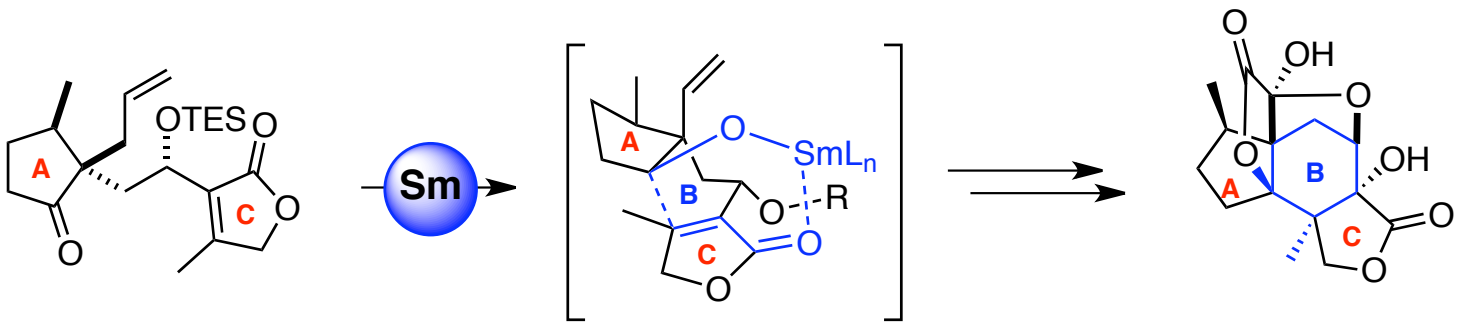
Total Synthesis of Jiadifenolide

Ian Paterson,* Mengyang Xuan, and Stephen M. Dalby

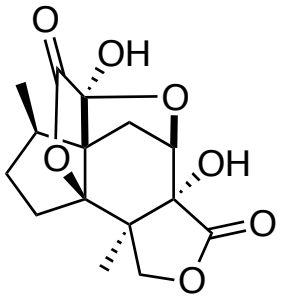
Angew. Chem. Int. Ed. **2014 May 23**. *doi: 10.1002/anie.201404224.*



Raffaele Colombo – 6/7/2014

Jiadifenolide

Jiadifenolide is a complex sesquiterpenoid first isolated from the fruit of the Chinese plant *Illicium* jiadifengpi by Fukuyama and coworkers in 2009.



Jiadifenolide

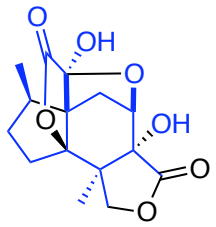
Potent neurotrophic activities: potential therapeutic treatment of neurodegenerative diseases.

Low natural abundance (1.5 mg/kg plant material)
Unkown structure–activity relationship (SAR)

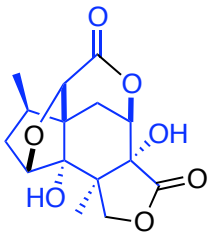
Attractive target for total synthesis

Jiadifenolide and related compounds

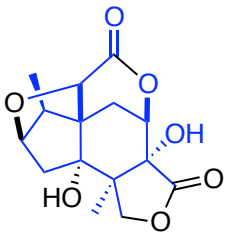
Natural products from *Illicium* species with potent neuropharmacological activities containing a *seco*-prezizaane core



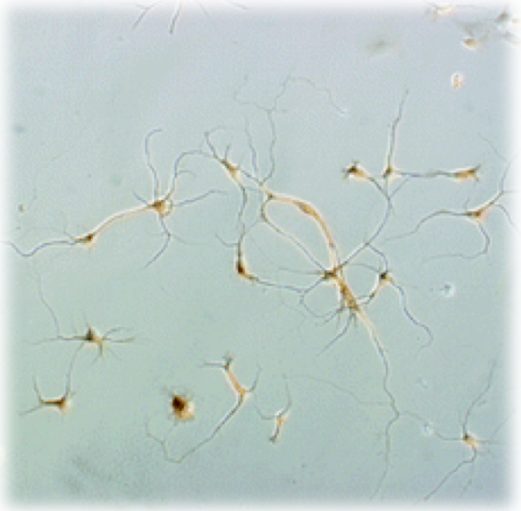
Jiadifenolide
Theodorakis 2011,
Sorensen 2014,
Paterson 2014

