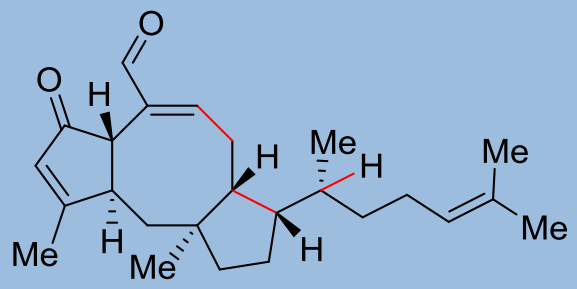
UNIVERSITÄT BERN

Enantioselective synthesis of an ophiobolin sesterpene via a programmed radical cascade

Presented by:

Sankar



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

Science, **2016**, *352*, 1078

Author Profile

Education

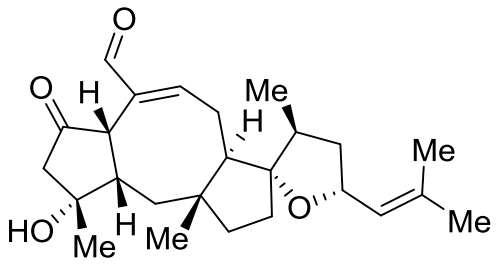
B.S. University of California, Berkeley with Prof. Dirk Trauner
Ph.D. The Scripps Research Institute, with Phil Baran
NIH Postdoctoral Fellow, MIT, with Steve Buchwald

Currently an assistant professor at UCB

Research interest
Synthesis of biologically active natural products

Introduction to ophiobolins

1. Ophiobolins belong to a expanding family of terpinoids
2. Possess stereo chemically rich and synthetically formidable 5-8-5 fused ring system
3. Shows potent cytotoxic effects against several cancer cell lines
4. More than 30 distinct members have been isolated to date



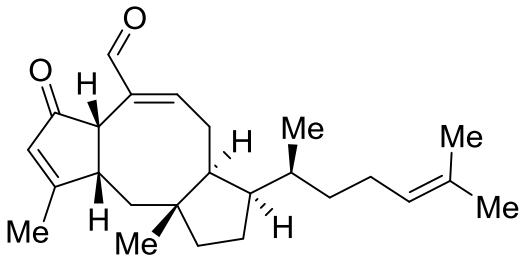
ophiobolin A

47 steps to synthesize

Kishi et al.

