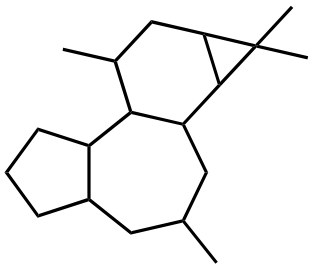
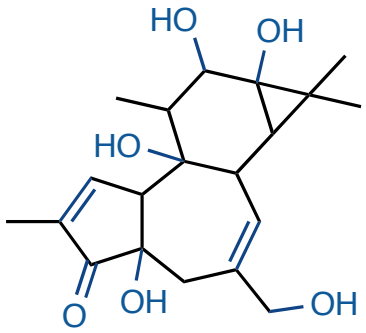
Nineteen-step Total Synthesis of (+) - Phorbol

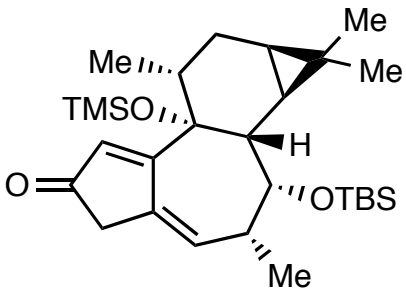
Shuhei Kawamura, Hang Chu, Jakob Felding, and Phil Baran



1 Cyclase Phase

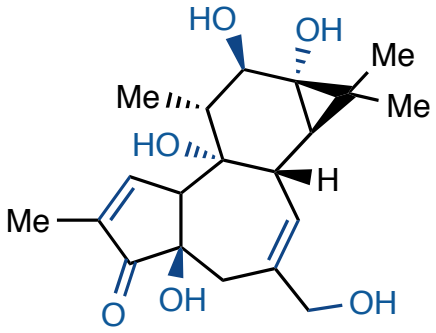


2 Oxidase Phase



Advanced Intermediate [1]

Oxidase Phase



(+) – Phorbol [2]

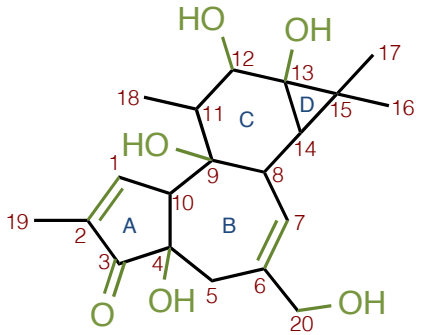
Evan Carder
Wipf Group Current Literature
April 09, 2016

[1] *Science* **2013**, 341, 878.
[2] *Nature* **2016**, 0, 1.

Phorbol Background

- Phorbol and phorbol derivatives are members of the tigliane diterpenoid family.

- The tigliane diterpenoid family are isolated from the *Euphorbiaceae* and the Thymelaeaceae family members [1]. Structural elucidation was confirmed by X-ray crystallography of a phorbol derivative in 1967 [2].



Structural characteristics:

- Tigliane diterpenoids have a 5/7/6/3- tetracyclic ring system consisting of a five-membered ring (A), a seven-membered ring (B), a six-membered ring (C), and a cyclopropane system (D).

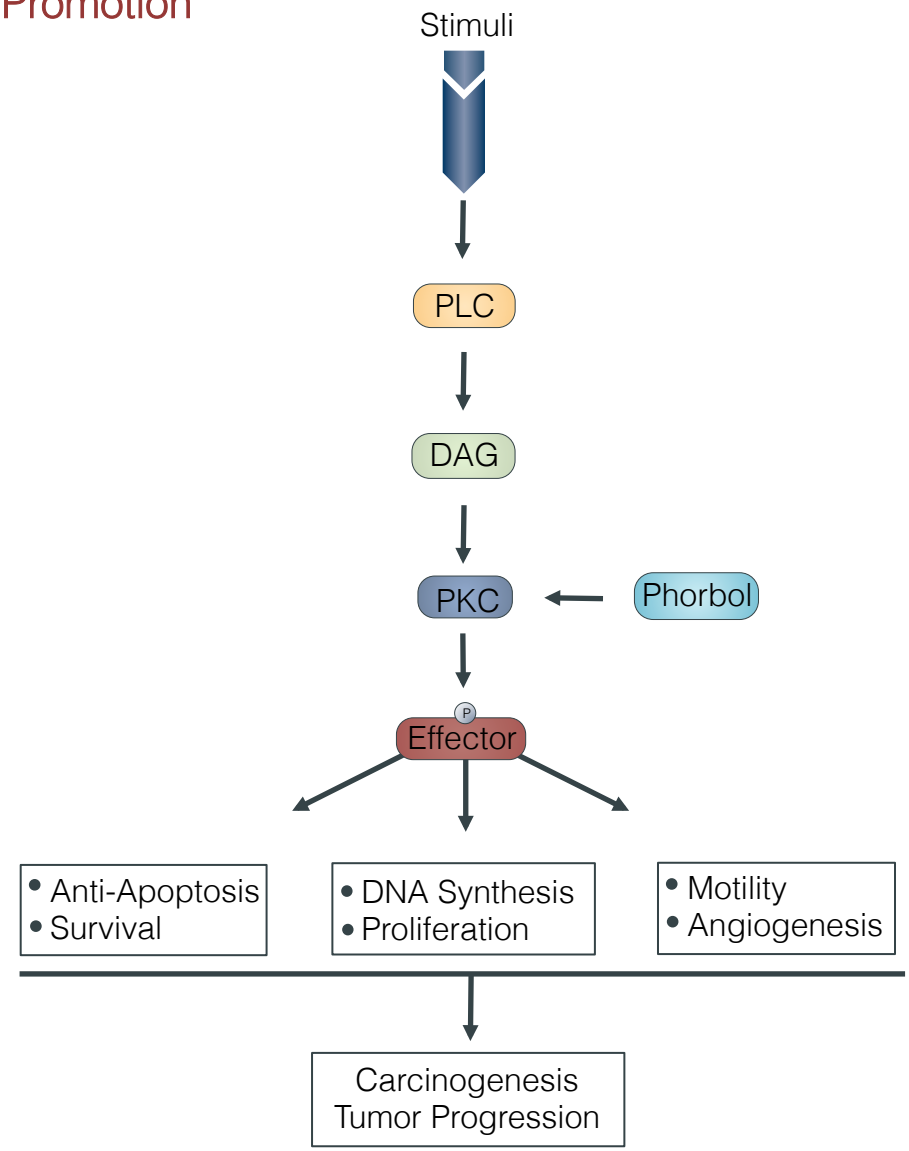
- Phorbol has a polyhydroxylated tigliane carbon skeleton that contains eight contiguous asymmetric centers, six of which are sited around the six-membered C ring.

