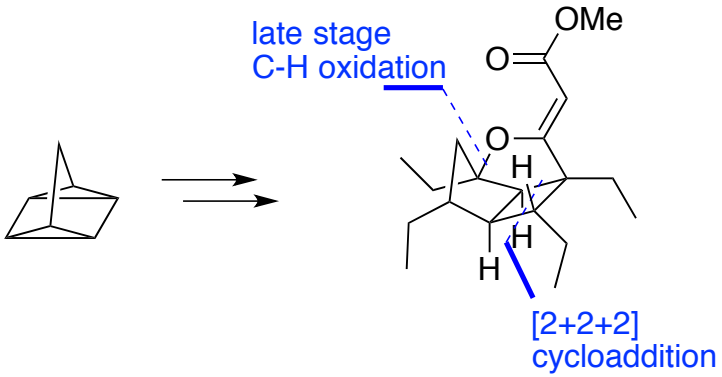
Collaborative Total Synthesis: Routes to (±)-Hippolachnin A Enabled by Quadricyclane Cycloaddition and Late-Stage C-H Oxidation



- Independent Routes by Wood and Brown Groups: 9 steps from Quadricyclane
- Collaborative Route by Wood/Brown Groups: 6 steps from Quadricyclane

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Samuel Rieder, 18. Feb 2016

John L. Wood
Biography

1980–85:	B.A. Chemistry, University of Colorado
1985–91:	Ph.D Organic Chemistry, **Prof. Smith** University of Pennsylvania
1991–93:	American Cancer Society Postdoctoral Fellow, **Prof. Schreiber**, Harvard University
1993–97:	Assistant Professor, Yale University
1997–98:	Associate Professor, Yale University
1998–06:	Professor, Yale University
2006–13:	Professor, Colorado State University
2013–:	Professor, Cancer Prevention Research Institute Scholar, Baylor University

M. Kevin Brown
Biography

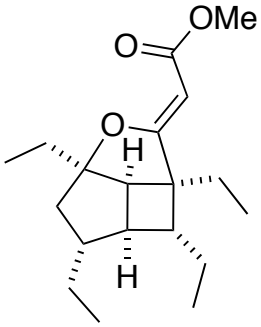
2002:	B.A. Chemistry, **Prof. Rosenstein**, Hamilton College
2002–08:	Ph.D Organic Chemistry, **Prof. Hoveyda** Boston College
2008–11:	National Institutes of Health Postdoctoral Fellow, **Prof. Corey**, Harvard University
2011–:	Assistant Professor, Indiana University

Research Interests

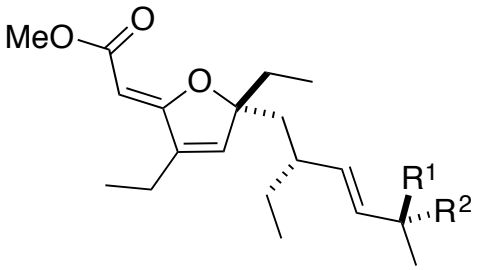
- Development of new methods/strategies for organic chemical synthesis
- "Inspiration from structures of important molecules that are currently difficult or impossible to access with current methods"
- Stereoselective [2+2] cycloaddition
- Cu-catalyzed cross-coupling/interrupted cross-coupling
- Stereoselective cross-coupling of C(sp^3)-nucleophiles by Pd/Cu catalysis

Hippolachnin A
General Information

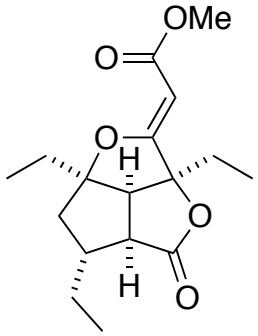
- First isolated in 2013 from *Hippospongia lachne* along with its proposed biogenic precursor
- 3.6 kg sponge for 5.1 mg (0.00014%)
- Six continuous stereocenters (two quaternary)
- Novel polyketide architecture
- Congested compact core
- Significant antifungal activity (*C. neoformans,* Cryptococcosis, second-most-common AIDS-defining illness in Africa)



