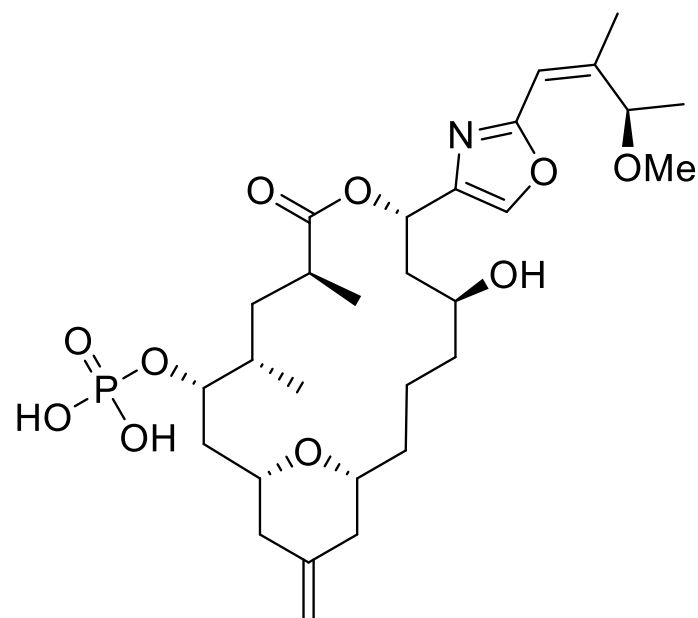


Total Synthesis of (–)-Enigmazole A¹



(–)-Enigmazole A

Presented by: Grace Hubbell

CEM 852

4/14/2018

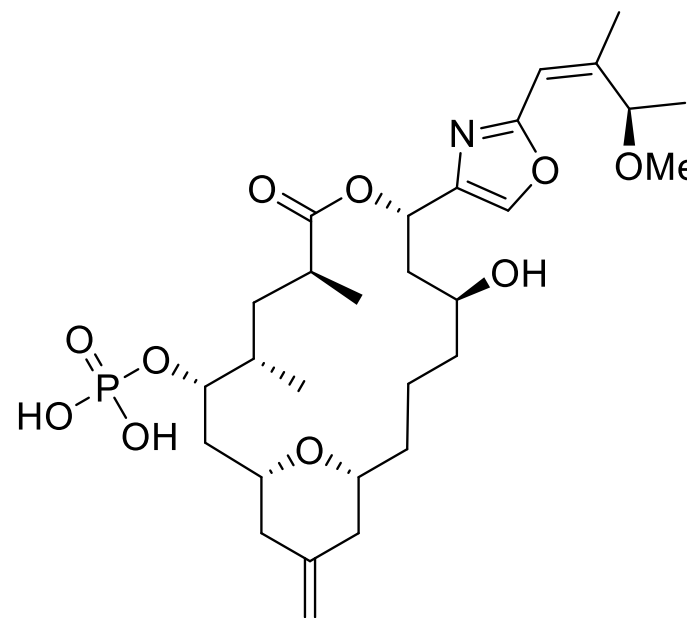
1. *J. Am. Chem. Soc.* **2015**, *137*,
15100–15100

Background

Marine macrolide isolated from the marine sponge *Cinachyrella enigmatica* in 2006.²

Cytotoxic towards NCI human tumor cell lines.³

First total synthesis achieved in 2010 by Molinski.⁴

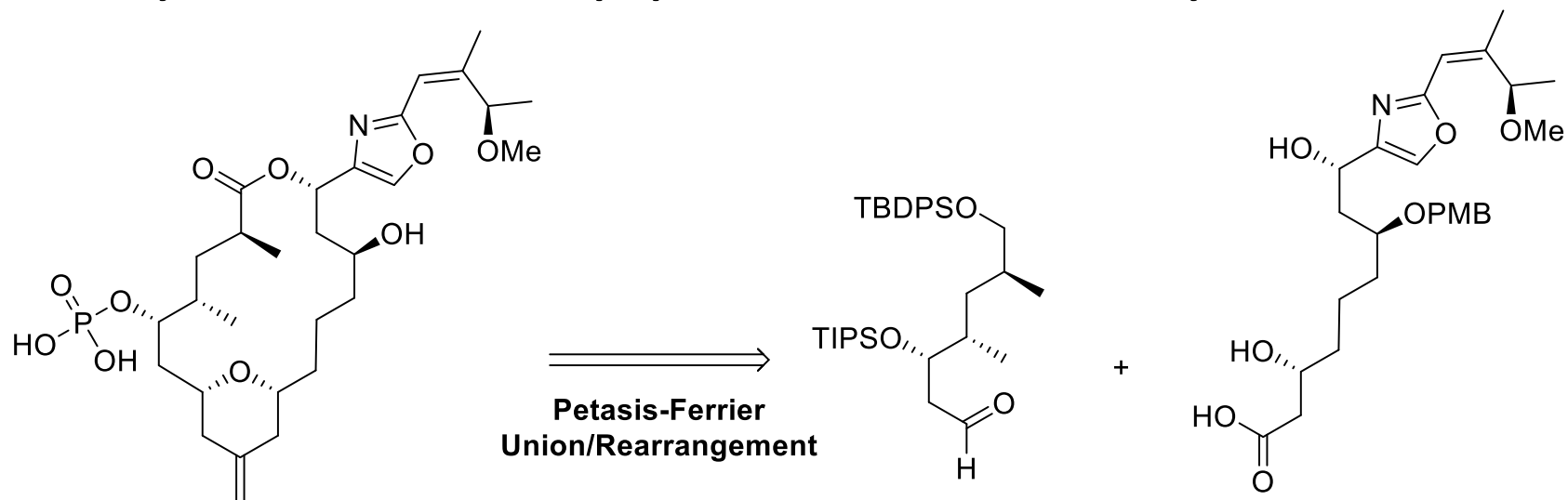


(±)-Enigmazole A

Oku, N.; Gustafson, K.R.; Fuller, R.W.; Wilson, J.A.; Panell, L.K.; McMahon, J.B. *Symposium on the Chemistry of Natural Products 2006*, 73.

