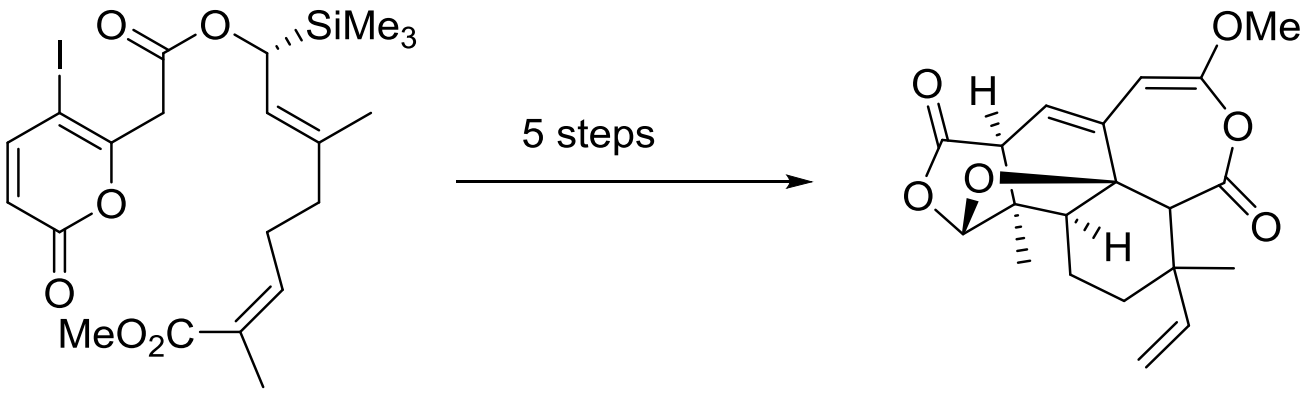
Asymmetric Total Synthesis of Transtaganolides A-D and Biosynthetic Implications



Nelson, H. M., Gordon, J. R., Virgil, S. C., and Stoltz, B. M.

ACIE Early View

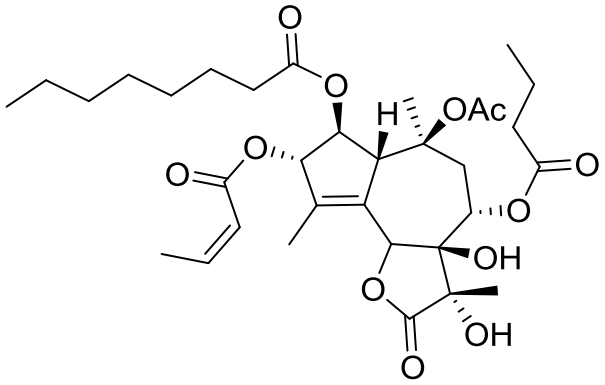
Wipf Group Current Literature 6/8/13

John Milligan

Deadly Carrots: Pick Your Poison

Thapsia garganica

http://en.wikipedia.org/wiki/File:Thapsia_garganica_(Bauer).jpg



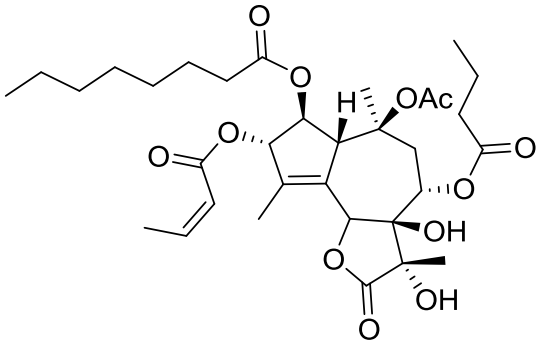
thapsigargin

1978

Deadly Carrots: Pick Your Poison

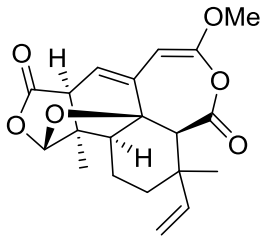
Thapsia garganica

http://en.wikipedia.org/wiki/File:Thapsia_garganica_(Bauer).jpg

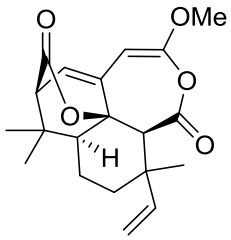


thapsigargin

1978



Transtaganolide A/B

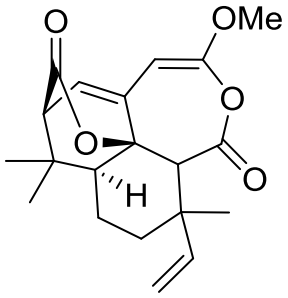


Transtaganolide C/D

2005

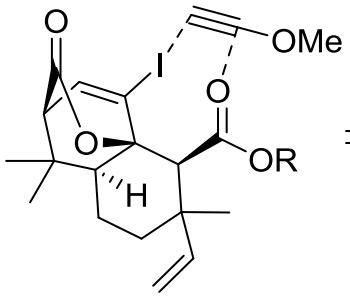
Mechanistically distinct calcium ATPase inhibitors!

Synthetic strategy

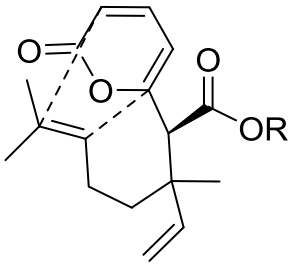


Transtaganolide C/D

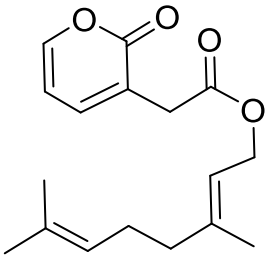
formal [5+2]



