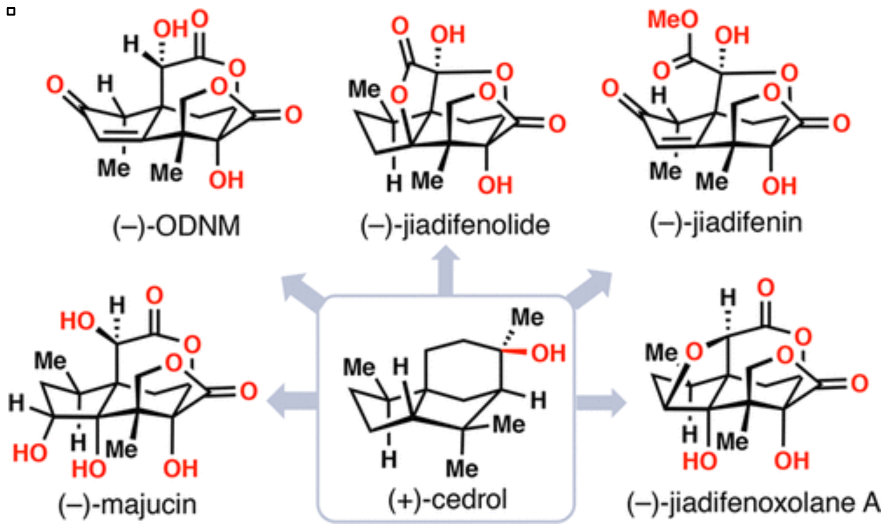
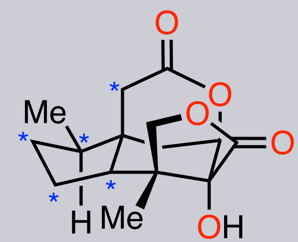
Total Syntheses of (–)-Majucin and (–)-Jiadifenoxolane A, Complex Majucin-Type *Illicium* Sesquiterpenes

Matthew L. Condakes, Kevin Hung, Stephen J. Harwood and Thomas J. Maimone
J. Am. Chem. Soc., 10.1021/jacs.7b11493



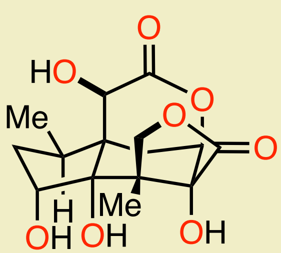
Steph McCabe
Wipf Group Current Literature
12/16/2017

The *Illicium* Family of Sesquiterpenes

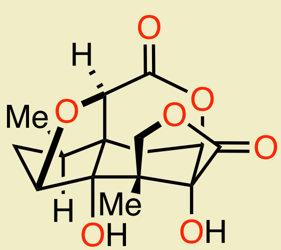


majucin core

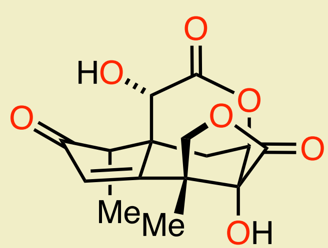
- The *Seco*-prezizaane family of sesquiterpenes are produced by *Illicium* evergreen shrubs/trees
- 20 members possess the majucin core with different oxygenation patterns
- Several members enhance neurite outgrowth: (–)-jiadifenolide (10 nM), (–)-jiadifenin, (–)-ODNM
- Axon degeneration and neuronal atrophy accompany chronic neurodegenerative diseases. Small molecules that promote growth of neurons are of interest



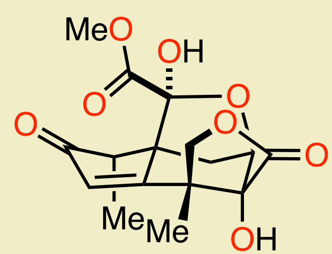
(–)-majucin



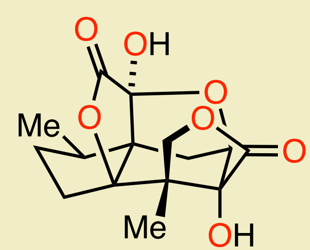
(–)-jiadifenoxolane A



(–)-ODNM

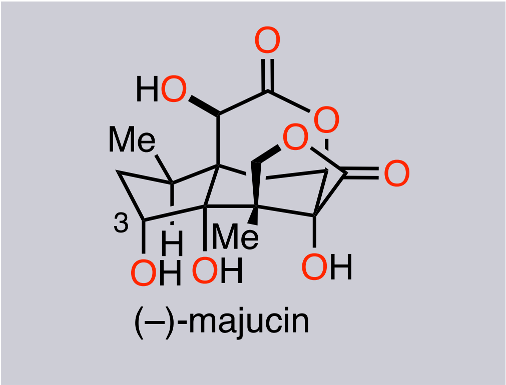


(–)-jiadifenin



(–)-jiadifenolide

(–)-Majucin



Illicium majus

Isolation: 1988 (Guangxi, China) by Sato

Illicium majus (Chinese flowering plant)

Characterization: 1D/2D NMR, IR, specific rotation, melting point, mass spectrometry, X-ray (*des*-C(3)-OH)

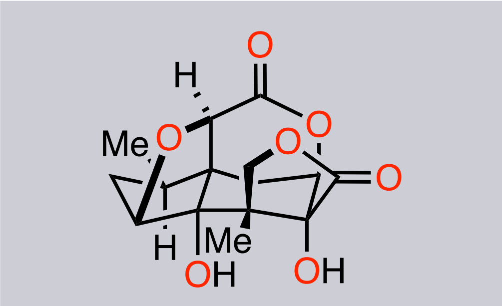
Structural features: fused γ-lactone, δ-lactone, and four stereodefined hydroxyl groups

Synthesis: Maimone (2017)

Bioactivity: None reported

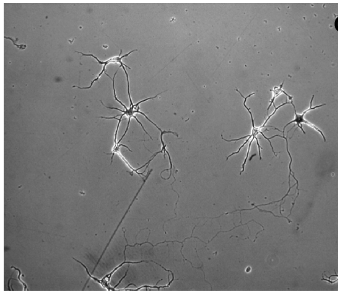
Yang, C.-S.; Kouno, I.; Kawano, N.; Sato, S. *Tetrahedron Lett.* 1988, *29*, 1165