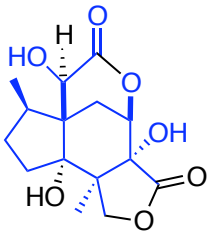


Jiadifenoxolane A

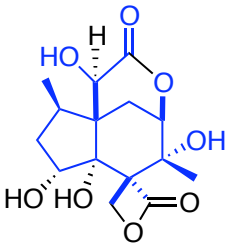


Jiadifenoxolane B

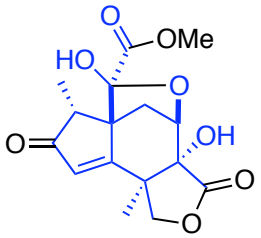




Neomajucin

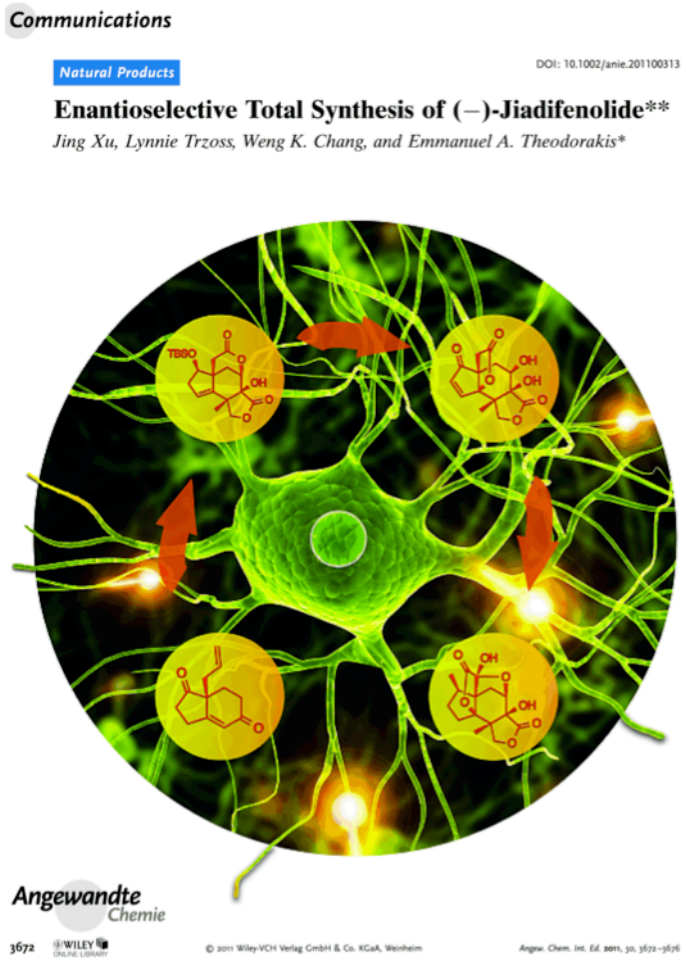


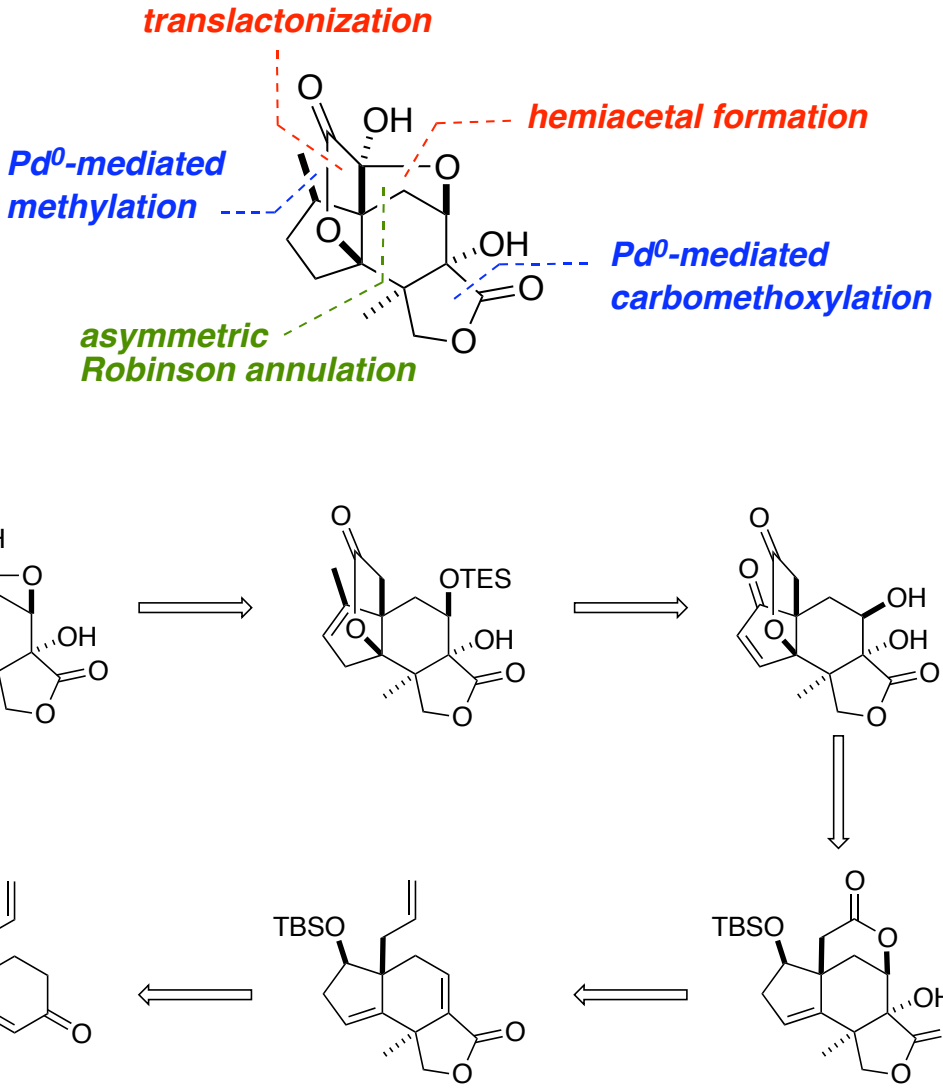
Anisatin
Yamada 1990,
Fukuyama 2012



Jiadifenin
Danishefsky 2006,
Theodorakis 2011,
Zhai 2012

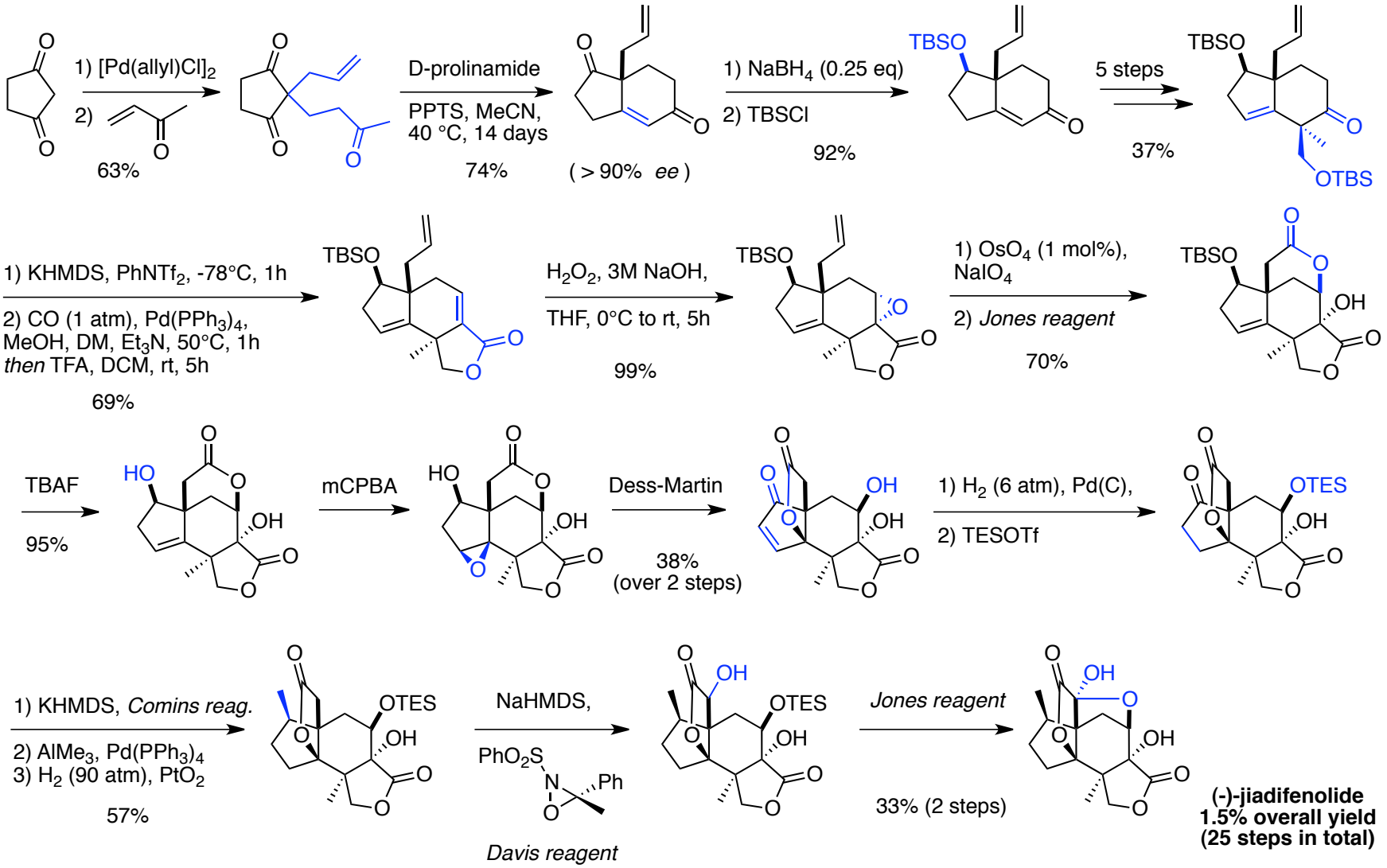
Previous total synthesis – Theodorakis (2011)





Angew. Chem. Int. Ed. **2011**, *50*, 3672 –3676

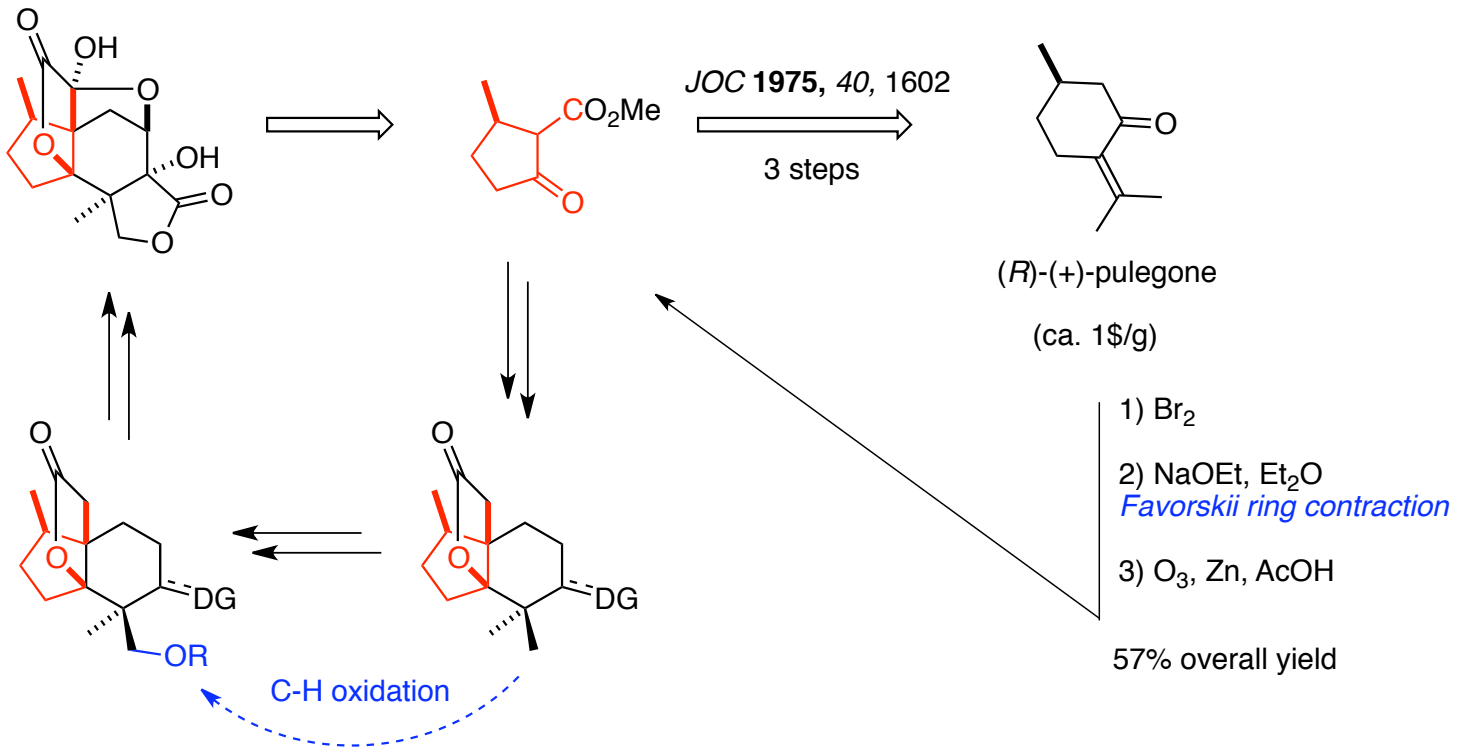
Previous total synthesis – Theodorakis (2011)



