Selective C-C Bond Activation/Cleavage of Pinene Derivatives and Application in Total Synthesis

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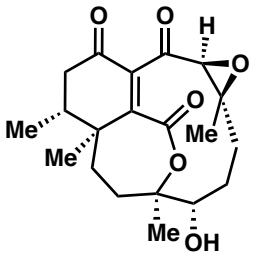
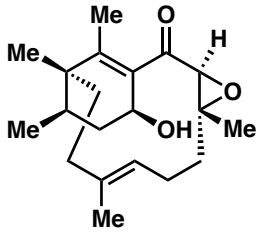
Outline

- Brief overview of C-C bond activation
- Selective C-C bond activation of pinene derivatives
- Application to synthesis of phomactin natural products



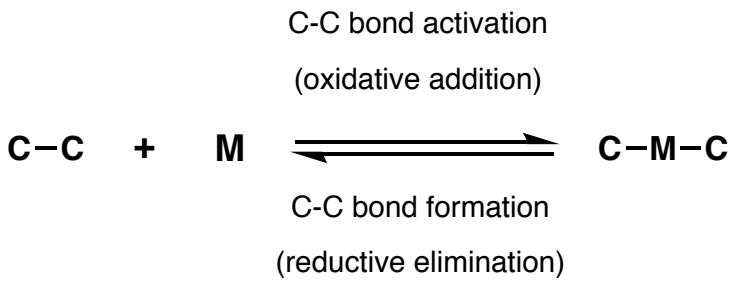
Phomactin T



Phomactin Q

C-C Bond Activation

- Either stoichiometric or catalytic metal
- 2 Basic Strategies



Strategy 1: Increase energy state of starting materials

-High energy starting materials such as strained 3- or 4- membered ring compounds

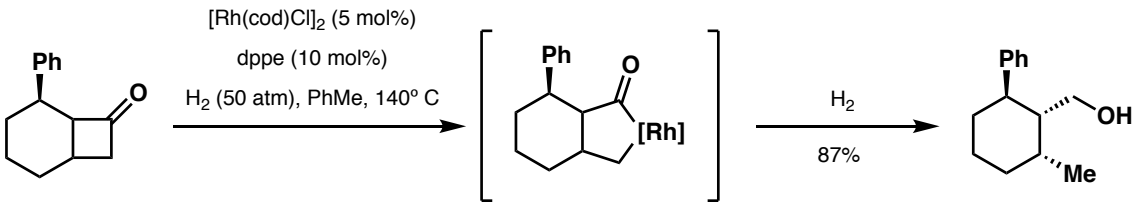
Strategy 2: Lower energy state of the C-C bond cleaved complexes

-Take advantage of driving forces (i.e. aromatic stabilization energy)

-Chelation assistance

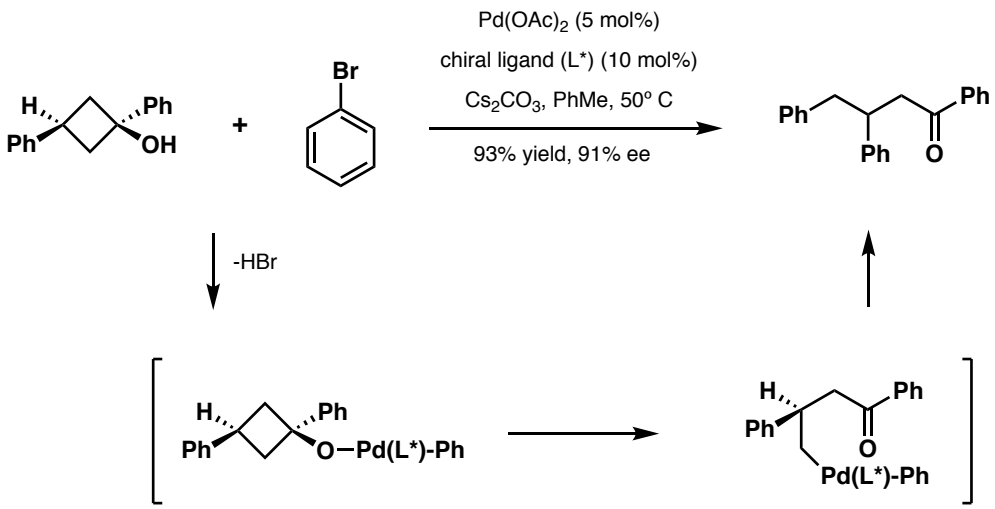
Strategy 1: Increase the energy state of starting materials

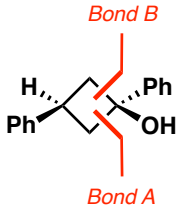
Direct cleavage of the C-C bond by transition metal catalysis

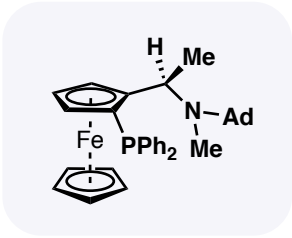


M. Murakami, *J. Am. Chem. Soc.*, **1998**, *120*, 9949-9950.

β-Alkyl elimination of a strained molecule





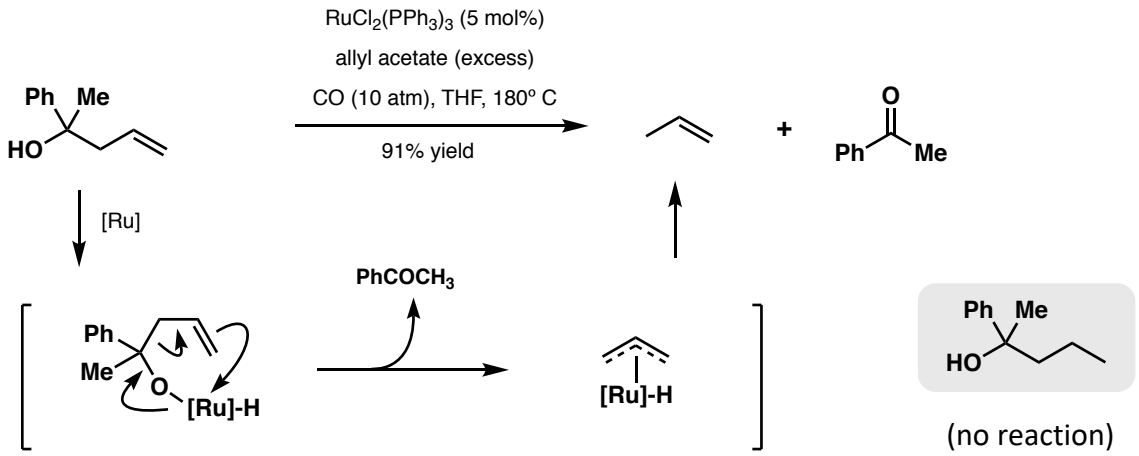


Chiral Ligand (L*)

S. Uemura, *J. Am. Chem. Soc.*, **2003**, *125*, 8862-8869.

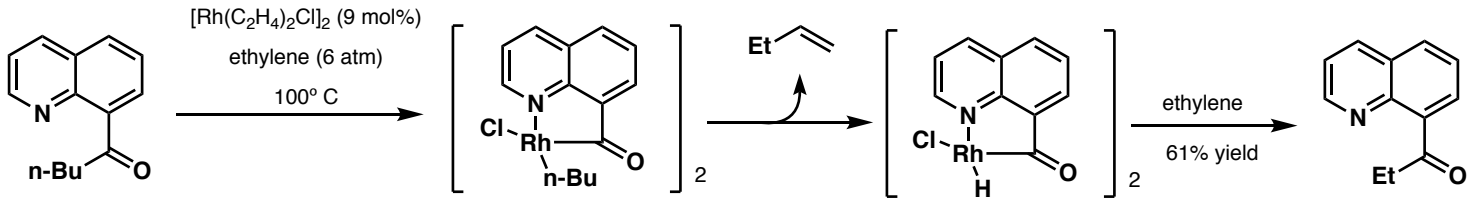
Strategy 2: Lower the energy state of the intermediate

