

Total Synthesis of Maoecrystal V

Reporter: **Wang Zhen**

Supervisor: **Prof. Motomu Kanai**

Yoichiro Kuninobu, Ph.D.

2013.09.28

■ Background

- Isolation of maoecrystal V
- Structural features and biological activity of maoecrystal V

■ Synthetic studies

- Nicolaou's model studies toward maoecrystal V
- Baran's model studies toward maoecrystal V
- Several other total synthesis of maoecrystal V

■ Conclusion

Brief introduction of prof. Sun Han-Dong(孙汉董)



1958–1962 B.S., Yunnan university

1980 –1982 Tokushima University(德岛大学,研修)

1988 Ph.D., Kyoto University, Japan(京都大学)

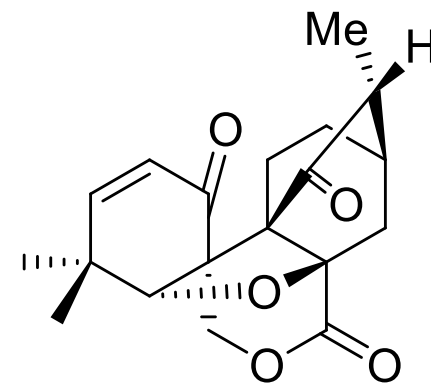
1983–1989 Kunming Institute of Botany, associate professor

1989 Kunming Institute of Botany, professor

2003 Academician of Chinese Academy of Sciences

Research field: phytochemistry and natural pharmaceutical chemistry

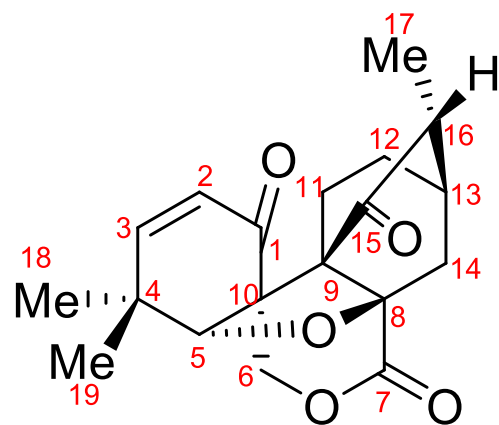
Background–*Isodon eriocalyx*(疏花毛萼香茶菜)



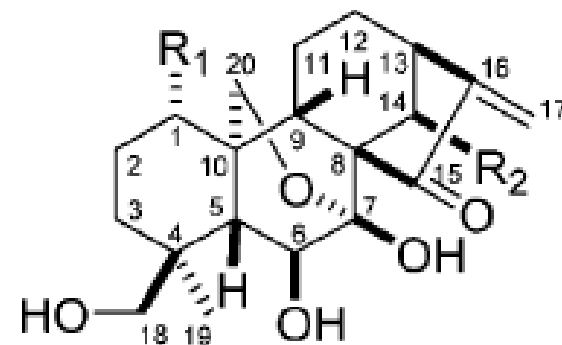
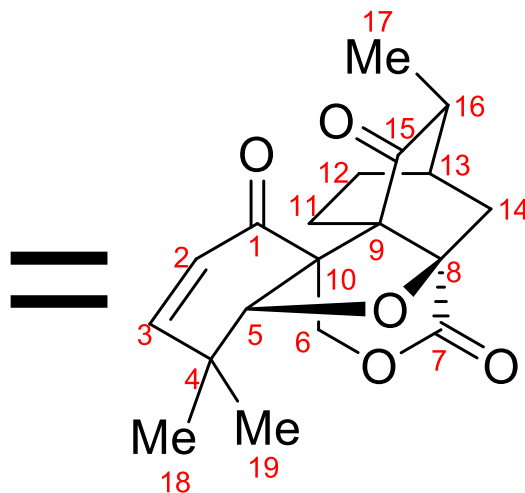
Maoecrystal V

- Perennial herb or shrub
- Widely distributed in southwestern China
- Used as a folk medicine for the treatment of sore throat, influenza, inflammation, hypertension, and dermatophytosis
- Rich in ent-kauranoids with different oxygenation and cleavage patterns, so far ca. 50 compound isolated, including over 30 new ones identified

