

Literature Report 1

Total Synthesis of (-)-Principinol C and (+)-Principinol E

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Checker: Li-Xia Liu

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Ma, T.; Cheng, H.; Pitchakuntla, M.; Ma, W.; Jia, Y. *J. Am. Chem. Soc.* **2022**, *144*, 20196
Kong, L.; Yu, H.; Deng, M.; Wu, F.; Jiang, Z.; Luo, T. *J. Am. Chem. Soc.* **2022**, *144*, 5268

CV of Prof. Dr. Yanxing Jia



Background:

- **1993-1997** B.S., Lanzhou University
- **1997-2002** Ph.D., Lanzhou University
- **2002-2007** Postdoctoral, French National Centre for Scientific Research
- **2007-2011** Associate Professor, Peking University
- **2011-now** Professor, Peking University

Research:

- ✓ **Total synthesis of biological activity natural products.**
- ✓ **Drug synthesis and structure-activity relationship studies.**
- ✓ **Research on new methods and strategies for organic synthesis.**

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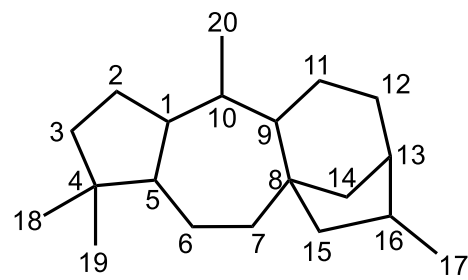
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2 Synthesis of (-)-Principinol C

3 Synthesis of (+)-Principinol E

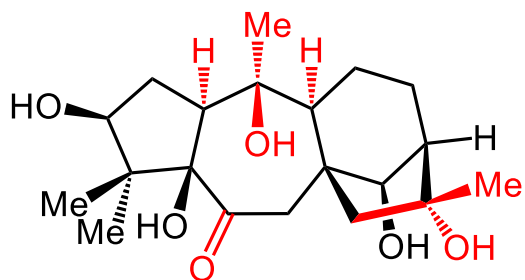
4 Summary

Introduction

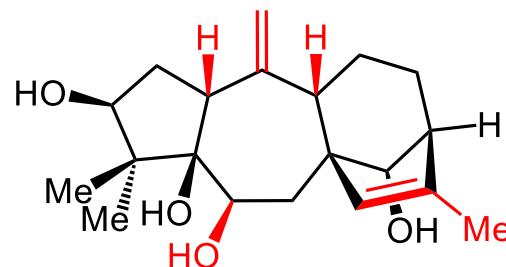


Grayanane

- ◆ Analgesic and sedative activities
- ◆ Inhibitory effect of PTP1B phosphatase
- ◆ Sodium channel modulating



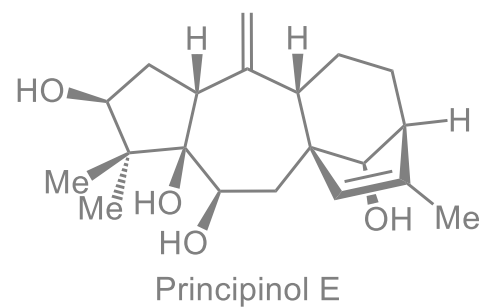
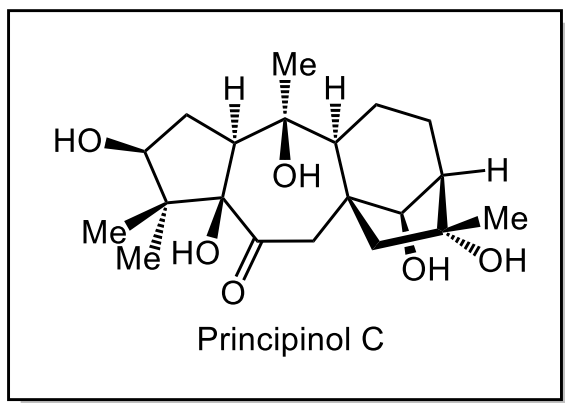
Principinol C



Principinol E

Liu, C.-C.; Hou, A.-J. *Tetrahedron Lett.* **2014**, *70*, 4317; Li, C.-H.; Gao, J.-M. *Eur. J. Med. Chem.* **2019**, *166*, 400

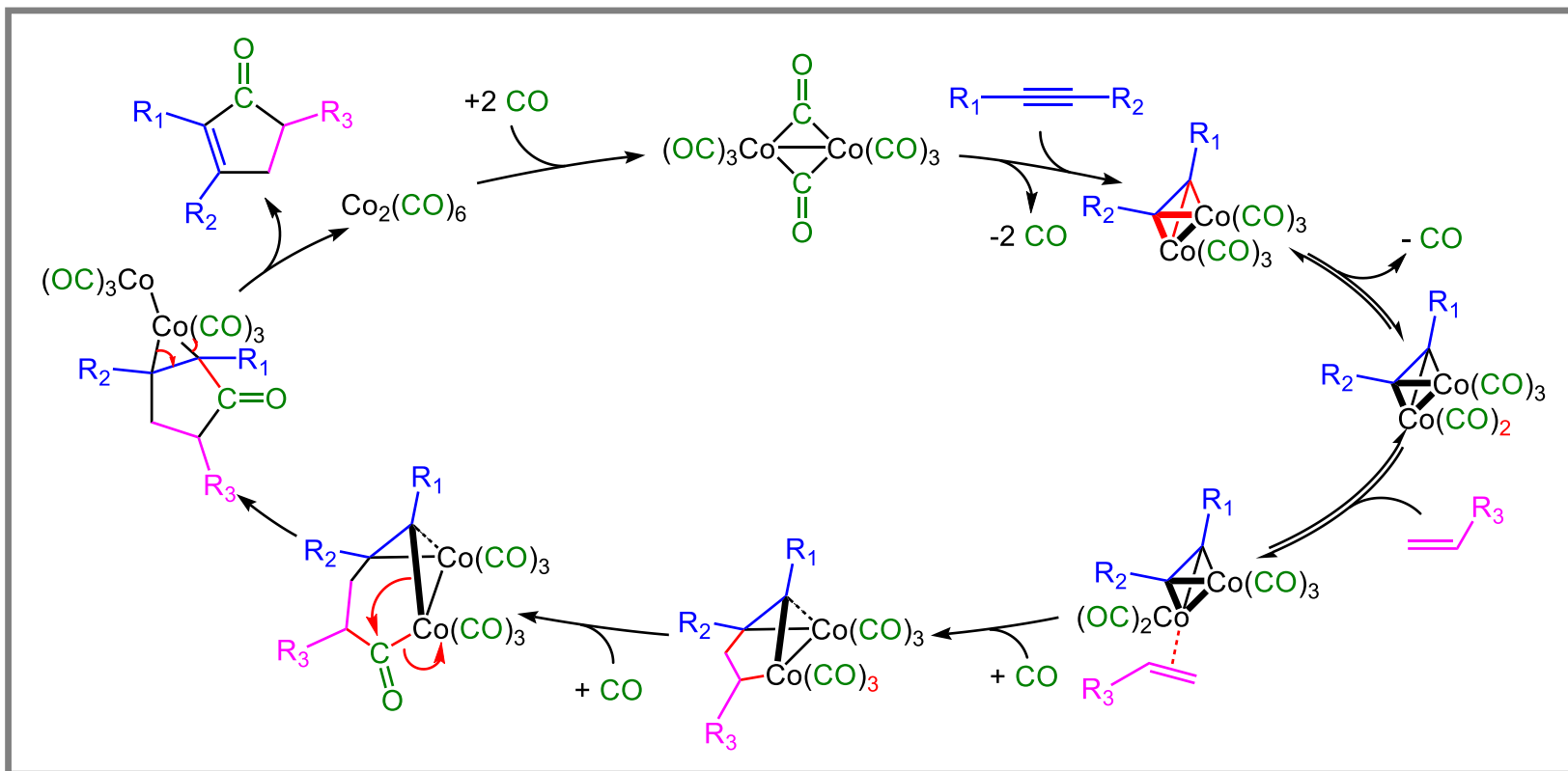
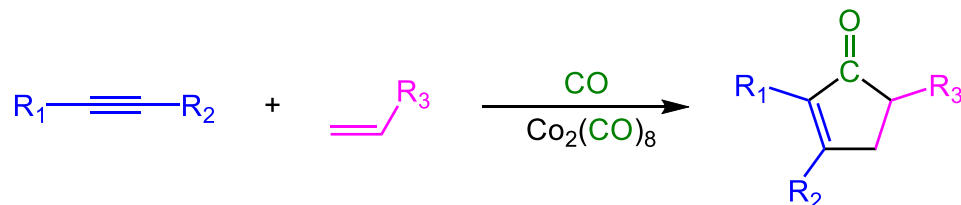
Synthesis of (-)-Principinol C



Jia, Y.

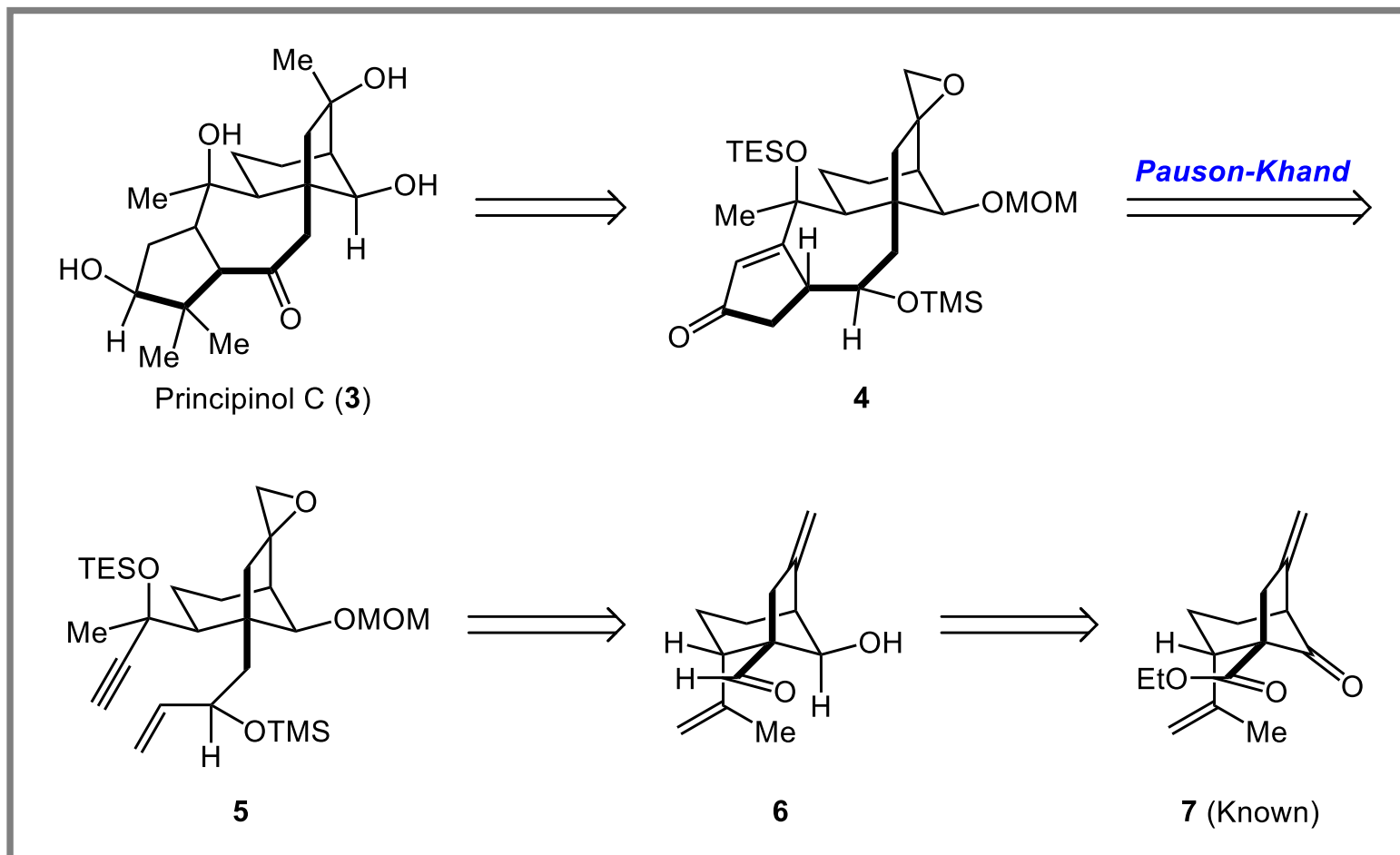
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Pauson-Khand Reaction

