Literature Review

Stereocontrolled Radical Bicyclizations of Oxygentaed Precursors Enable Short Synthesis of Oxidized Abietane Diterpenoids

Darius Vrubliauskas, Benjamin M. Gross, and Christopher D. Vanderwal

Presented by Xin Gao
Sorensen Group Meeting
02/19/2021

Christopher D. Vanderwal

1995: B.S. in Biochemistry, University of Ottawa

1998: M.S. in Chemistry, University of Ottawa. PI: Prof. Tony Durst

2003: Ph.D., The Scripps Research Institute. PI: Prof. Erik Sorensen

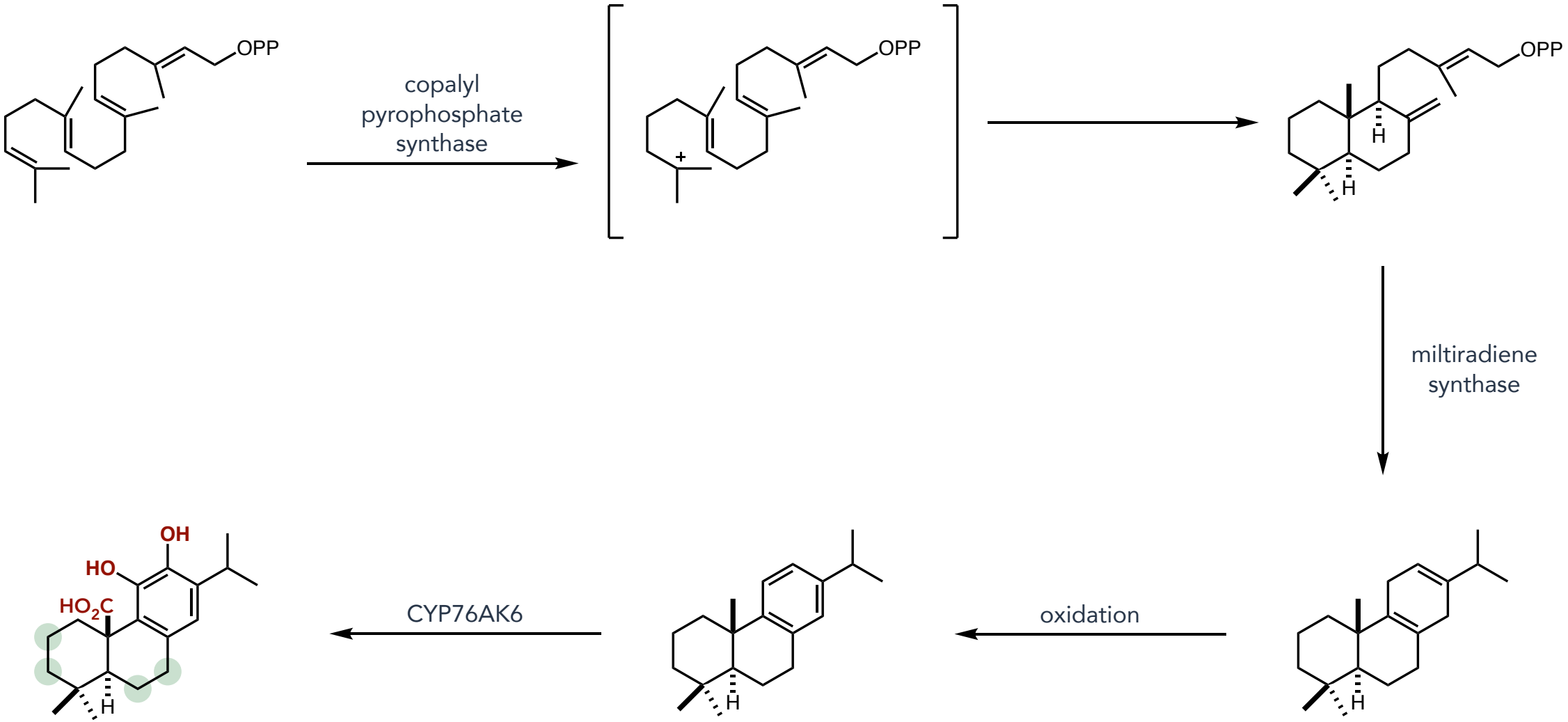
2003-2005: Harvard University. PI: Prof. Eric Jacobsen

2005: Assistant Professor, UC Irvine

2011: Associate Professor, UC Irvine

2013: Professor, UC Irvine

Biosynthesis of Aromatic Abietane Diterpenoids



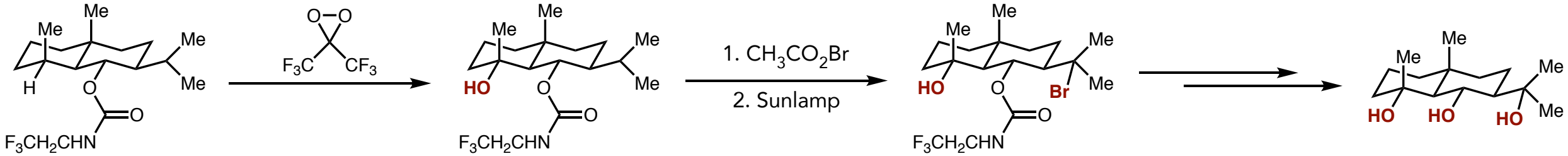
carnosic acid
precursor for aromatic abietanes

Nat. Commun. **2016**, 7, 12942.