Structure features of maoecrystal V



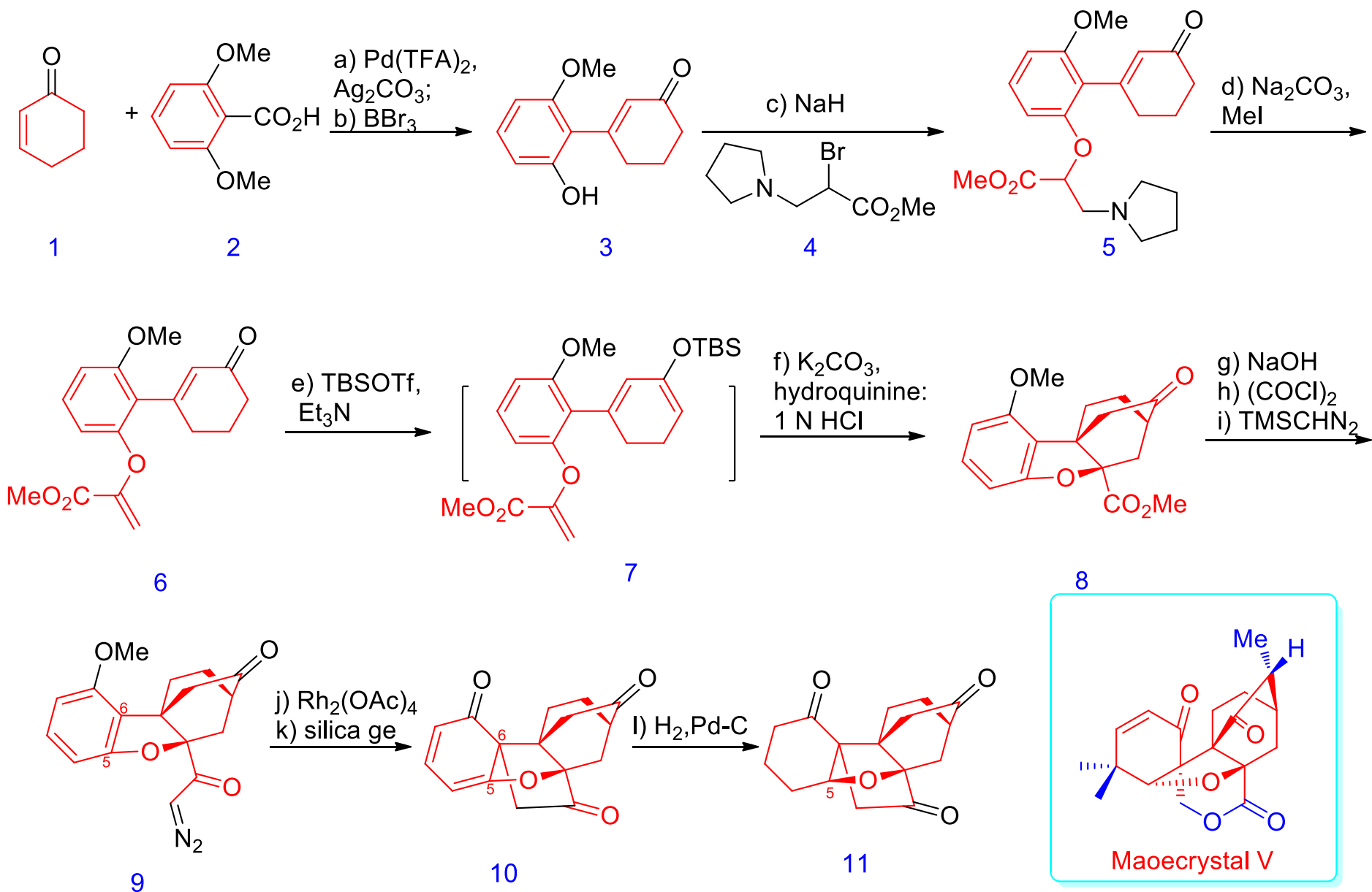
maoecrystal V



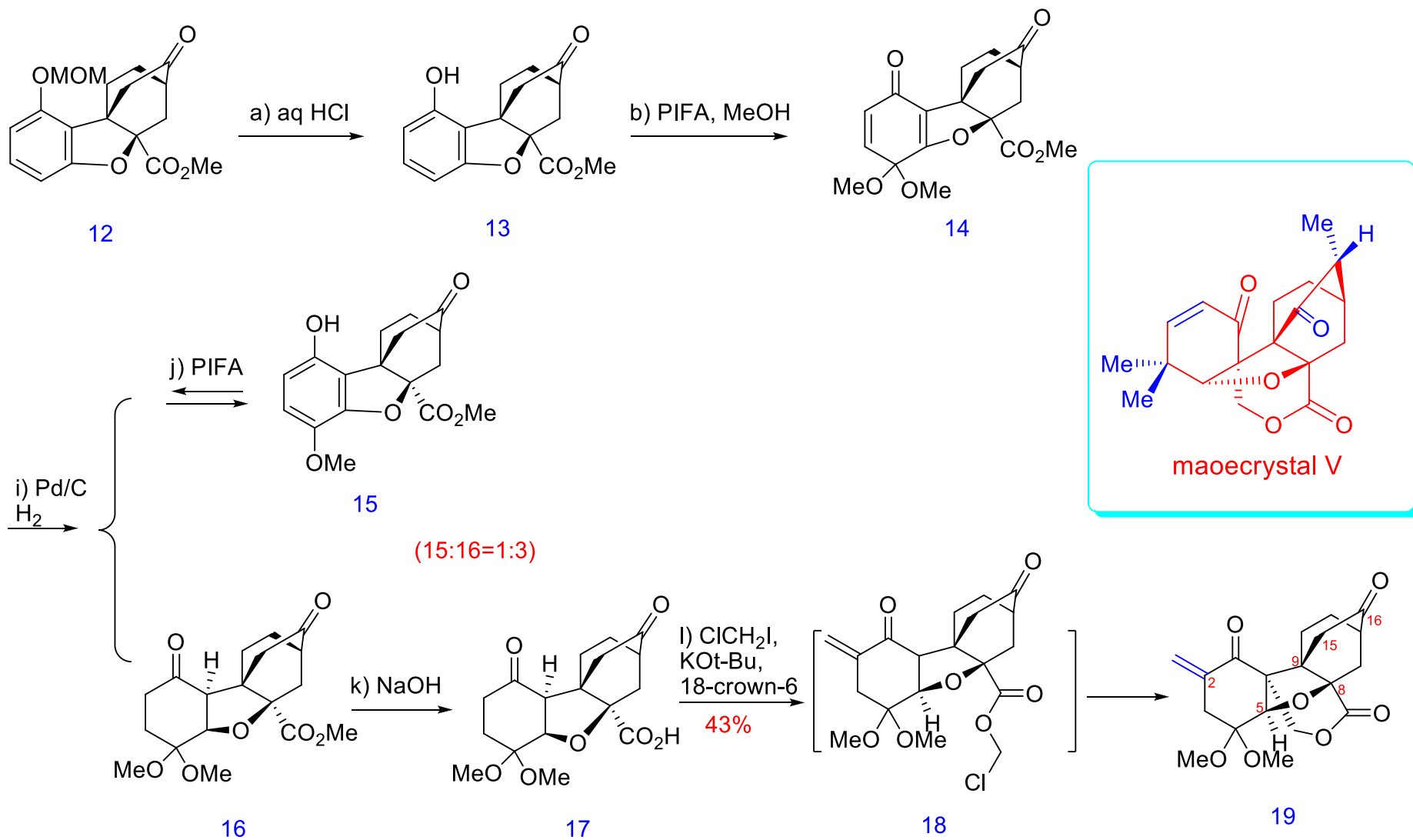
Compound 1

- C19 diterpenoid; An unprecedented and highly congested pentacyclic framework
- Six stereocenters, three of which are vicinal quaternary centers; [2.2.2]Bicyclic octanone moiety
- Isolated in 1994, Confirmed by X-ray crystallography in 2004.
- Display potent and selective inhibitory activity against HeLa cell (IC₅₀ = 60 nM)

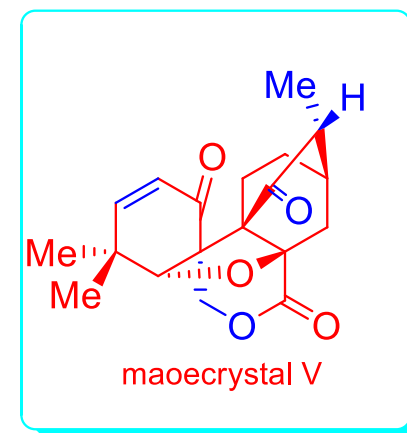
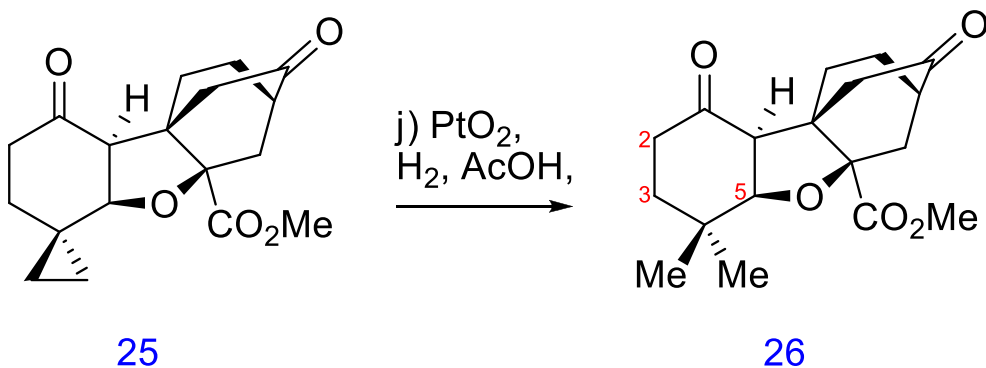
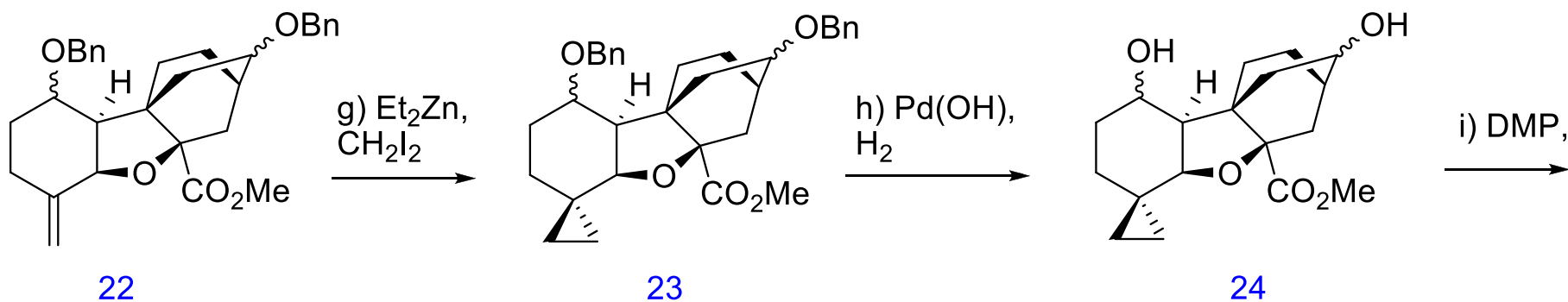
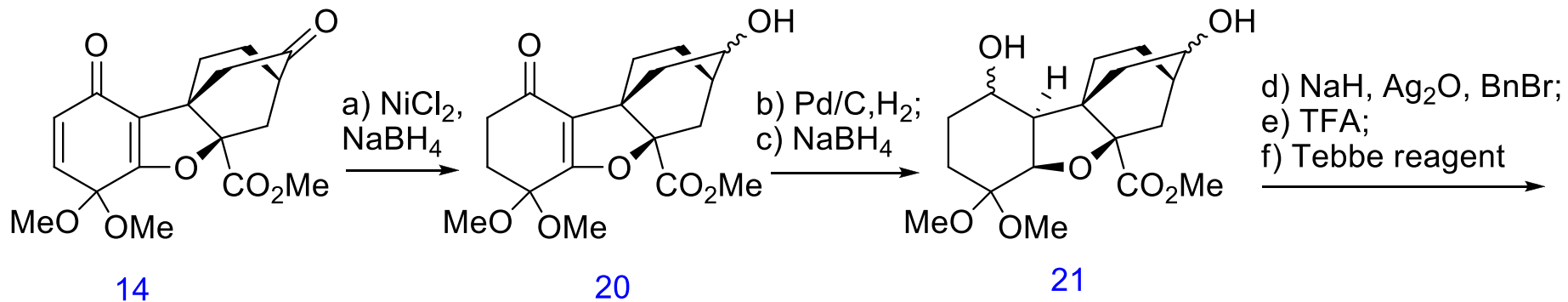
Nicolaou's model studies toward maoecrystal V