J. Am. Chem. Soc. 1989, 111, 2735

Powerful inhibitor of colmodulin

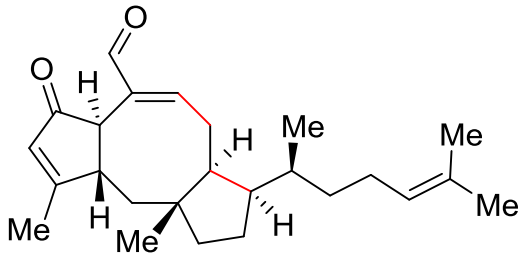


ophiobolin C

38 steps to synthesize

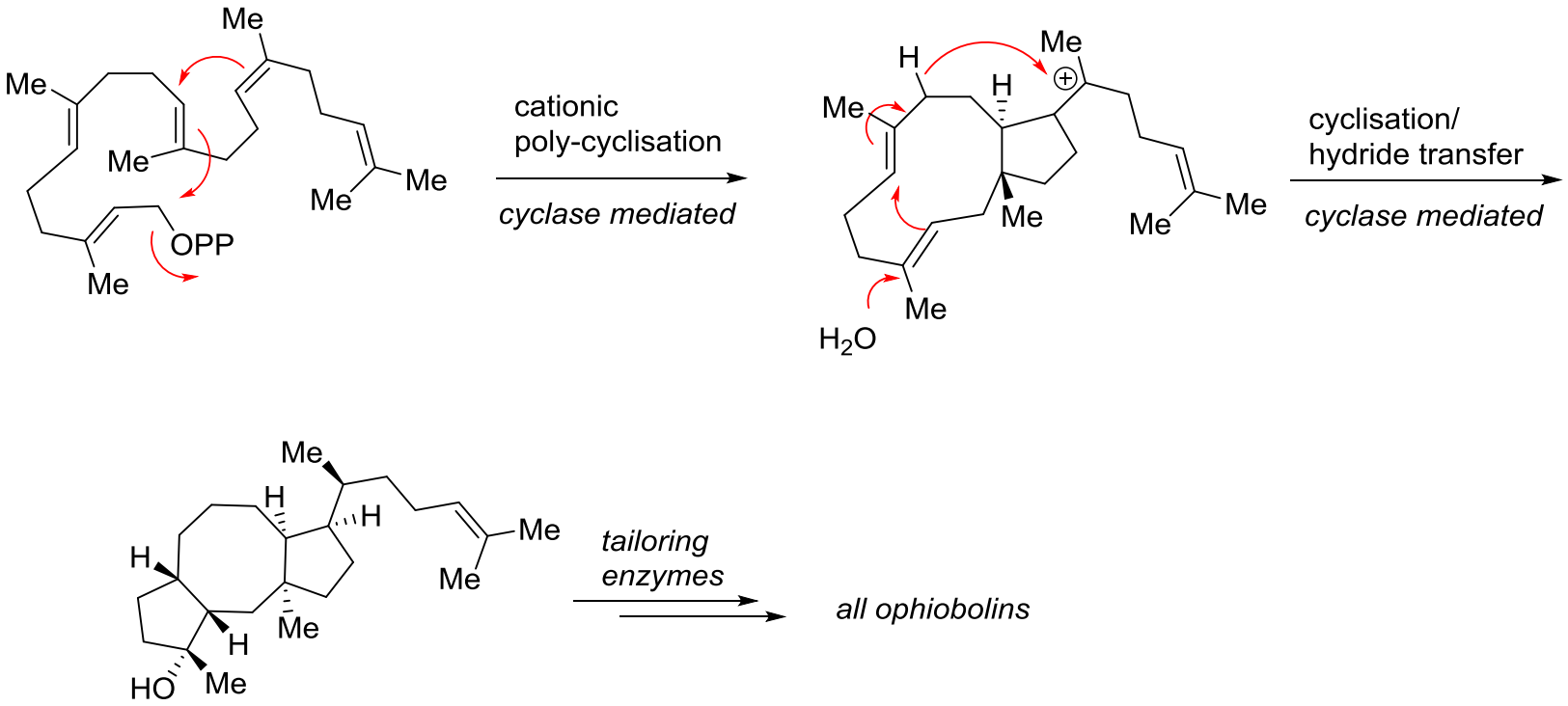
Nakada et al.

