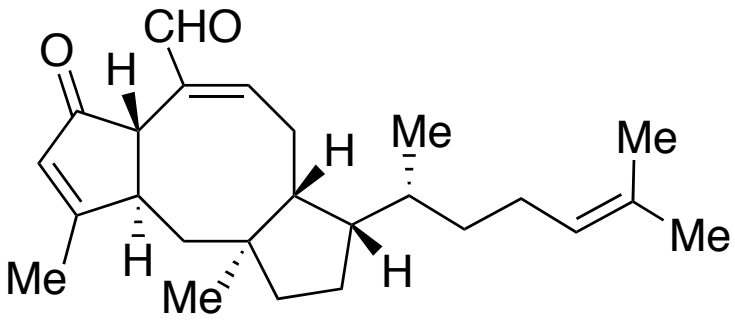
Enantioselective synthesis of an ophiobolin sesterterpene via a programmed radical cascade

Zachary G. Brill, Huck K. Grover, Thomas J. Maimone

Science. **2016**, 1078-1082



(-)-6-epi-ophiobolin N

Ruiting Liu
Wipf Group Current Literature
06/18/2016

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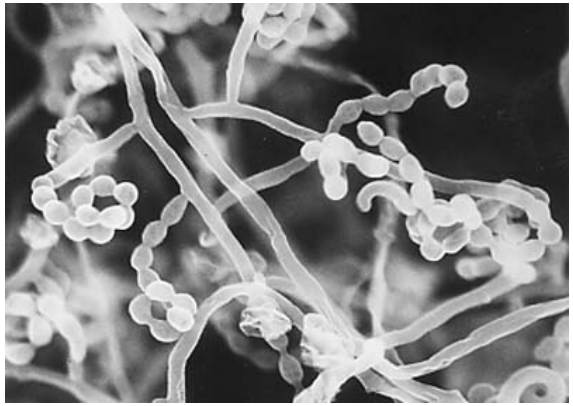
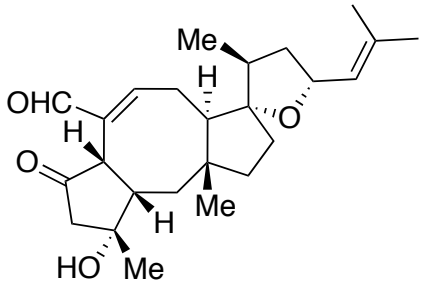
Ophiobolins

- Ophiobolins are a group of naturally occurring sesterterpenes isolated from pathogenic fungi
- More than 30 members so far
- Having potent cytotoxic effects against multiple cancer cell lines
- Stereochemically rich 5-8-5 fused ring system