Oku, N.; Takada, K.; Fuller, R.W.; Wilson, J.A.; Peach, M.L.; Panell, L.K.; McMahon, J.B.; Gustafson, K.R. *J. Am. Chem. Soc.* 2010, 132, 10070.

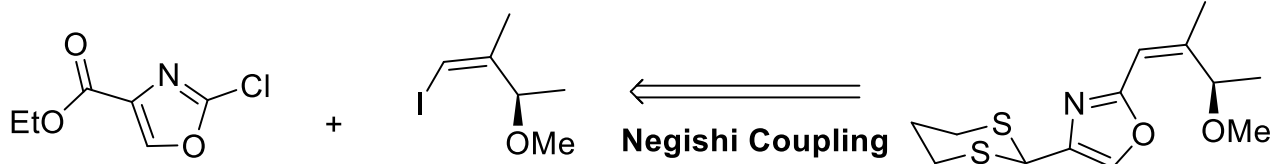
Retrosynthetic Approach & Key Reactions



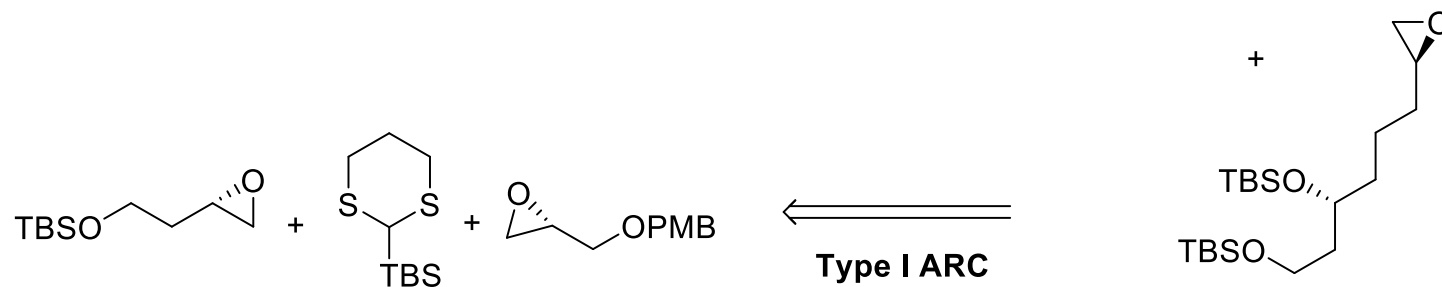
(-)-Enigmazole A

**Petasis-Ferrier
Union/Rearrangement**

Dithiane-Epoxyde Union



Negishi Coupling

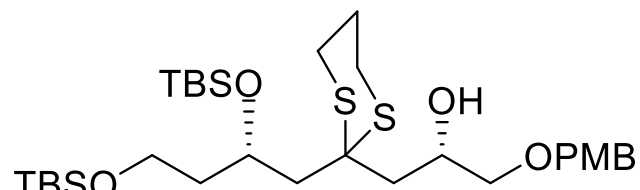


Type I ARC

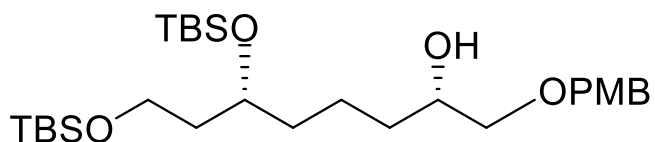