Angew. Chem. Int. Ed. 2011, 50, 9452



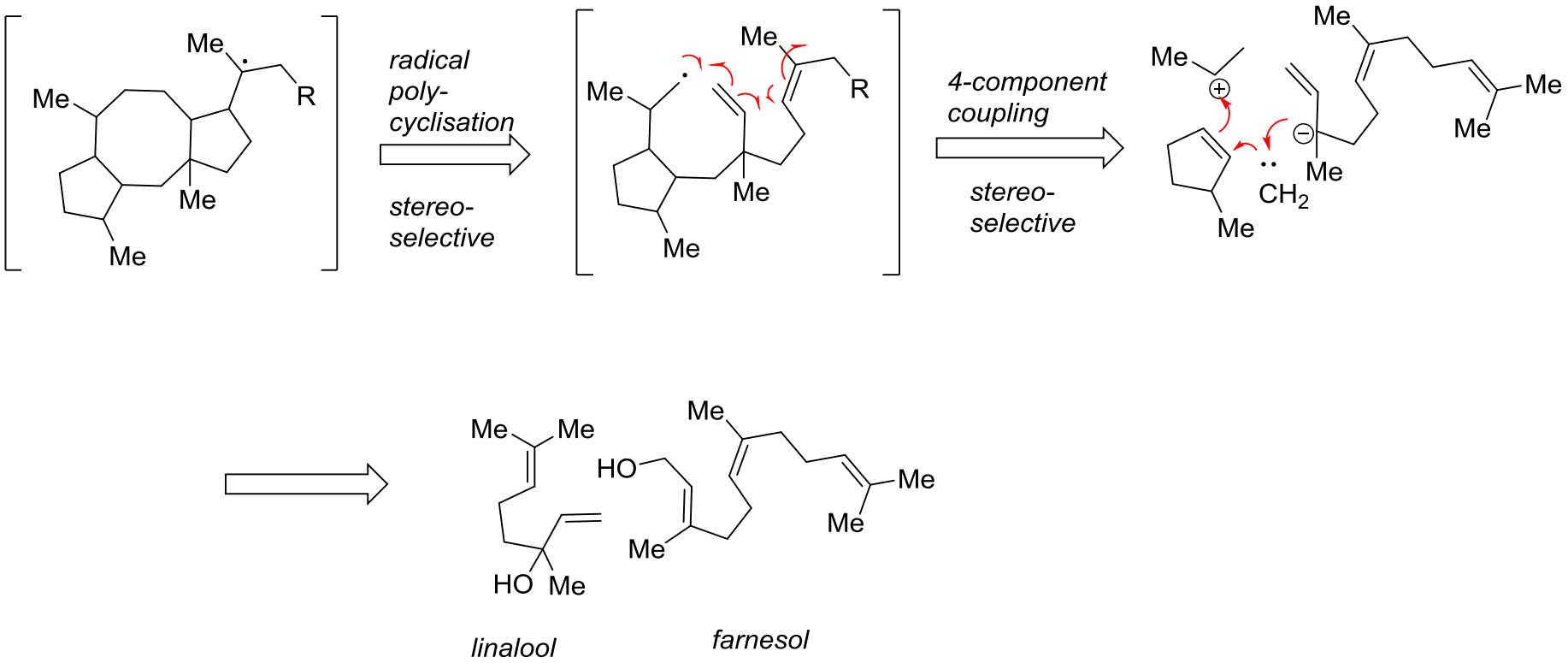
6-*epi*-ophiobolin N

Biosynthesis of ophiobolins

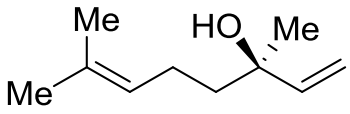


See also: Oikawa , H. et al, Org. Lett. **2013**, *15*, 594

Retrosynthetic analysis with a strategic radical cascade



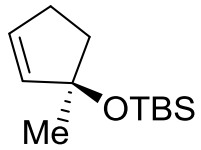
Efficient convergent four-step entry into complex 5-8-5 fused ring systems



(-)-linalool

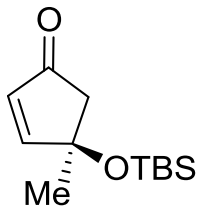
1. HG-II (0.1 mol%)
25 °C , 1 h

then NaH (3.0 equiv)
TBSCl (1.5 equiv), 65 oC
2 h, 98%

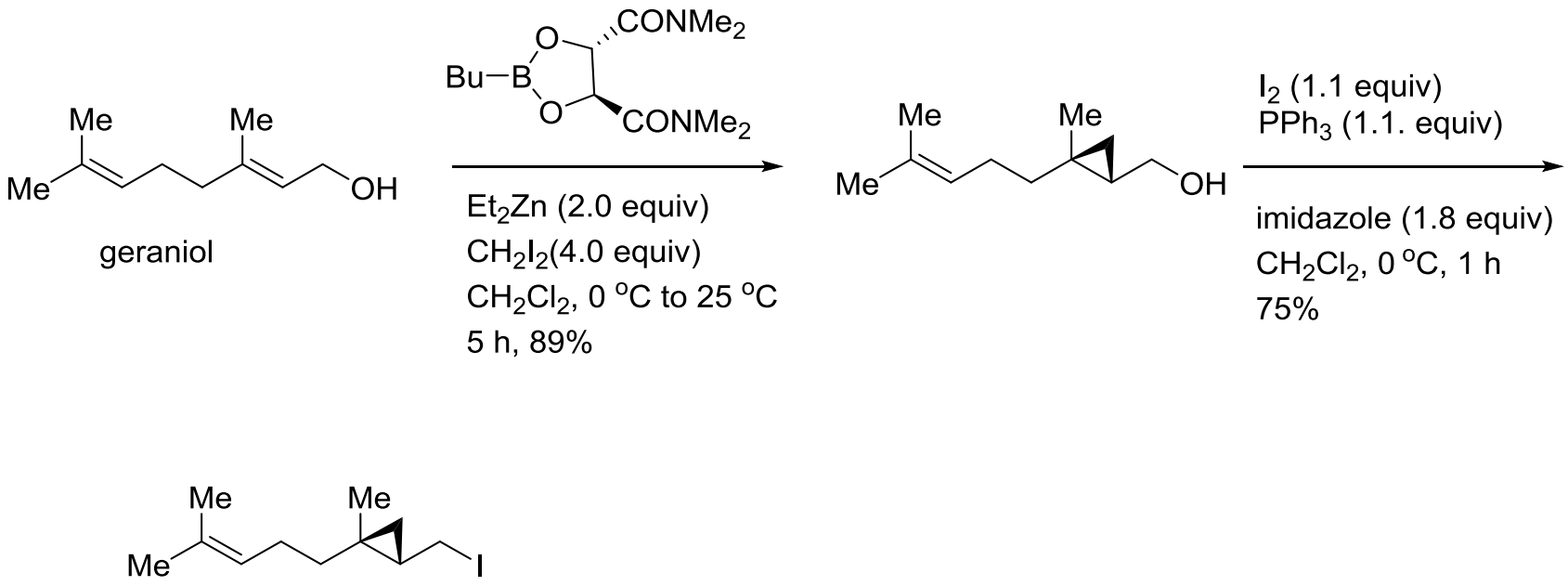


$RuCl_3$ (1 mol%)
$Mg(OAC)_2.4H_2O$ (2.0 equiv)