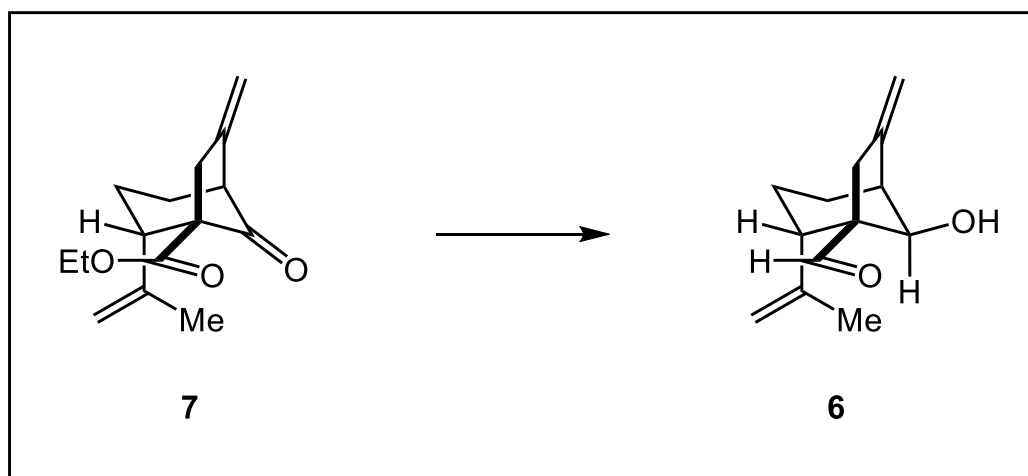


Magnus, P. *Tetrahedron* **1985**, *41*, 5861

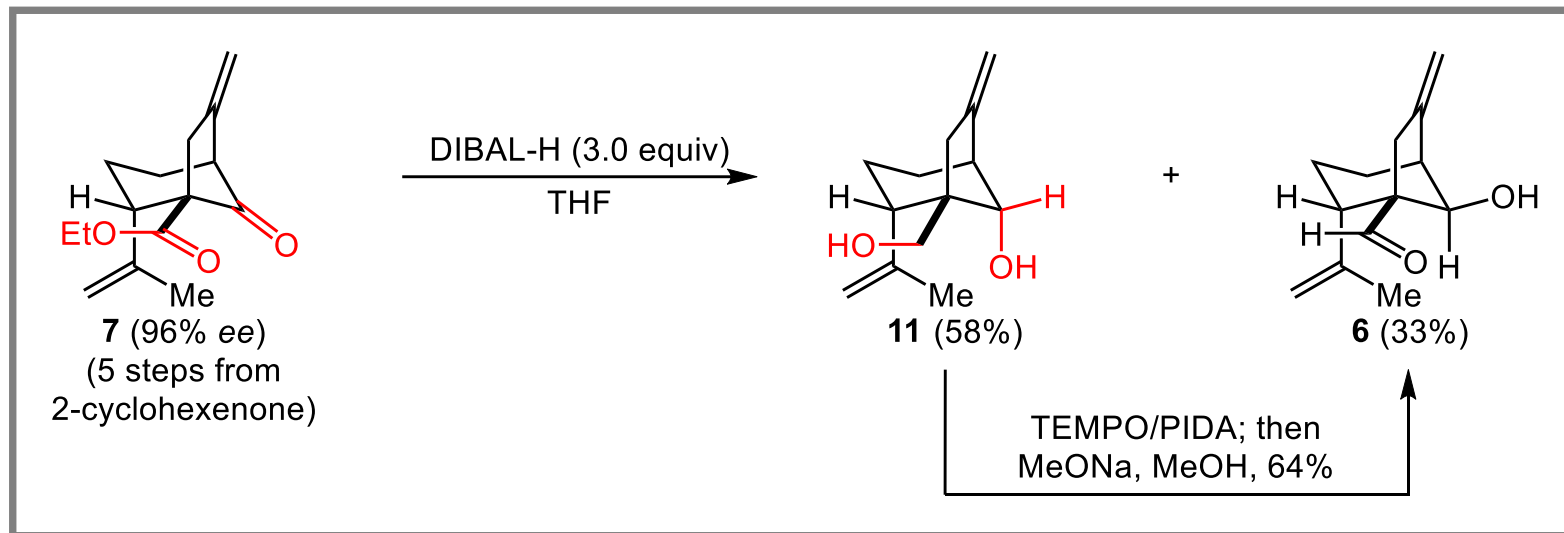
Retrosynthetic Analysis of (-)-Principinol C