(–)-Jiadifenoxolane A



(–)-jiadifenoxolane A

Illicium jiadifengpi



Morphology of neurons: 10 µM of (–)-jiadifenoxolane A

<u>*Isolation*</u>: 2009 (Yunnan, China) by Fukuyama

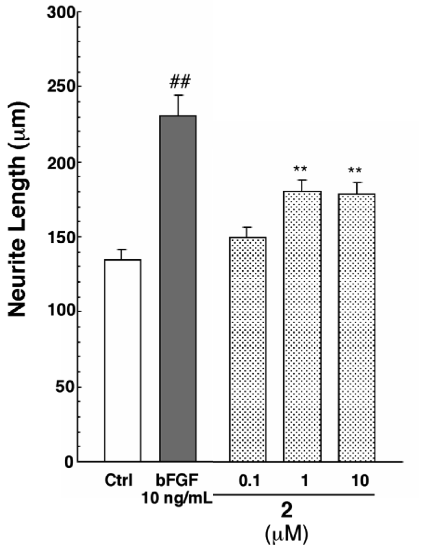
Illicium jiadifengpi (Chinese flowering plant)

<u>*Characterization*</u>: 1D/2D NMR, IR, specific rotation, mass spectrometry

<u>*Structural features:*</u> fused γ-lactone, δ-lactone, two stereodefined tertiary hydroxyl groups, strained bridging tetrahydrofuran ring

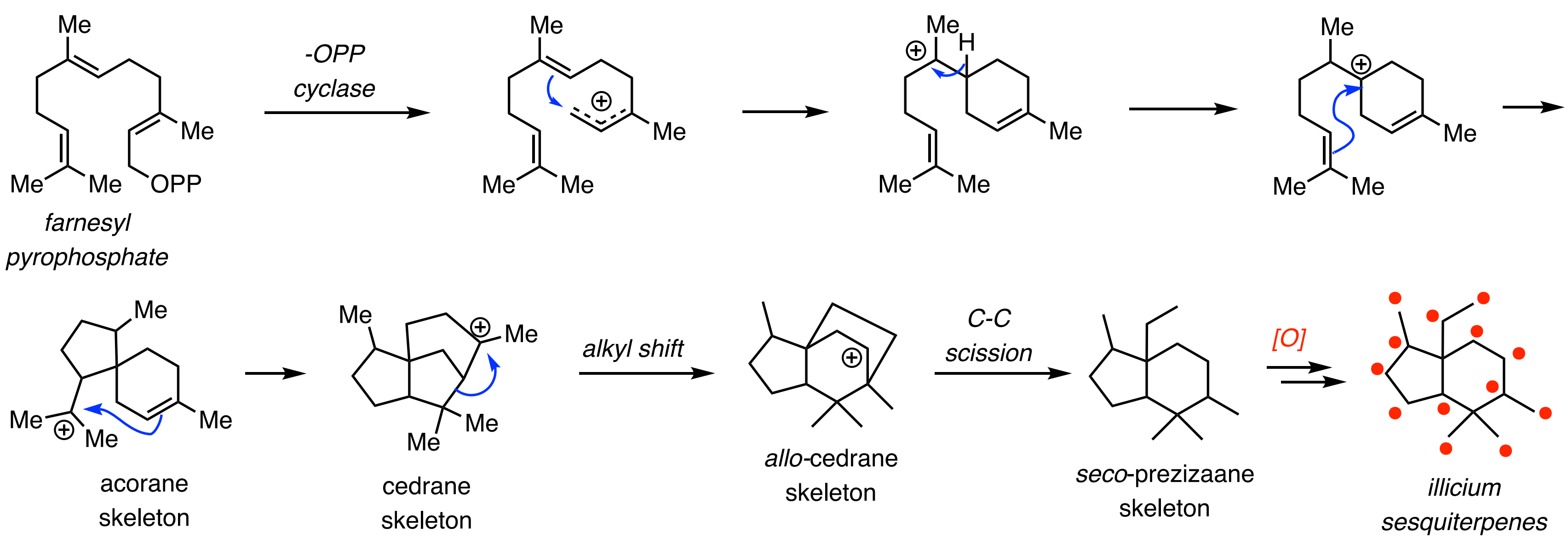
<u>*Synthesis:*</u> Maimone (2017)

<u>*Bioactivity*</u>: Promotes neurite outgrowth in primary cultured rat cortical neurons

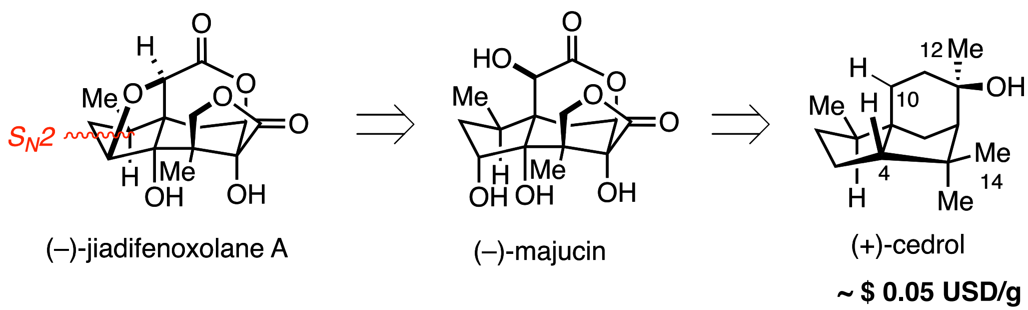


Kubo, M.; Okada, C.; Huang J.-M.; Harada, K.; Hideaki, H.; Fukuyama, Y. *Org. Lett.*, 2009, *11*, 5190