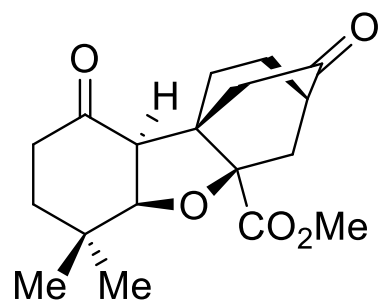
Nicolaou's model studies toward maoecrystal V



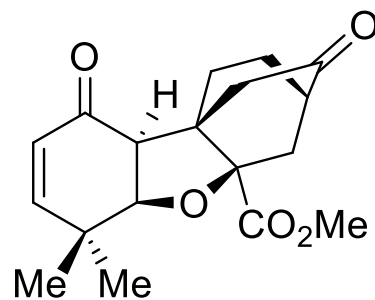
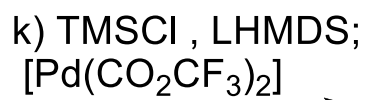
Nicolaou's model studies toward maoecrystal V



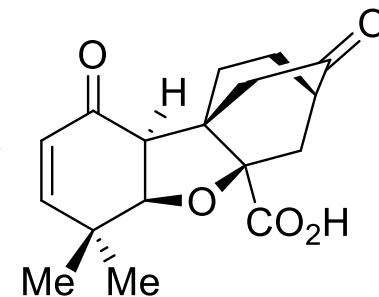
Nicolaou's model studies toward maoecrystal V



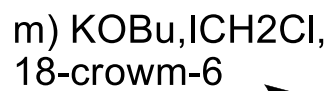
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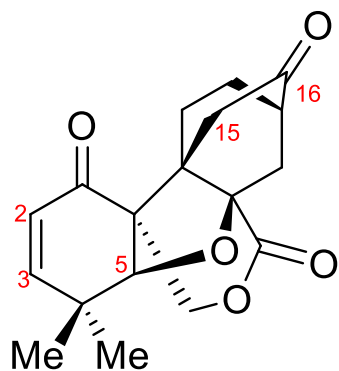
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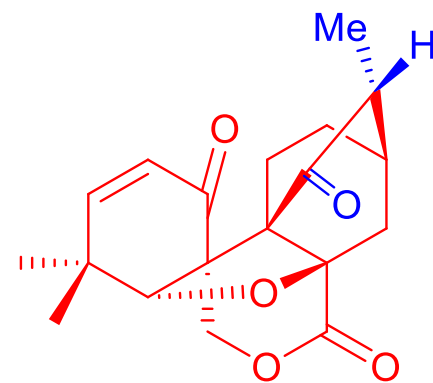
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23%

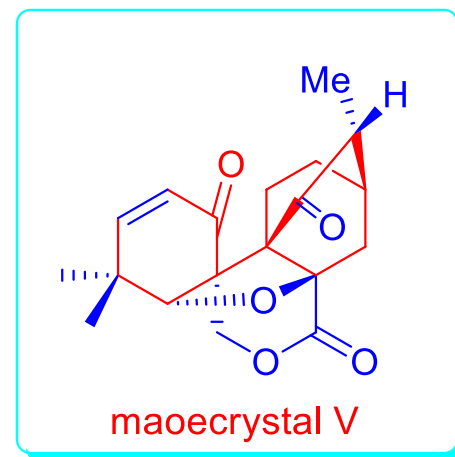
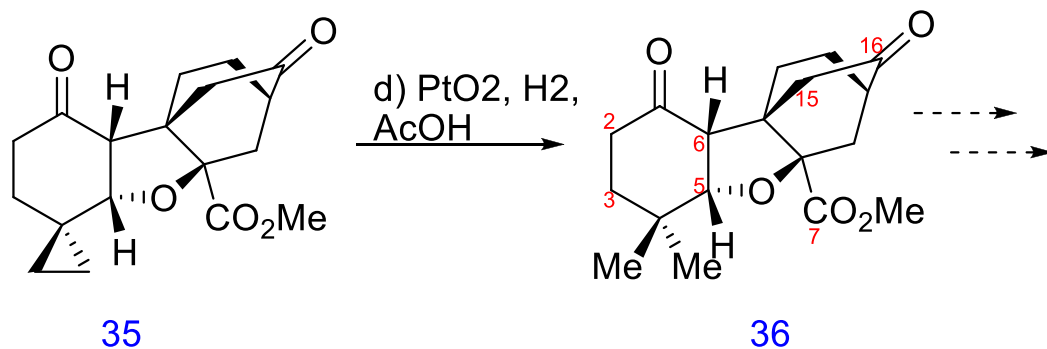
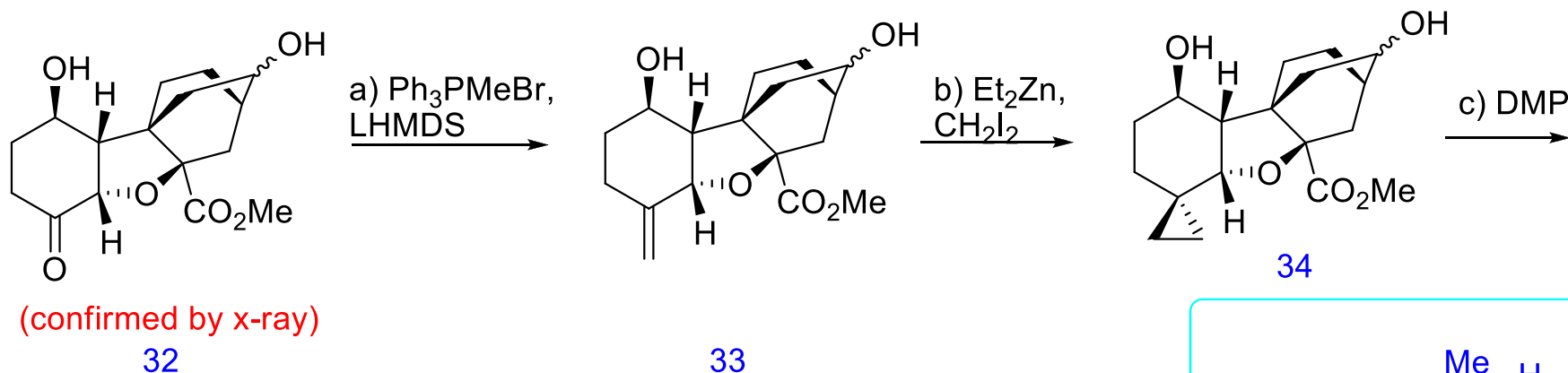
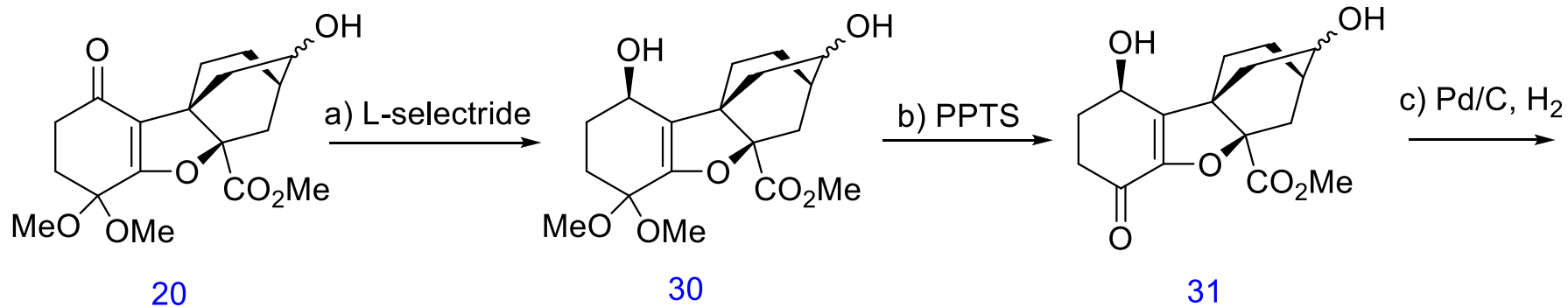


