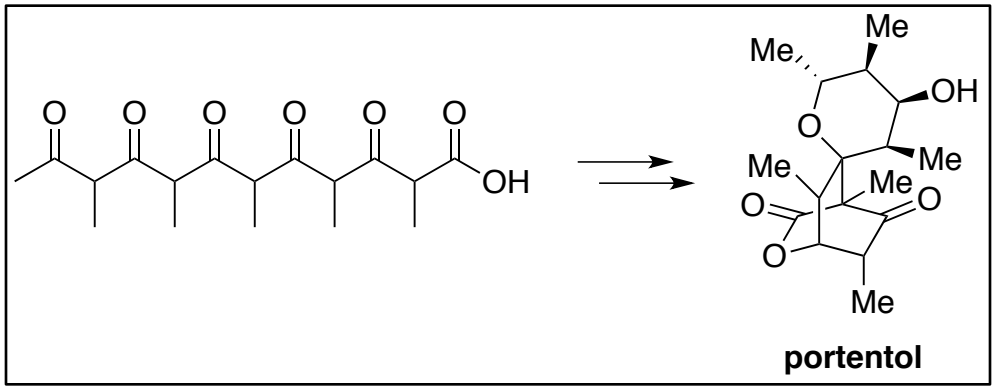
A Highly Convergent and Biomimetic Total Synthesis of Portentol



B. Cheng, D. Trauner,

J. Am. Chem. Soc. **2015**, *137*, 13800–13083

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Samuel Rieder, 25th Nov. 2015

Dirk Trauner

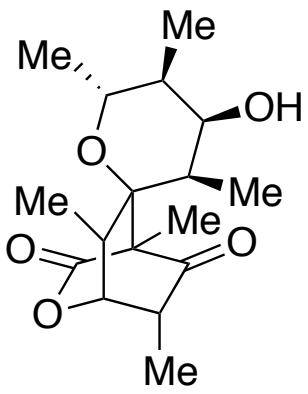
- **1967**: Born in Linz, Austria
- **1986-88**: Studied Biology, Vienna
- **1988-91**: Studied Biochemistry, Vienna
- **1992-95**: Studied Chemistry, Berlin
- **1995-97**: PhD, Prof. J. Mulzer, Berlin & Vienna
- **1998-00**: Postdoc, Prof. S. Danishefsky, New York
- **2000-06**: Assistant Professor, Berkeley
- **2006-10**: Associate Professor, Berkeley
- **2008-** : Full Professor, Munich

Research Interest:

- Chemical Synthesis
- Cell Biology
- Natural Product Chemistry
- Neuroscience
- Photopharmacology

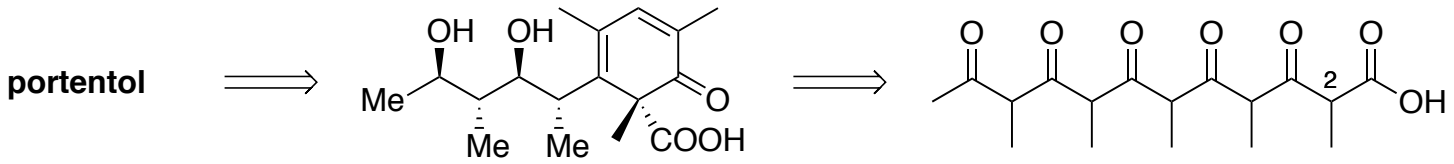
Portentol

Isolation and Characterisation



- First isolated in **1967** from *Roccella portentosa* (lichen)
- Moderate growth inhibition against several cancer cell lines
- Densley functionalized spiro tricyclic core (9 consecutive stereocenters)

