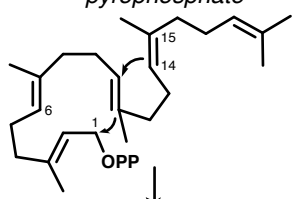
Ophiobolins

Sophie Shevick

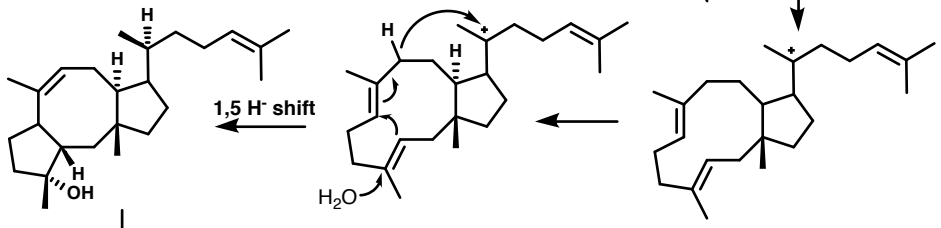
The **ophiobolins** are a class of sesterterpenes isolated from fungi that possess a 5-8-5 ring system. The **ceroplastins** are similar but are found in insects and display different sterochemistry at the ring junctions. **Fusicoccin** diterpenes have the same ring system but have a shorter side chain.

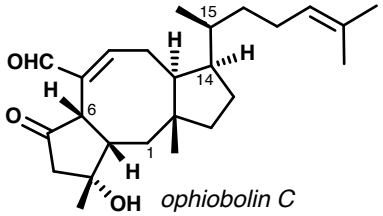
1958 - isolation from plant fungus (*J. Agr. Chem. Soc. Jpn.* **1958**, *32*, 739-744)
1965 - structural identitfication (*JACS*, **1965**, *87*, 4968-4970)
1968 - structural identification of ceroplastol I (*JACS*, **1968**, 1092-1093)
1977 - ophiobolin A shown to be phytotoxin
1982 - ophiobolin A shown to be inhibitor of calmodulin (9μm)
1989 - synthesis of (+)-ophiobolin C (Kishi)
1996 - synthesis of (-)-cotylenol (Kato)
2000s - cytotoxic to human cancer cell lines
2011 - synthesis of (+)-ophiobolin A (Nakada)
2016 - synthesis of (-)-6-*epi*-ophiobolin N (Maimone)

geranylgeranyl pyrophosphate

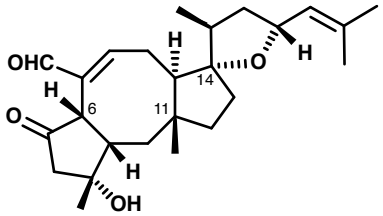


Possible biosynthesis -
JCS Perkin Trans 1, **1975**, 1405-1410

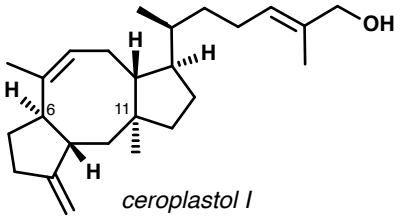




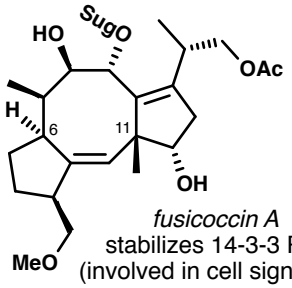
ophiobolin C



ophiobolin A



ceroplastol I

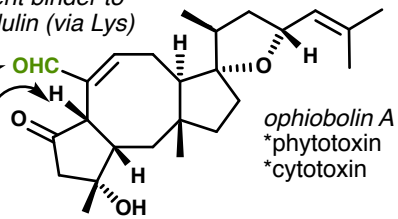


fusicoccin A
stabilizes 14-3-3 PPI
(involved in cell signaling)

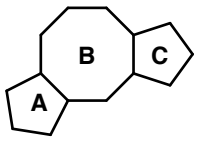
Why make them?
*biological significance
*structural features

covalent binder to calmodulin (via Lys)

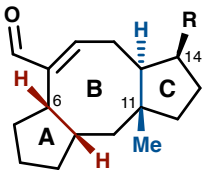
different reports on *epi* activity



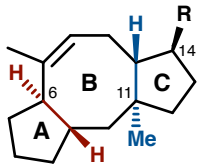
ophiobolin A
*phytotoxin
*cytotoxin



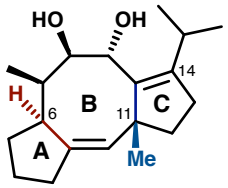
5-8-5 ring system



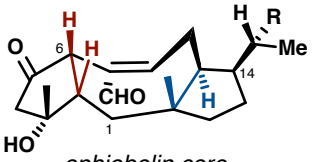
ophiobolin core
cis-syn-*trans*



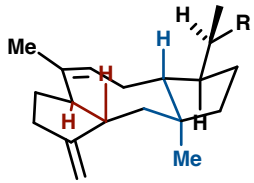
ceroplastin core
trans-anti-*trans*



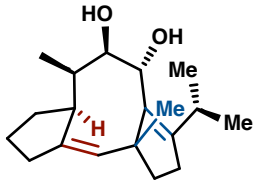
fusicoccin core
8β,9α glycol



ophiobolin core

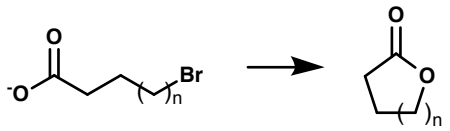


ceroplastin core



fusicoccin core

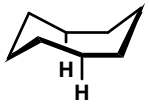
(1) **Ring strain** and (2) **transannular strain** make medium-sized rings difficult to synthesize.