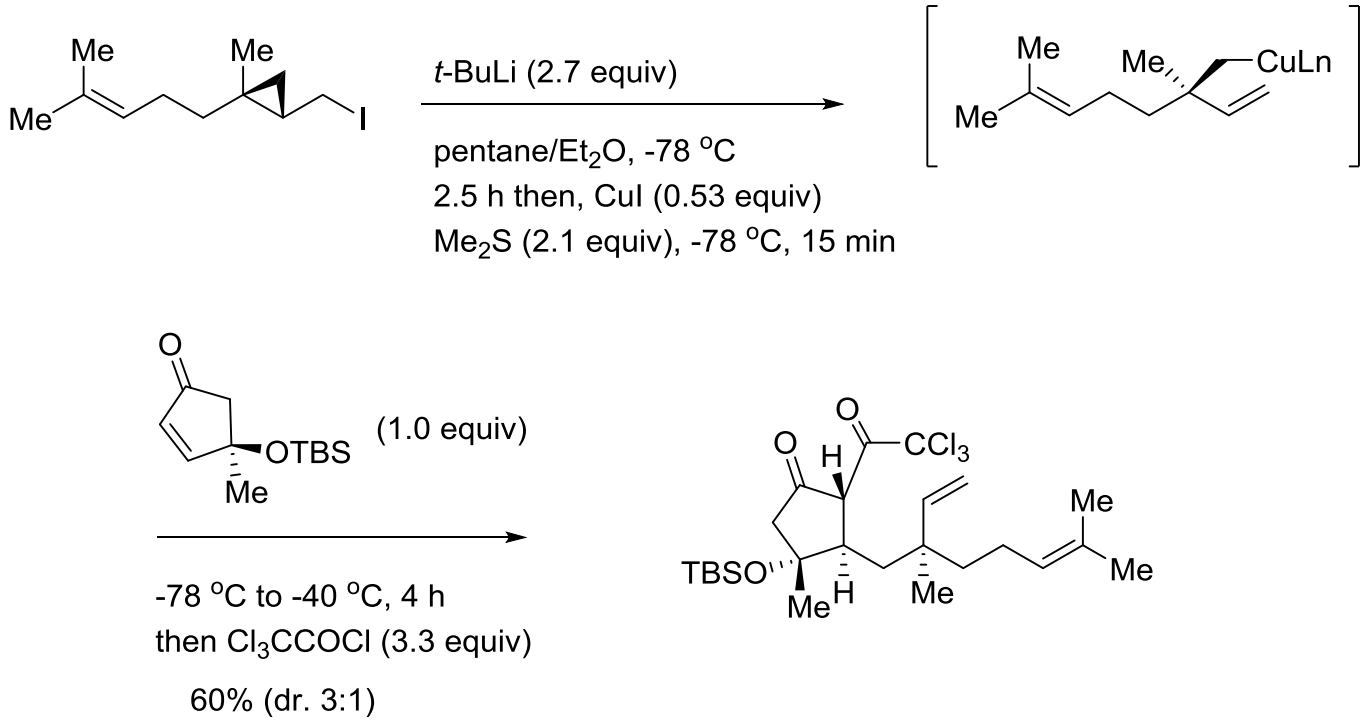
t-BuOOH (10.9 equiv)
CH_2Cl_2/H_2O, 25 °C, 57%



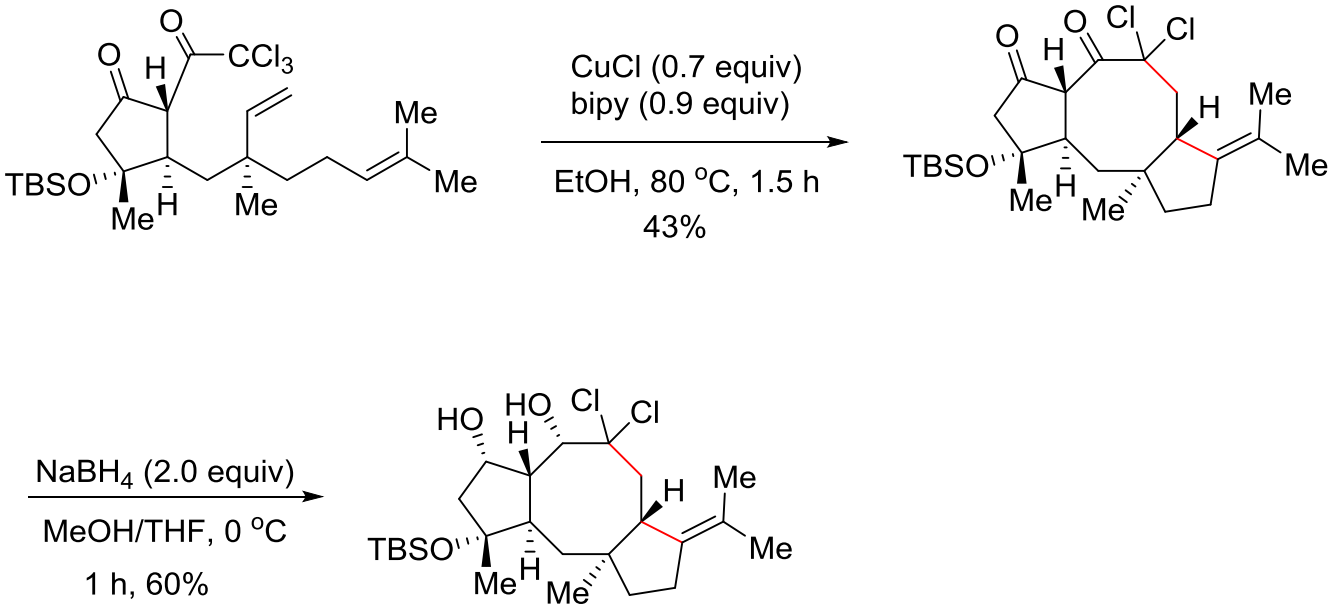
Four-step entry into complex 5-8-5 fused ring systems



