Scalable Total Synthesis of (-)-Berkelic Acid by Using a Protecting-Group-Free Strategy

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Tamara Arto, Baris Temelli, and Felix Rodríguez

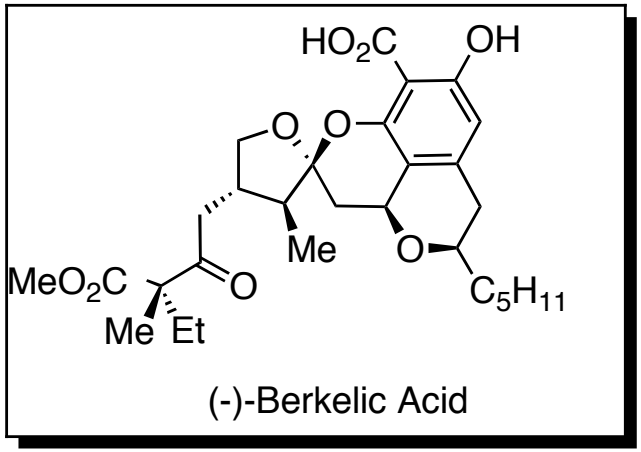
ACIE 2012, 124, 5014

Presented by:

Jared Hammill

Berkeley Pit Lake

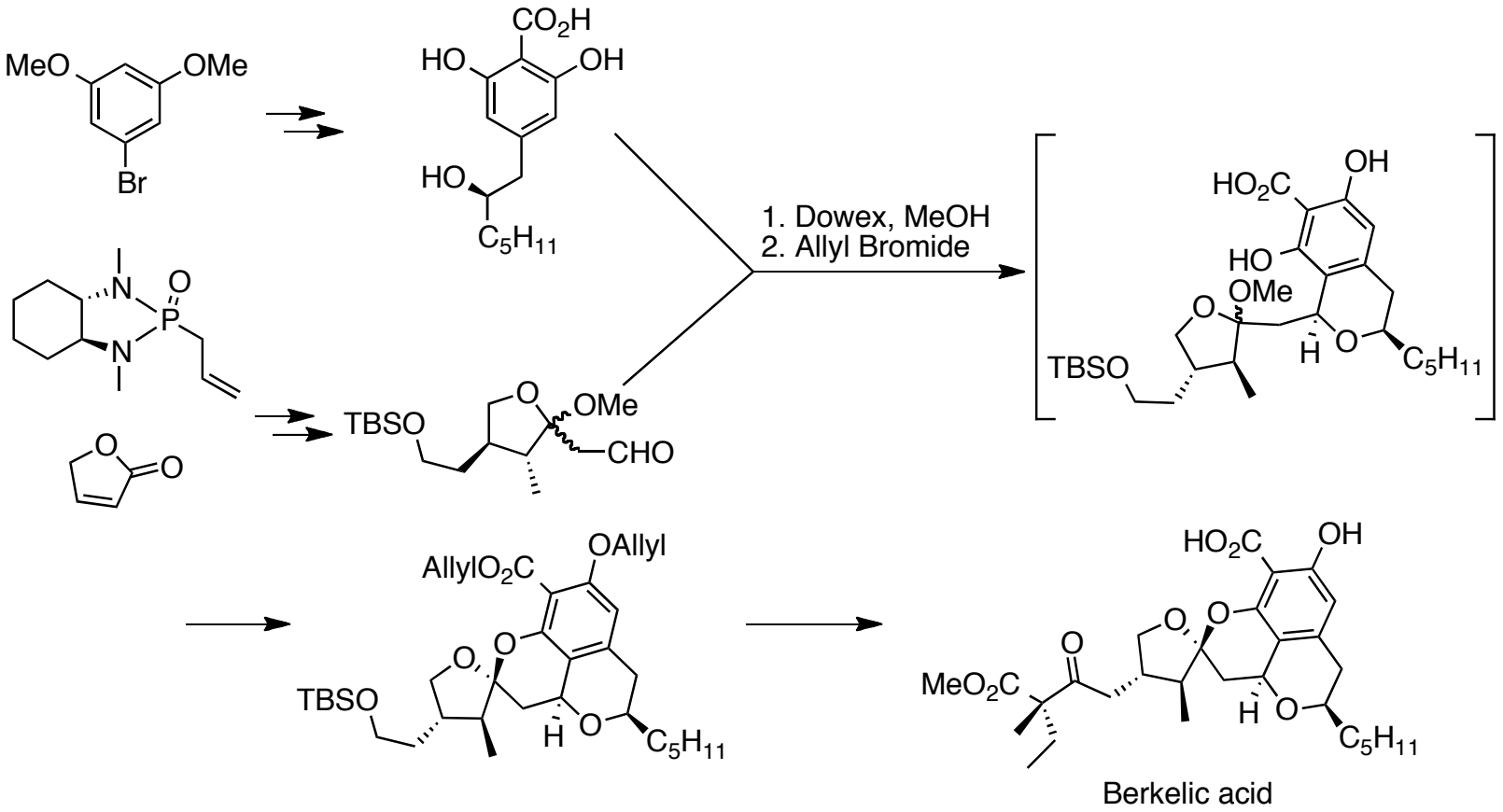
- Butte, Montana
- Formed by flooded copper mine
- pH = 2.5 (lemon juice)
- Contains high levels of arsenic, cadmium, zinc, sulfuric acid, and copper
- Home to extremophiles



(-)-Berkelic Acid

- GI_{50} = 91 nM (ovarian cancer)
- Contradictory bioactivity studies
- Limited access