J. Am. Chem. Soc. **2016**, 138, 34, 10905–10915.

Strategies for Terpenoids Synthesis

- Chemoselective Late-Stage Oxidation



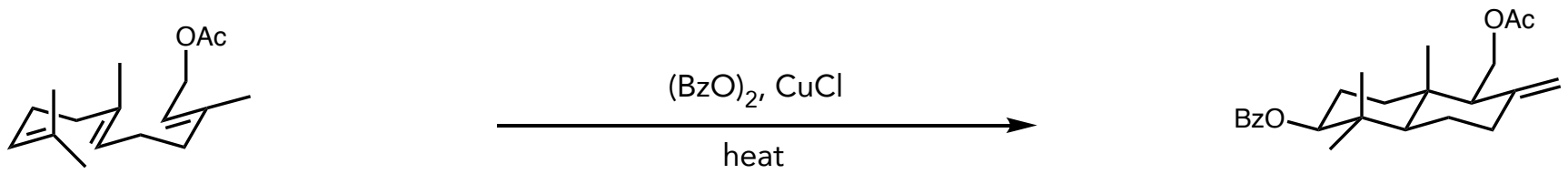
82%

52%

Nature **2009**, 459, 824–828.

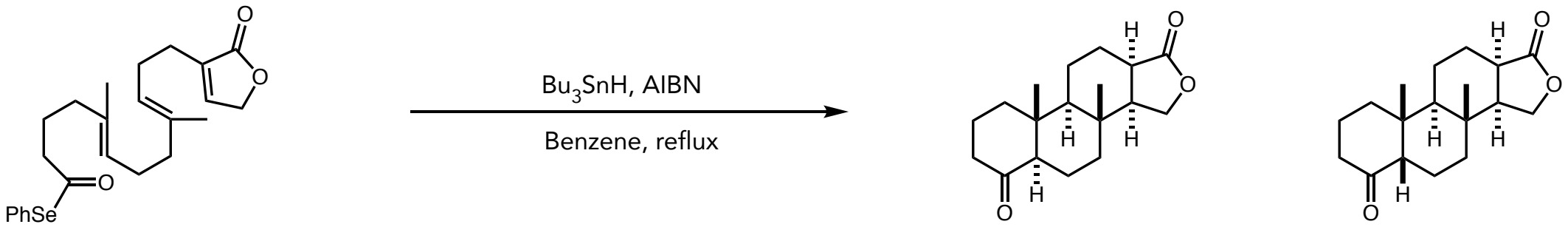
- Oxidation of Carbon Skeletons Followed by Cyclization

Radical Polyene Cyclization



20%-30%

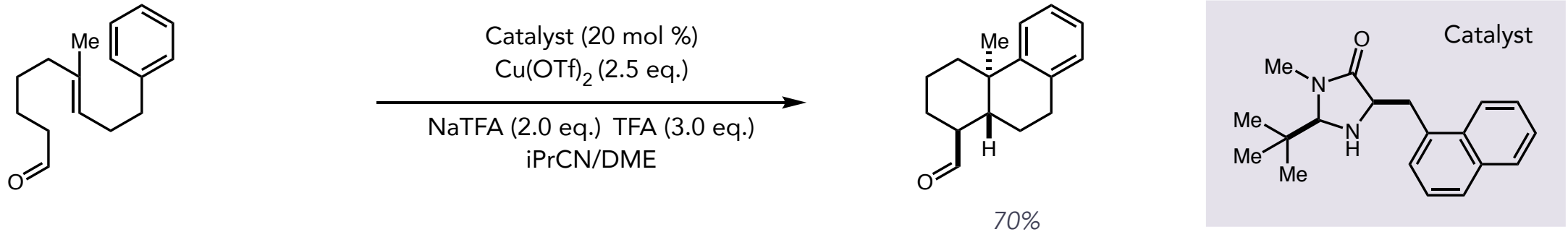
Tetrahedron Lett. **1968**, 9, 1837–1840.



53%

minor

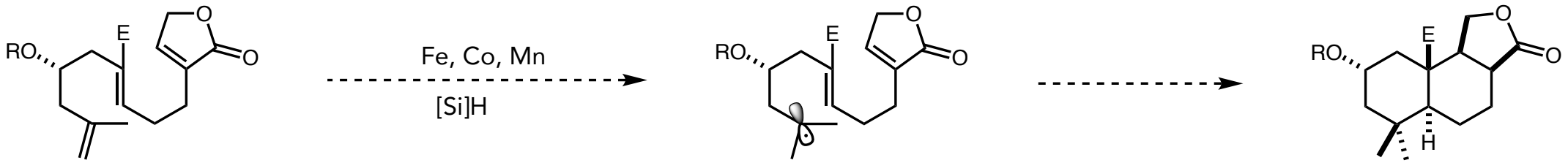
J. Chem. Soc. Perkin Trans. **1998**, 1, 863–865.



