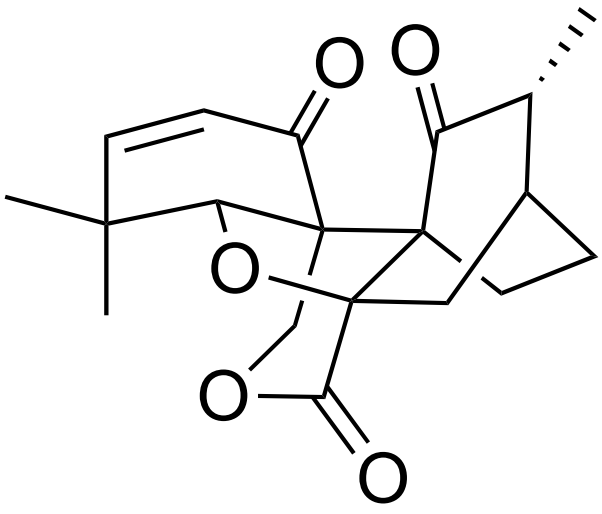
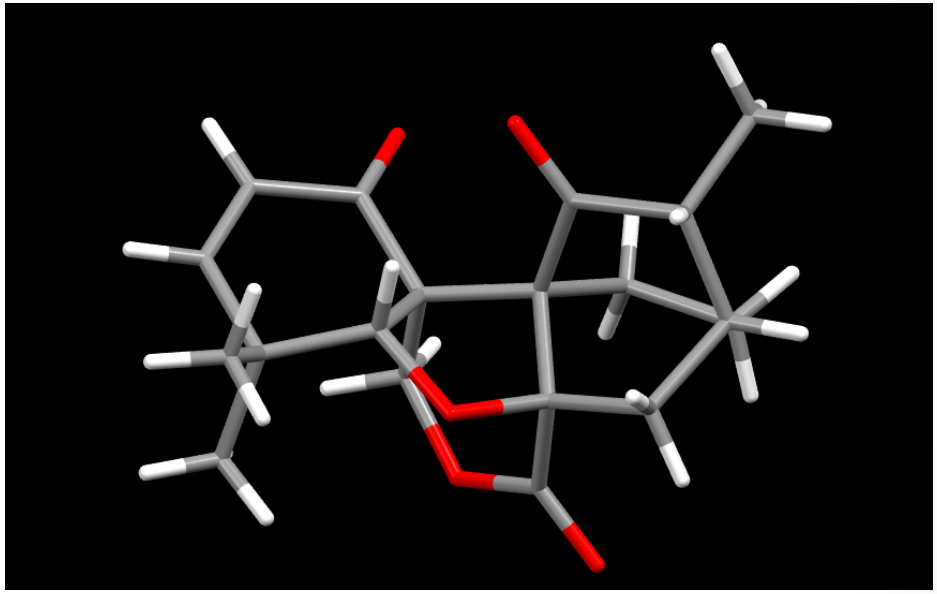
11-Step Total Synthesis of (–)-Maoecrystal V



(–)-maoecrystal V

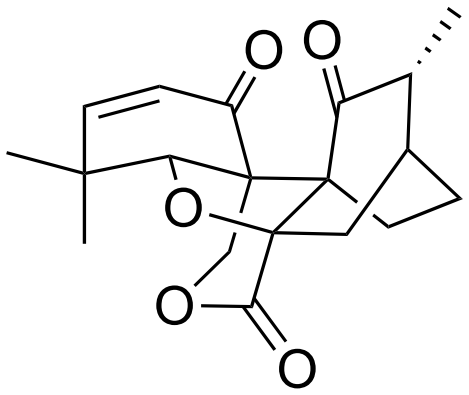


Cernijenko, A.; Risgaard, R.; Baran, P. S. *J. Am. Chem. Soc.* **2016**, *138 (30)*, 9245-9428

John Milligan
Wipf Group Meeting

Current Literature
August 6, 2016

Maoecrystal V

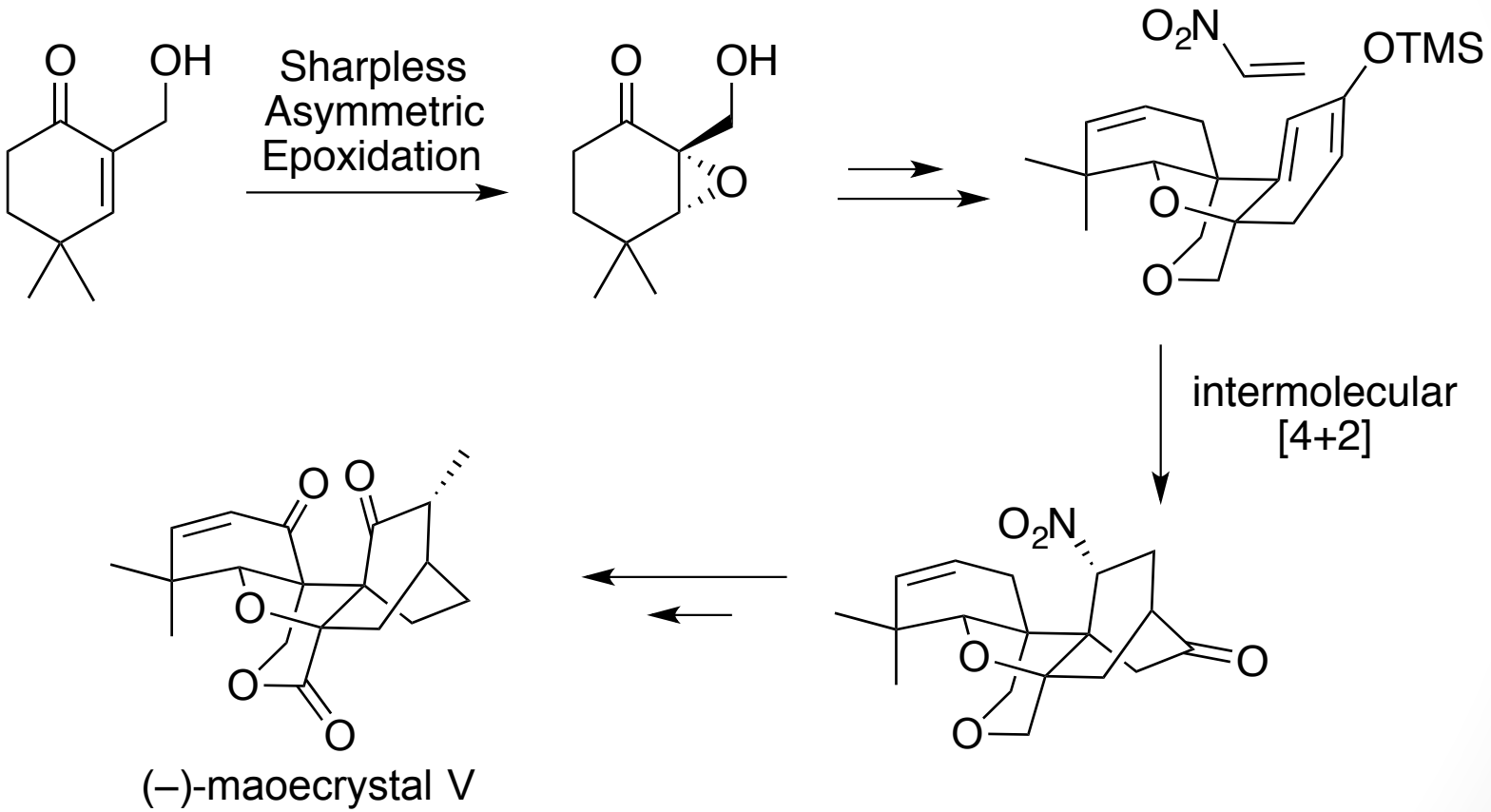


(–)-maoecrystal V

- Isolated from *Isodon eriocalyx*, a perennial shrub common in southwestern China
- Reported in 2004 with X-ray structure (isolation claimed to be prior to this date)
- Dense tetracyclic framework including adjacent all C quaternary centers
- Potent and selective inibitor of HeLa cancer cells