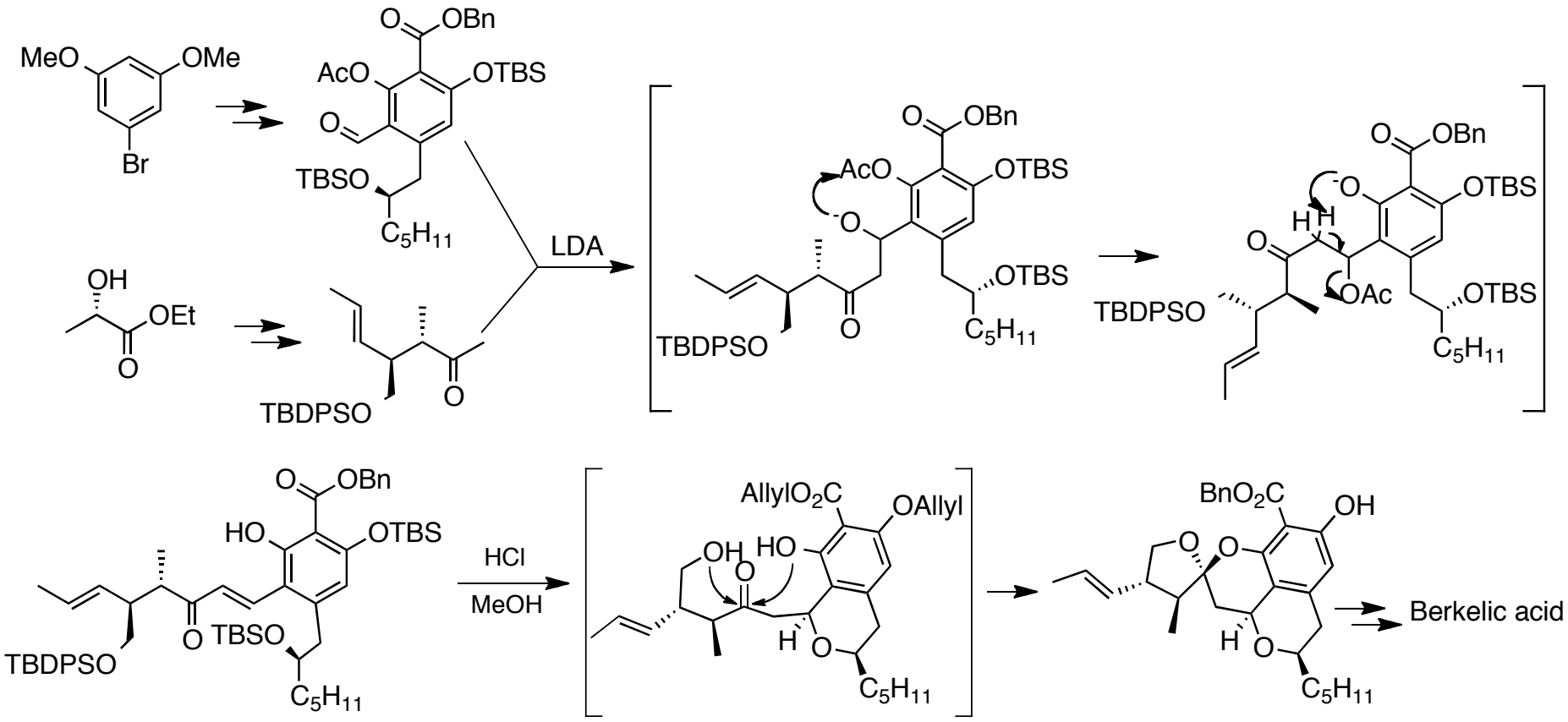
Snider's synthesis



- Key Oxa-Pictet-Spangler reaction
- 13 steps (longest linear) and 1.7% overall yield

