THE FLIGHT OF THE (+)-DACTYLOLIDE

N-HETEROCYCLIC CARBENE CATALYZED OXIDATIVE MACROLACTONIZATION: TOTAL SYNTHESIS OF (+)-DACTYLOLIDE

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Presented by James Johnson

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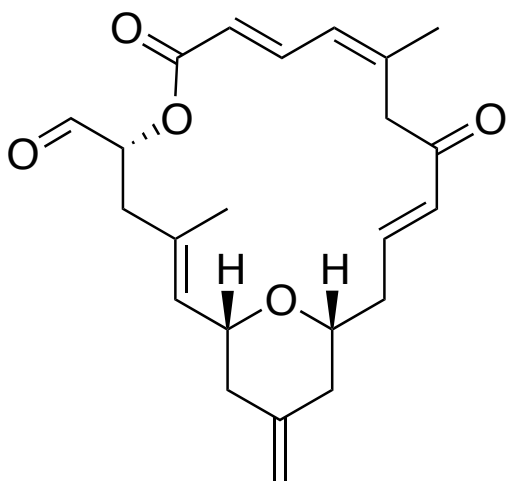
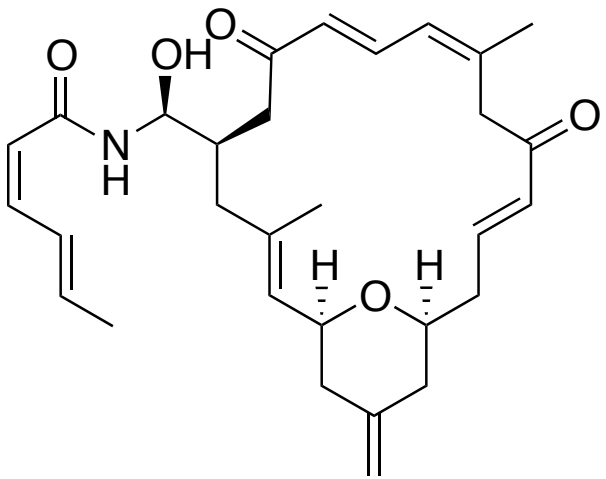
Current Literature



