Progress in the Total Synthesis of Cyclic Natural Products

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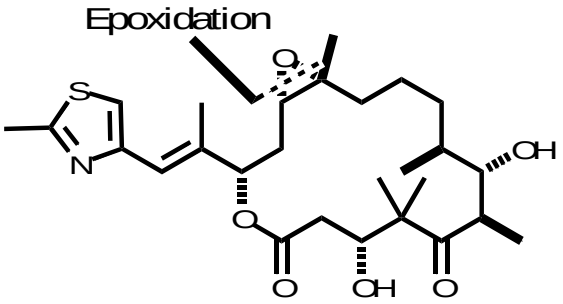
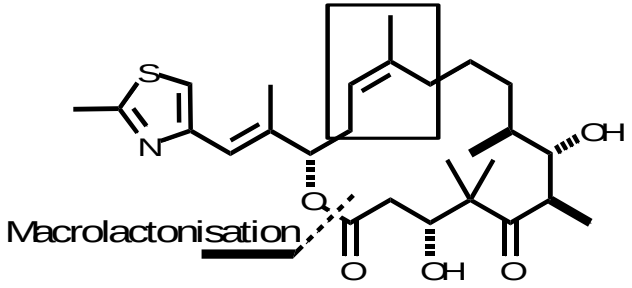
IASOC 2006