β-Alkyl elimination of unstrained molecules



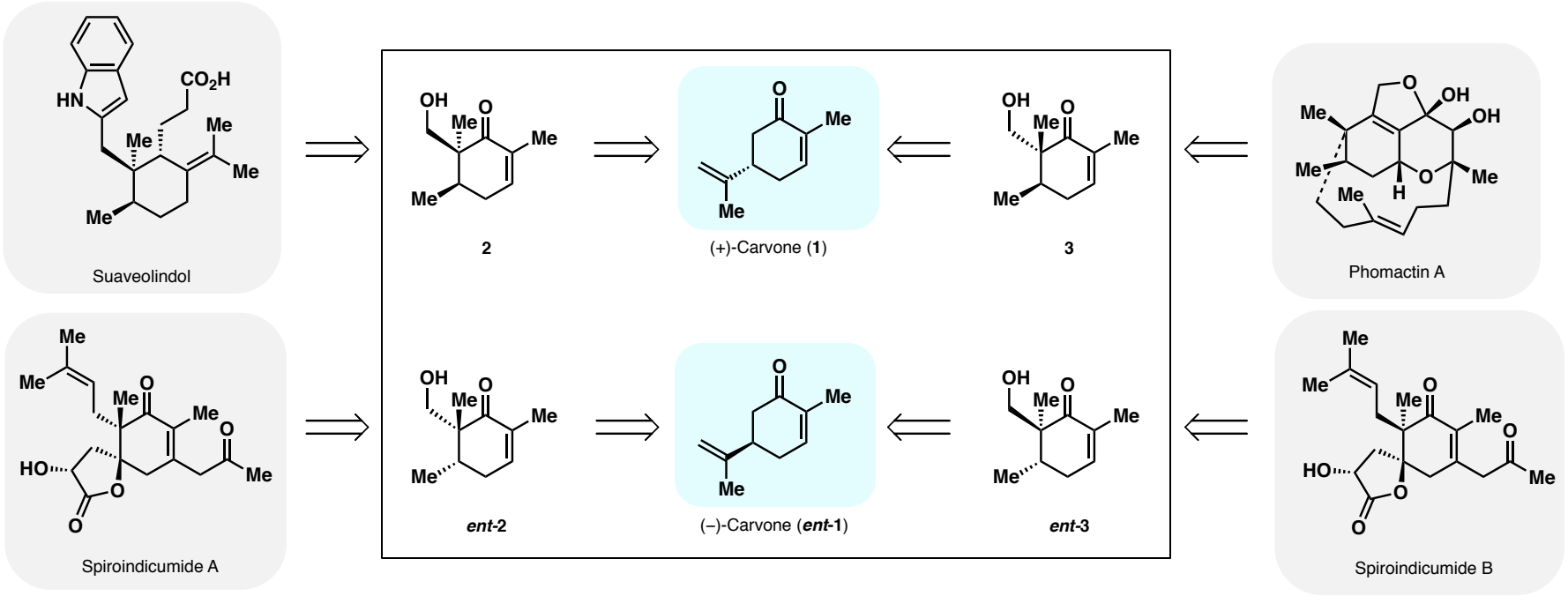
T. Mitsudo, *J. Am. Chem. Soc.*, **1998**, *120*, 5587-5588.

C-C bond activation by chelation assistance

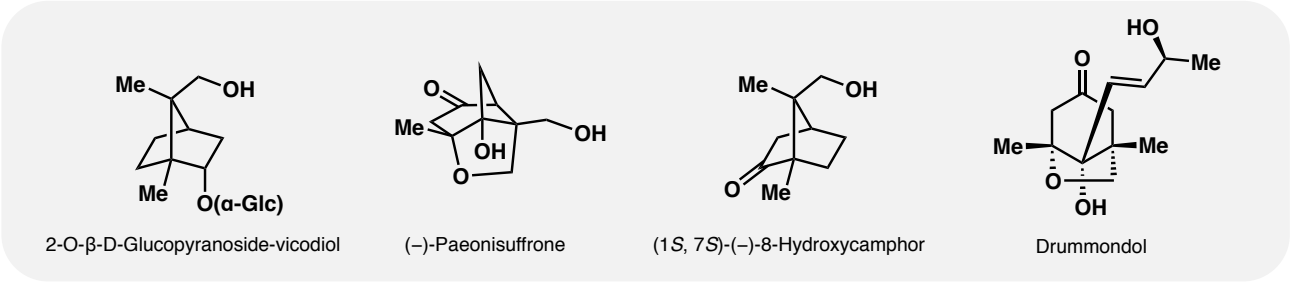


C.-H. Jun, *J. Chem. Soc., Chem. Commun.*, **1985**, 92-93.

Selective C-C bond activation of pinene derivatives

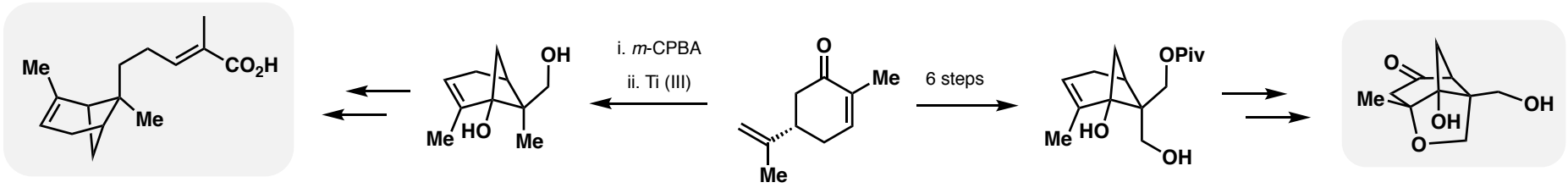


Unified, carvone based strategy to natural product core scaffolds



R. Sarpong, *J. Am. Chem. Soc.*, **2015**, *137*, 6327-6334.

Selective C-C bond activation of pinene derivatives



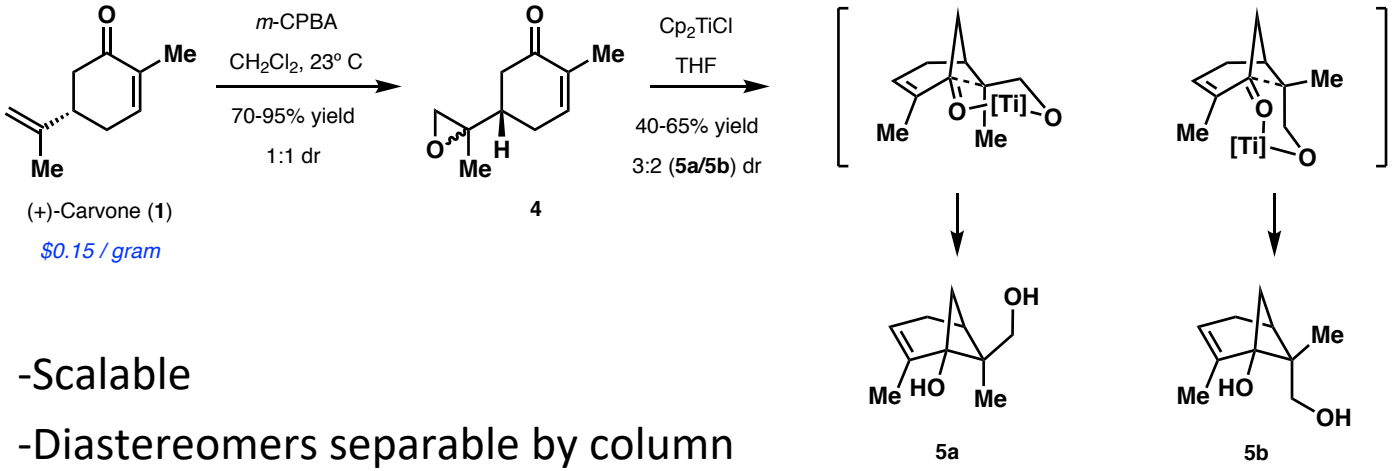
(E)-*endo*-bergamoten-12-oic acid

+ diastereomer (3:2 mixture)