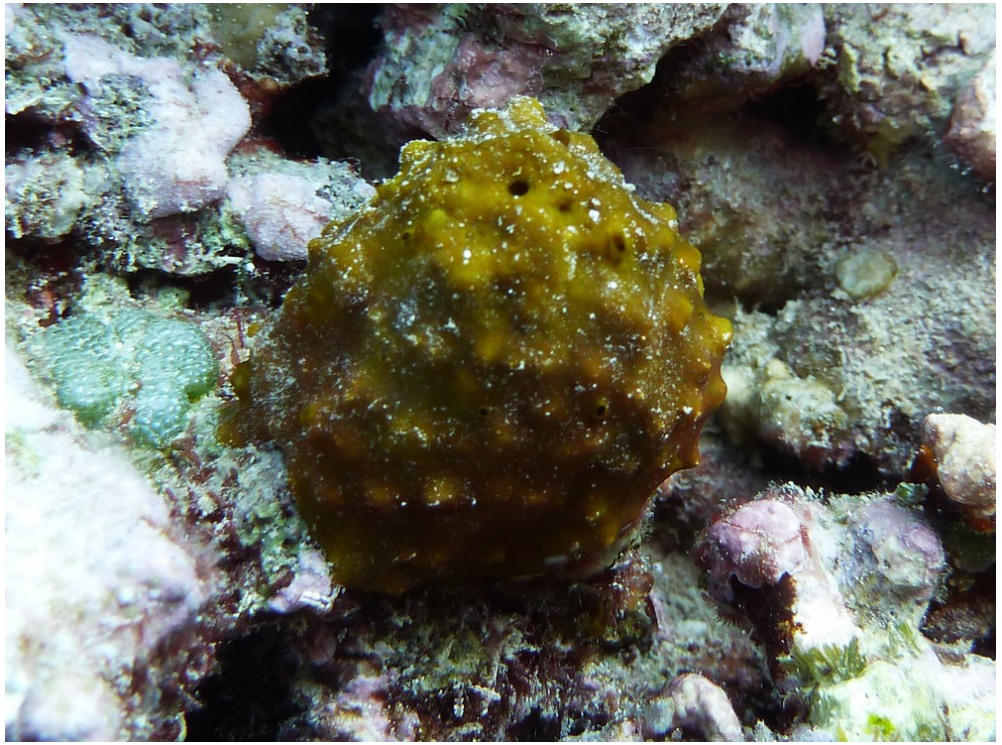
(+)-Dactylolide



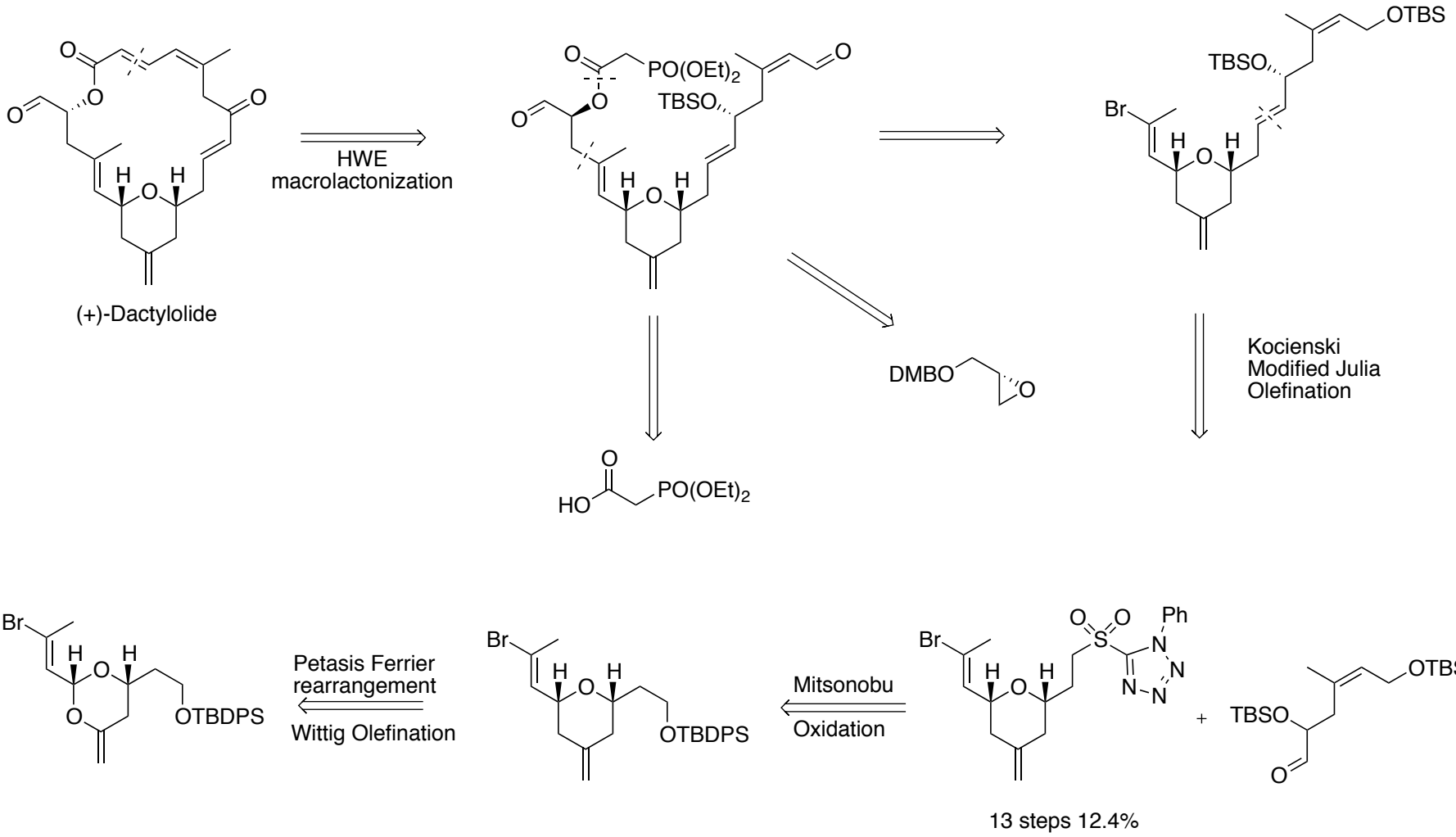
(-)-Zampanolide

Isolation

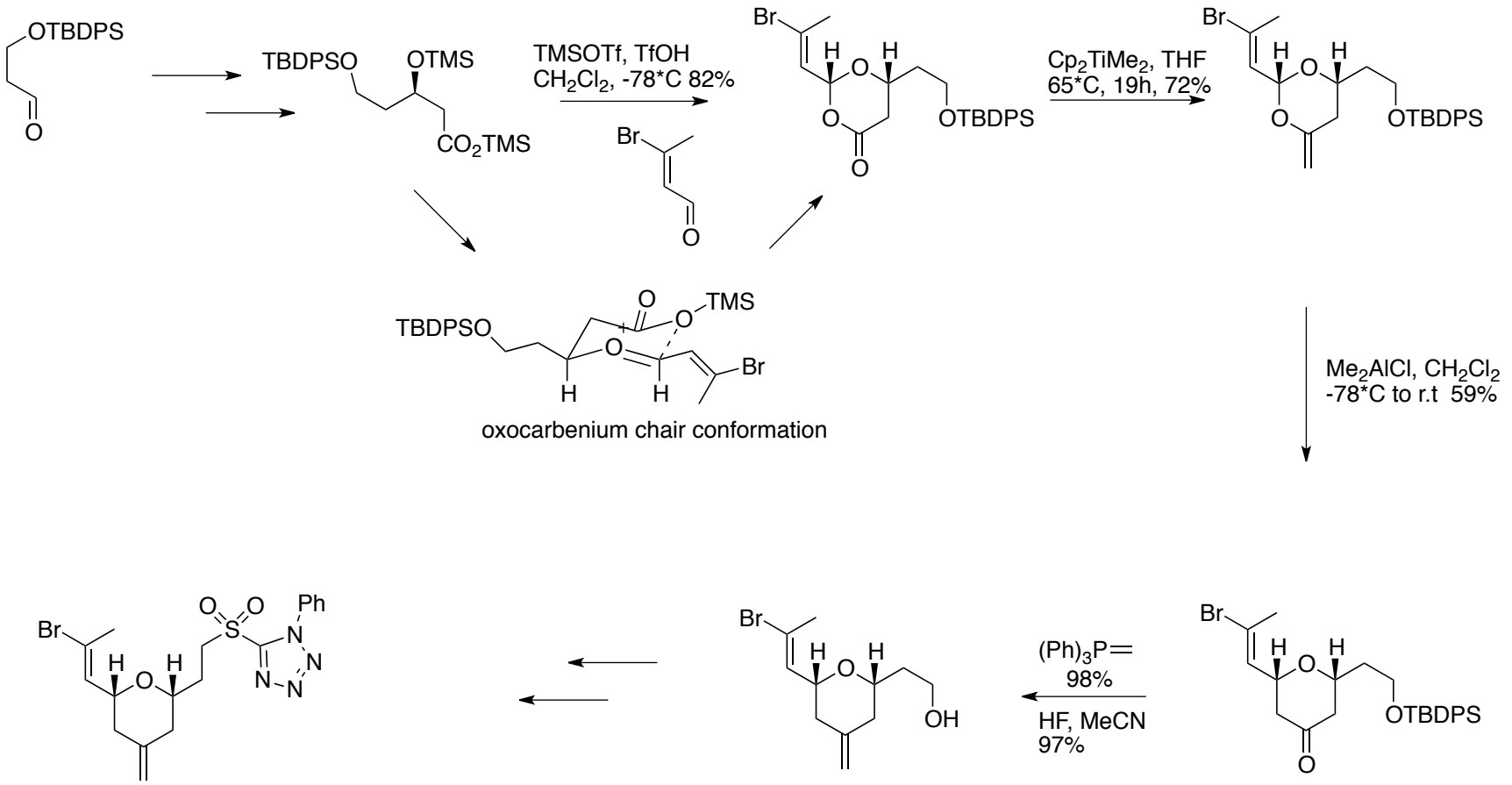
- Isolated from the Vanuatu sponge Dactylospongia by Riccio and co-workers
- Showed cytotoxic activity against the L1210 and SK-OV-3 tumor cell lines (63% and 40% inhibition at 3.2 µg/mL).
- Mechanism of action thought to be a microtubulin stabilizer