70%
87% ee

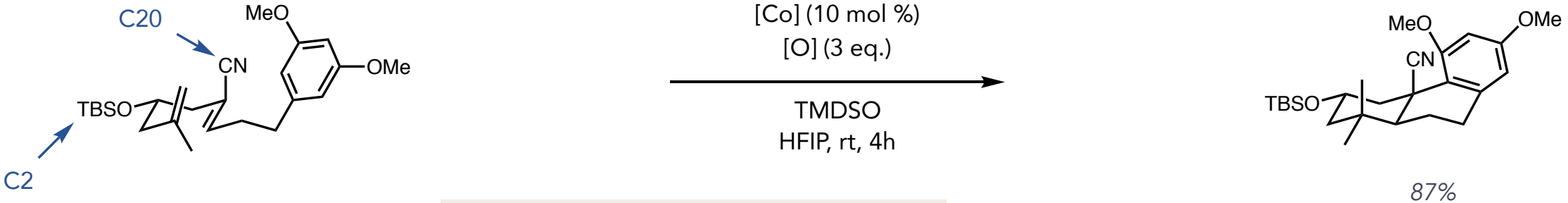
J. Am. Chem. Soc. **2010**, 132, 14, 5027–5029.

Radical Polycyclization Enabled by Metal-Catalyzed Hydrogen Atom Transfer

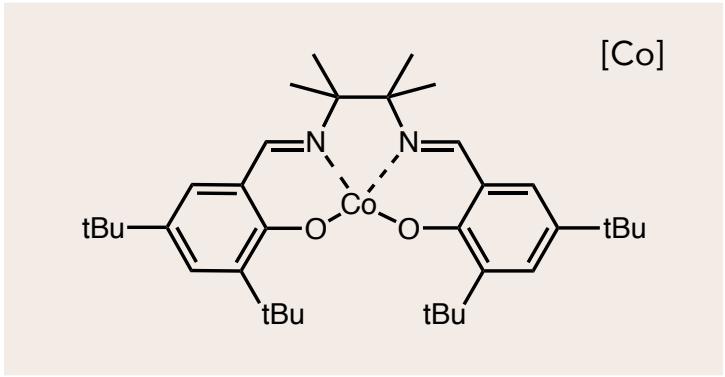


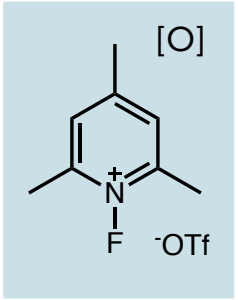
Angew. Chem. Int. Ed. **2017**,*56*, 5849–5852.