Preparation of Epoxide (–)-7

a) n-BuLi, Et₂O, 0°C
b) (–)-10, Et₂O, -30°C

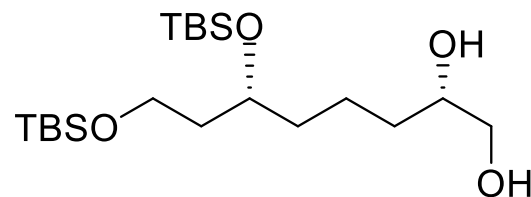
c) (–)-12, DMPU,
-78 °C to rt, 90%



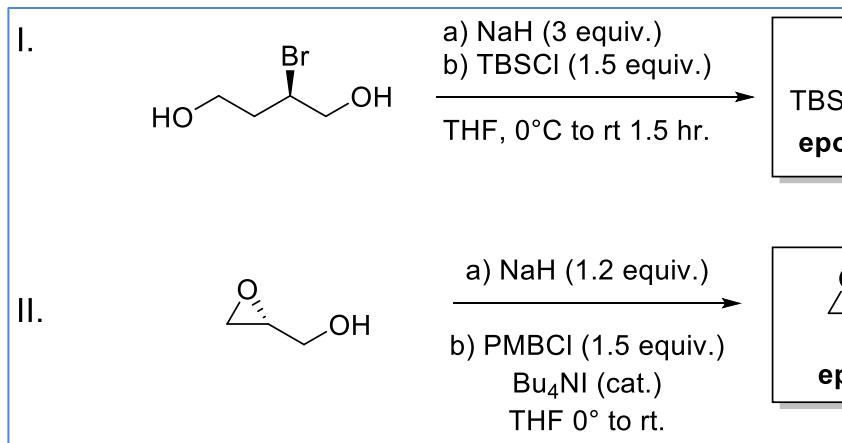
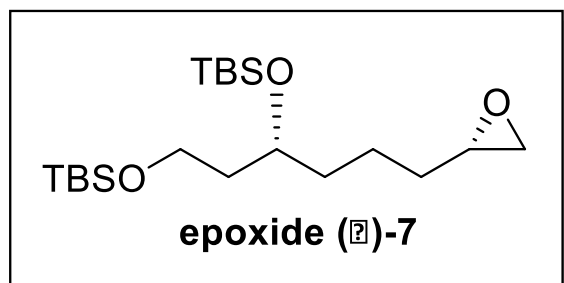
Raney Ni
(1 atm.)
THF, 80°C
95%



Raney Ni
H₂ (1 atm.)
EtOH, 80°C
87%



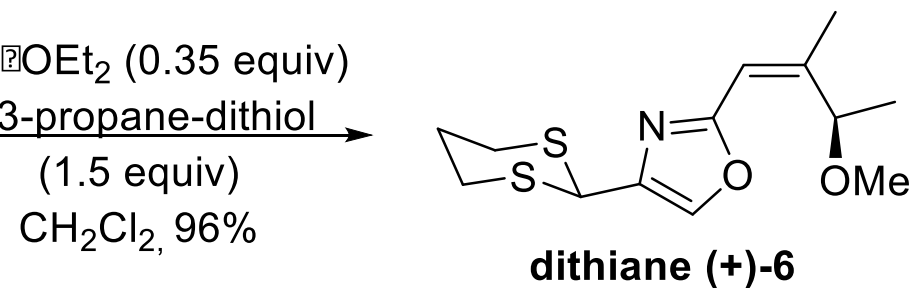
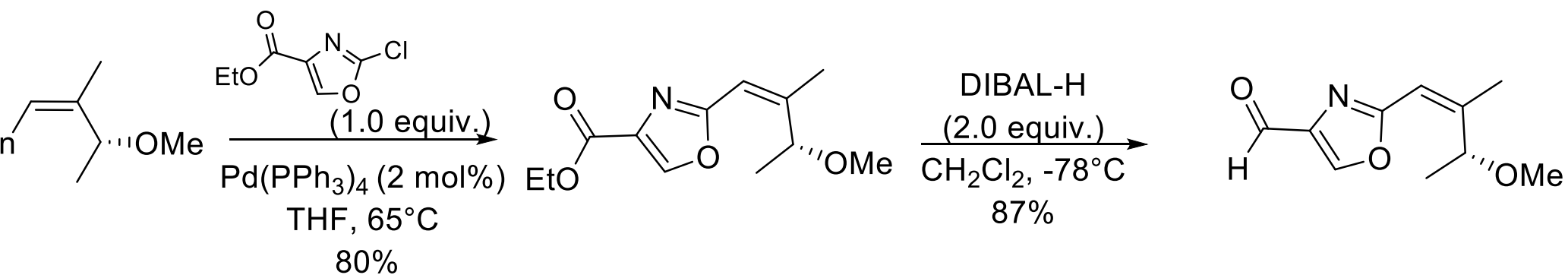
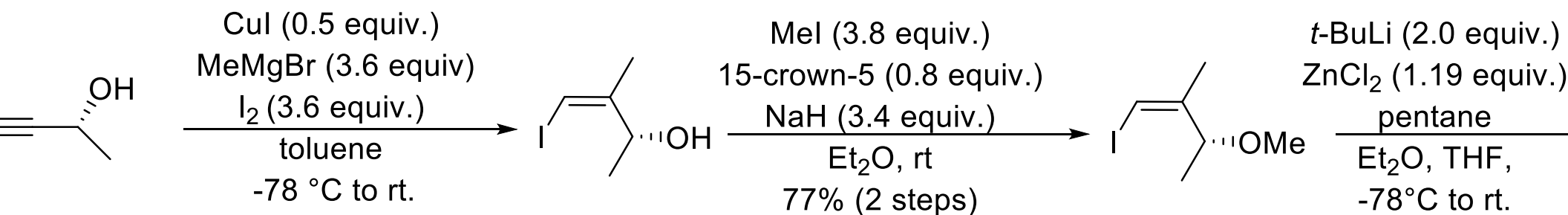
NaH (2.28 equiv.)
TBAI (1.2 equiv.)
THF, 0°C
quant.