(+)-Carvone (**1**)

(+)-Paeonisuffrone

F. Bermejo, *Tetrahedron*, **2006**, *62*, 8933-8942; F. Bermejo, *J. Org. Chem.*, **2009**, *74*, 1798-1801.



(+)-Carvone (**1**)

$0.15 / gram

4

5a

5b

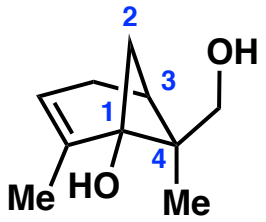
-Scalable

-Diastereomers separable by column chromatography

R. Sarpong, *J. Am. Chem. Soc.*, **2015**, *137*, 6327-6334.

Selective C-C bond activation of pinene derivatives

-Selectivity in C-C activation? (C1-C2 vs C1-C4)

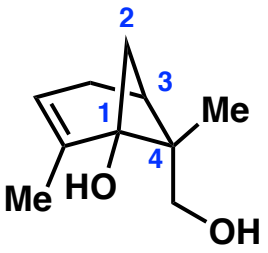


5a

-C1-C4 bond is weaker, longer:

5a C1-C2 = 1.551 Å C1-C4 = 1.567 Å

5b C1-C2 = 1.535 Å C1-C4 = 1.589 Å

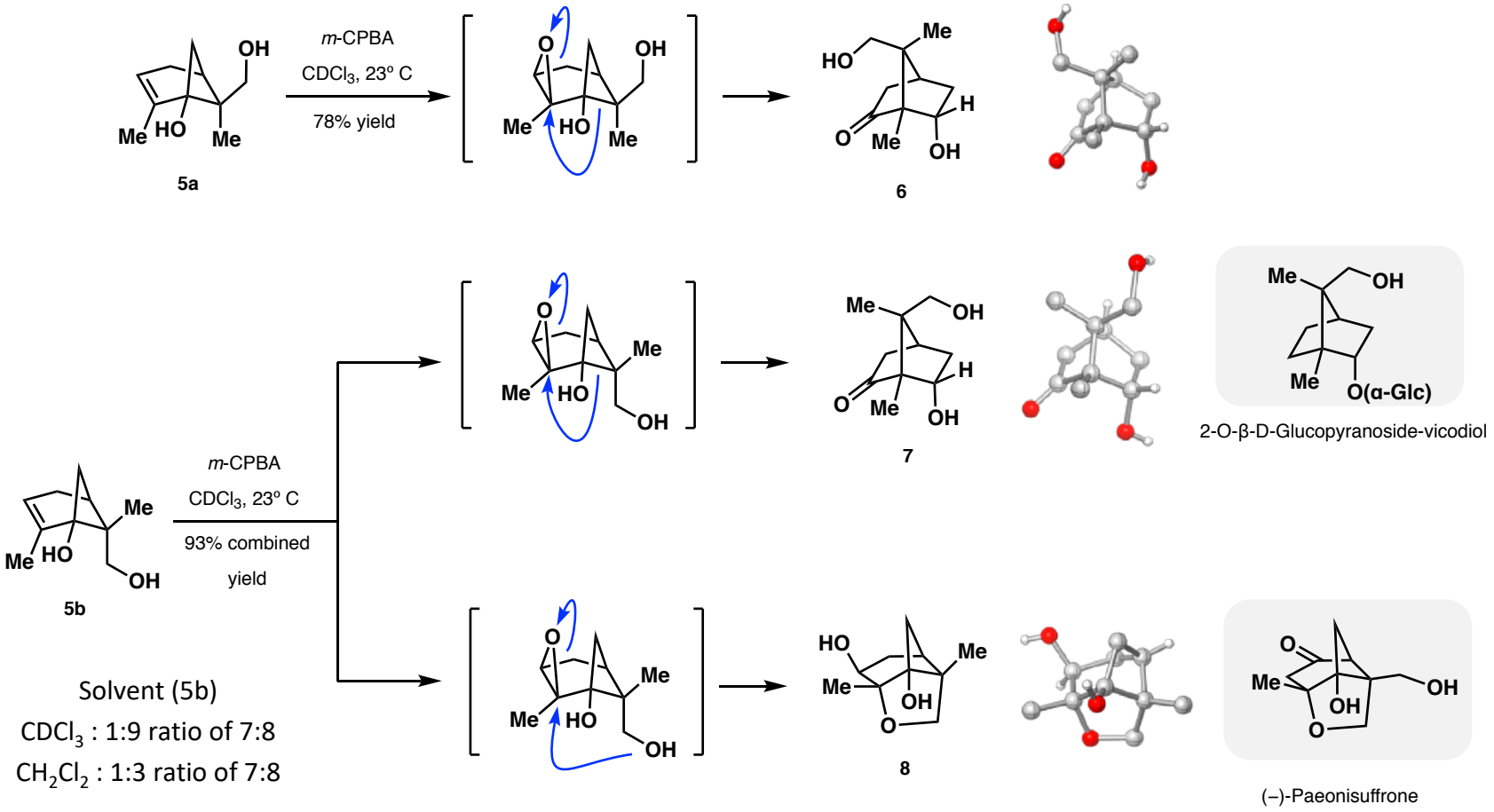