- Cobalt-Catalyzed MHAT Induced Radical Bicyclization



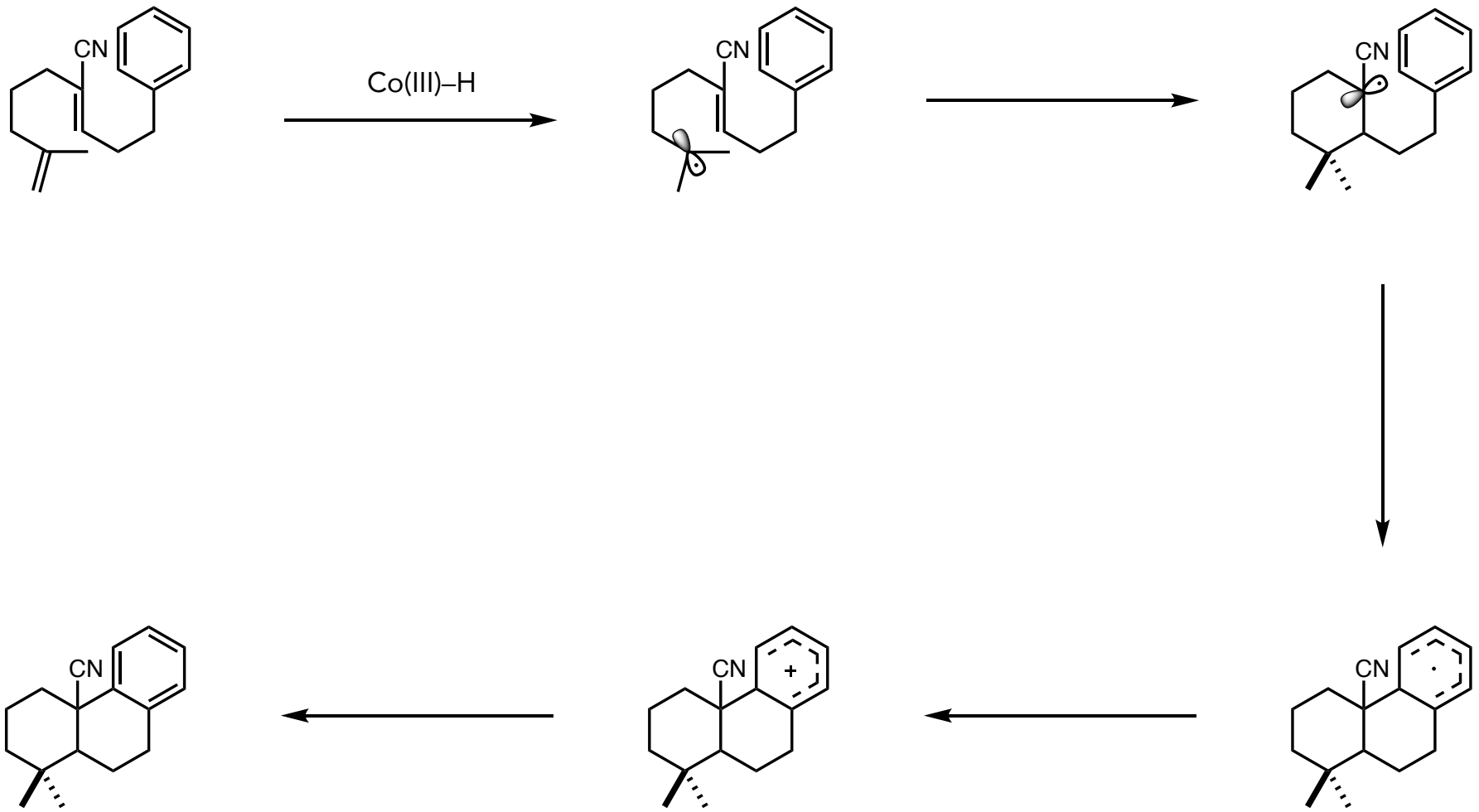
87%
>20:1 dr





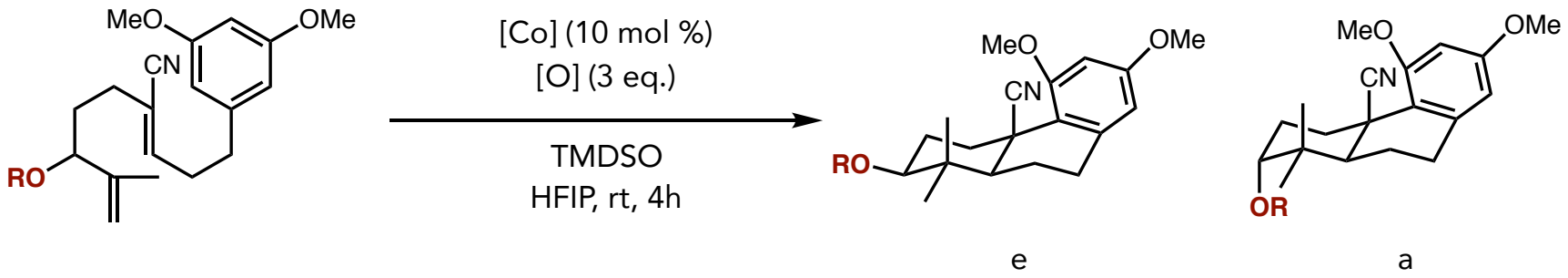
Angew. Chem. Int. Ed. **2020**,*9*, 1837–1840.

