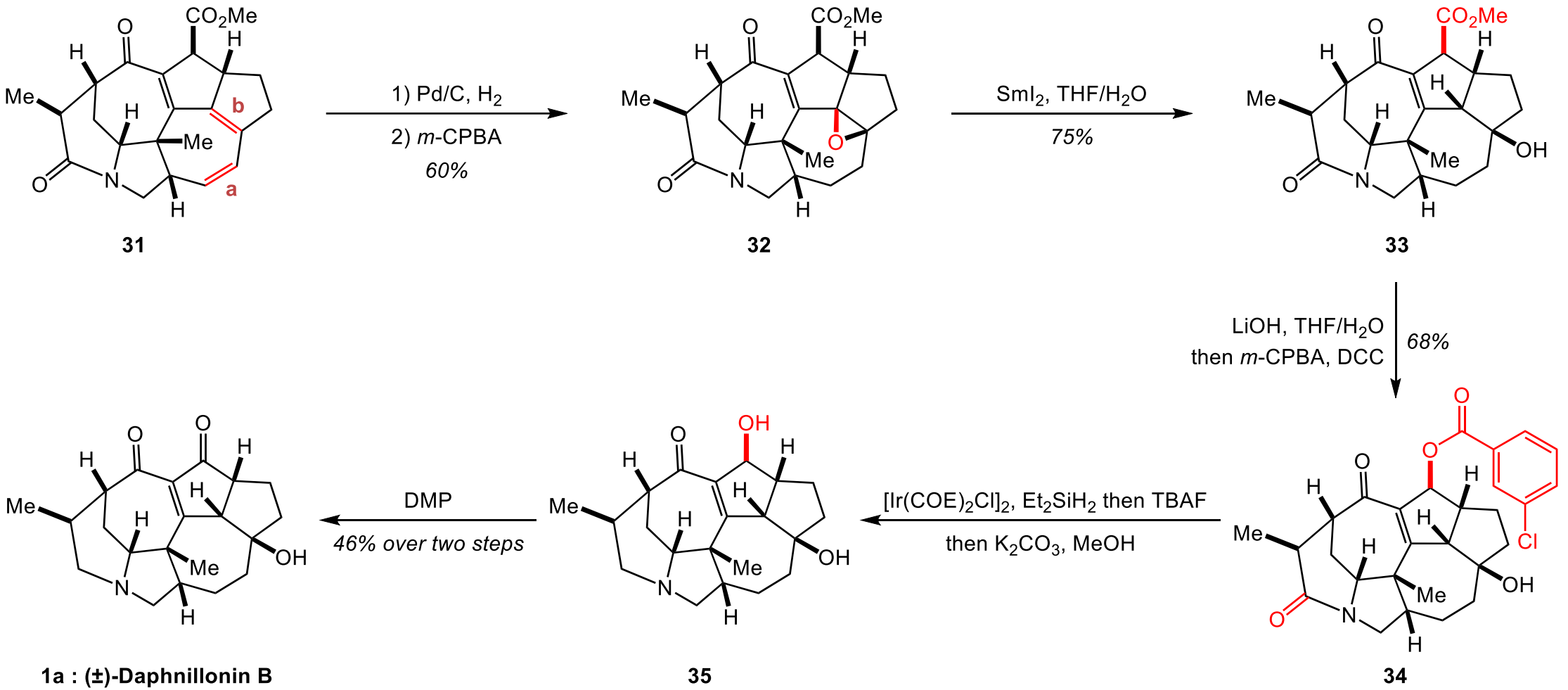
Synthesis of Compound 31



Synthesis of (±)-Daphnillonin B



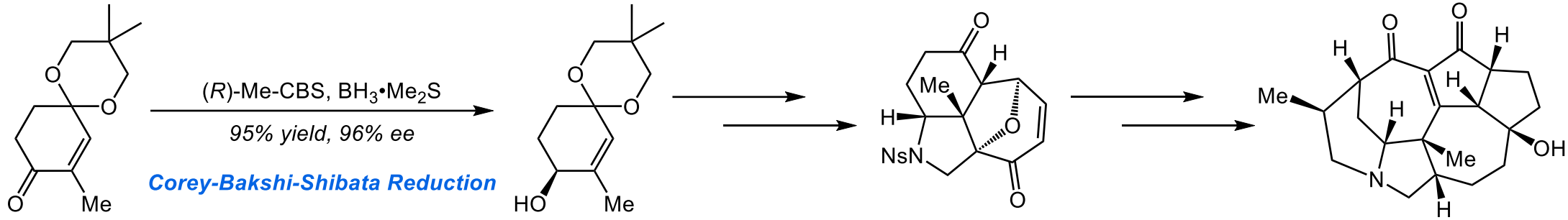
Synthesis of (±)-Daphnillonin B



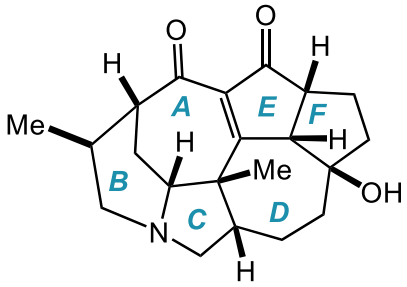
31 **32** **33** **34** **35**

1a : (±)-Daphnillonin B

Synthesis of (−)-Daphnillonin B

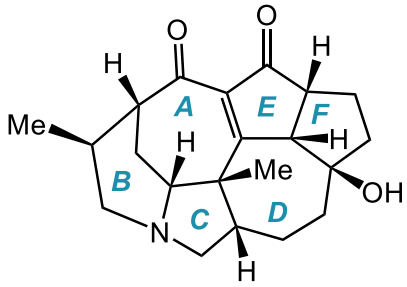


Summary



(±)-Daphnillonin B

28 steps
0.05% overall yield



(-)-Daphnillonin B

28 steps
0.11% overall yield

- C1 → C13 Rearrangment (A ring);
- Type I [5+2] Reation (C/D rings);
- Corey-Bakshi-Shibata Asymmetric Reduction.
- Radical Cyclization (B ring);
- Pauson-Khand Reation (E/F rings);

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Writing Strategy

Introduction

Source and Physiological Activity

- Daphniphyllum alkaloids (>13 subfamilies, >300 members), which have complex and diverse structures and interesting biological activities, have attracted considerable attention from the chemical synthesis community.

Examples of Synthesis

- Following Heath-cock's ground-breaking work, the groups of Carreira, A. Li, Smith, Fukuyama, Hanessian, Dixon, Zhai, Qiu, Xu, Gao, Sarpong, C. Li, and Lu have accomplished the outstanding total syntheses of several Daphniphyllum alkaloids.

Structural Features

- Remarkably, most of the polycyclic Daphniphyllum alkaloids synthesized previously have a [6-7] fused carbocyclic core.

Writing Strategy

Last paragraph