- Phorbol derivatives are isolated as mixed esters, most commonly existing as 12,13 or 13,20-diesters.

[1] *Arch. Exp. Pathol. Pharmakol.* **1935**, 177, 212.
[2] *Angew. Chem. Int. Ed. Engl.* **1967**, 6, 809.

Protein Kinase C (PKC) Activation and Tumor Promotion

- As a downstream effector of G-protein coupled receptors and receptor tyrosine kinases, PKC propagates important signaling events.
- Deregulation of PKC has been associated with multiple cancer-promoting pathways, which can lead to an array of adverse phenotypes.
- Therefore, PKC has been implicated in the development and progression of disease.
- PKC is commonly activated by second messenger molecule 1,2-diacylglycol (DAG) at the cellular surface.
- Phorbol esters have been shown to strongly activate PKC and potently promote tumor development - tetradocecanoyl phorbol acetate is active at 20 nM. Paradoxically, deoxygenated derivatives can inhibit tumor formation; therefore, synthesis of phorbol and phorbol derivatives may provide therapeutically active agents toward the treatment of cancer.



[1] Nature Review **2011**, 11, 937.
[2] *J. Bio. Chem.* **2000**, 275, 12136.

Efforts toward the synthesis of Phorbol

- Paul Wender and co-workers:

  Racemic total synthesis, 52 steps, 0.16% overall yield [1]

  Racemic formal synthesis, 42 steps, 0.02% overall yield [3]

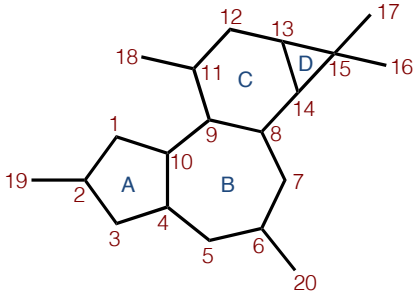
  Asymmetric formal synthesis; 36 steps, 1.2% overall yield [4]

- Jin Kun Cha and co-workers:

  Asymmetric formal synthesis, 43 steps, 0.4% overall yield [5]

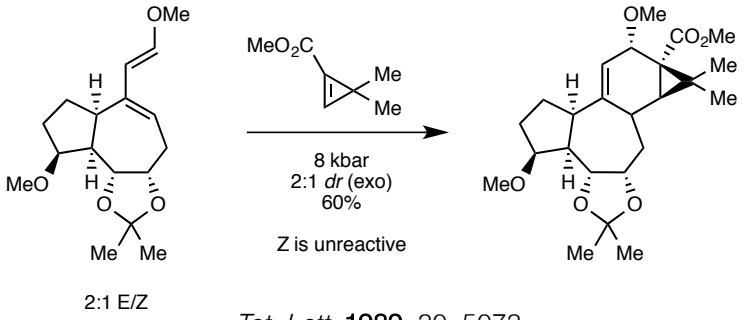
- Work from the labs of Shibasaki, Wilson, Rigby, Harwood, Little, Page, Dauben, McMills, Paquette, Singh, Ovaska, West, Evans, Li, and others.

  A-B-C-D, B-C-D, A-B-C skeletal components



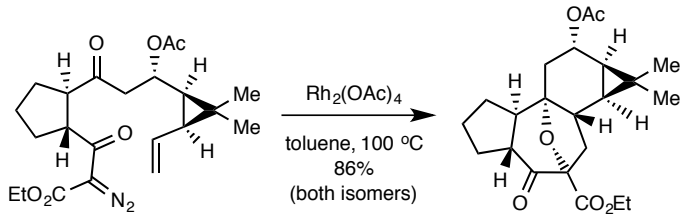
[1] *J. Am. Chem. Soc.* **1989**, 111, 8954. [2] *J. Am. Chem. Soc.* **1989**, 111, 8957.
[3] *J. Am. Chem. Soc.* **1990**, 112, 4956. [4] *J. Am. Chem. Soc.* **1997**, 119, 7897.
[5] *J. Am. Chem. Soc.* **2001**, 123, 5590.

Rigby Lab – [4+2] cycloaddition



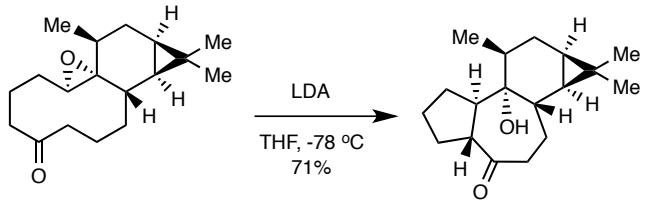
Tet. Lett. **1989**, 30, 5073.

Dauben Lab – carbonyl ylide cycloaddition



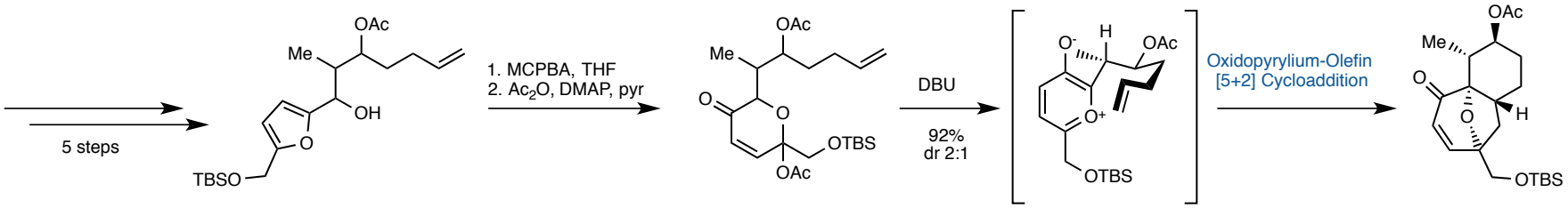
J. Org. Chem. **1993**, 58, 7635.