(conditions employed by the Danishefsky group toward the synthesis of jiadifenin)

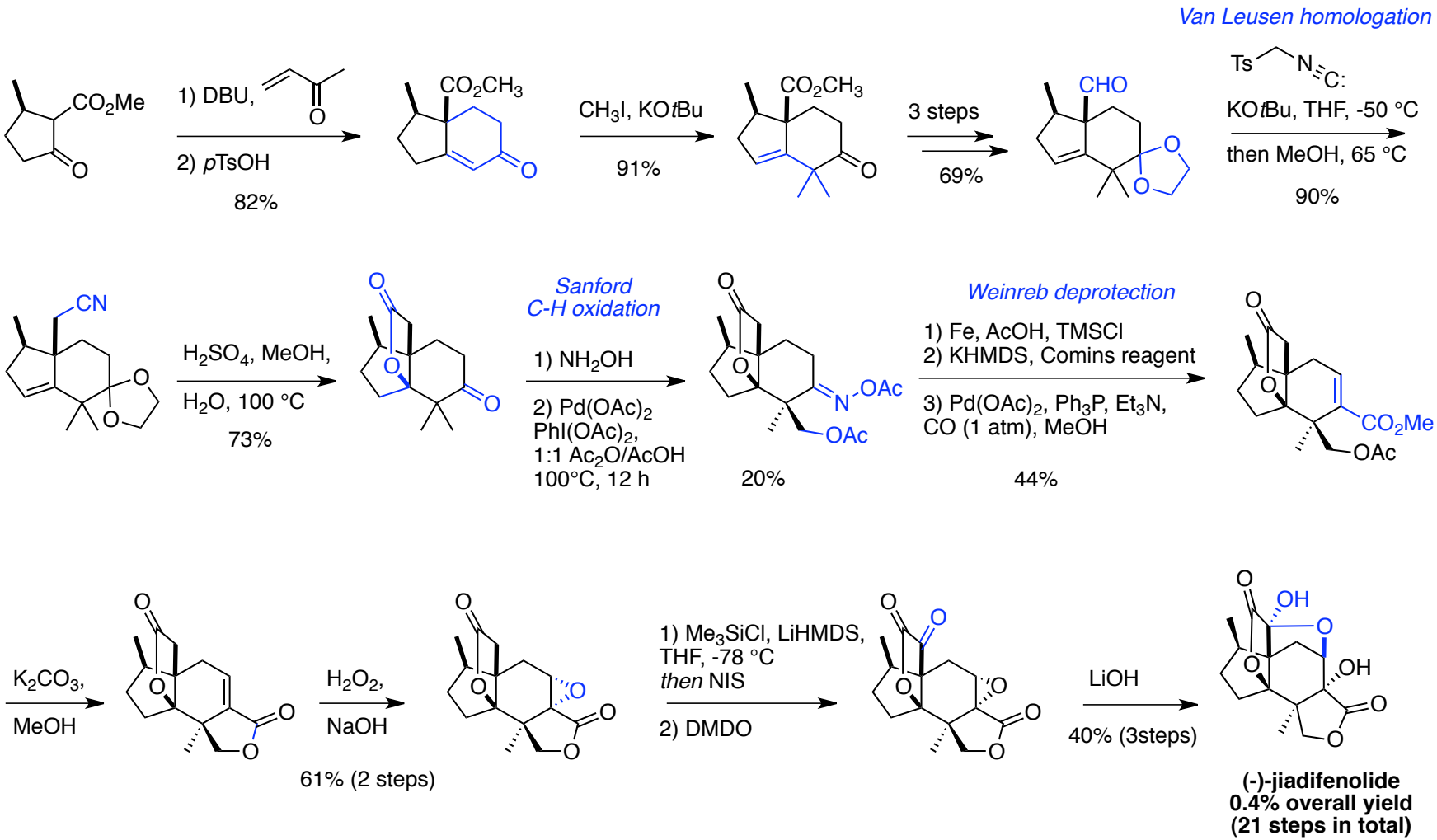
Angew. Chem. Int. Ed. **2011**, *50*, 3672 –3676

Previous total synthesis – Sorensen (2014)



Angew. Chem. Int. Ed. **2014**, *53*, 5332 – 5335

Previous total synthesis – Sorensen (2014)

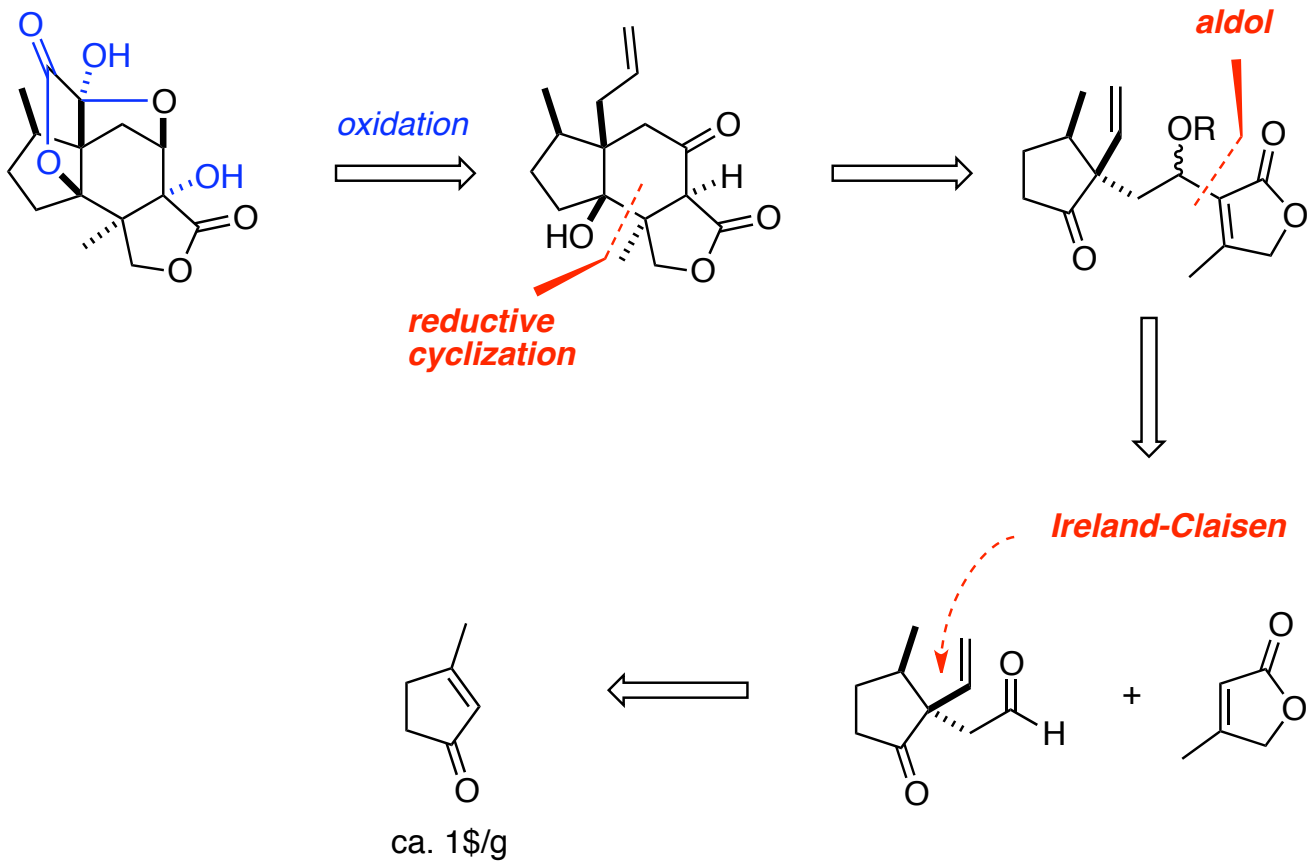


for Sanford's C-H oxidation see:
J. Am. Chem Soc. **2004**, *126*, 9542-9543
Org. Lett. **2010**, *12*, 532-535
Acc. Chem. Res. **2012**, *45,* 936-946.