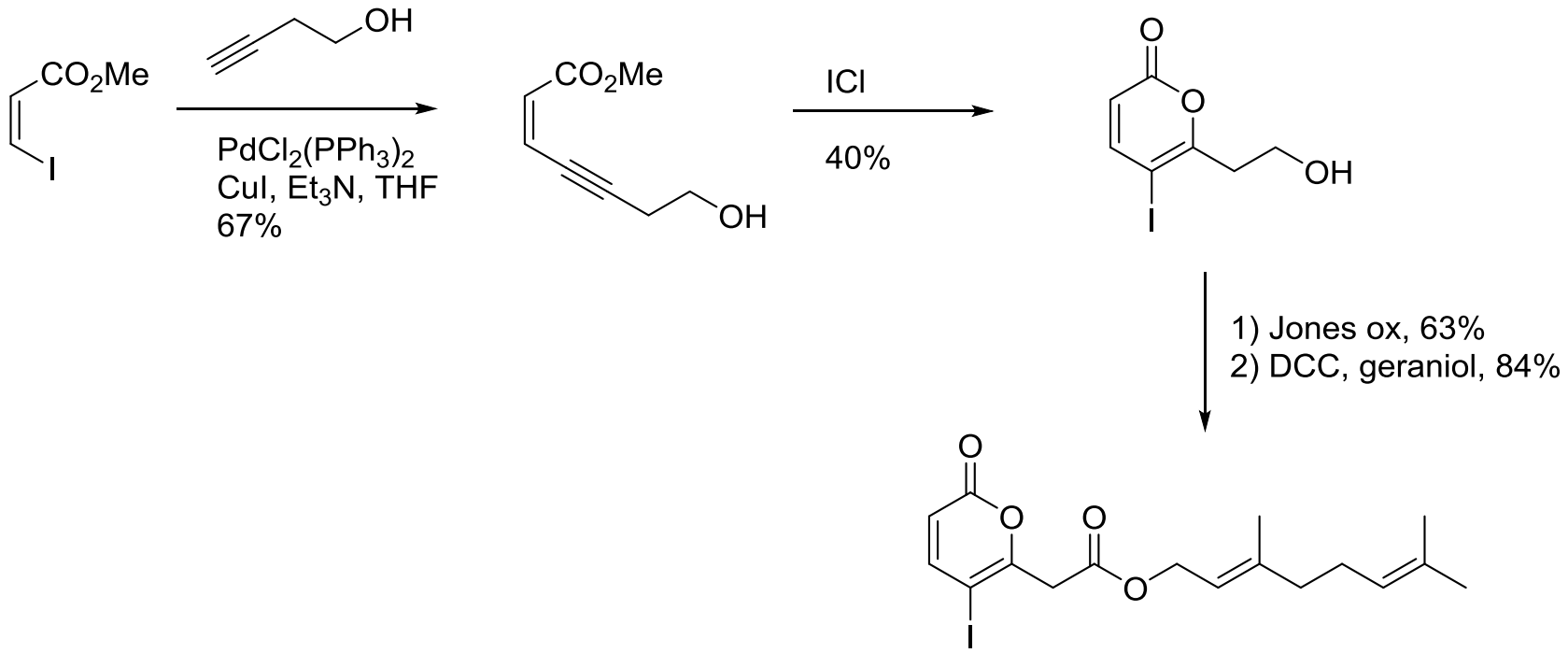
Diels-Alder



Ireland-Claisen
biomimetic?