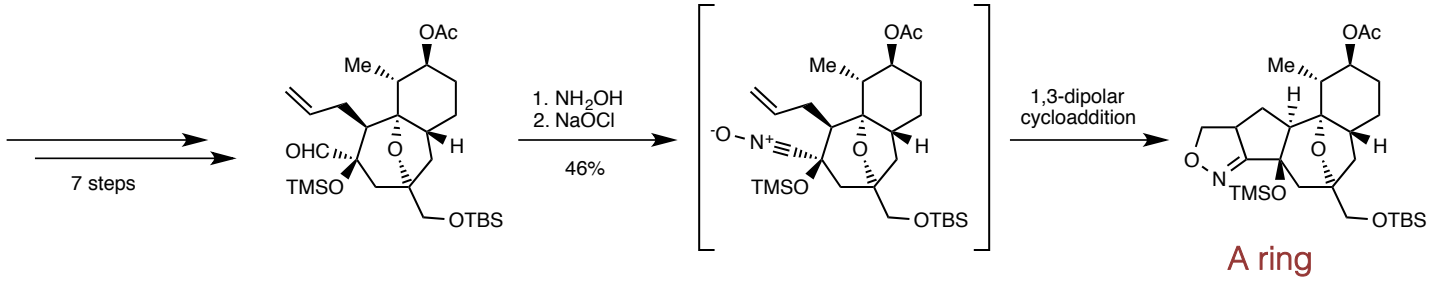
Paquette Lab – anionic oxy-Cope

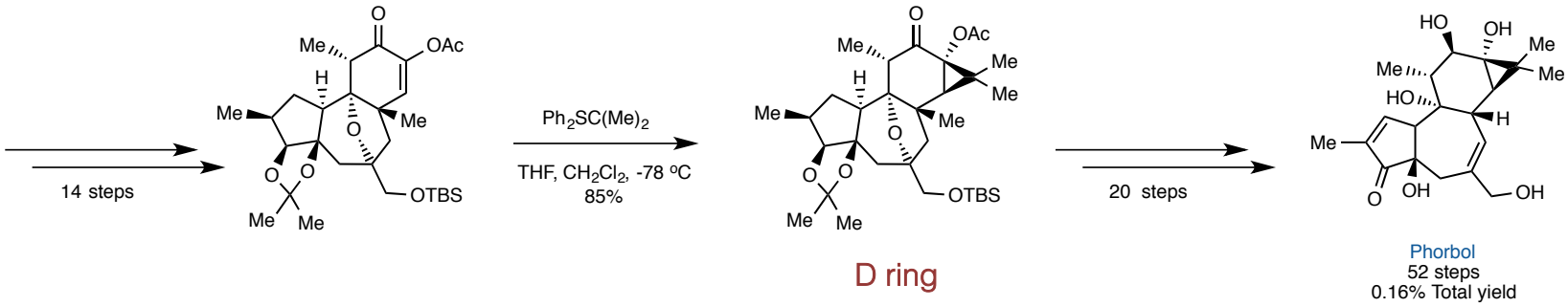


Tet. **1994**, 50, 4071.

Wender's racemic total synthesis

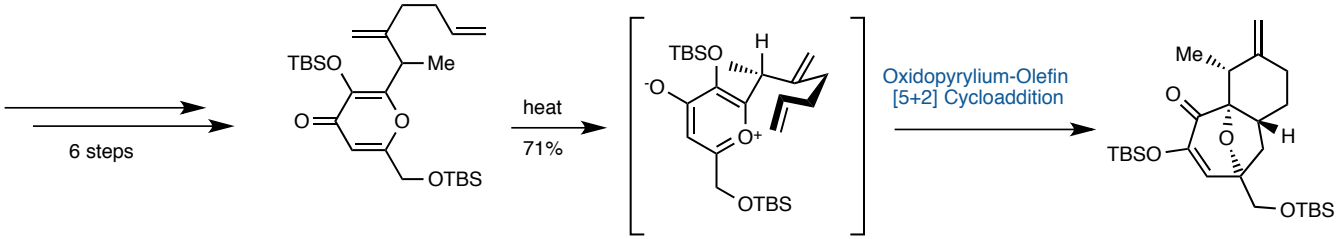




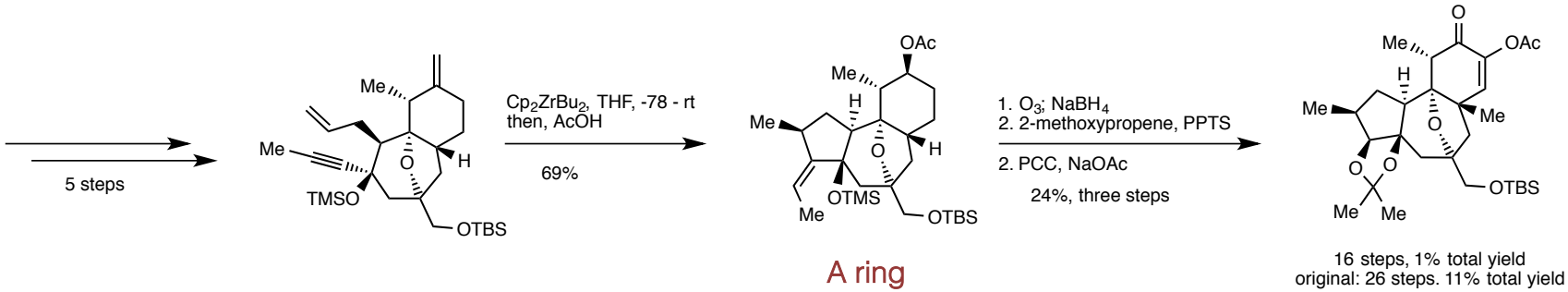


[1] *J. Am. Chem. Soc.* **1989**, 111, 8954.
[2] *J. Am. Chem. Soc.* **1989**, 111, 8957.