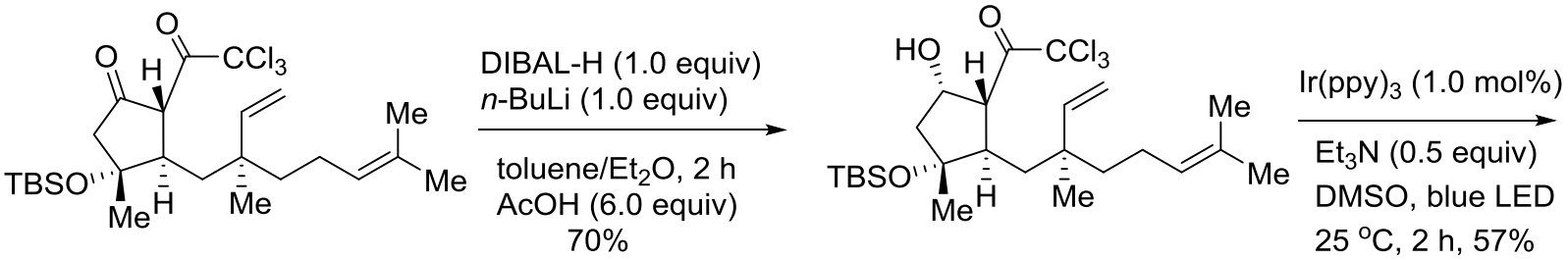
Four-step entry into complex 5-8-5 fused ring systems