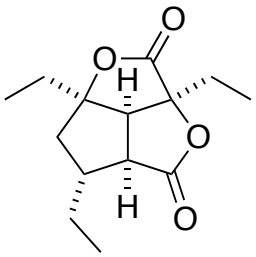
hippolachnin A



$R^1 = R^2 = H$; unnamed precursor
$R^1 = R^2 = O$; gracilioether B
$R^1 = OH$, $R^2 = H$; gracilioether C



gracilioether E

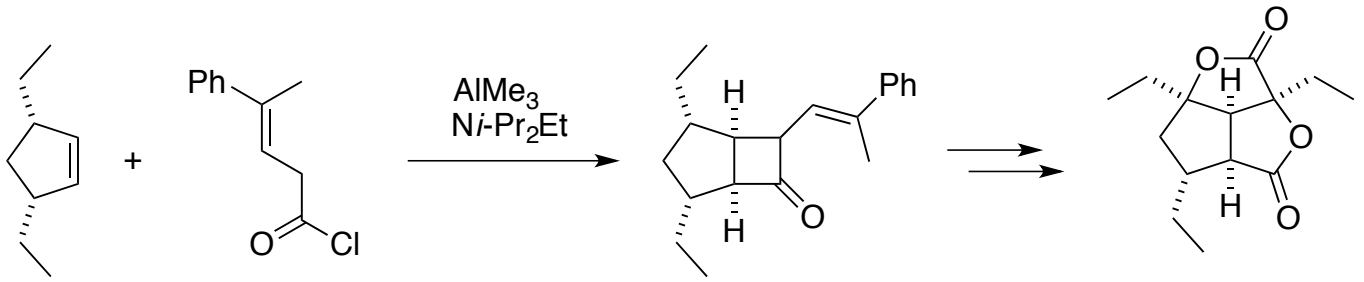


gracilioether F

Hippolachnin A and Related Marine Polyketides

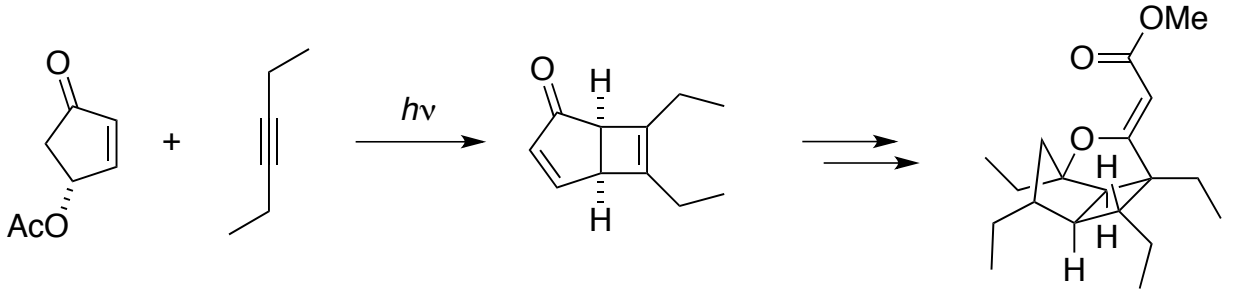
Previous Synthetic Strategies

- **Brown 2014**



(±)-gracilioether F

- **Carreira 2015**