for Weinreb acetyl-oxime deprotection see:
Tetrahedron Lett. **2010**, *51*, 3555-3557

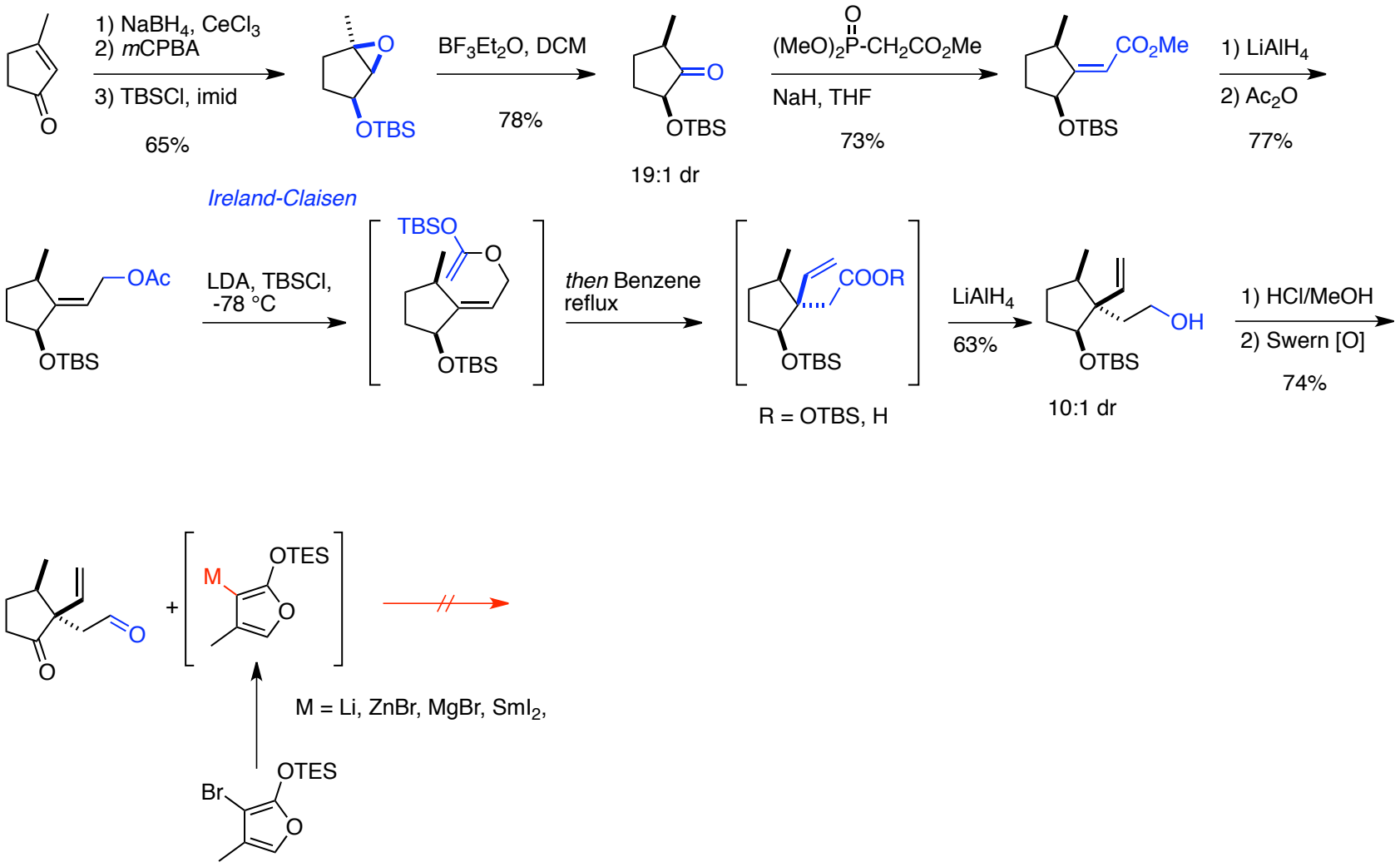
Angew. Chem. Int. Ed. **2014**, *53*, 5332 – 5335

Current work – retrosynthetical analysis

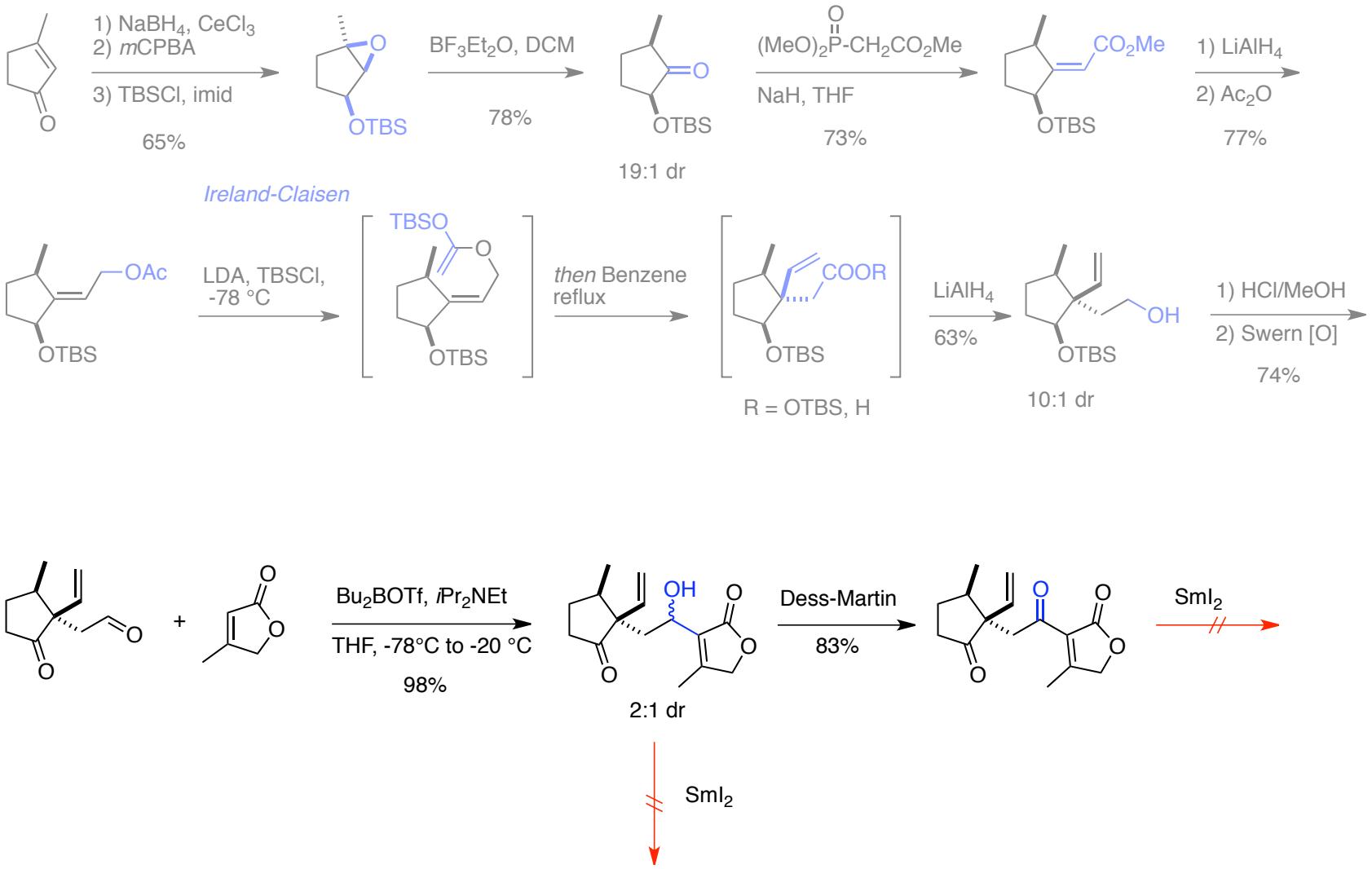


Paterson *et al., Angew. Chem. Int. Ed.* . **2014 May 23**. *doi: 10.1002/anie.201404224.*