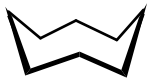
Relative Rates	
n = 1	10^6
n = 2	10^4
n = 3	100
n = 4	1

ACR, **1981**, *14*, 95-102

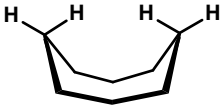
Confirmations of 8-membered rings -



boat-chair



crown



boat-boat

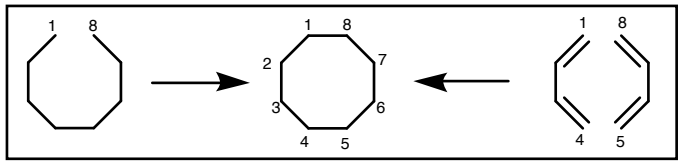
Strategies to synthesize these rings include
1) Intramolecular C–C bond formation
2) ring expansion
3) fragmentation

Recommended reviews:
Petasis, *Tet*, **1992**, *48*, 5757-5821
Singh, *Chem. Rev.*, **1999**, *99*, 881-930
Yet, *Chem. Rev.*, **2000**, *100*, 2963-3007

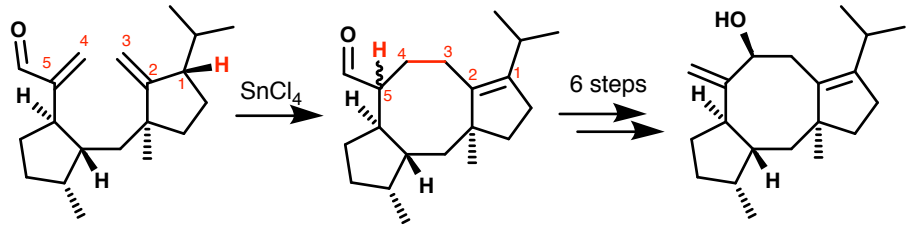
Ophiobolins: Synthesis of Medium-Sized Rings

Sophie Shevick

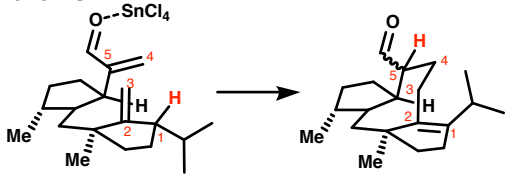
Intramolecular C–C bond formation



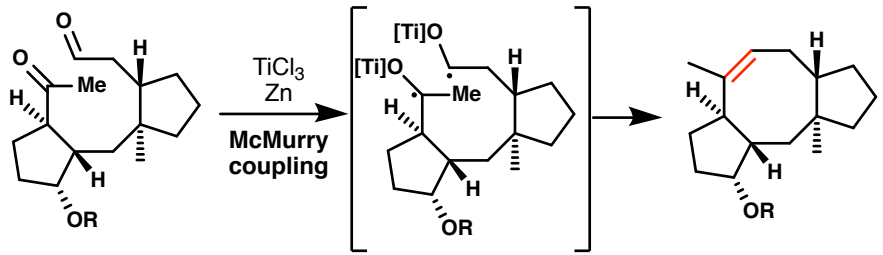
*addition into Michael acceptor (ene reaction)
Synthesis of **hydroxycycloaraneosene** (Kato, *CL*, **1989**, 91)



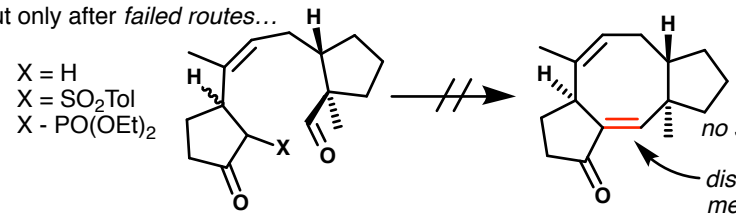
ene TS:



*carbonyl coupling
Synthesis of ceroplastin nucleus (Snider, *JOC*, **1992**, *57*, 3615-3626)

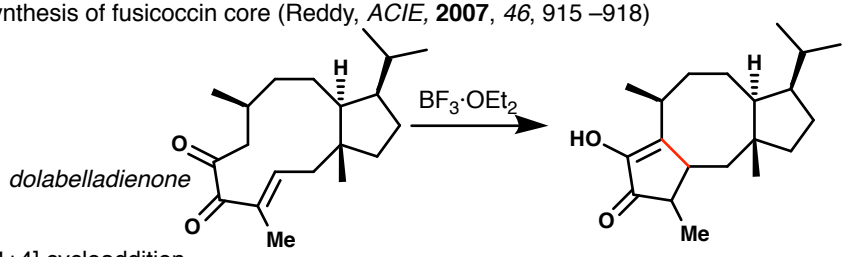


but only after *failed routes…*

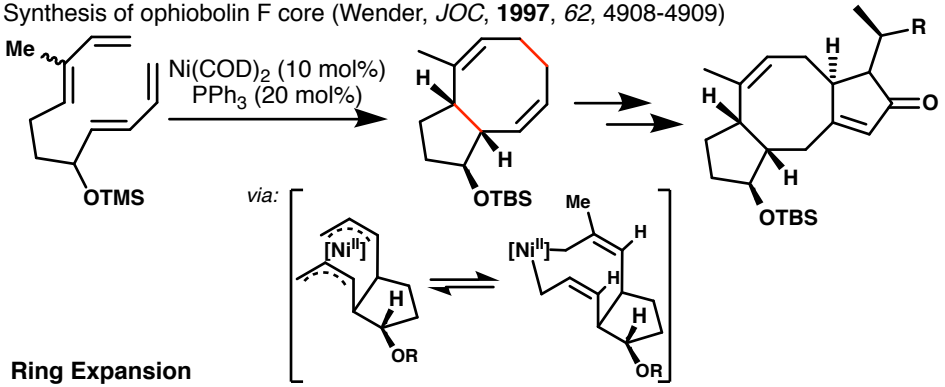


no successful routes make this disconnection for 8-mem ring formation

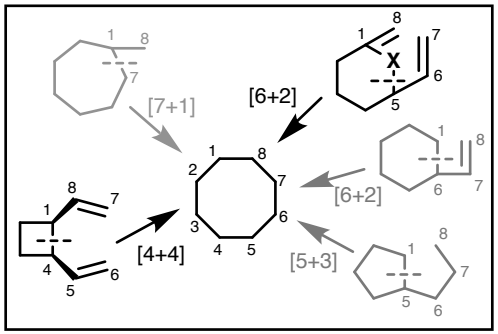
*Nazarov cyclization
Synthesis of fusicoccin core (Reddy, *ACIE,* **2007**, *46*, 915 –918)



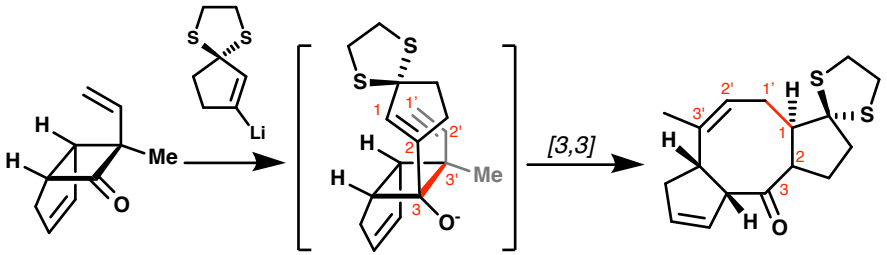
*[4+4] cycloaddition
Synthesis of ophiobolin F core (Wender, *JOC*, **1997**, *62*, 4908-4909)