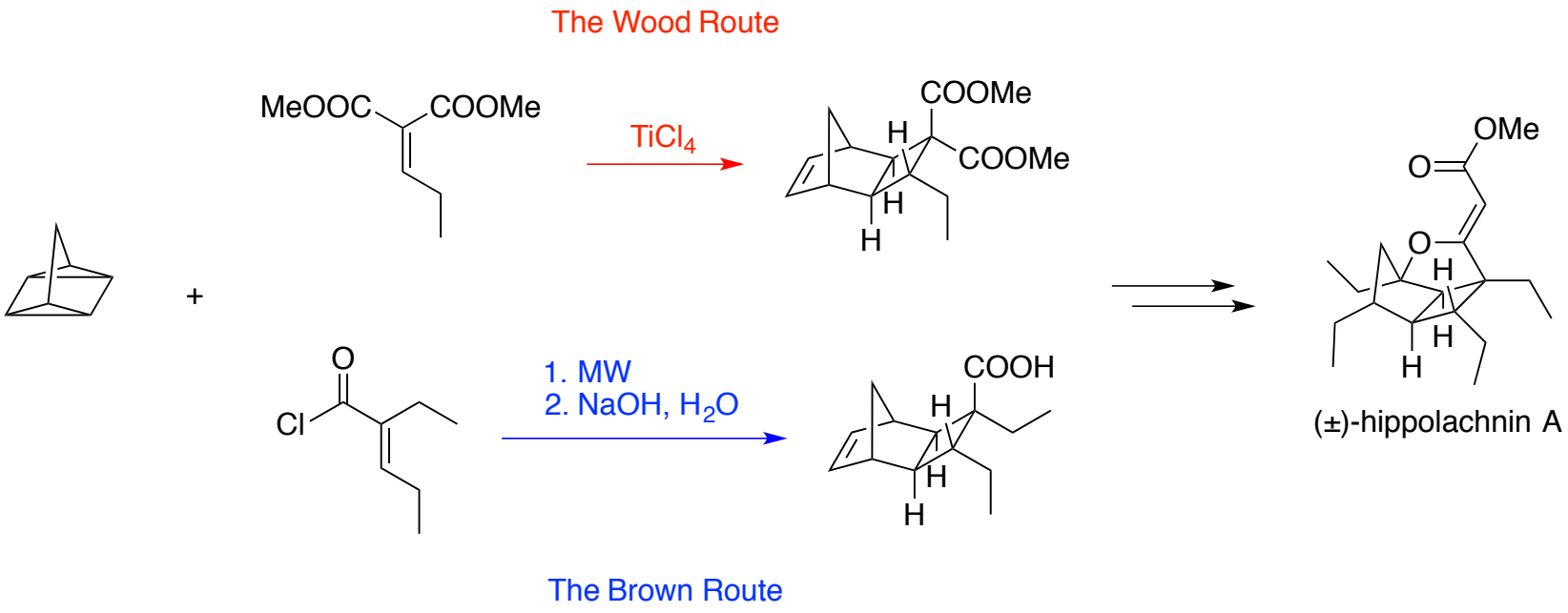


(±)-hippolachnin A

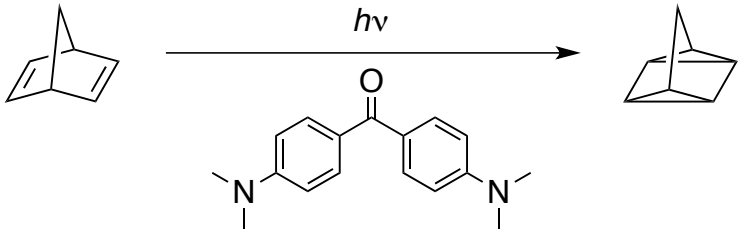
C. M. Rasik, M. K. Brown, *Angew. Chem. Int. Ed.* **2014**, *53*, 14522–14526
S. A. Ruider, T. Sandmeier, E. M. Carreira, *Angew. Chem. Int. Ed.* **2014**, *54*, 2378–2382

Hippolachnin A and Related Marine Polyketides

This Paper



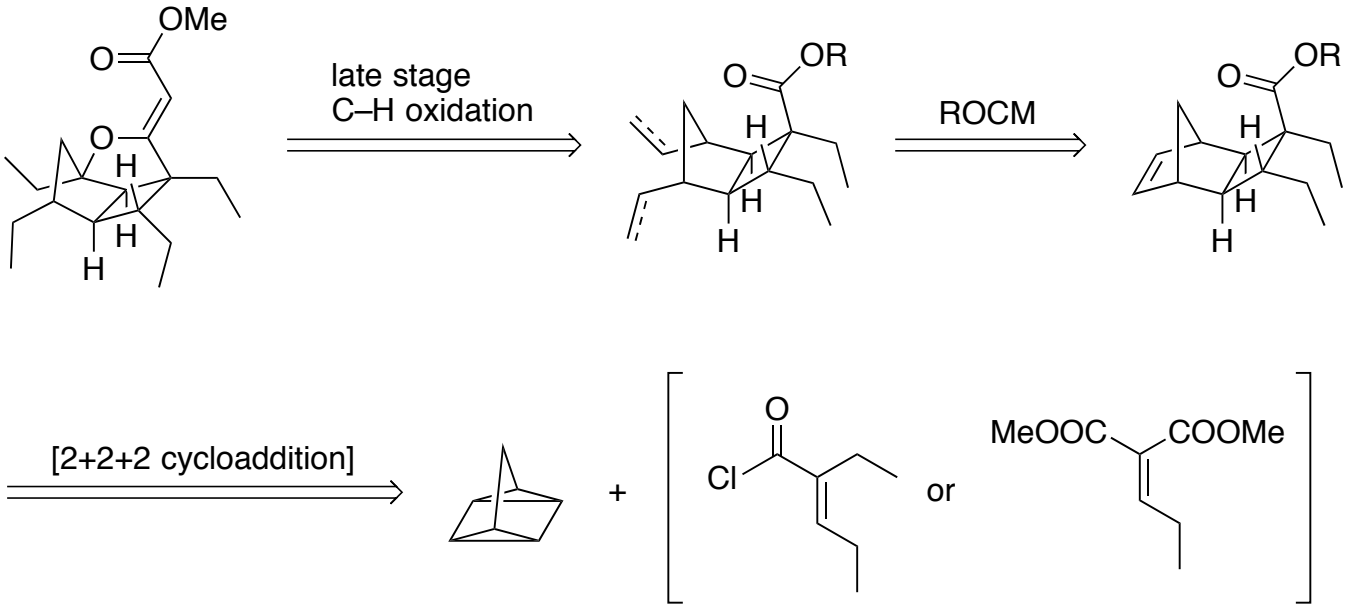
- Both routes use quadricyclane as starting material