5b

-Methods for fragmentation/rearrangement of pinene: *m*-CPBA, Brønsted acid, NBS

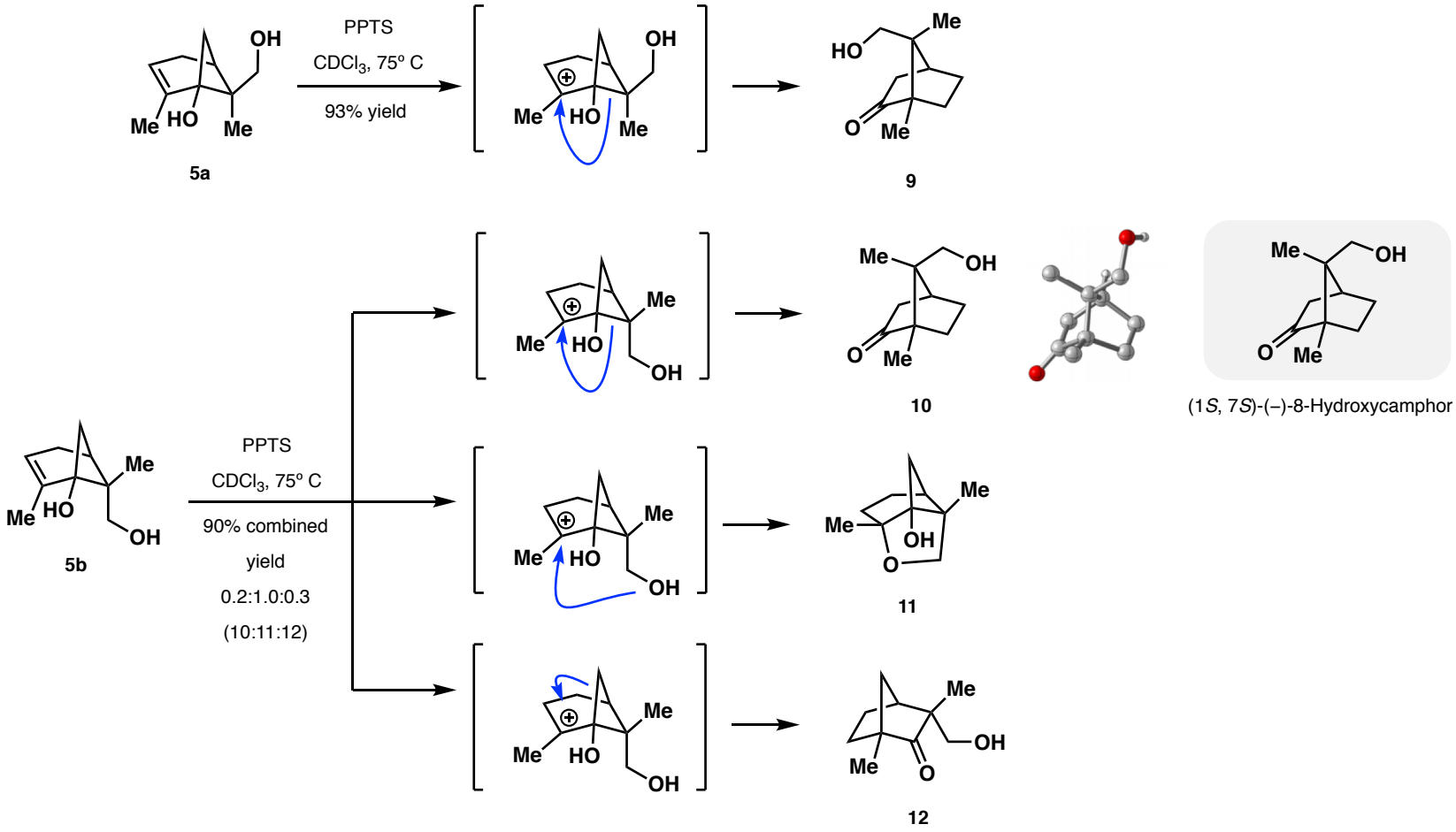
R. Sarpong, *J. Am. Chem. Soc.*, **2015**, *137*, 6327-6334.

m-CPBA promoted C-C bond cleavage



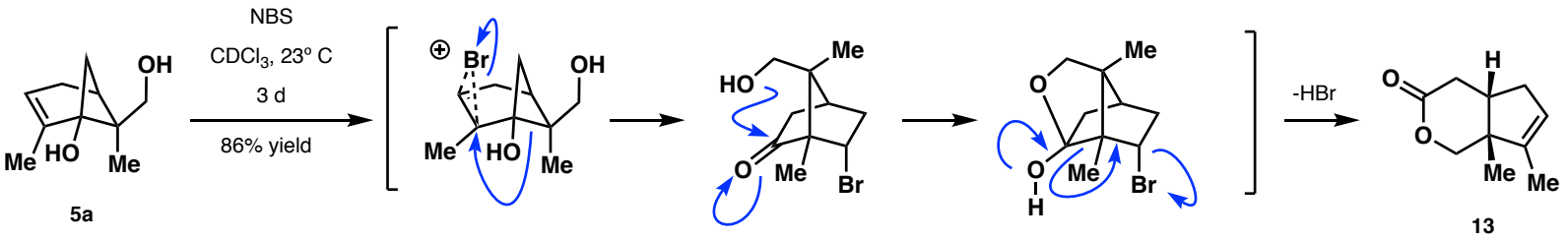
R. Sarpong, *J. Am. Chem. Soc.*, **2015**, *137*, 6327-6334.

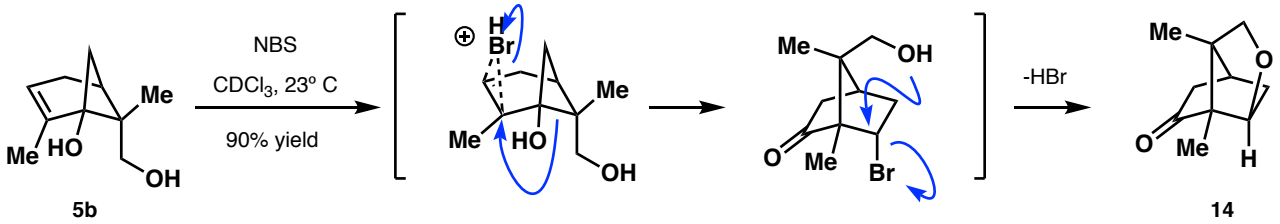
PPTS promoted C-C bond cleavage



R. Sarpong, *J. Am. Chem. Soc.*, **2015**, *137*, 6327-6334.

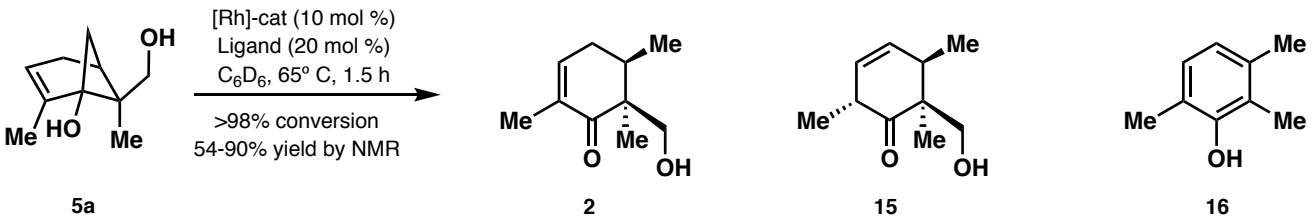
NBS promoted C-C bond cleavage





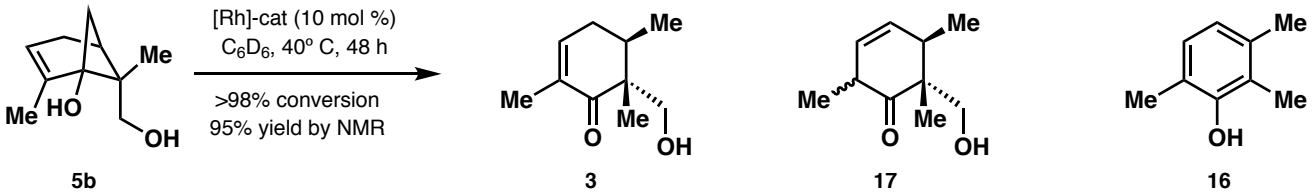
R. Sarpong, *J. Am. Chem. Soc.*, **2015**, *137*, 6327-6334.