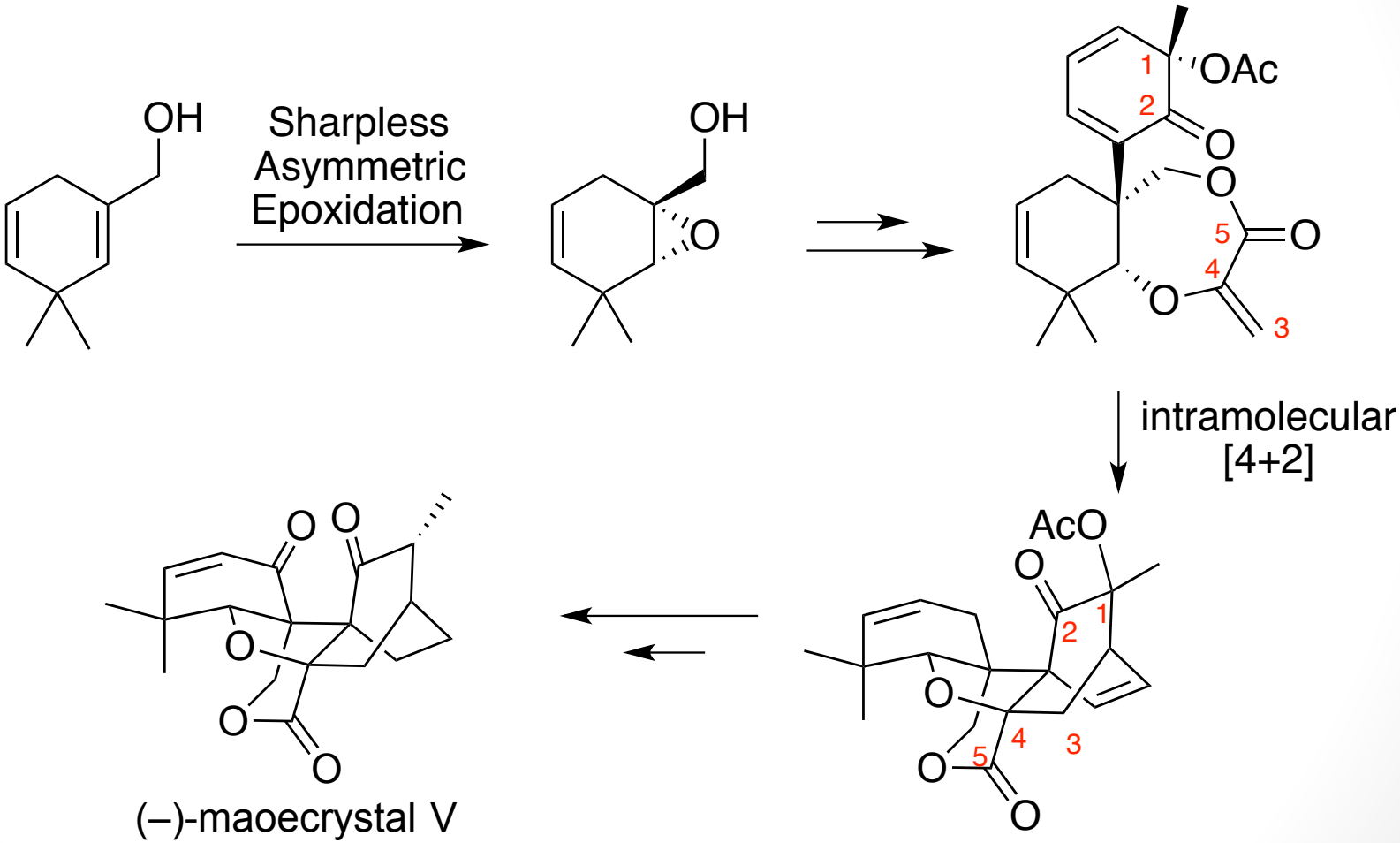
Li, S.-H.; Wang, J.; Niu, X.-M.; Shen, Y.-H.; Zhang, H.-J.; Sun, H.-D.; Li, M. L.; Tian, Q.-E.; Lu, Y.; Cao, P.; Zheng, Q.-T. *Org. Lett.* **2004**, *6*, 4327.

Previous Enantioselective Total Syntheses



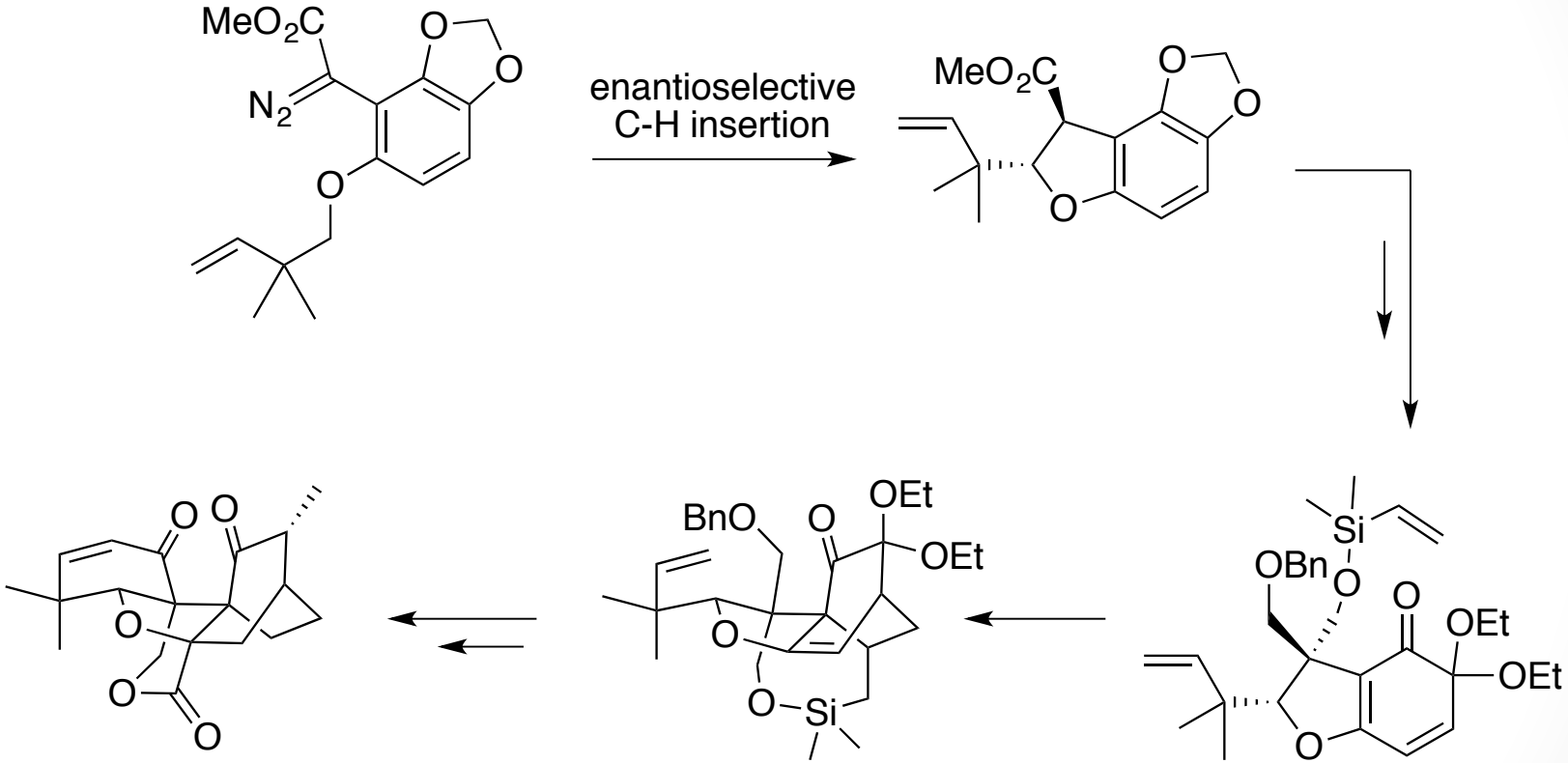
Zheng, C.; Dubovyk, I.; Lazarski, K. E.; Thomson, R. J. *J. Am. Chem. Soc.* **2014**, *136*, 17750-17756.