Cahill, Paul A.; Steppel, Richard N. (**2003**): „Process of driving a non-polymerization solution-phase photochemical transformation“. United States of America.

Hippolachnin A

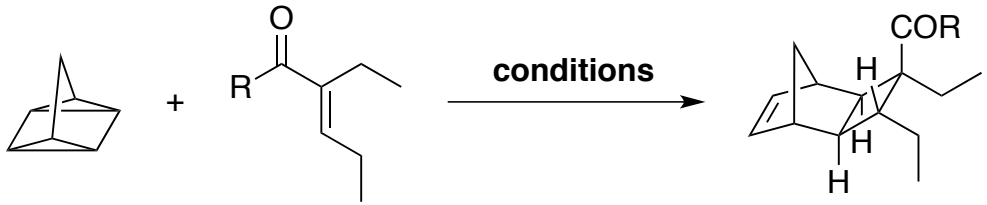
Retrosynthesis



The Brown Route

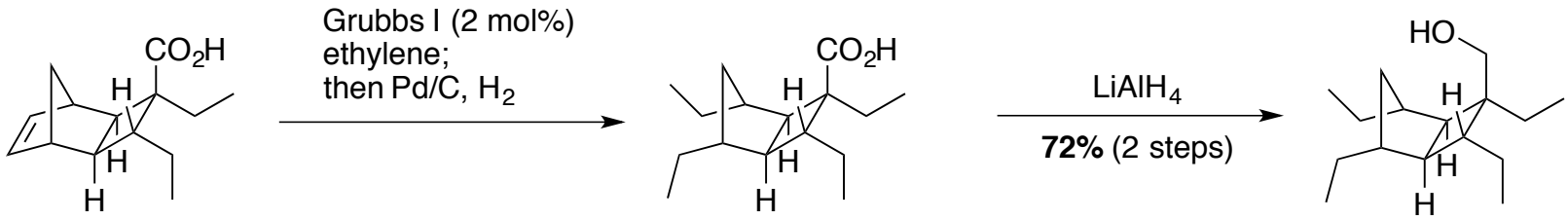
[2+2+2] Cycloaddition; ROCM

- Screening the conditions



entry	R	conditions	product	yield (dr)
1	OEt	140 °C, 4 equiv. quadricyclane, 48 h	OEt	<2%
2	Cl	120 °C, 4 equiv. quadricyclane, 72 h	Cl	73% (3:1)
5	Cl	MW, 140 °C, 4 equiv. quadricyclane, 4 h	Cl	74% (5:1)

- Work-up with NaOH furnished acid; Recrystalization 50% (>20:1 dr)
- Ring opening cross metathesis (in situ hydrogenation, cat. Pd/C)