Ring Expansion



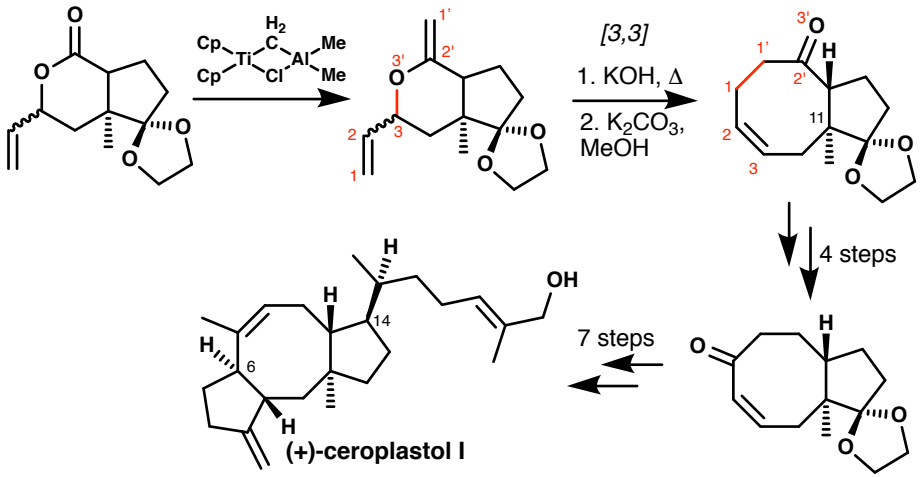
*[4+4] ring expansion
ophiobolin F core (Paquette, *JOC*, **1985**, *50*, 201-205; *JOC*, **1983**, *48*, 1147-1149)



Ophiobolins: Synthesis of Medium-Sized Rings

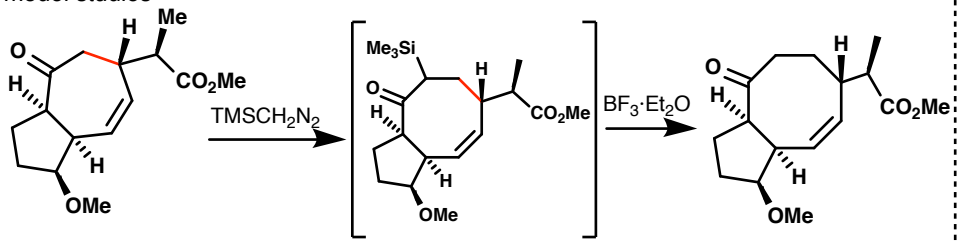
Sophie Shevick

*[6+2] ring expansion
Synthesis of **(+)-ceroplastol I** (Paquette, *JACS*, **1993**, *115*, 1676-1683; *JACS*, **1991**, *113*, 2762-2764)

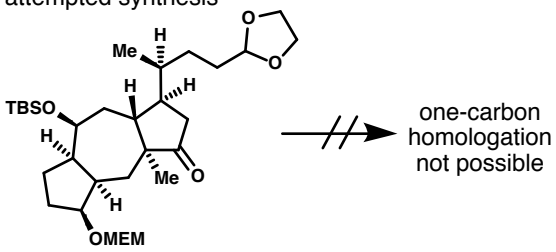


*[7+1] ring expansion
Attempted ophiobolin ring system (Rigby, *JOC*, **1987**, *52*, 4634-4635;*JCS Perkins Trans. 1*, **1994**, 3449-3457)

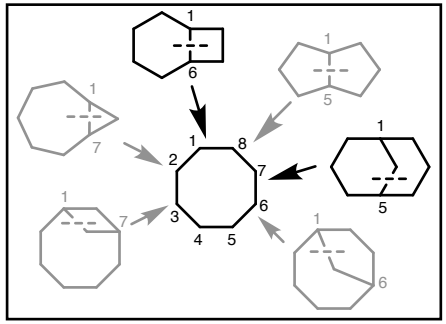
model studies -



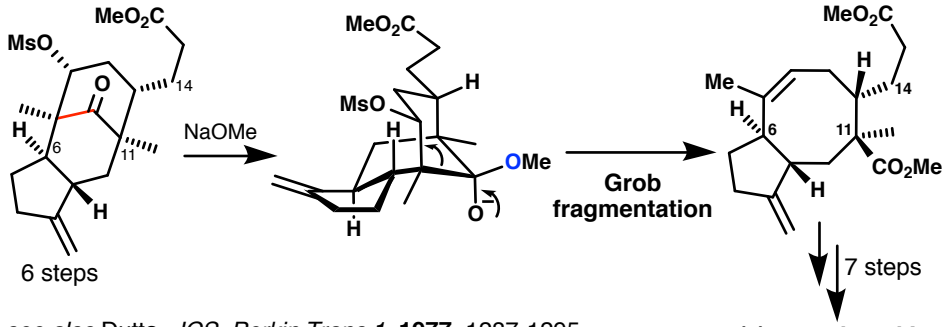
attempted synthesis -



Fragmentation

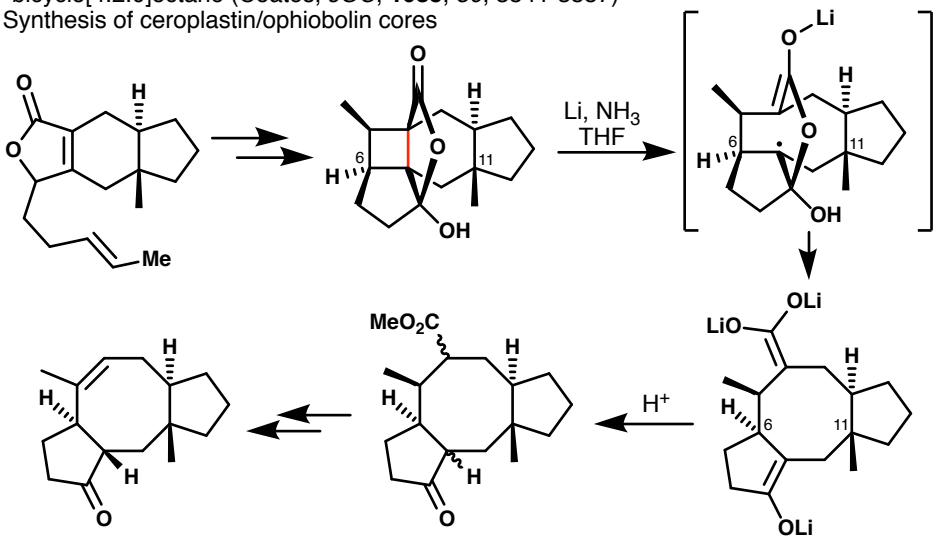


*bicyclo[3.3.1]nonane
Synthesis of **ceroplastol I** (Boeckman, *JACS*, **1989**, *111*, 2737-2739)