- **Biosynthetic Speculation (Overton)**

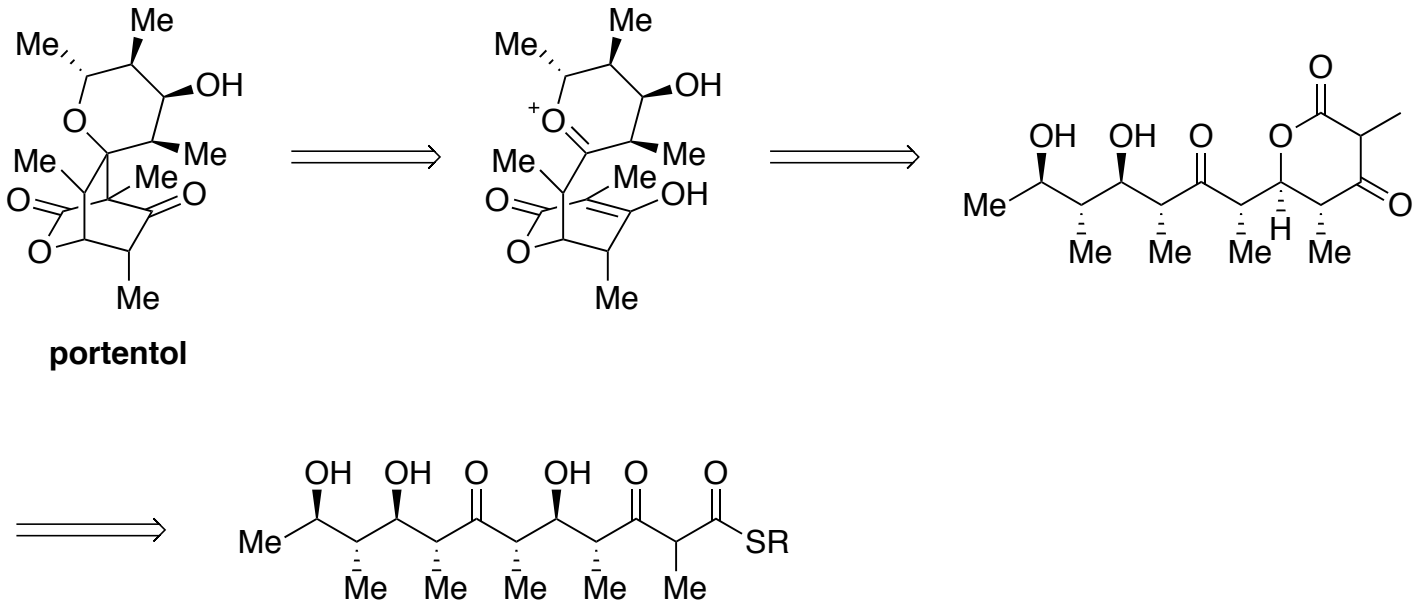


- ^{14}C labelling: Carbon chain from acetate and malonate
- C2 Me from acetate, other Me from methionine

D. J. Aberhart, K. H. Overton, S. Huneck, *J. Chem. Soc., C* **1970**, 1612–1623.
D. J. Aberhart, A. Corbella, K. H. Overton, *J. Chem. Soc. D* **1970**, 664–665.

Biosynthetic Analysis
Speculations

- Cationic Cyclization Cascade

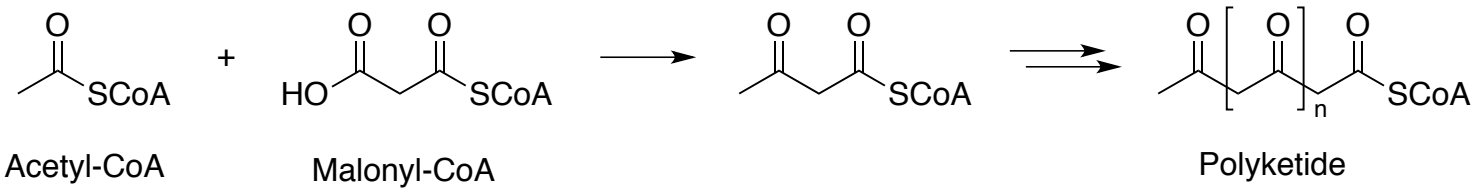


- Lactone assembled by **type II polyketide synthase (PKS)**
- Containing two ***anti-anti*** **triads** (synthetically challenging)
- PKS (thioesterase domain) might also catalyze subsequent cationic cyclization

Polyketides

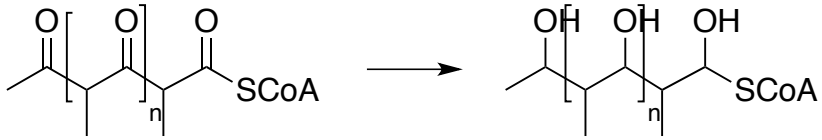
Stereotriades; Propionate Triades

- Biosynthesis (polyacylation)