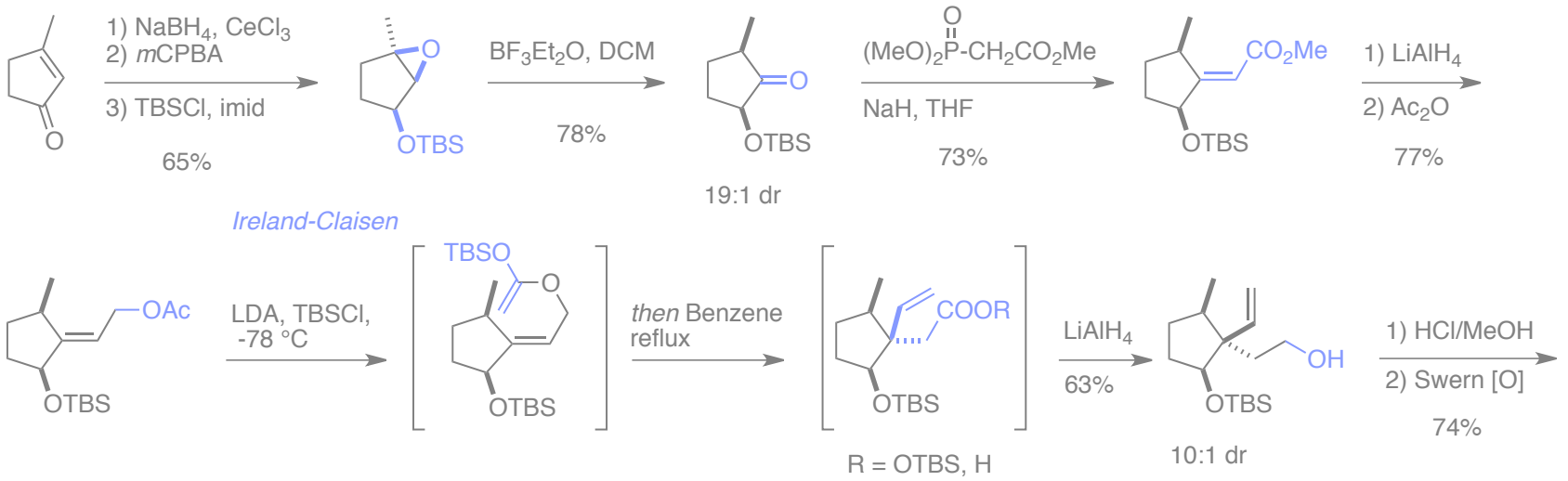
Synthesis – first steps

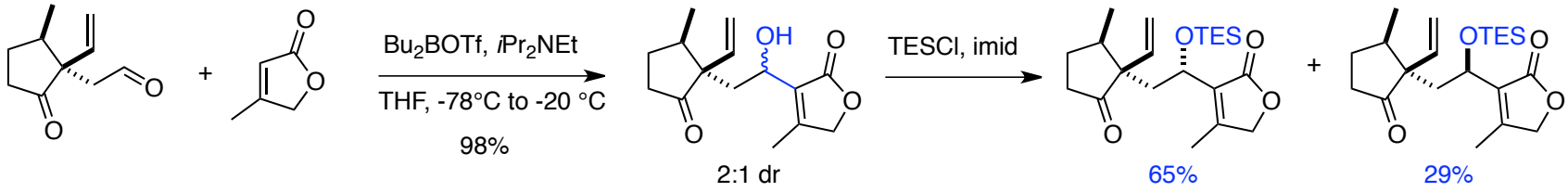


Unsuccessful Sm-mediated coupling

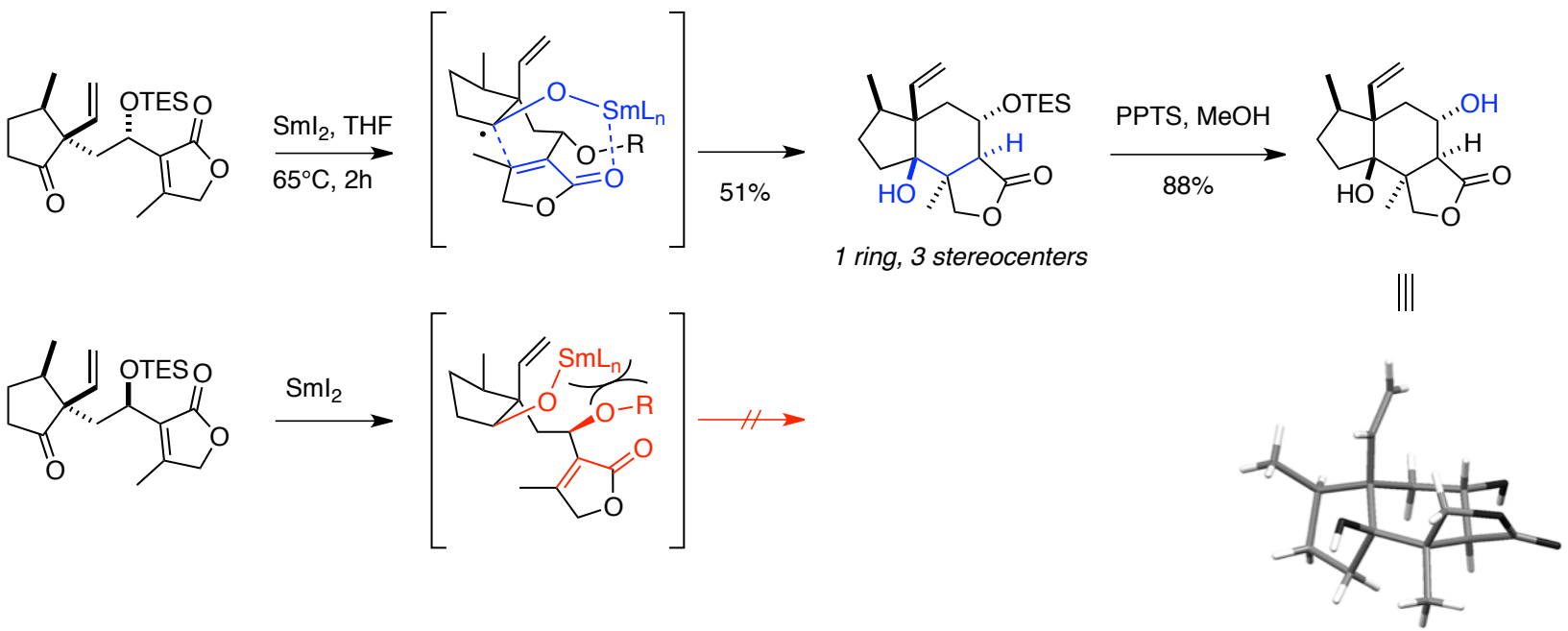


Key step: Sm-mediated reductive cyclization



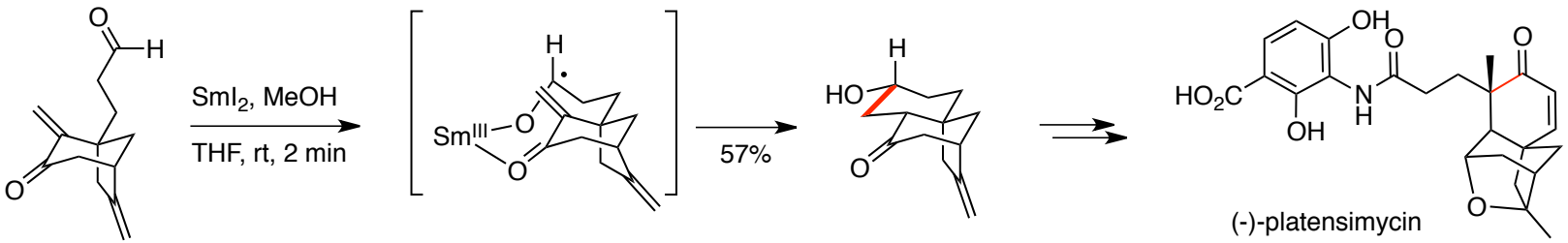


Proposed mechanism: chelated intermediate

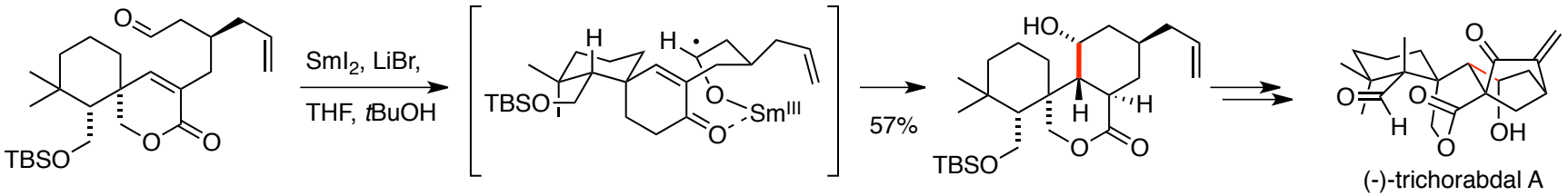


Previous Sm-mediated cyclization

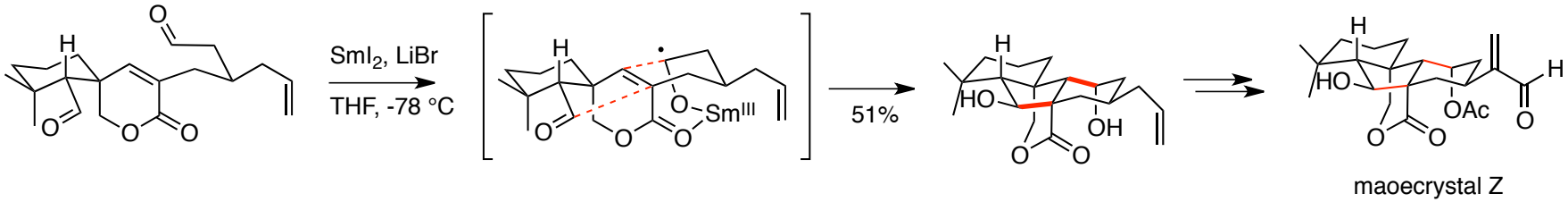