Selective Rh-catalyzed C1-C2 bond cleavage/activation



5a 2 15 16

1. $[Rh(COD)OH]_2$, no added ligand: 1 : 1 : 1
2. $[Rh(COD)OH]_2$, *S*-BINAP added: 0 : 1 : 0
3. $[Rh(COD)OH]_2$, no ligand, 40 °C: 1 : 0 : <0.04



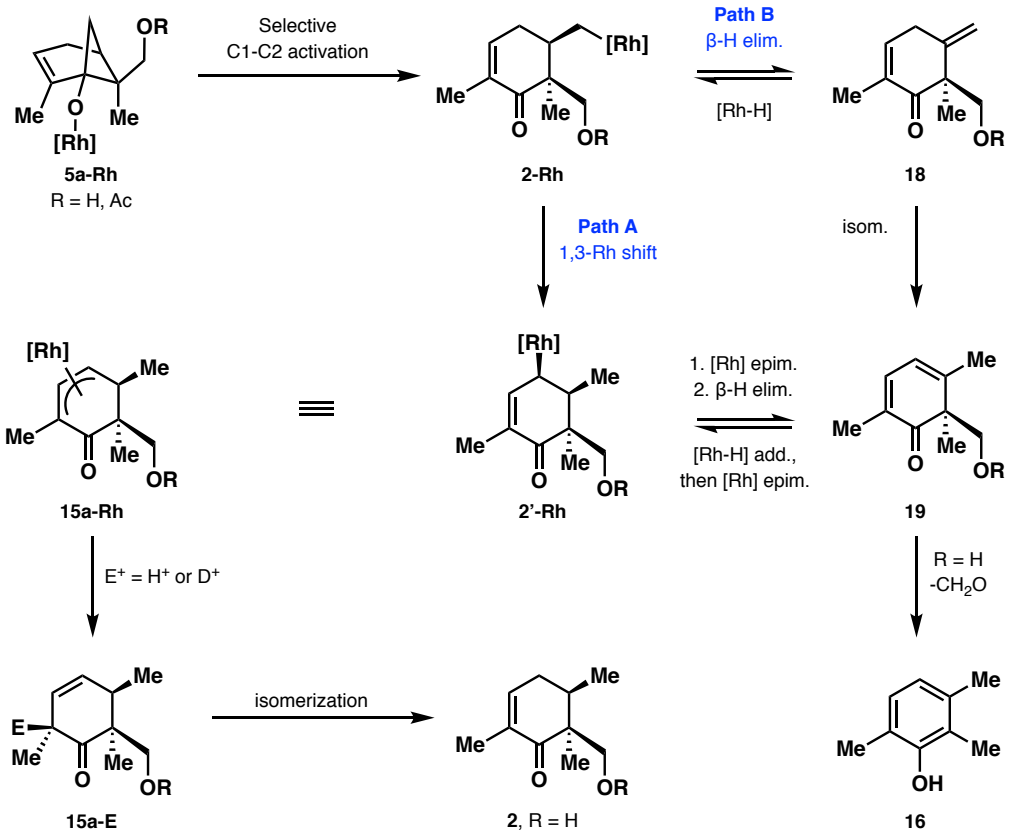
5b 3 17 16

1. $[Rh(COD)OH]_2$, no added ligand: 1 : <0.05 : 0.1

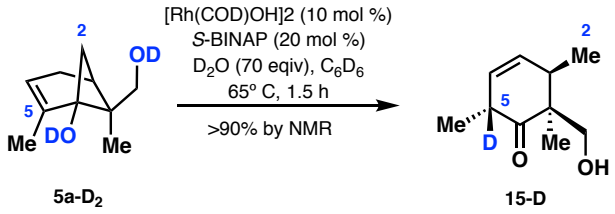
R. Sarpong, *J. Am. Chem. Soc.*, **2015**, *137*, 6327-6334.

Mechanistic analysis: selective Rh-catalyzed cleavage

Mechanistic hypothesis



Deuteration study



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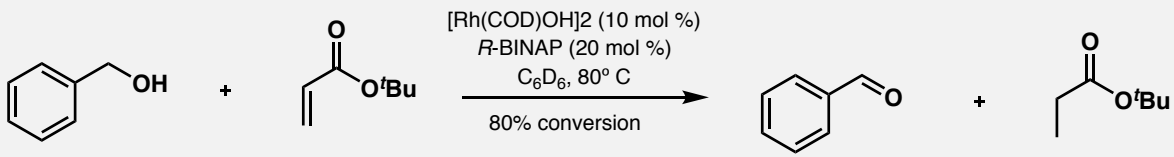
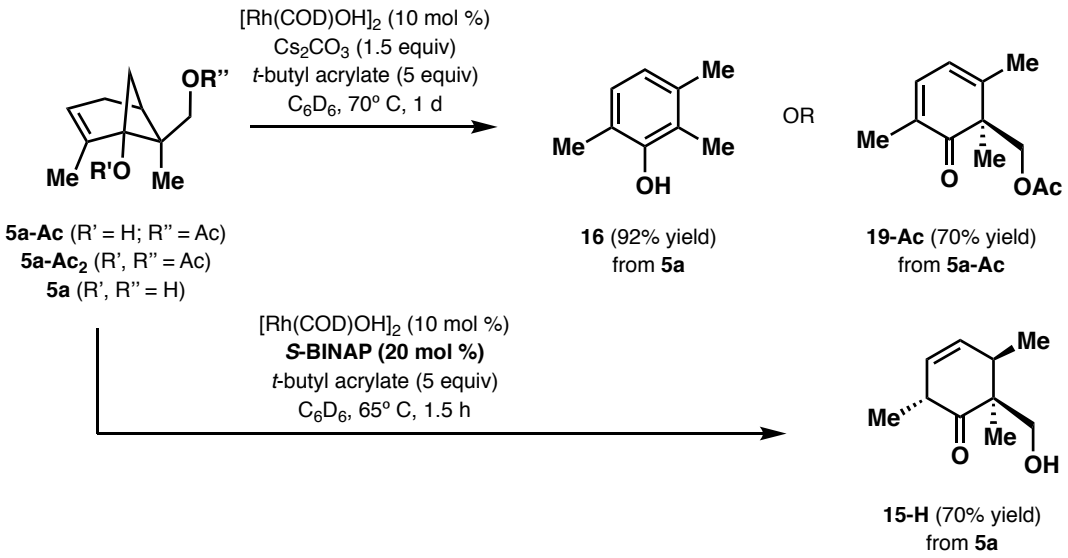
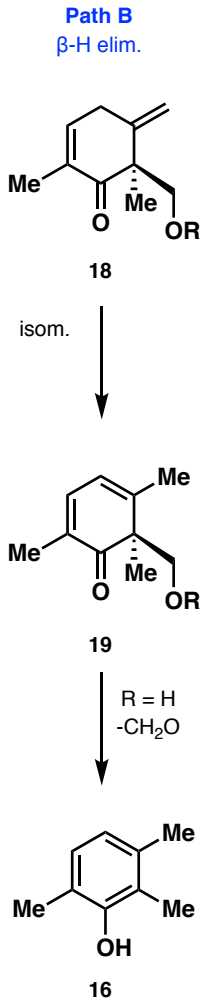
Mechanistic analysis: selective Rh-catalyzed cleavage