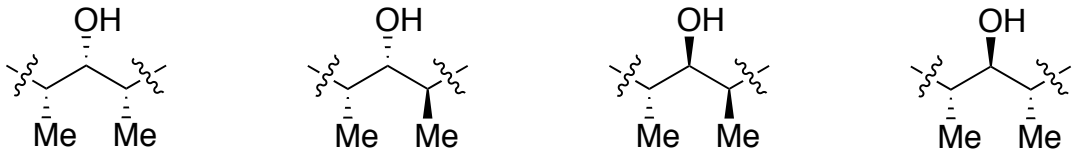


Acetyl-CoA Malonyl-CoA Polyketide

- Biosynthesis (Methylation, Reduction)



- Biosynthesis (Selectivity)

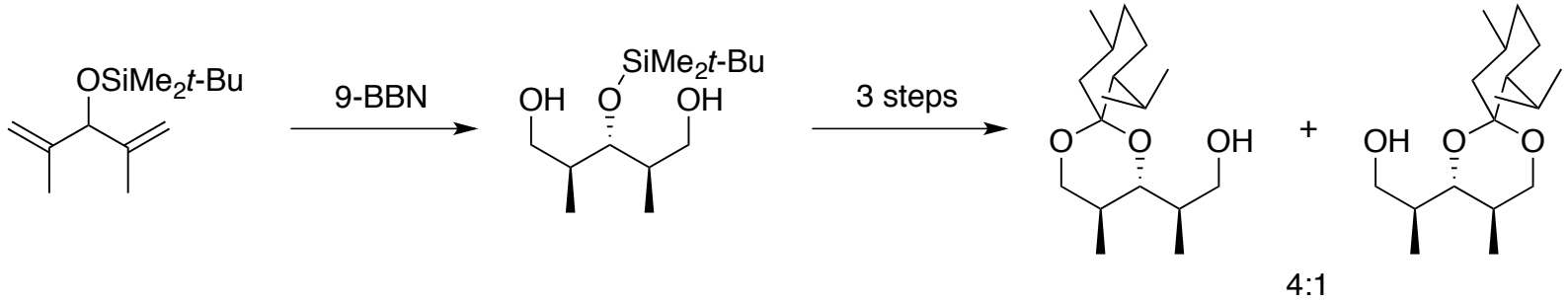


syn, syn *syn, anti* *anti, syn* *anti, anti*

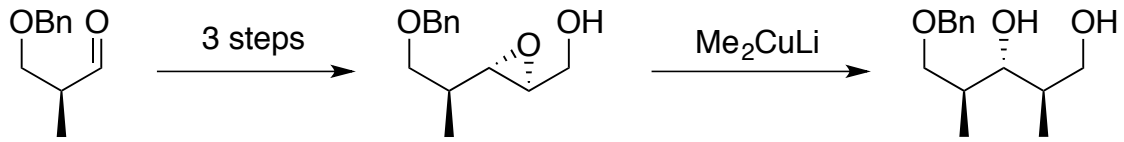
anti,anti-Triade

Previous Approaches

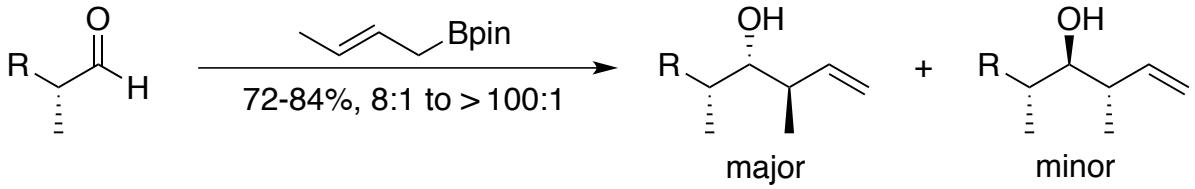
- Desymmetrization (Mesoforms)