Wender's racemic formal synthesis

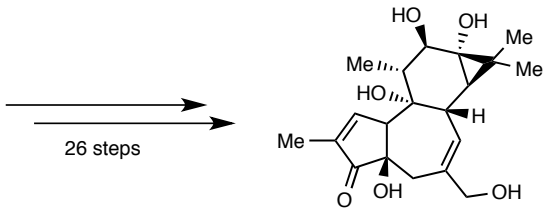


B and C ring



A ring

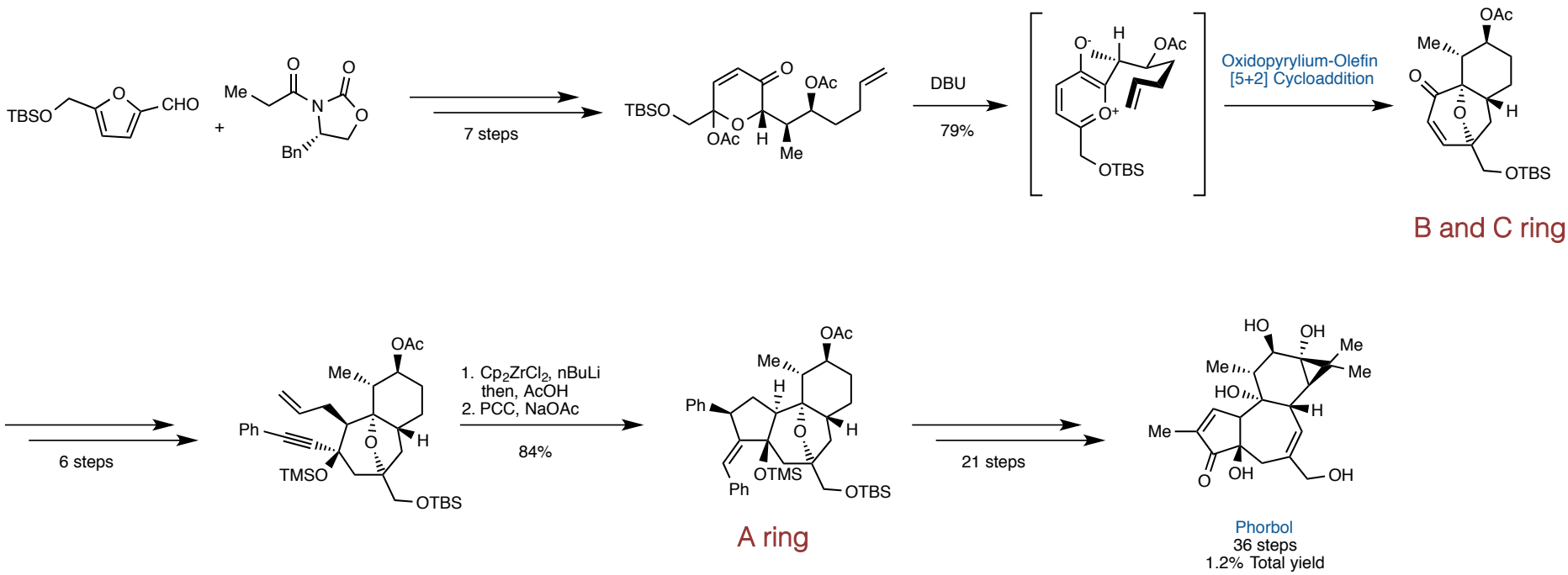
16 steps, 1% total yield
original: 26 steps. 11% total yield



Phorbol
42 steps
0.02% Total yield

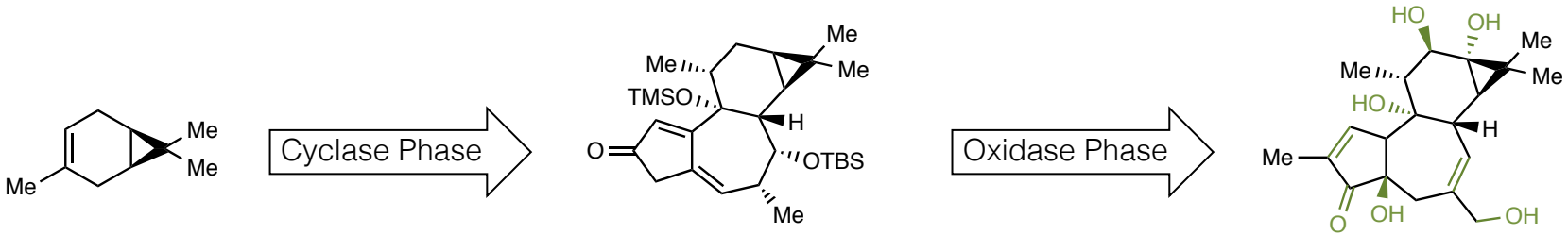
[1] *J. Am. Chem. Soc.* **1990**, 112, 4956.

Wender's asymmetric formal synthesis



[3] *J. Am. Chem. Soc.* **1997**, 119, 7897.

Current work: Two phase synthetic strategy



(+) – 3-Carene

Advanced Intermediate [1]

(+) – Phorbol [2]

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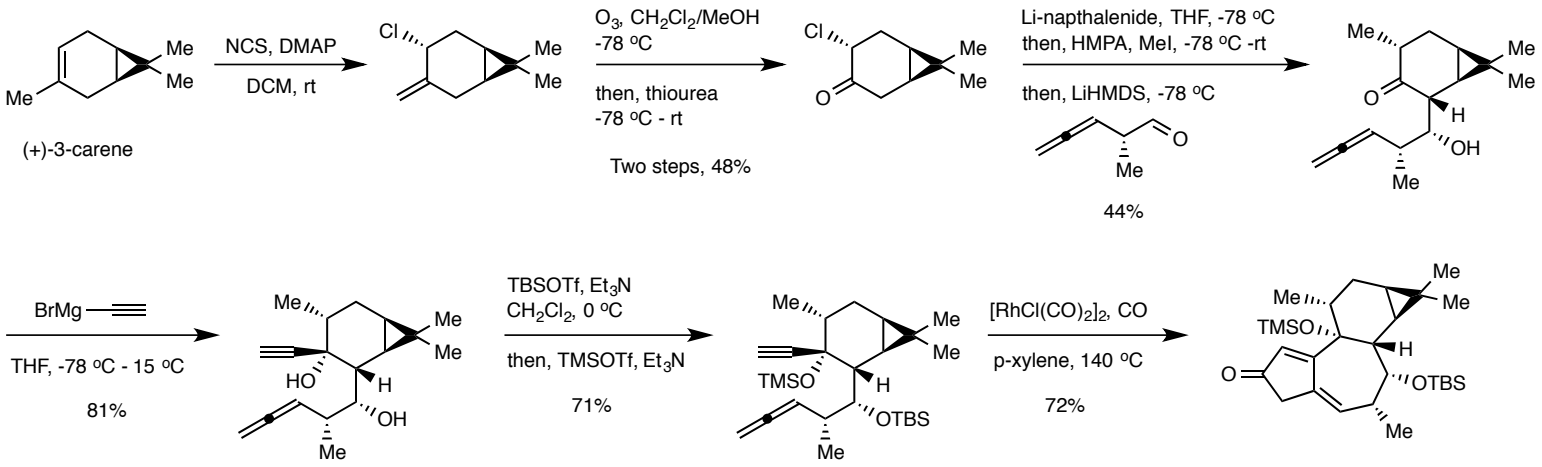
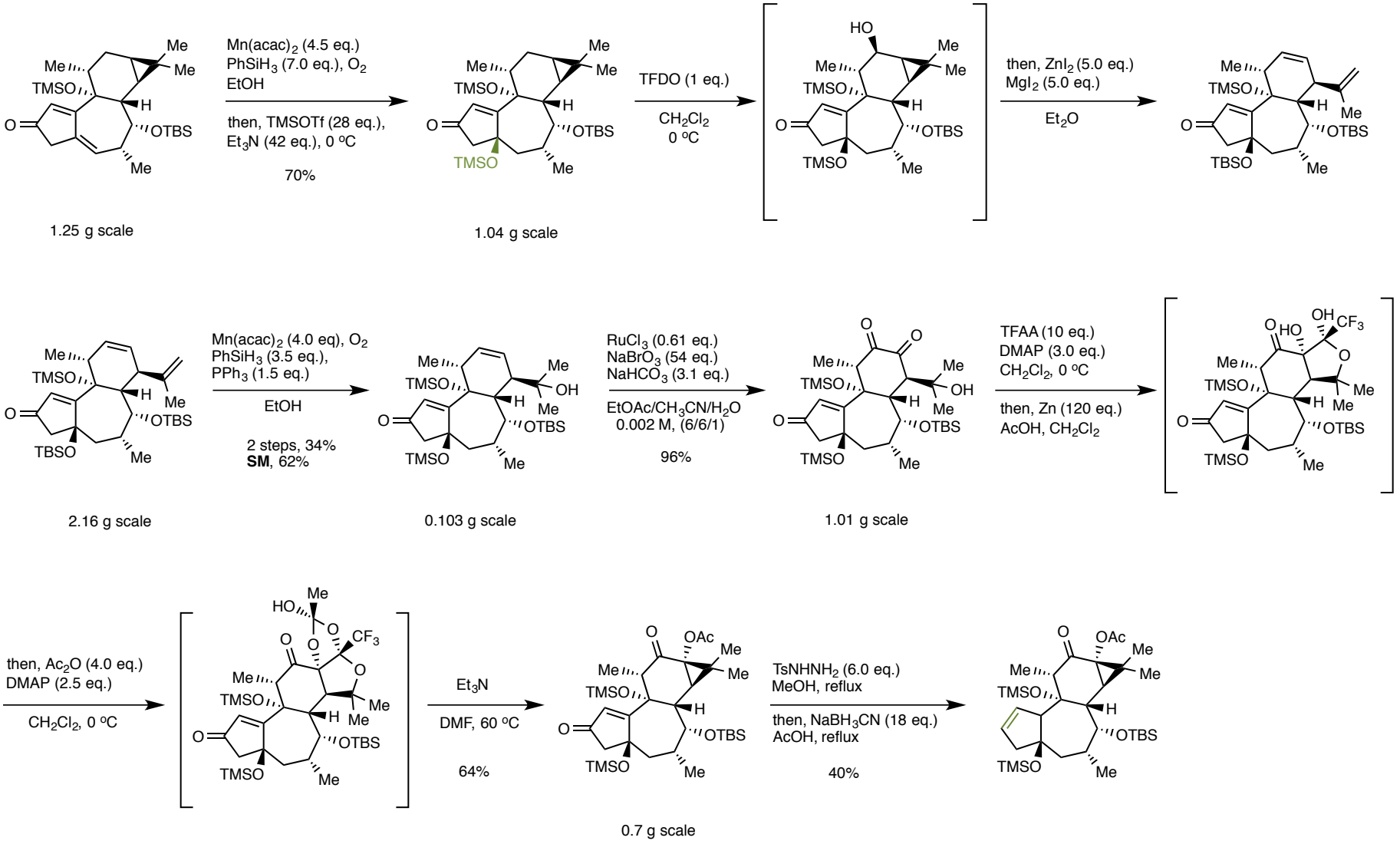
1 Cyclase Phase