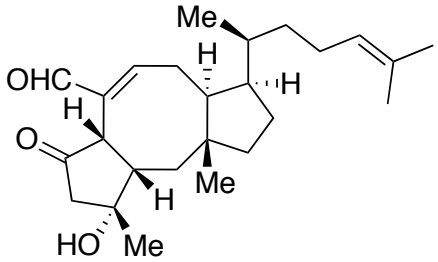


Streptomyces sp



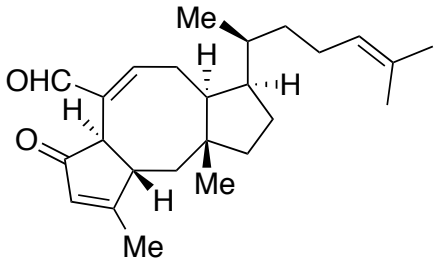
ophiobolin A

48 steps from Nakada



ophiobolin C

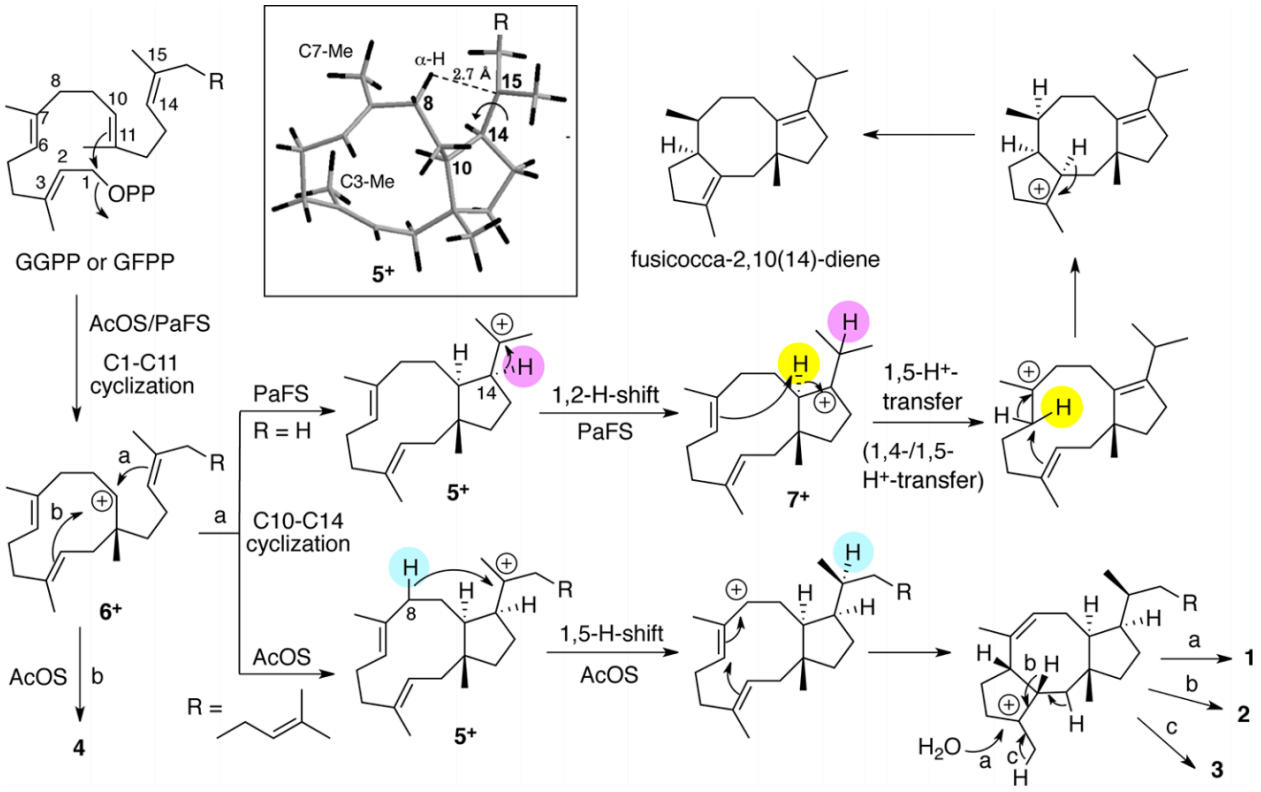
37 steps from Kishi



6-epi-ophiobolin N

Proposed biosynthesis

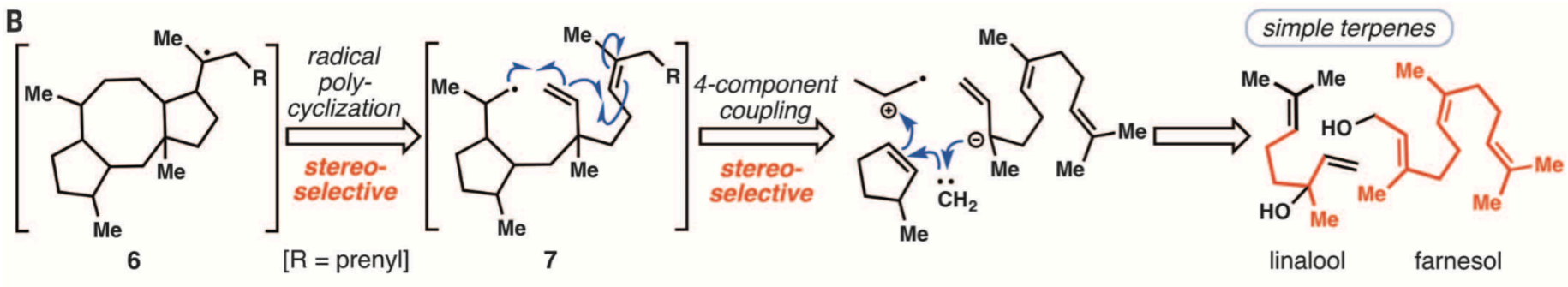
Scheme 1. Proposed Mechanism of Bifunctional Class-I Diterpene Synthases AcOS and PaFS[a]