Nicolaou et al., *Angew. Chem. Int. Ed.* **2008,** *47,* 944



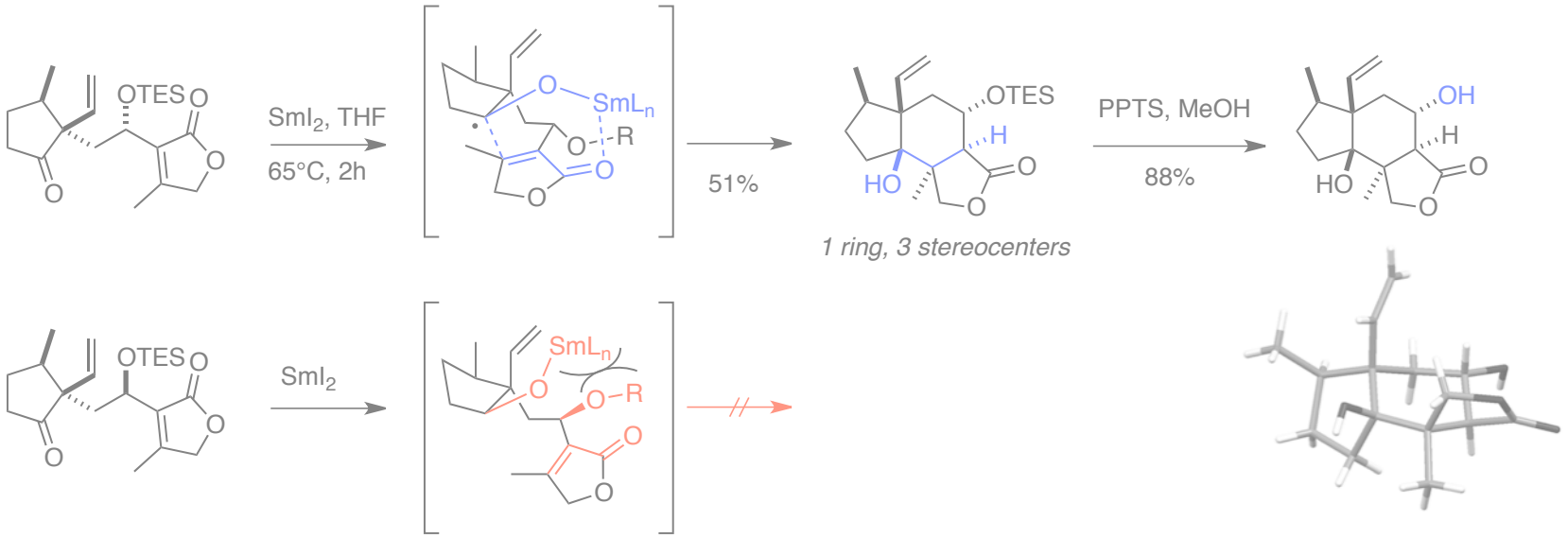
Reisman et al., *J. Am. Chem. Soc.* **2013,** *135,* 11764

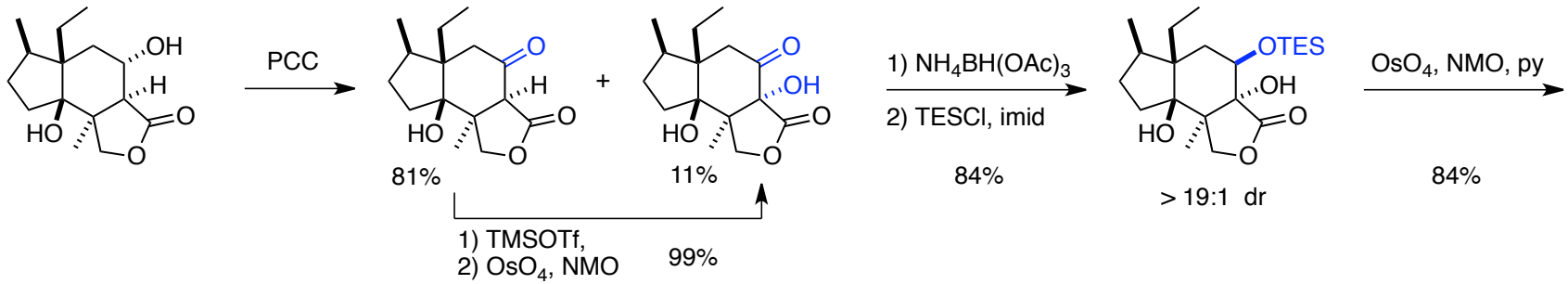


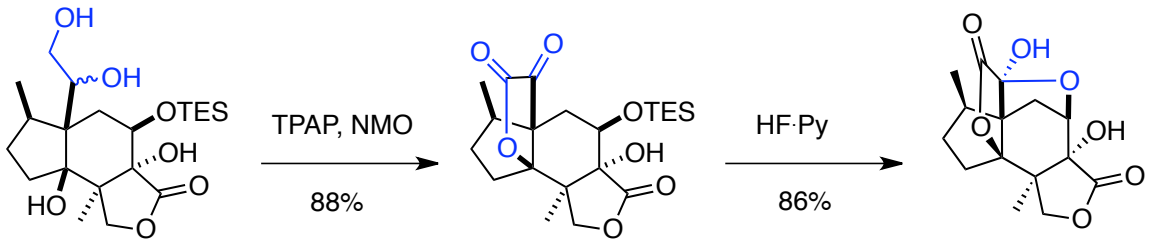
Reisman et al., *J. Am. Chem. Soc.* **2011,** *133,* 14964



Final steps – oxidase phase







jiadifenolide
2.3% overall yield
(23 steps in total)