t-Butyl acrylate as an additive



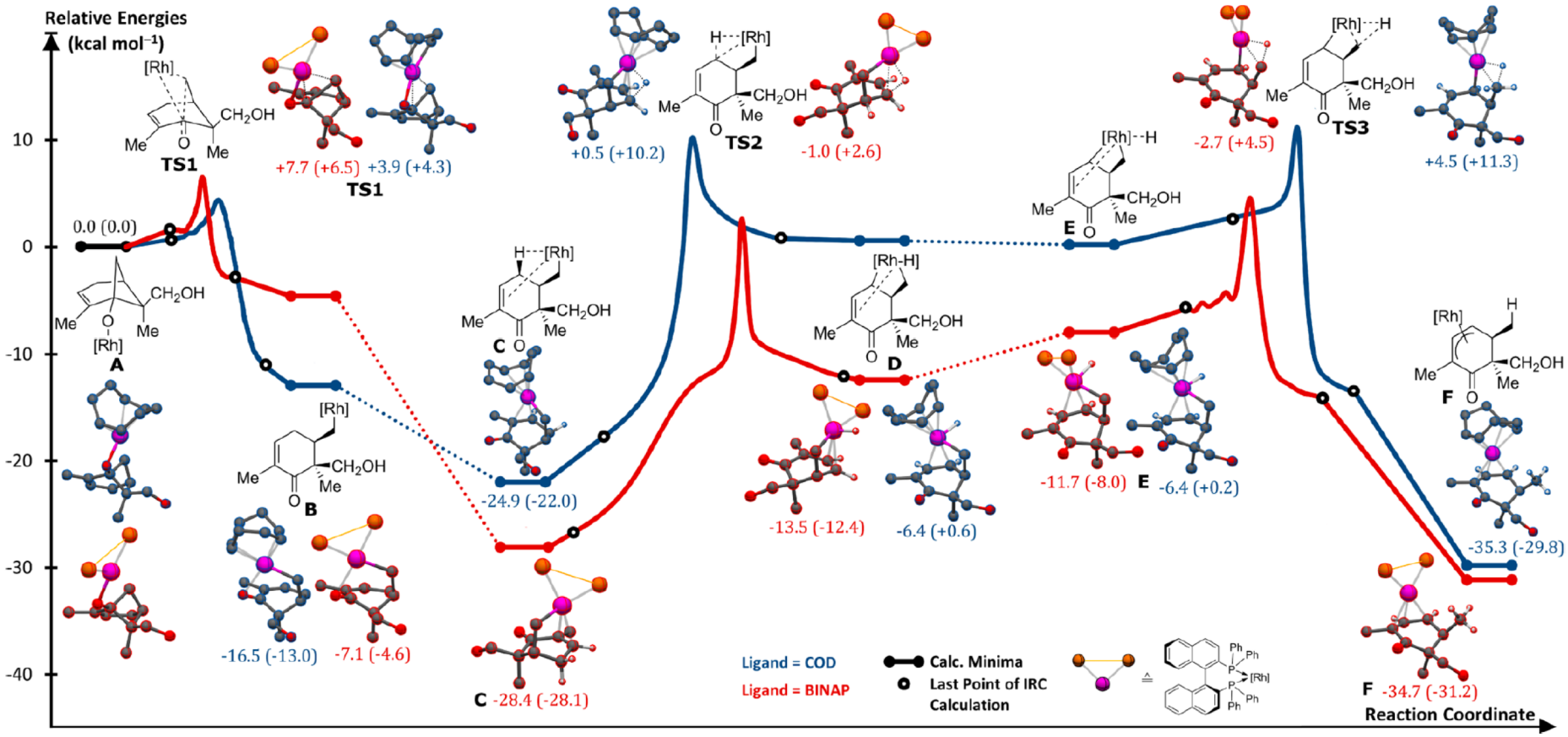
Mechanistic hypothesis



R. Sarpong, *J. Am. Chem. Soc.*, **2015**, *137*, 6327-6334.

Selective Rh-catalyzed C1-C2 bond cleavage/activation

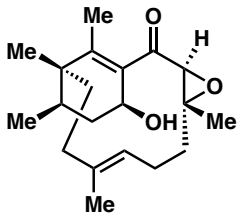
Energy profile of the C-C/C-H activation and reductive elimination steps



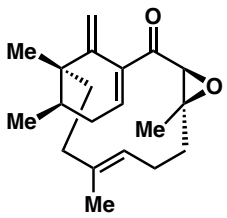
Numbers represent relative energies in kcal mol^{-1} . Numbers in brackets are calculated gas-phase energies.

R. Sarpong, *J. Am. Chem. Soc.*, **2015**, *137*, 6327-6334.

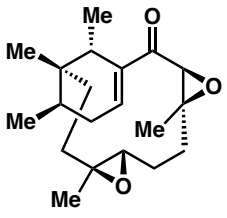
Phomactin terpenoids



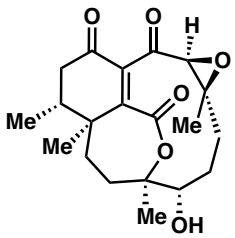
Phomactin Q



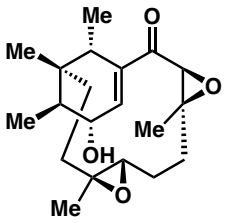
Phomactin R



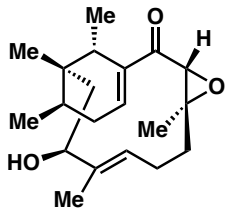
Phomactin S



Phomactin T



Phomactin U



Phomactin V

-27 Phomactins

-First isolated in 1991 from *Phoma* sp.

(A-G, phomacta-1(14),3,7-triene, and Sch 49027)

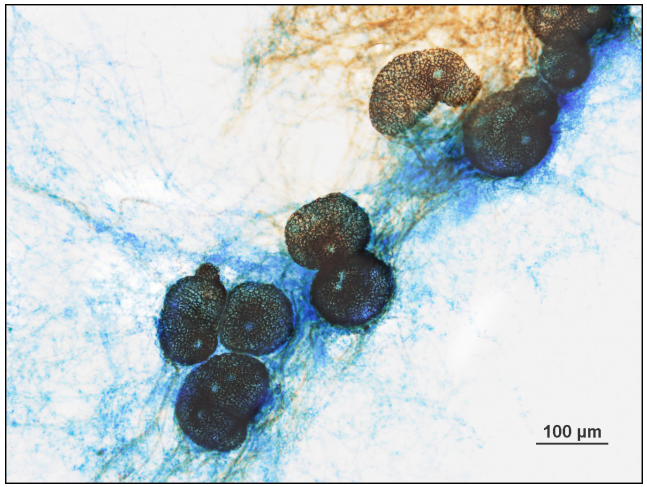
-Phomactins H-P isolated from fungus MPUC 046

-Q-V from *Biatriospora* sp.