- Asymmetric Epoxidation



- Crotylboration

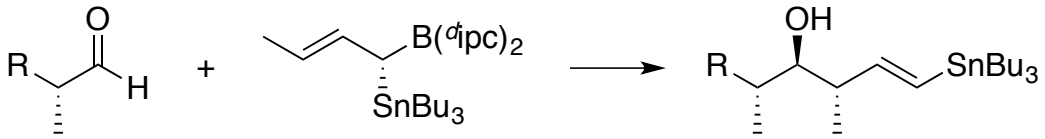


T. Harada, A. Inoue, I. Wada, J. Uchimura, S. Tanaka, A. Oku, *J. Am. Chem. Soc.* **1993**, *115*, 7665–7674.

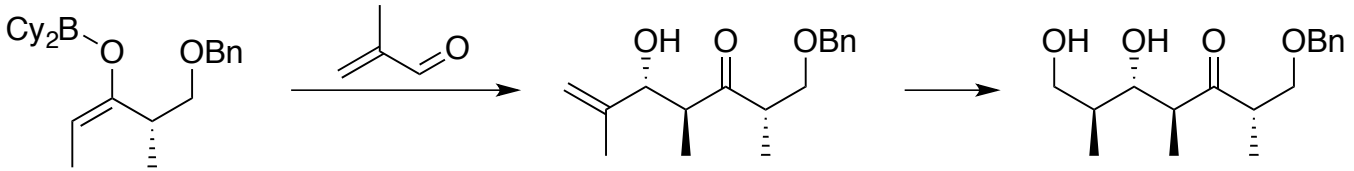
anti,anti-Triade

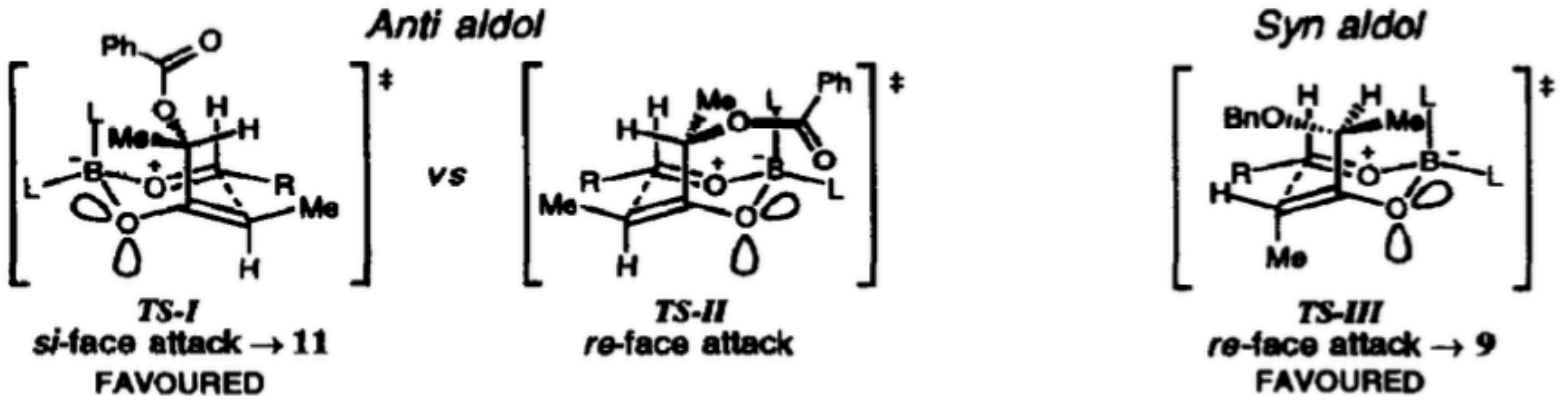
Previous Approaches

- Double Mismatched Crotylboraion



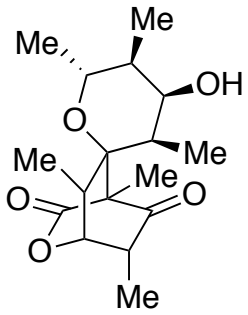
- Aldol reaction (*anti*-selective)





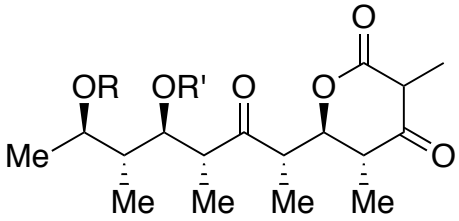
I. Paterson, D. J. Wallace, S. M. Velázquez, *Tetrahedron Lett.* **1994**, *35*, 9083–9086.
M. Chen, W. R. Roush, *J. Am. Chem. Soc.* **2012**, *134*, 3925–3931.