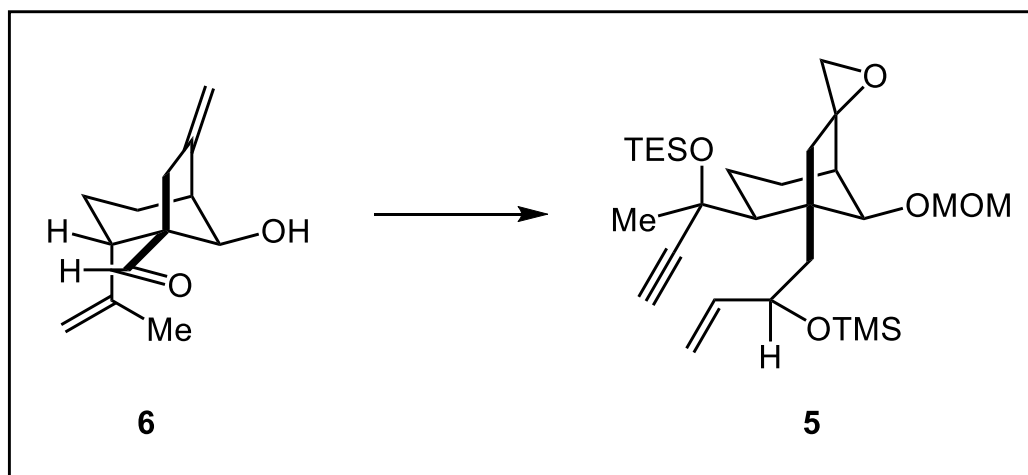
Synthesis of Compound 6



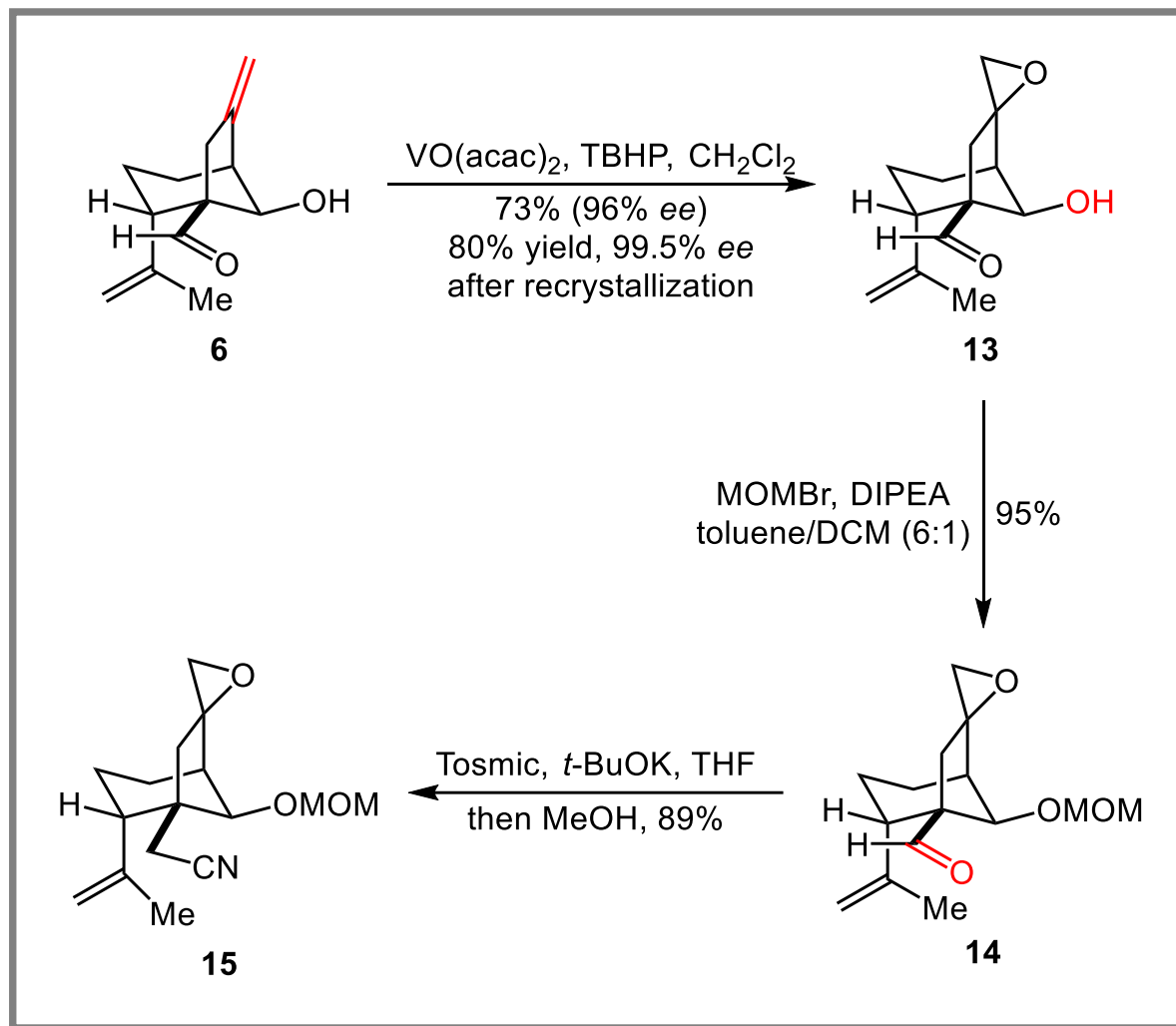
Synthesis of Compound 6



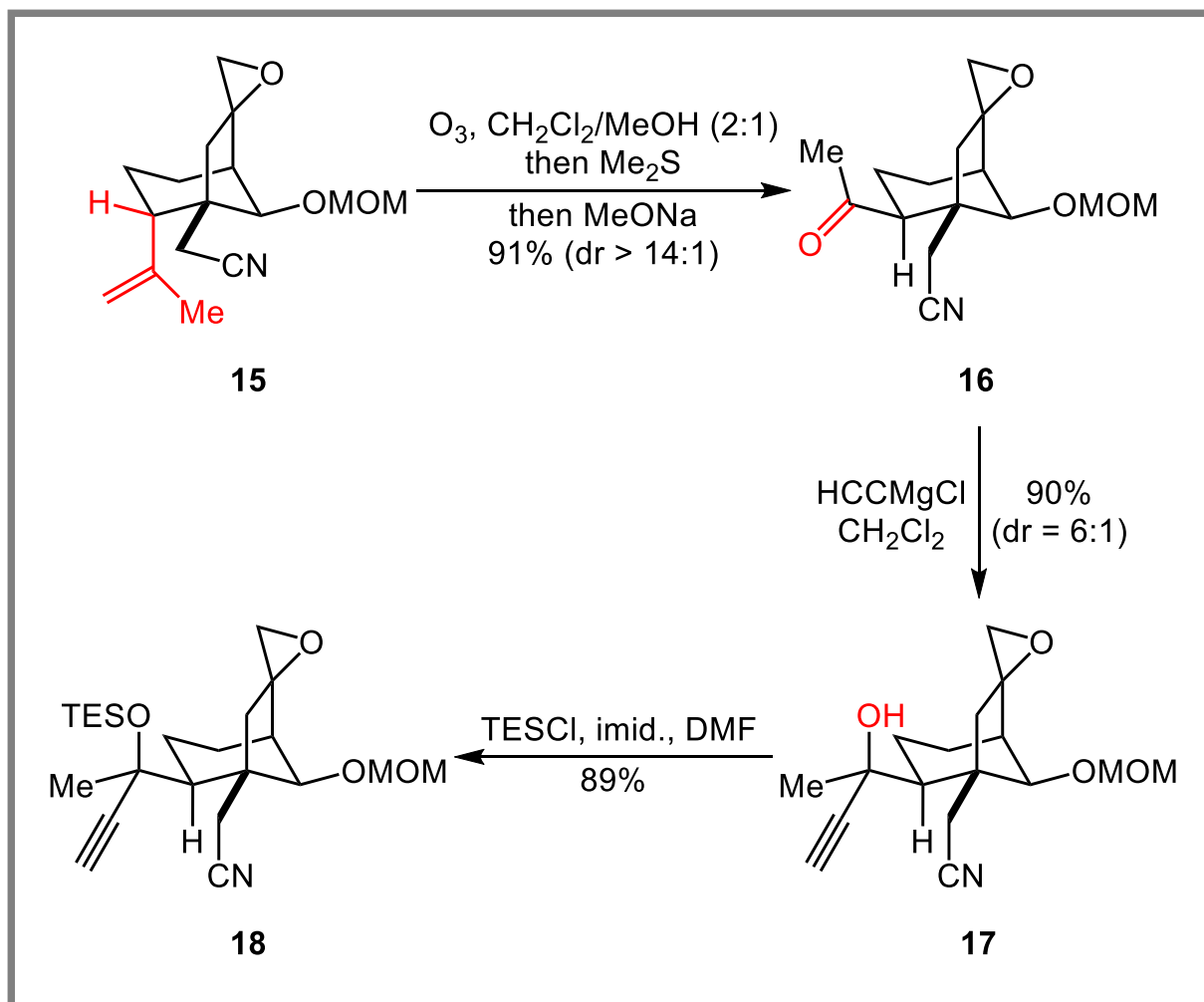
Synthesis of Key Intermediate 5



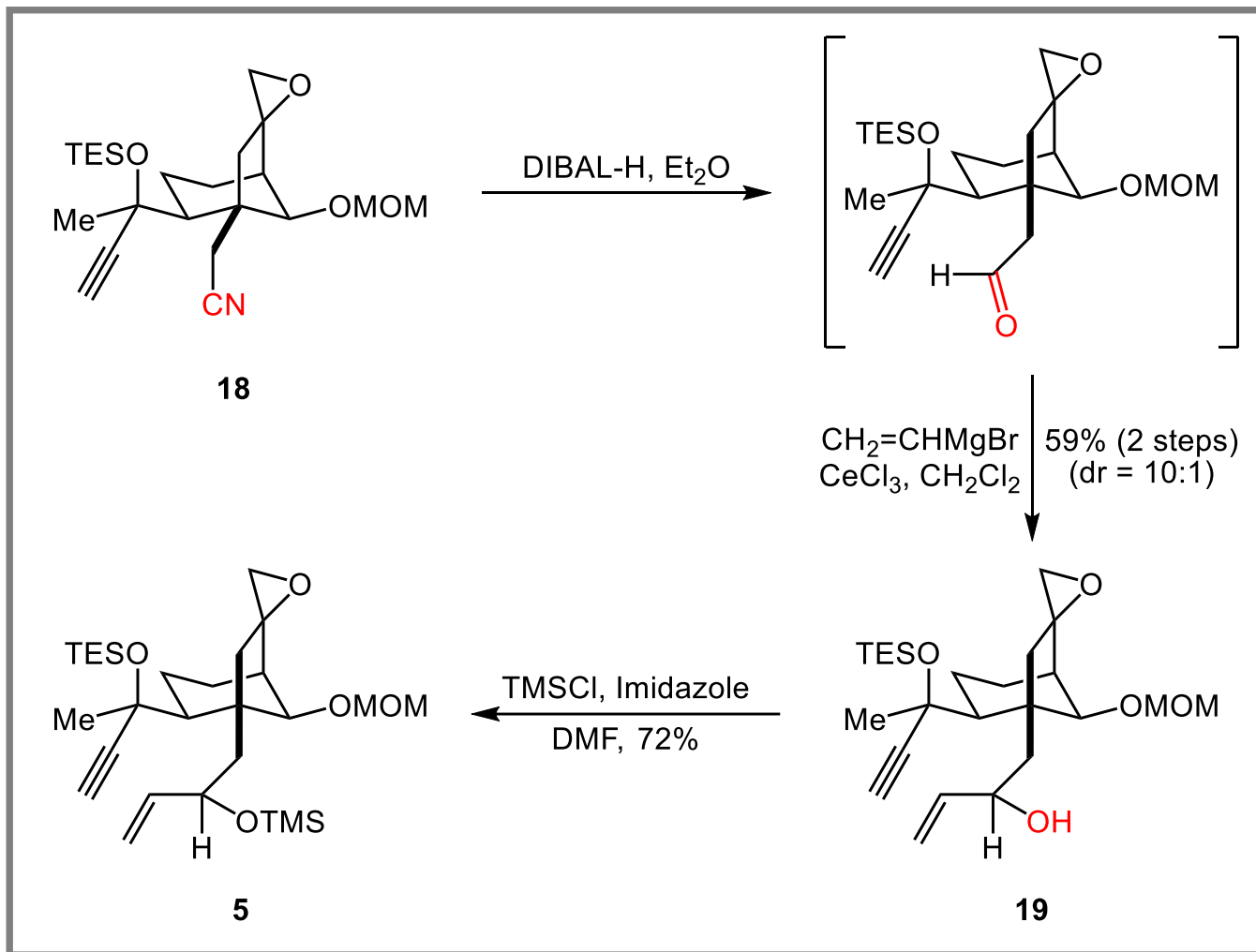
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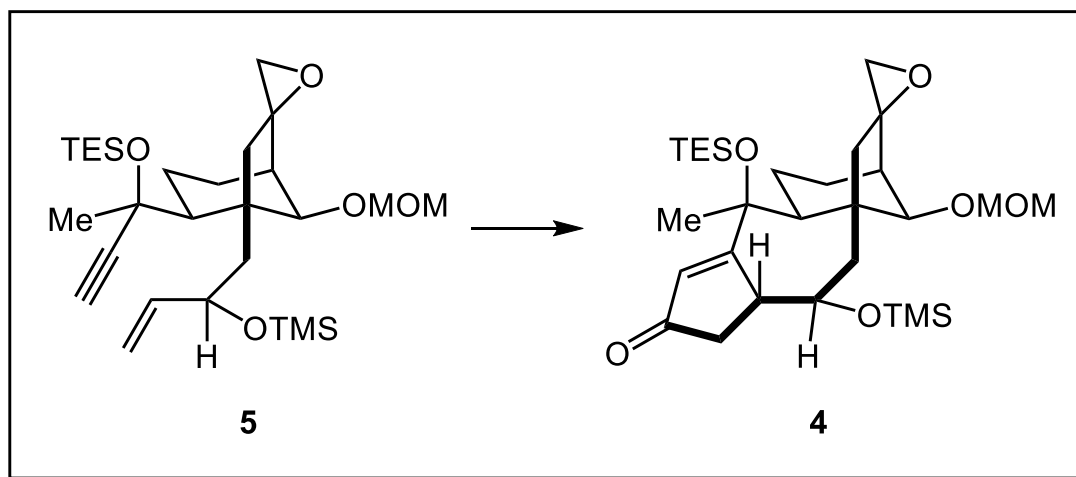
Synthesis of Key Intermediate 5