see also Dutta, *JCS, Perkin Trans 1*, **1977**, 1287-1295

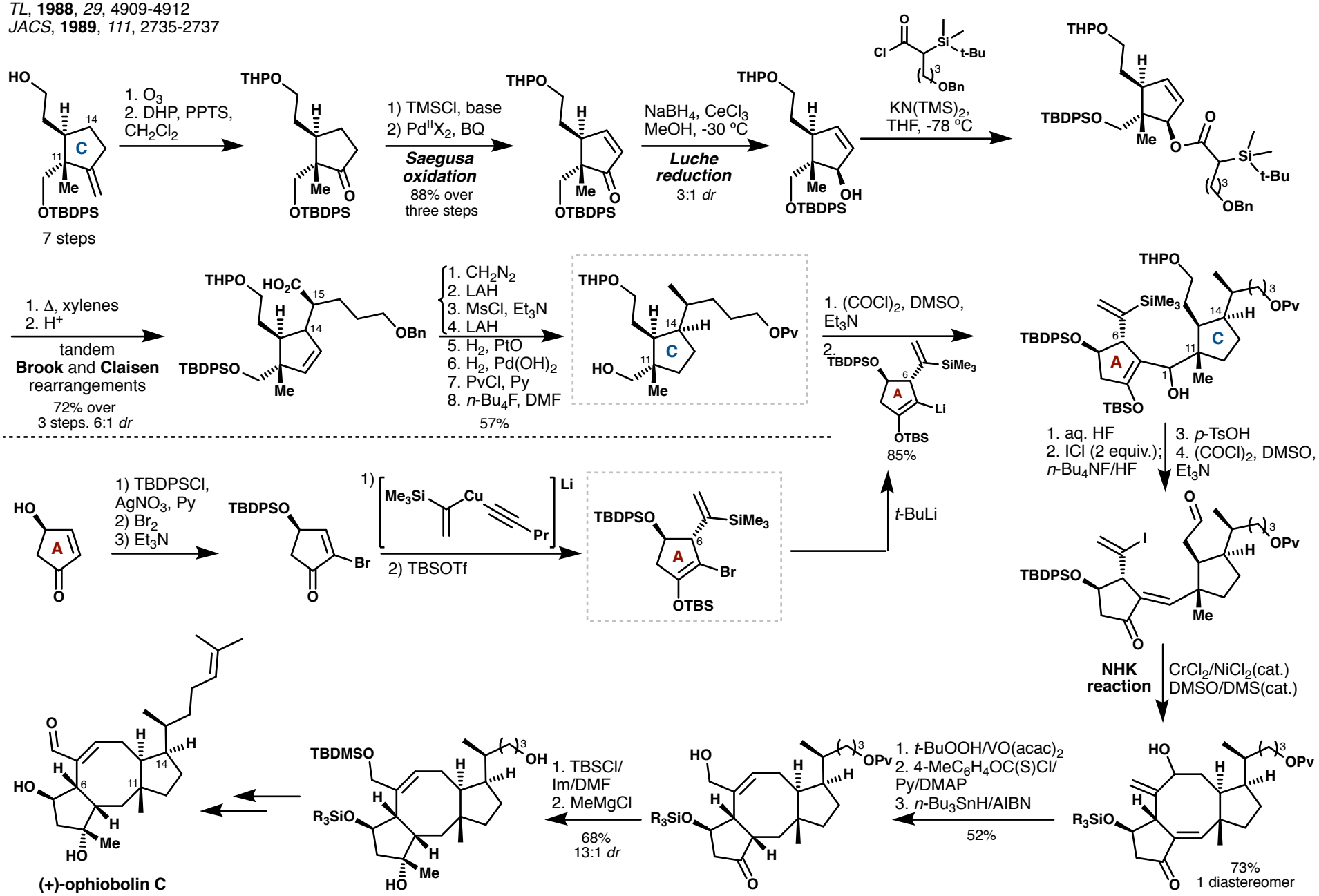
*bicyclo[4.2.0]octane (Coates, *JOC*, **1985**, *50*, 3541-3557)
Synthesis of ceroplastin/ophiobolin cores