Wu, X.; Zhou, J.; Snider, B. Angew. Chem. **2009**, *121*, 1309-1312

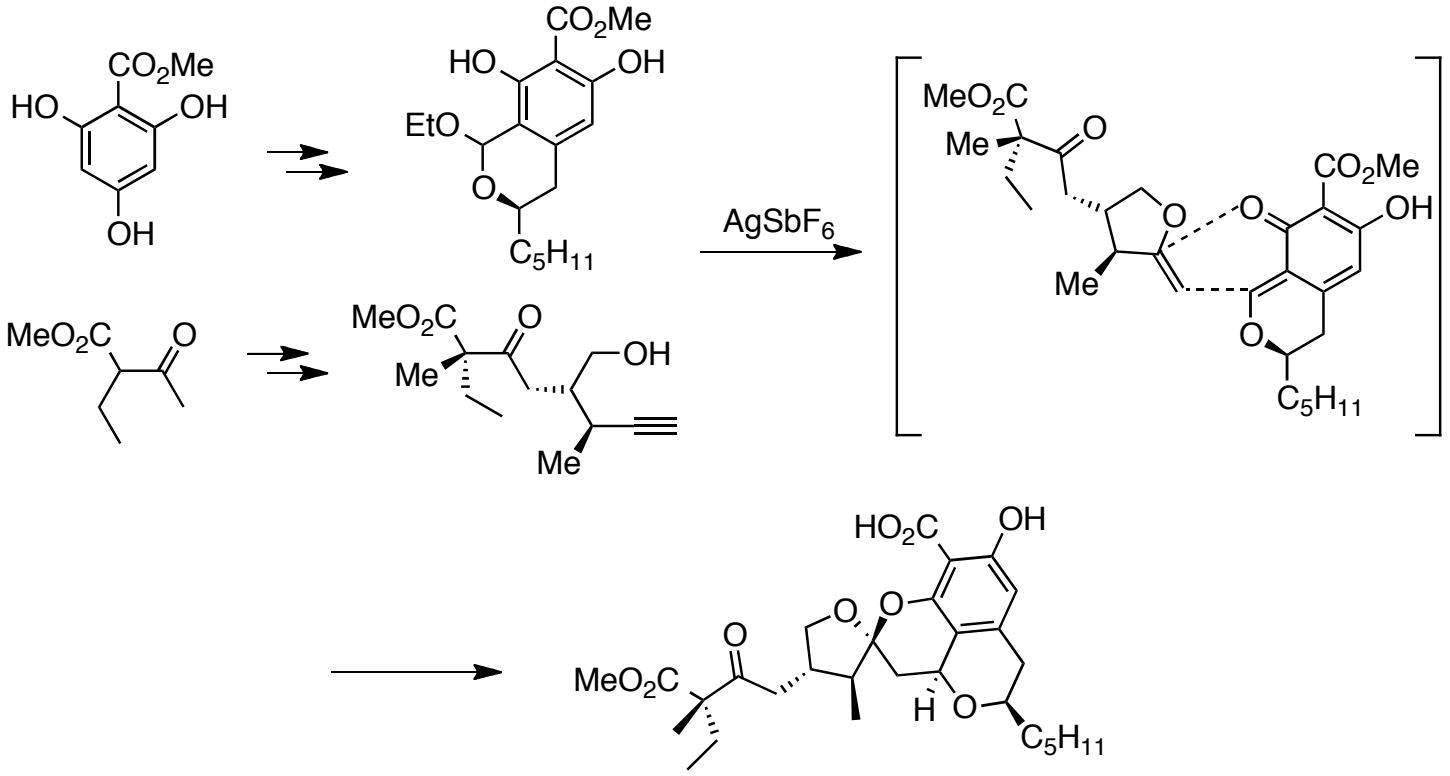
Furstner's Synthesis



- Key triple-deprotection,1,4-addition/spiroketalization cascade
- 19 steps (longest linear) 5% overall yield

Snaddon, T. N.; Buchgraber, P; Schulthoff, S.; Wirtz, C.; Mynott, R.; Furstner, A. Chem Eur. J. **2010**, *16*, 12133

De Brabander Synthesis

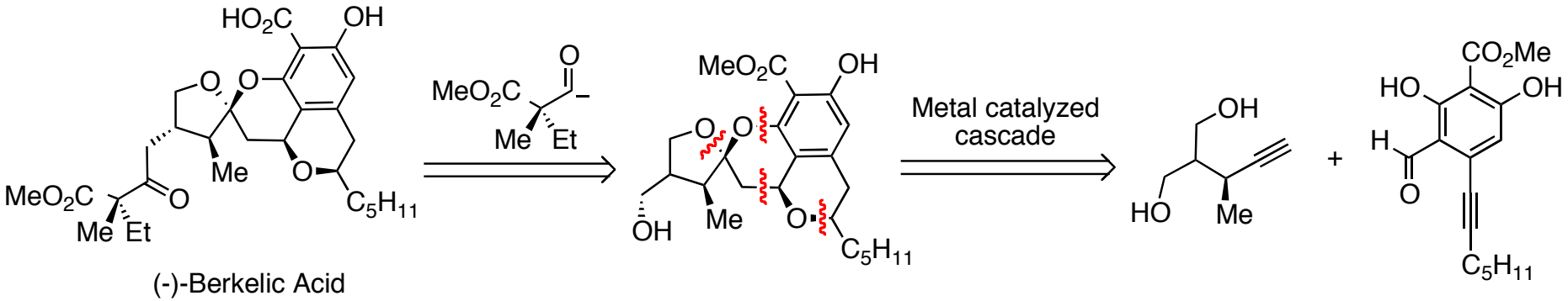


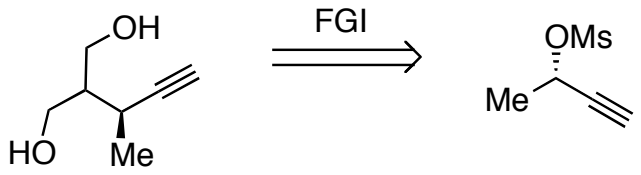
Berkelic Acid

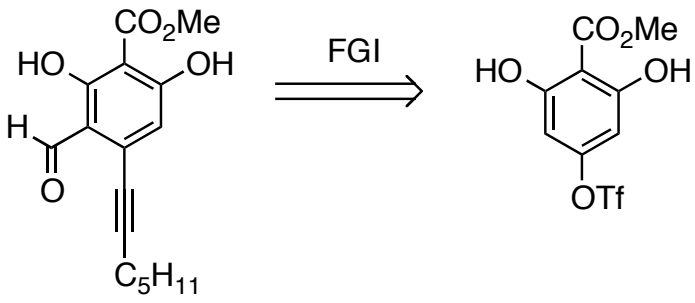
- Ag catalyzed dearomatization-cycloisomerization-cycloaddition cascade
- 10 steps (longest linear) 11-27% yield

Bender, C. F.; Yoshimoto, F. K.; Paradise, C. L.; De Brabander, J. K.
J. Amer. Chem. Soc. **2009**, *131*, 11350