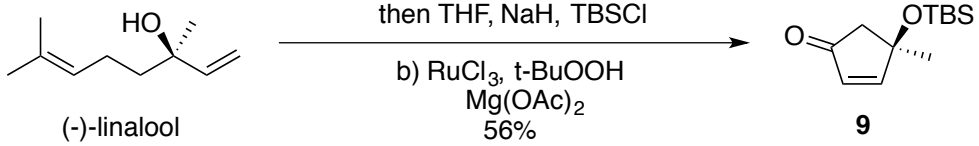
[a] The conformation of carbocation intermediate $\mathbf{5}^{+}$ for the 1,5-H shift from C8 to C15 is shown within the square. The distance between proximate 8H and C15 in the carbocation is shown.

Org. Lett. **2013**, 594–597

Retrosynthesis

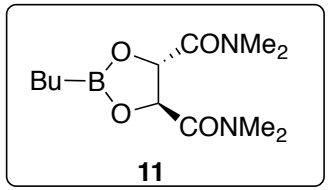


(B) Retrosynthetic analysis with a strategic 8-endo/5-exo-cascade cyclization

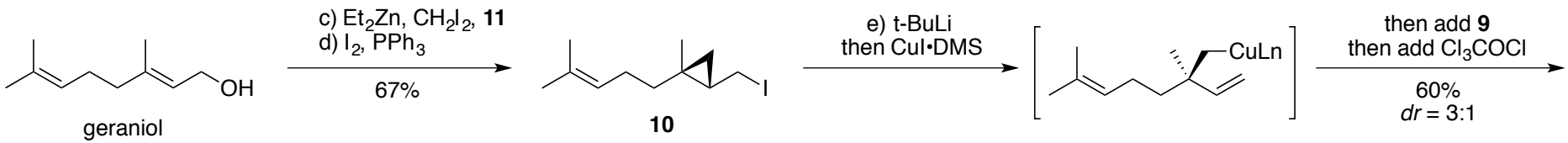


(-)-linalool

9

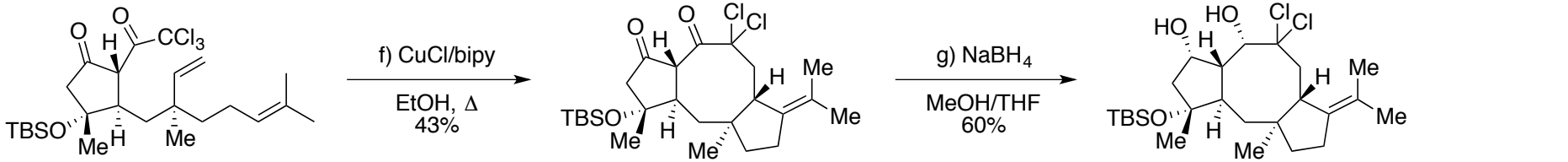


11



geraniol

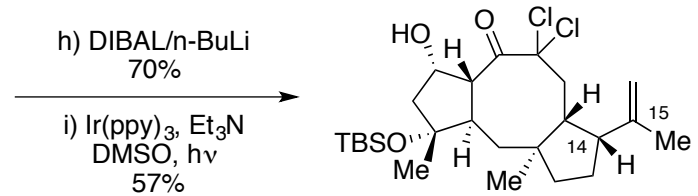
10



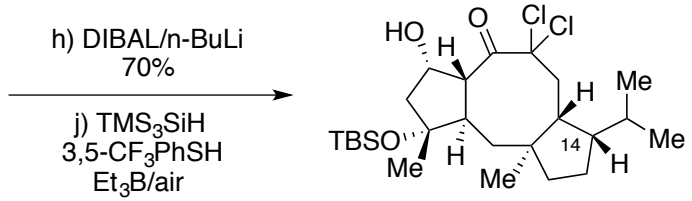
13

14

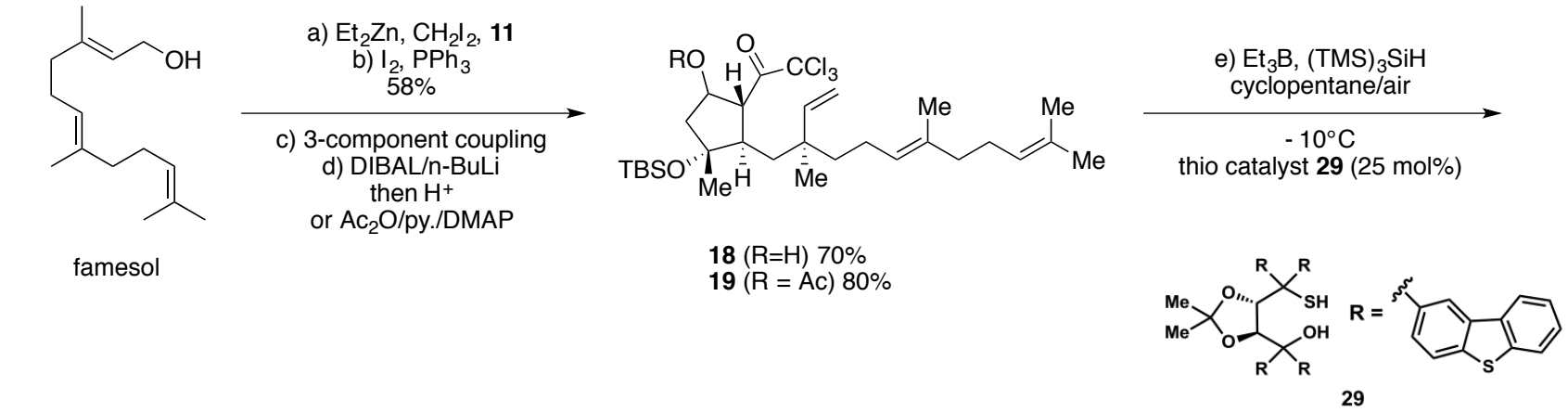
15



16 (+ 10% **17** + 15% $\Delta_{14\text{-}15}$ alkene)