Part 1:
The (Z)-12,13-double bond in epothilone B

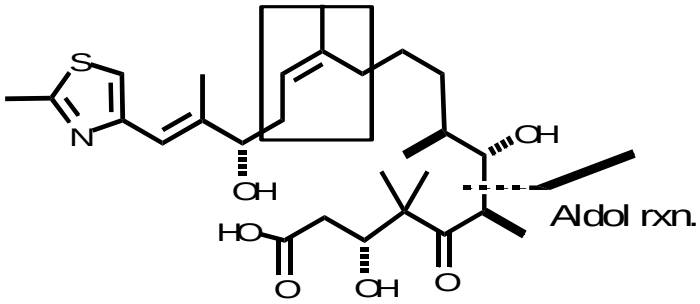
Retrosynthetic analysis



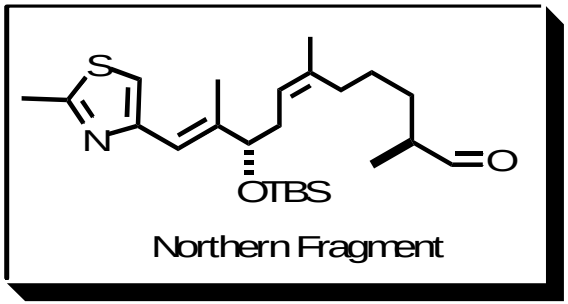
Epothilone B

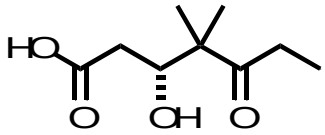


Epothilone D



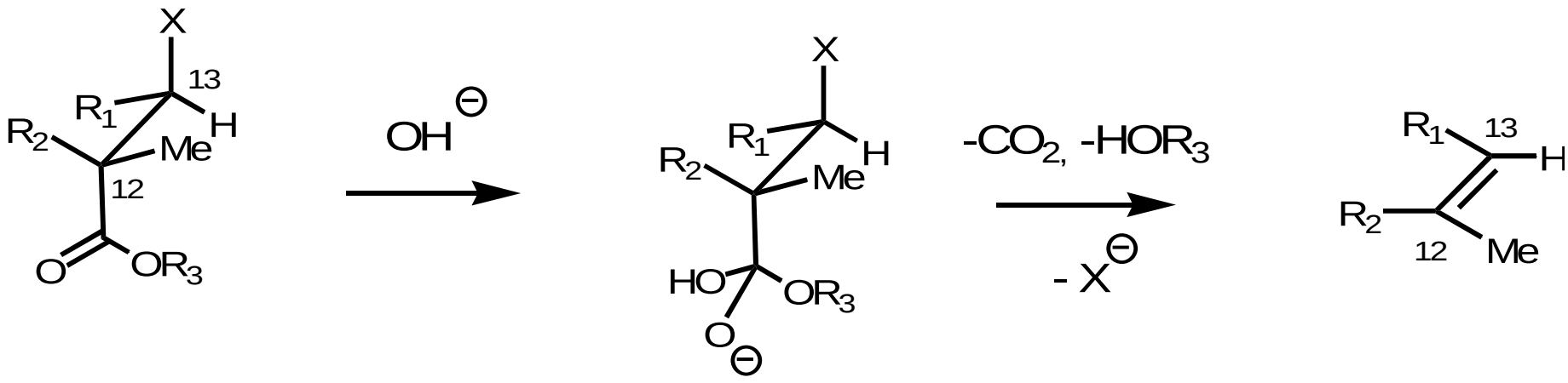
Epothilone B
seco acid