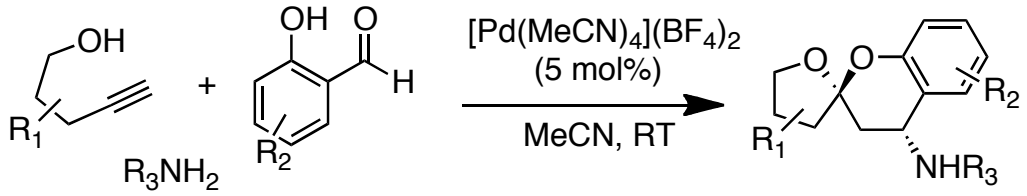
Title Paper


HO2C
OH
O
O
Me
O
C5H11
MeO2C
O
Me Et
(-)-Berkelic Acid
MeO2C
O
Me Et
MeO2C
OH
O
O
OH
Me
O
C5H11
Metal catalyzed
cascade
OH
HO
Me
+
CO2Me
HO
OH
H
O
C5H11

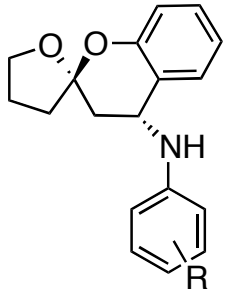

OH
HO
Me
FGI
OMs
Me


CO2Me
HO
OH
H
O
C5H11
FGI
CO2Me
HO
OH
OTf

Methodology

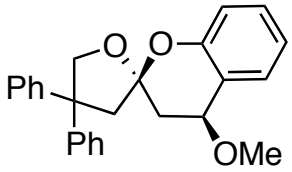


18 examples, 70-06% yield