Synthesis of (+)-Ophiobolin C

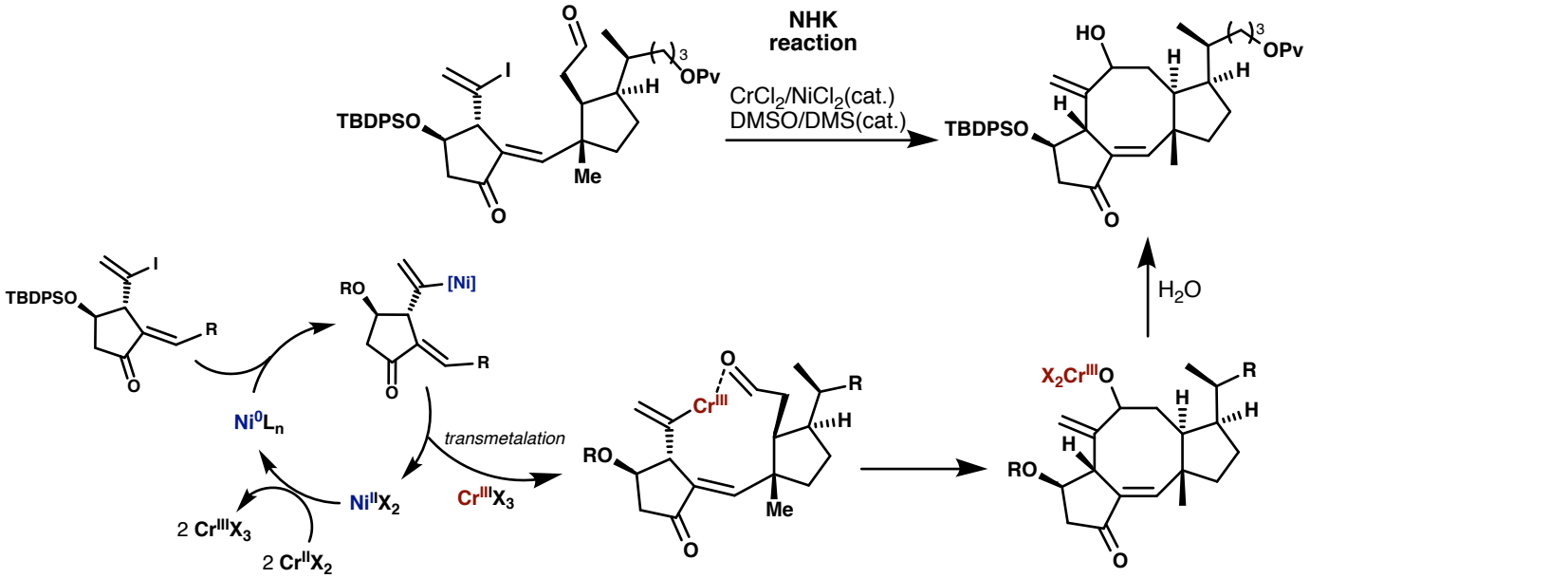
Sophie Shevick

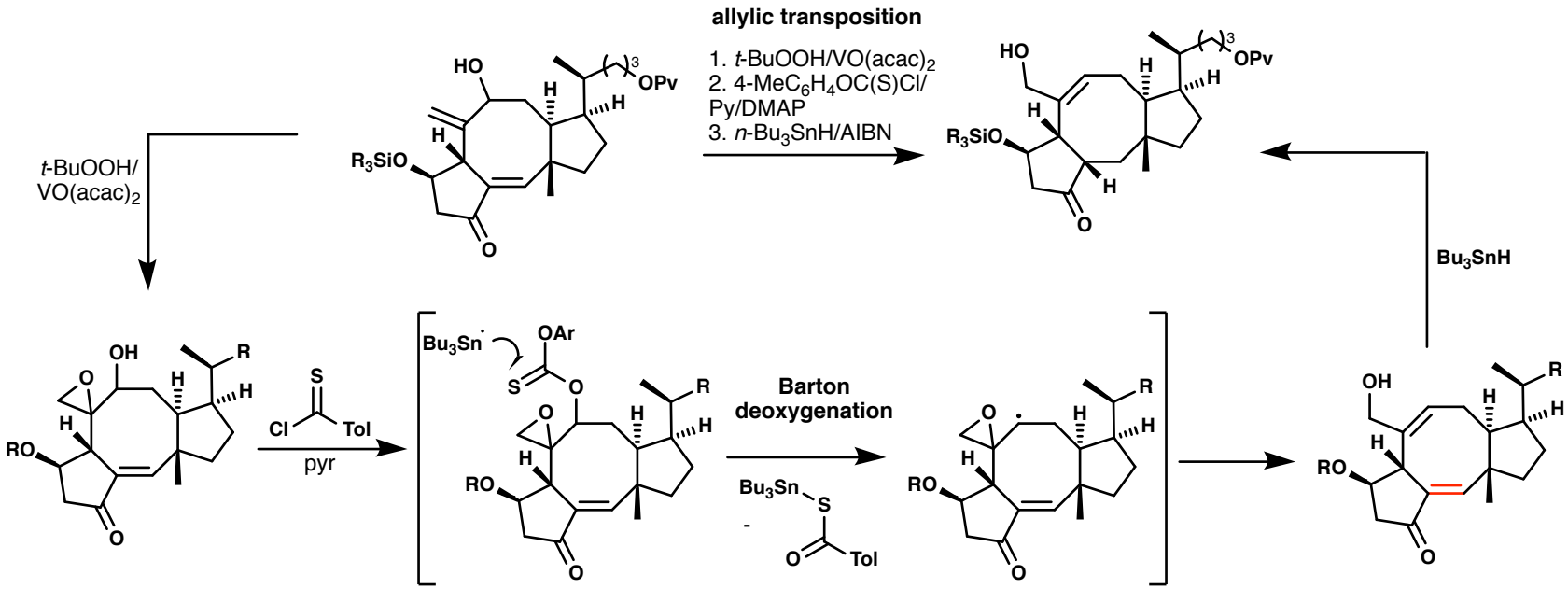
Ophiobolin C (Kishi, 1989)
TL, **1988**, *29*, 4909-4912
JACS, **1989**, *111*, 2735-2737