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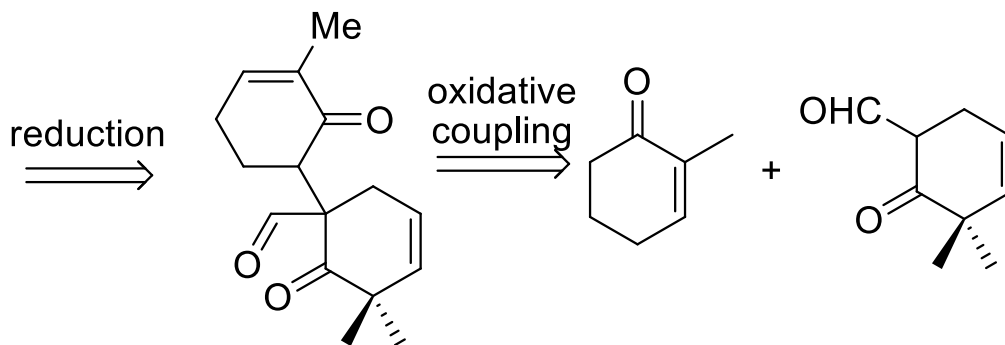
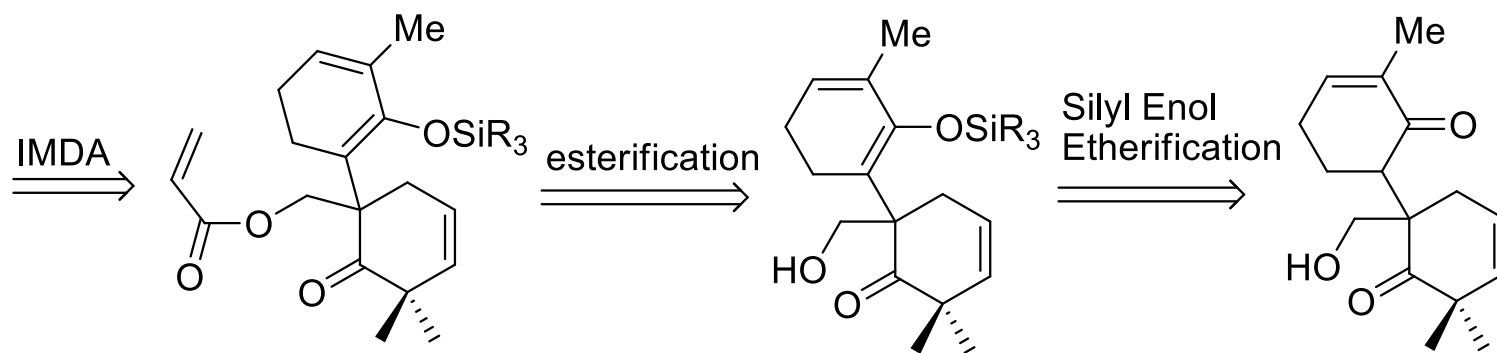
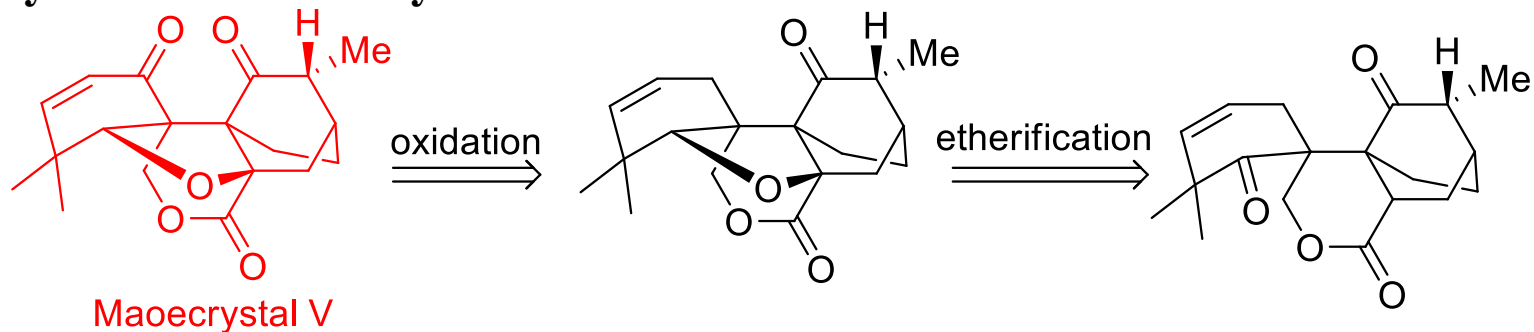
Maoecrystal V