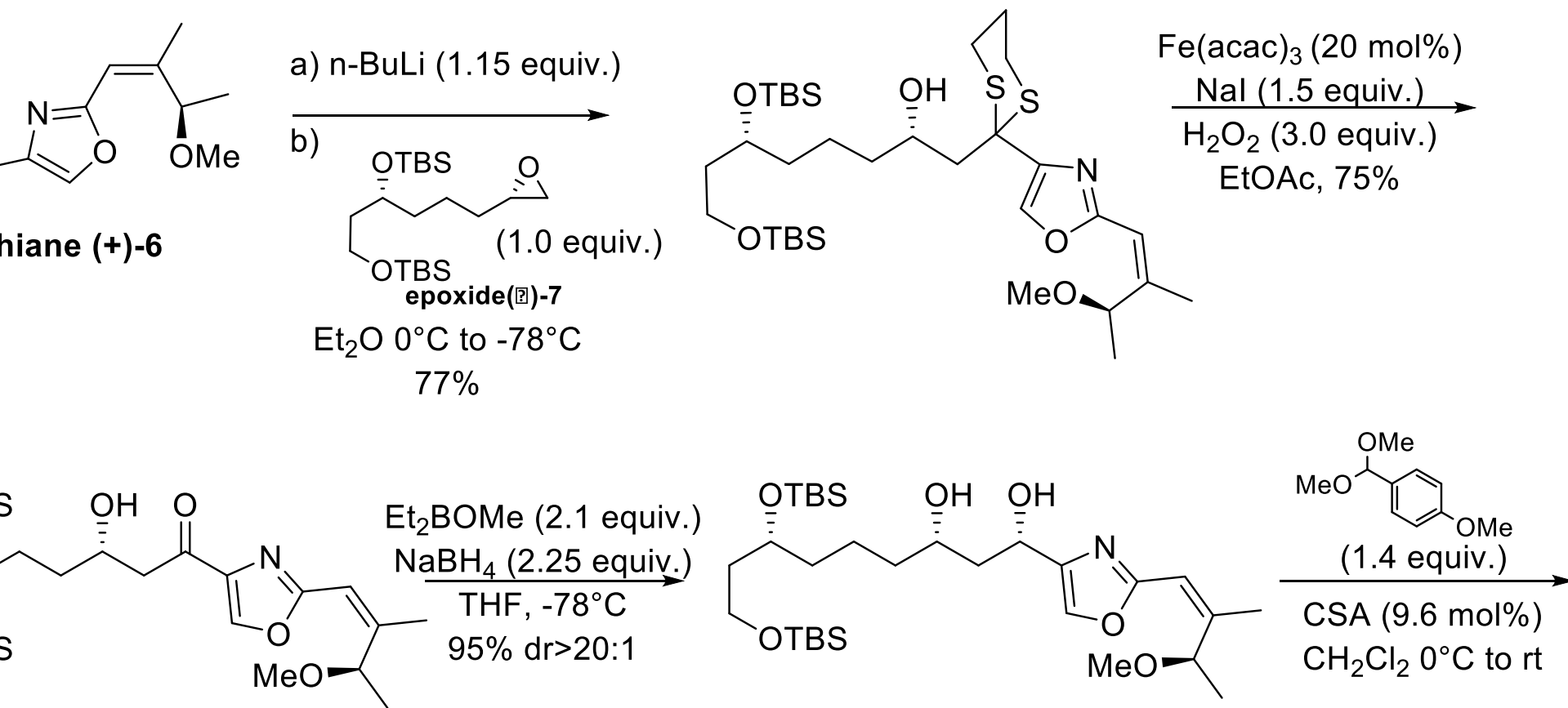
Chem. Eur. J. **2014**, *20*(30) 9336.

Chem. Eur. J. **2012**, *18*(52) 16868.