Synthesis of (+)-Ophiobolin C

Sophie Shevick

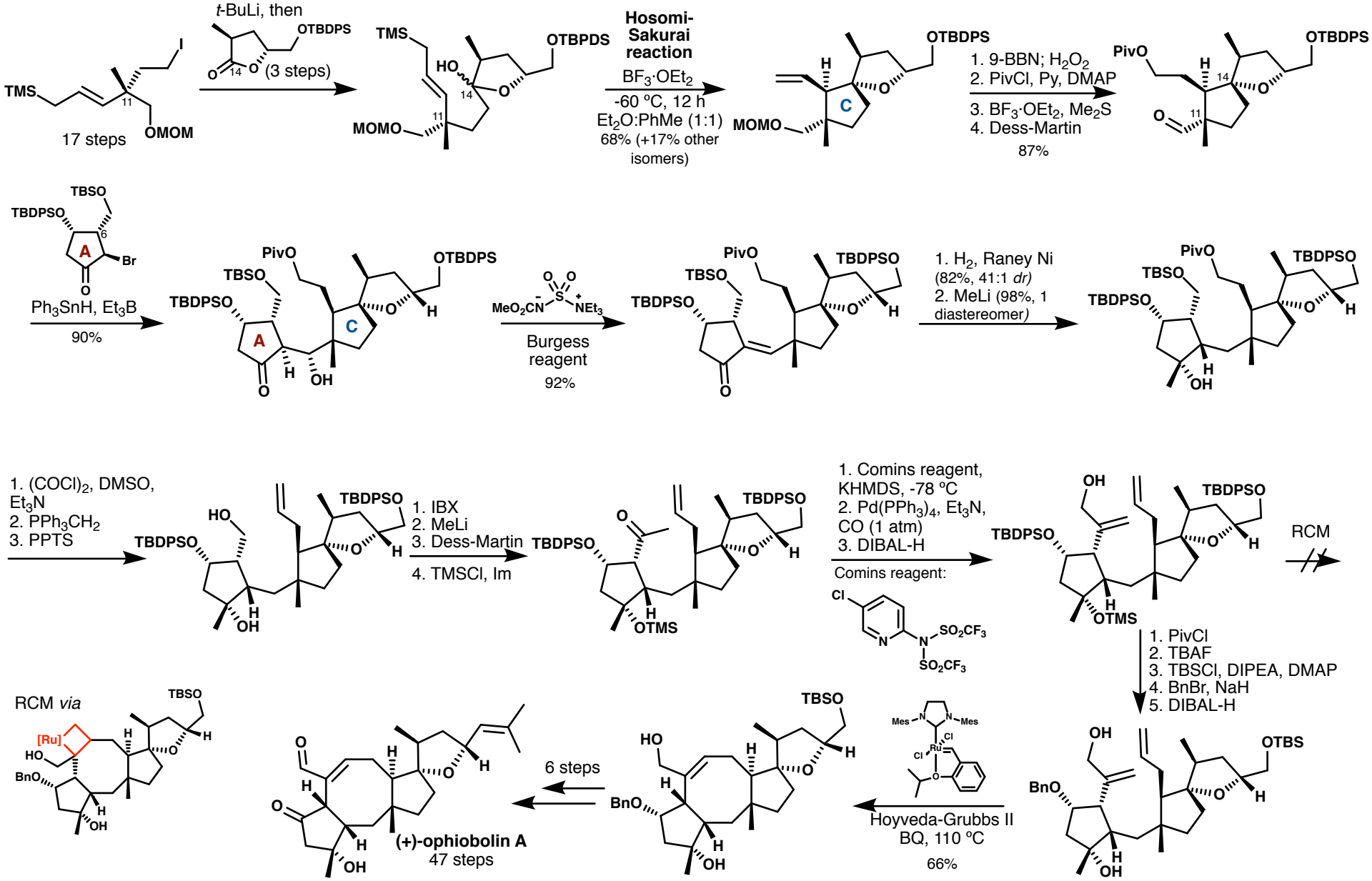




Synthesis of (+)-Ophiobolin A

Sophie Shevick

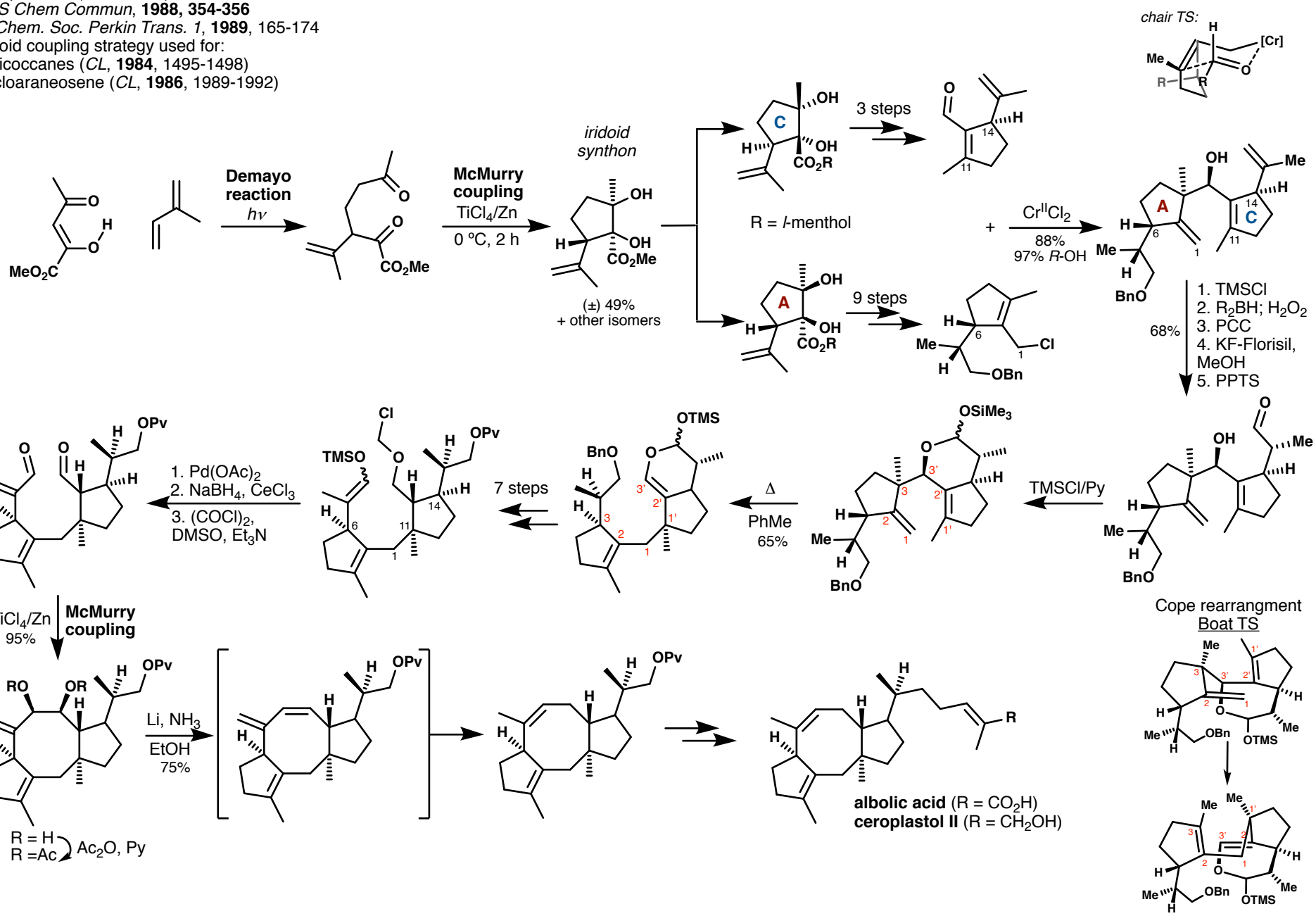
Ophiobolin A (Nakada, 2011)
Chem Eur. J., **2013**, *19*, 5476-5486
ACIE, **2011**, *50*, 9452-9455
OL, **2006**, *8*, 2039-2042



Synthesis of Ceroplastol II

Sophie Shevick

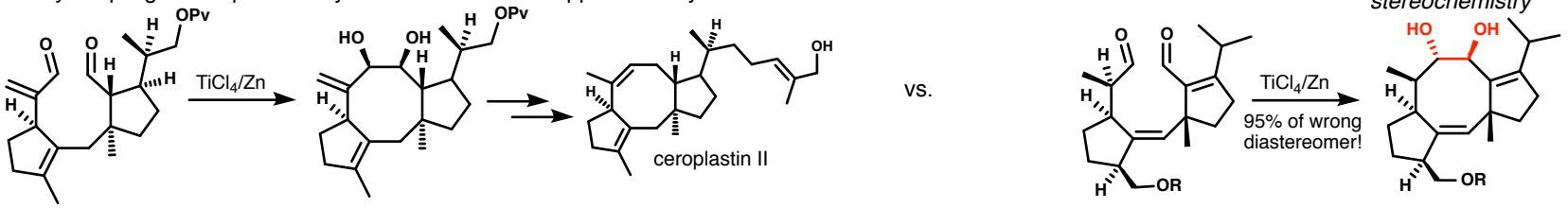
ceroplastol II (Kato, 1988)
JCS Chem Commun, **1988, 354-356**
J. Chem. Soc. Perkin Trans. 1, **1989**, 165-174
iridoid coupling strategy used for:
fusicoccanes (*CL*, **1984**, 1495-1498)
cycloaraneosene (*CL*, **1986**, 1989-1992)