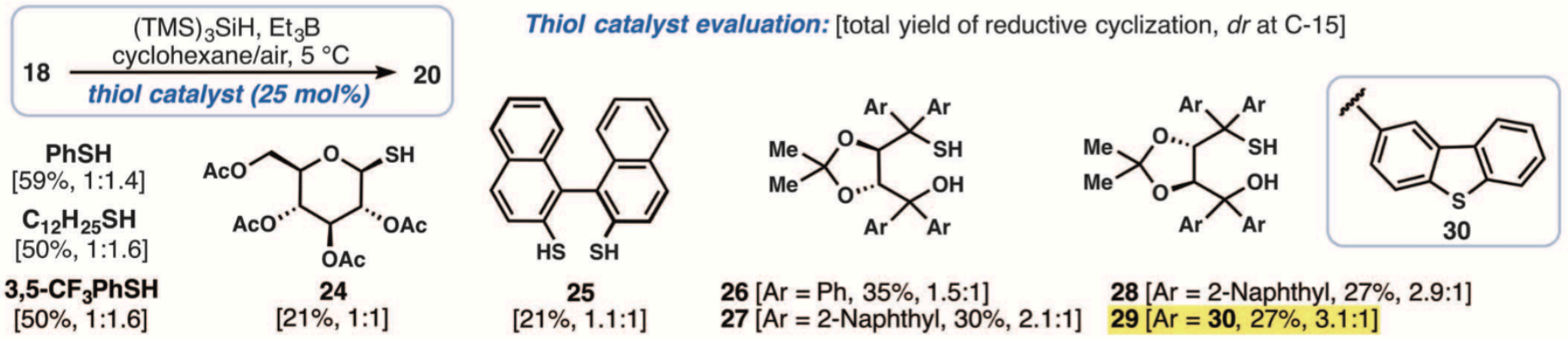


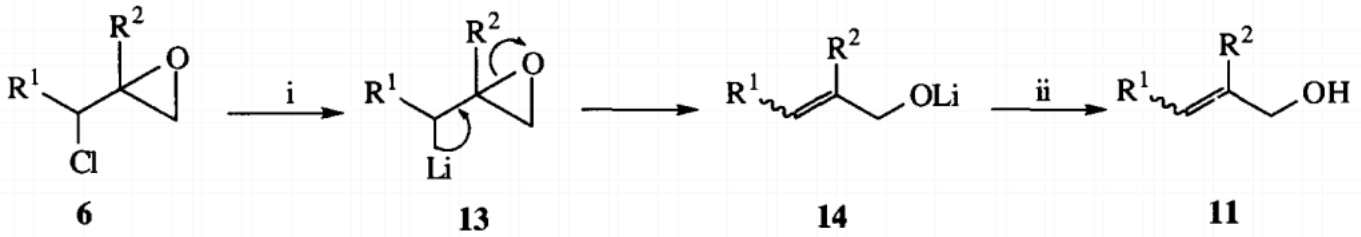
17


OH
famesol
a) Et2Zn, CH2I2, 11
b) I2, PPh3
58%
c) 3-component coupling
d) DIBAL/n-BuLi
then H+
or Ac2O/py./DMAP
RO
H
O
CCl3
TBSO
Me
H
Me
Me
Me
Me
18 (R=H) 70%
19 (R = Ac) 80%
e) Et3B, (TMS)3SiH
cyclopentane/air
- 10°C
thio catalyst 29 (25 mol%)
R
R
SH
Me
Me
O
O
OH
R
R
R =
S
29
RO
H
O
Cl
Cl
H
Me
15
Me
TBSO
Me
H
14
Me
H
Me
20 (R=H)
21 (R = Ac) 56%
C-14 dr = 5.3:1
C-15 dr = 3.4:1
f) Me3SI
g) Li-niphthalenide