Previous Enantioselective Total Syntheses



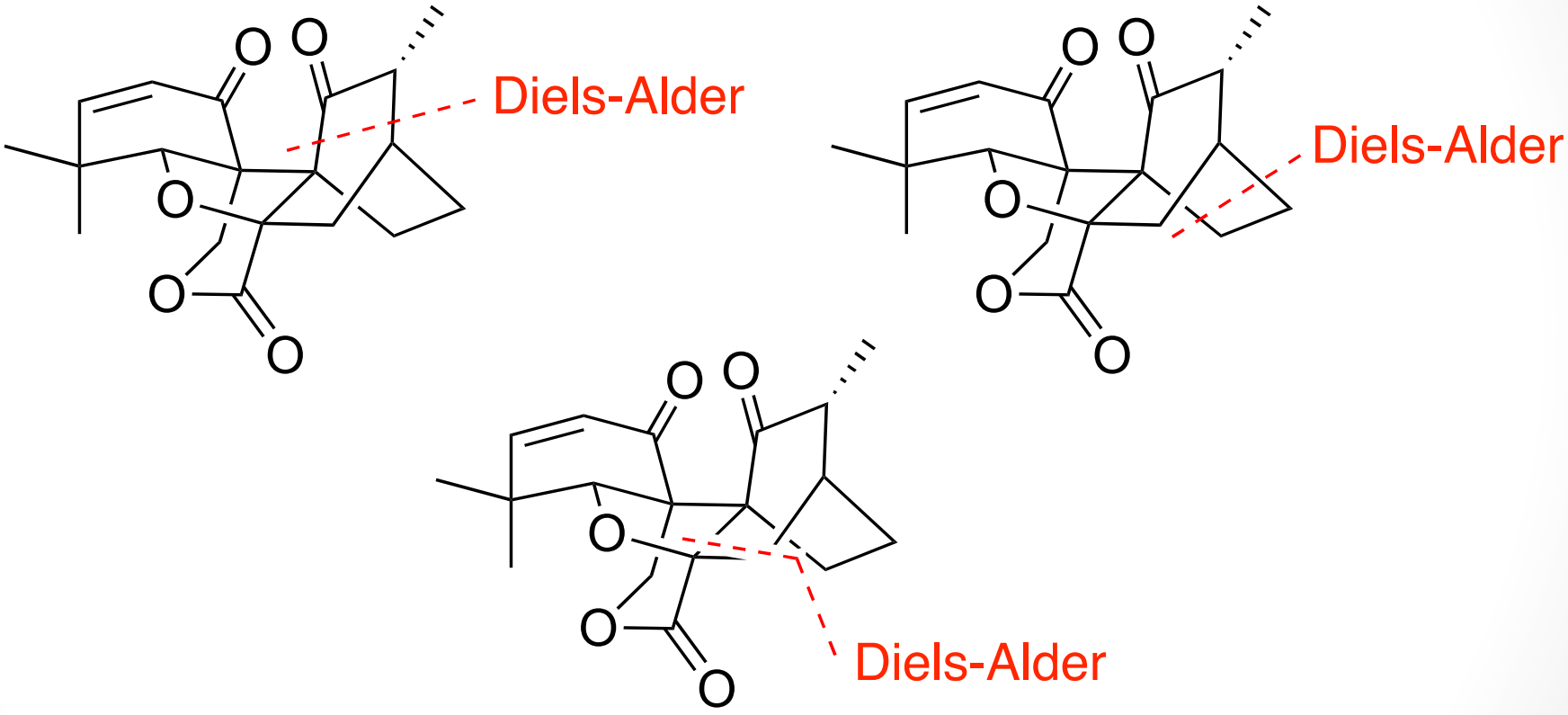
Zhang, W.; Shao, W.; Li, F.; Gong, J.; Yang, Z. *Chem. Asian J.* **2015**, *10*, 1874-1880.

Previous Enantioselective Total Syntheses

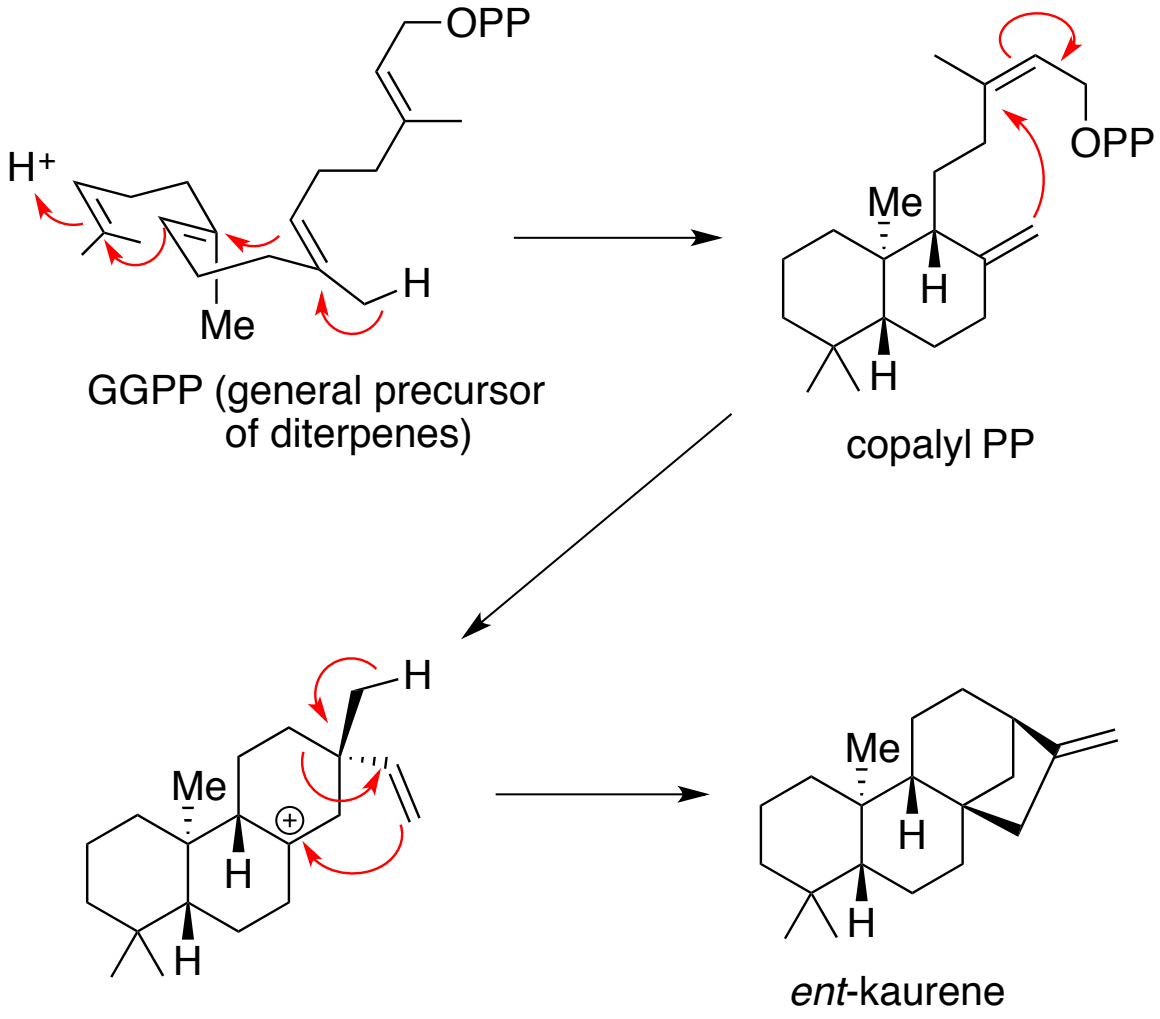


Lu, P.; Milyan, A.; Gu, Z.; Guptill, D. M.; Wang, H.; Davies, H. M. L.; Zakarian, A. *J. Am. Chem. Soc.* **2014**, *136*, 17738-17749.