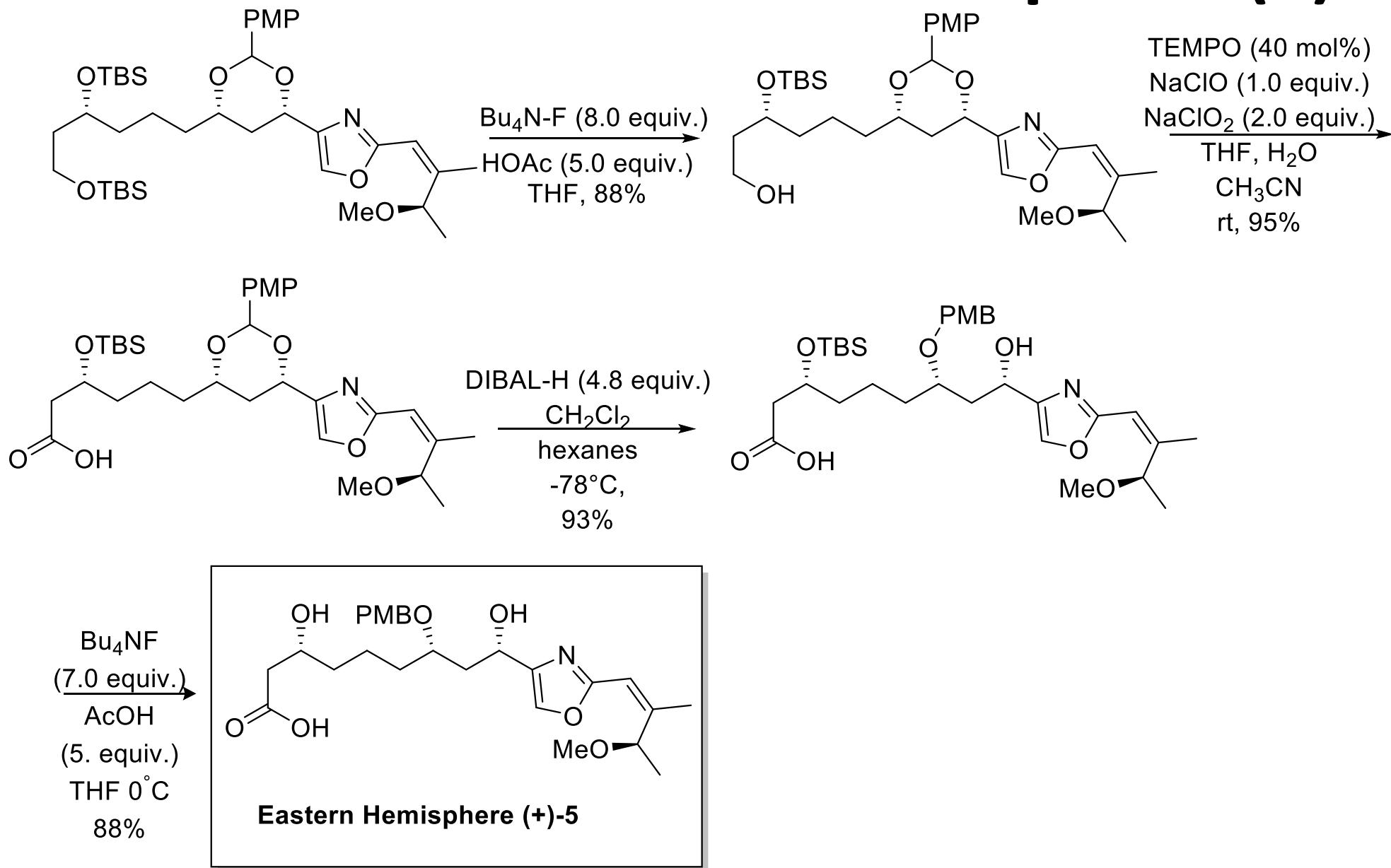
Preparation of **Dithiane (+)-6**



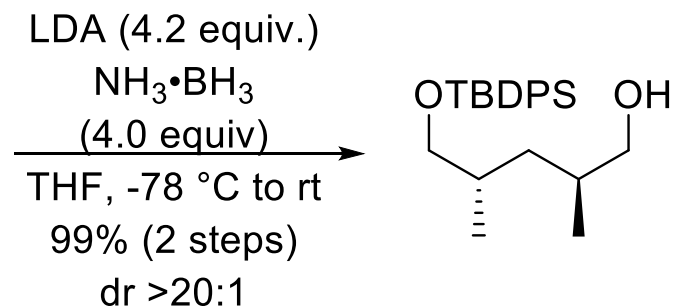
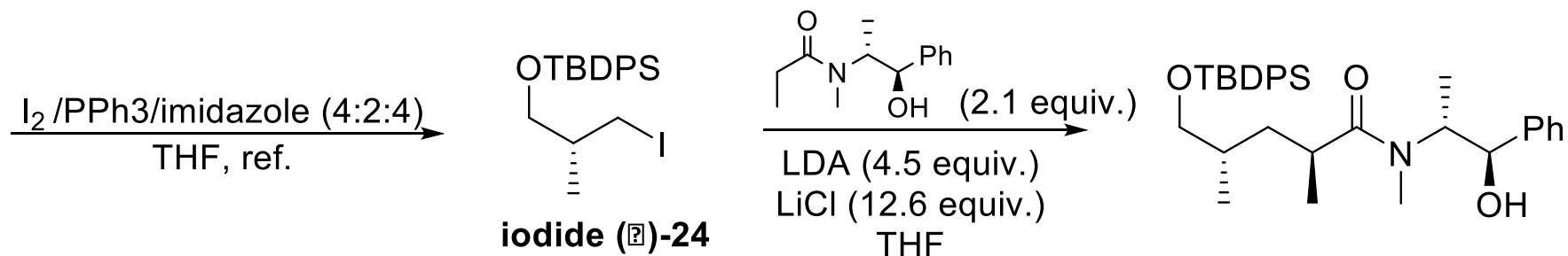
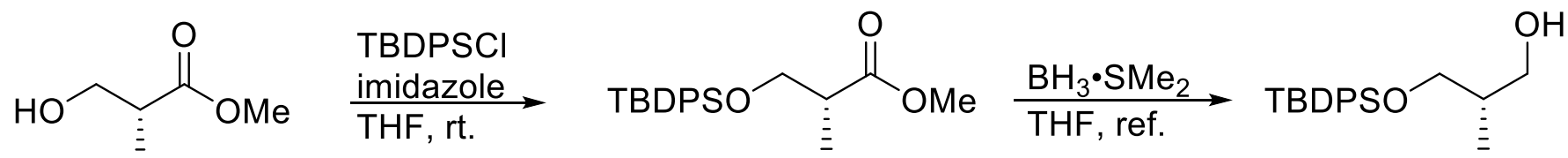
Construction of Eastern Hemisphere (+)-5