Retrosynthetic Analysis

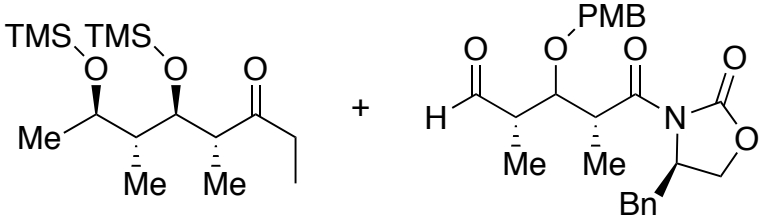


portentol

oxocarbenium/
β-keto lactone cyclization

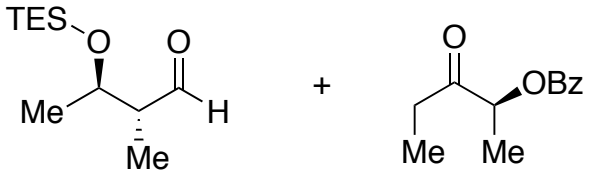


aldol

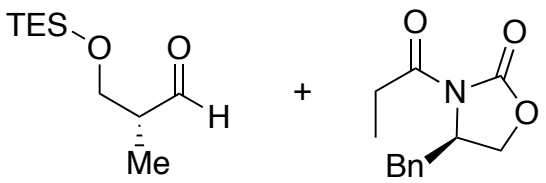


A **B**

aldol aldol



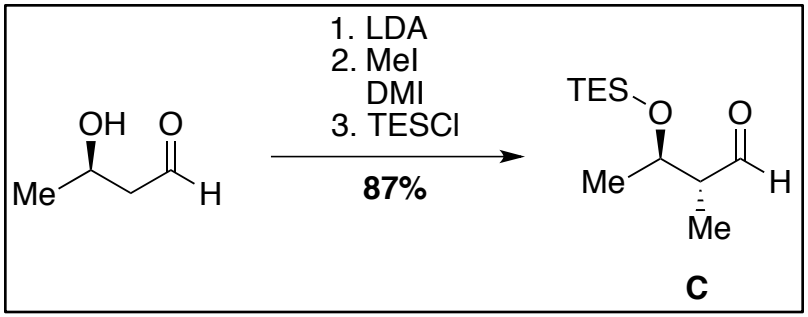
C **D**

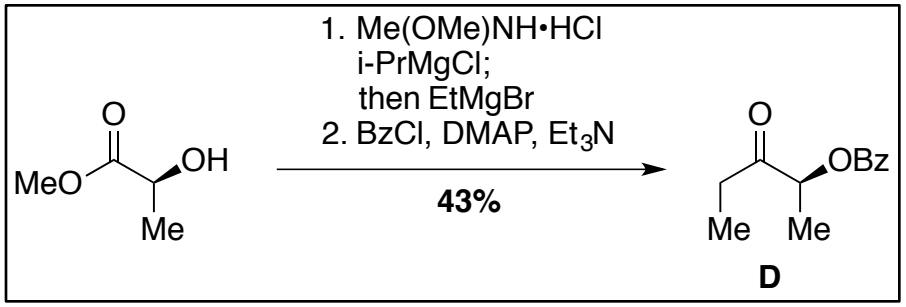