Proposed Mechanism



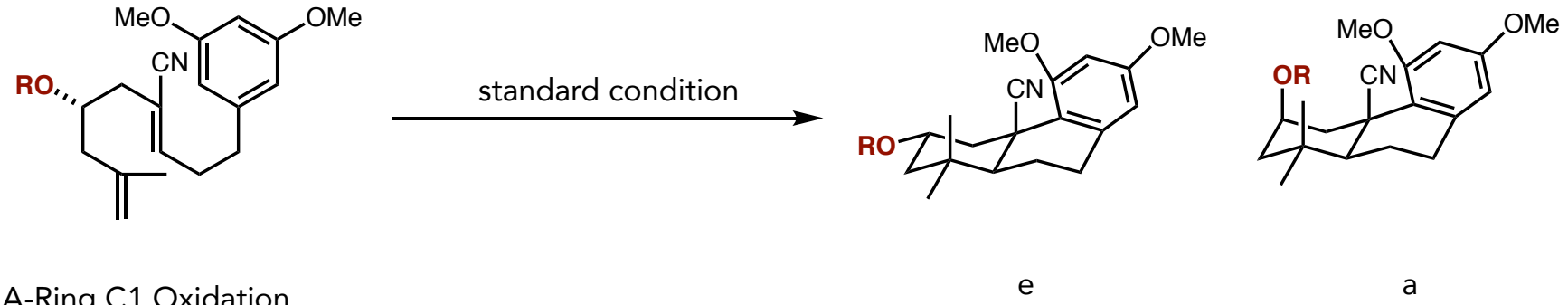
Stereochemical Control by Oxygenation

- A-Ring C3 Oxidation



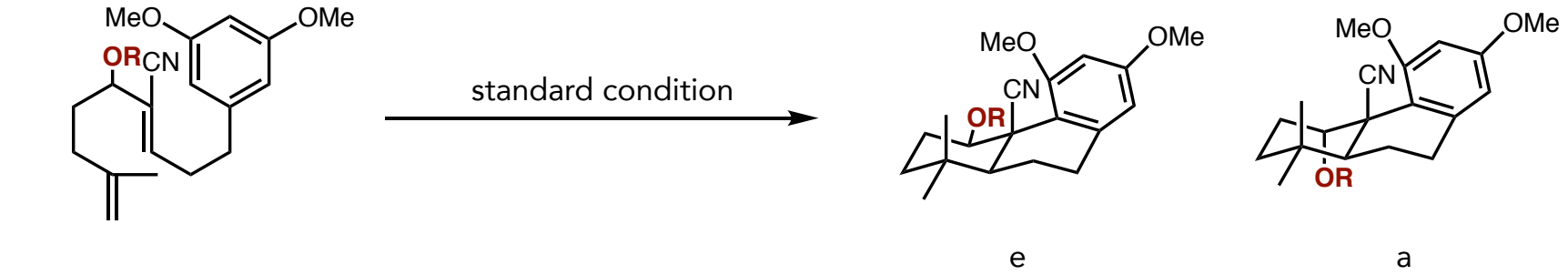
R	dr (e:a)	yield
H	3:1	81%
Ac	1.3:1	75%
MOM	1:1.3	69%
TBDMS	1:8	71%

- A-Ring C2 Oxidation



R	dr (e:a)	yield
H	>20:1	81%
TBDMS	>20:1	87%

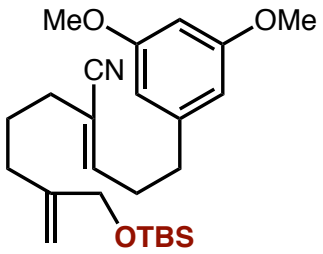
- A-Ring C1 Oxidation



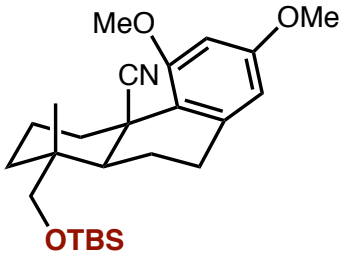
R	dr (e:a)	yield
H	3:1	80%
TBDMS	nd	<5%

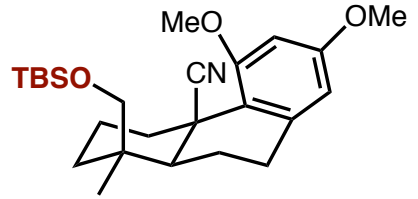
Stereochemical Control by Oxygenation

- A-Ring C18 Oxidation

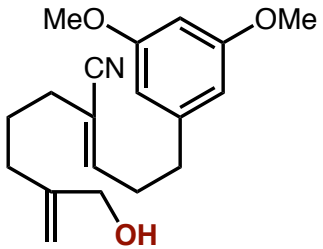


standard condition

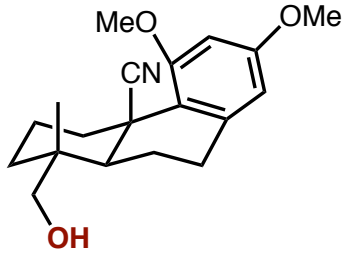


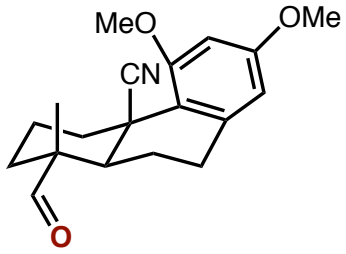


not observed



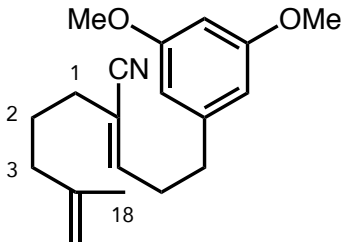
standard condition





74% (2:1)

- A-Ring Summary



C3: OH (e), OTBDMS (a)

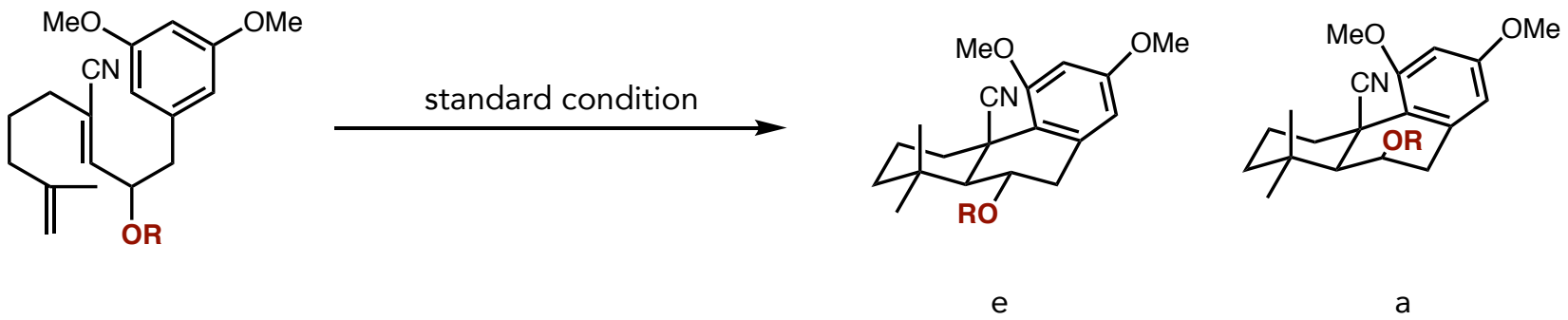
C2: e

C1: OH (e)