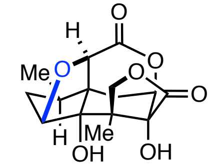
Biosynthetic Pathway

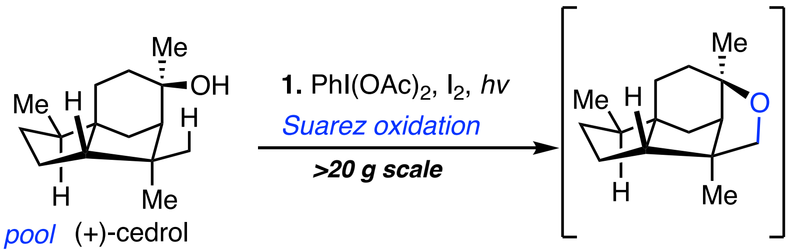


This Work



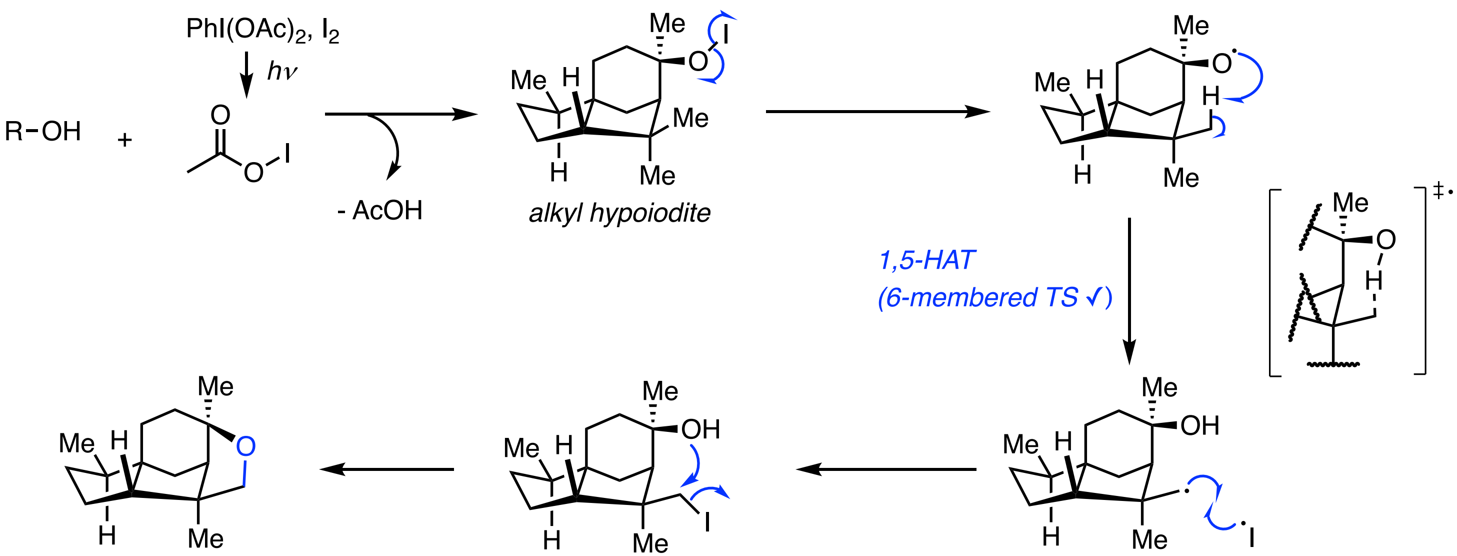
Double Suárez Oxidation





chiral pool (+)-cedrol
~ $ 0.05 USD/g

<u>*Mechanism?*</u>

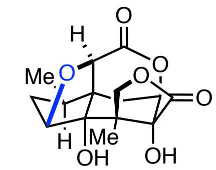


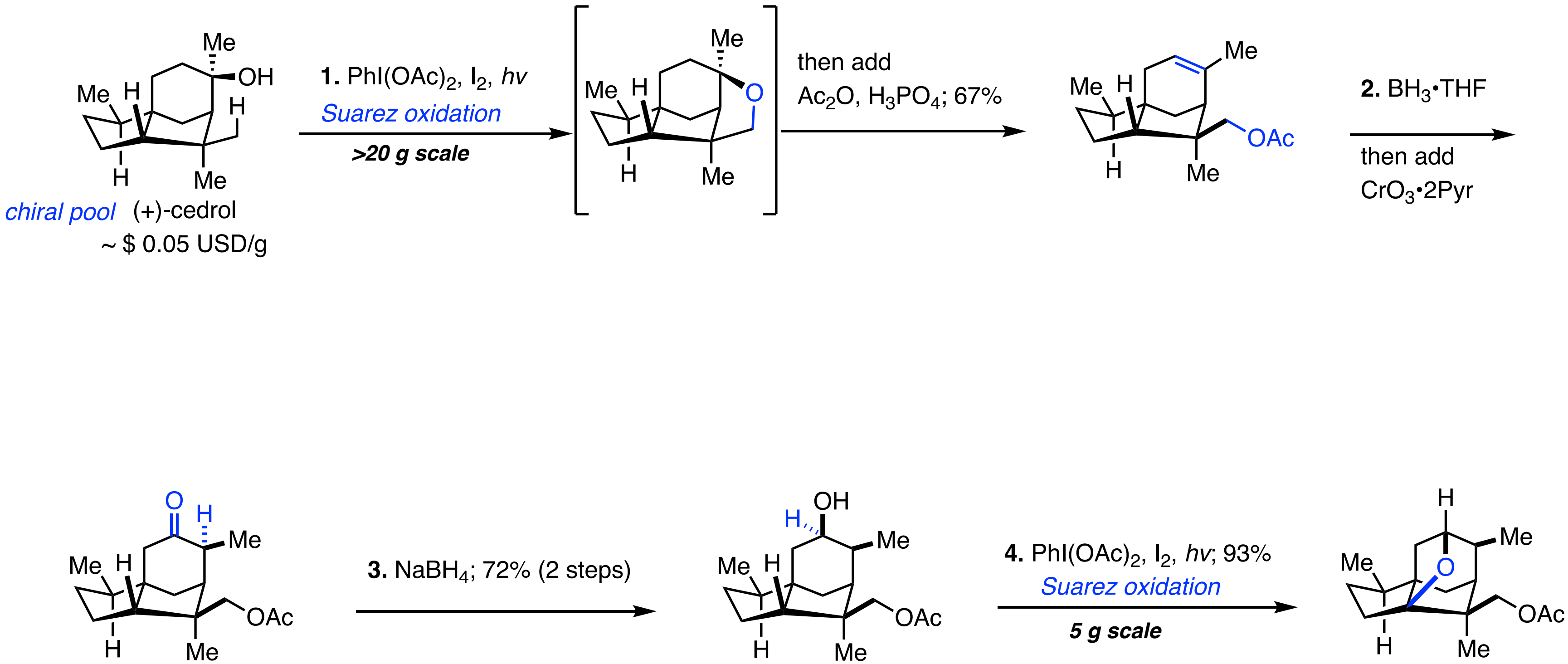
<u>*for HAT reactions*</u>

- Ideal arrangement of C-H—X is close to 180°
- Distance between X• and C-H is < 3Å