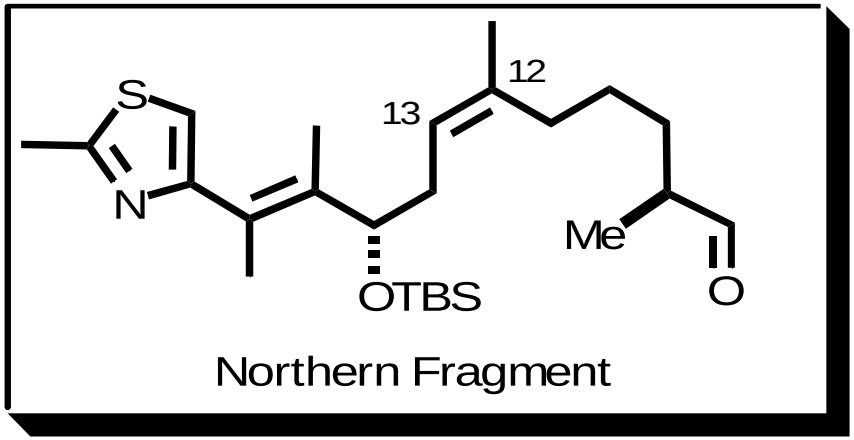




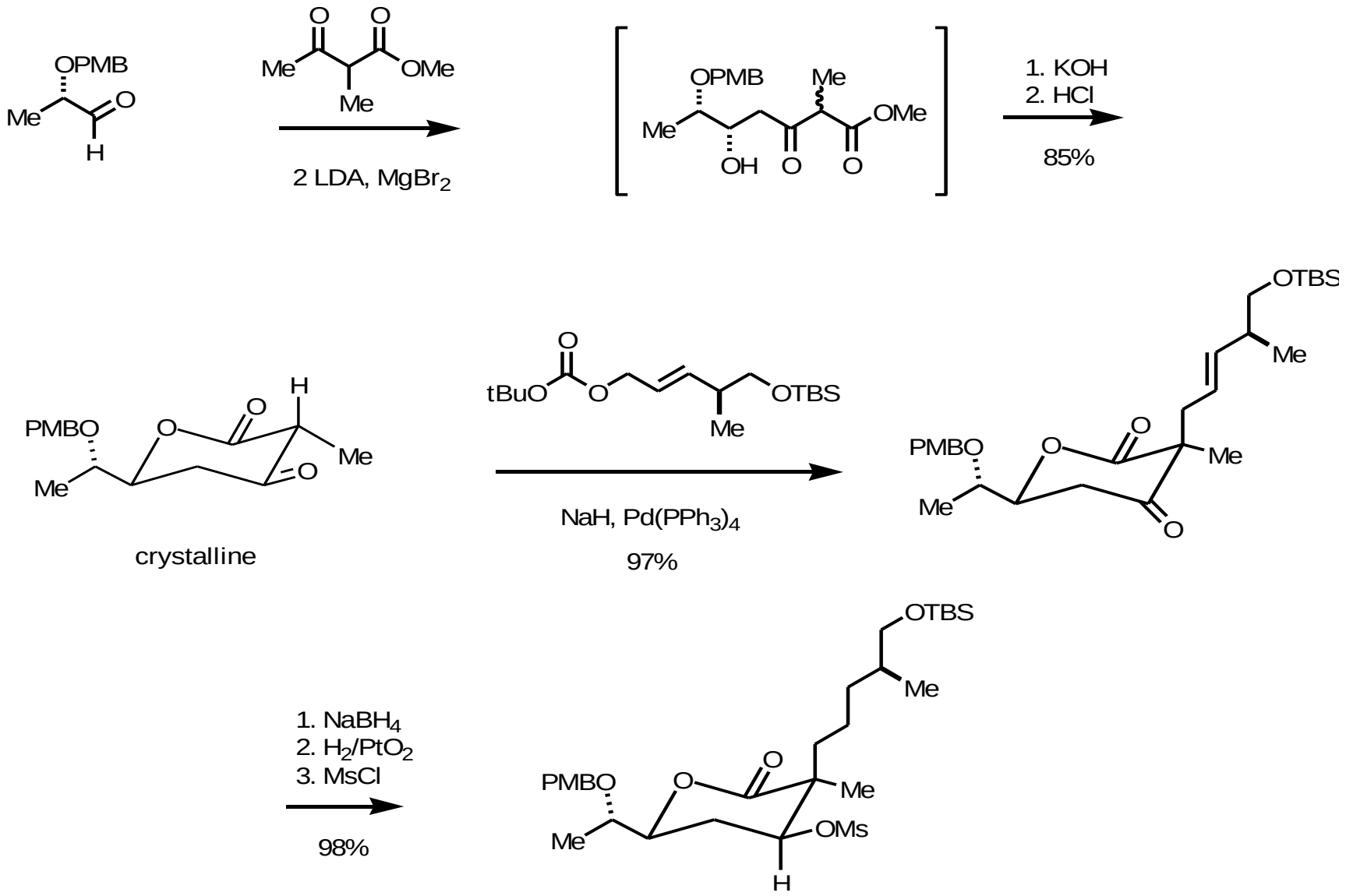
Southern Fragment

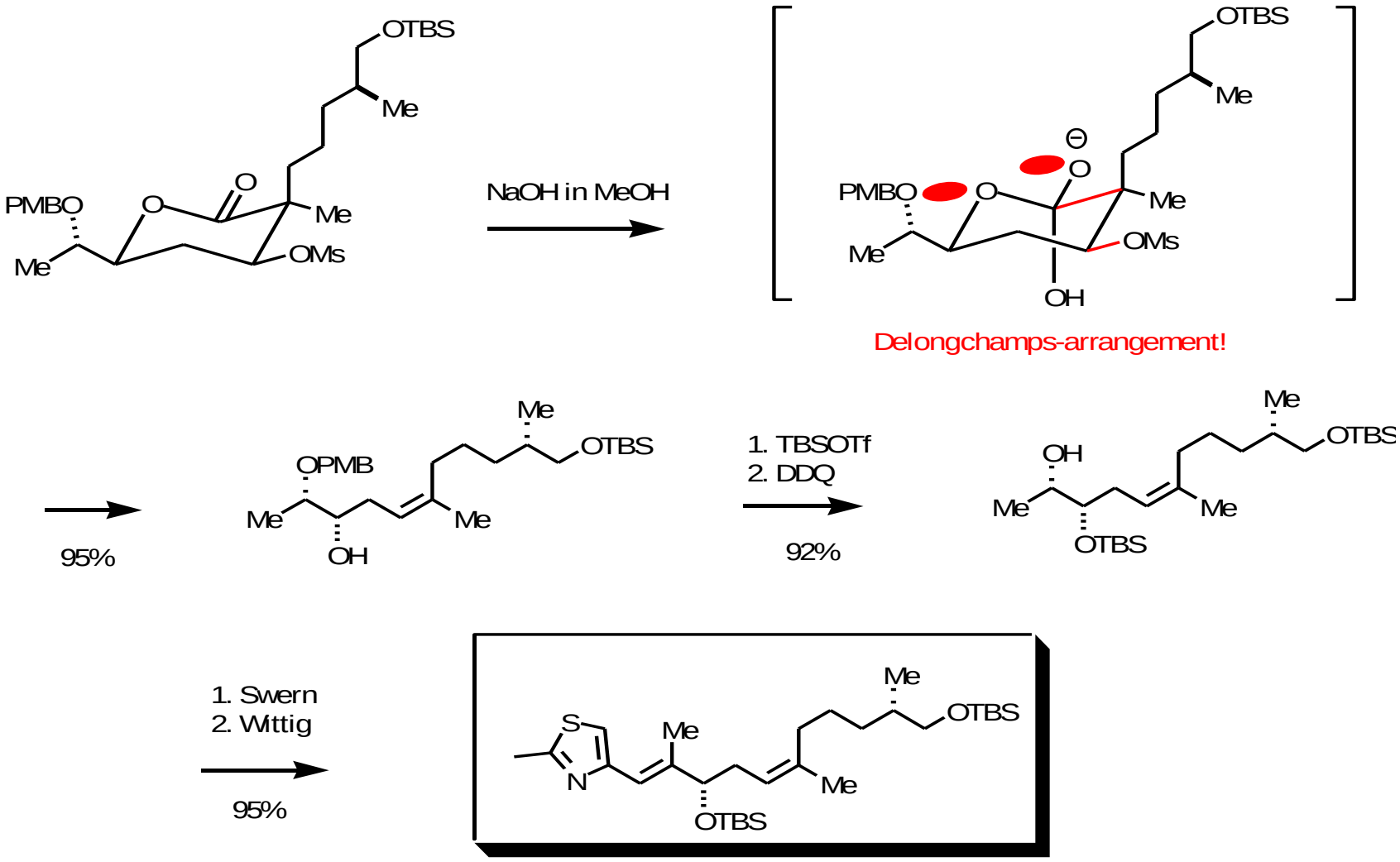
A novel concept: fragmentation of -hydroxy-esters





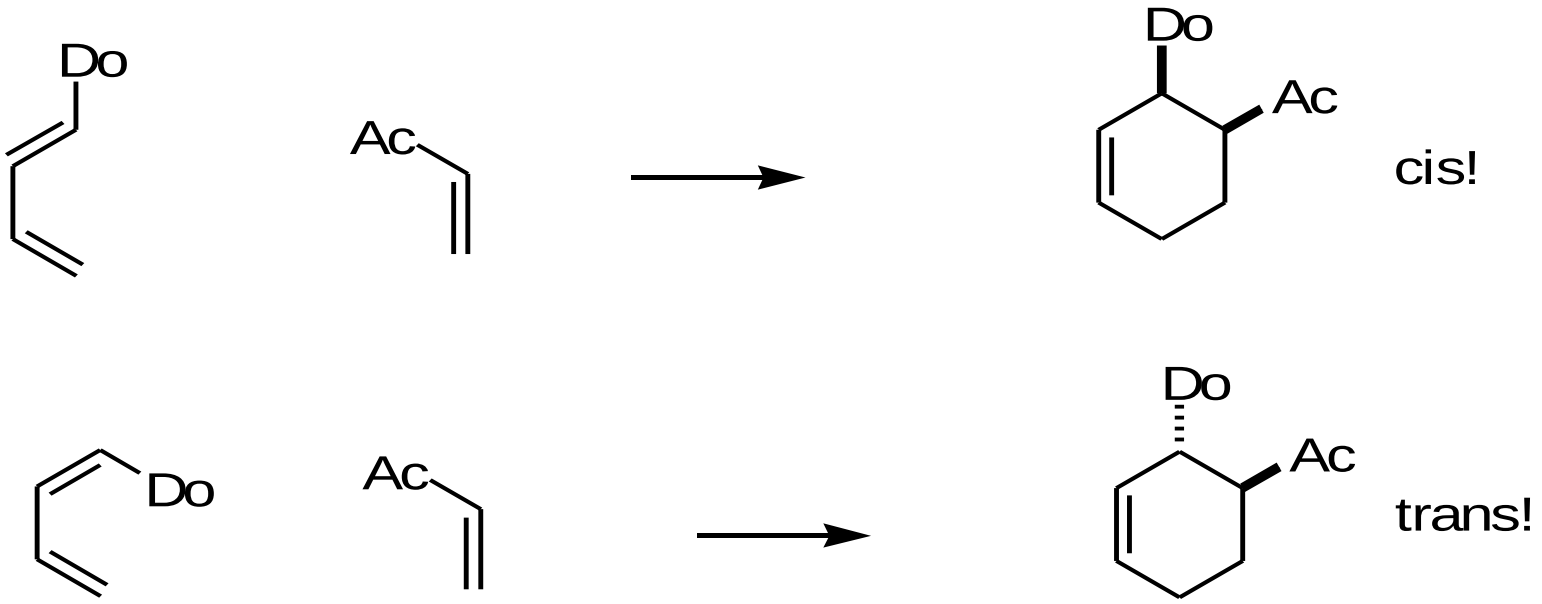
To enforce antiperiplanar geometry, better use a cyclic template !