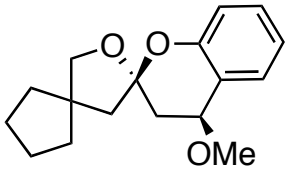


R = OMe, F, Br, Cl, TBu

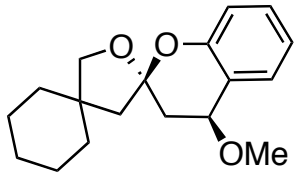
71%-90%



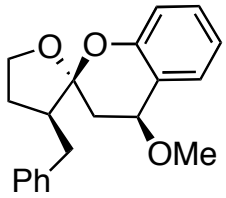
96%



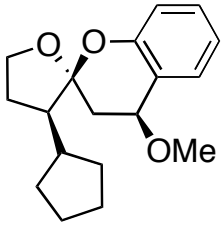
90%



70%



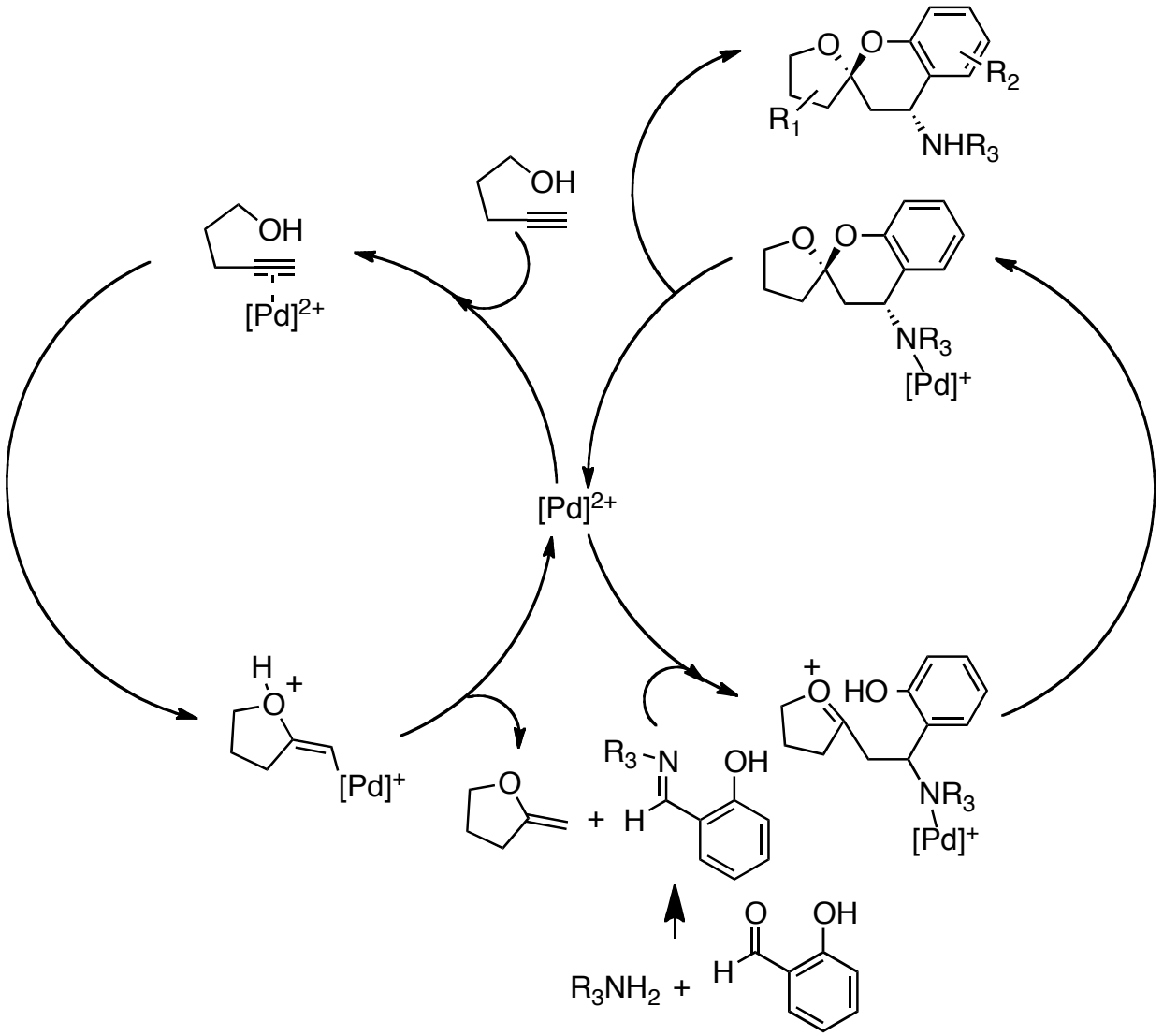
72%



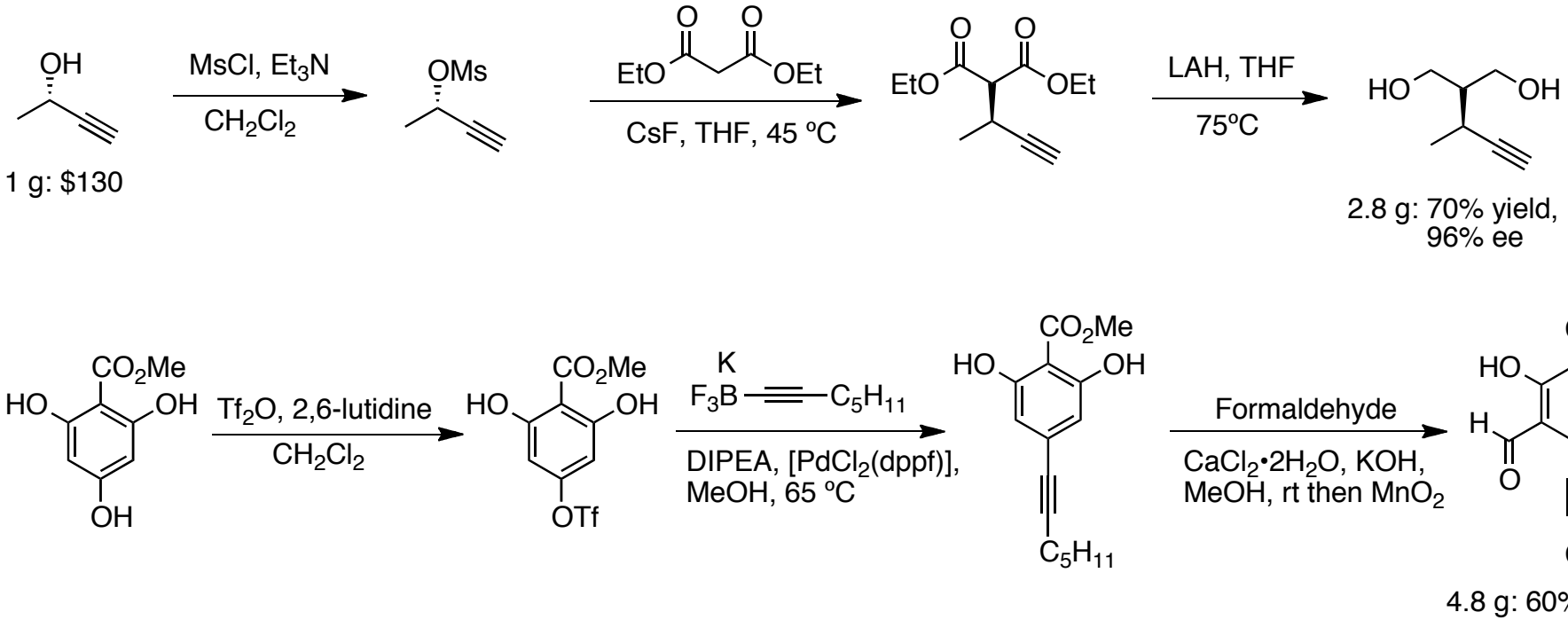
74%

Barluenga, J.; Mendoza, A.; Rodriguez, F.; Fananas, F. J.
Angew. Chem. Int. Ed. **2009**, *48*, 1644