Courtneidge J. L.; Lusztyk, J.; Page, D.; *Tetrahedron Lett.*, 1994, *35*, 1003; Mowbray, C., E.; Pattenden, G. *Tetrahedron Lett.*, 1993, *34*, 127; Dorta, R. L.; Francisco, C. G.; Freire, R.; Suaŕez, E. *Tetrahedron Lett.* 1988, *29*, 5429.

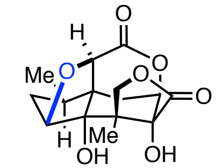
Double Suárez Oxidation

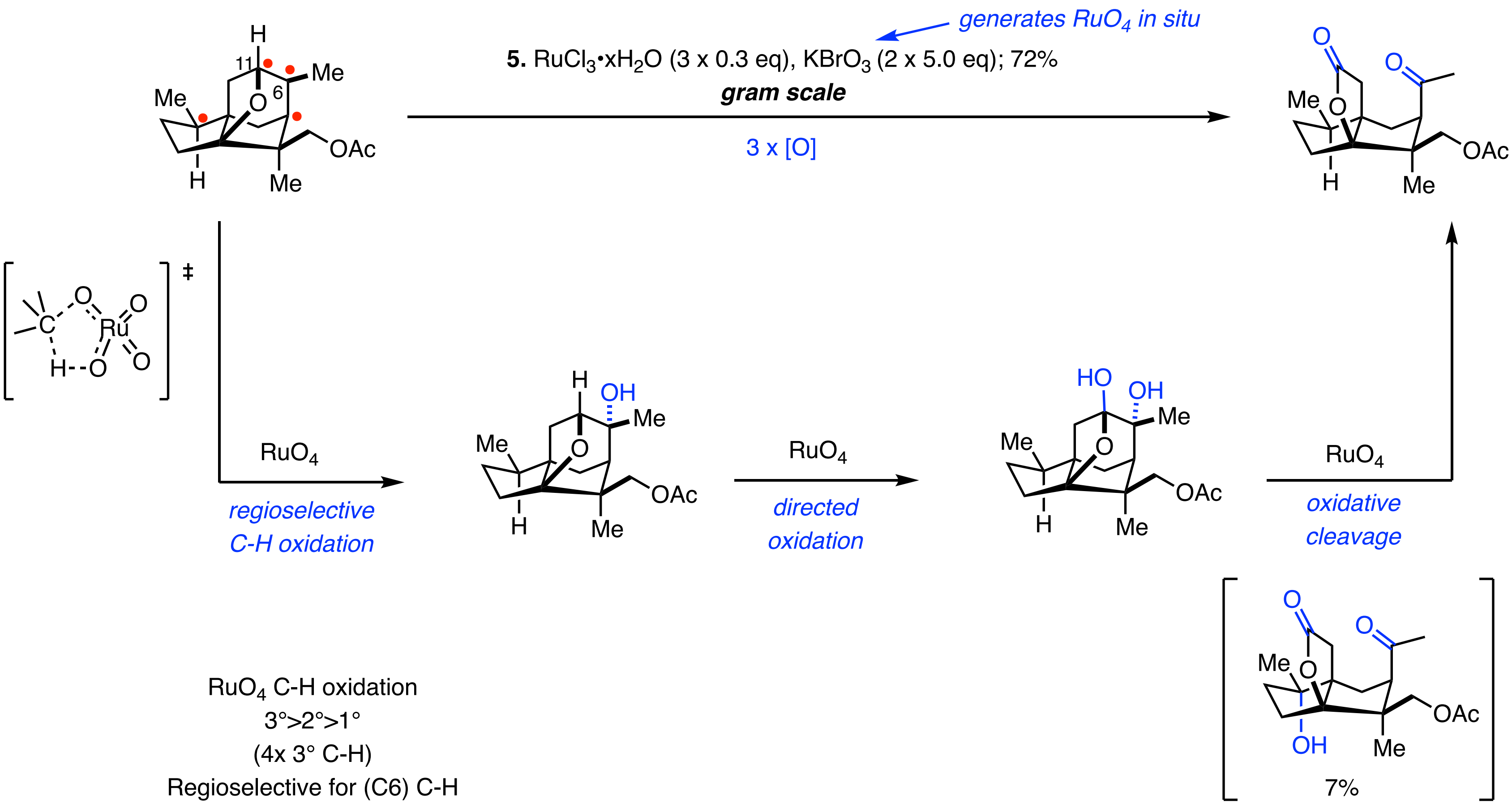




Courtneidge J. L.; Lusztyk, J.; Page, D.; *Tetrahedron Lett.*, 1994, *35*, 1003; Mowbray, C., E.; Pattenden, G. *Tetrahedron Lett.*, 1993, *34*, 127; Dorta, R. L.; Francisco, C. G.; Freire, R.; Suaŕez, E. *Tetrahedron Lett.* 1988, *29*, 5429.