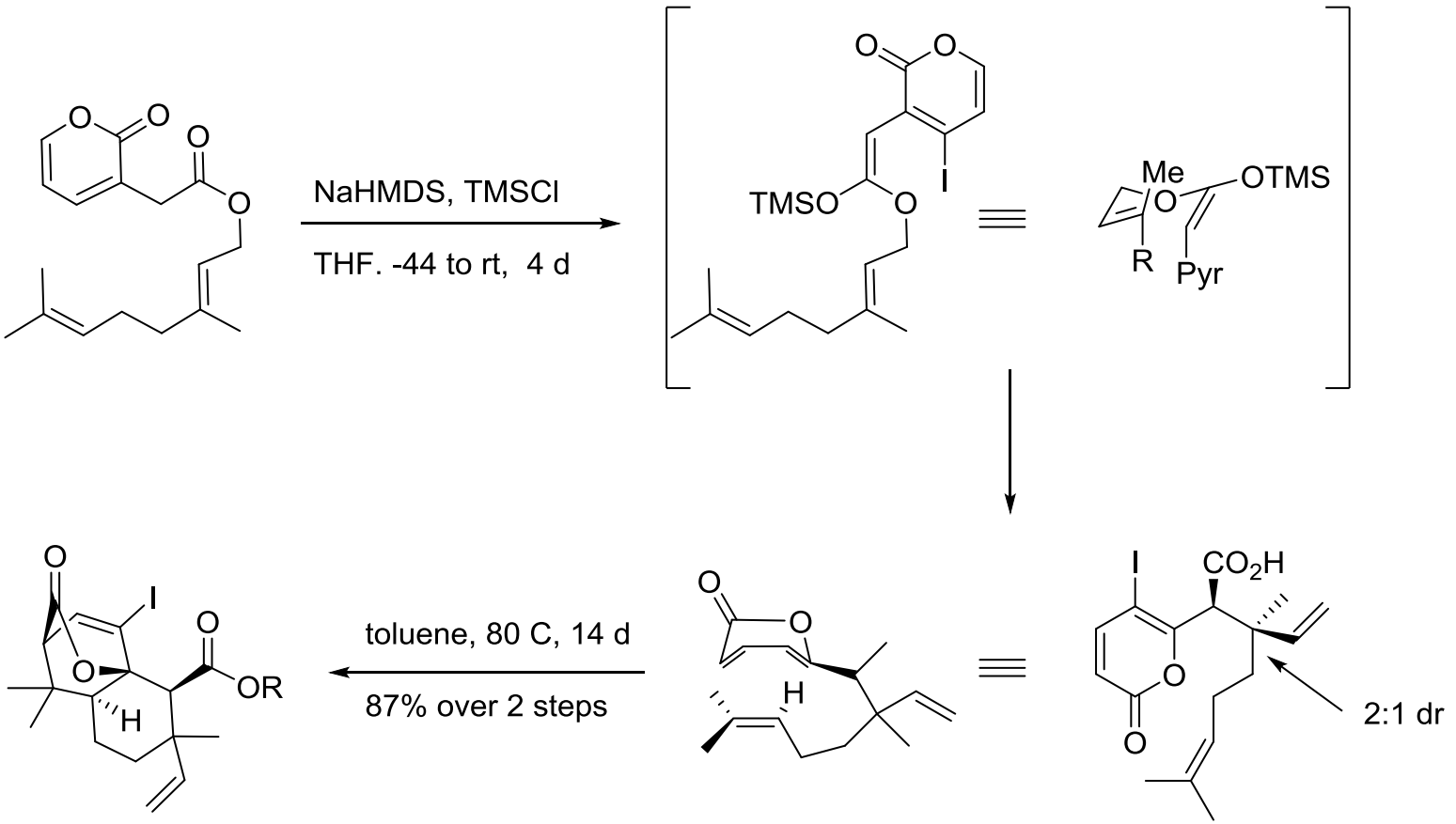


Pyrone preparation



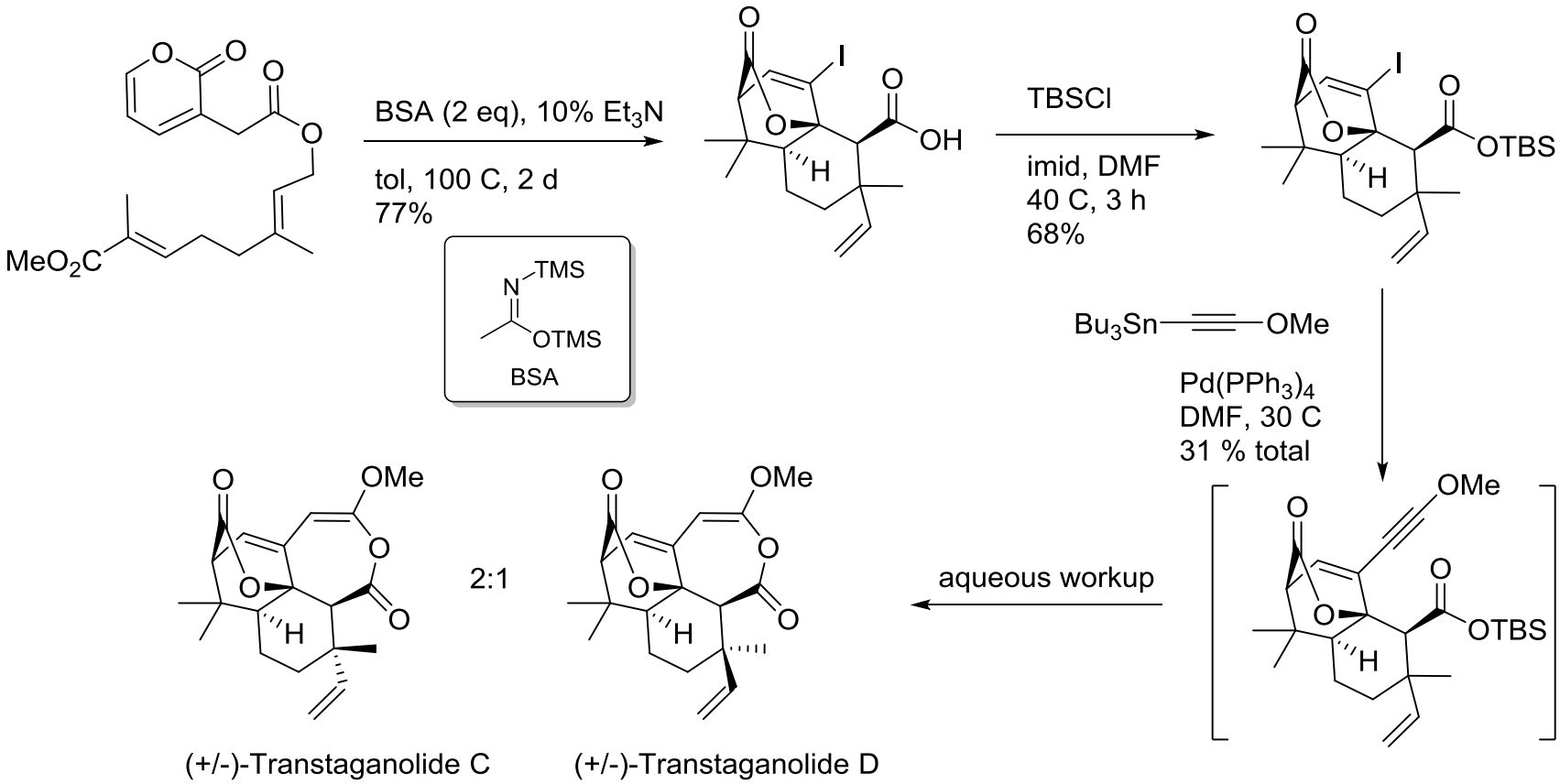
Joansson *Org. Lett*. **2009**, *11*, 657
Stoltz *Tet. Lett*. **2009**, *50*, 1699