Nicolaou's model studies toward maoecrystal V

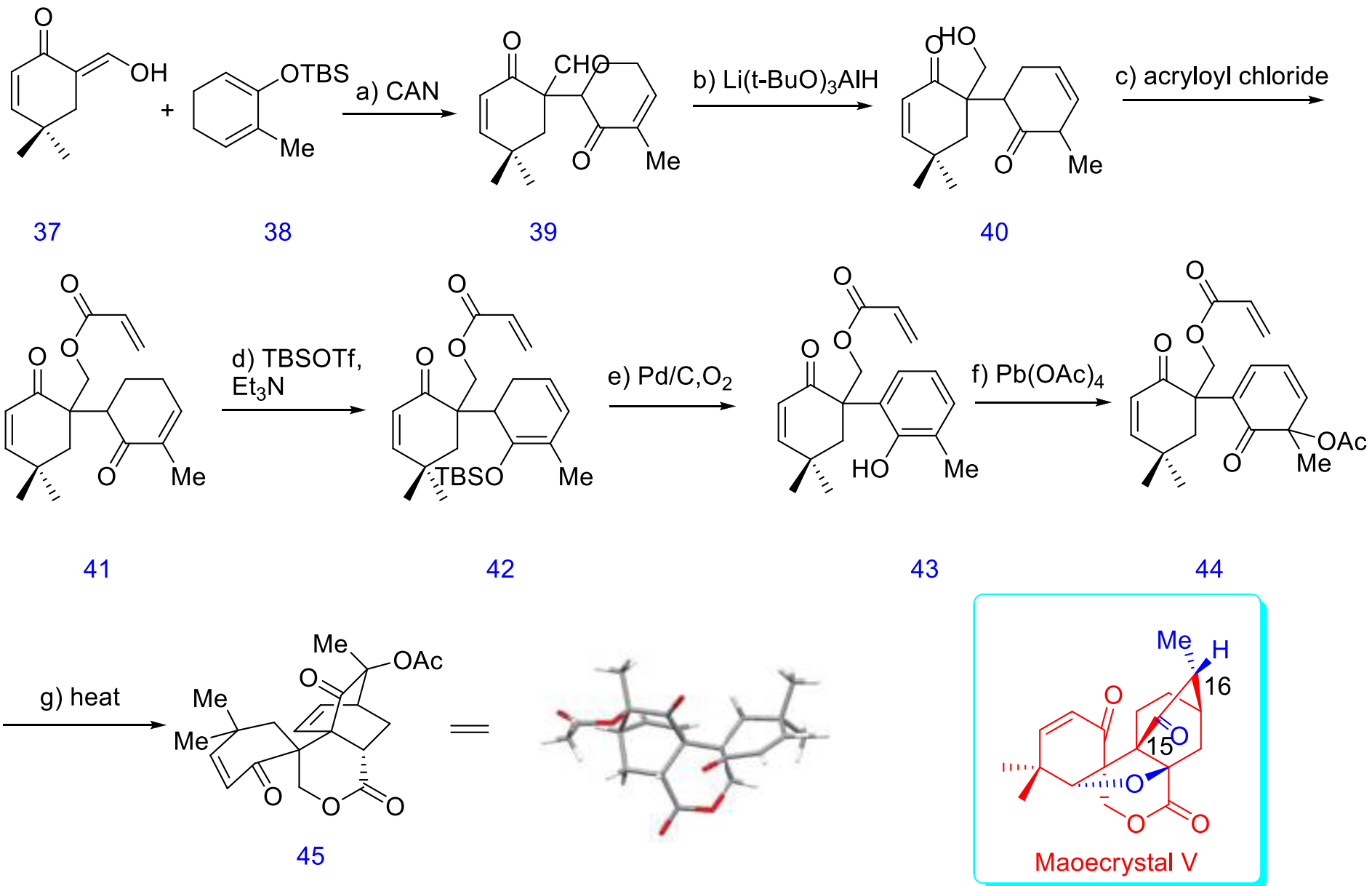


Baran's model studies of maoecrystal V

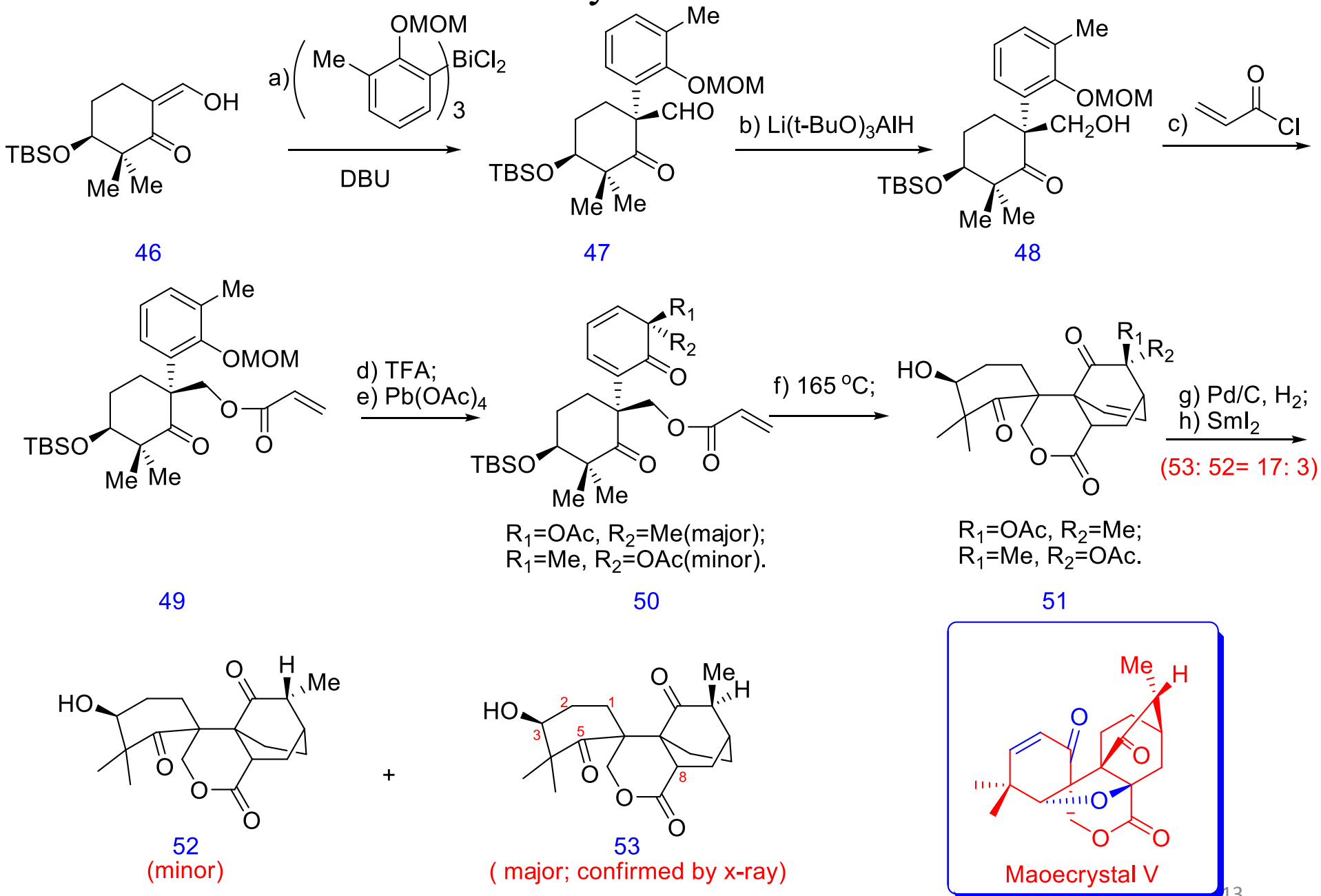
Retrosynthetic of Maoecrystal V



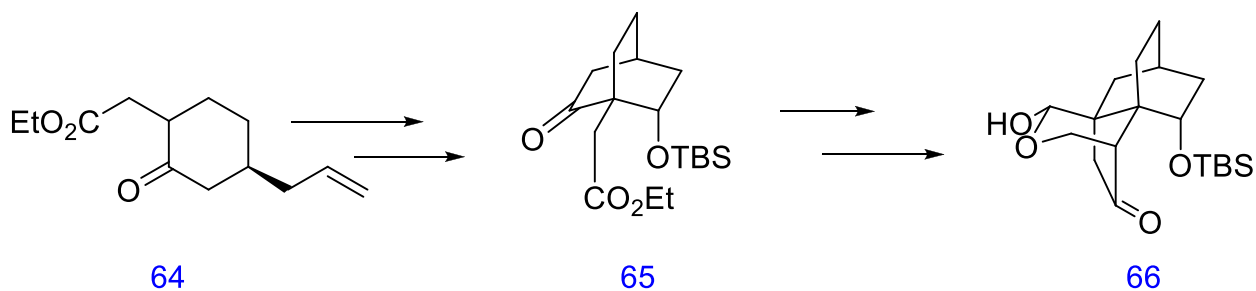
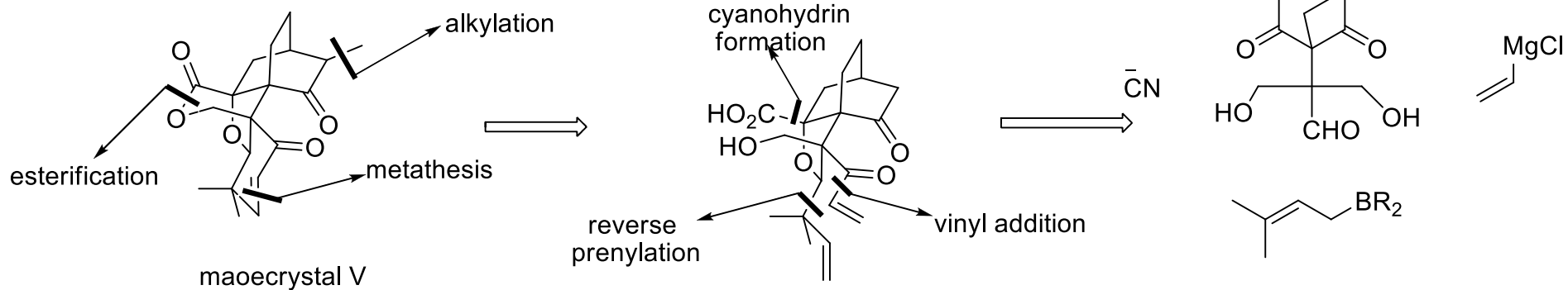
Baran's model studies of maoecrystal V



Baran's model studies of maoecrystal V



Trauner's model studies of maoecrystal V



First Total Synthesis of Maocrystal V

Introduction of Prof. Yang

EDUCATION

1989–1992, Ph. D., The Chinese University of Hong Kong, advisor: prof. Henry N.C. WONG.