C18: e

Stereochemical Control by Oxygenation

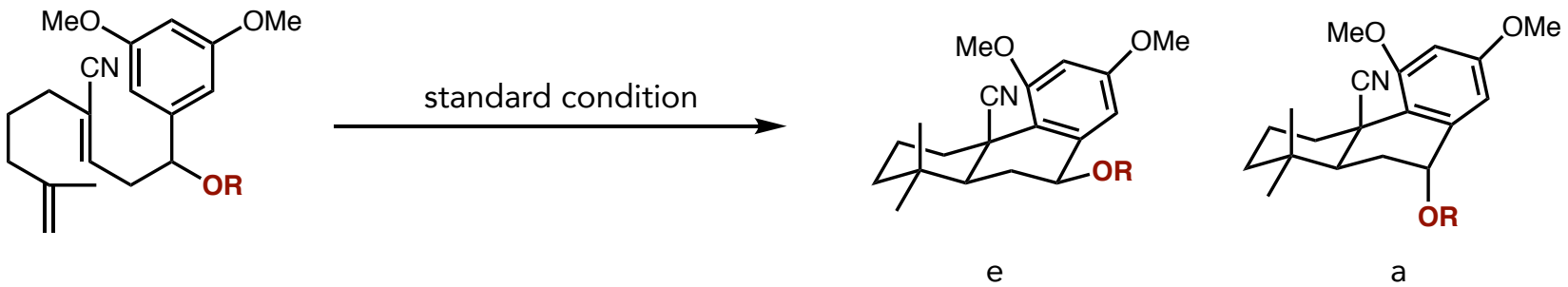
- B-Ring C6 Oxidation



e a

R	dr (e:a)	yield
Ac	1:1	64%
TBDMS	nd	<5%

- B-Ring C7 Oxidation



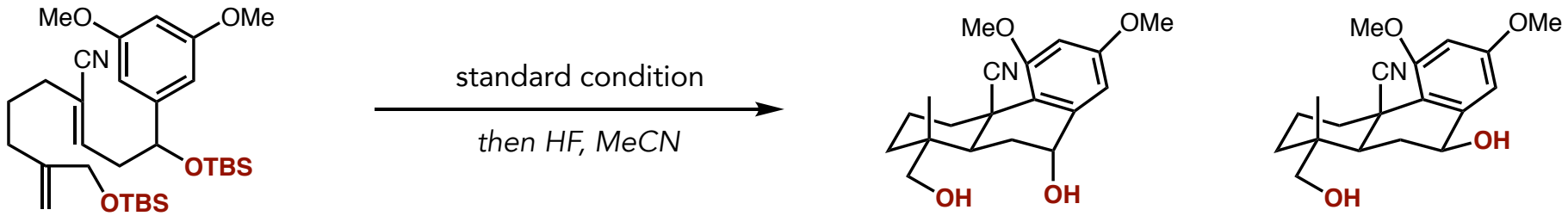
e a

R	dr (e:a)	yield
H	1:1.3	65%
TBDMS	1:1	73%

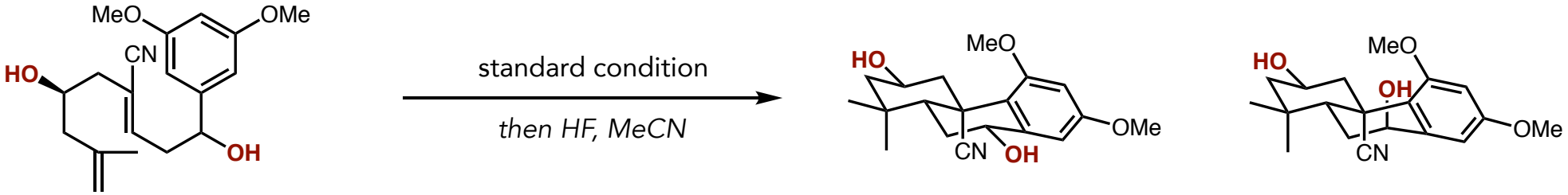
B-ring oxygenation has negligible impact on stereoselectivty.