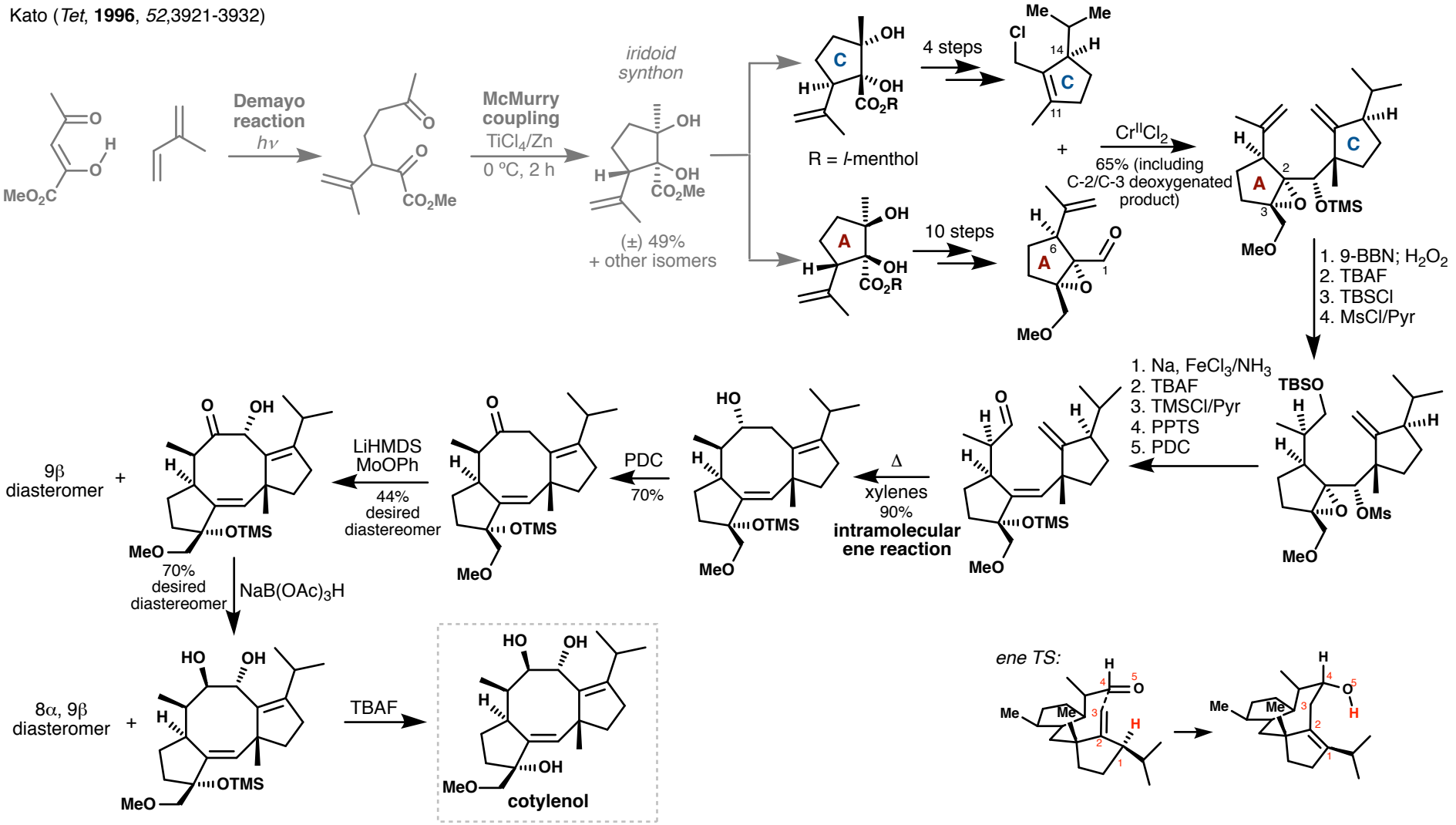
Synthesis of (-)-Cotylenol

Sophie Shevick

*McMurry coupling in ceroplastin II synthesis could not be applies to cotylenol route