-Phomactin A emerged from PAFR antagonist assay

-PAFR antagonists as adjuvants in cancer therapy

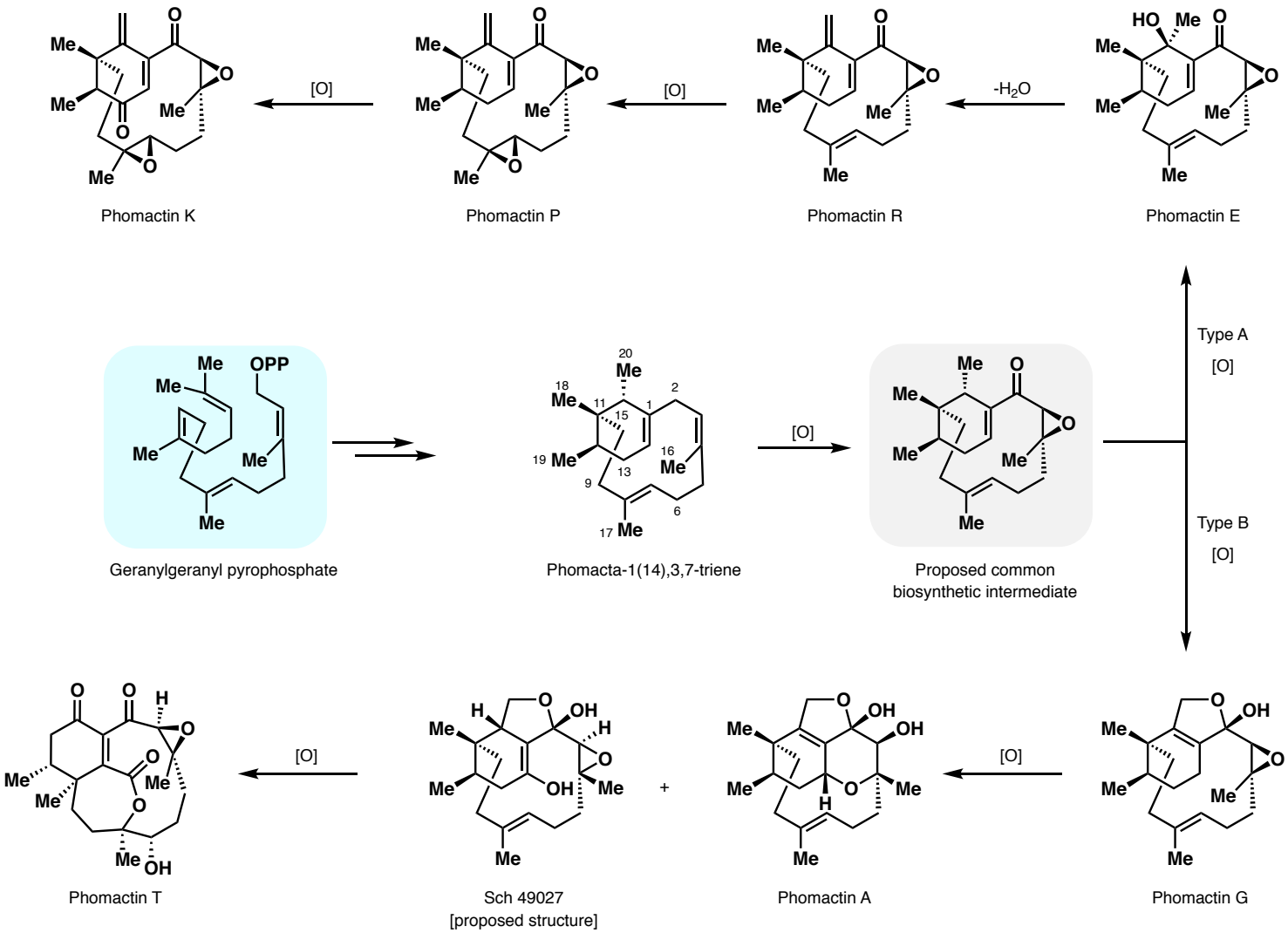
-Six total synthesis reported so far (4 racemic, 18-37 steps)



Phoma glomerate. (https://www.inspq.qc.ca/en/moulds/fact-sheets/phoma-glomerate)

R. Sarpong, *Nat. Chem.*, **2018**, *10*, 938-945.

Phomactin terpenoids



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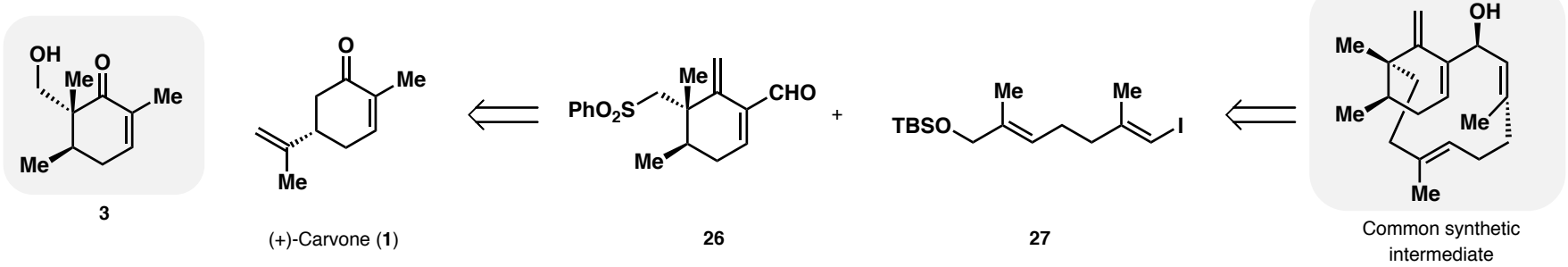
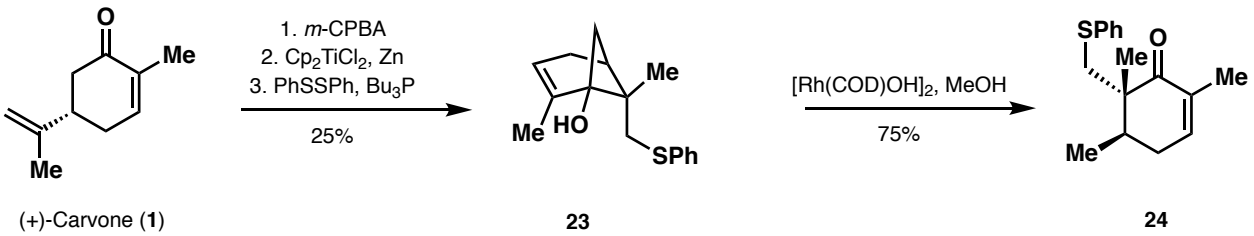
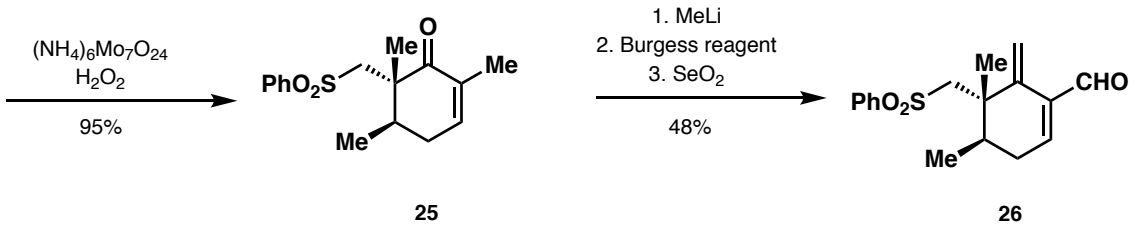
Phomactin terpenoids