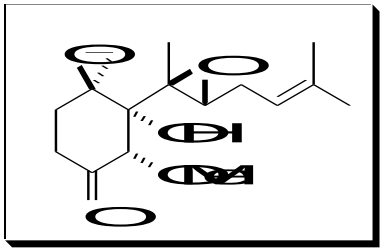
10 steps, overall yield 67%

Part 2: Diels-Alder-Reactions: the *endo*-principle

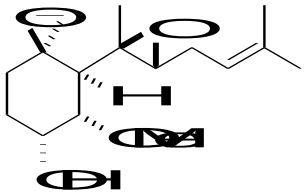


endo-selectivity:
acyclic < *IMDA* < *TADA*
in general increase with Lewis-acid catalysis

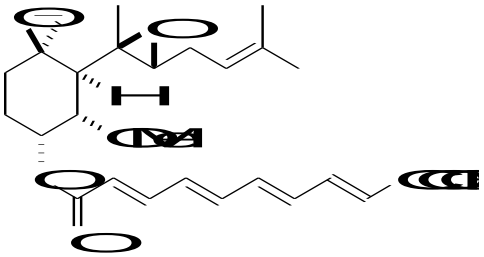
Diels Alder Approach Towards (-)-Ovalicin



(-)-Ovalicin



(-)-Fumagillol



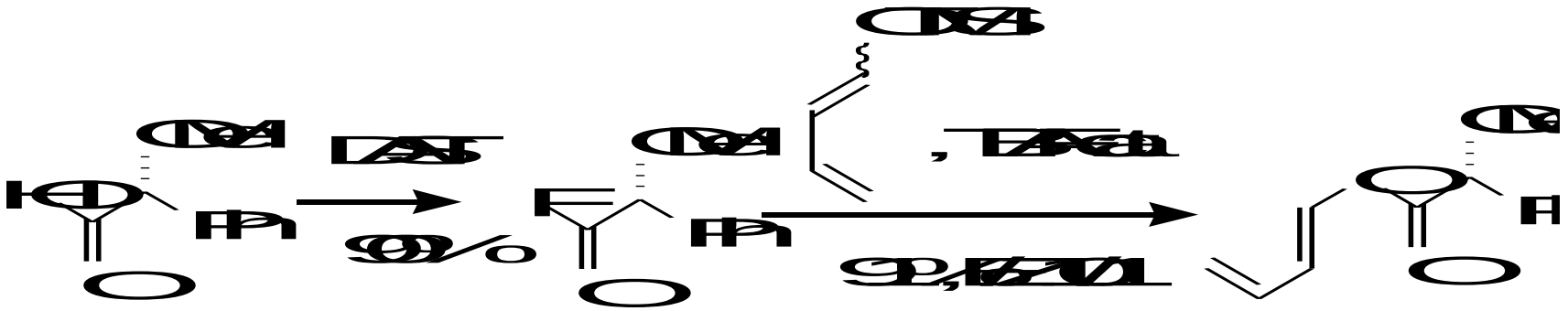
(-)-Fumagillin

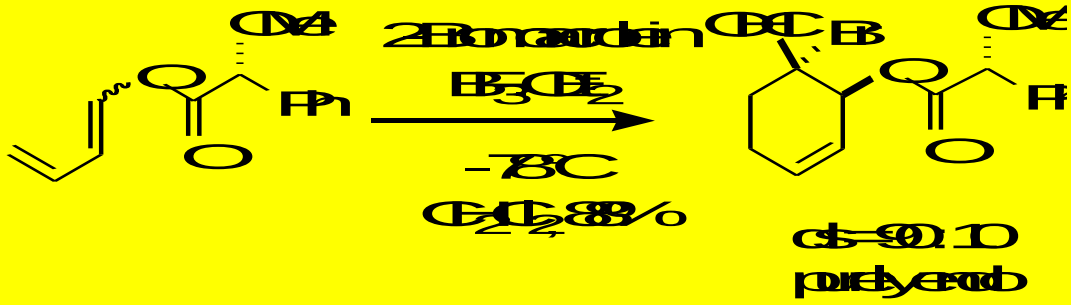
- Ovalicin: first isolated from fungus *Pseudorotium ovalis* Stolk[1] in 1968
- Antibiotic, antitumor and immunosupressive activity[2]
- Potent anti-angiogenic activity, stable, nontoxic and more potent as Fumagillol[3]

[1] Sigg et al. *Helv. Chim. Acta* 1968, *51*, 1395; [2] Zimmerman et al. *Eur. J. Biochem.* 1981, *118*, 143; [3] Ingber et al. *Nature* 1990, *348*, 555.