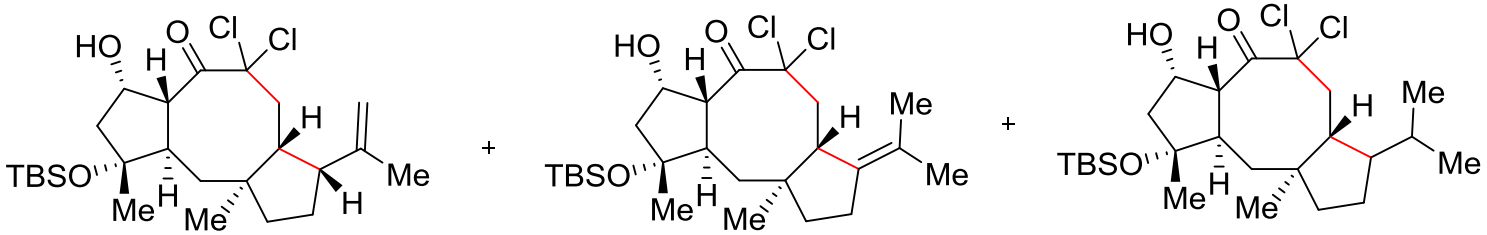


Four-step entry into complex 5-8-5 fused ring systems



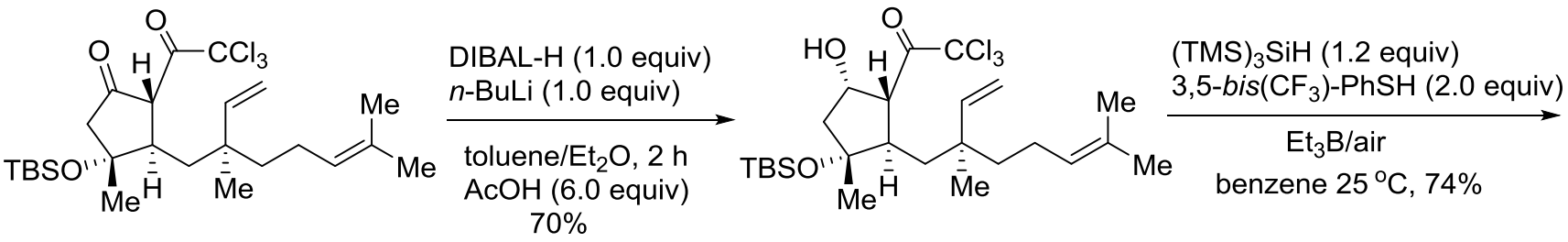
Four-step entry into complex 5-8-5 fused ring systems

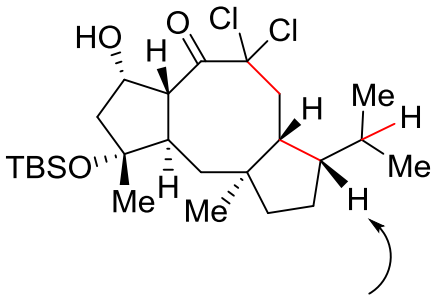




d.r : 3:1 + **10%** + **15%**

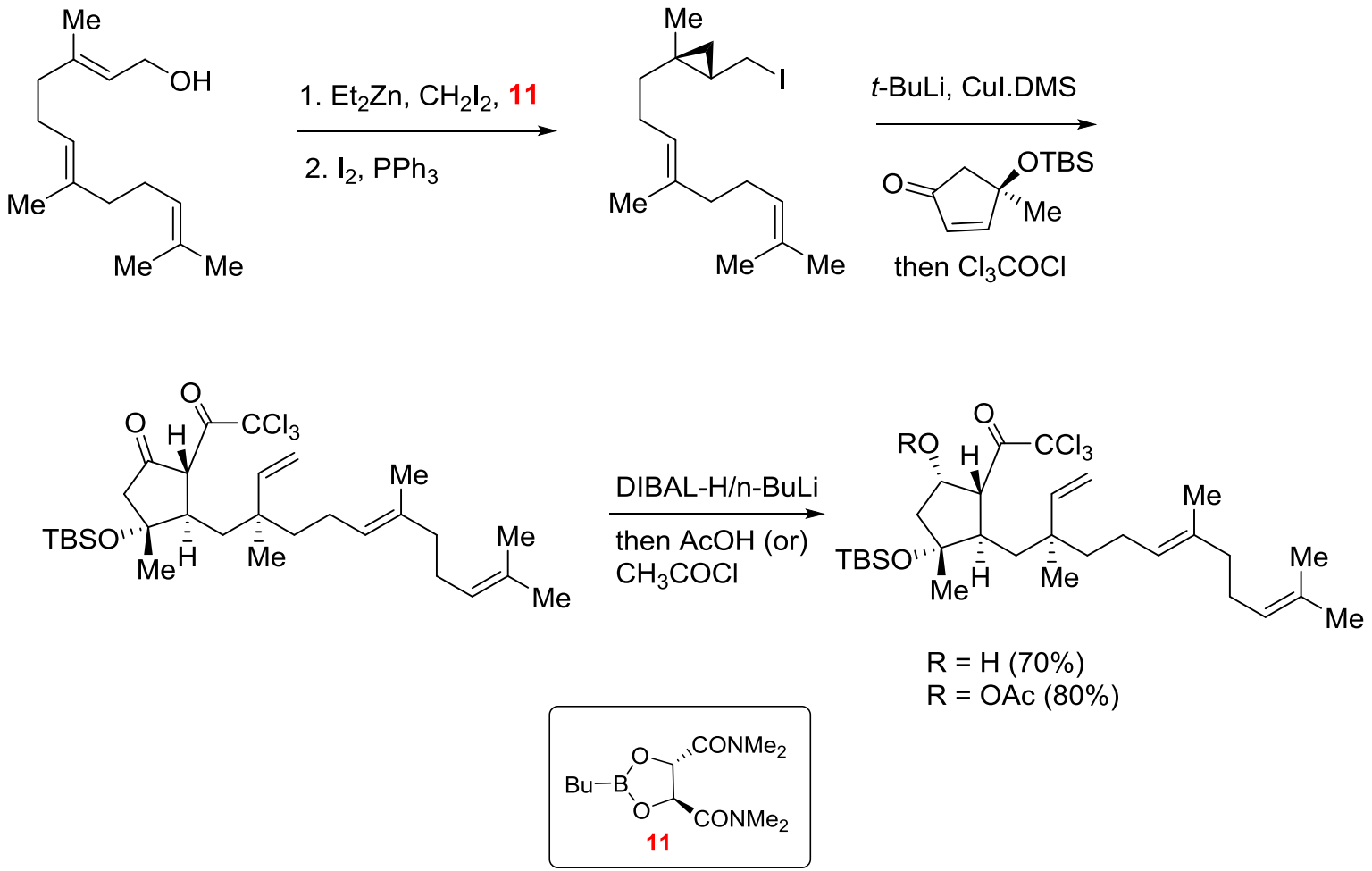
Four-step entry into complex 5-8-5 fused ring systems