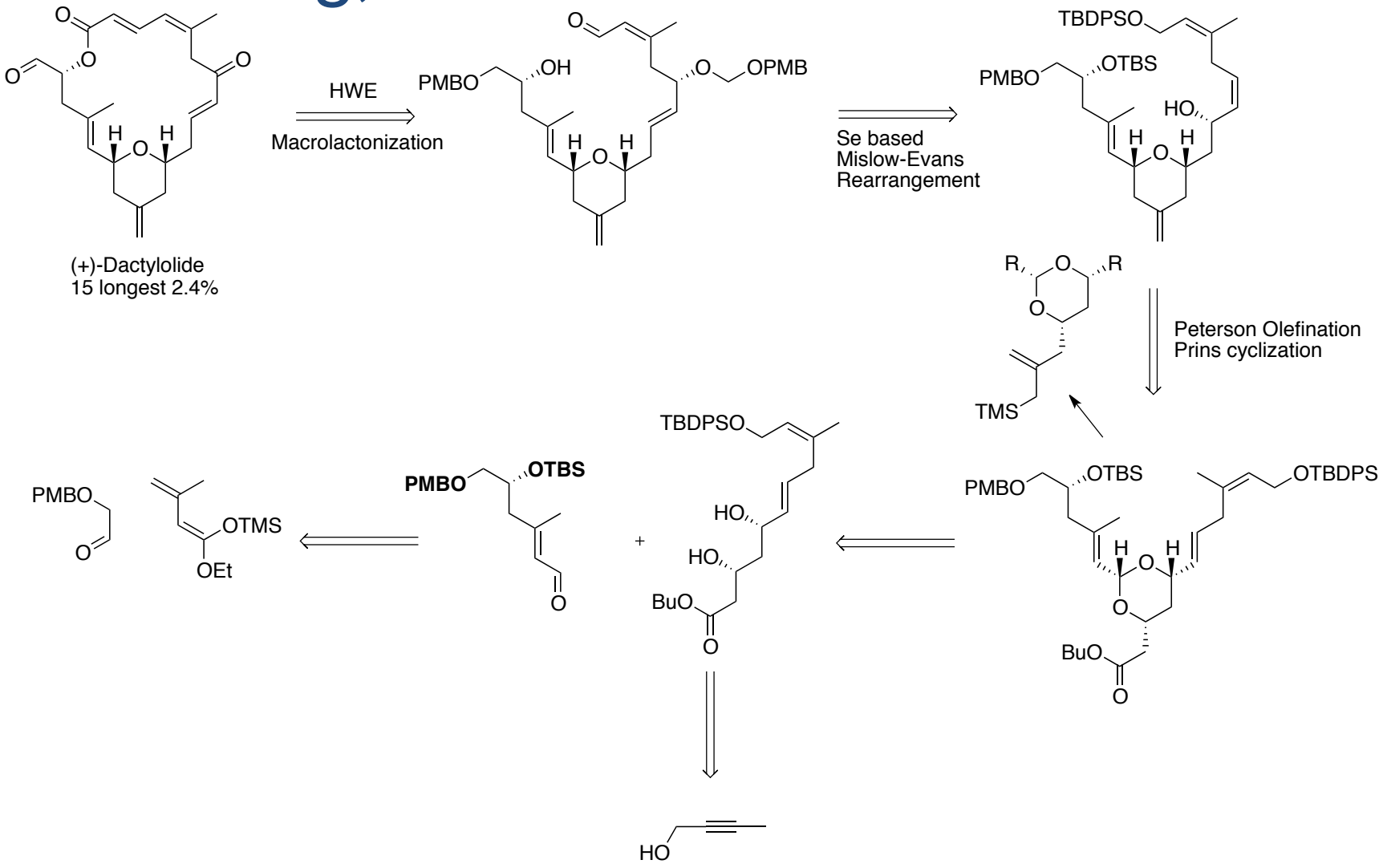
Previous Synthesis
Smith, et. al



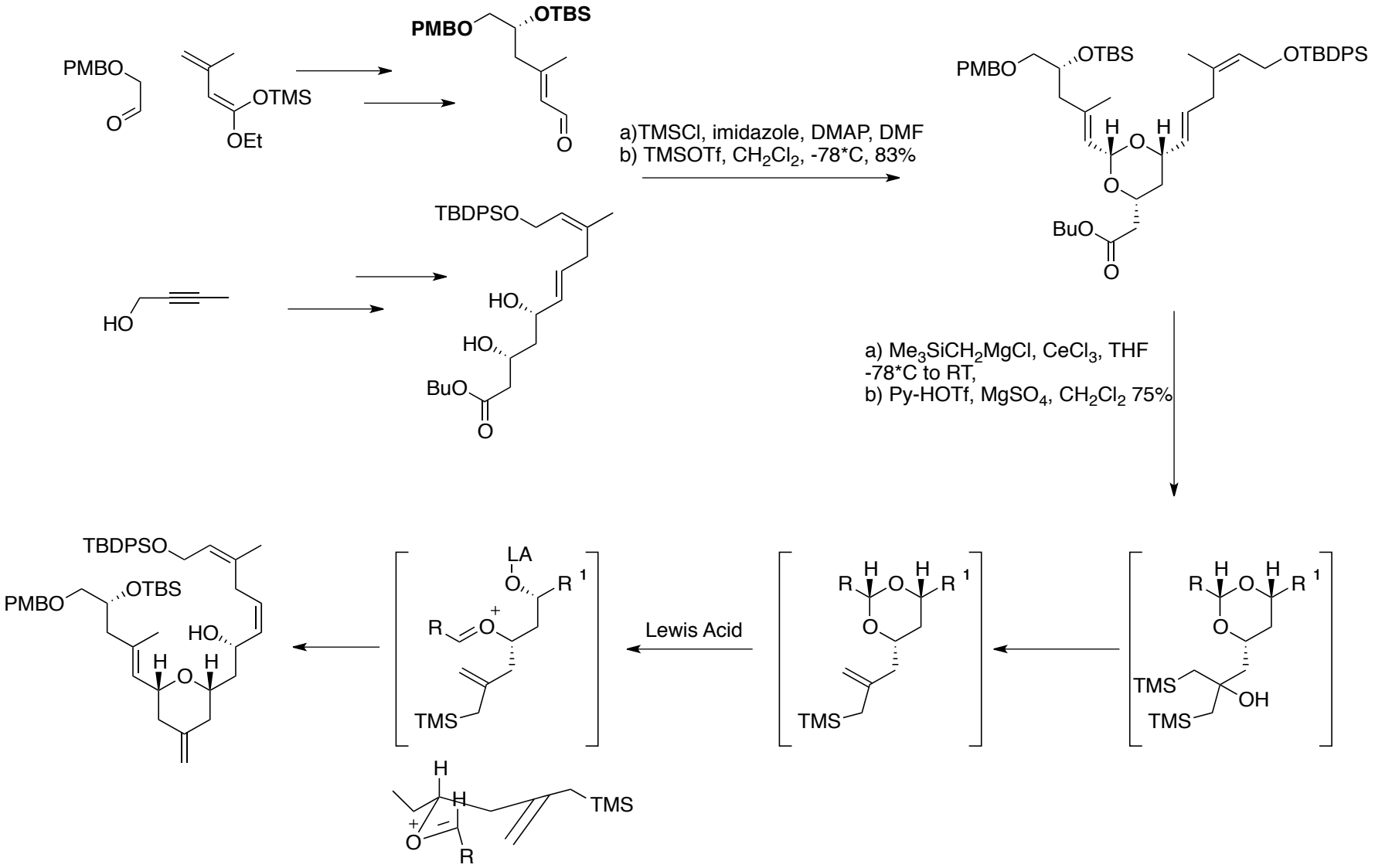
Smith Tetrahydropyran Formation