Summary

- In summary, we have achieved the first total synthesis of (±)- and (−)-daphnillonin B with a longest linear sequence of 28 steps and an overall yield of 0.045%, from commercially available staring material (ocresol).

Committed Steps

- A mild [5+2] cycloaddition enabled diastereoselective and efficient synthesis of the C/D ring system. A radical cyclization allowed diastereoselective construction of a bridged B ring. A diastereoselective intramolecular Pauson−Khand reaction efficiently installed the fused E/F ring system.

Prospect

- This approach could be applied to synthesize other members of the calyciphylline A-type and daphnicyclidin-type subfamilies of alkaloids and their analogs, enabling further biological research. This work is ongoing and will be described subsequently.

Representative Examples

- Therefore, the total synthesis of **1** poses a daunting challenge. (adj. 使人畏惧的，使人气馁的)

- As part of our continuing efforts toward the total syntheses of biologically active natural products, including yuzurine-type Daphniphyllum alkaloids, we herein describe the first total synthesis of (±)- and (−)-Daphnillonin B. (引出目的)

- This Pauson−Khand reaction is challenging for two reasons: the unfavorable steric hindrance of the two fully substituted carbon centers (C5 and C10) next to the electron-poor trisubstituted double bond (C8 and C9) in **4**. (阐述挑战)

Acknowledgement

Thanks for your attention