RuO_4 Triple Oxidation

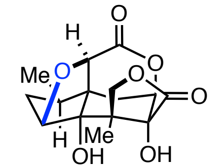


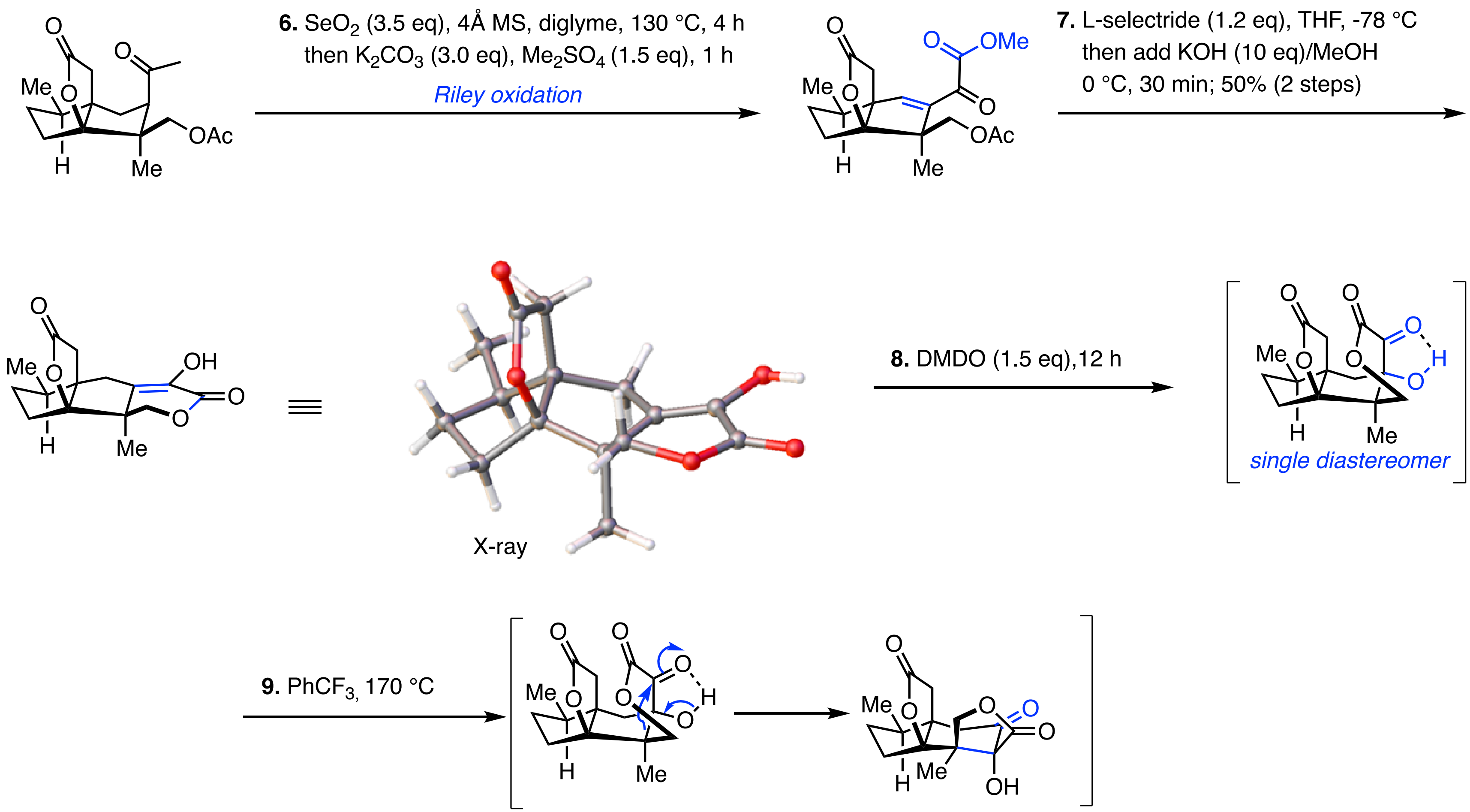


RuO_4 C-H oxidation
3°>2°>1°
(4x 3° C-H)
Regioselective for (C6) C-H

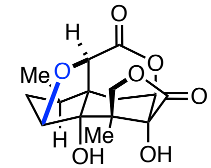
Bakke, J., M.; Frøhaug, A., E. *J. Phys. Org. Chem.*, 1996, **9**, 507