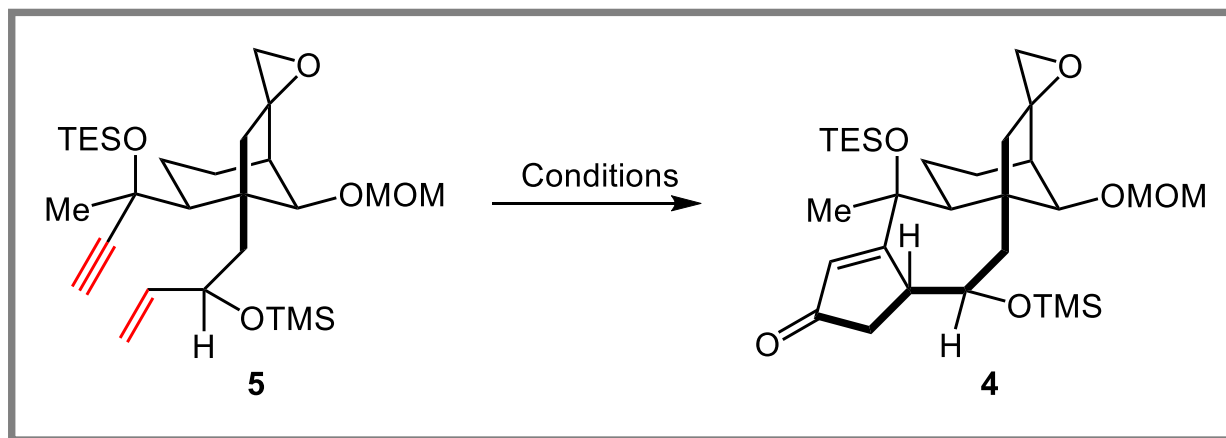
Synthesis of Key Intermediate 5



Synthesis of Compound 4

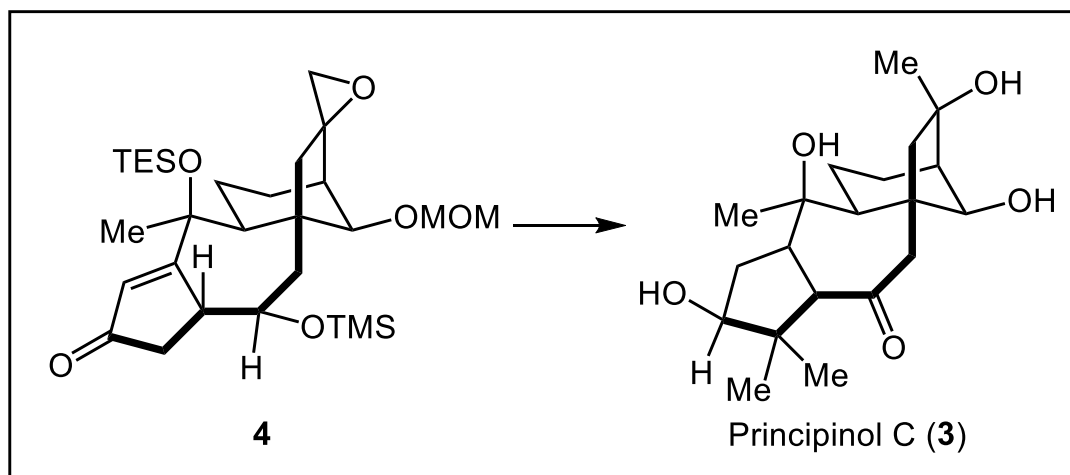


Optimization of the IMPK

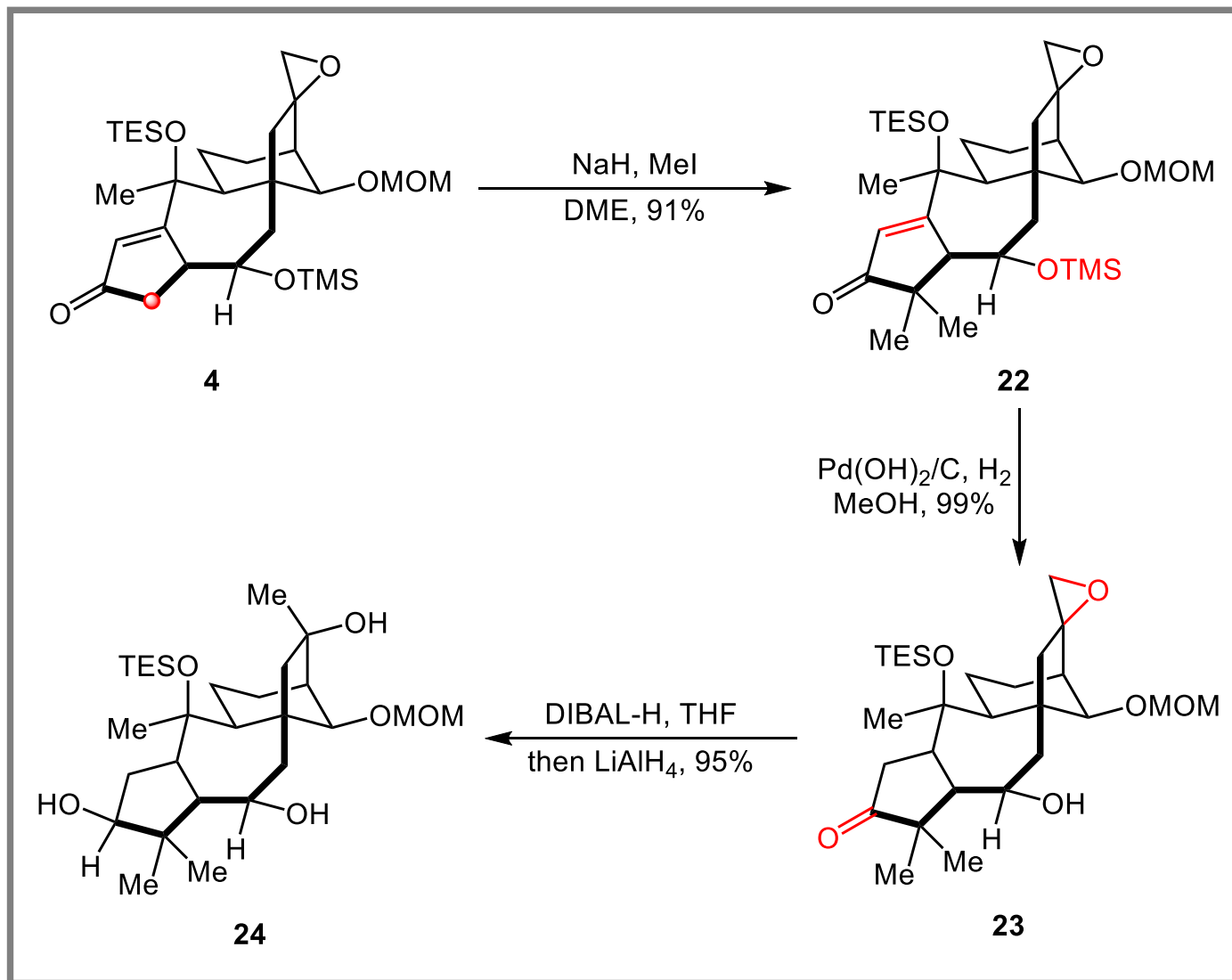


Entry	Conditions	Yield (%)
1	Co ₂ (CO) ₈ , toluene, 40 °C	<5
2	Co₂(CO)₈, toluene, 40 to 60 °C	45
3	Co ₂ (CO) ₈ , toluene, 40 to 110 °C	21
4	Co ₂ (CO) ₈ , THF, 40 to 60 °C	20
5	Co ₂ (CO) ₈ , toluene, 40 °C; then NMO, 60 °C	<5
6	Co ₂ (CO) ₈ , toluene, 40 °C; then TMTU, rt	<5
7	Co ₂ (CO) ₈ , toluene, 40 °C; then TMAO, rt	<5
8	Co ₂ (CO) ₈ , toluene, 40 °C; then DMSO, rt	<5
9	[RhCl(CO) ₂] ₂ (5 mol %), CO, toluene, 90 °C	<5