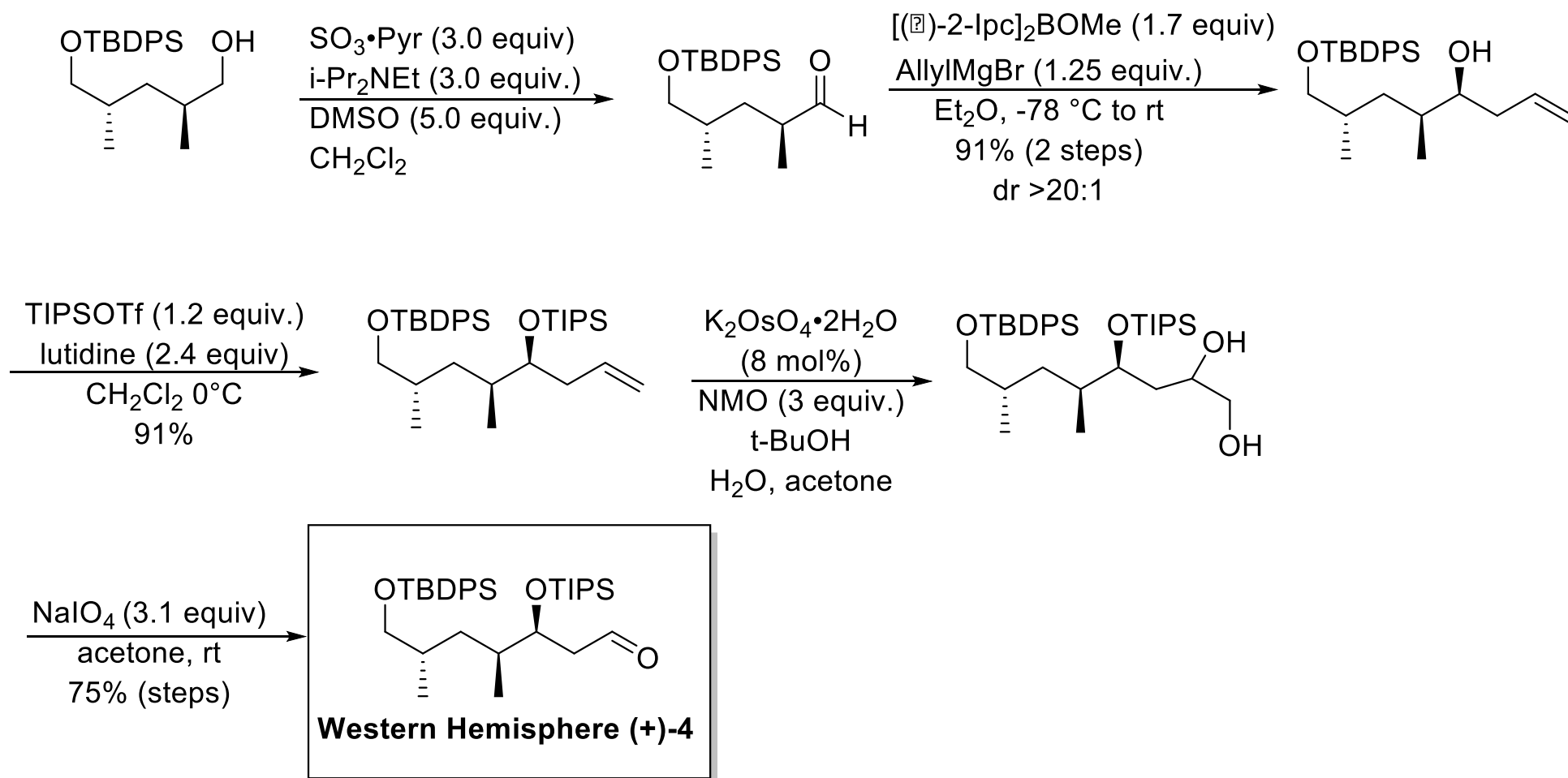
Construction of Eastern Hemisphere (+)-5



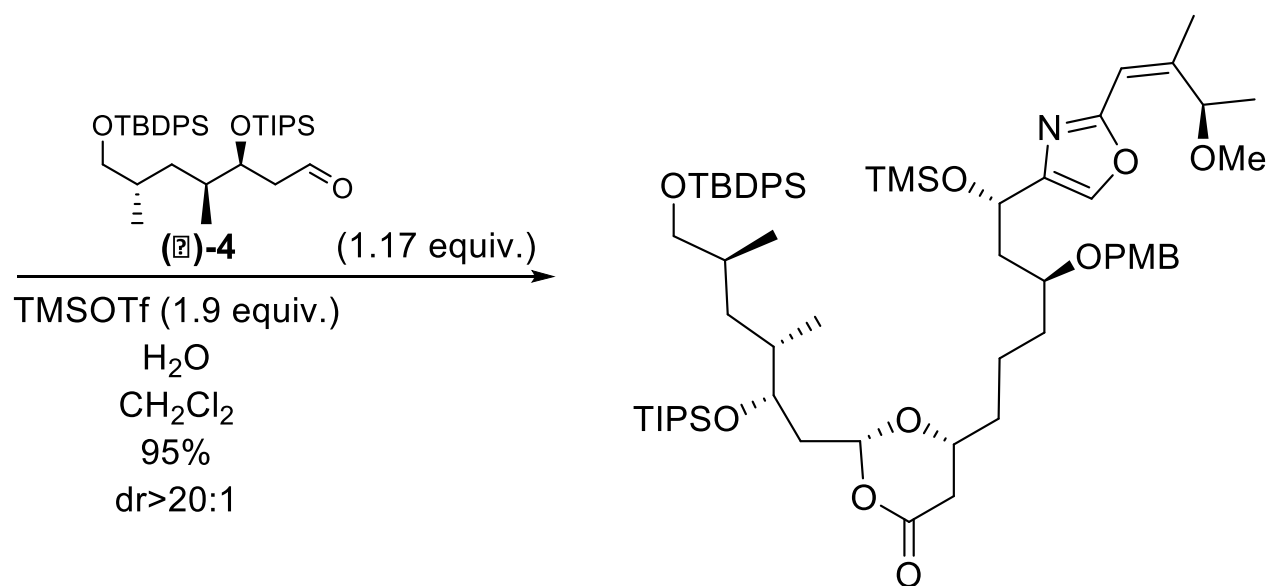
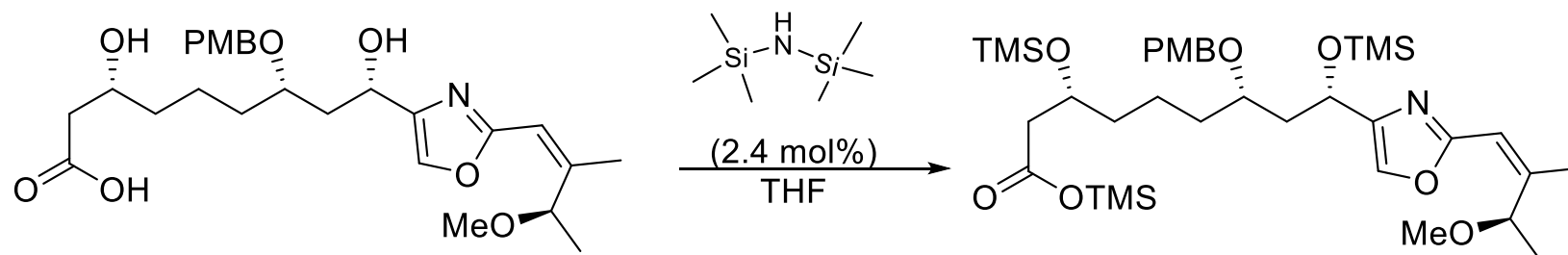
Construction of **Western Hemisphere (-)-4**