1978–1986, B.S., and M.S., Shenyang College of Pharmacy

Professional experience

2001–present, Professor, Peking University

1998–2001, Institute fellow, Harvard University

1995–1998, Assistant Professor, The Scripps Research Institute

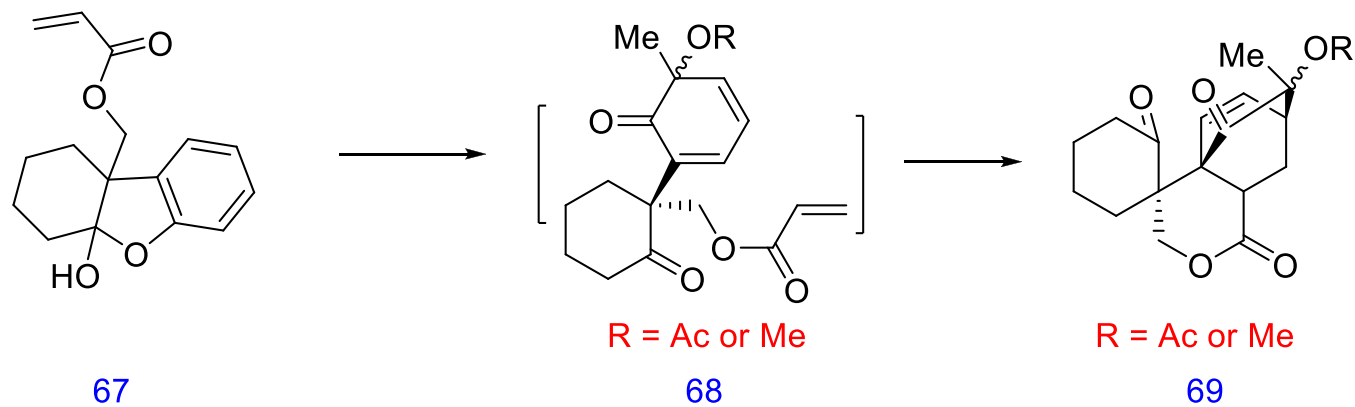
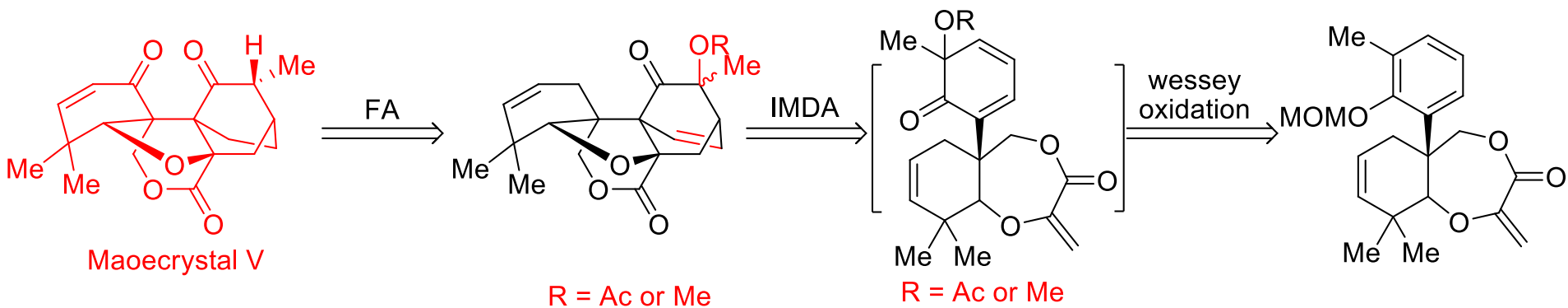
1992–1995, Postdoctoral Fellow, The Scripps Research Institute (total syntheses of Taxol, brevetoxin A, epothilone A and zaragozic acid). advisor: prof. K.C. Nicolaou.

Research Interest:

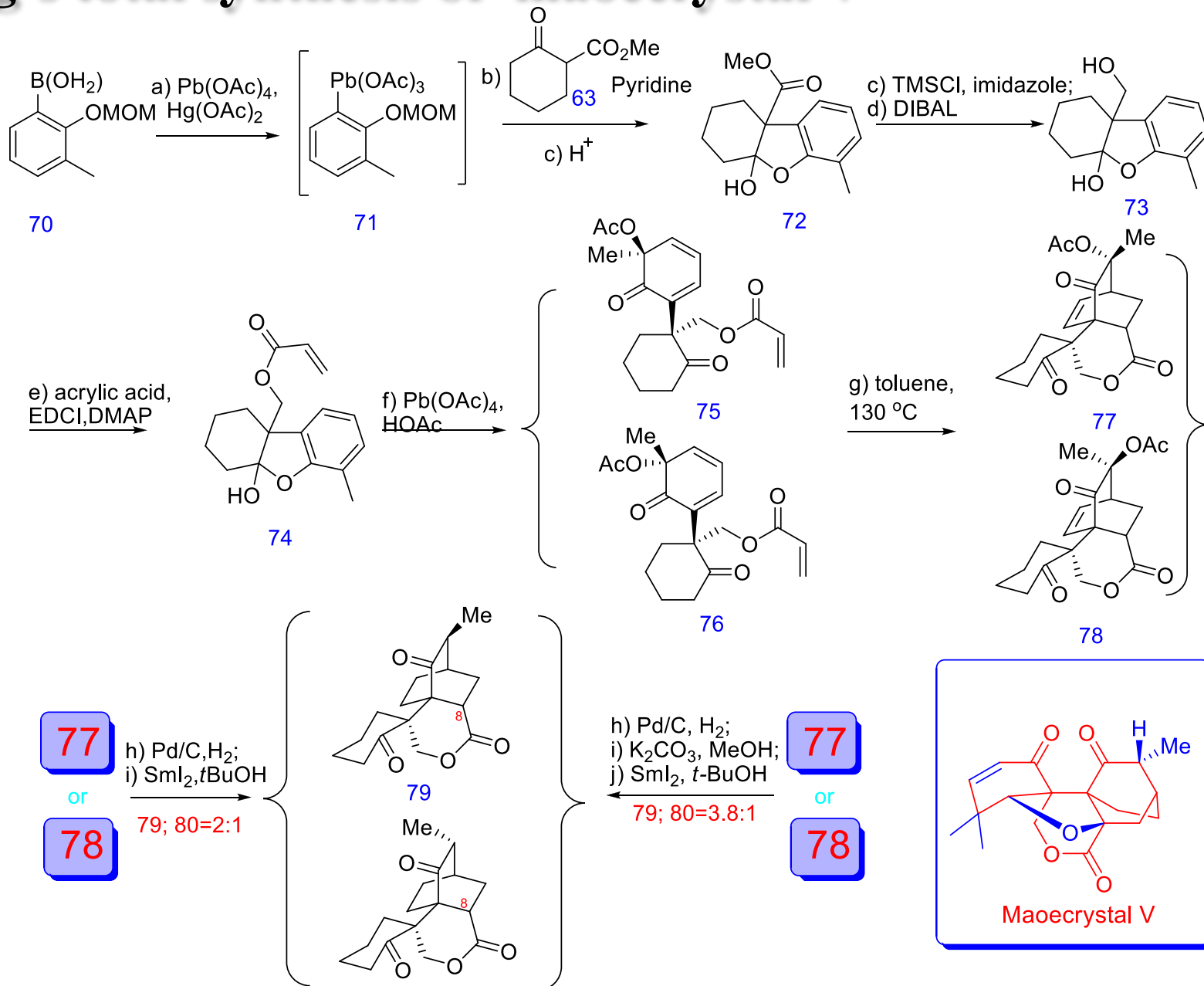
Total Synthesis of Natural Products, organometallic chemistry, diversity oriented synthesis, and chemical biology.



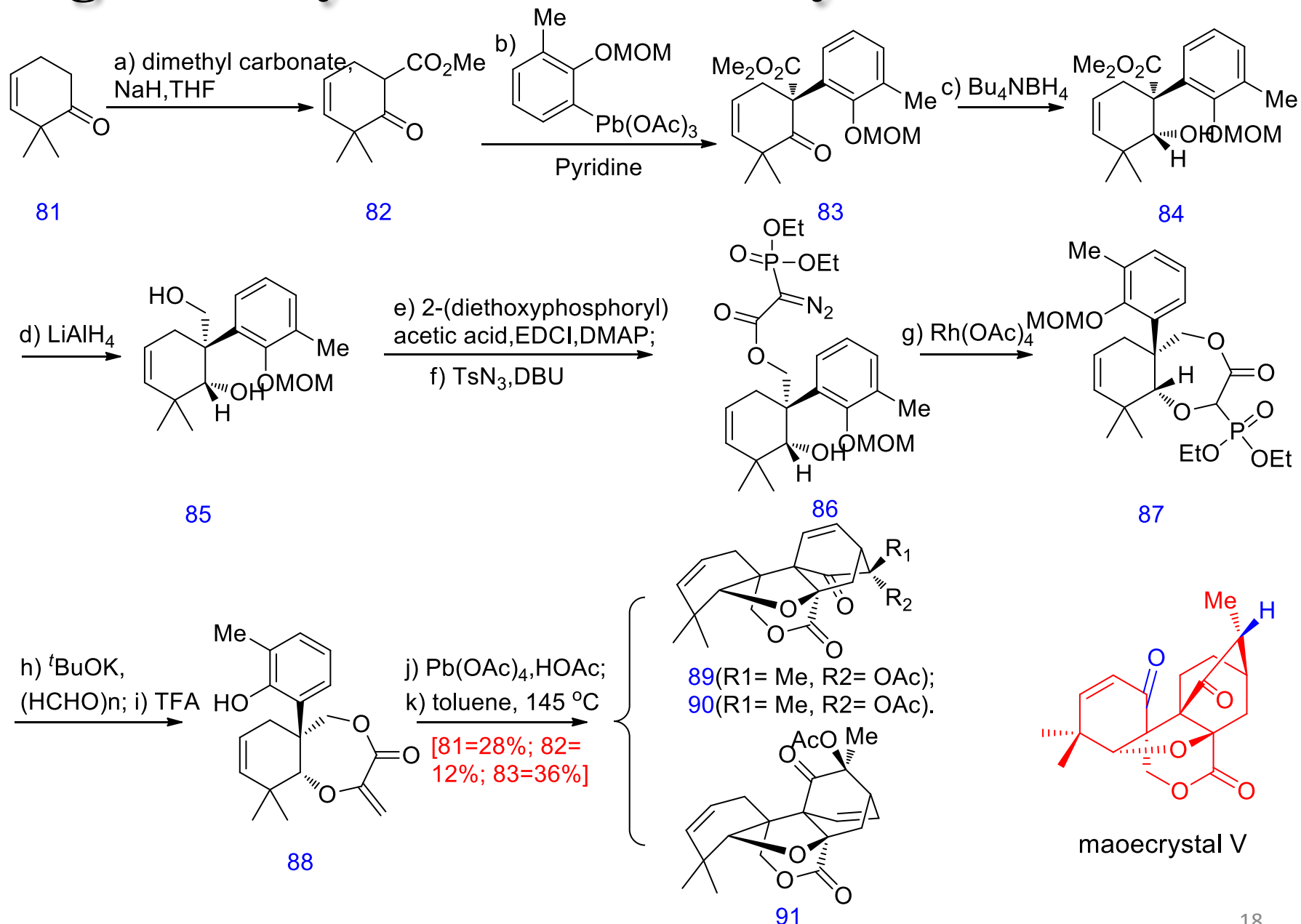
Yang's retrosynthetic analysis of maoecrystal V