Auxiliary-controlled Diels Alder Reaction

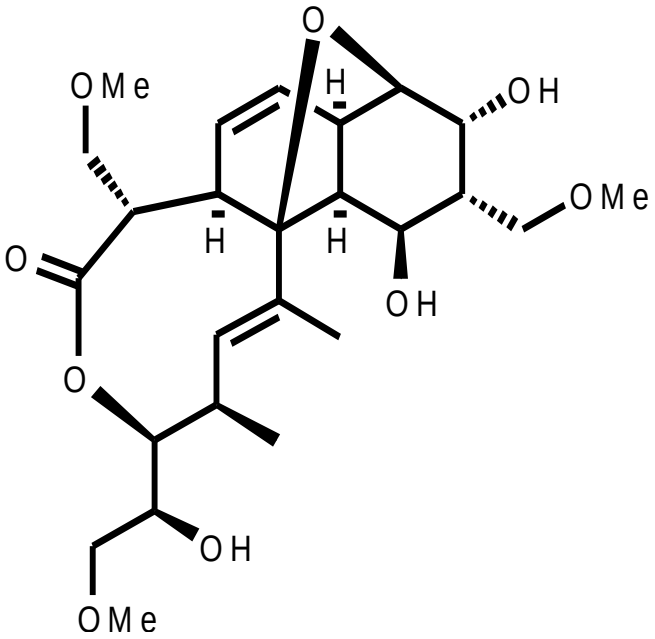
Trost's diene





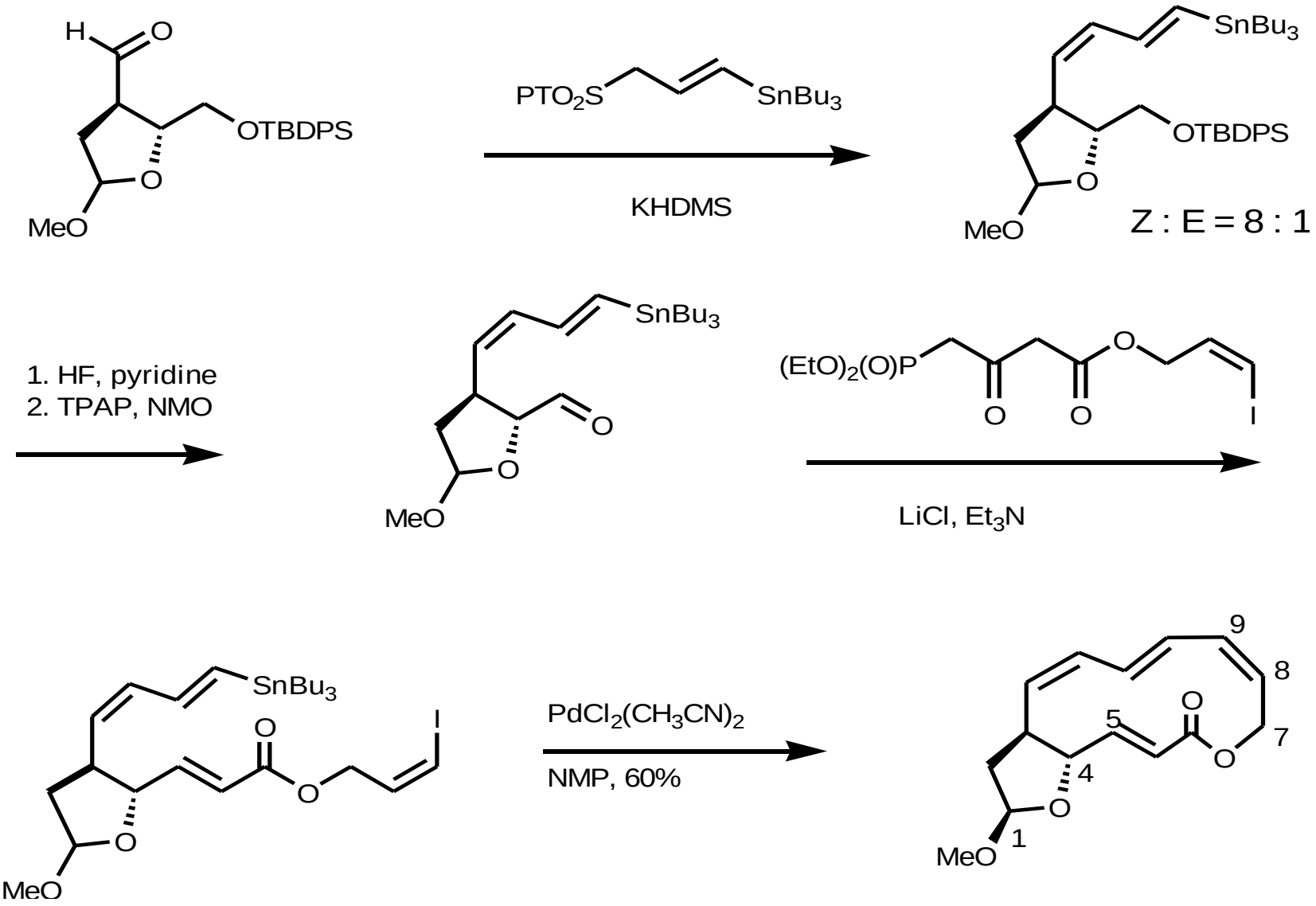
no reaction with bromoacrylic acid ester (DCM, up to rt) !