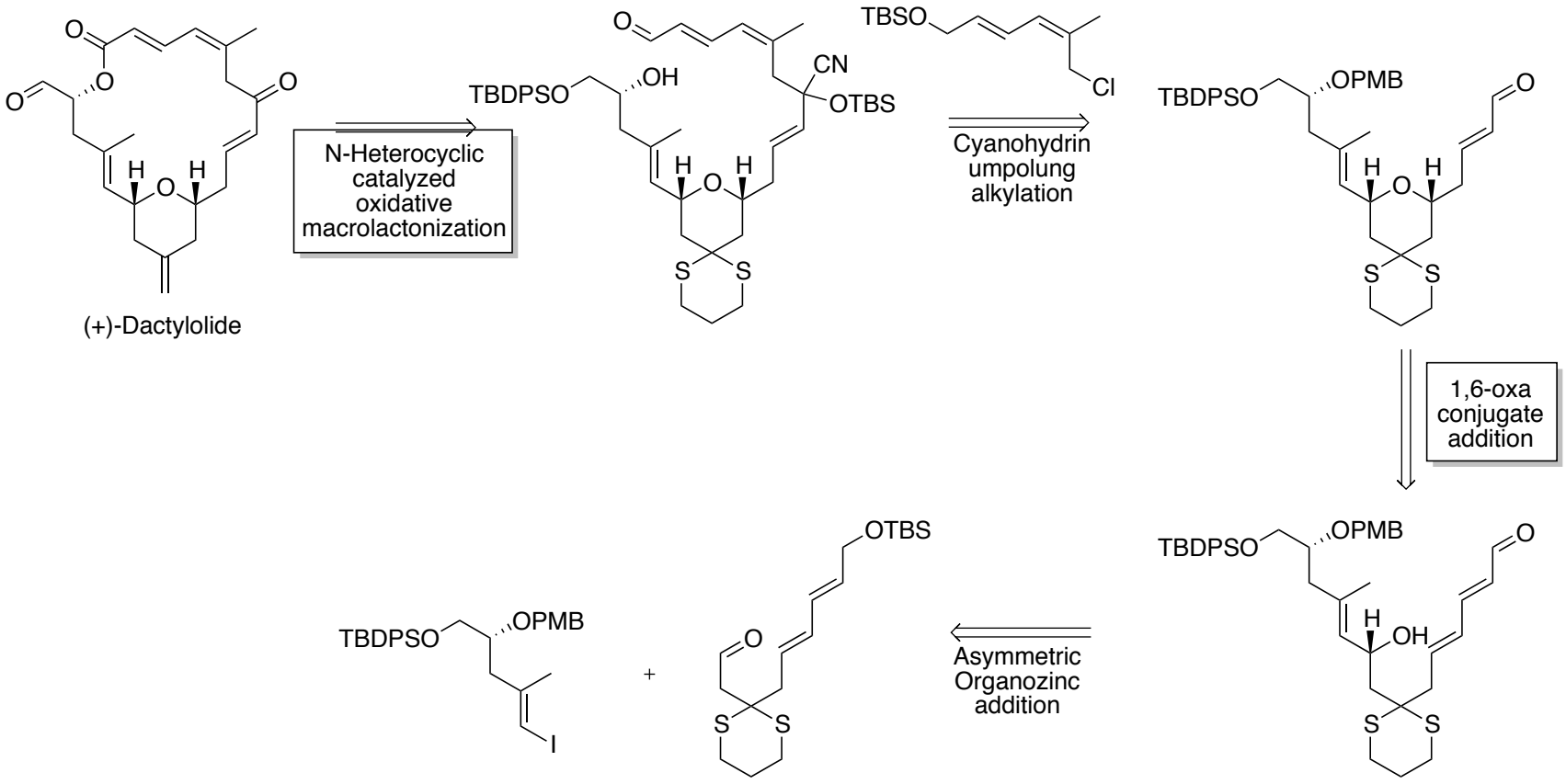
Previous Synthesis
Floreancig, et. al



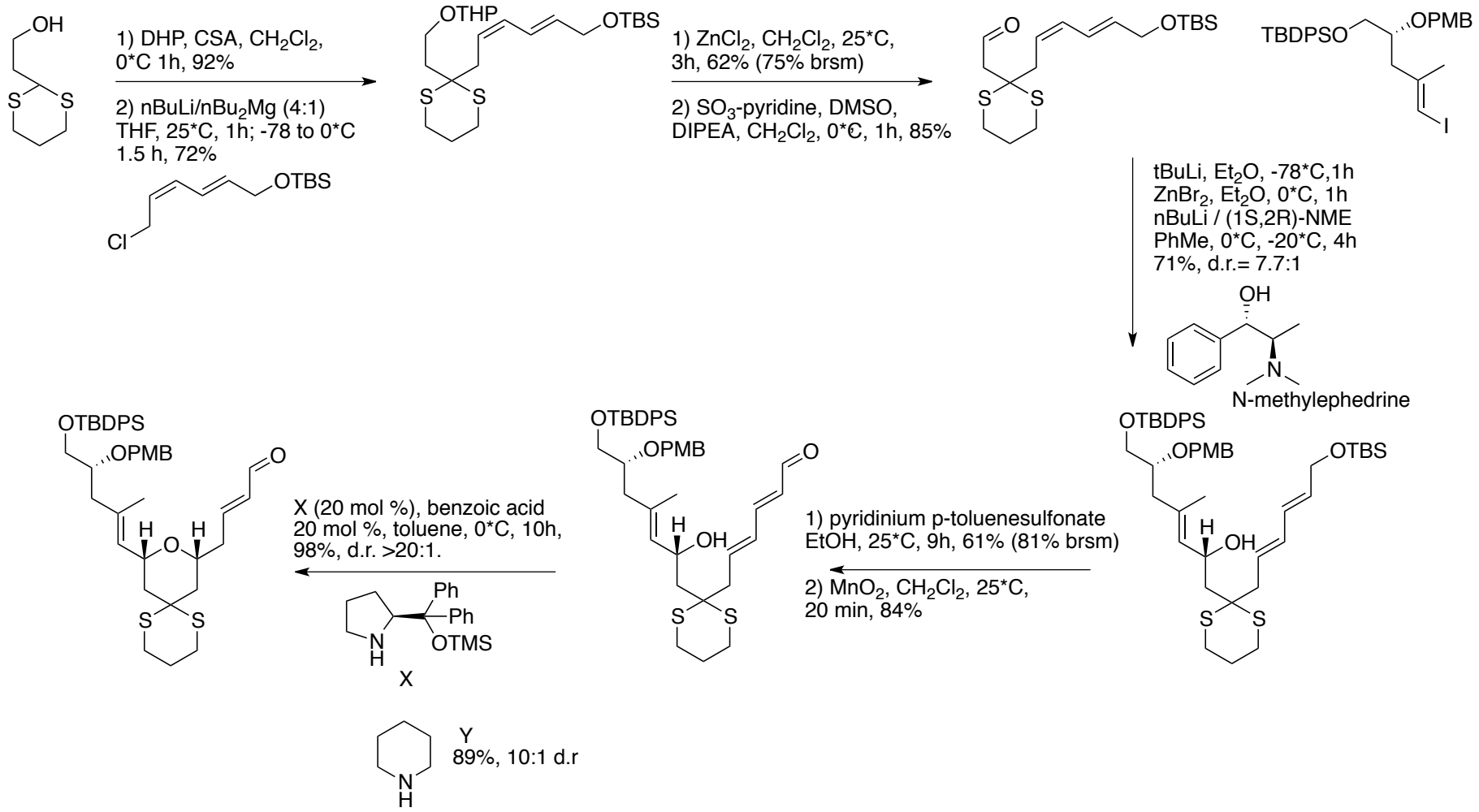
Floreancig Tetrahydropyran Formation