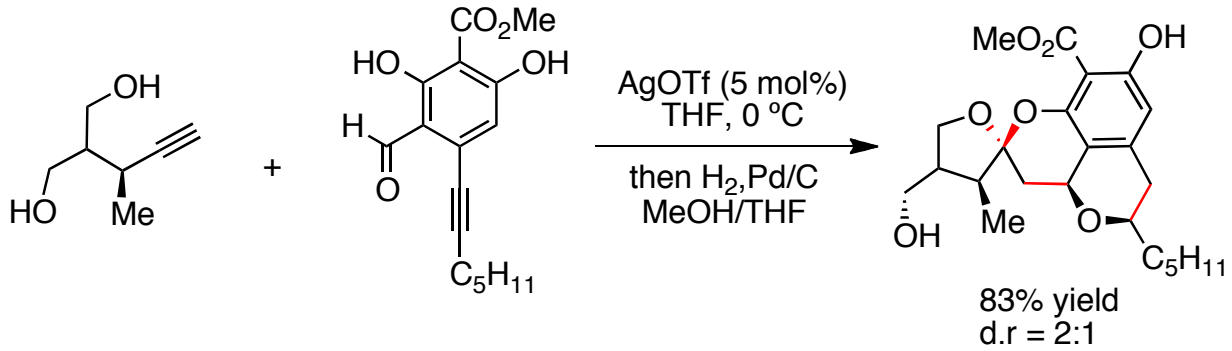
Methodology



Starting Material Synthesis

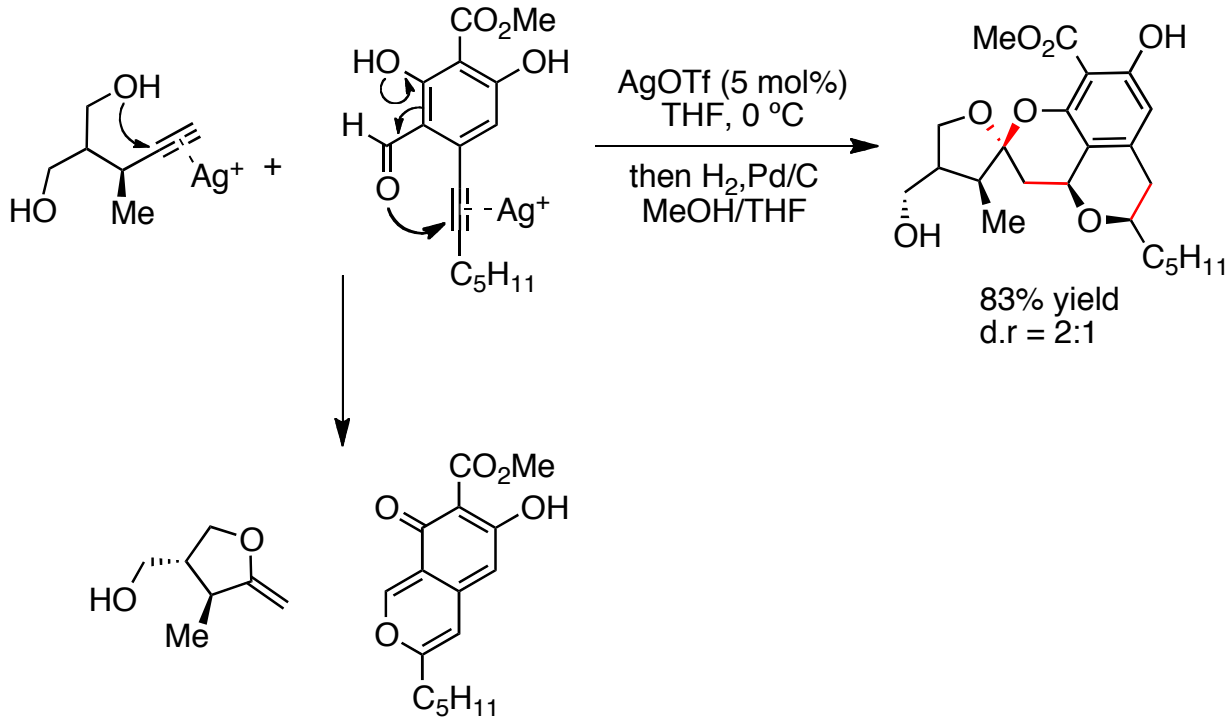


Key Transformation

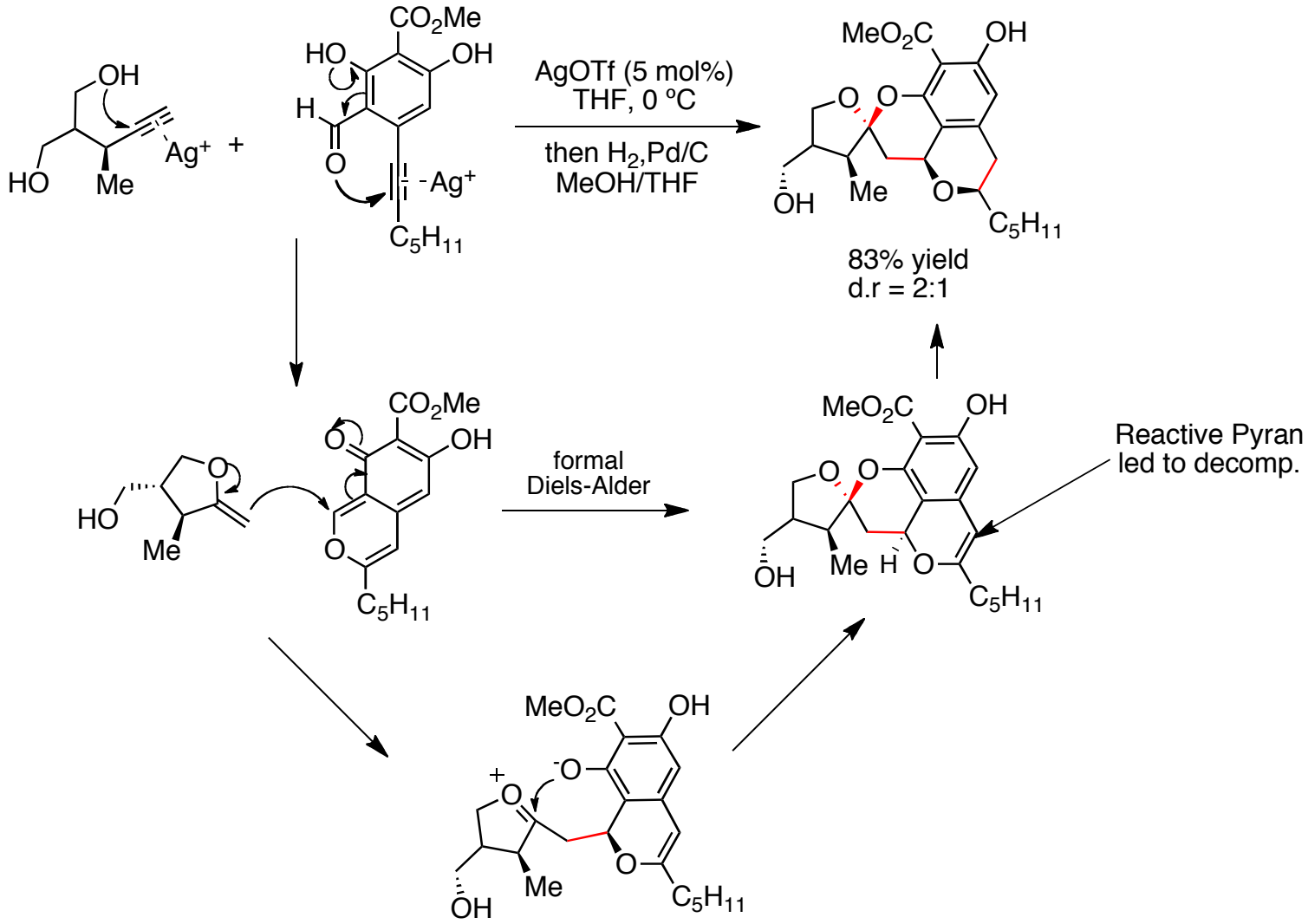


83% yield
d.r = 2:1

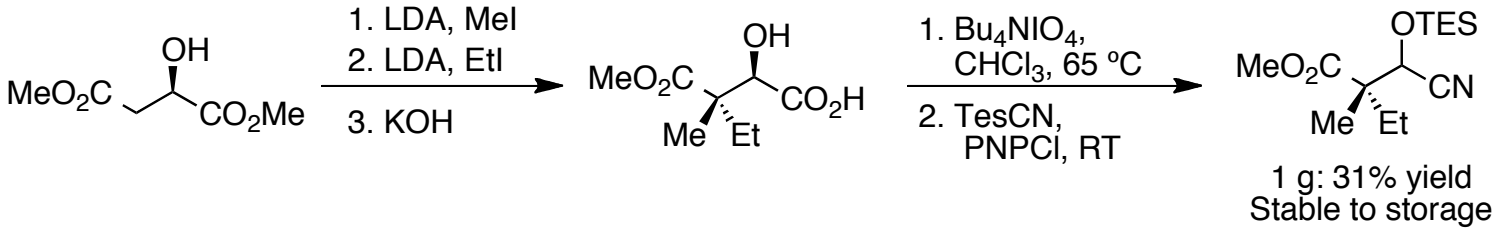
Key Transformation

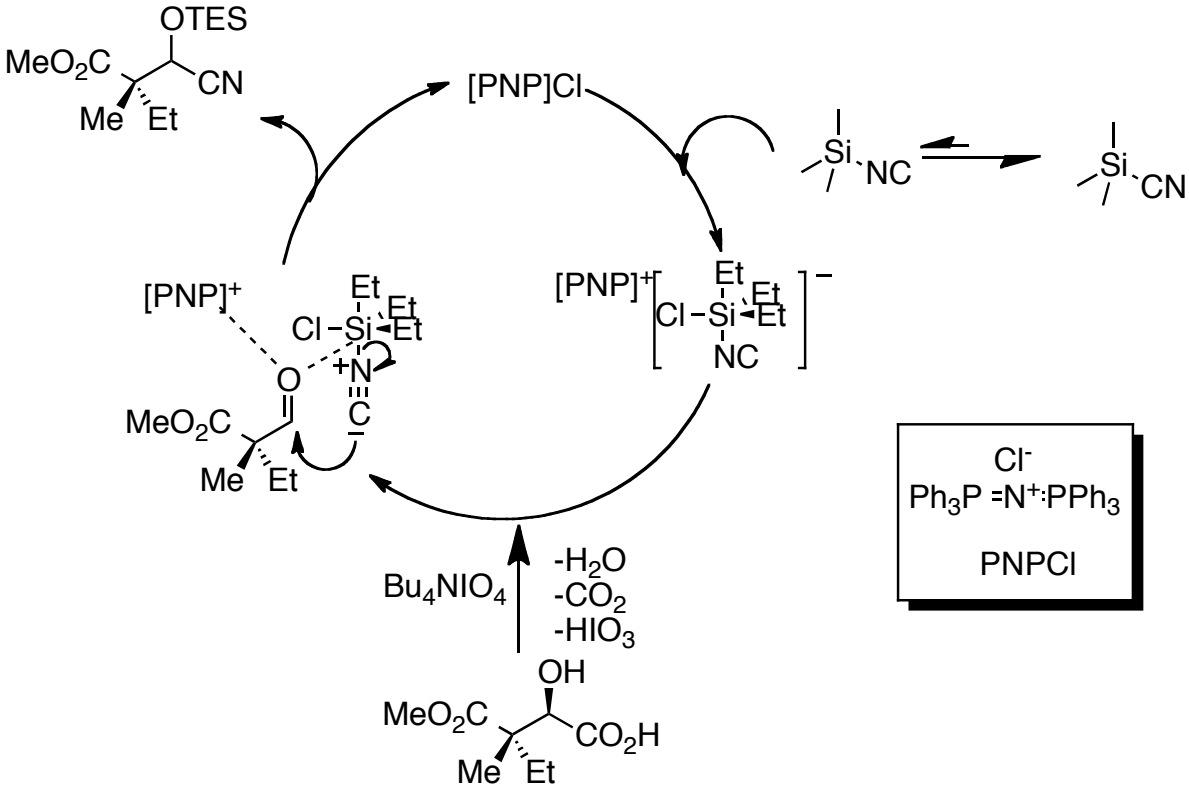


Key Transformation