Branimycin

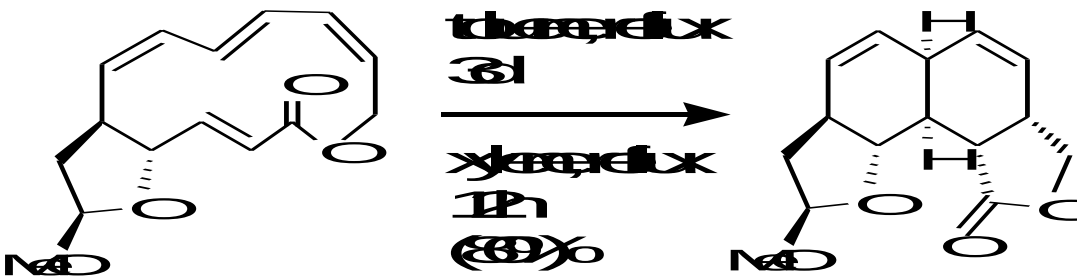


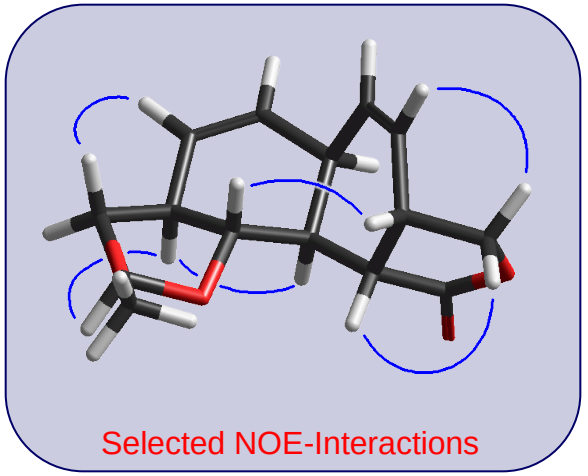
- Isolated by the Laatsch group at the Universität Göttingen
- Highly active against *streptomyces viridochromogenes*
- structurally related to Nargenicin antibiotics

Synthesis of the TADA-precursor



TADA!