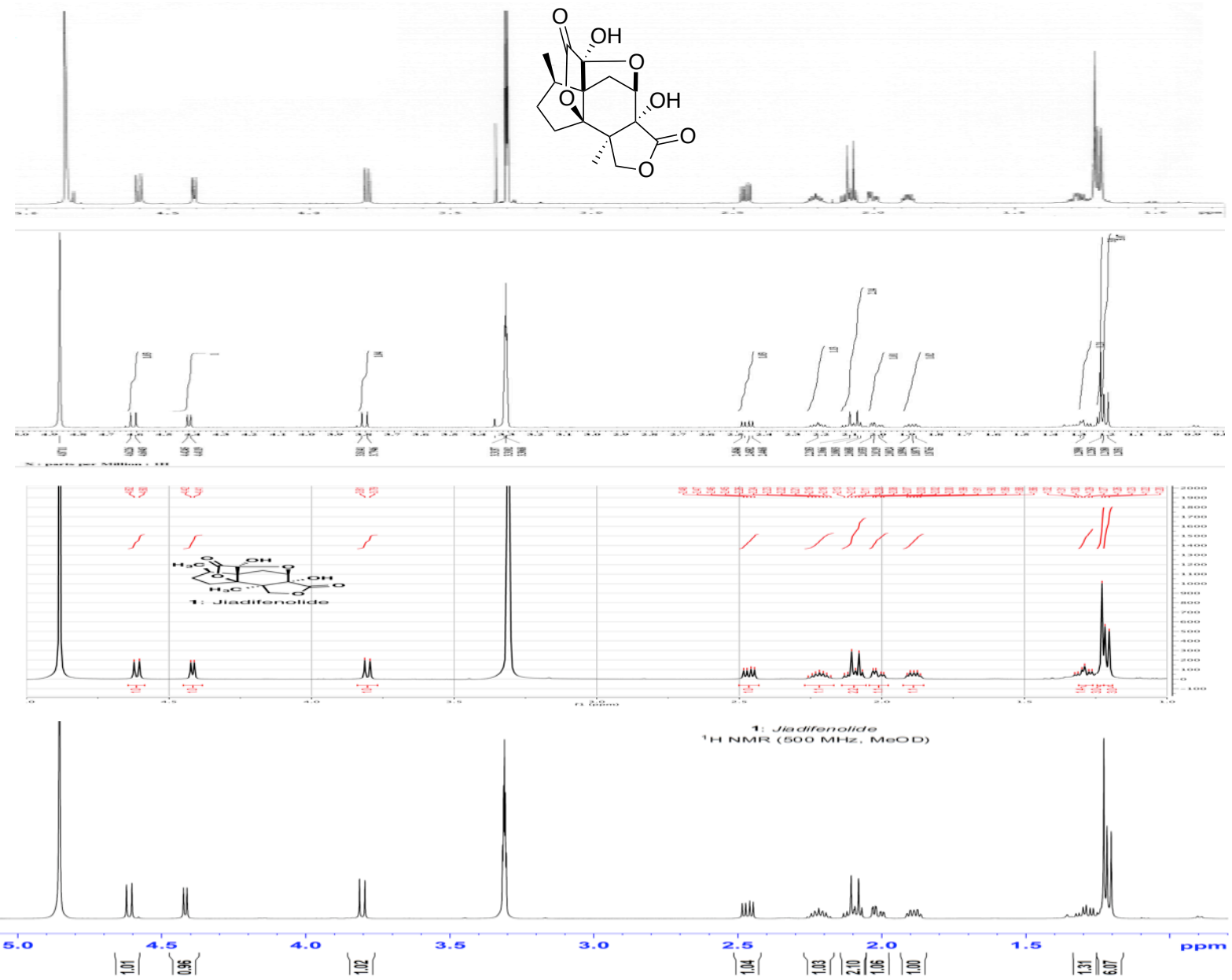
NMR spectra comparison

Fukuyama (2009)

Theodorakis (2011)

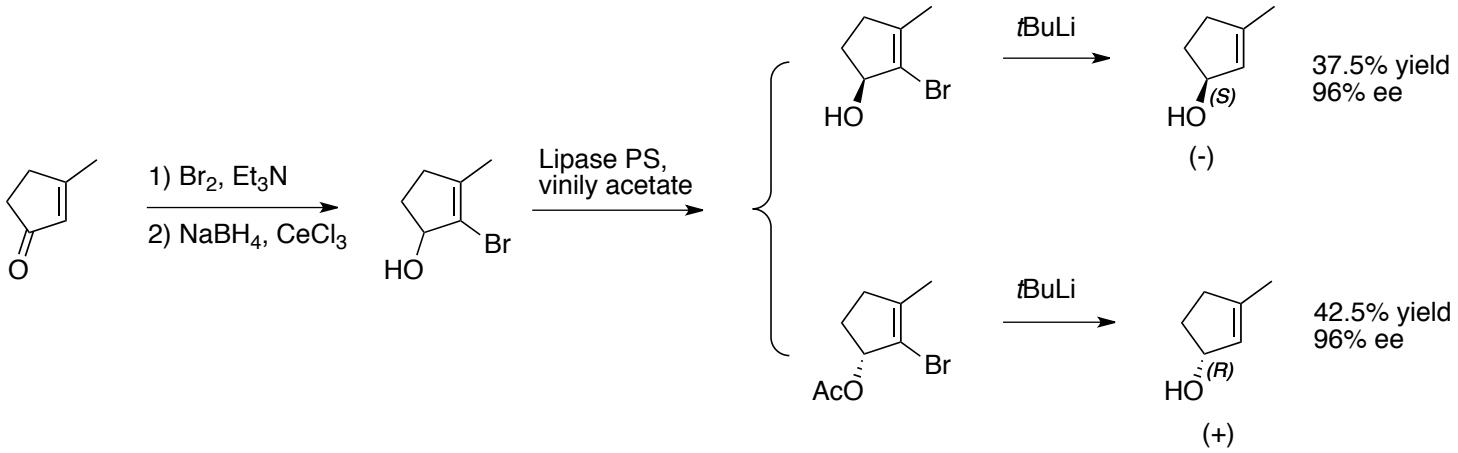
Sorensen (2014)

Paterson (2014)



Paterson future work

Enantiomeric version of the synthesis



X. Zhou, P. J. De Clercq, J. Gawronski*, Tetrahedron: Asymmetry*, **1995**, *6*, 1551.

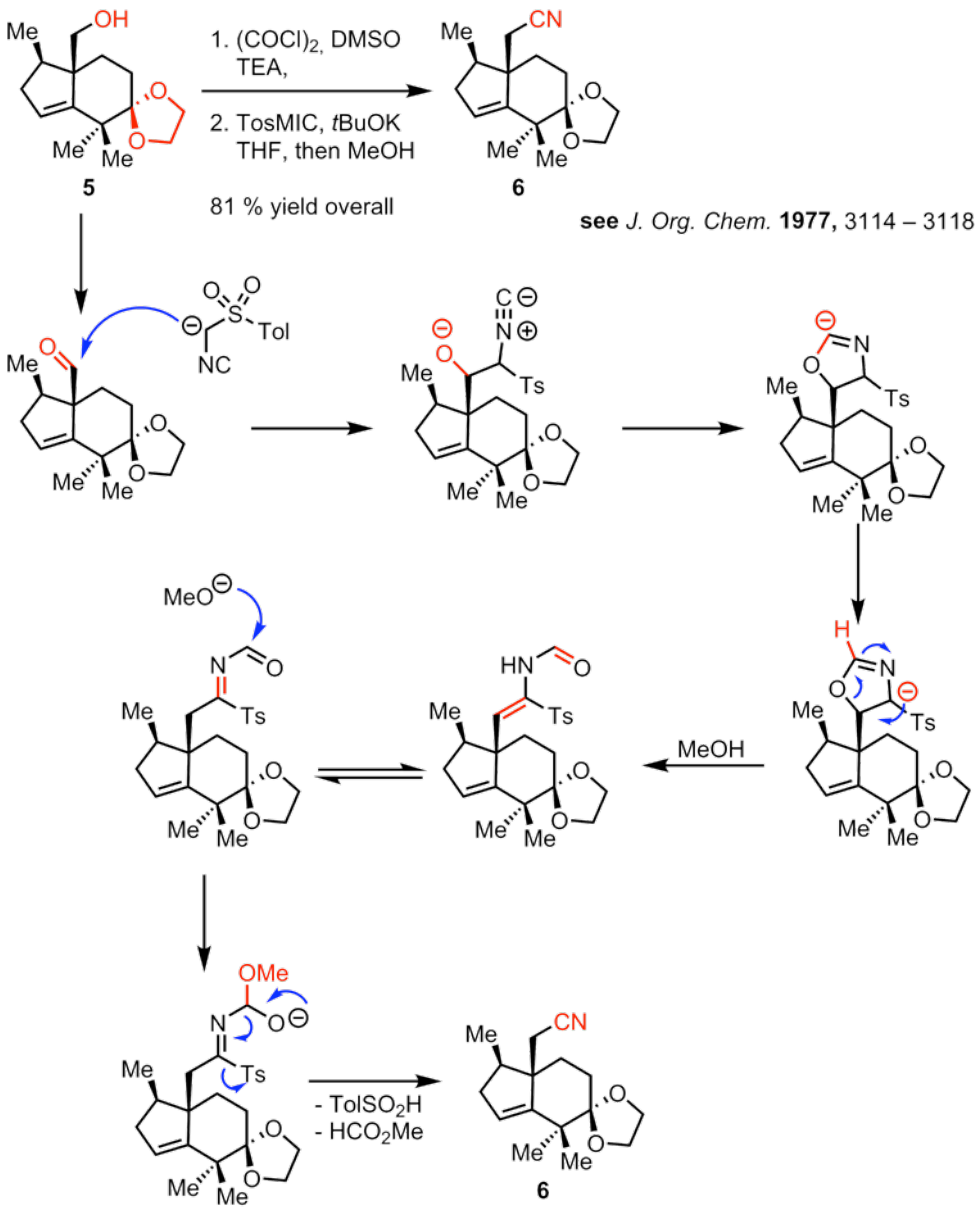
Analogues for biologiacal screening

Conclusion

Total synthesis of Jiadifenolide:

- 23 steps, 2.3 % overall yield
- Sm-mediated reductive cyclization as key step
- 2:1 mixture of diasteroisomers in the aldol reaction
- Tedious oxidation-oxidation-reduction-oxidation-oxidation in the last steps
- Racemic synthesis

Van Leusen


1. (COCl)2, DMSO
TEA,
2. TosMIC, tBuOK
THF, then MeOH
81 % yield overall
see J. Org. Chem. 1977, 3114 – 3118
5
6
MeOH
- TolSO2H
- HCO2Me

Sanford's C-H activation

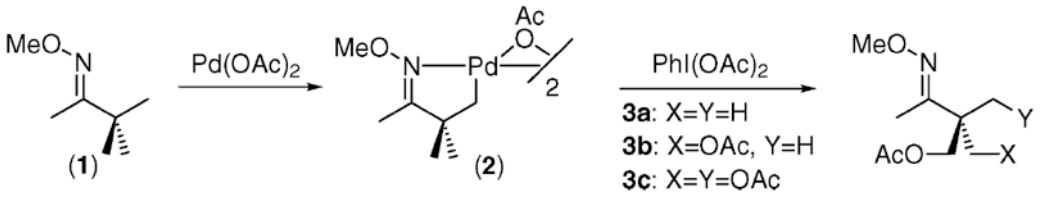
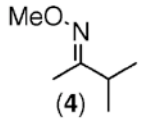
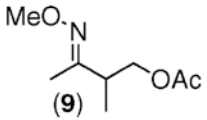
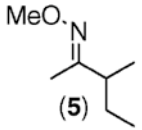
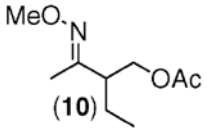
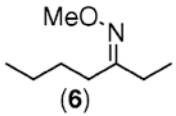
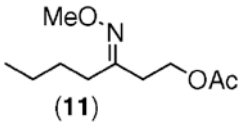
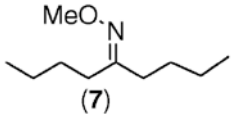
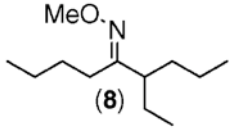
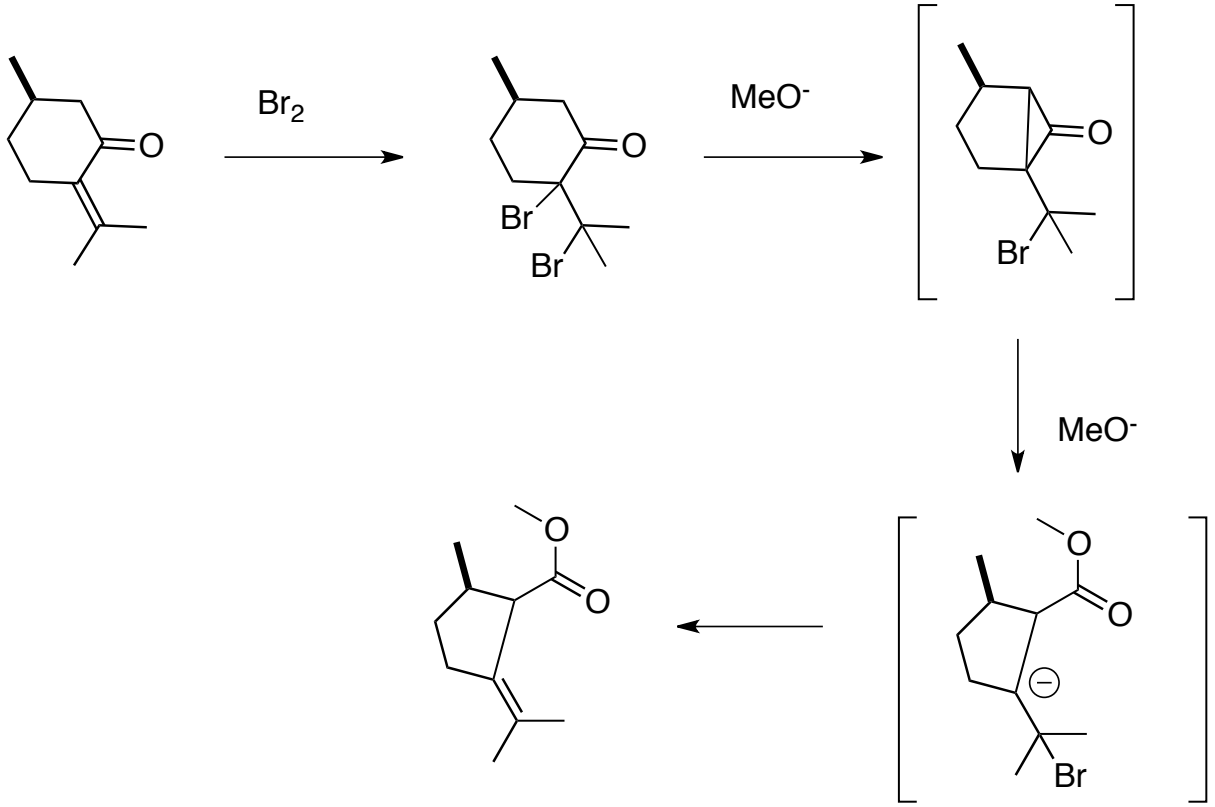


Table 1. Selectivity of Unactivated sp^3 C−H Bond Oxidation[a]

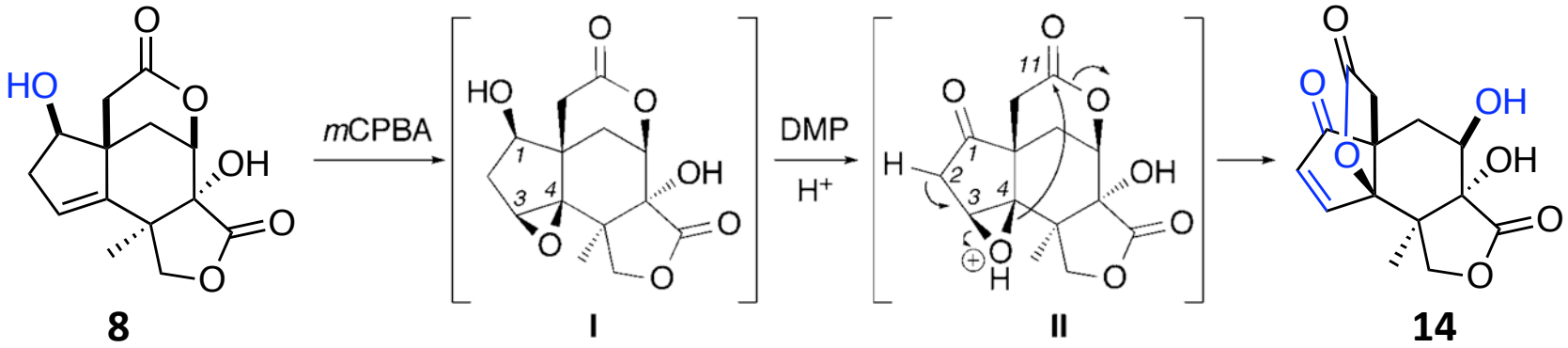
Entry	Substrate	Major Product	Yield[b]
1	 (4)	 (9)	74%[c]
2	 (5)	 (10)	78%[c]
3	 (6)	 (11)	39%[c]
4	 (7)	No Reaction	0%
5	 (8)	No Reaction	0%

[a] 1 equiv of substrate (0.12 M), 1.1 equiv of $PhI(OAc)_2$, 5 mol % $Pd(OAc)_2$, 50% AcOH/50% Ac_2O, 100 °C, 1.5−3.5 h. [b] Isolated yields. [c] Isolated as a mixture of oxime *E*/*Z* isomers.

Favorskii ring contraction



Theodorakis – key step



Scheme 4. Plausible mechanistic scenario for the conversion of **18** into **8**.

Jiadifenin – Danishefsky approach