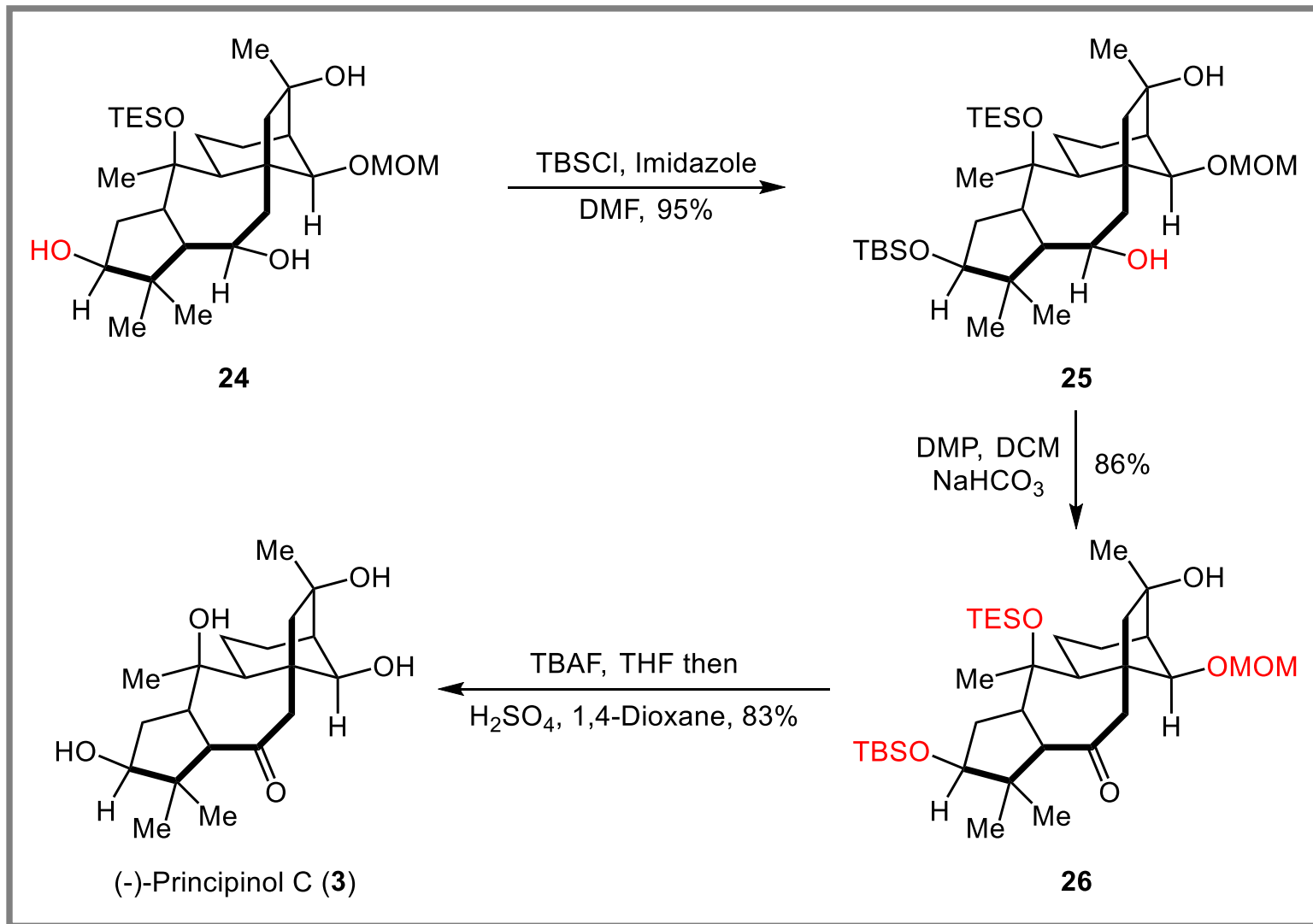
Synthesis of (-)-Principinol C



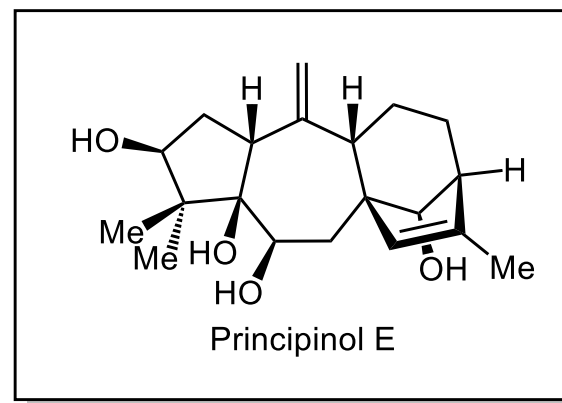
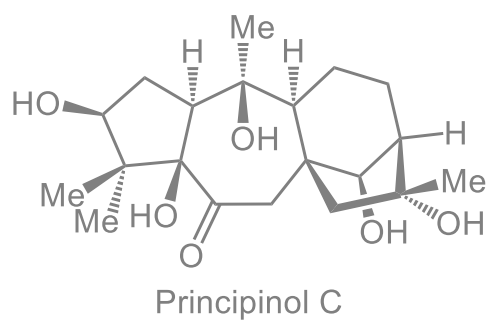
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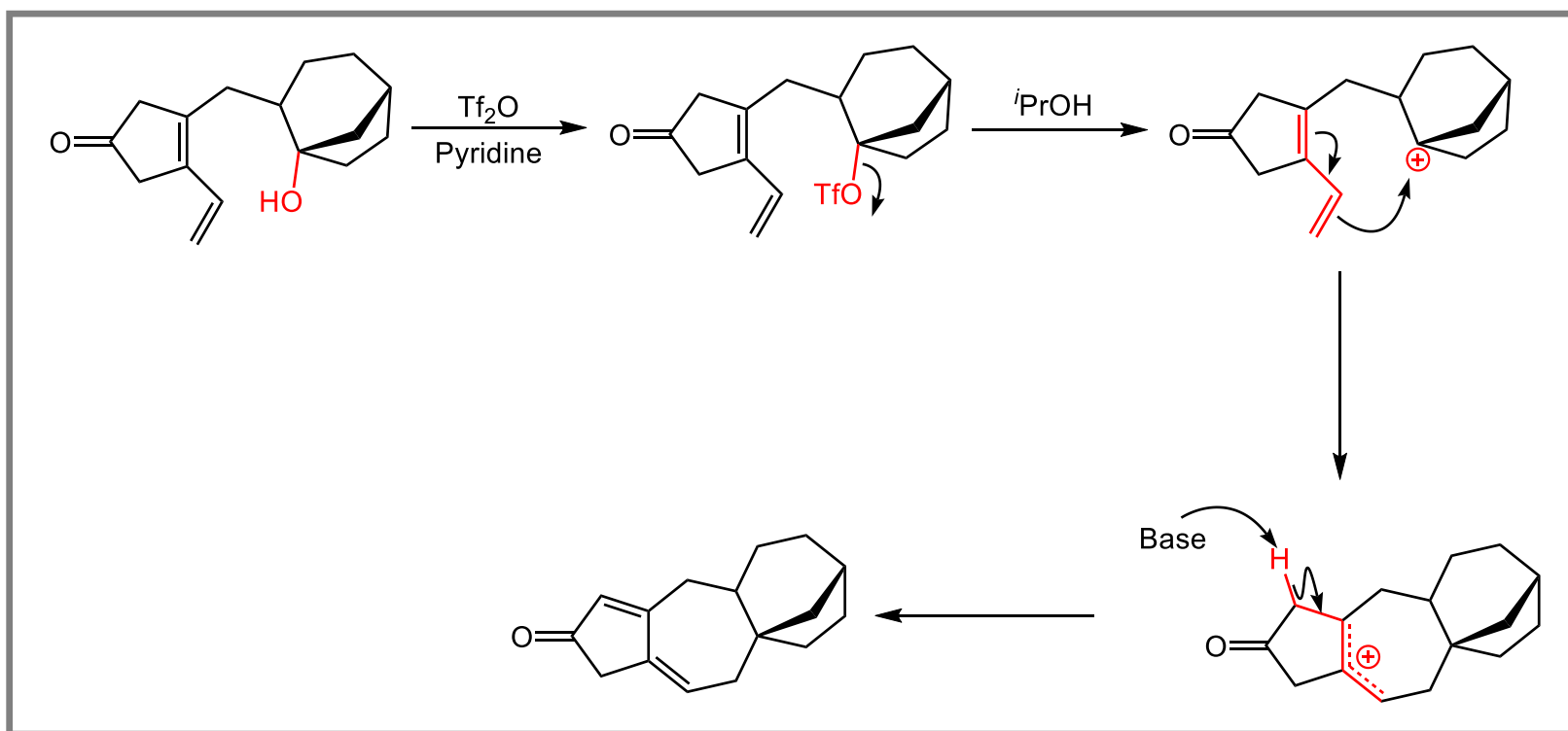
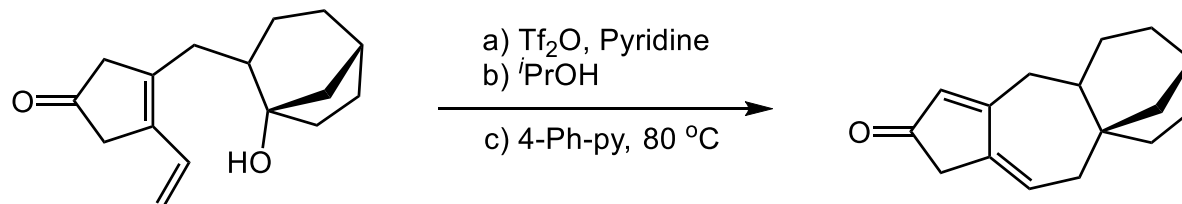


Synthesis of (+)-Principinol E

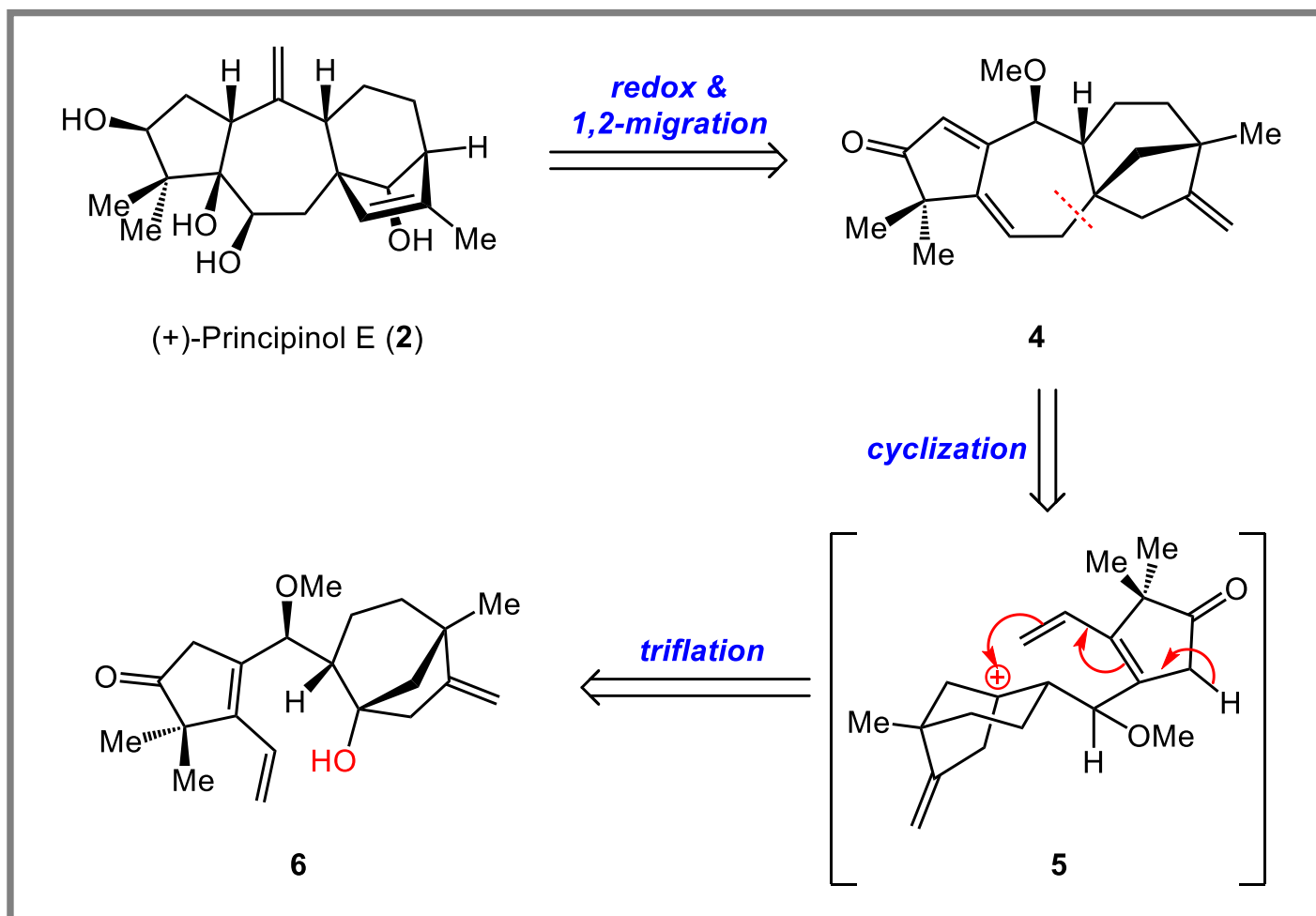


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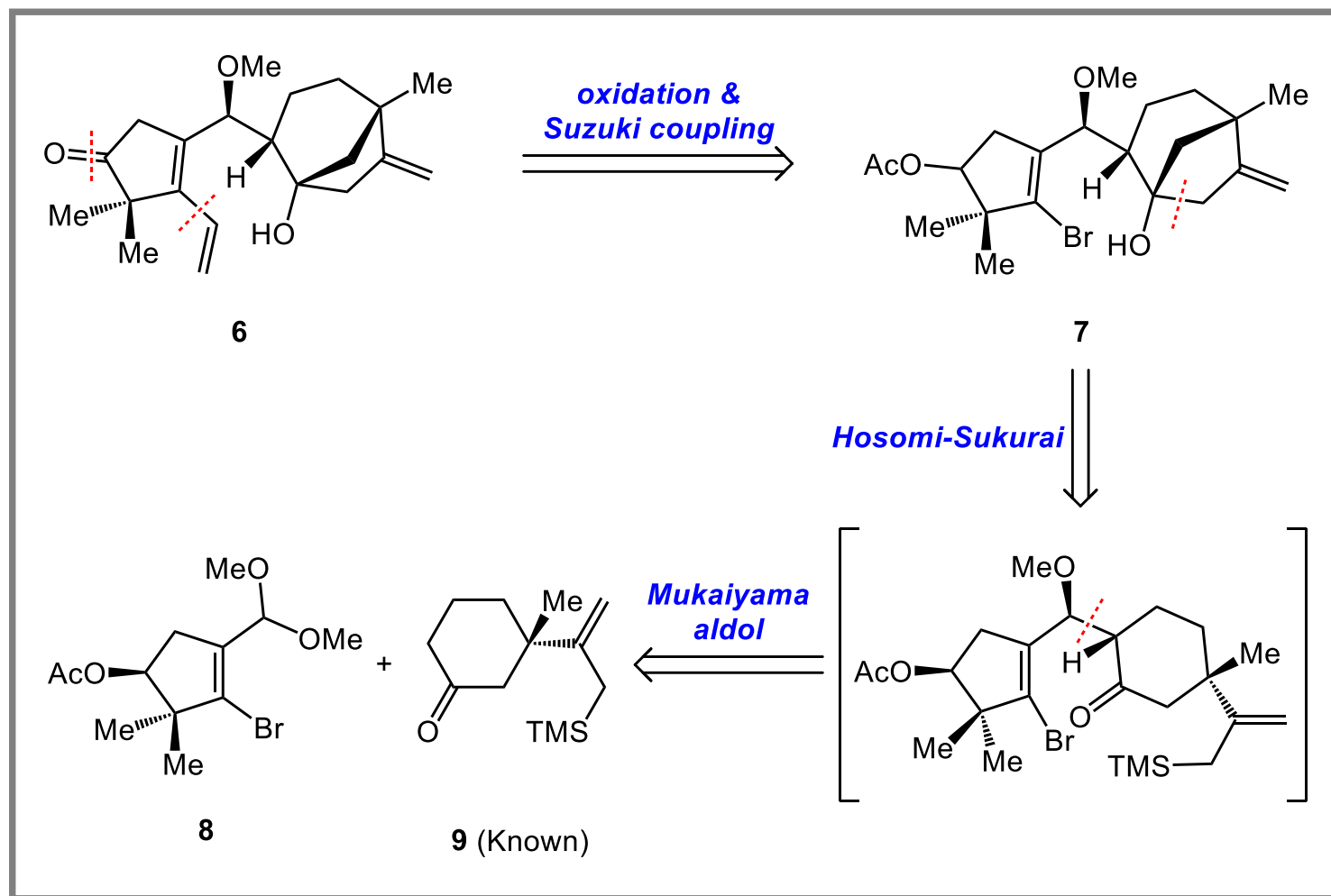
7-endo-trig Cyclization