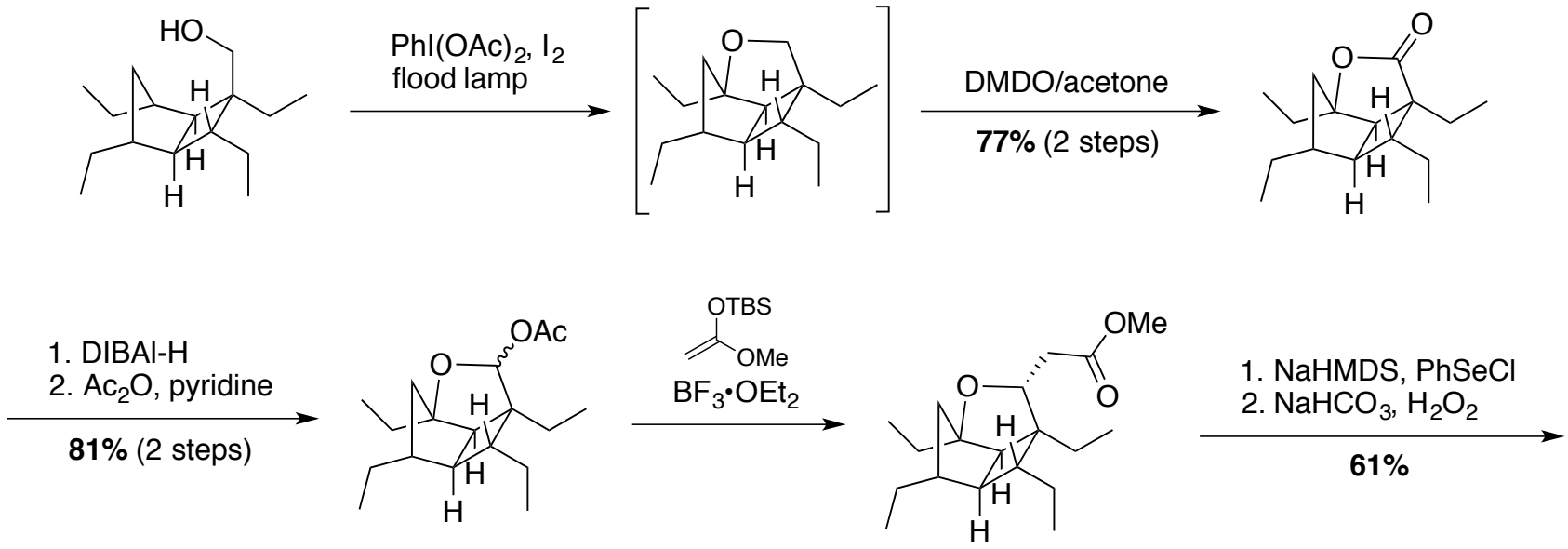


- Synthesis of the alcohol for oxidation

The Brown Route

C–H Oxidation; Finishing the Synthesis

- **COOH**:
  - Cu promoted oxidation not working,
  - Fe C–H oxidation --> product; low yield, overoxidation, complete consumption
- Surez Oxidation



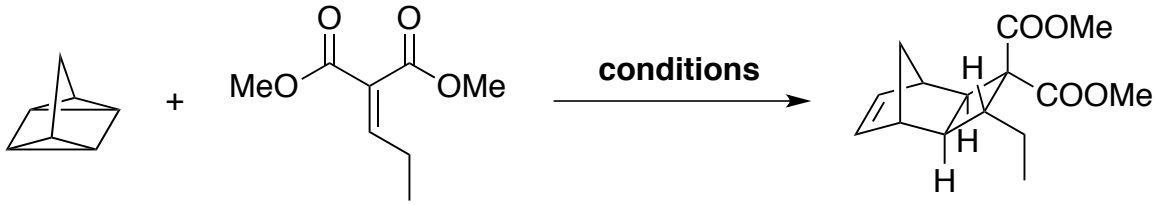
S. A. Ruider, T. Sandmeier, E. M. Carreira, *Angew. Chem. Int. Ed.* **2014**, *54*, 2378–2382

A. L. Baumstark, F. Kovac, P. C. Vasquez, *Can. J. Chem.* **1999**, *77*, 308–312

The Wood Route

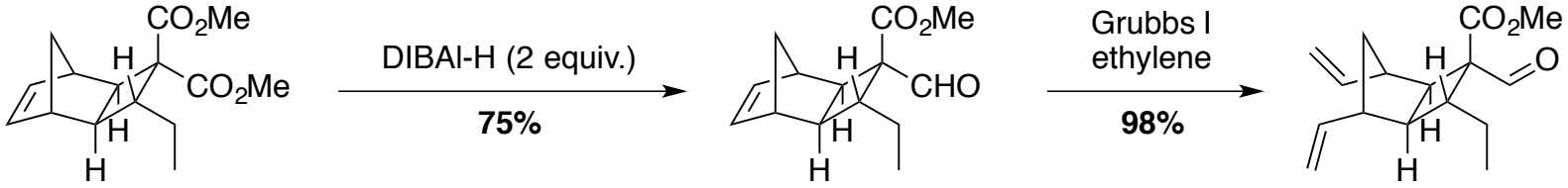
[2+2+2] Cycloaddition; ROCM

- Screening the conditions



entry	solvent	catalyst	time (h)	dr (1H NMR)	% conversion
1	EtOH	–	144	9.1:1	52
7	DCE	TiCl4 (10 mol%)	4	2.9:1	>95
8	CH2Cl2	TiCl4 (5 mol%)	4	3.4:1	>95
9	CH2Cl2	TiCl4 (5 mol%)	1	3.7:1	>95

- Ring Opening Cross Metathesis (Grubbs I)