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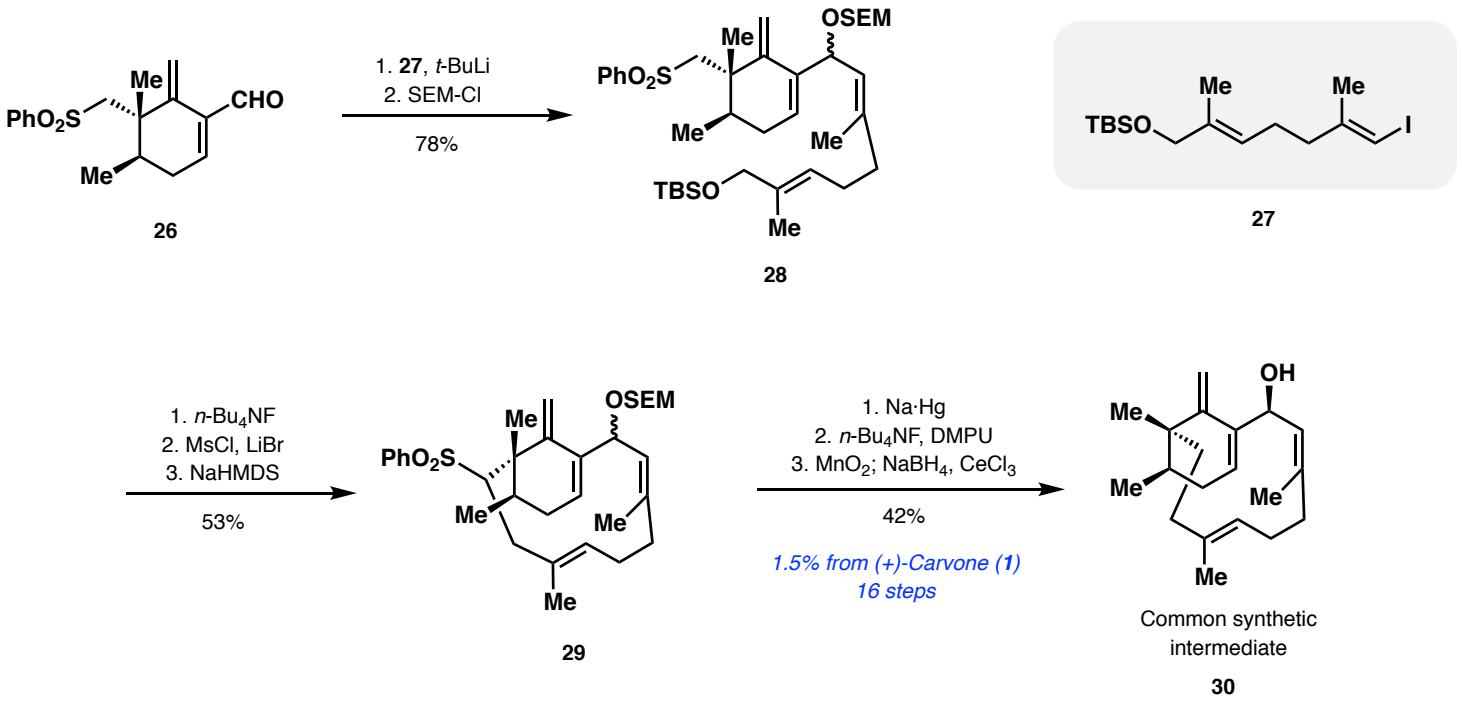
Phomactin terpenoids



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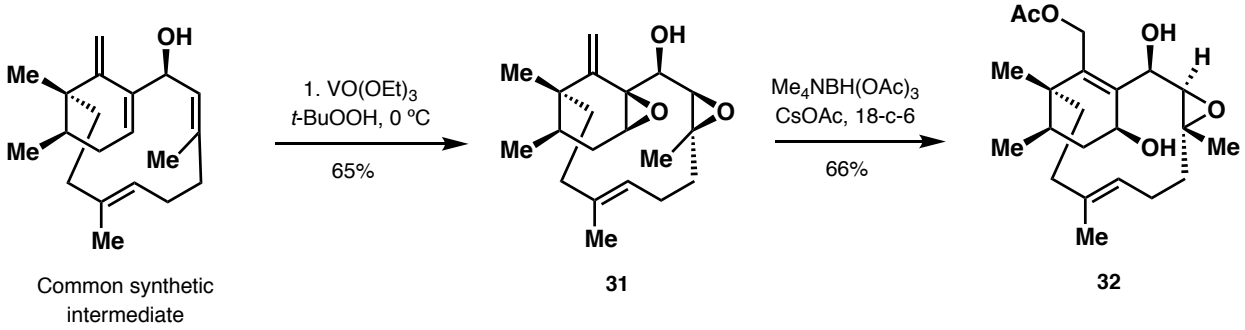
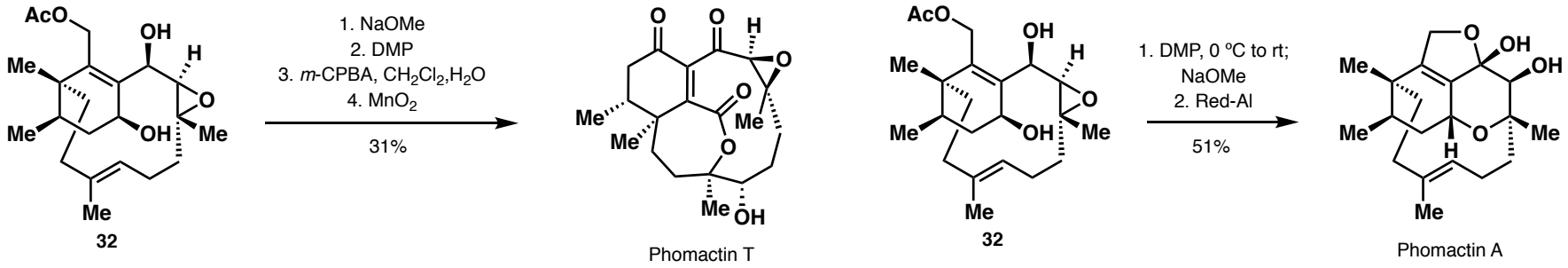
Phomactin terpenoids



Common synthetic intermediate

31

32

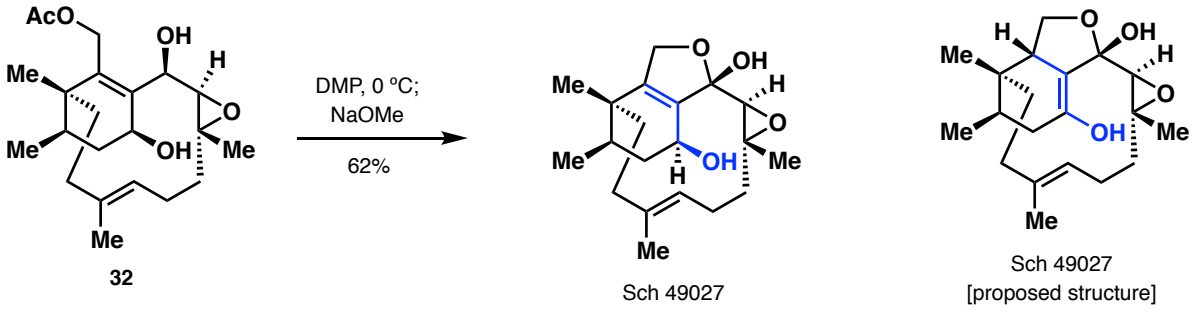


32

Phomactin T

32

Phomactin A



32

Sch 49027

Sch 49027
[proposed structure]

R. Sarpong, *Nat. Chem.*, **2018**, *10*, 938-945.

Phomactin terpenoids

Table 1 | PAFR-inhibitory concentration (IC_{50}) of phomactins (μM)

Phomactins	IC_{50}
Phomactin A	3.8
Phomactin F	2.7
Phomactin I	3.2
Phomactin P	3.0
Phomactin R	2.5
Phomactin S	2.8
Phomactin U	10.0
Phomactin V	3.1
WEB 2170	3.2

Concentration of phomactins or WEB 2170 (in μM) that reduced 50% of the response to 10 nM of cPAF (IC_{50}). Inhibitory doses were generated using three-parameter non-linear regression analysis from $n = 3$ independent experiments (see the 'Biological assays' and 'Statistical analysis' sections for more details). cPAF, carbamoyl-PAF (1-hexadecyl-2-N-methylcarbamoyl glycerophosphocholine).

Table 2 | Inhibition of tumour cell repopulation by phomactin congeners

Phomactins	% inhibition of RLU*
Phomactin A	55 ± 11
Phomactin R	83 ± 7
Phomactin S	68 ± 2
Phomactin P	29 ± 5
Phomactin U	34 ± 5
Phomactin F	77 ± 3
Phomactin V	47 ± 2
Phomactin I	49 ± 6
WEB 2170	71 ± 2

*% inhibition of RLU by 10 μM of phomactin compounds or WEB 2170 relative to untreated control irradiated at 8 Gy. Data are from $n \geq 3$ independent experiments and are presented as mean ± standard error of the mean (s.e.m.).

R. Sarpong, *Nat. Chem.*, **2018**, *10*, 938-945.