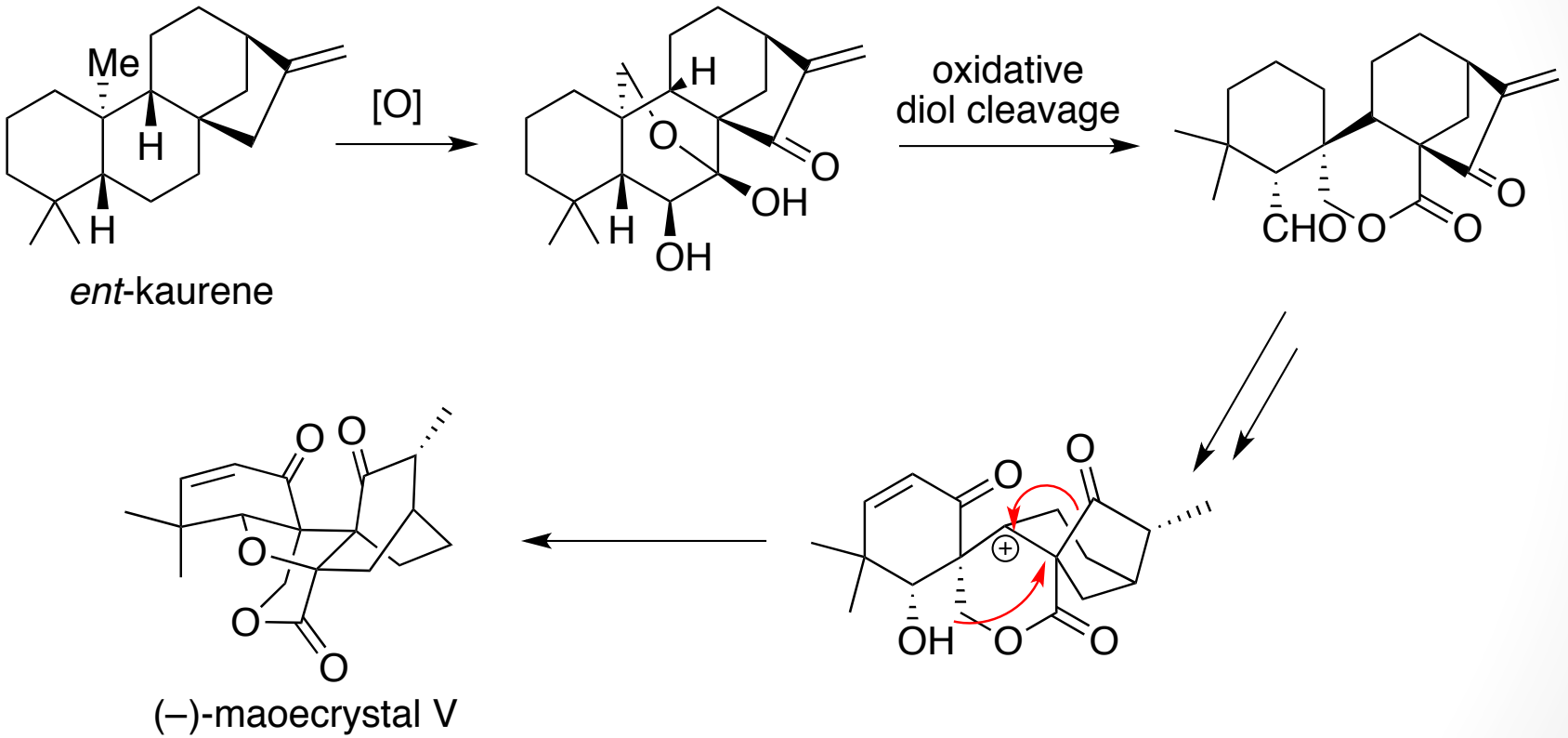
Common Disconnection



Proposed Biosynthesis: Inspiration for a Novel Synthetic Approach



Proposed Biosynthesis: Inspiration for a Novel Synthetic Approach

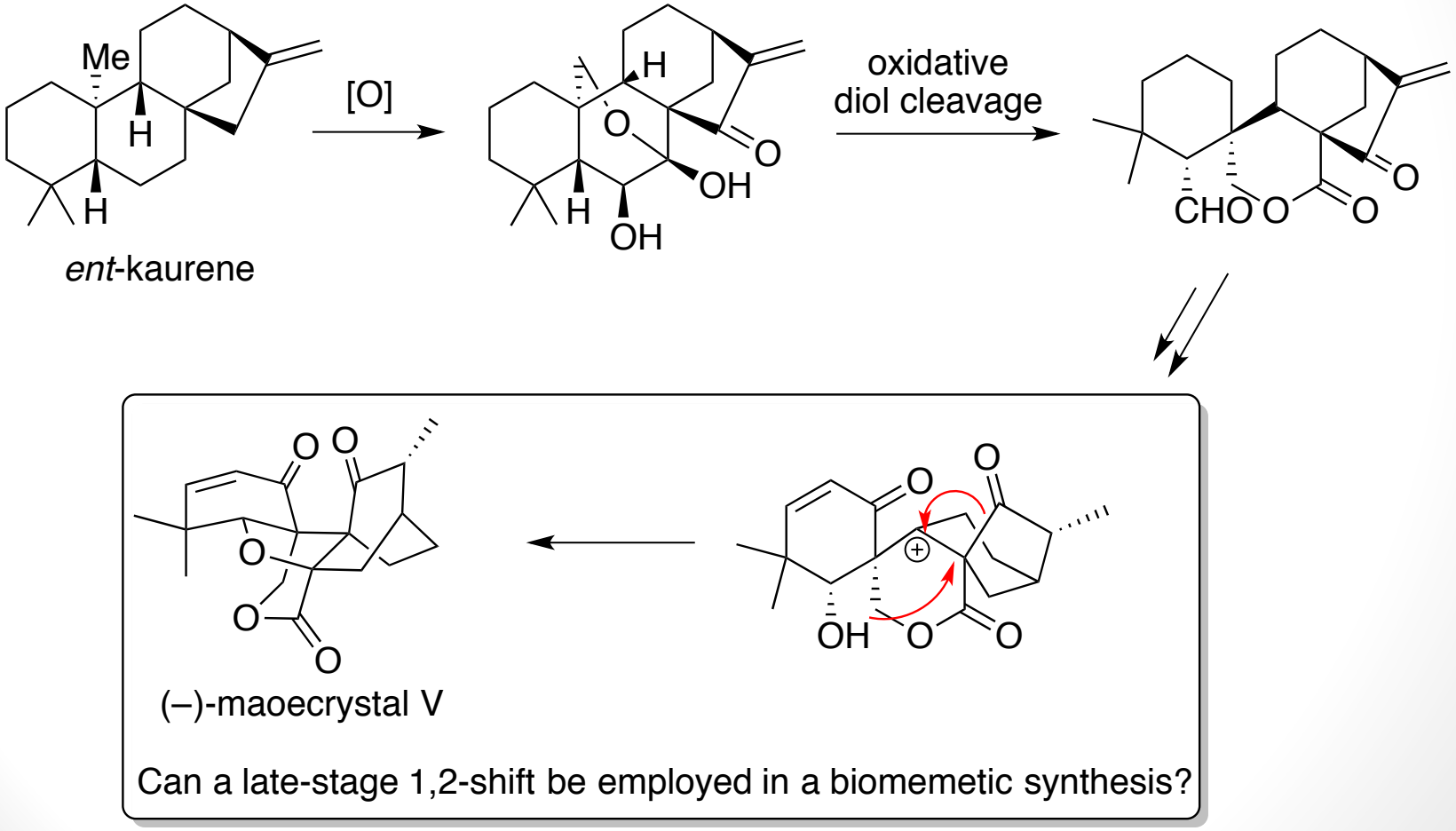


ent-kaurene

(–)-maoecrystal V

Han, Q.-B.; Cheung, S.; Tai, J.; Qiao, C.-F.; Song, J.-Z.; Tso, T.-F.; Sun, H.-D.; Xu, H.-X. *Org. Lett.* **2006**, *8,* 4727.