Stereochemical Control by Oxygenation

- Double Oxygenation

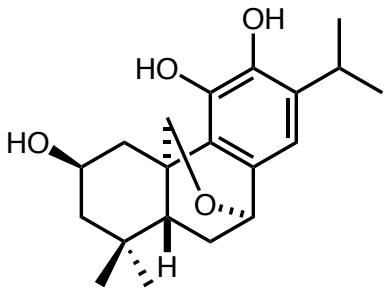


52%, 4:3 dr at C7

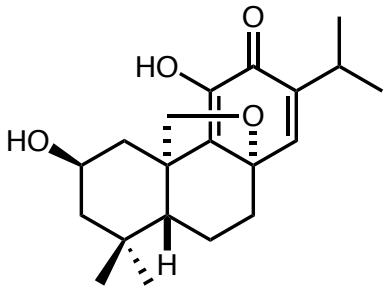


74%, 1:1 dr at C7

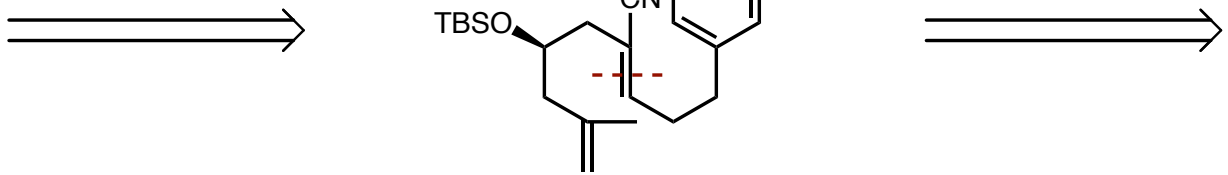
Application in Total Synthesis

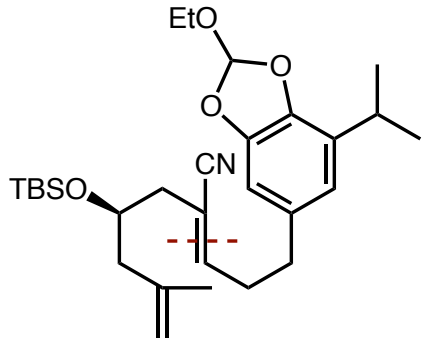


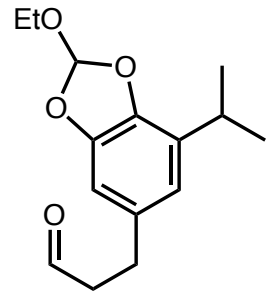
(+)-2-O-deacetyl plebedipene C

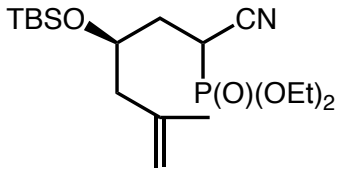