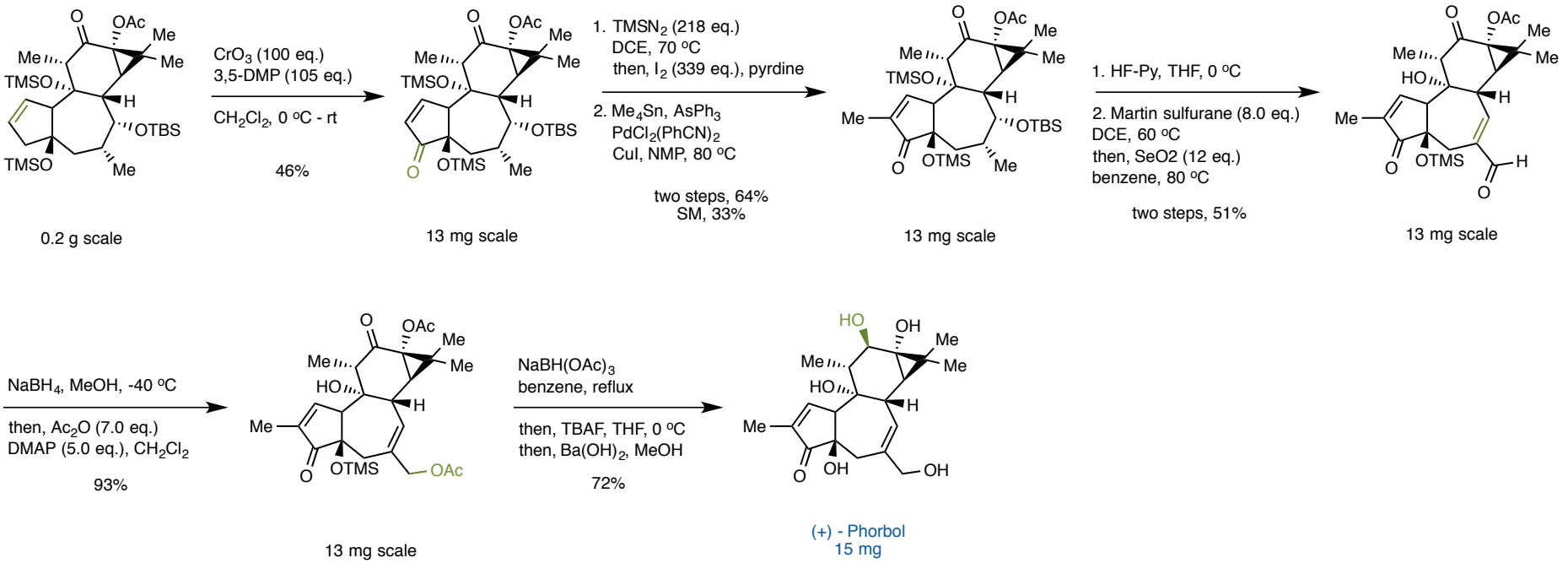
Advanced Intermediate
LEO Pharmaceutics
> 100 grams

[1] *Science* **2013**, 341, 878.
[2] *Nature* **2016**, 0, 1.