Proposed Biosynthesis: Inspiration for a Novel Synthetic Approach

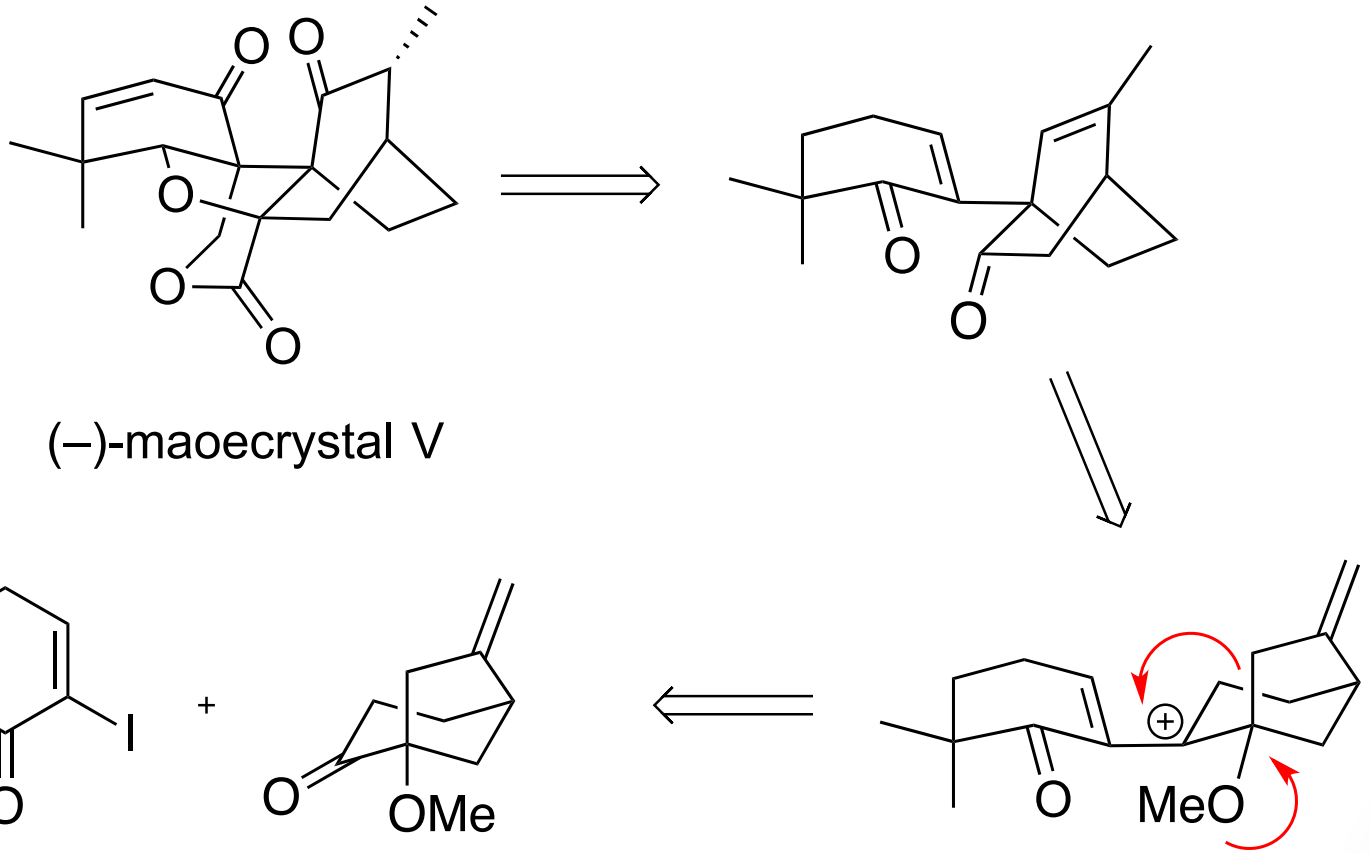


ent-kaurene

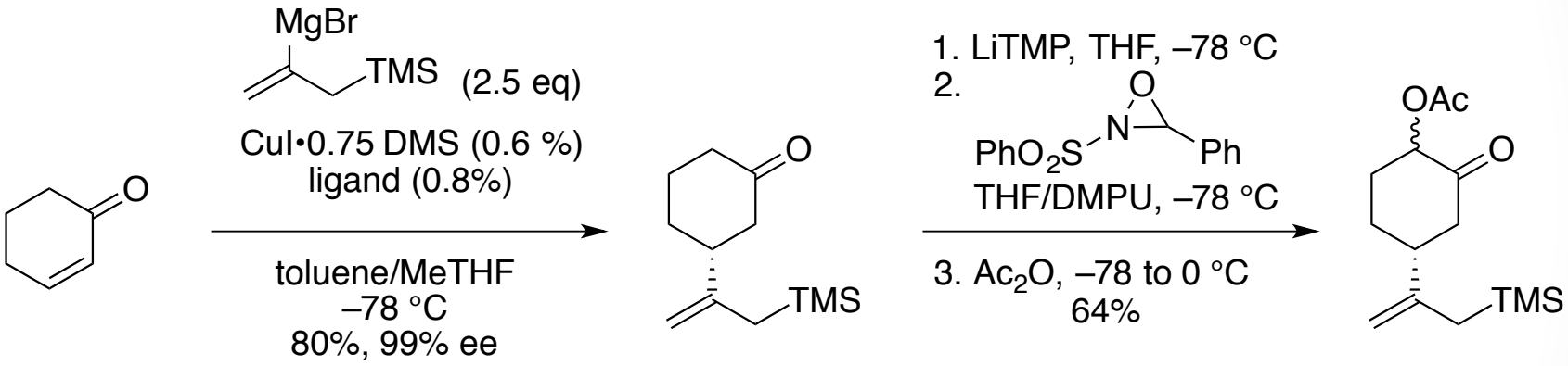
(–)-maoecrystal V

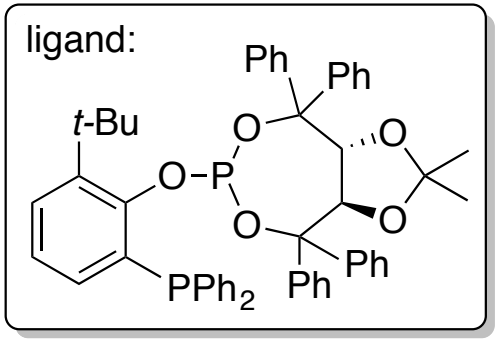
Can a late-stage 1,2-shift be employed in a biomemetic synthesis?

Retrosynthesis

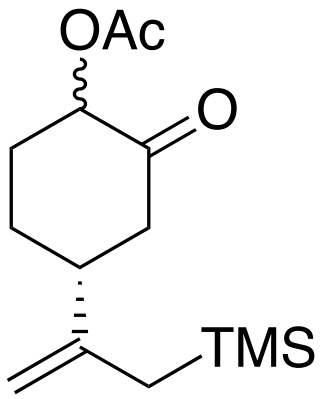


Conjugate Addition/Oxidation



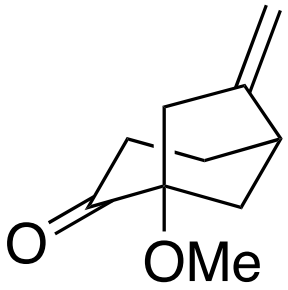


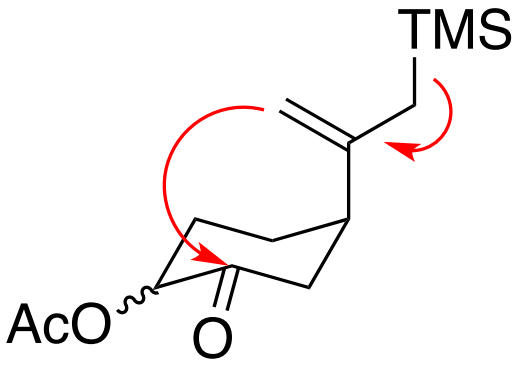
Ring Closure



1. $EtAlCl_2$ (2.0 eq)
   toluene, 0 °C, 77%
2. NaH, Me_2SO_4, Bu_4NI;
   aq. LiOH (8.5 eq)

3. $Py{\cdot}SO_3$, Et_3N
   DMSO, CH_2Cl_2
   81% (2 steps)