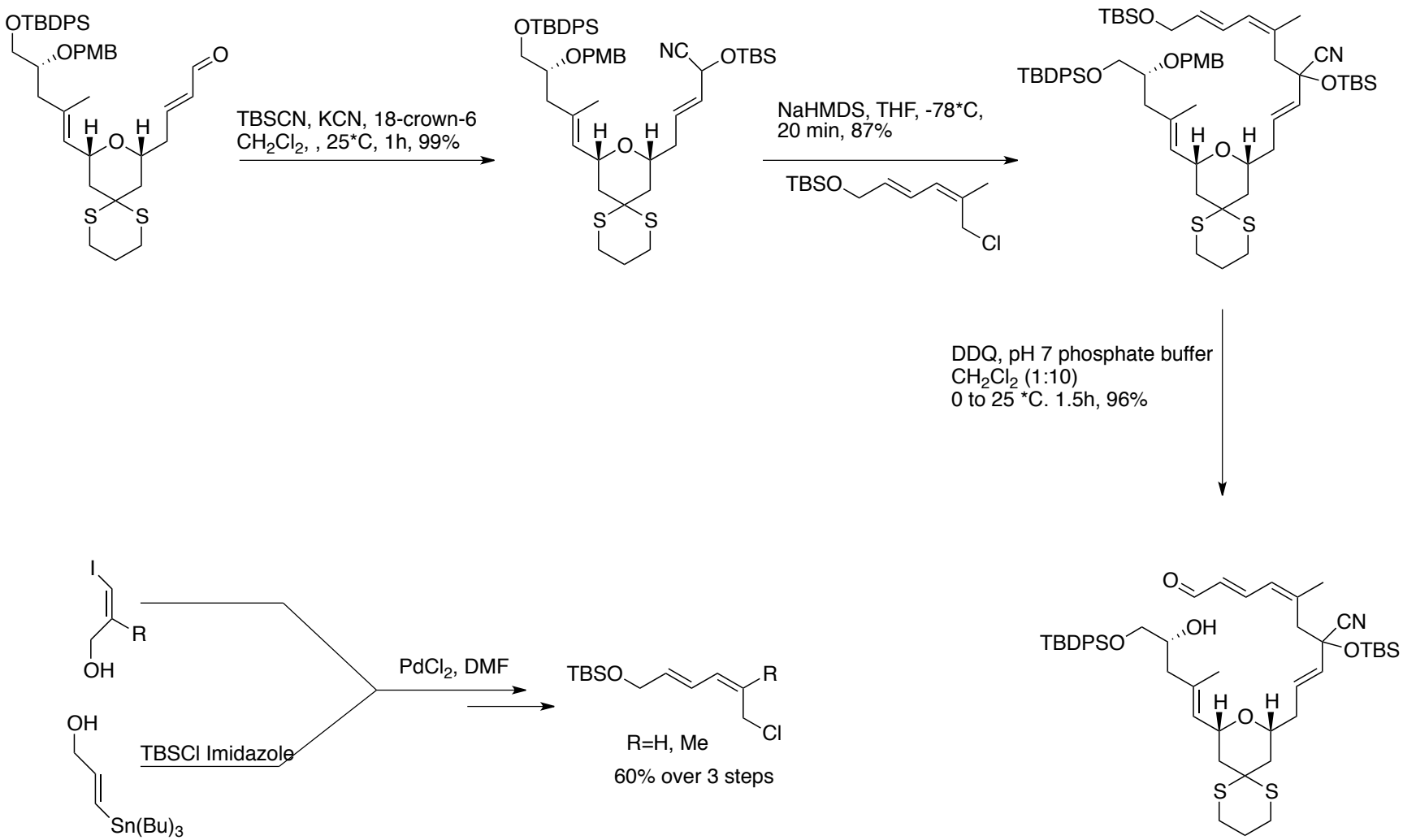
Title Paper


(+)-Dactylolide
N-Heterocyclic catalyzed oxidative macrolactonization
TBDPSO
OH
CN
OTBS
TBSO
Cl
Cyanohydrin umpolung alkylation