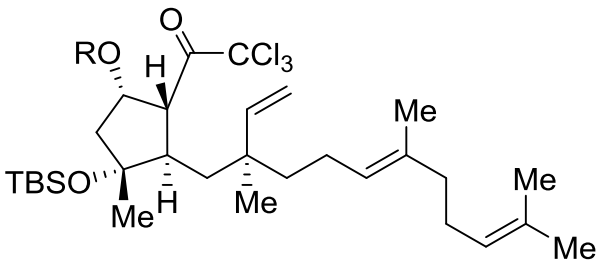


dr 3:1

Total synthesis of an ophiobolin sesterpene



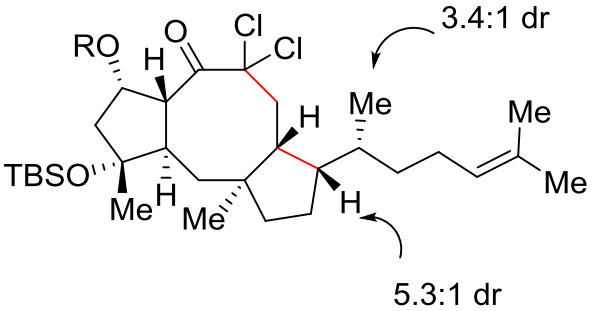
Total synthesis of an ophiobolin sesterpene



A, R = H (70%)
B, R = OAc (80%)

Et_3B (1.0 equiv)
$(TMS)_3SiH$ (1.0 equiv)

cyclopentane/air
-10 °C
thiol catalyst (25 mol%)



C, R= H
D, R =OAc, 56%

A → **C**

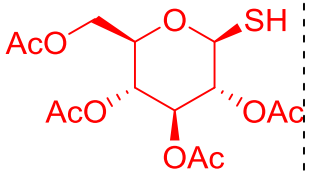
Et_3B (1.0 equiv)
$(TMS)_3SiH$ (1.0 equiv)

cyclopentane/air
-10 °C
thiol catalyst (25 mol%)