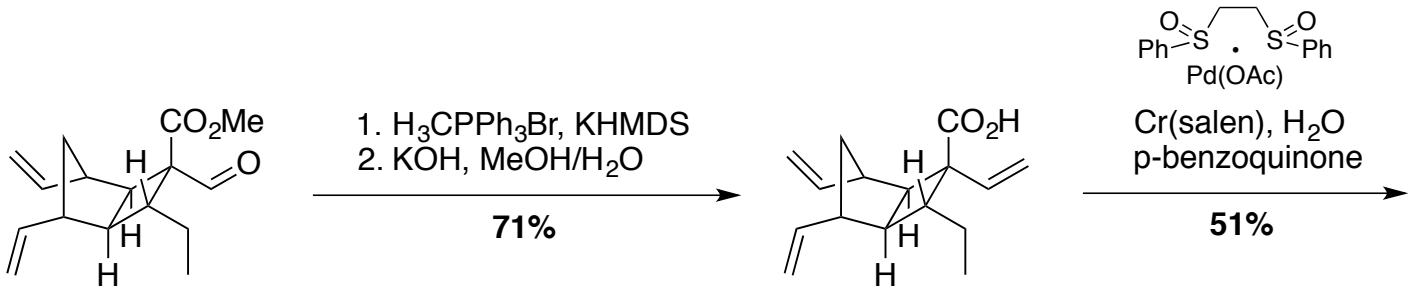


C. Yuan, L. Jiao, Z.-X. Yu, *Tetrahedron Lett.* **2010**, *51*, 5674–5676.

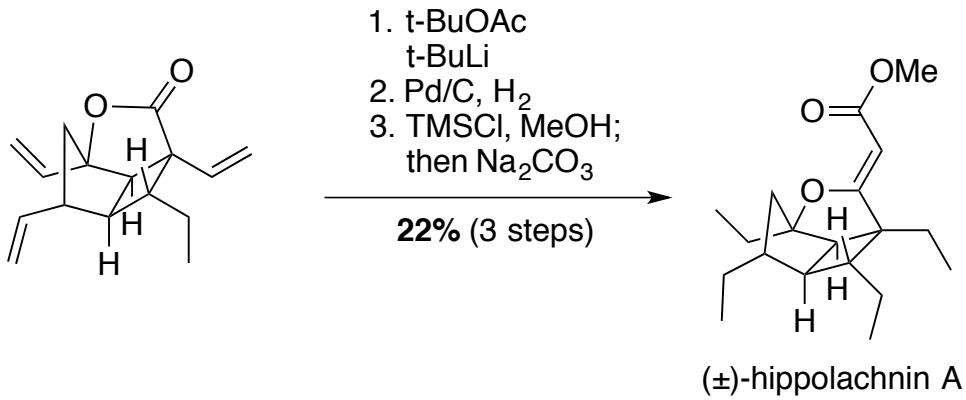
The Wood Route

C–H Oxidation; Finishing Synthesis

- Pd/Cr Oxidation of intermediate carboxylic acid



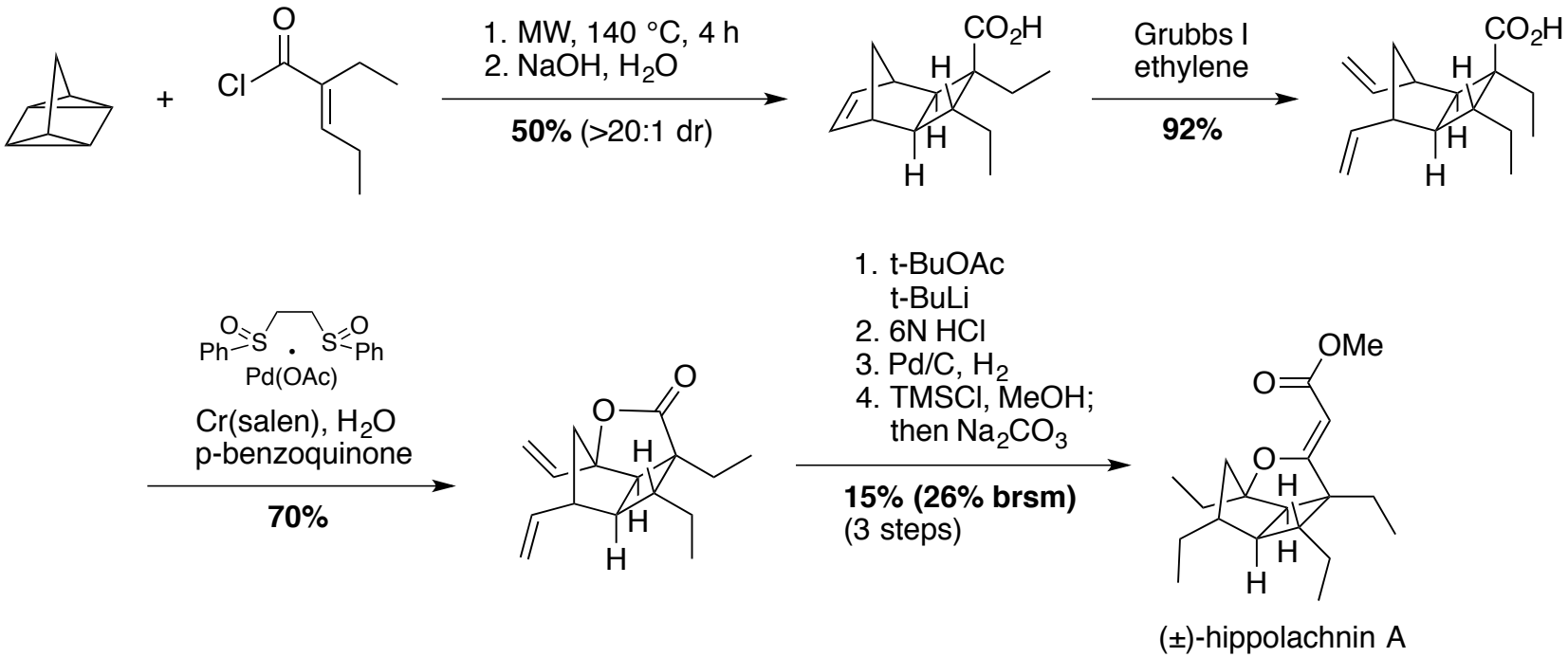
- Final step



(±)-hippolachnin A

Collaborative Route

“ ... the Wood and the Brown group became aware of each other‘s work during a poster session at the National Organic Symposium. Given the similarities [...] and the fact