OPMB
1,6-oxa conjugate addition
Asymmetric Organozinc addition
I

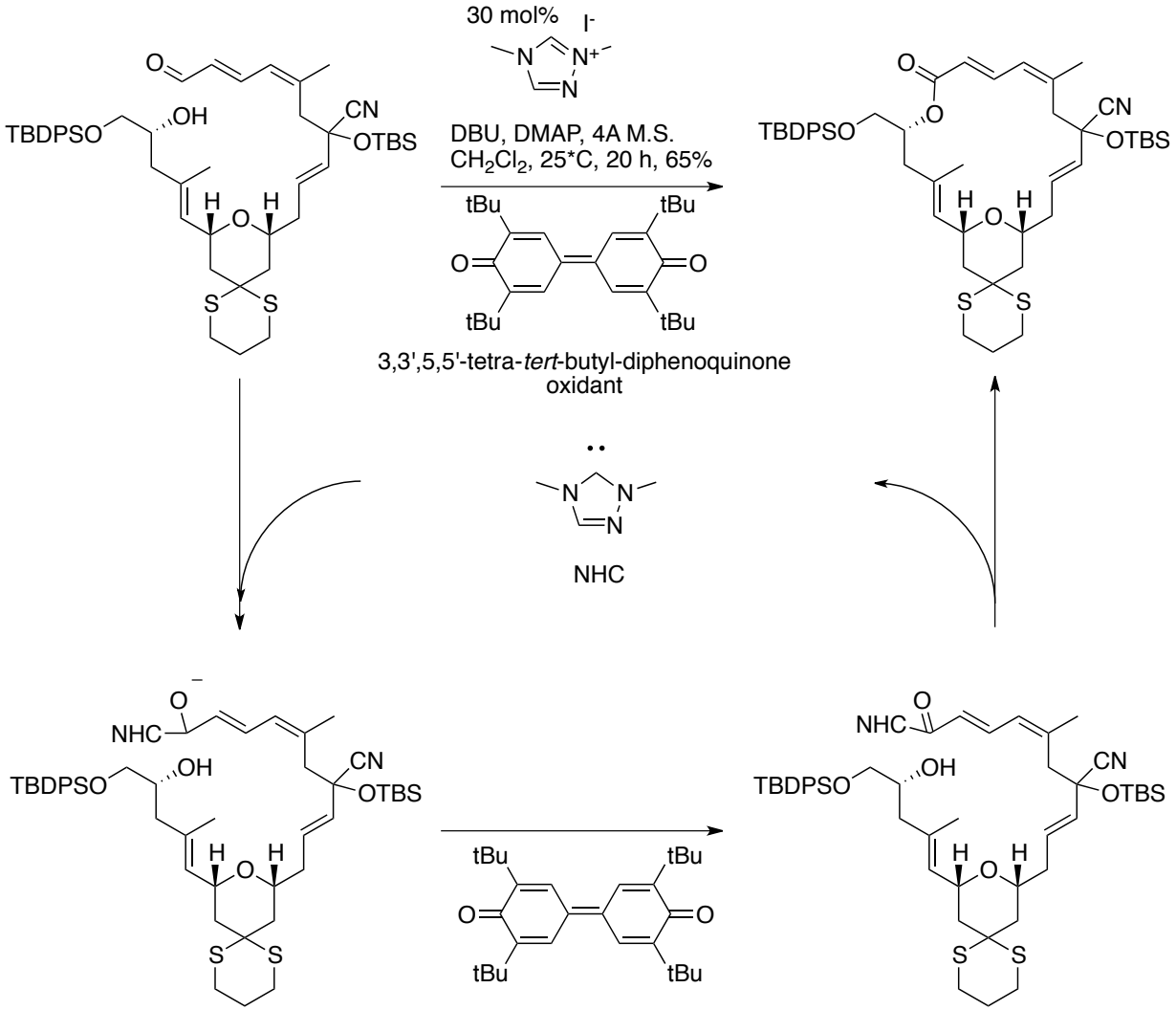
Synthesis: 2,6-cis-2-(4-oxo-2-butenyl)tetrahydropyran