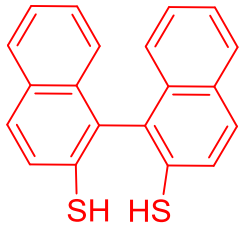
PhSH
59%, 1:1.4

$C_{12}H_{25}SH$
50%, 1:1.6

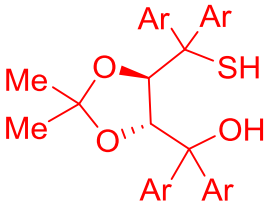
$3,5\text{-}CF_3PhSH$
50%, 1:1.6



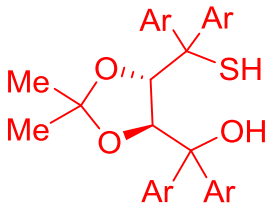
21%,1:1



21%, 1.1:1

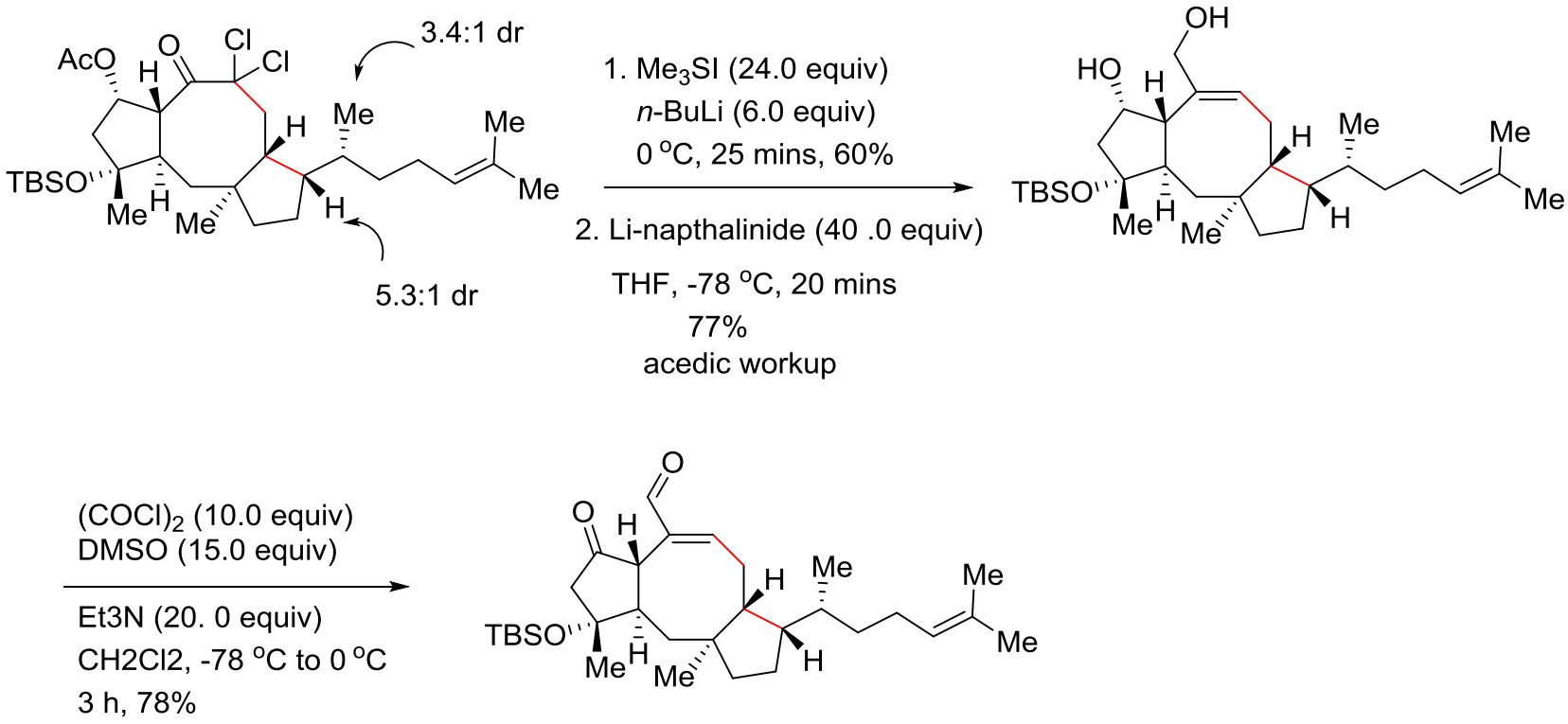


Ar = Ph, 35%, 1.5:1
Ar = 2-Napthyl,
30%, 2.1:1

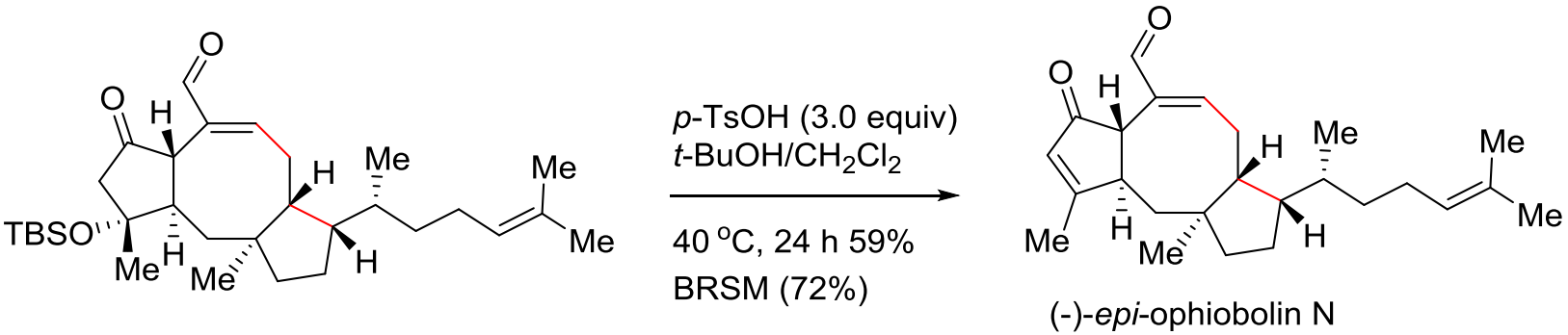


Ar = 2-Napthyl, 27%, 2.9:1
Ar = benzothiophene,
27%, 3.1:1

Total synthesis of an ophiobolin sesterpene



Total synthesis of an ophiobolin sesterpene



(-)-*epi*-ophiobolin N

Conclusion

1. Very elegant enantioselective Synthesis of 6-epi-ophiobolin was achieved in 9 steps with 2% overall yield
2. Efficient construction of 5-8-5 fused ring system using reductive cyclisation cascade

Flaws

1. Lack of complete diastereocontrol in several steps

Thank you...!!