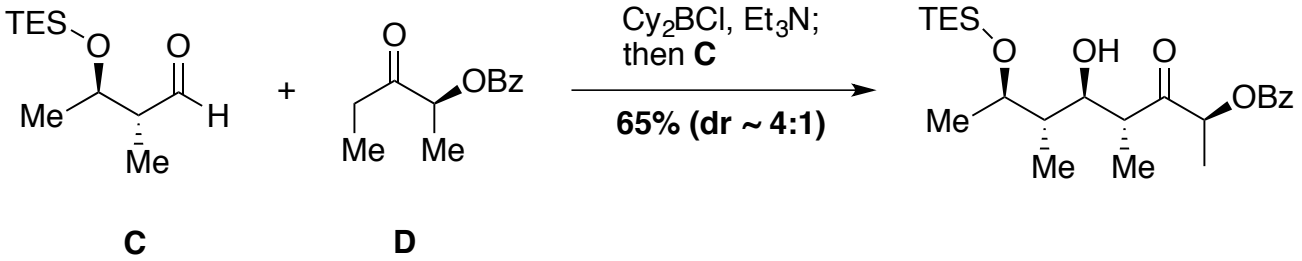
E **F**

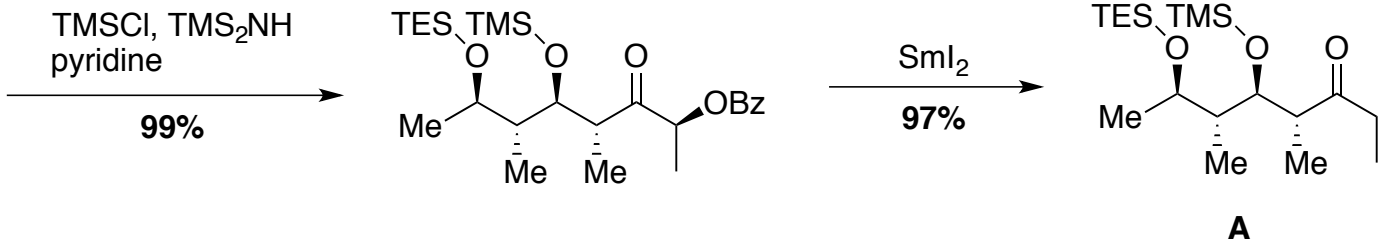
Synthesis of Fragment A

Synthesis of C & D; Paterson Aldol Reaction





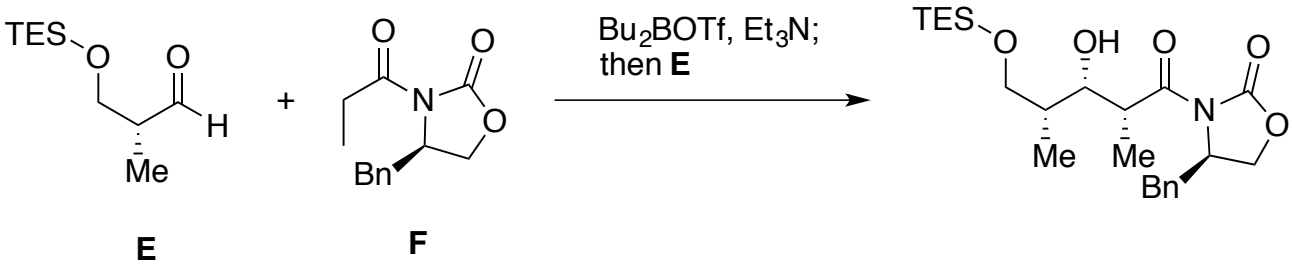




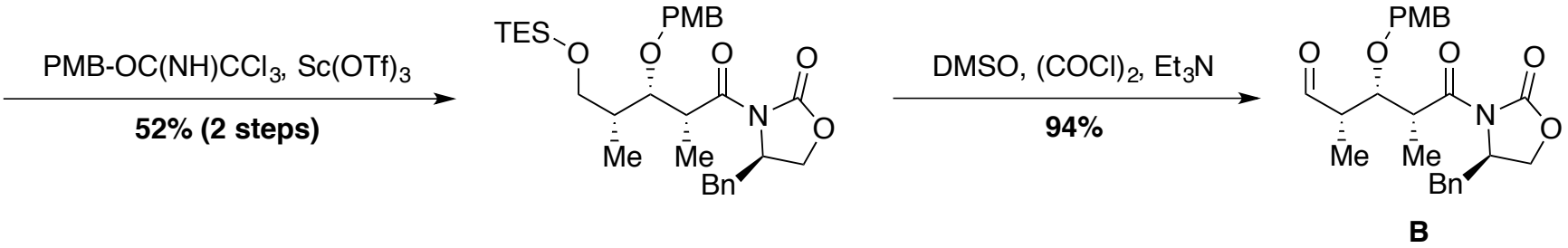
I. Paterson, D. J. Wallace, S. M. Velázquez, *Tetrahedron Lett.* **1994**, *35*, 9083–9086.