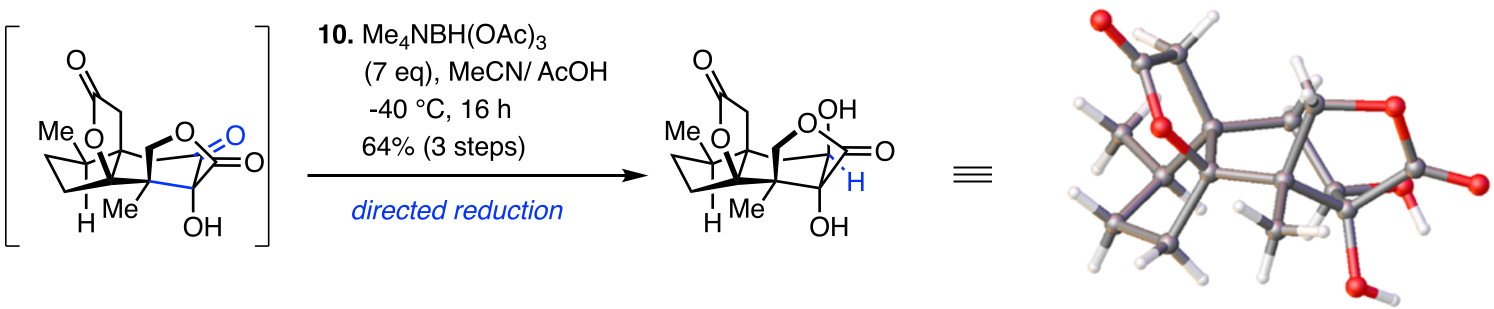
Rearrangement



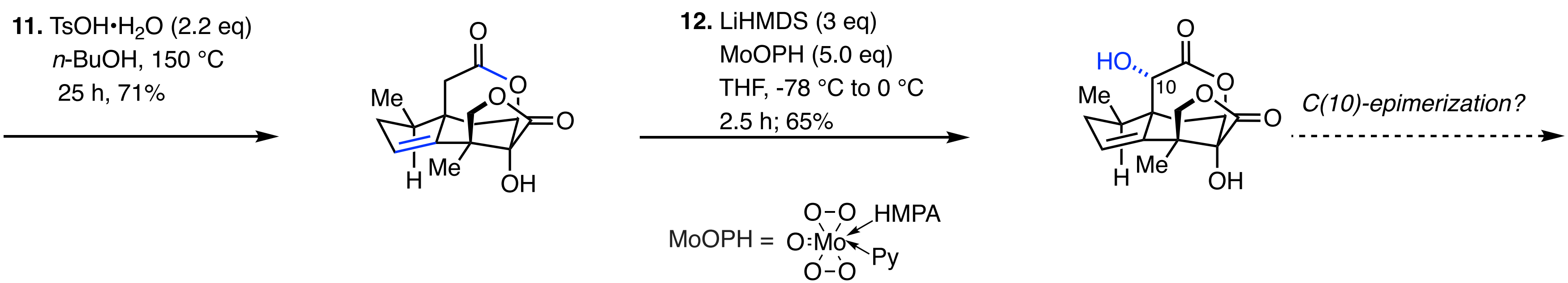


Formation of the δ-Lactone Ring

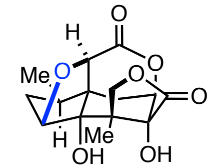




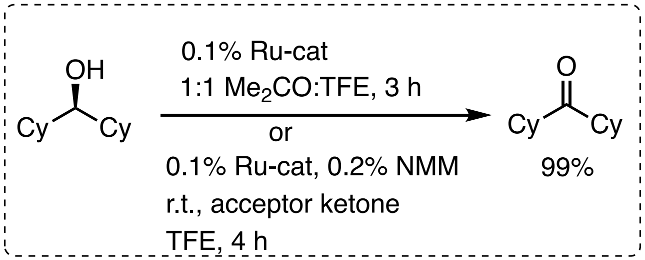
X-ray

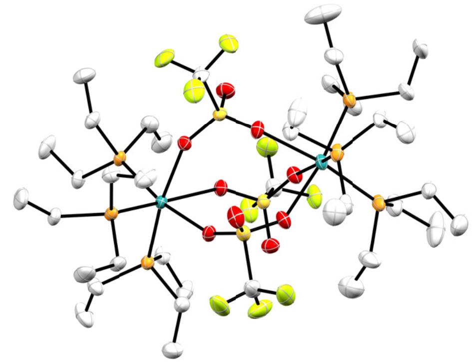


Epimerization of C(10)-OH



- $[Ru_2(PEt_3)_6(OTf)_3][OTf]$ catalyzes the selective oxidation of secondary alcohols

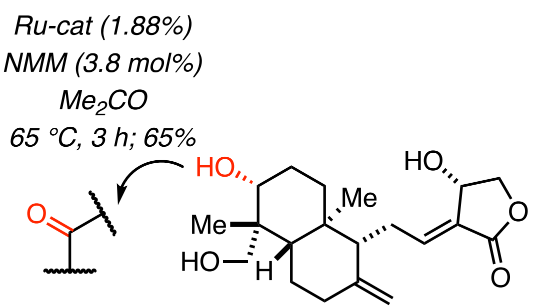


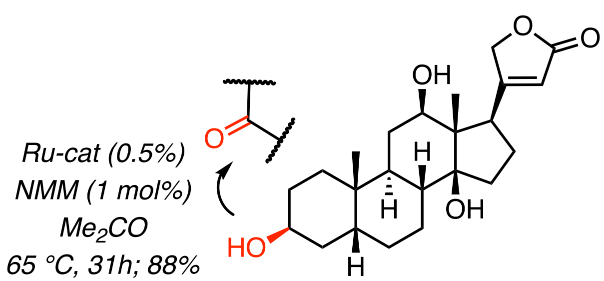


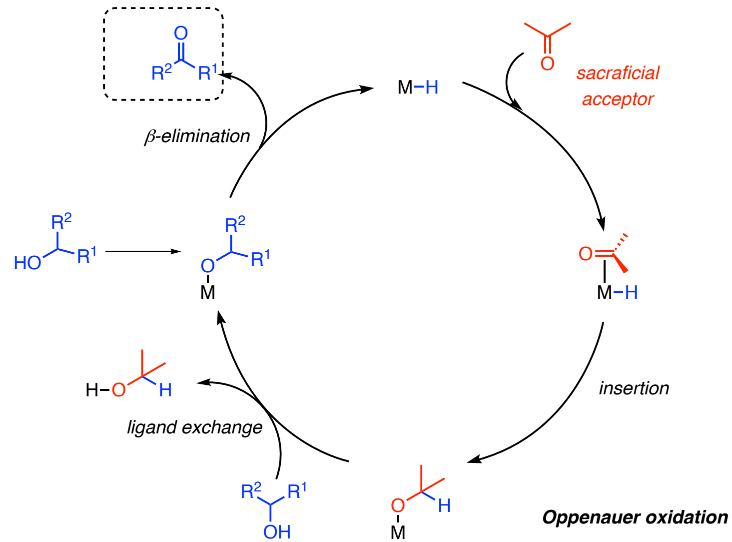
Ru-cat = $[Ru_2(PEt_3)_6(OTf)_3][OTf]$

Catalyst is more selective for:

- electron rich 2° OH
- less hindered alcohols

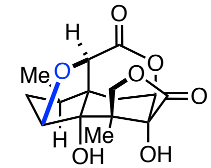




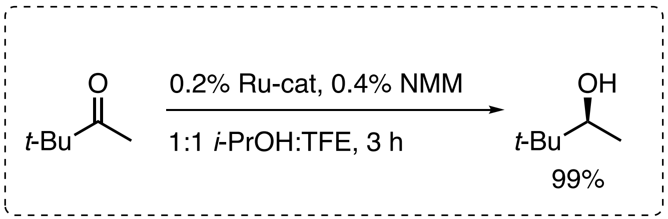


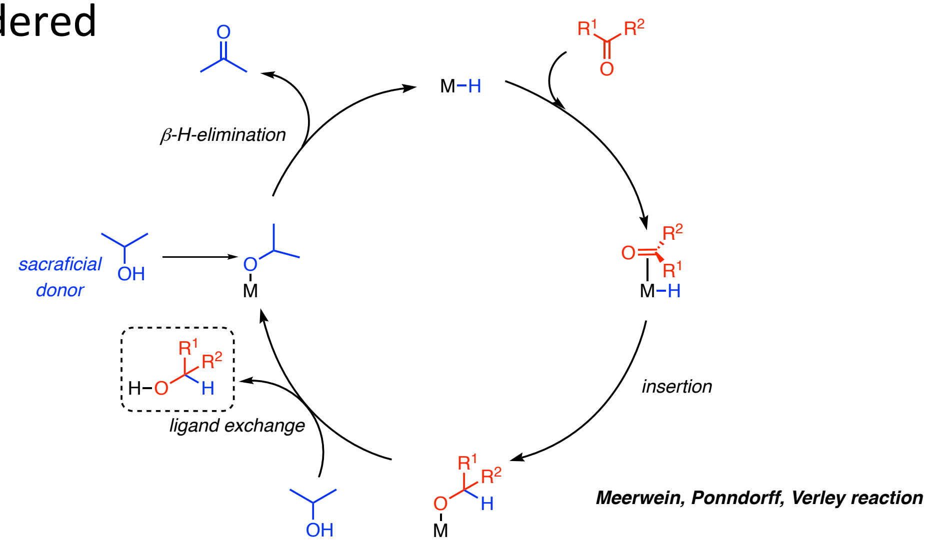
Hill, C.K.; Hartwig, J.F. *Nature Chem.* **2017**, 9, 1213

Epimerization of C(10)-OH

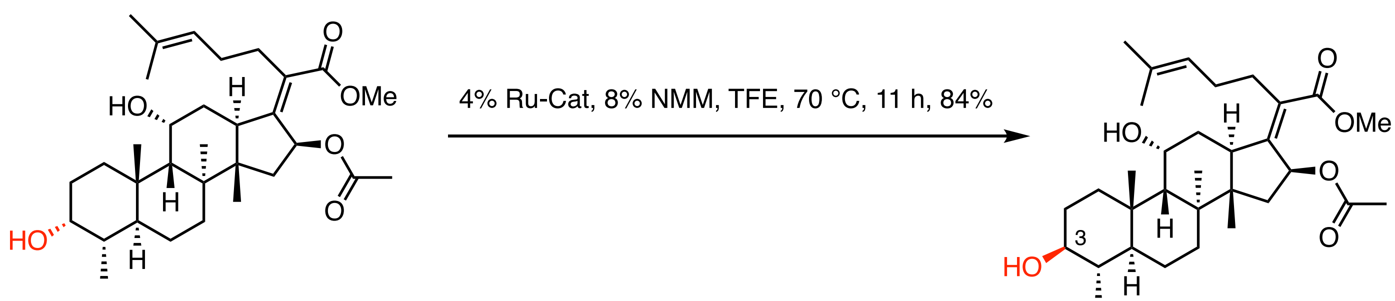


- Ru complex catalyzes the reverse transfer hydrogenation from isopropanol to hindered ketones





- Ru complex catalyzes the site selective one-step epimerization of secondary alcohols in the absence of an acceptor