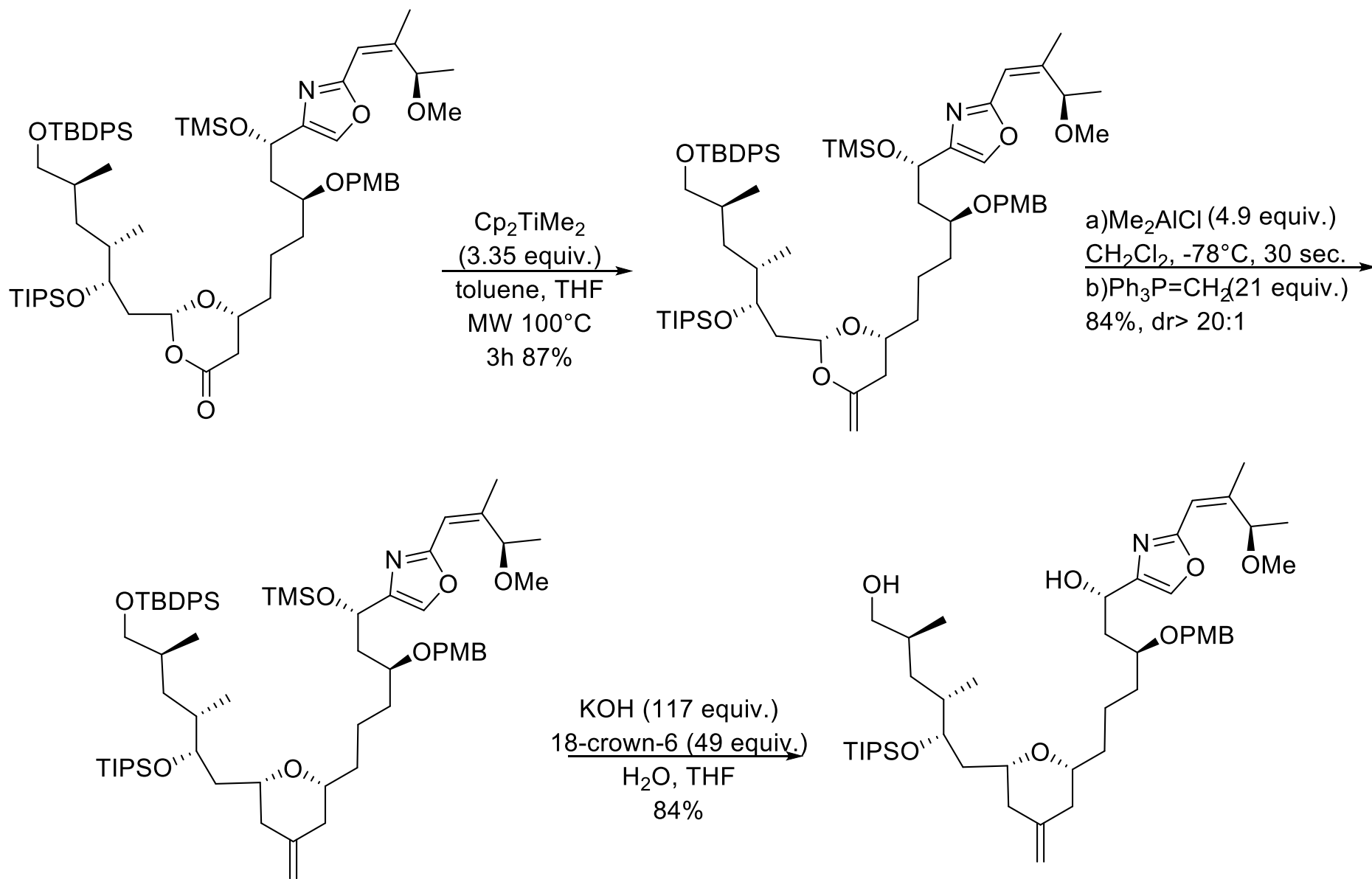
Construction of **Western Hemisphere (-)-4**