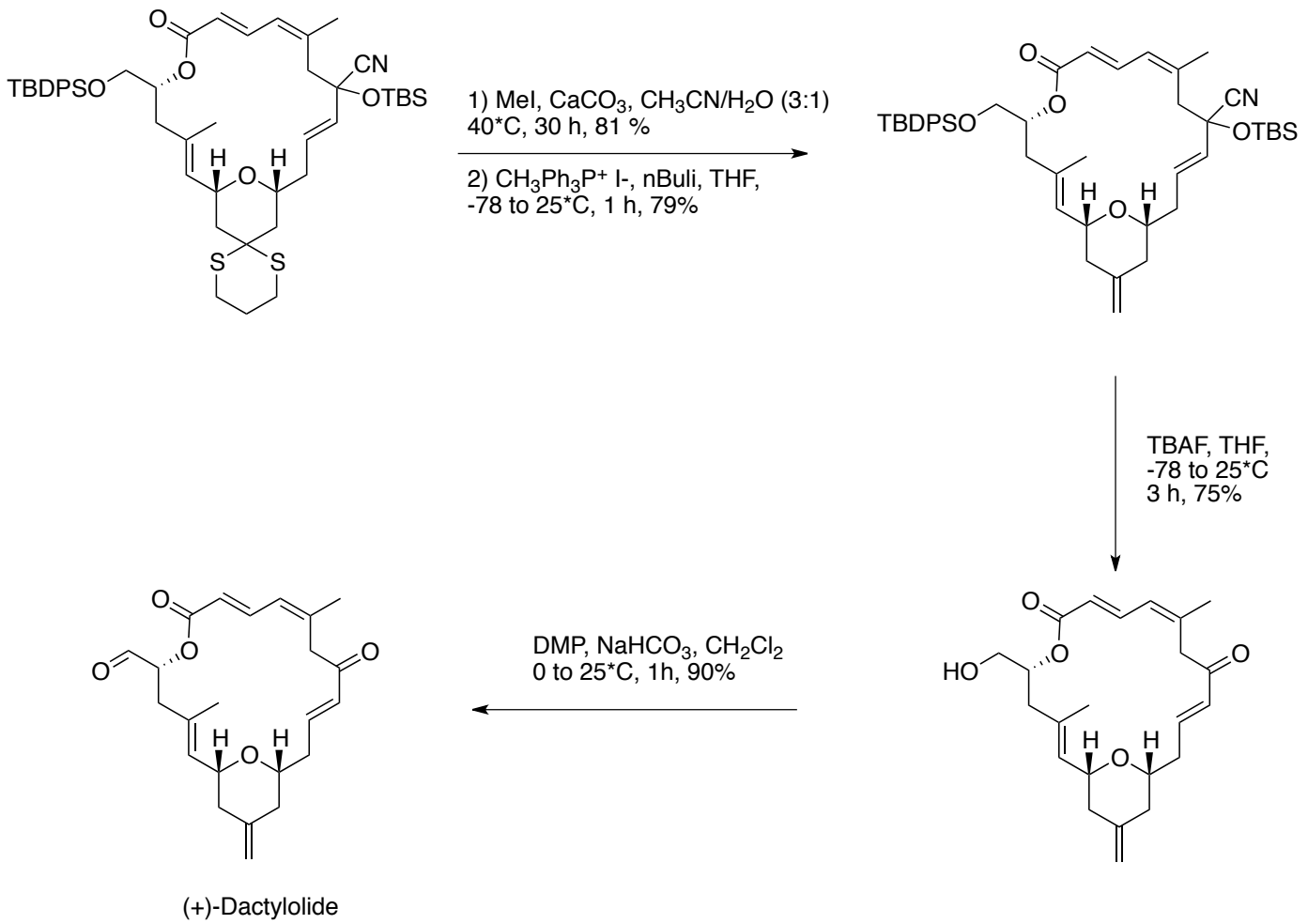
Preparation for NHC macrolactonization



NHC-Catalyzed Oxidative Macrolactonization



Completion of Total Synthesis



(+)-Dactylolide

Conclusions

- Total Synthesis of (+) Dactylolide in 19 steps longest linear, with an overall yield of 1.4 % (1.9% brsm)
- First recorded 1,6 intramolecular conjugate addition to form a 2,6-cis tetrahydropyran.
- First recorded use of an NHC catalyzed oxidative macrolactonization of a ω-hydroxy aldehyde