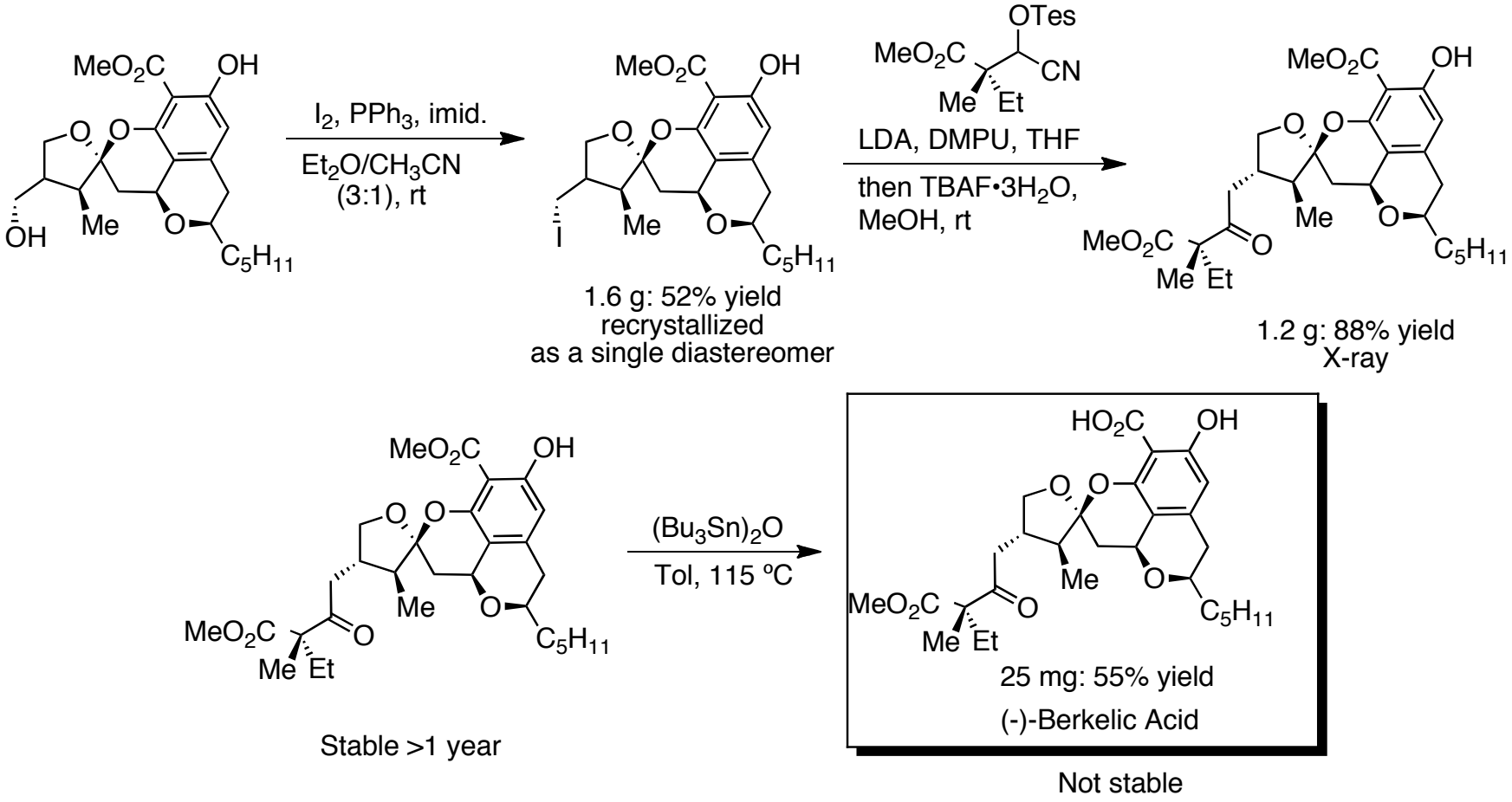


Final Starting Material Synthesis





End Game


MeO2C
OH
OH
Me
O
C5H11
I2, PPh3, imid.
Et2O/CH3CN
(3:1), rt
I
1.6 g: 52% yield
recrystallized
as a single diastereomer
OTes
MeO2C
CN
Me
Et
LDA, DMPU, THF
then TBAF•3H2O,
MeOH, rt
1.2 g: 88% yield
X-ray
(Bu3Sn)2O
Tol, 115 ºC
Stable >1 year
HO2C
25 mg: 55% yield
(-)-Berkelic Acid
Not stable

Conclusions

- 14 steps (longest linear) and 12.5 % overall yield
- Key cascade sets 5 stereocenters in 83% yield (2:1 dr)
- Selective crystalization removes need for chiral chromatography
- "Protecting group free" strategy with minimal oxidation/ reduction steps
- All but last step done on gram scale
- Convergent, modular synthesis allows for SAR