Synthesis of Fragment B

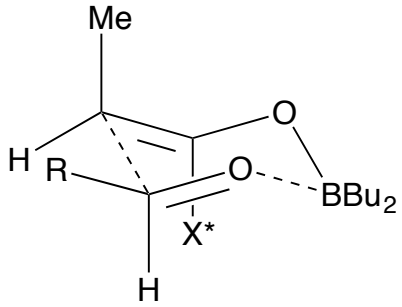
Evans Aldol Reaction



E **F**

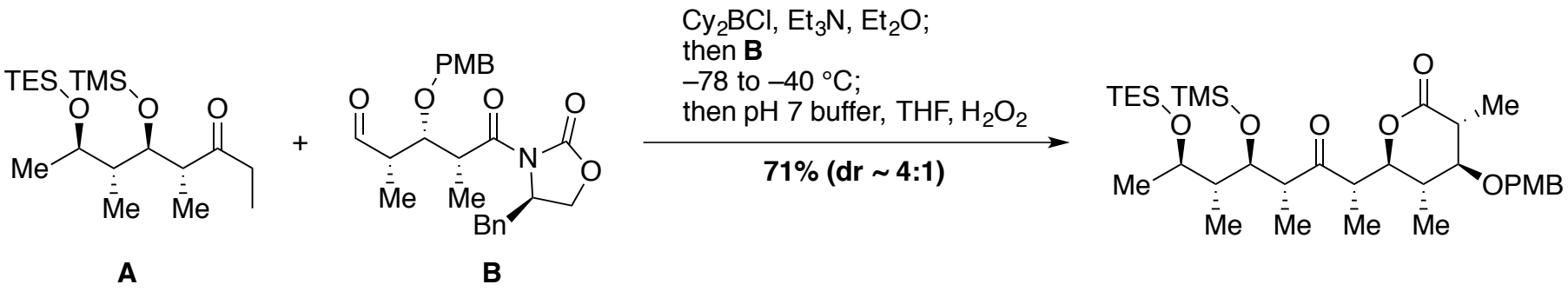


B



Synthesis Lactone Precursor

Key Coupling Reaction

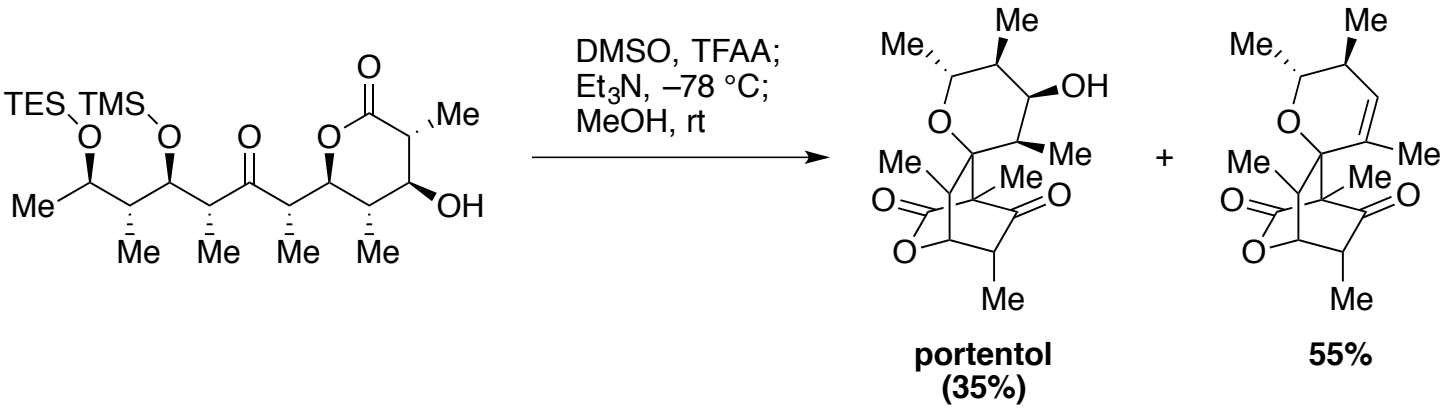


A **B**

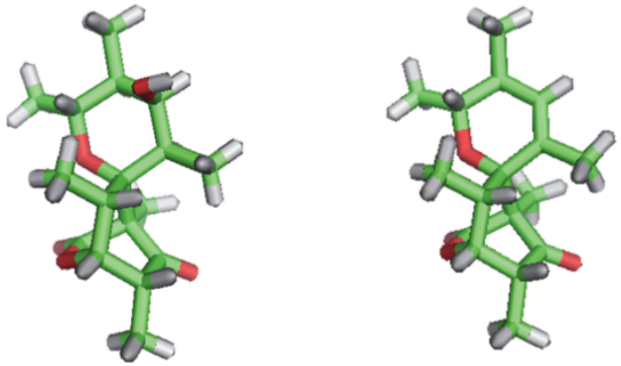
- Lactone directly obtained after removal of auxiliary when adding THF during wu
- Separation by FC (recovered fragment **A**)
- Confirmation of stereochemistry by NMR
- Removing PMB with DDQ (**84%**) → adding H_2O or pH 7 buffer lead to byproduct formation