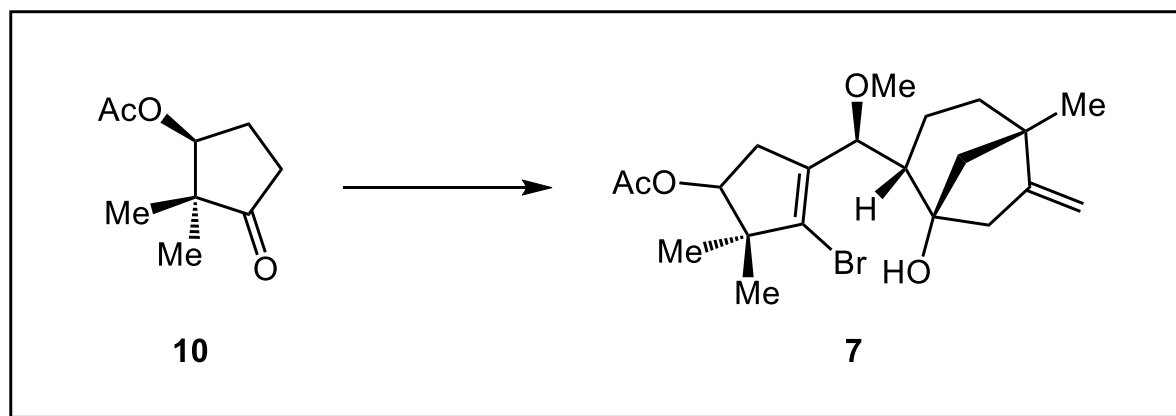
Retrosynthetic Analysis of (+)-Principinol E



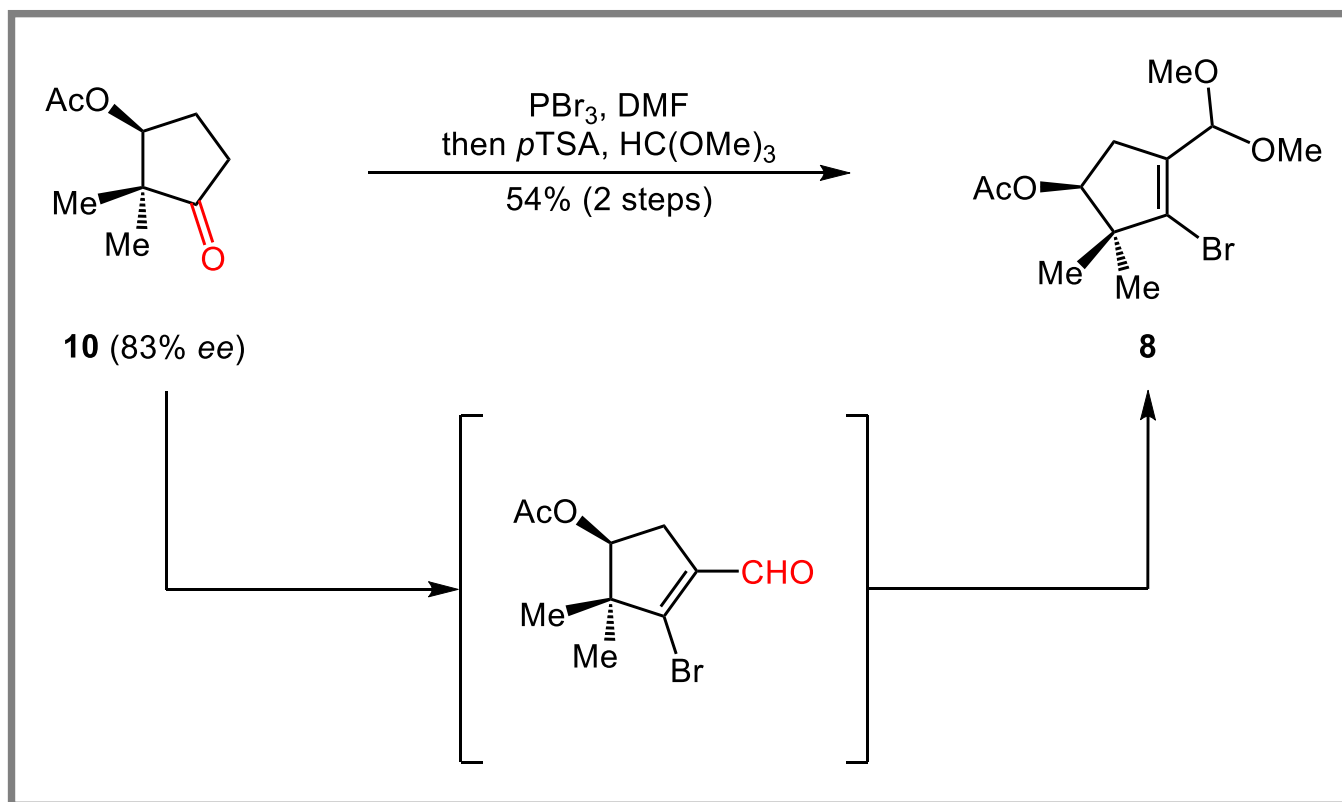
Retrosynthetic Analysis of (+)-Principinol E