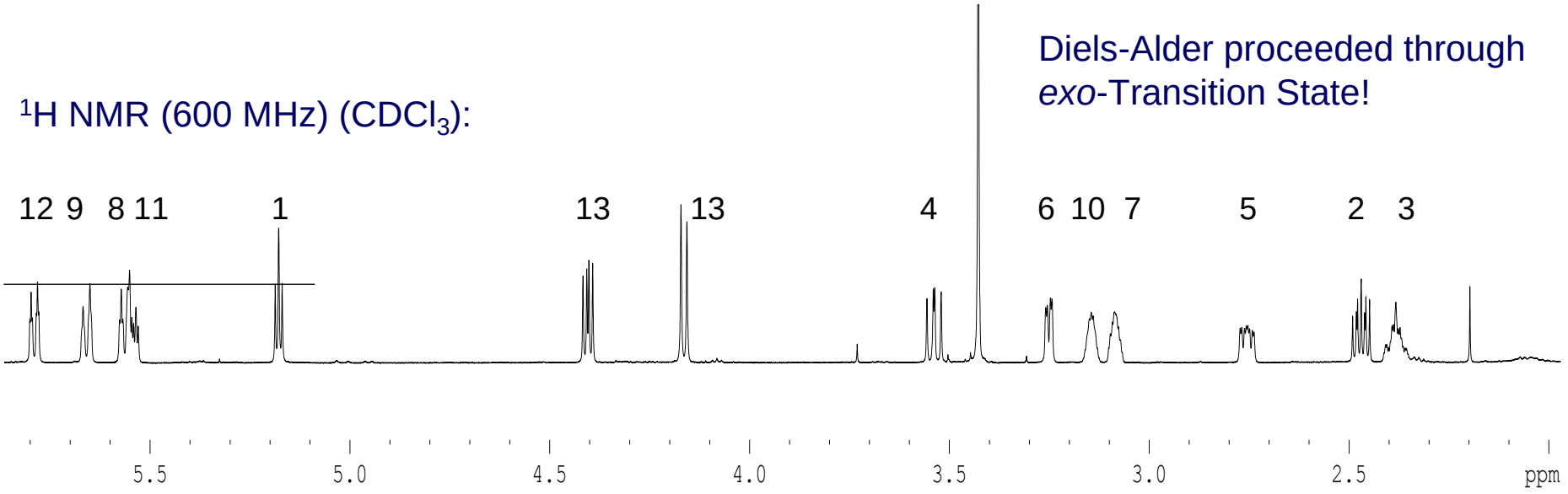




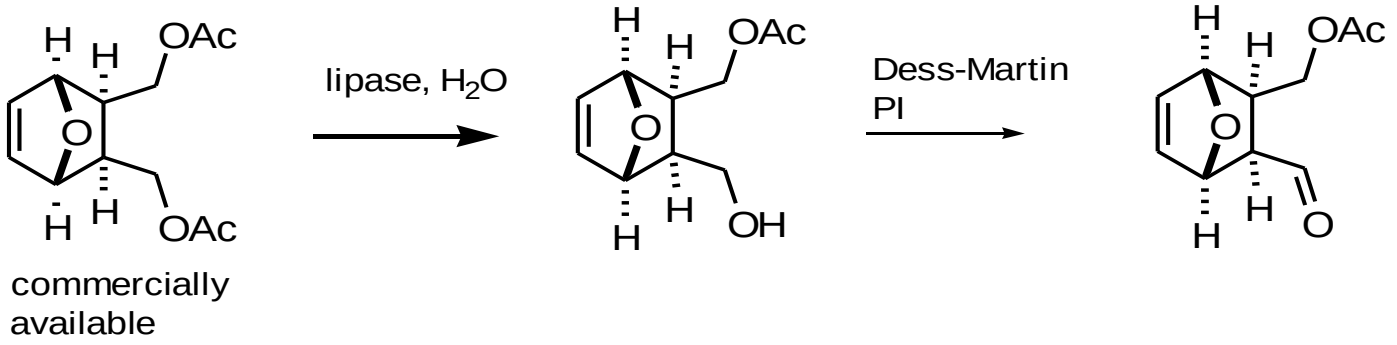
$J_{5,10}$ = 6 Hz

Diels-Alder proceeded through *exo*-Transition State!

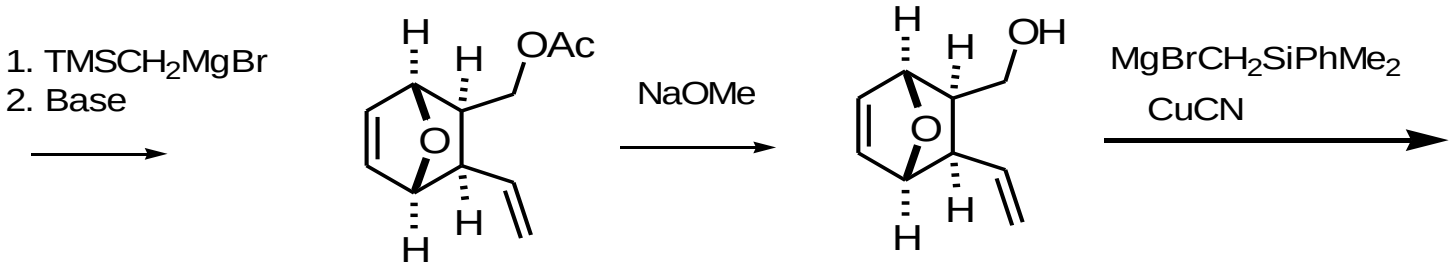
^{1}H NMR (600 MHz) ($CDCl_3$):