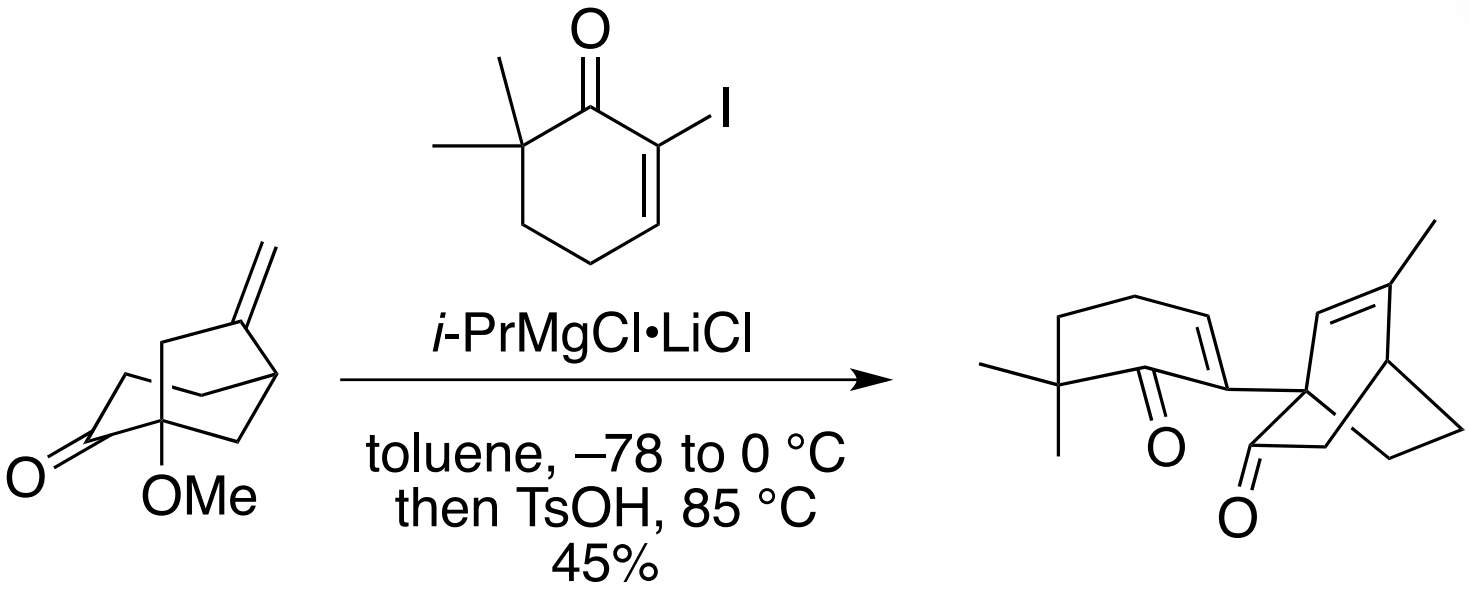


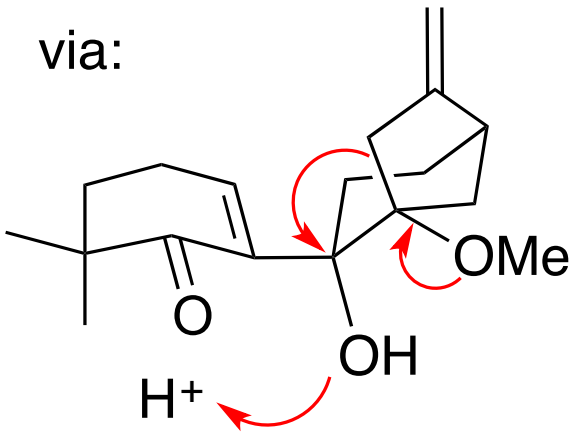


5-(enolendo)-exo-trig:
Disfavored by Baldwin rules

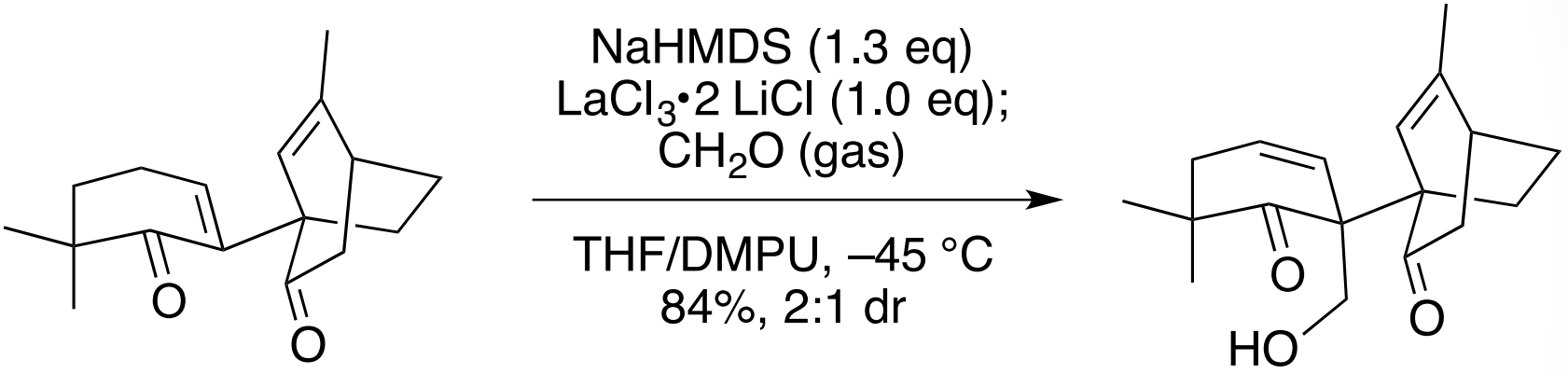
$EtAlCl_2$ was singularly
effective (out of > 50 Lewis acids)