Final Step
Double Cyclization Cascade

- Oxidation of β-hydroxy lactone under Swern conditions



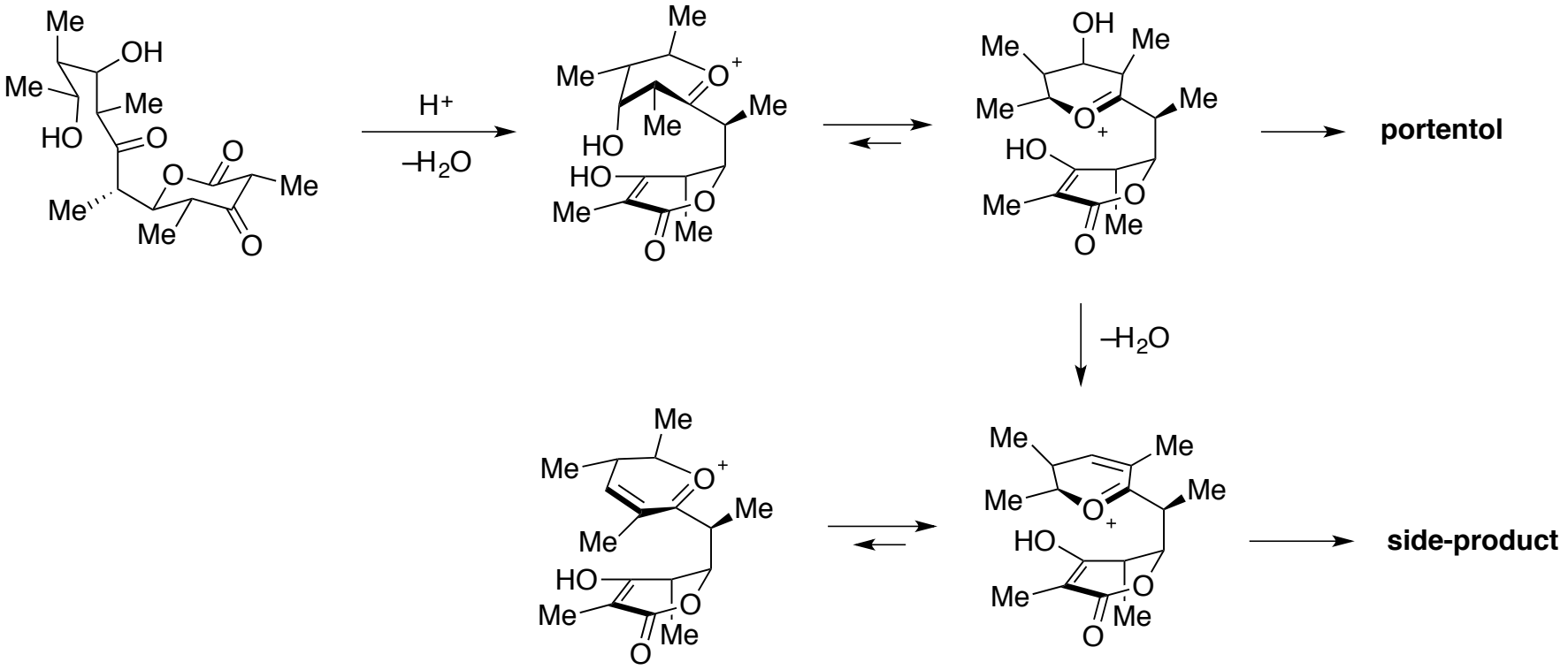
- Acid formed in-situ during wu
- Spectroscopic data and X-ray structures



N. Sakai, Y. Ohfune, *J. Am. Chem. Soc.* **1992**, *114*, 998–1010.

Cationic Cascade

Mechanism



- C2 and C7 bond formation slow (steric hindrance)
- $A^{1,3}$-strain of C6 and C8 methyl groups

Conlusion

- Due to high yield and ease of the cascade → similar process in nature

- Enzymatic vs. Spontaneous
  - Side-product never isolated → points to catalysis

- Brief, and efficient synthesis due to biomimetic key step and convergent synthetic plan

- Three diastereoselective boron aldol reactions (one *syn*, two *anti*)

- First total synthesis

Boron Enolate