that each had complementary strengths, rather than compete, we launched a collaborative effort …”



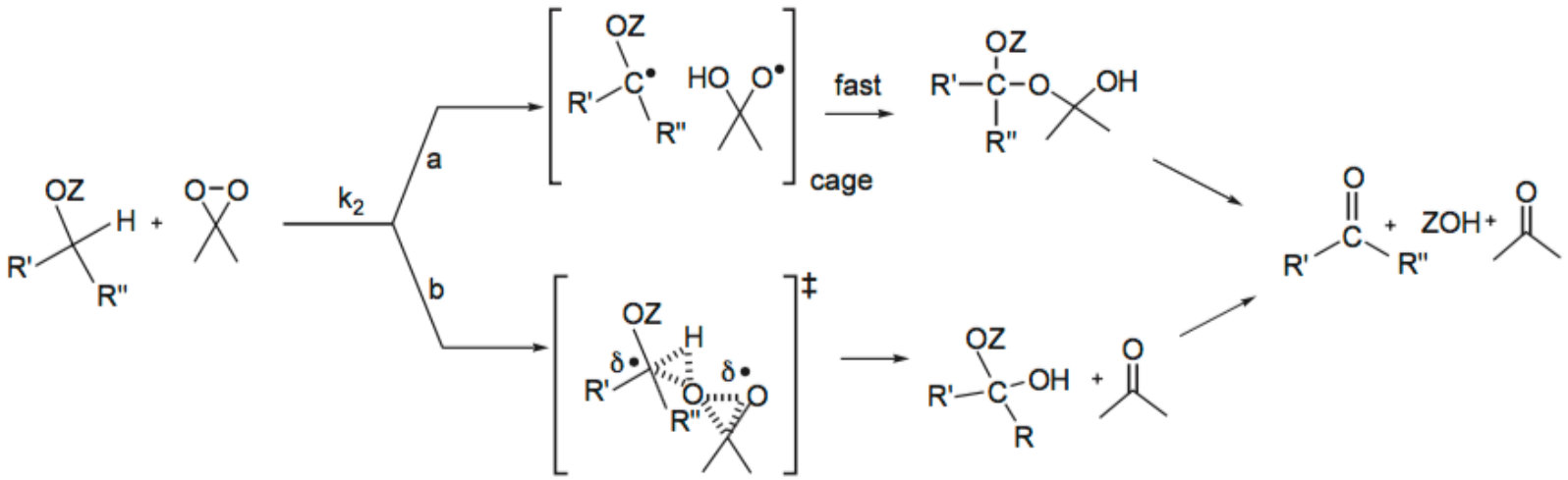
Conclusion

- Three syntheses of (±)-hippolachnin A
  - Brown Route: 9 steps, 12%
  - Wood Route: 9 steps, 4.8%
  - Collaborative Route: 7 steps, 4.8%
- First time [2+2+2] cycloaddition of quadricyclane in complex molecule synthesis
- B. route greater insights in electronics required for quadricyclane
- W. route illustrates potential utility of LA-promoted reactions of quadricyclane