Key Pinacol Rearrangement



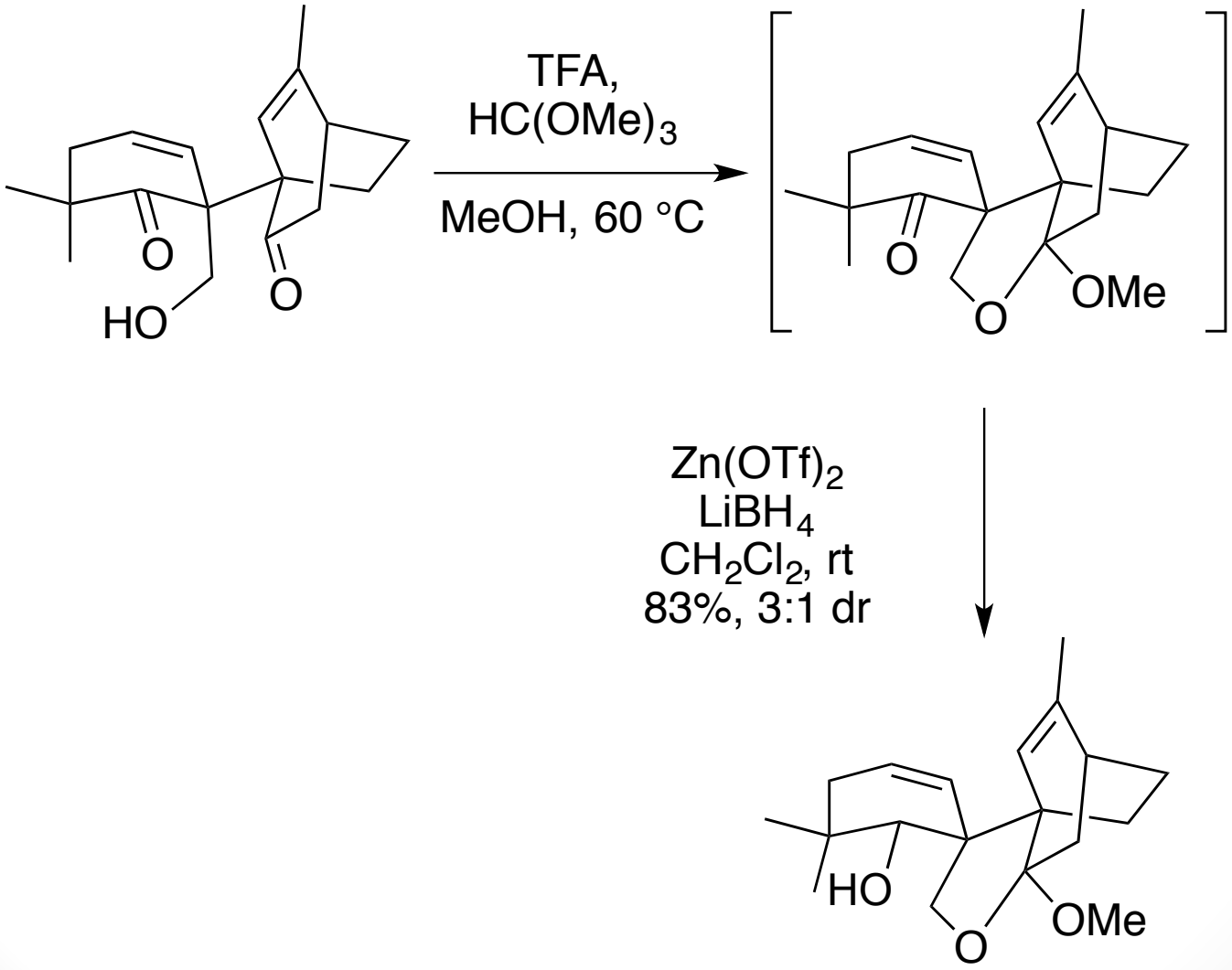


Hydroxymethylation: A challenge of selectivity

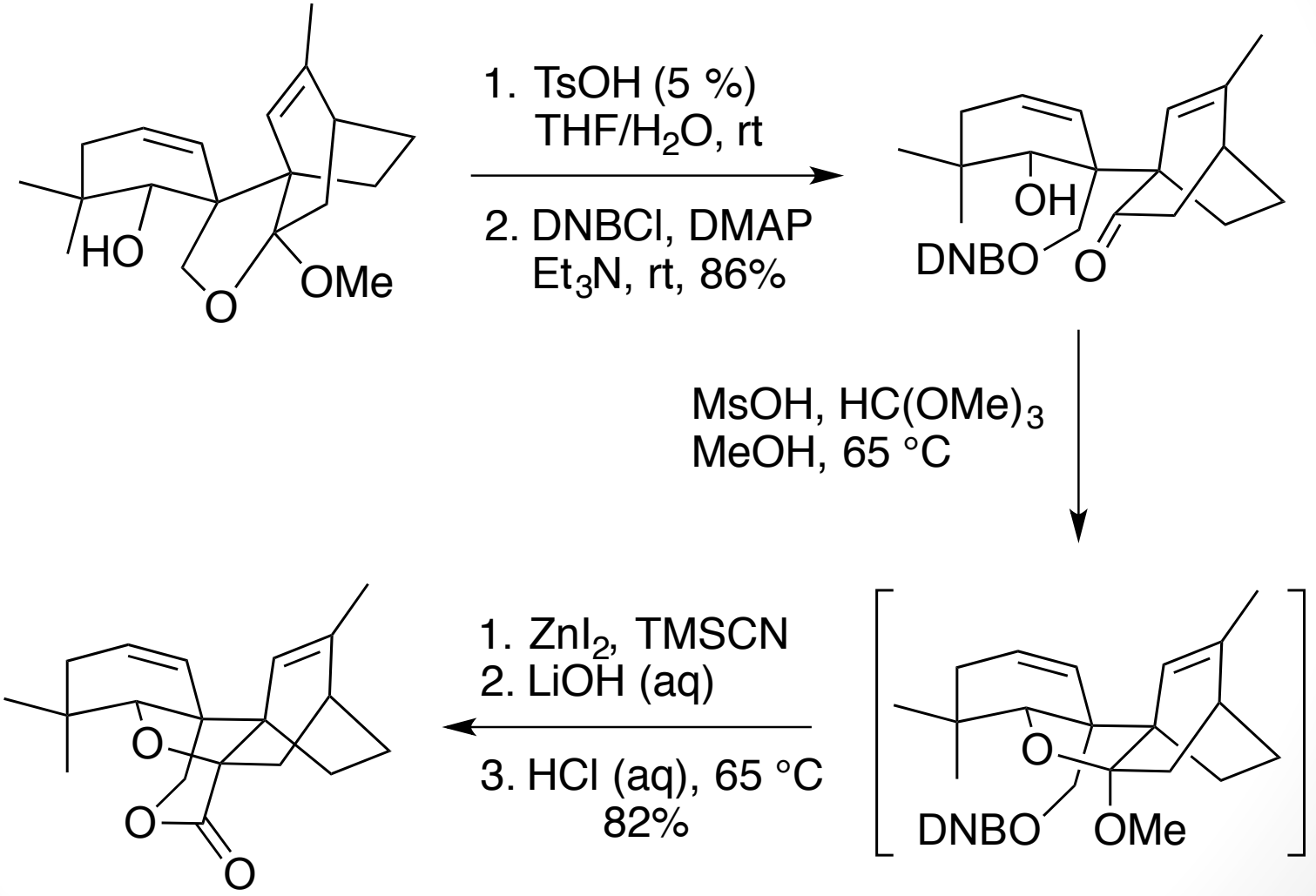


about ~1000 iterations attempted!