Claisen / Diels-Alder



Stoltz *Tetrahedron Lett*. **2009**, 50, 1699

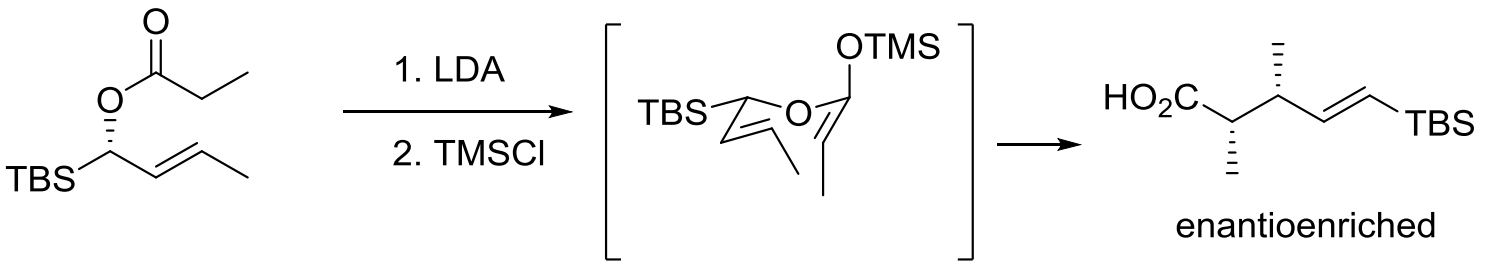
Transtaganolides C/D



Stoltz *Angew. Chem. Int. Ed*. **2011**, *50*, 1688

Enantioselective cascade

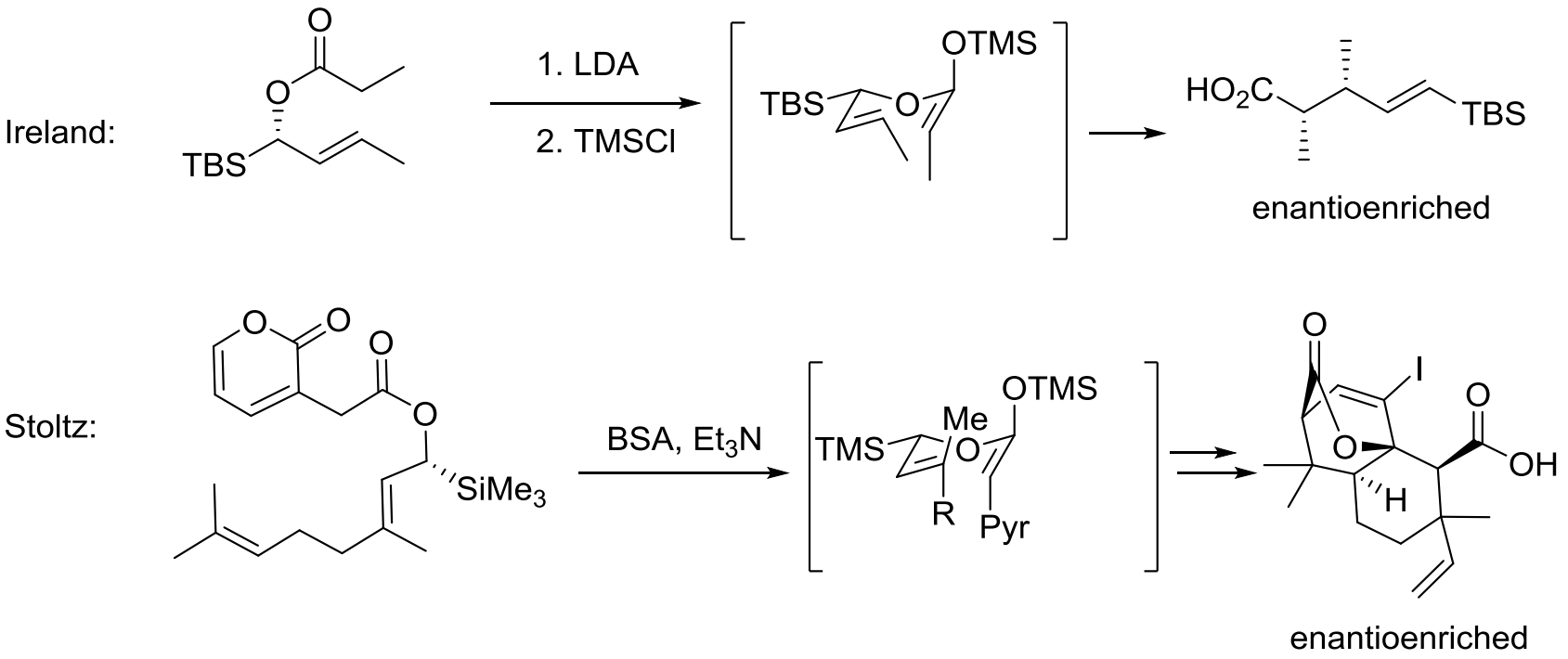
Ireland:



Ireland *J. Am. Chem. Soc.* **1984**, *106*, 3668

Stoltz *Angew. Chem. Int. Ed*. **2013**

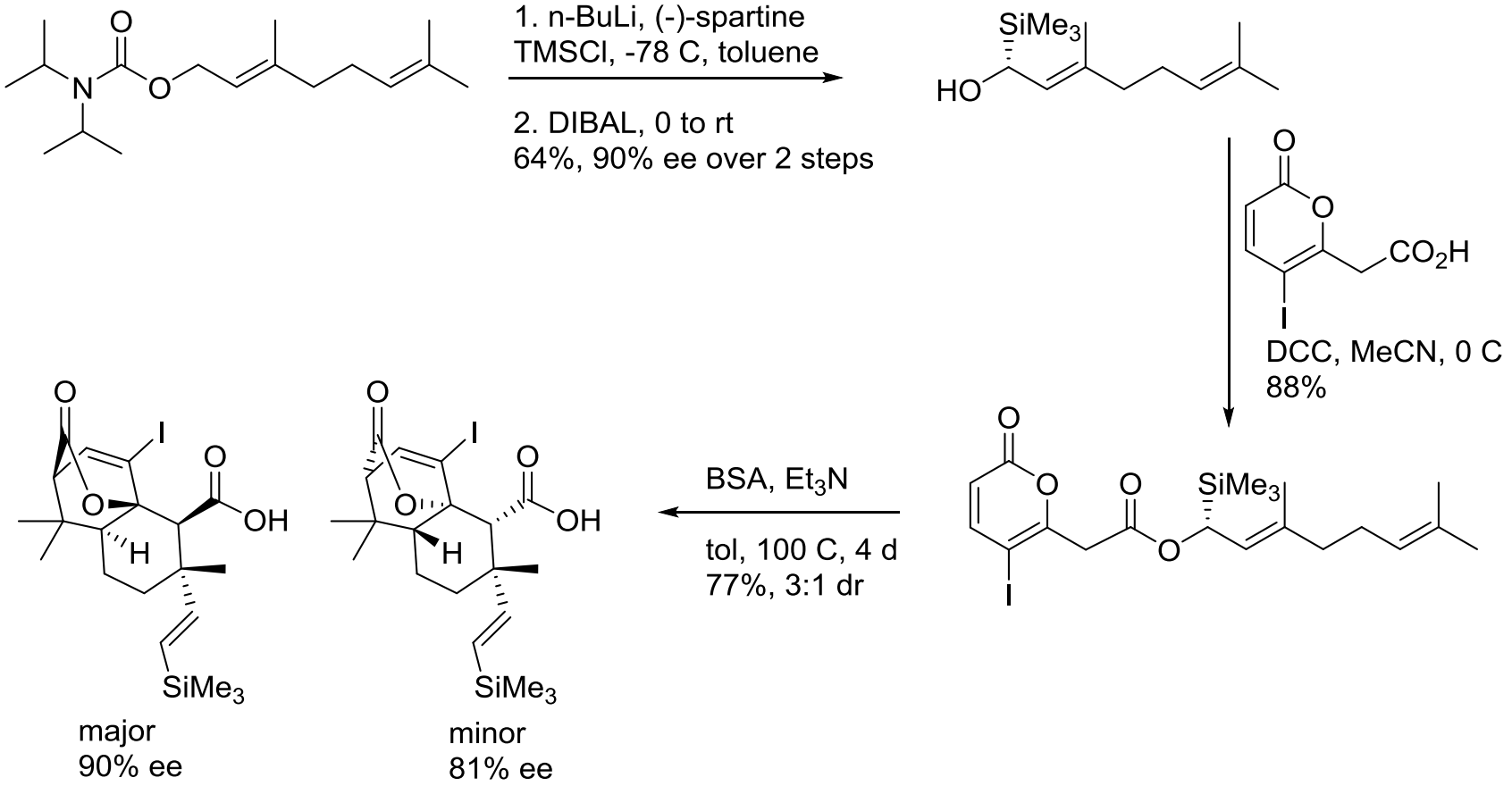
Enantioselective cascade



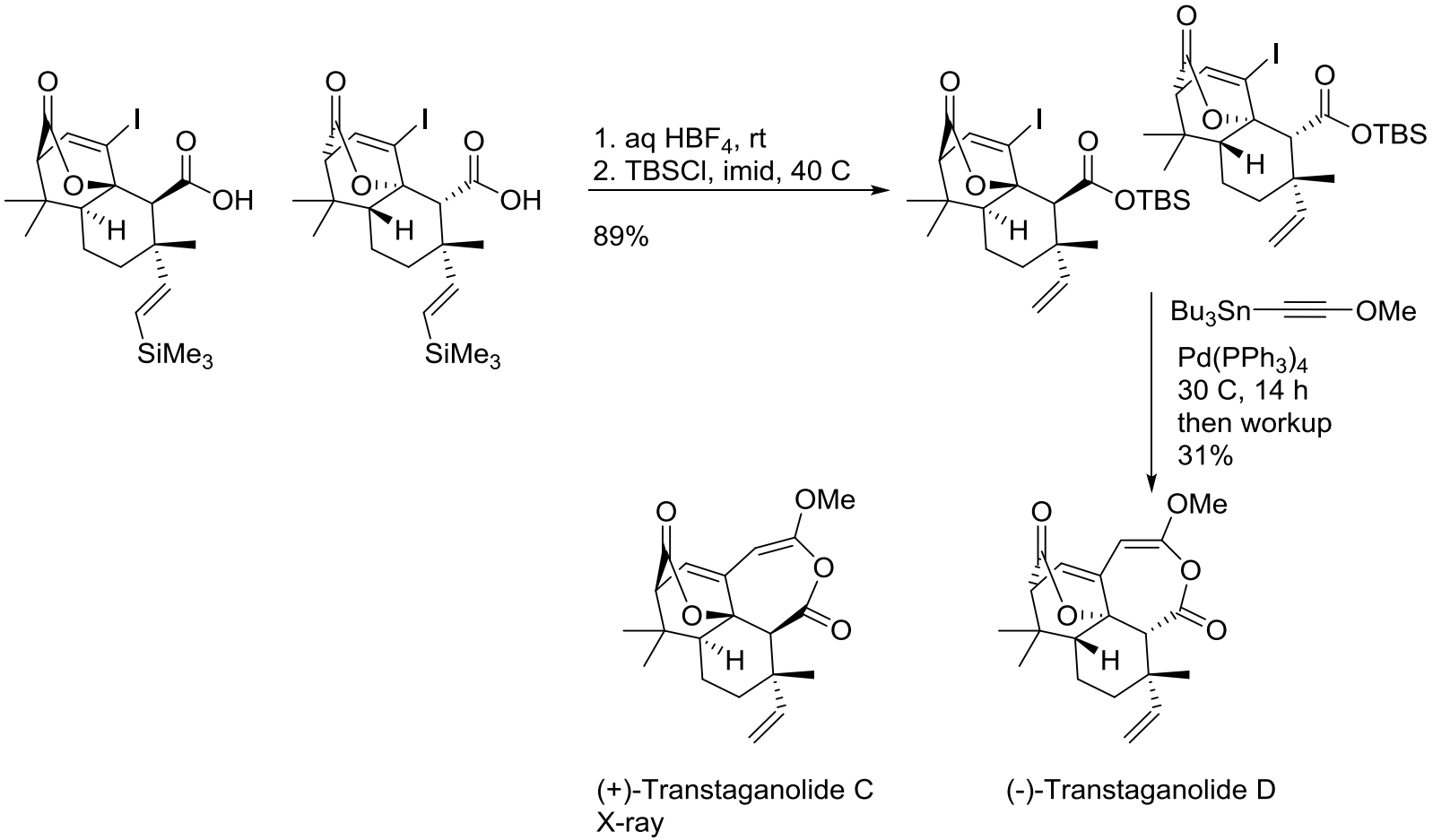
Ireland *J. Am. Chem. Soc.* **1984**, *106*, 3668