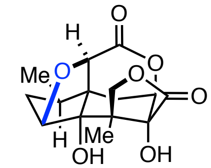


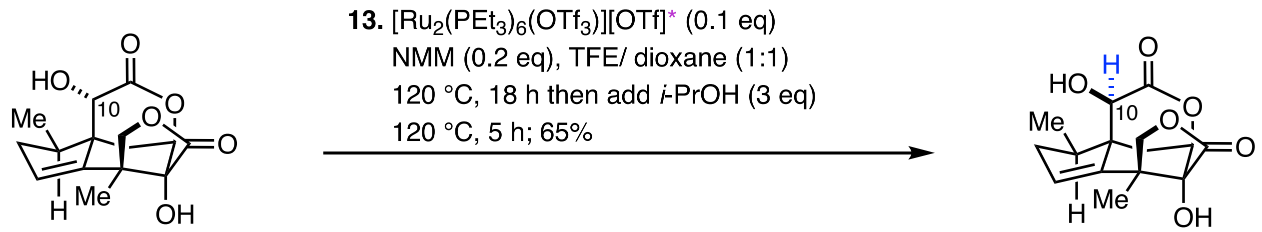
fusidic acid methyl ester

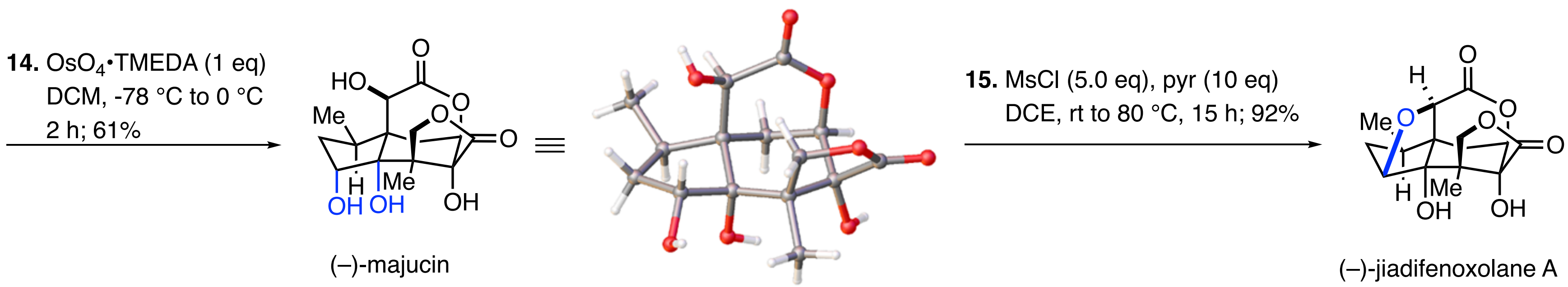
3-*epi*-fusidic acid methyl ester

Hill, C.K.; Hartwig, J.F. *Nature Chem.* **2017**, 9, 1213

Epimerization of C(10)-OH/ Completion of the Syntheses







(–)-majucin
7.5 mg

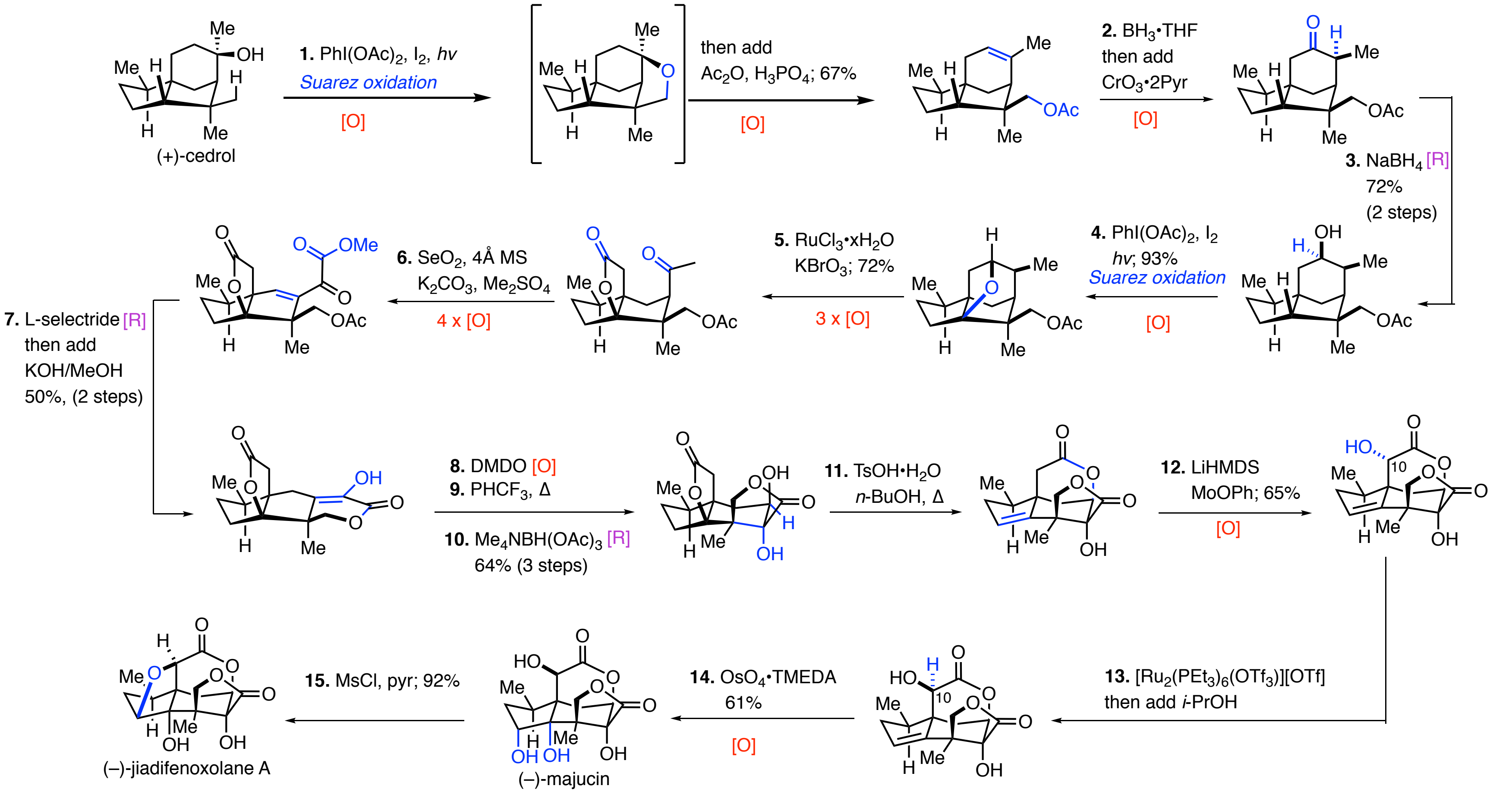
X-ray

(–)-jiadifenoxolane A
2.6 mg

* provided by Hartwig group;

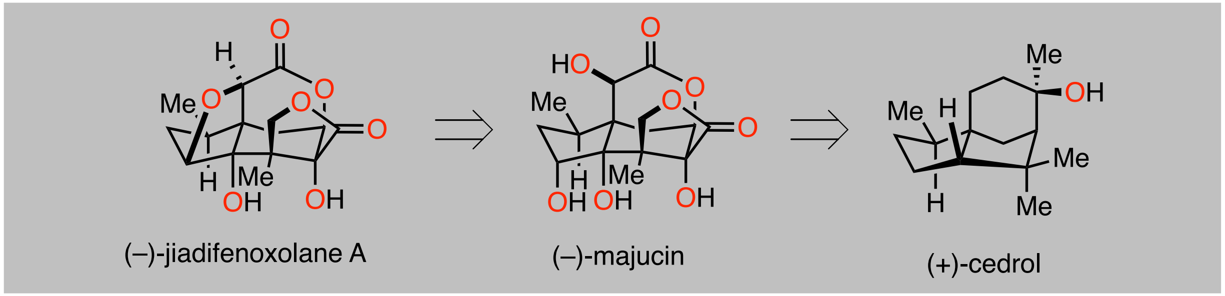
Hill, C.K.; Hartwig, J.F. *Nature Chem.* **2017**, 9, 1213

Summary of Synthesis



- 13 oxidation reactions [O]
- 3 reduction reactions [R]

Summary



- The first total synthesis of (–)-majucin (7.5 mg) was accomplished in 14 steps and 2.2% overall yield
- The first totals synthesis of (–)-jiadifenoxolane A (2.6 mg) was accomplished in 15 steps and 2.0% overall yield
- Exhaustive oxidation of (+)-cedrol scaffold (13 [O] reactions)
  - Site-selective C(sp^3)–H bond oxidation
- However, 3 reductive steps were necessary for oxidation state and stereo-chemical adjustments
- First application of $[Ru_2(PEt_3)_6(OTf)_3][OTf]$ catalyzed 2° alcohol epimerization in total synthesis