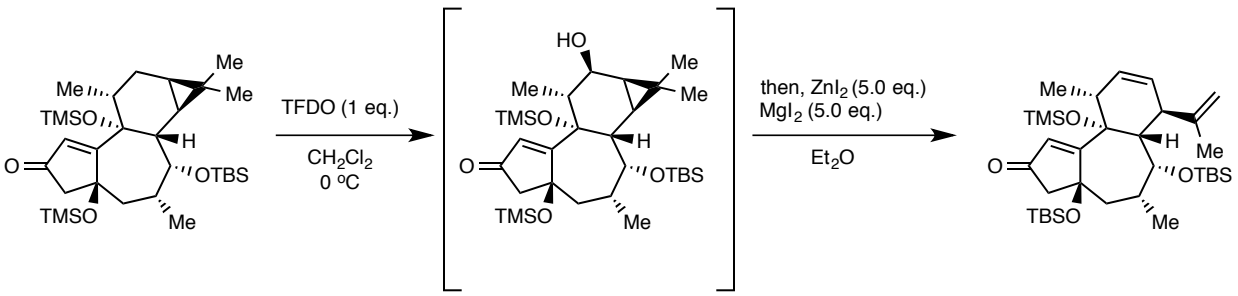
② Oxidase Phase



② Oxidase Phase

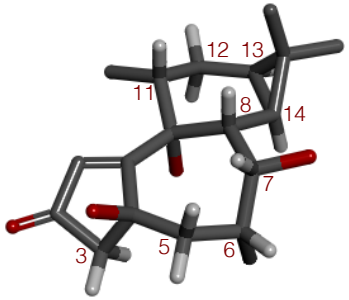


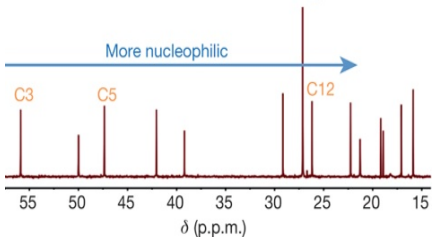
Notable steps: C-H Activation



C-H Activation Considerations

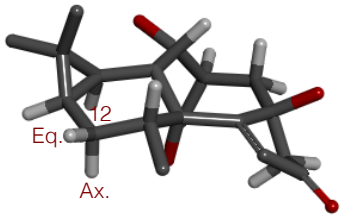
- Steric shielding of C6, C7, C8, and C11.
- Higher s-character of tertiary cyclopropane C-H bonds (C13/C14).
- Compared to the remaining carbon centers, C^{13} NMR suggests C12 is the most nucleophilic position.
- Hyperconjugation from the pi-like cyclopropane system should facilitate oxidation.

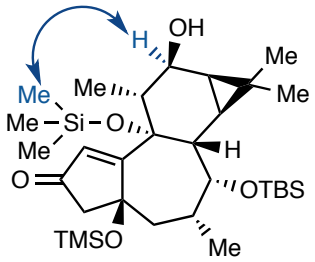




Eq. vs Ax. Considerations

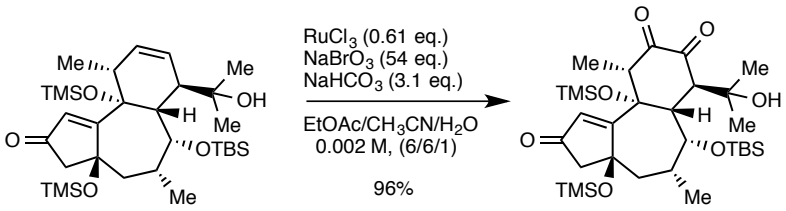
- Activation by cyclopropane occurs through electron donation of its C-C σ bonding orbital to neighboring C-H σ antibonding orbitals.
- Proper orbital overlap is required in order for activation through cyclopropane hyperconjugation.
- Hindered C-H bonds can experience reduced rates of oxidation.





Angew. Chem. Int. Ed. **2011**,50, 3362.

Notable steps: 1,2 –Diketone



0.103 g scale

Evaluated conditions were reported by The Baran Laboratory Blog:

PCC or PDC, MS4A, DCM, 0 C or rt, not scalable (<1 mg), nonreproducible
PCC or PDC, Celite, DCM, 0 C or rt,not clean, not scalable, nonreproducible
PCC or PDC, Al2O3 (neutral or basic), DCM, 0 C or rt, not clean
PCC or PDC, SiO2, DCM, clean but different product
PCC or PDC, Fluorisil, DCM, not scalable, nonreproducible

IBX, DMSO, rt, 40 C or 60C, not clean, slow
TFAA, DMSO, Et3N, DCM, -78 C to rt, alpha-hydroxyketone (low conversion)
PySO3, DMSO, Et3N, DCM, 0 C to rt, no reaction
DMP, DCM, no reaction at rt, complex mixture at 40 C
4-acetamido TEMPO, PTSA, DCM, 0 C to rt, no reaction
TPAP, NMO, MS4A, DCM, no desired product
CrO3, 3,5-DMP, DCM, 0 C to rt, diketone, not clean

OsO4 (in t-BuOH), DCE, 40 C, then, TBHP, DCE, no reaction
OsCl3, oxone, NaHCO3, EtOAc/MeCN/water (6:6:1), no reaction
OsCl3, oxone, EtOAc, water, no reaction

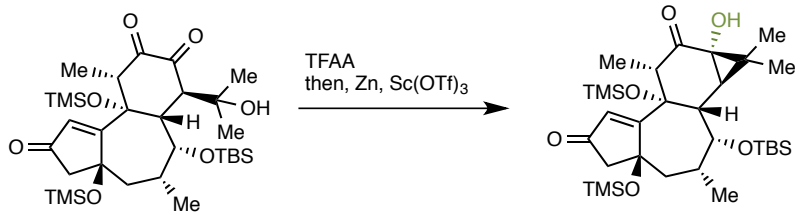
KMnO4, Ac2O, 0 C to rt, epoxide (quant)
KMnO4, MeCN, rt or 60 C, no reaction
KMnO4, acetone, rt or 60 C, no reaction
KMnO4, MeCN, then left on TLC, SM, diketone, alpha-hydroxyketone, epoxide
KMnO4, SiO2, MeCN, no reaction
KMnO4, CuSO4, DCM/water, no reaction
KMnO4, CuSO4, DCM/t-BuOH/water, epoxide
KMnO4, t-BuOH, no reaction
KMnO4, acetone/AcOH/H2O, no reaction
KMnO4, AC2O/MeCN, expoxide

RuCl3, oxone, NaHCO3, EtOAc/MeCN/water (6:6:1), 0 C, rt, 40 C, or 60 C, alphahydroxykeone, diketone, not clean
RuCl3, NaIO4, NaHCO3, EtOAc/MeCN/water (6:6:1), not clean
RuCl3, oxone, NaHCO3, EtOAc//water (6:1), not clean
RuCl3, oxone, NaHCO3, tBuOH/MeCN/water (6:6:1), not clean
RuCl3, oxone, NaHCO3, DCM/MeCN/water (6:6:1), not clean
RuCl3, oxone, NaHCO3, diethylcarbonate/MeCN/water (6:6:1), alpha-hydroxyketone, diketone
RuCl3, oxone, NaHCO3, EtOAc/acetone/water (6:6:1), alpha-hydoxyketone, diketone
RuCl3, oxone, NaHCO3, EtOAc/MeCN/water (6:6:1), alpha-hydroxyketone, diketone
RuCl3, oxone, NaHCO3 (excess), EtOAc/MeCN/water (6:6:1), slow, alpha-hydroxyketone, diketone
RuCl3, oxone, NaHCO3, EtOAc/acetone/water (6:6:1), alpha-hydoxyketone, diketone
RuCl3, oxone, NaHCO3, EtOAc/MeCN/water (1:1:1), not clean
RuCl3, oxone, NaHCO3, EtOAc/MeCN/water (36:36:1), diketone (0.5 mg scale, quant.), not scalable
RuCl3, oxone, NaHCO3, EtOAc/MeCN/water (36:36:1), reagents made first, fast, slightly messier
RuCl3, oxone, NaHCO3, EtOAc/acetone/water (36:36:1), alpha-hydroxyketone, diketone, not clean
RuCl3, oxone, EtOAc/MeCN/water (72:72:1), not clean