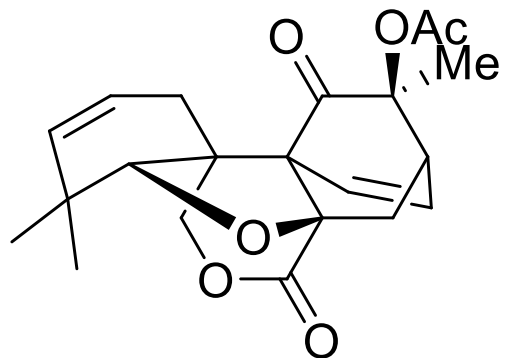
Yang's total synthesis of maoecrystal V



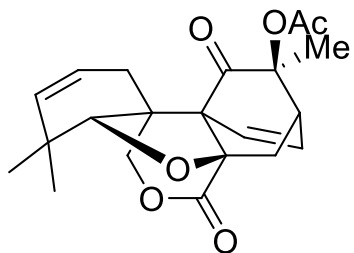
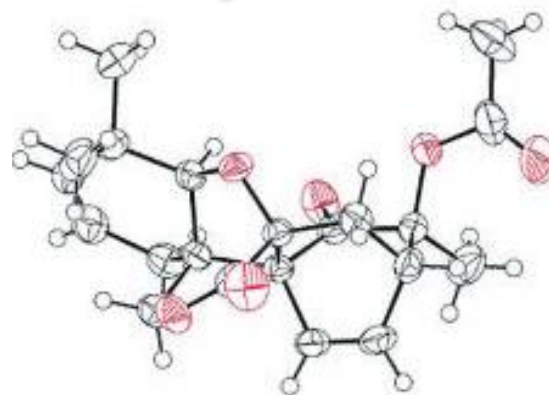
Yang's total synthesis of maoecrystal V



Yang's total synthesis of maoecrystal V



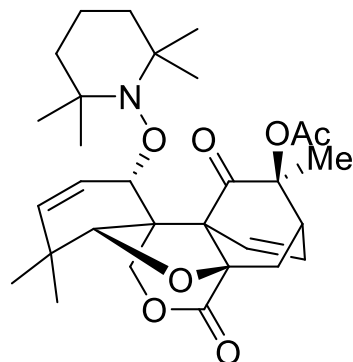
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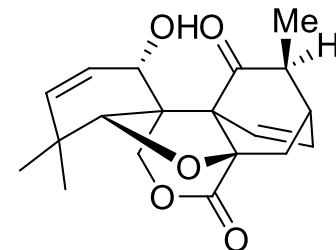
a) NBS, (PhCO₂)₂O,
CCl₄, reflux

b) Bu₃SnH, TEMPO,
PhH, reflux, 2 h,

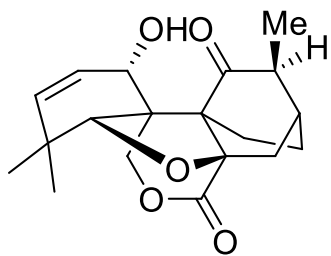


c) Zn, HOAc, THF, H₂O

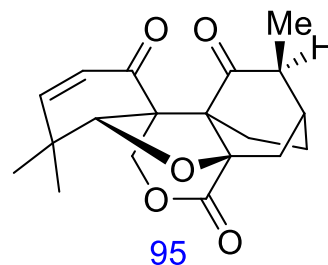
d) SmI₂, MeOH, THF



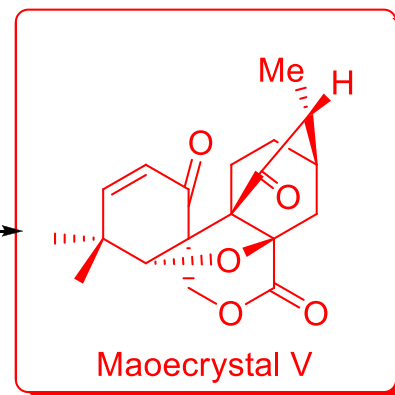
e) Lindlar Pd,
H₂;



f) DMP



g) DBU



nature

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NATURE | RESEARCH HIGHLIGHT:

Organic chemistry:

Nature 468, 871 (16 December 2010)
Published online 15 December 2010

Subject terms: [Biochemistry](#) • [Drug Discovery](#)

Highly read in November on <http://www.nature.com/nature/journal/v468/n7326/full/468871f.html>

The complex molecule maoecrystal laboratory, after six years of intense Yang and his colleagues at Peking sought-after compound — which sh — in a concise 16-step synthesis. I herb (*Isodon eriocalyx*) that has long and inflammation, and has already produced a number agents. By varying the laboratory synthesis, chemists



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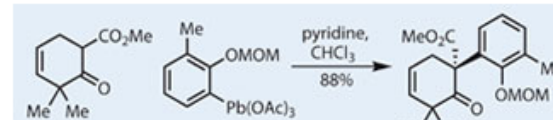
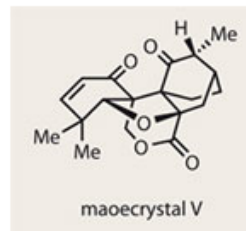
Column: Totally Synthetic

Maoecrystal V

In a conversation at the beginning of this year, a friend and I considered the most challenging targets available to the total-synthesiser - and maoecrystal V was at the top of the list. A quick inspection reveals a trio of contiguous quaternary stereocentres, along with an extremely congested pentacyclic ring system. Little wonder, then, that this target has been so popular. Add to that an impressive biological profile (potent and selective inhibitory activity against HeLa cancer cells (IC50 = 60nM)) and it's no surprise that over ten 'studies towards' papers have been published since its isolation in 2004,¹ including work by some of the most prolific scientists in the field.^{2,3}

News that the beast has fallen will be received with dismay in those labs - doubly so since this route is so concise. Sixteen steps were all that were required for Zhen Yang's team at Peking University in China⁴ - leaving little to be desired from subsequent routes.

Starting with a rather unconventional coupling, the group quickly built the first quaternary stereocentre. This oxidative coupling reaction is unfortunately not discussed in any detail, and neither is the synthesis of the aryllead intermediate, so we'll have to wait for a full paper to understand their rationale for using such exotic - and presumably toxic - conditions (figure 1).