Thank you for your attention

Backup Slide

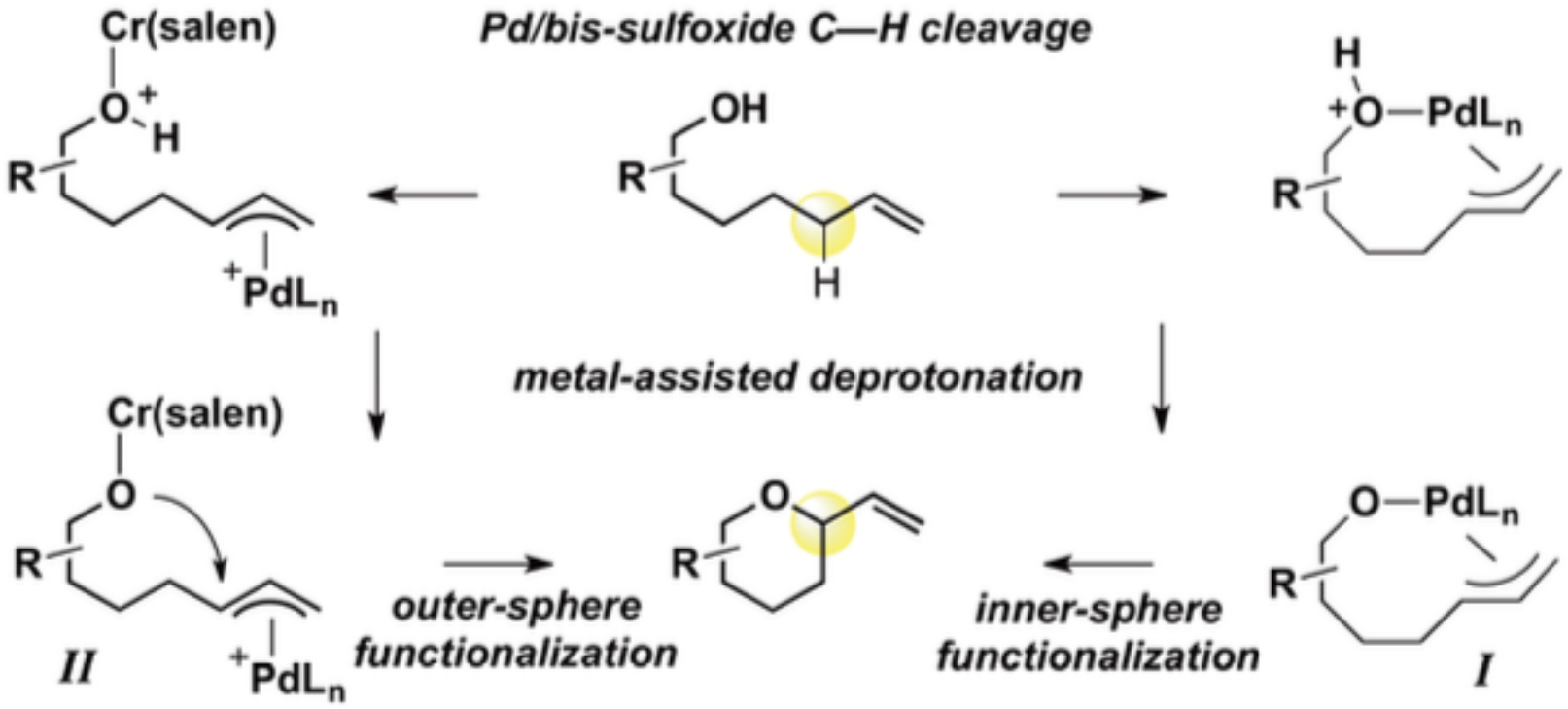
Oxidation of ethers with DMDO



A. L. Baumstark, F. Kovac, P. C. Vasquez, *Can. J. Chem.* **1999**, *77*, 308–312.

Backup Slide

Allylic $Pd(OAc)_2$ Oxidation



S. E. Ammann, G. T. Rice, M. C. White, *J. Am. Chem. Soc.* **2014**, *136*, 10834–10837