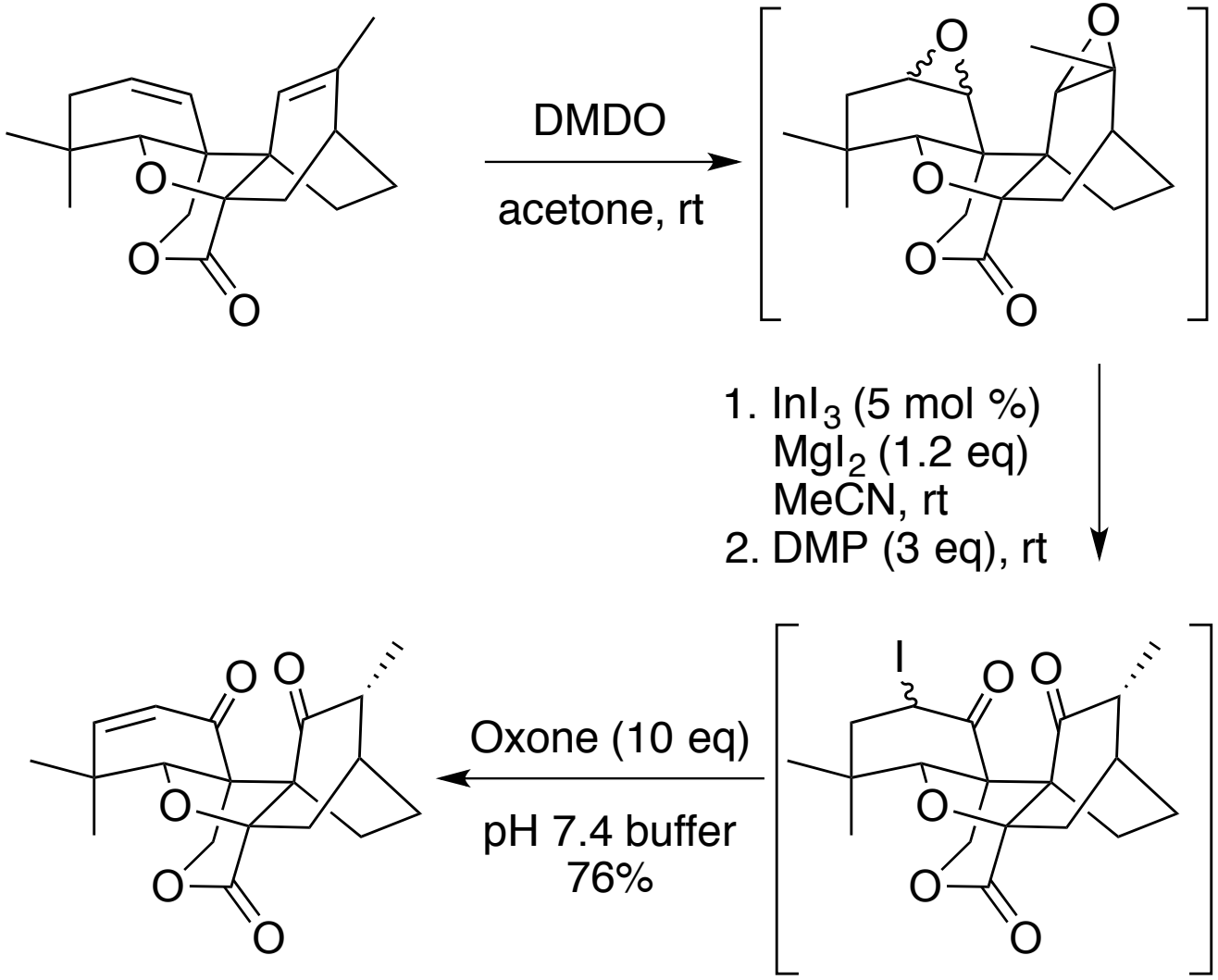
Temporary Protection/Reduction



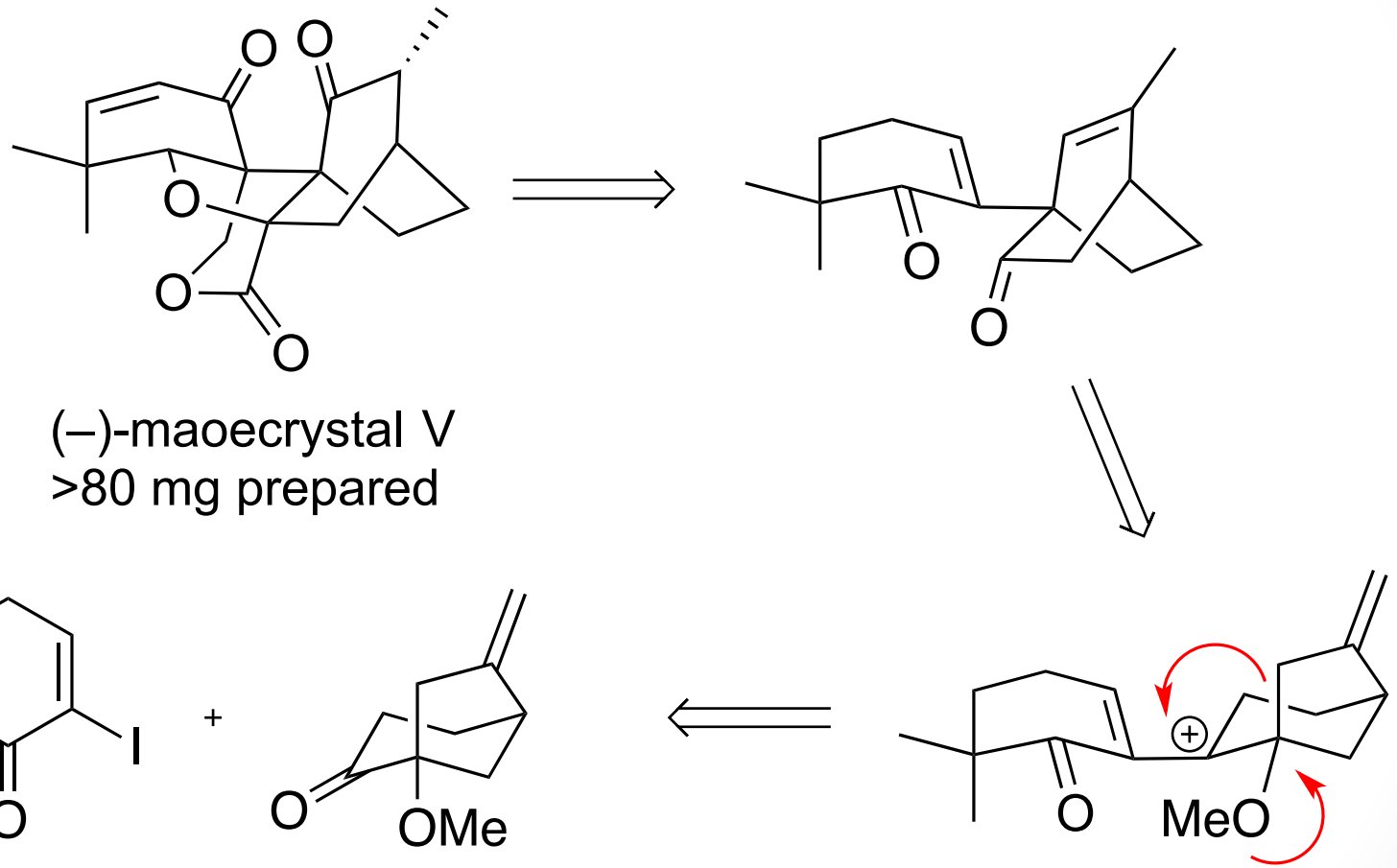
Tetrahydrofuran Ring Closure



End Game


DMDO
acetone, rt
1. InI_3 (5 mol %)
MgI_2 (1.2 eq)
MeCN, rt
2. DMP (3 eq), rt
Oxone (10 eq)
pH 7.4 buffer
76%
(–)-maoecrystal V

Recap



Biological Activity: A Mysterious Disappointment

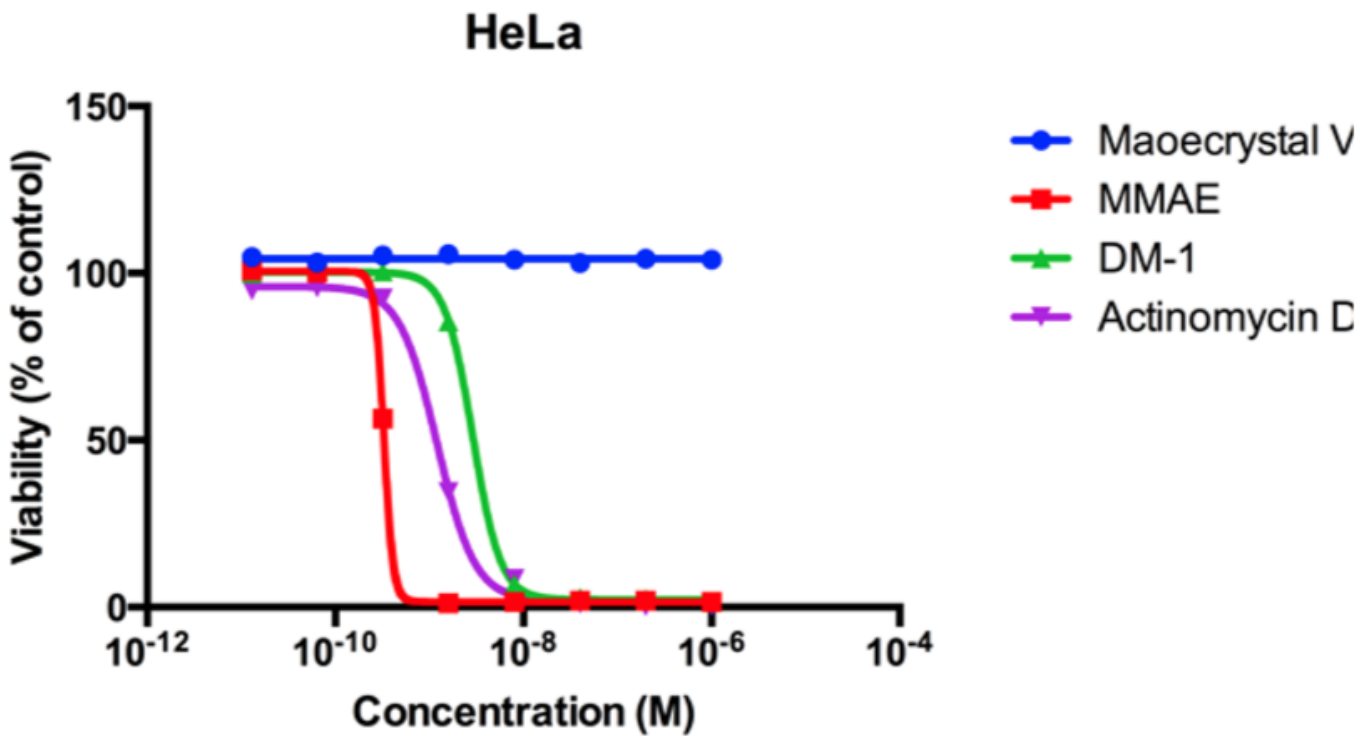
IC_{50} (μg/mL) reported by Sun et al. (isolation paper, 2004)

Cell line	K562	A549	BGC-823	CNE	HeLa
(–)-maoecrystal V	6430	26300	1470	(—)	**0.02**
cis-platin	0.38	1.61	0.25	2.31	0.99

Li, S.-H.; Wang, J.; Niu, X.-M.; Shen, Y.-H.; Zhang, H.-J.; Sun, H.-D.; Li, M. L.; Tian, Q.-E.; Lu, Y.; Cao, P.; Zheng, Q.-T. *Org. Lett.* **2004**, *6*, 4327.

IC_{50} (μg/mL) reported by Sun et al. (isolation paper, 2004)

Cell line	K562	A549	BGC-823	CNE	HeLa
(–)-maoecrystal V	6430	26300	1470	(—)	**0.02**
cis-platin	0.38	1.61	0.25	2.31	0.99



32 cell lines tested in 4 different labs: No activity!

Conclusions

- An 11 step enantioselective total synthesis of maeocrystal V was completed with an overall yield of ~5%
- The synthesis was strategically distinct
- Key steps include *anti*-Baldwin ring closure, La-mediated aldol
- A total of ~80 mg of the target was produced, allowing thorough confirmation of its biological inactivity

- Interesting blog posts on the synthesis
  - In the Pipeline (D. Lowe): 7/27/16
  - Open Flask (Baran group blog): 7/26/16