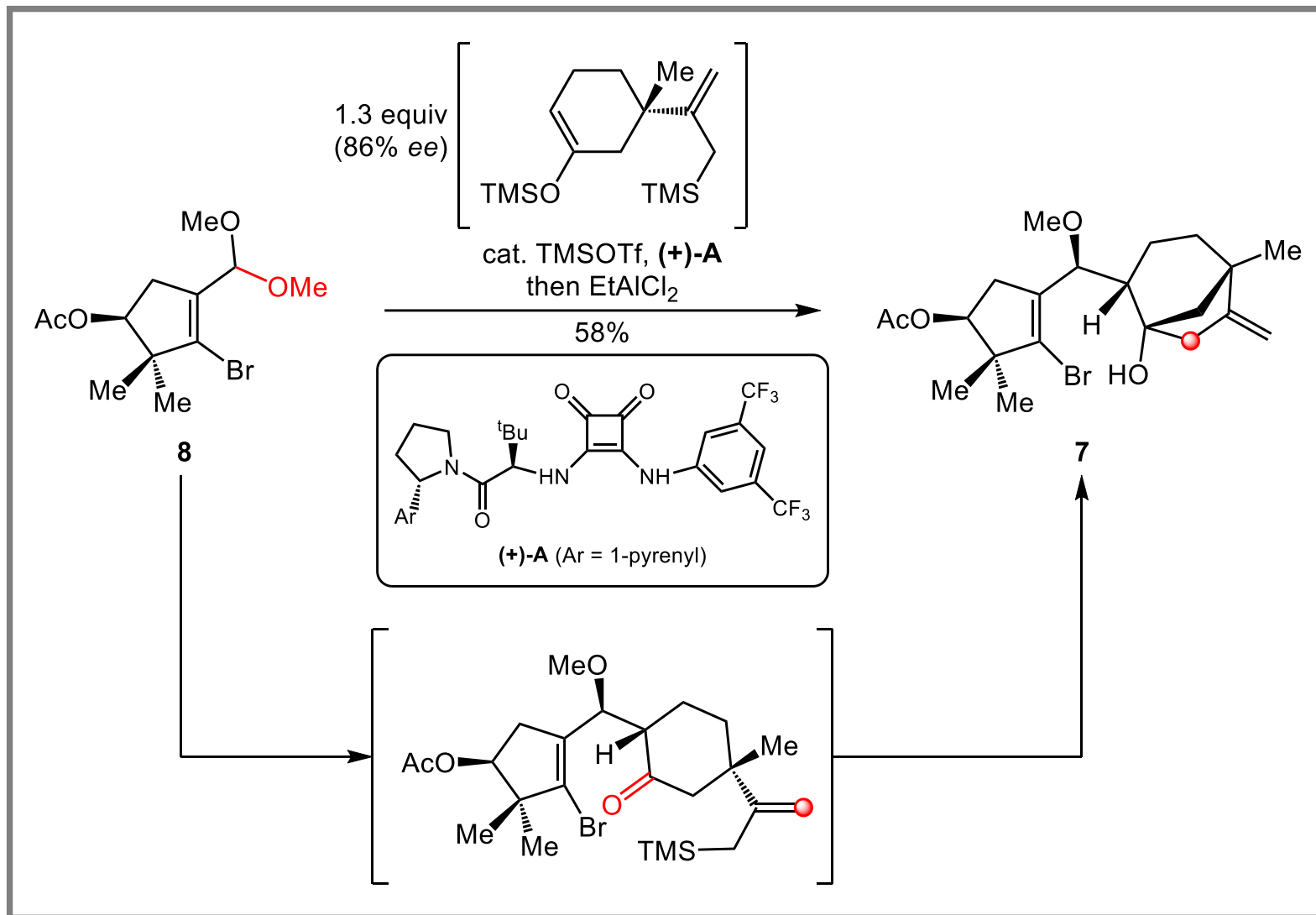
Synthesis of Compound 7



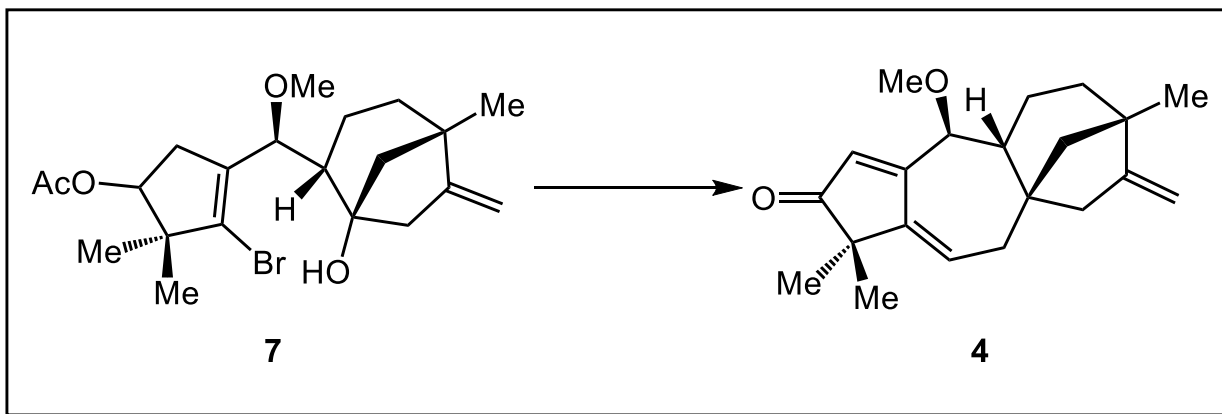
Synthesis of Compound 7



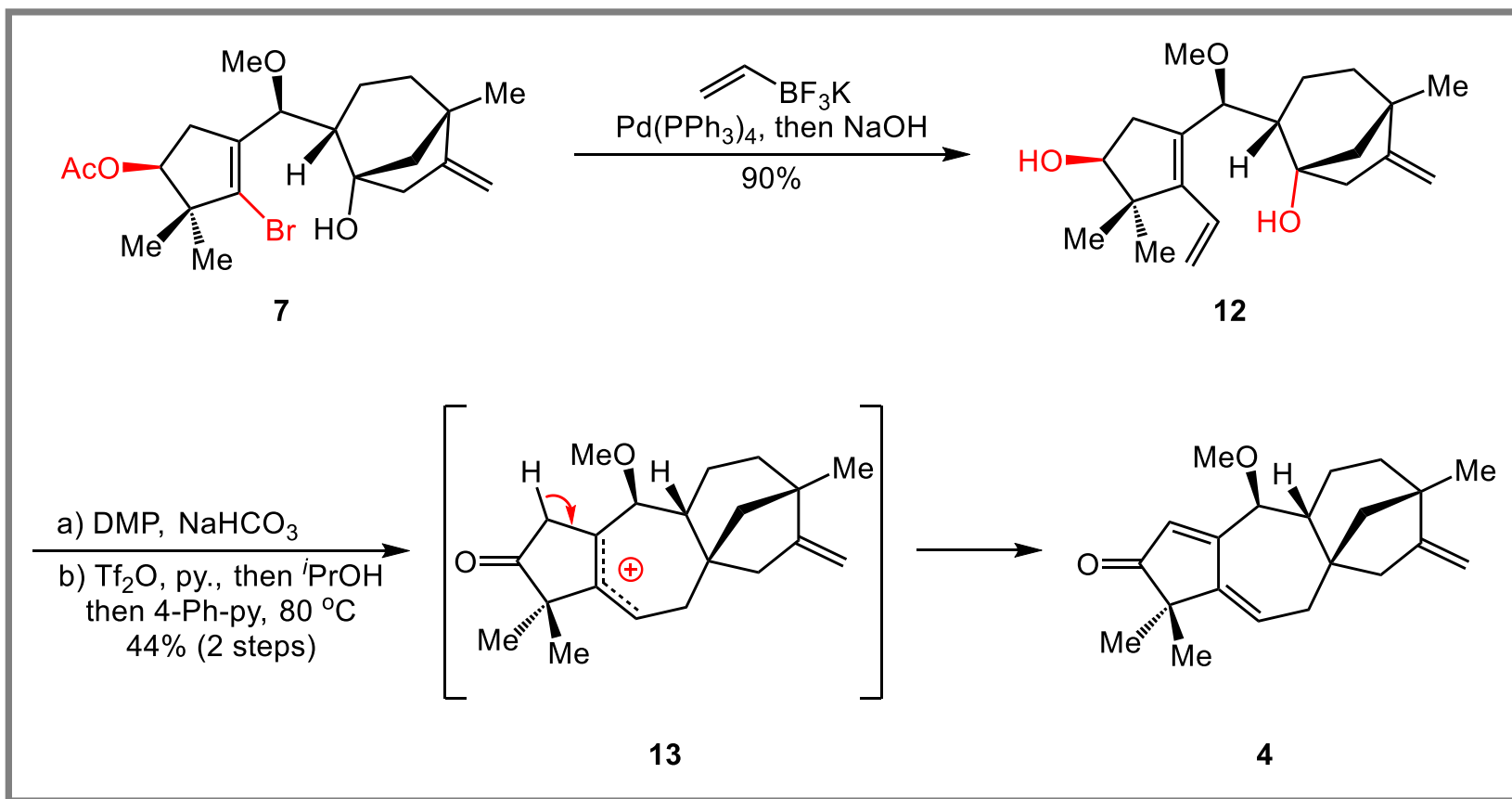
Synthesis of Compound 7



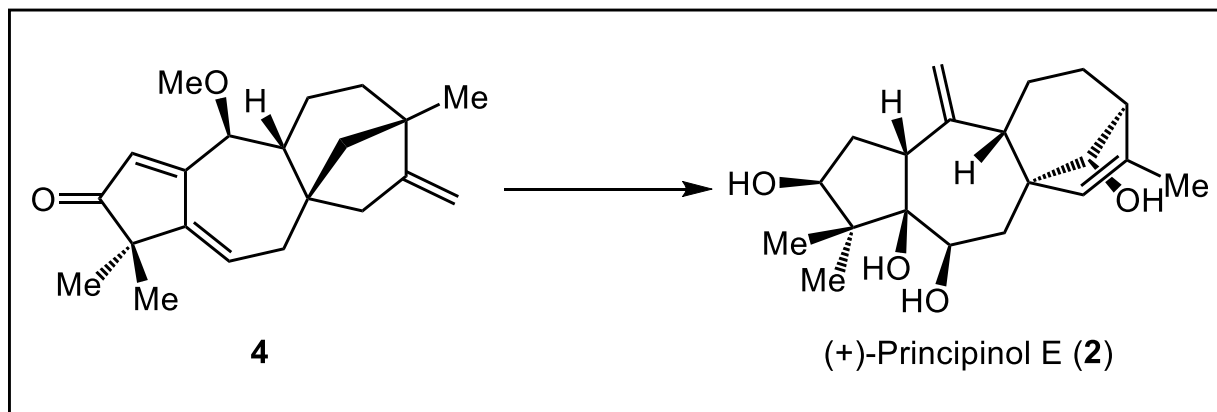
Synthesis of Compound 4



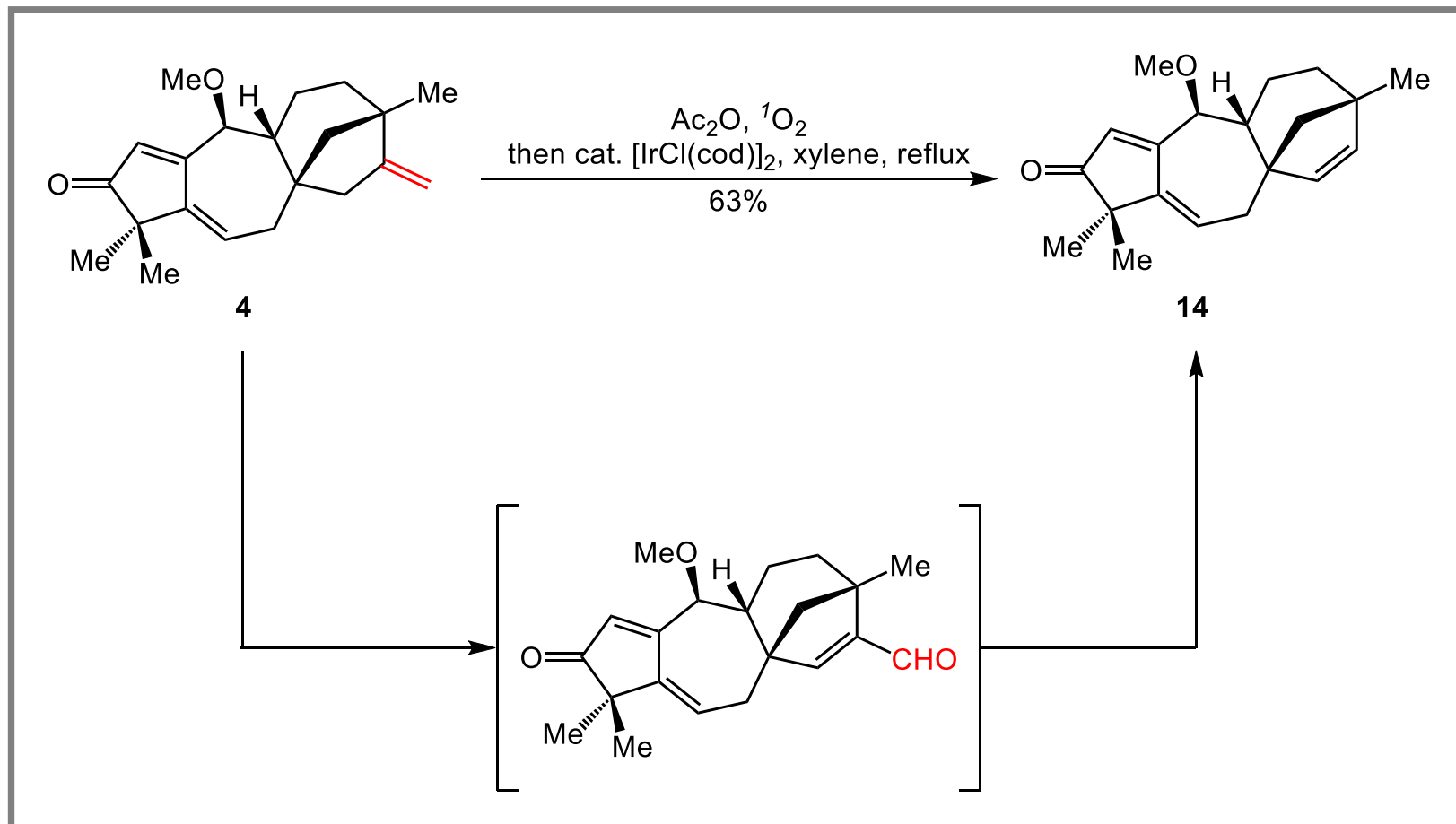
Synthesis of Compound 4



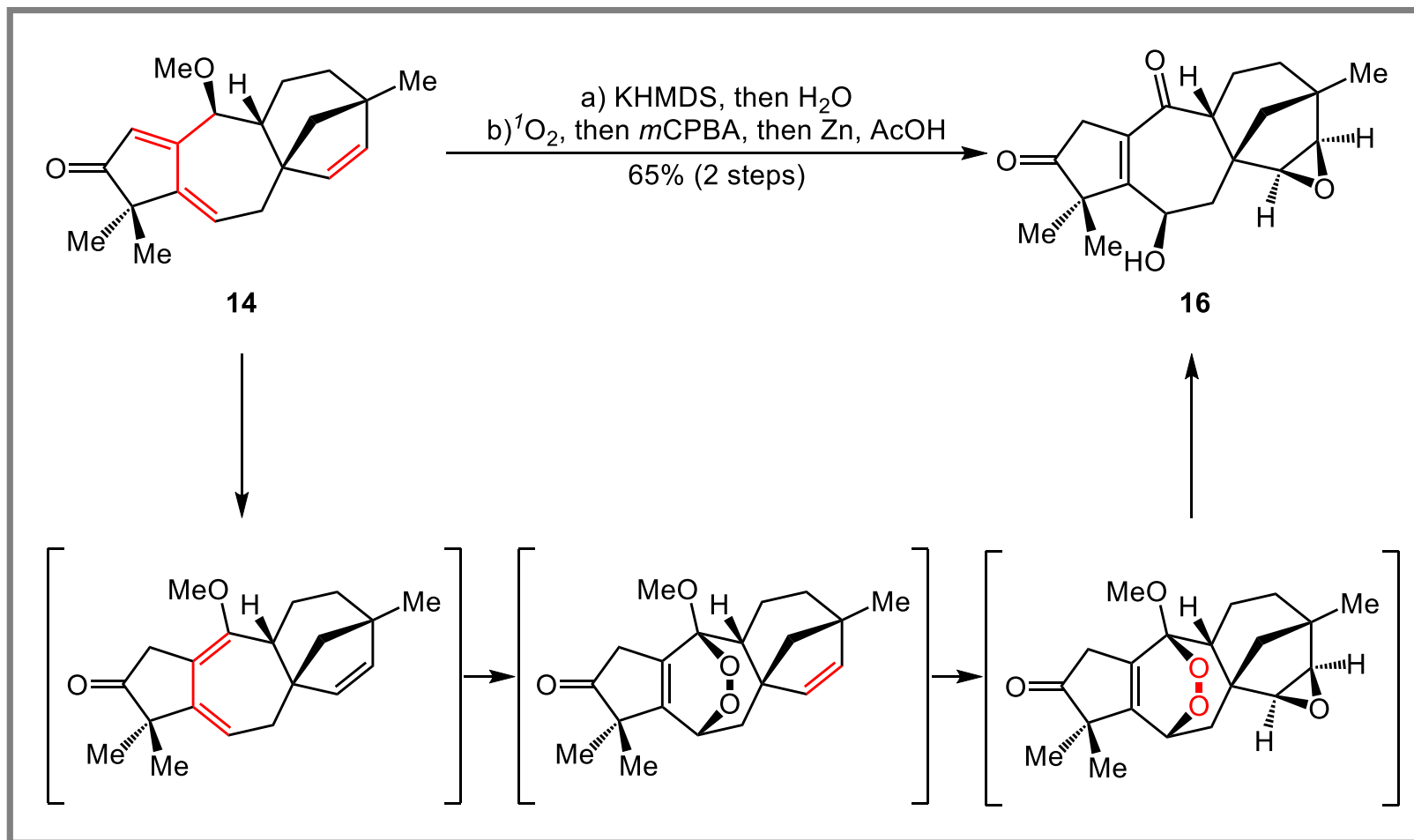
Synthesis of (+)-Principinol E



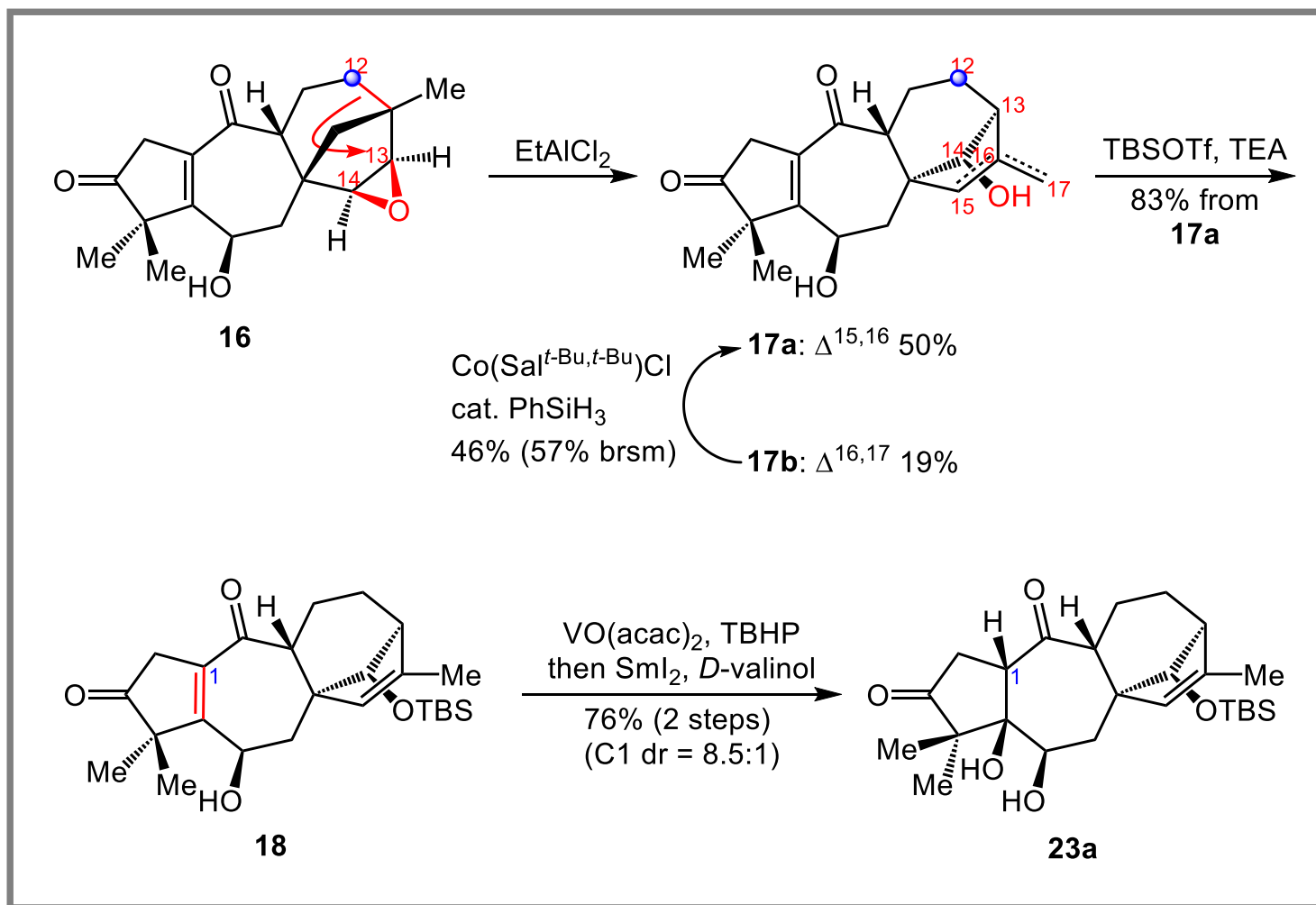
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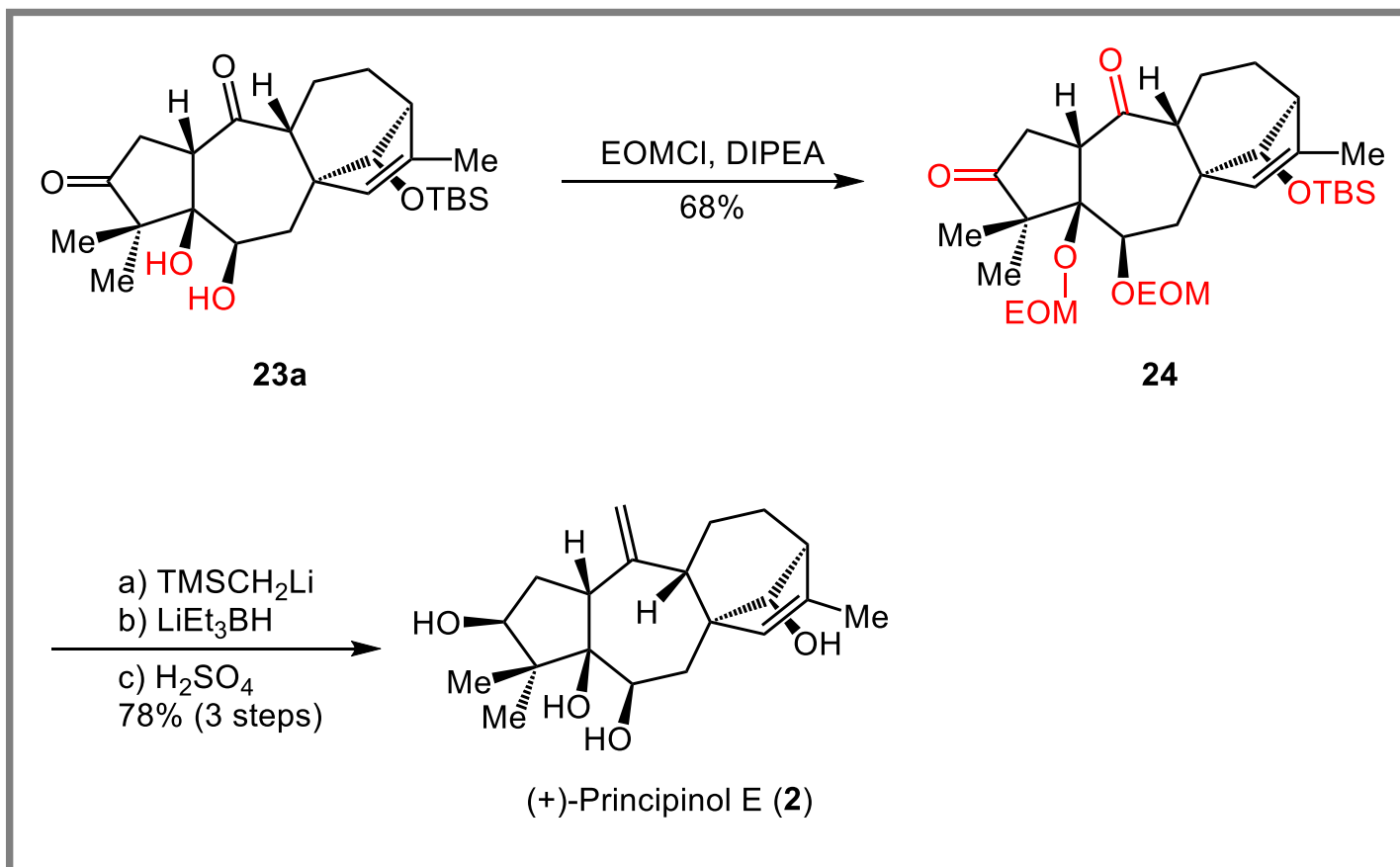
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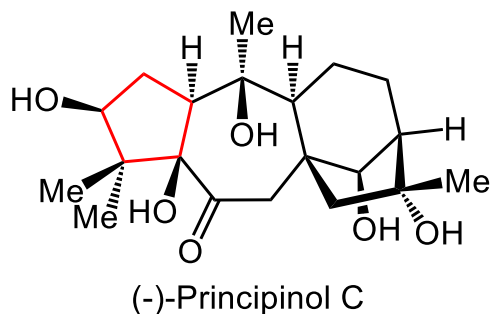
Synthesis of (+)-Principinol E



Synthesis of (+)-Principinol E

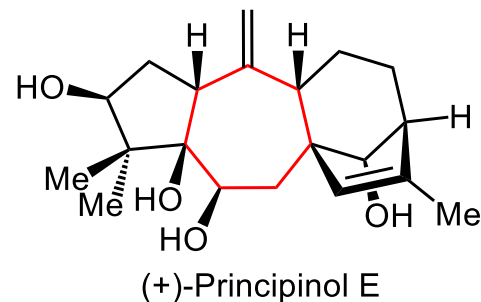


Summary



- ◆ Achieved the first total synthesis of Principinol C in 16 steps (2.8% overall yield)
- ◆ Applied IMPK of enyne in constructing the 7/5-bicyclic ring of the 5/7/6/5 tetracyclic skeleton

- ◆ Achieved the total synthesis of (+)-Principinol E in 17 steps (1.0% overall yield)
- ◆ Applied unique 7-endo-trig cyclization based on a bridgehead carbocation forged the 5/7/6/5 tetracyclic skeleton



The First Paragraph

写作思路

Grayanotoxin 的来源



Grayanane 的结构以及生理活性



合成 Grayanane 的研究进展

The First Paragraph

- ✓ Grayanotoxins such as grayanotoxin I and grayanotoxin II are the toxic constituents of the leaves of various Ericaceae species, and they have been the subject of numerous investigations for over a century.