Petasis-Ferrier Union/Rearrangement

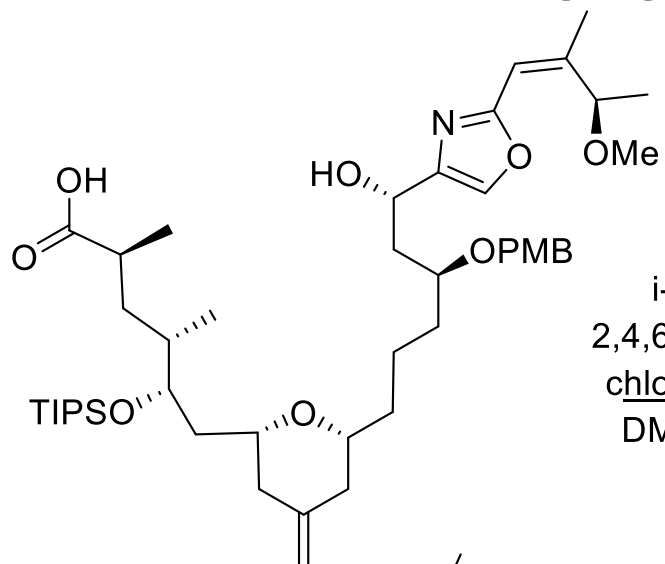


Petassis-Ferrier Union/Rearrangement

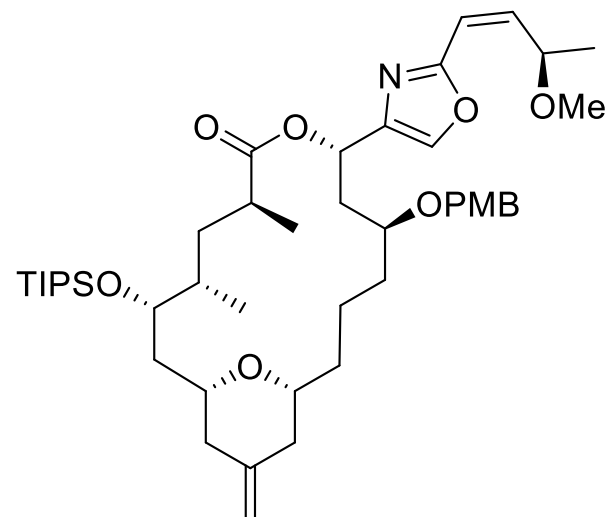


Macrolactone (+)-33 Formation

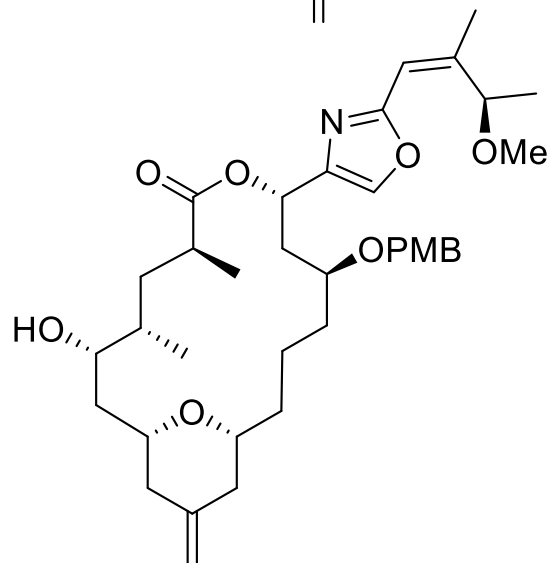
TEMPO (1.1 equiv.)
NaClO (1.8 equiv.)
NaClO₂ (3.4 equiv.)
t-BuOH
CH₃CN, H₂O rt
75%



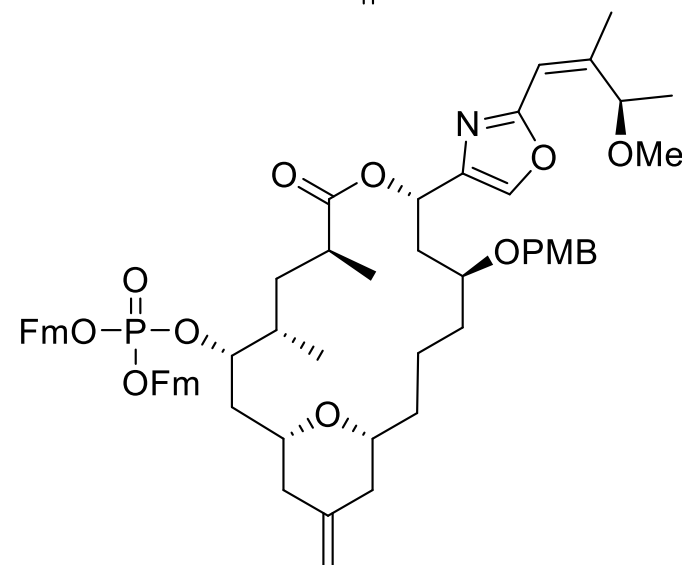
i-Pr₂NEt (cat.)
2,4,6-trichlorobenzoyl
chloride (7.5 equiv.)
DMAP (33 equiv.)
toluene, ref.
89%



HF/Pyridine (1:6)
THF
70%



i-Pr₂NP(OFm)₂
(20 equiv.)
1H-tetrazole
(16 equiv.)
MeCN/CH₂Cl₂
H₂O₂



Phosphoric Acid Formation