Stoltz *Angew. Chem. Int. Ed*. **2013**

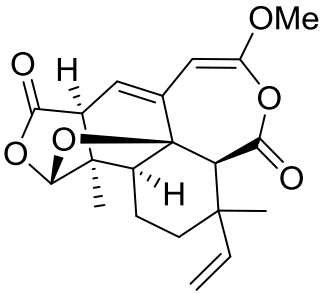
Enantioselective C/D



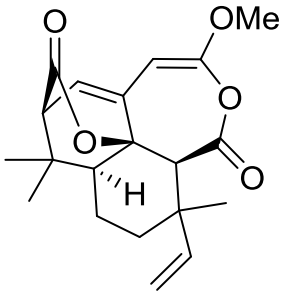
Enantioselective C/D



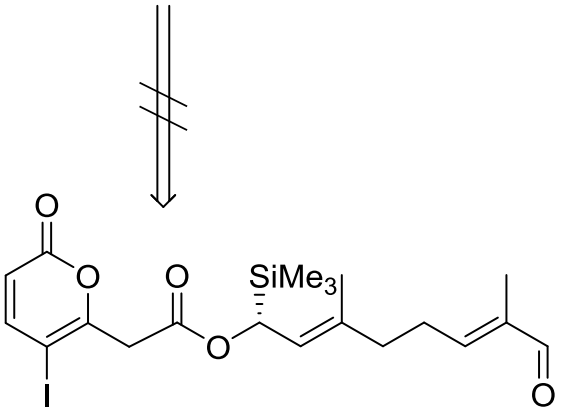
Comparison



Transtaganolide A/B

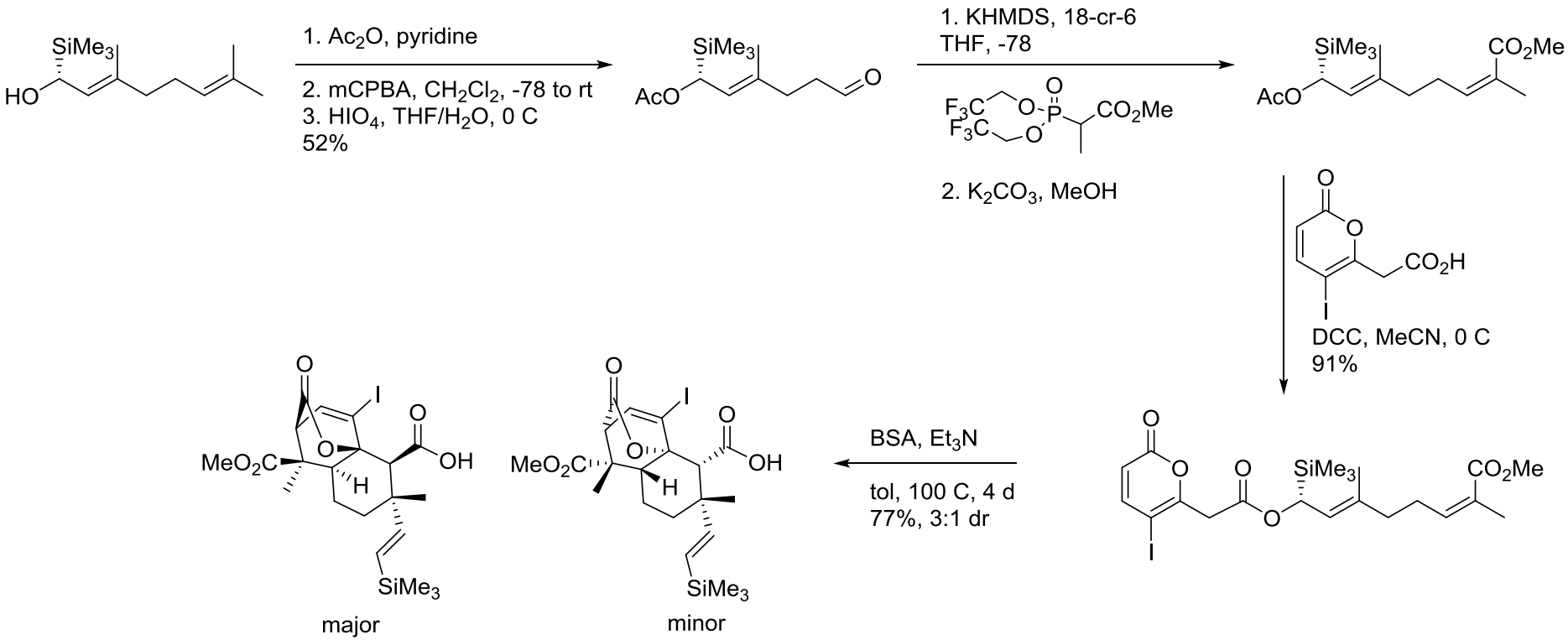


Transtaganolide C/D

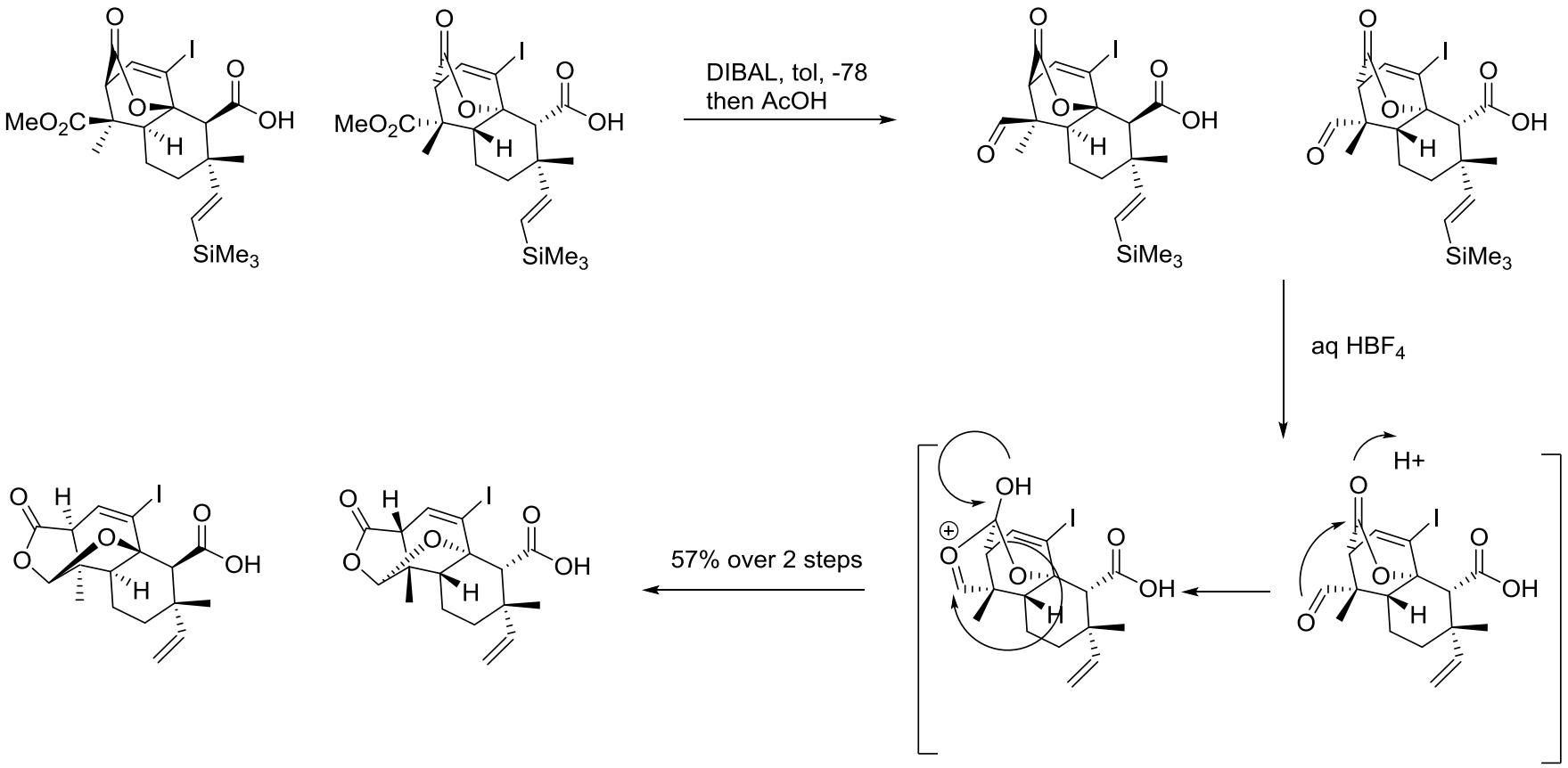


prone to isomerization

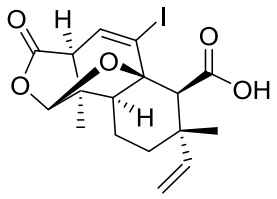
Enantioselective A/B