- ✓ Some of them show interesting bioactivities, including sodium channel modulating, analgesic, and sedative activities and inhibitory effect of PTP1B phosphatase. Structurally, grayanane diterpenoids possess a unique 5/7/6/5 tetracyclic skeleton bearing polyhydroxyl groups and harboring 7–11 stereocenters.
- ✓ However, only eight total syntheses of grayanane diterpenoids have been accomplished, and the major breakthroughs were achieved after 2019.

The Last Paragraph

写作思路

总结工作：完成Principinol C的全合成



阐述亮点：通过IMPK构建关键7/5-二环结构



进行展望：合成其他Grayanane二萜类化合物

The Last Paragraph

- ✓ In summary, we have achieved the first total synthesis of (-)-principinol C in 16 steps (2.8% overall yield) from the known bicyclo[3.2.1]octane ring system 7 or in 21 steps (0.6% overall yield) from the 2-cyclohexenone.
- ✓ The central strategic step in the synthesis was an intramolecular Pauson–Khand reaction of enyne to construct the 7/5-bicyclic ring of the 5/7/6/5 tetracyclic skeleton. This is the first application of IMPK of enyne in constructing the 7,5-bicyclic ring system in natural product synthesis.
- ✓ The present strategy could also be applied to the synthesis of other grayanane diterpenoids.

Representative Examples

To date, more than 200 grayanane diterpenoids have been isolated and identified from the Ericaceae plants. (迄今为止, 可替换 so far)

In sharp contrast, a 7,5-bicyclic ring system has not been easily realized from the corresponding enyne derivatives, except for a few specific enynes that have an aromatic ring as a template. (形成鲜明对比)

Reduction of **22** with Pd(OH)₂/C and H₂, accompanied with the simultaneous removal of TMS, gave ketone **23** in 99% yield. (同时)

Acknowledgement

Thanks for your attention