(+)-2-O-deacetyl plebedipene A

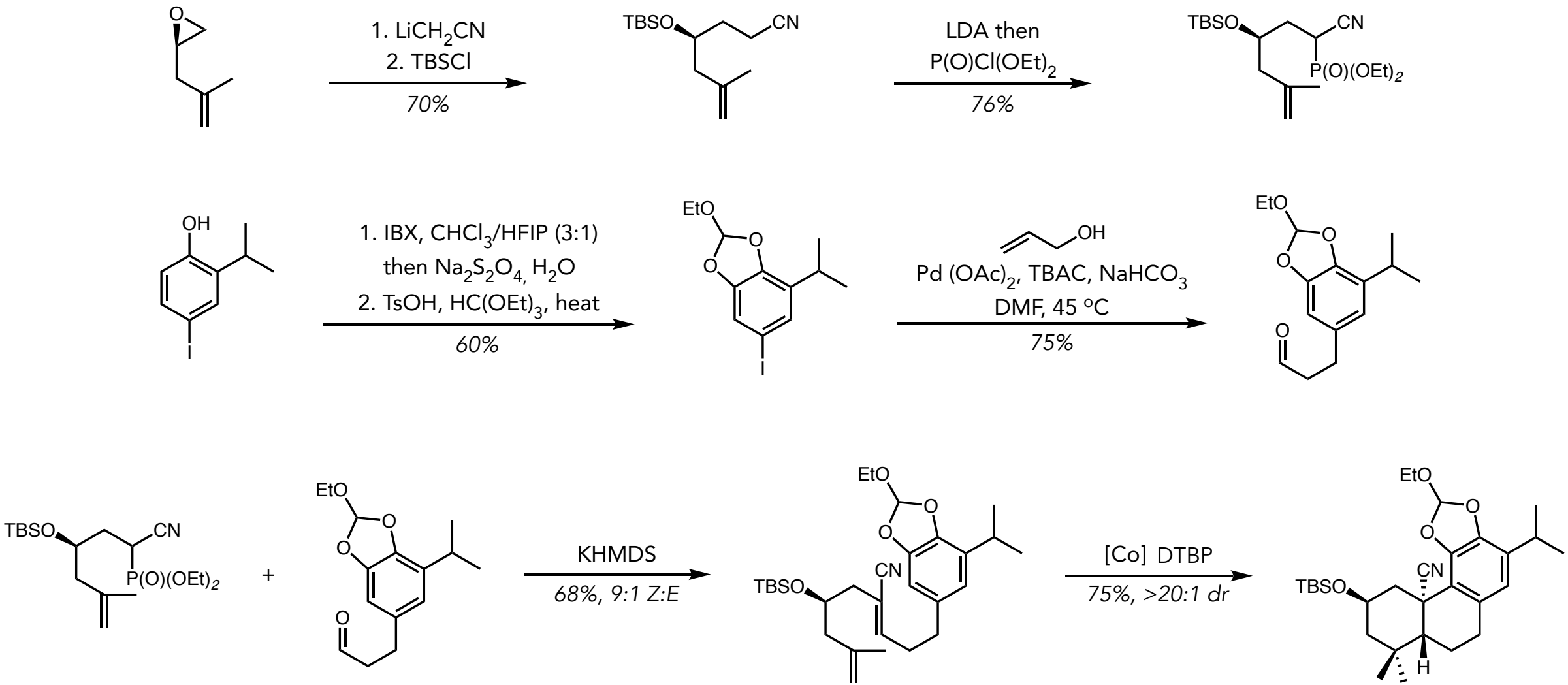




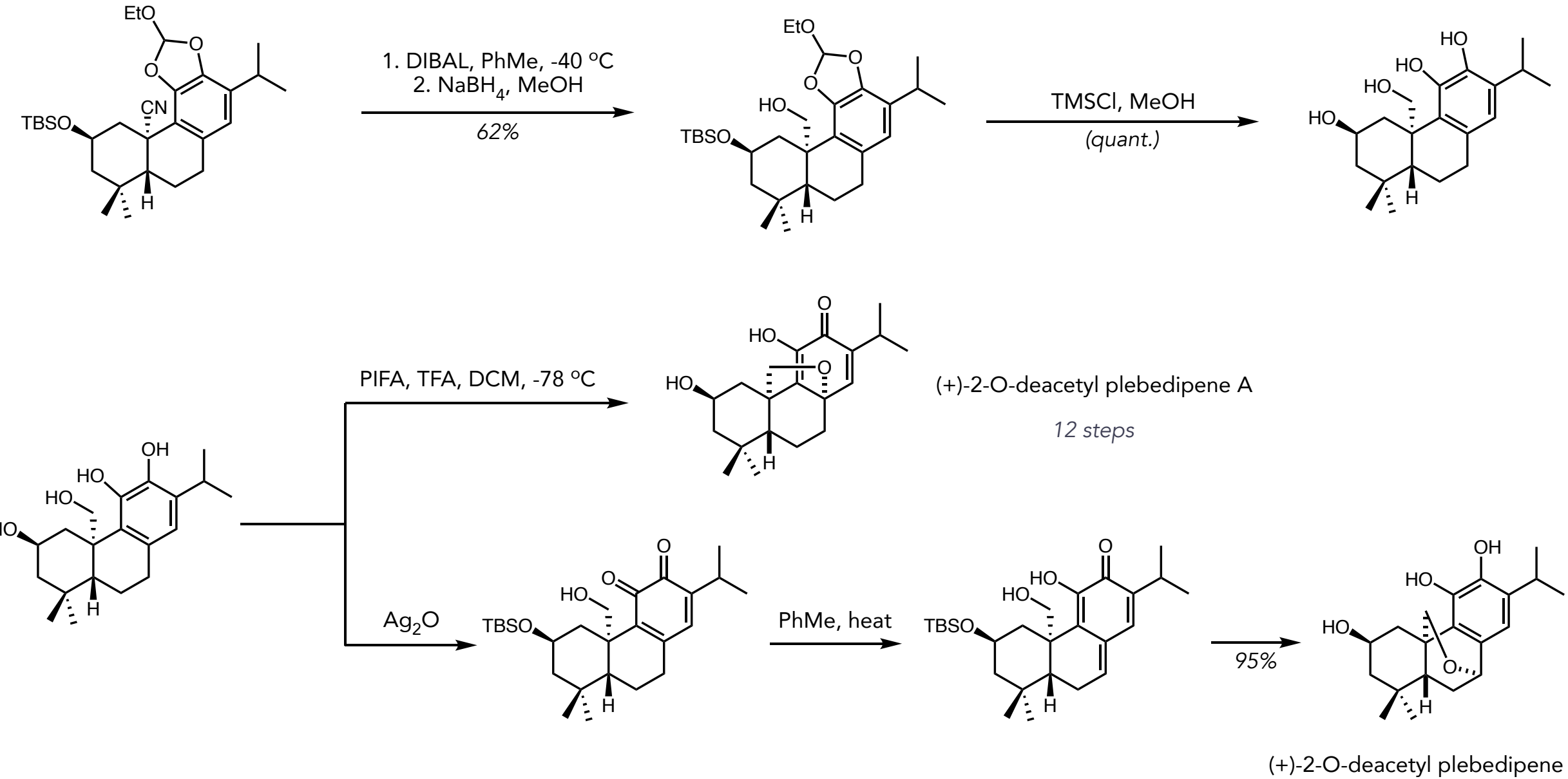




Forward Synthesis



Forward Synthesis



Summary

- Investigated stereochemical outcome of MHAT induced cyclization of preoxidized polyene precursors
- Oxygenation at various C is tolerated. A-ring oxygenation results in useful stereoselectivity.
- Completed the first total synthesis of plebedipene A, C.