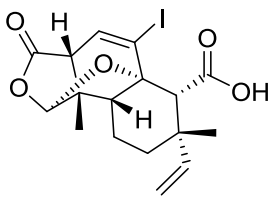


Enantioselective A/B



Enantioselective A/B

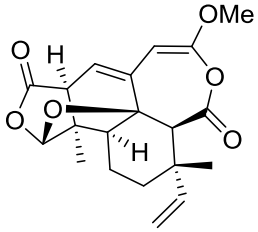




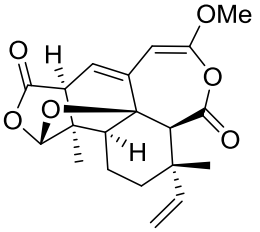
1. TBSCl, imid, DMF
67%

2. Bu_3Sn—≡—OMe

$Pd(PPh_3)_4$, DMF, 40 C
then workup
35%, 2.5: 1 dr

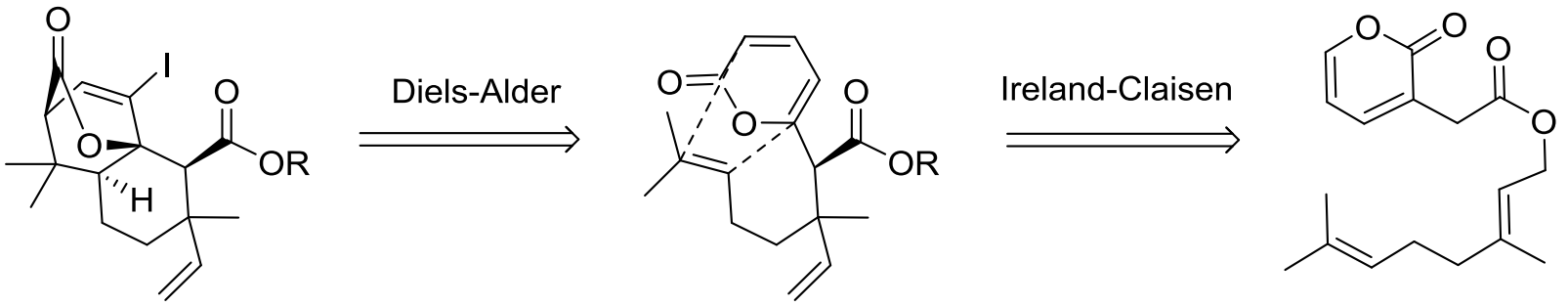


(+)-Transtaganolide B
(major, 81% ee)

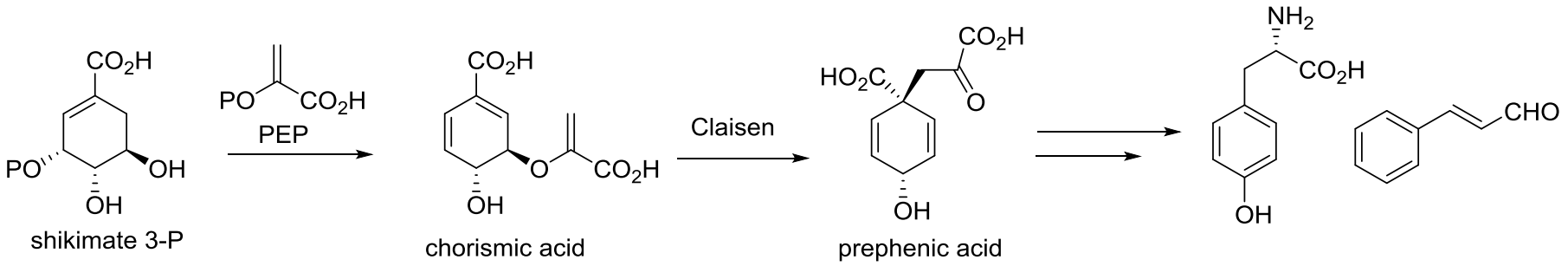


(-)-Transtaganolide A
(minor, 90% ee)