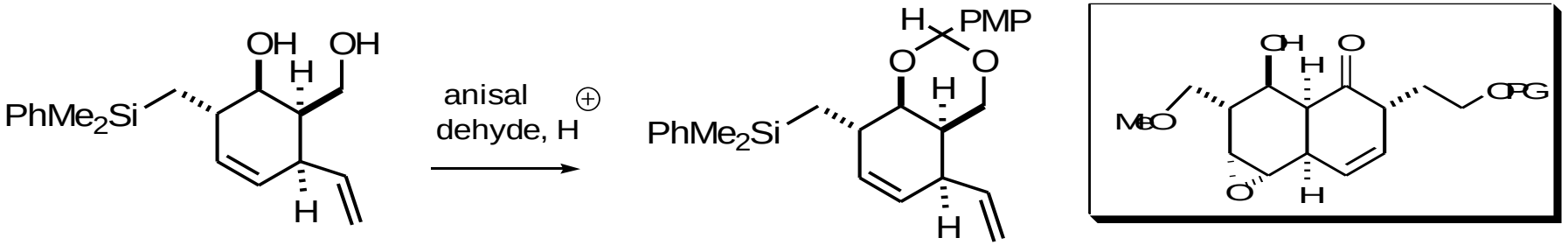


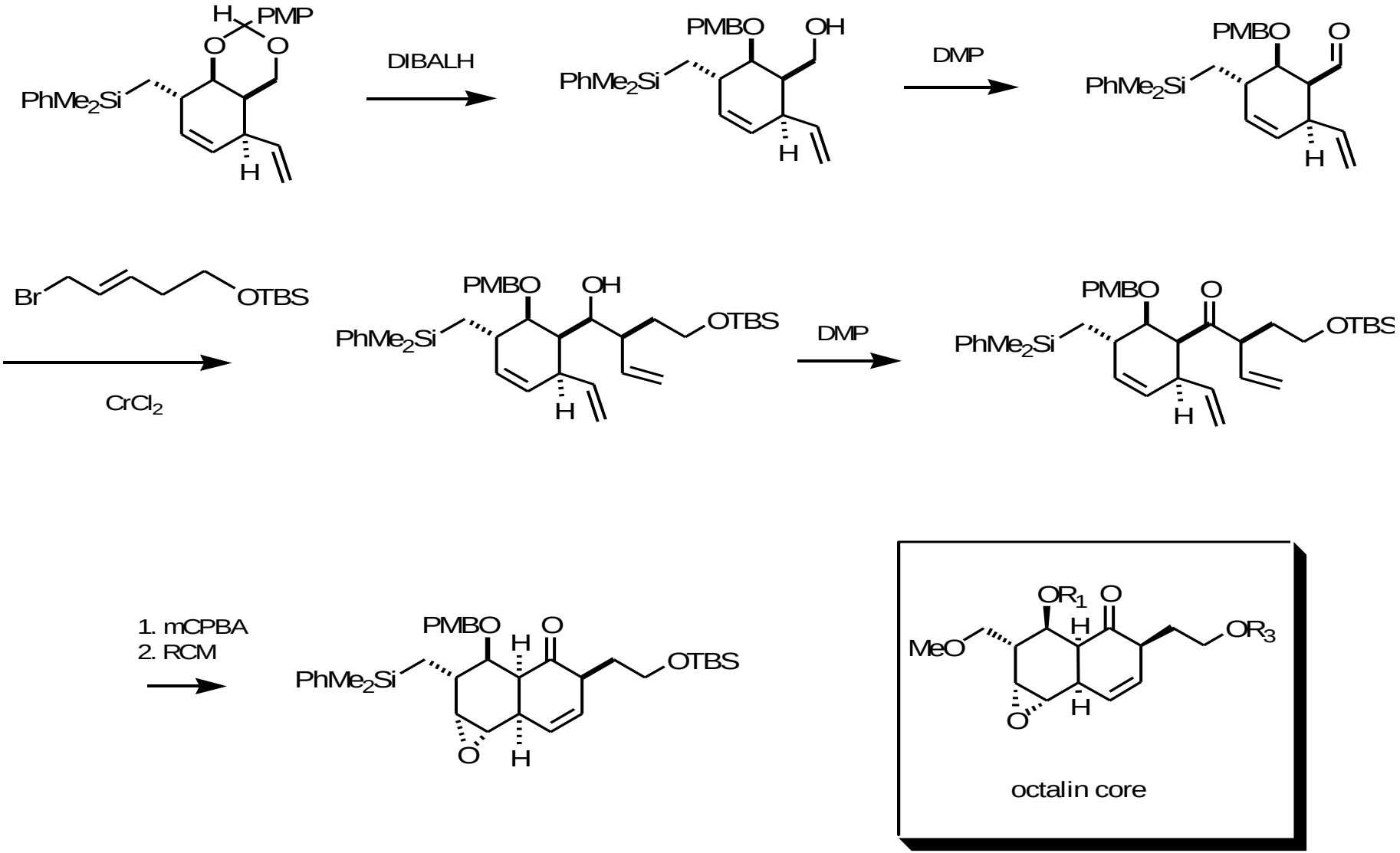
Shorter Access via Desymmetrization



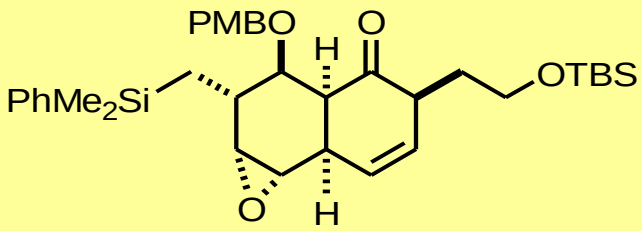
commercially available

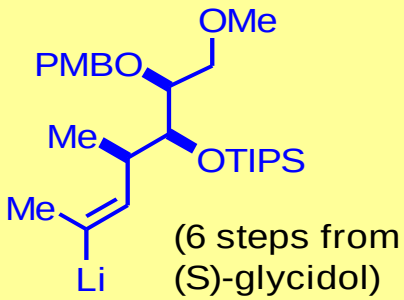




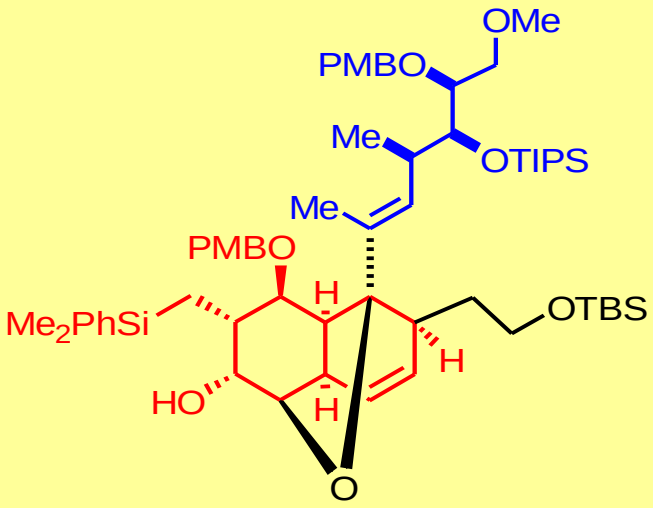

H
PMP
O
O
PhMe2Si
H
DIBALH
PMBO
OH
PhMe2Si
H
DMP
PMBO
O
PhMe2Si
H
Br
OTBS
CrCl2
PMBO
OH
PhMe2Si
OTBS
H
DMP
PMBO
O
PhMe2Si
OTBS
H
1. mCPBA
2. RCM
PMBO
H
O
PhMe2Si
OTBS
O
H
OR1
O
MeO
H
OR3
O
H
octalin core

Coupling





LiCl



13 steps, ca 10% overall yield