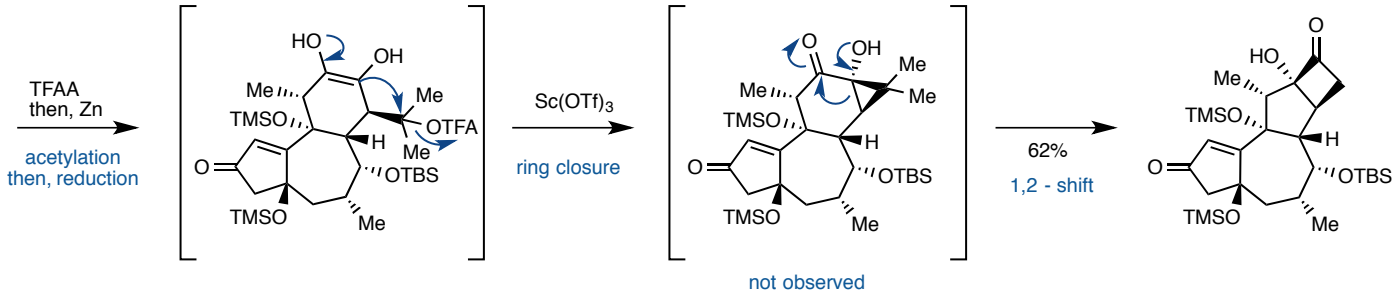
RuCl3, oxone, NaHCO3, EtOAc/MeCN/water (6:6:1), alpha-hydroxyketone, diketone, not clean, not scalable
RuCl3, oxone, NaHCO3, EtOAc/MeCN/water (6:6:1), -20 C to -15 C, diol, alpha-hydroxyketone
RuCl3, oxone, NaHCO3, EtOAc/MeCN/water (6:6:1), 0 C, diol, alpha-hydroxyketone, diketone
RuCl3 (excess), oxone, NaHCO3, EtOAc/MeCN/water (6:6:1), diketone (major), alpha-hydroxyketone
RuCl3 (excess), oxone (excess), NaHCO3, EtOAc/MeCN/water (6:6:1), diketone, not scalable, nonreproducible
RuCl3, NaIO4, NaHCO3, EtOAc/MeCN/water (6:6:1), 0 C, no desired product
RuCl3, oxone, NaHCO3, EtOAc/water (3:1), complex mixture

RuCl3, NaBrO3, NaHCO3, EtOAc/MeCN/water (6:6:1), 0.001 M, diketone (quant.)
RuCl3, NaBrO3, NaHCO3, EtOAc/MeCN/water (6:6:1), 0.004 M, diketone, slightly messier than 0.001 M
RuCl3, NaBrO3, NaHCO3, EtOAc/MeCN/water (6:6:1), 0.008 M, slow, diketone, slightlymessier than 0.001 M
RuCl3, NaBrO3, NaHCO3, EtOAc/MeCN/water (6:6:1), 0.01 M, slow, not clean, diketone, low conversion
RuCl3, NaBrO3, NaHCO3, EtOAc/MeCN/water (6:6:1), 0.02 M, slow, not clean, diketone, low conversion
RuCl3, NaBrO3, NaHCO3, EtOAc/MeCN/water (6:6:1), 0.001M, low conversion, diketone

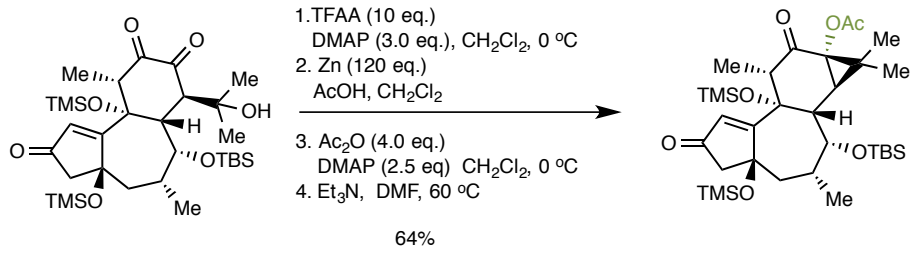
Notable steps: Reforming the cyclopropane ring