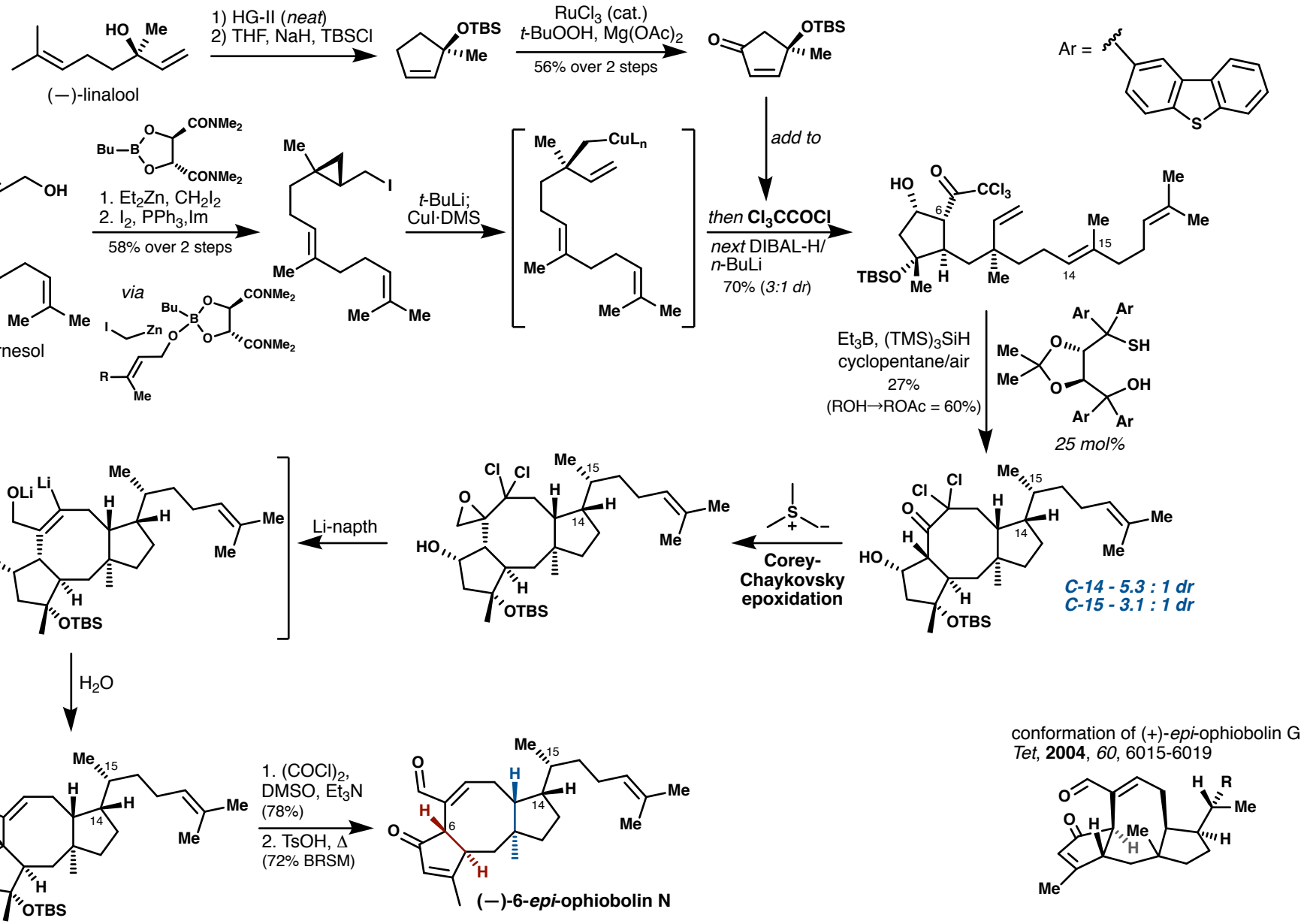
Kato (*Tet*, **1996**, *52*,3921-3932)



Synthesis of (-)-6-*epi*-ophiobolin N

Sophie Shevick

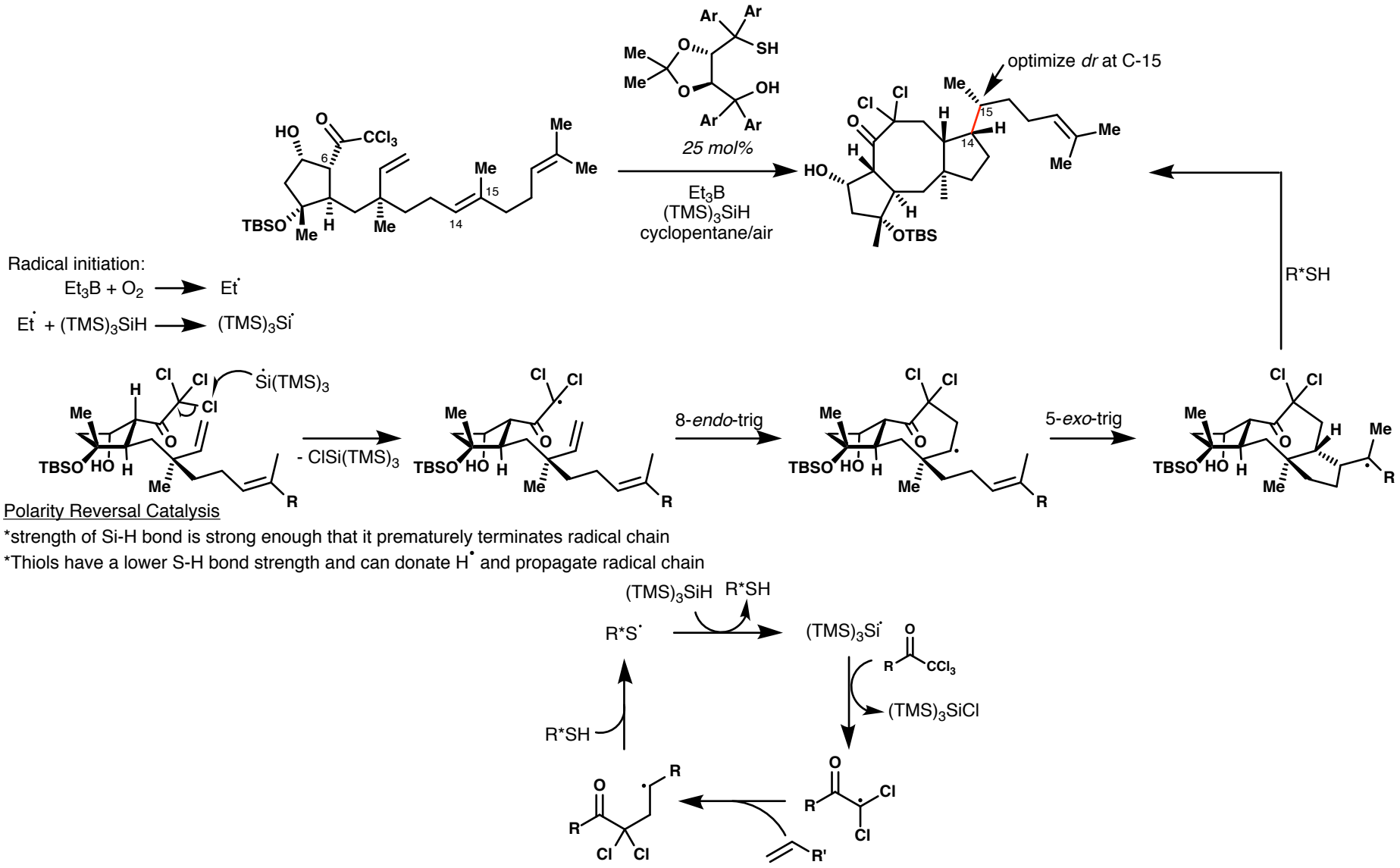
(—)-6-*epi*-ophiobolin N (Maimone, 2016)
Science, **2016**, *352*, 1078-1082



conformation of (+)-*epi*-ophiobolin G
Tet, **2004**, *60*, 6015-6019

Synthesis of (-)-6-*epi*-ophiobolin N

Sophie Shevick



Conclusion

*potential biological significance and questions makes these targets worth pursuing
*medium-sized rings display changes in reactivity based on *transannular* interactions, not as important in small or large ring systems

Future Directions

*synthetic potential for this class of molecules exists, particularly with new C-C bond forming reaction methods
*conformational rigidity important for stereoselective transformations