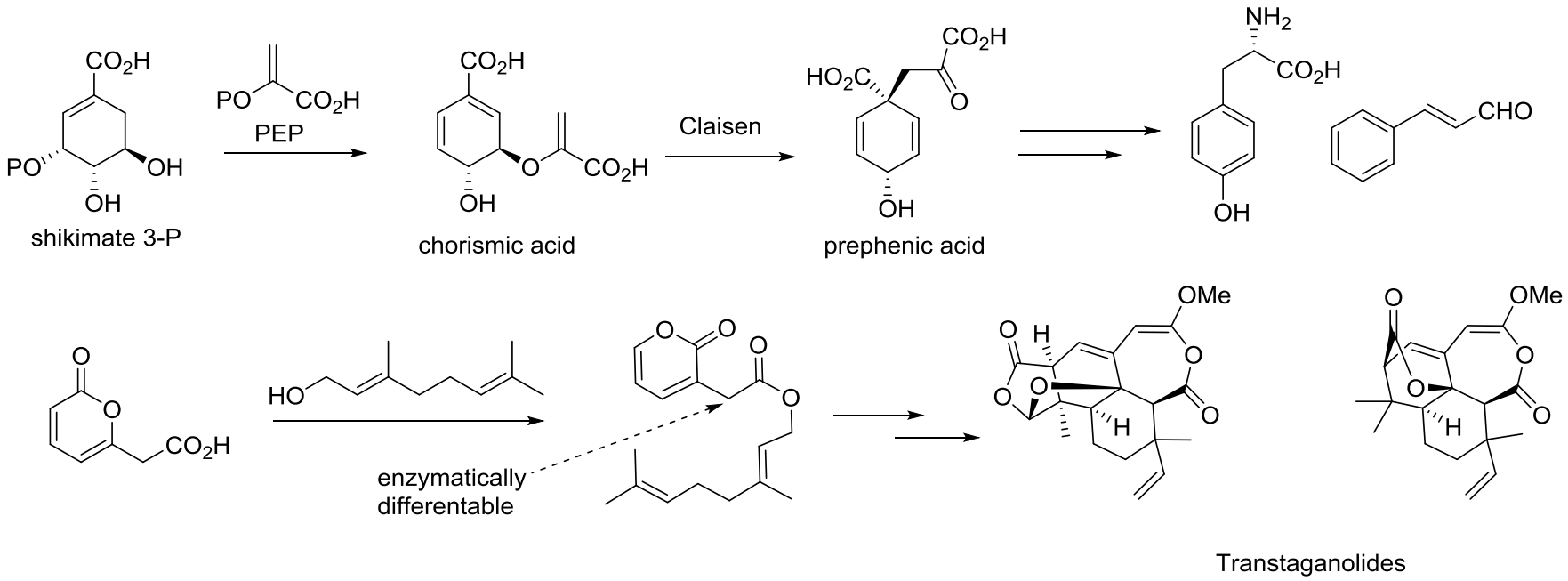
Biomimetic?



Claisenases



Claisenases

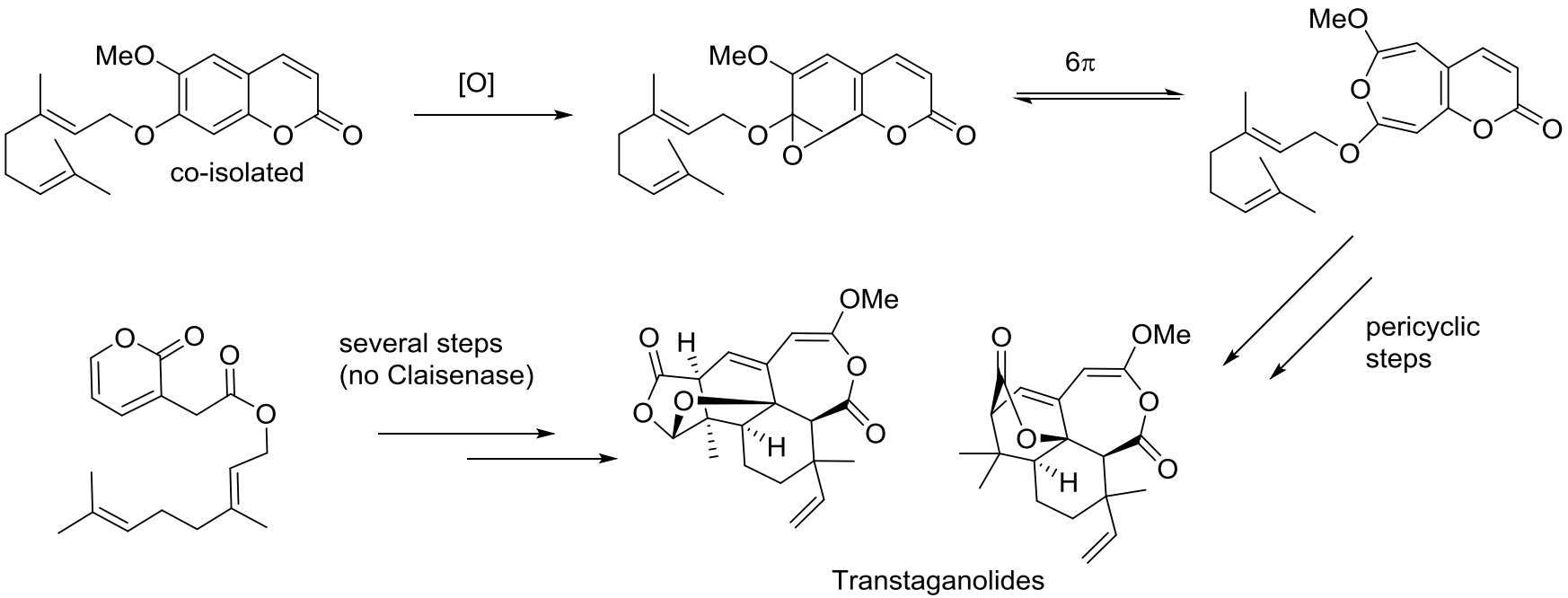


Optical Rotation Data

	A	B	C	D
Synthetic	-98.8 (90% ee)	+207.9 (81% ee)	+120.7 (96% ee)	-51.6 (92% ee)
Natural	-44.8	-25.8	-10	-14.2

Data does not support the existence of a Claisenase

Proposed Biosynthesis



Conclusion

- Enantioenriched transtaganolides A-D prepared in 10 steps or less and 3-12% overall from chiral gerinol
- Demonstration of robust and stereospecific Ireland/Claisen-Diels/Alder cascade
- Stereochemical based revision of biosynthetic origin