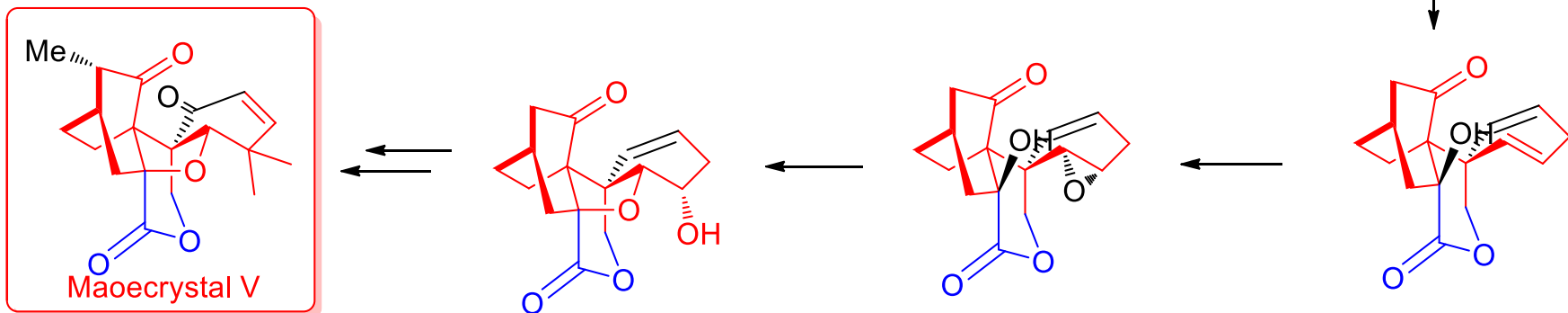
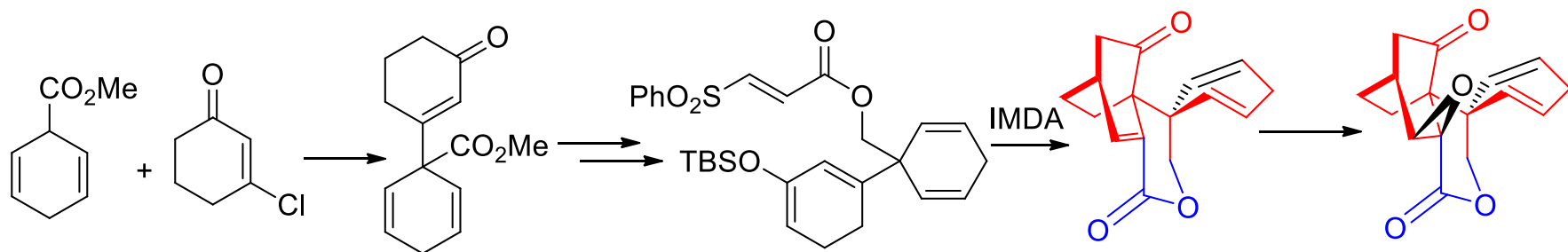
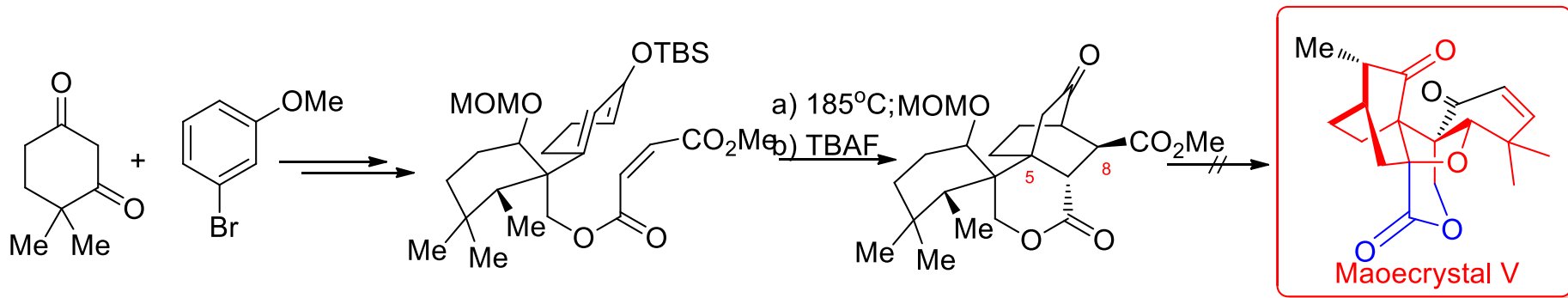


<http://www.nature.com/nature/journal/v468/n7326/full/468871f.html>;

<http://totallysynthetic.com/blog/?s=maoecrystal+V&x=0&y=0>;

<http://www.rsc.org/chemistryworld/Issues/2010/December/ColumnTotallySynthetic.asp>.

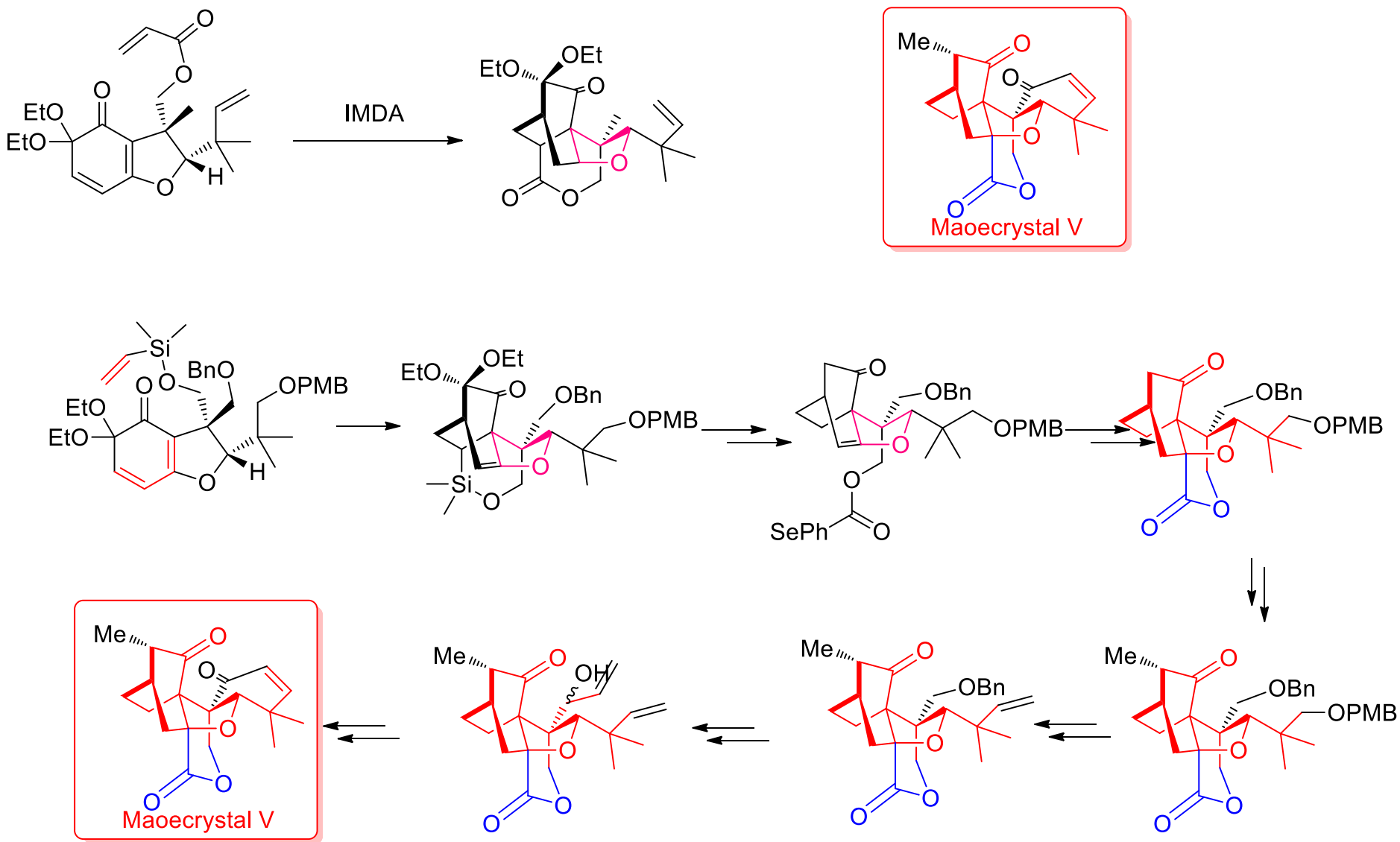
Second Total Synthesis of Maoecrystal V by Prof. Danishefsky



F. Peng, M. L. Yu, S. J. Danishefsky, *Tetrahedron Lett.* **2009**, *50*, 6586;

F. Peng, S. J. Danishefsky. *J. Am. Chem. Soc.* **2012**, *134*, 18860.

Third Total Synthesis of Maoecrystal V by A. Zakarian



Zhenhua Gu, A. Zakarian, *Org. Lett.* **2010**, *12*, 5656 – 5659;

Ping Lu, Zhenhua Gu, A. Zakarian. *J. Am. Chem. Soc.* [dx.doi.org/10.1021/ja408231t](https://doi.org/10.1021/ja408231t) ..

Conclusion

Nicolaou, Baran, Danishefsky, Zakarian , and Thomson all employed intramolecular Diel–Alder Strategy(IMDA) to construct[2, 2, 2] bicyclic ring system.

Trauner proposed a conceptual different strategy to construct the bicyclic ring system, which proved to be fruitless in his practice.

Yang utilized Rh–catalyzed O–H bond insertion to furnish a fully functional precursor for IMDA, which smoothly solved both THF and lactone problems in one pot.

Thanks for your attention!