60%
OLi
LiO
H
Li
H
Me
Me
TBSO
Me
H
Me
H
Me
H+
OH
HO
H
H
Me
Me
TBSO
Me
H
Me
H
Me
h) COCl2, DMSO, Et3N
78%
i) TsOH, Δ
72% (BRSM)
O
H
CHO
H
Me
Me
Me
H
Me
H
Me
(-)-6-epi-ophiobolin N

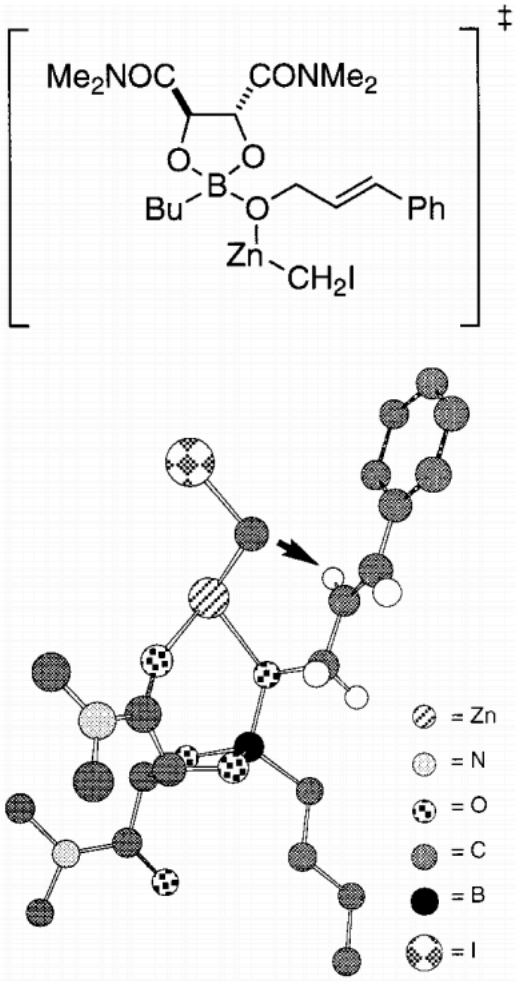
Conclusion

- 9 steps, 2%
- Abiotic radical cascade cyclization
- Termination of the cascade using a chiral thiol reagent





Scheme 9. *Reagents and conditions*: i, Li, -78 to 20°C; ii, HCl-H_2O.


Me2NOC
CONMe2
O
O
B
Bu
O
Ph
Zn
CH2I
‡
= Zn
= N
= O
= C
= B
= I