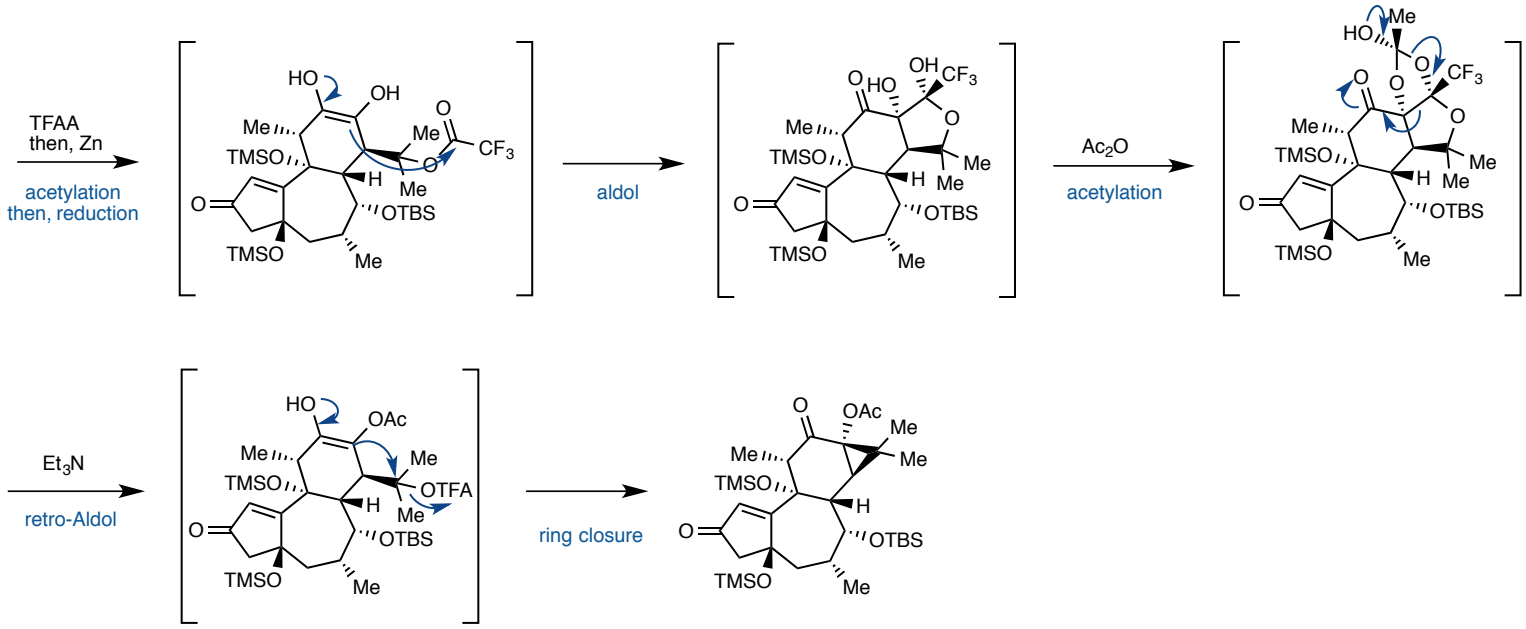
Alternative product

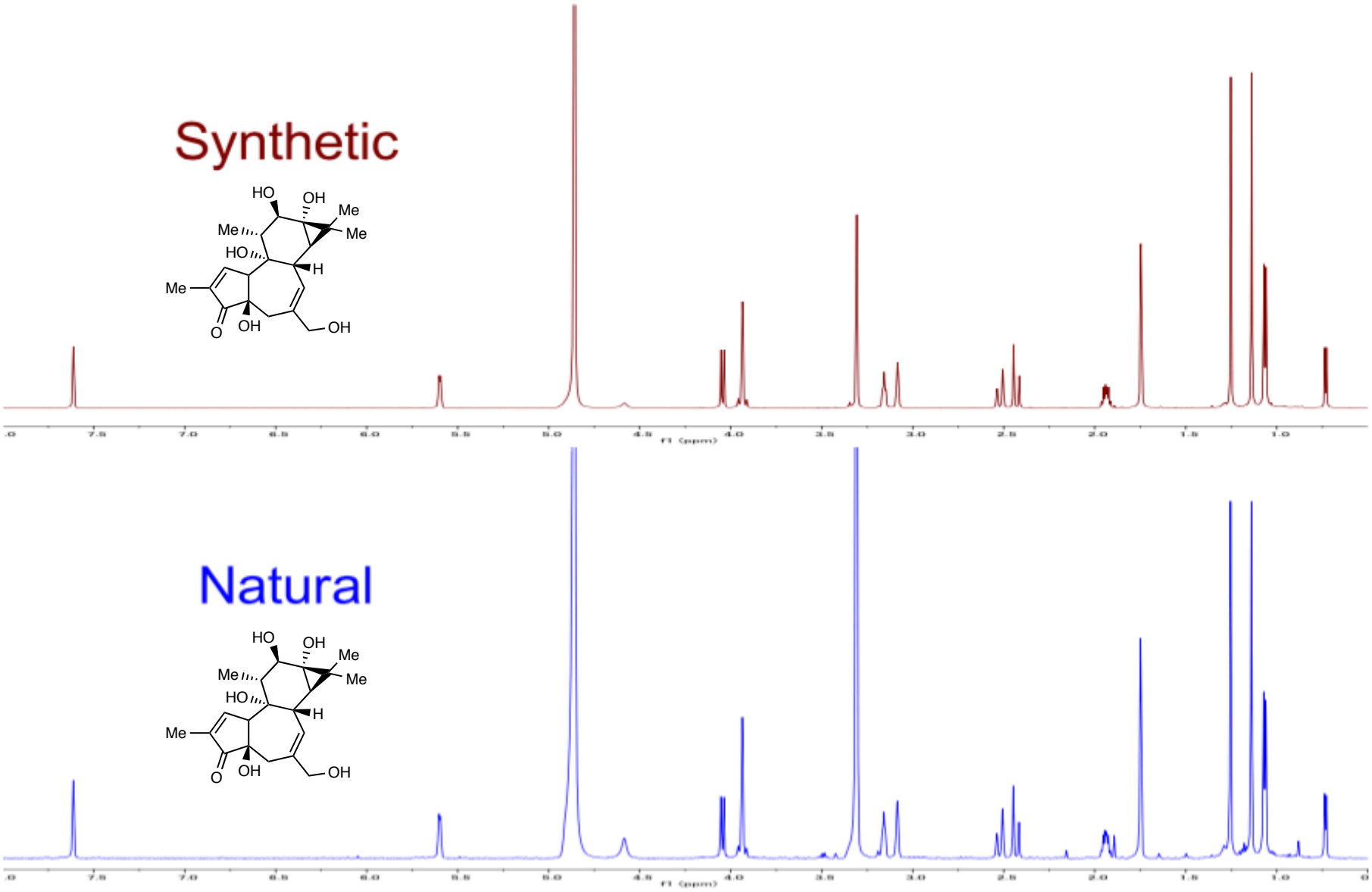


Notable steps: Reforming the cyclopropane ring



Desired product




Synthetic
HO
OH
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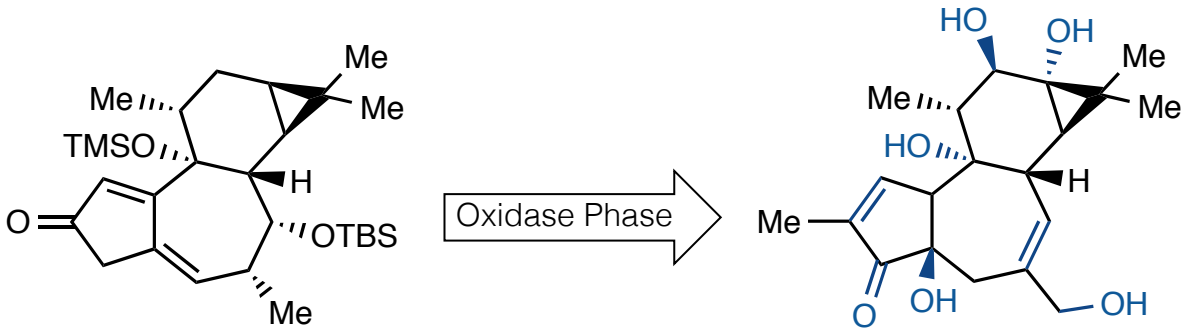
OH



Advanced Intermediate [1]

(+) – Phorbol [2]

Conclusions

- Accomplished an enantiospecific total synthesis of (+) – Phorbol in 19 steps.
- Demonstrated an effective, symbiotic relationship between an academic organic chemist and a pharmaceutical company in a collaborative pursuit toward a complex natural product synthesis.