An Enantioconvergent and Concise Synthesis of Lasonolide A

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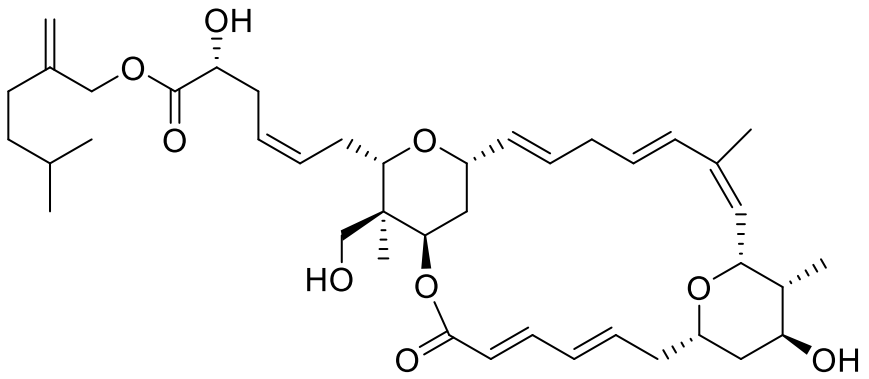
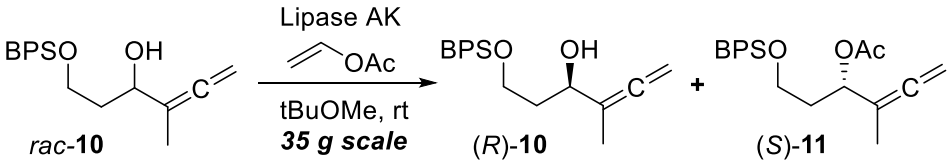
- Lasonolide A (**4**) was identified by McConnell and coworkers from the Caribbean orange-red marine sponge *Frocepia* sp.
- The complex macrolide exhibited promising activity for the treatment of pancreatic cancer, with a mode of action (MOA) distinct from that of most other cancer drugs, which highlights its potential as a valuable drug in the treatment of multidrug-resistant cancer cell lines.
- This synthesis uses alkylborane as a traceless protecting group for protecting alcohol and carboxylic acid functional groups.
- Stereocenters are initially introduced through an initial enzymatic kinetic resolution, where each resolved stereoisomer is used to synthesize half of the target molecule The two halves, as well as additional components, are put together through Wittig, Horner-Wadsworth-Emmonds, and Julia olefinations.

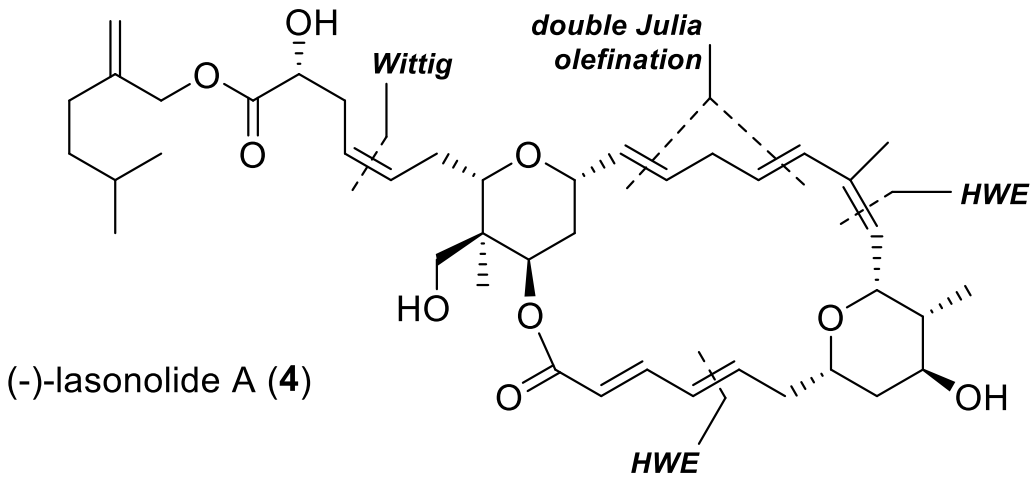


(-)-lasonolide A (**4**)



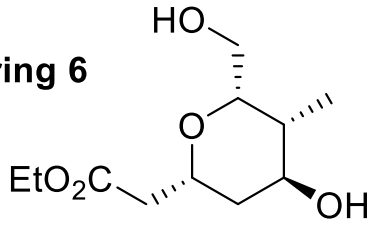
Ricky Alvarado
December 13th, 2018
Liu Group

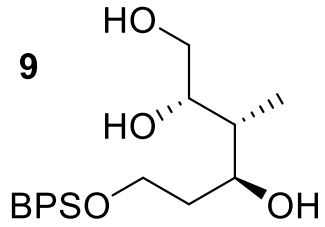
Retrosynthesis



(-)-lasonolide A (**4**)

THP B-ring 6





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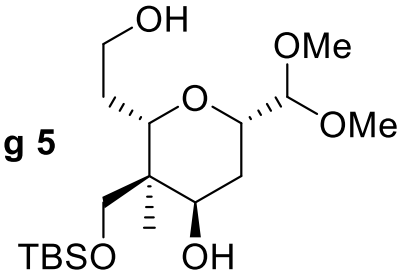
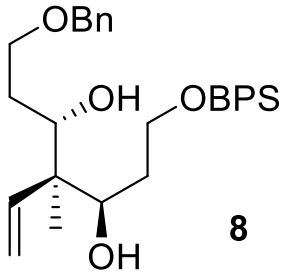
THP A-ring 5





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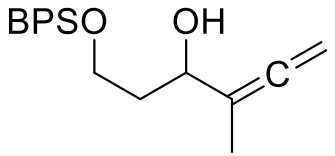

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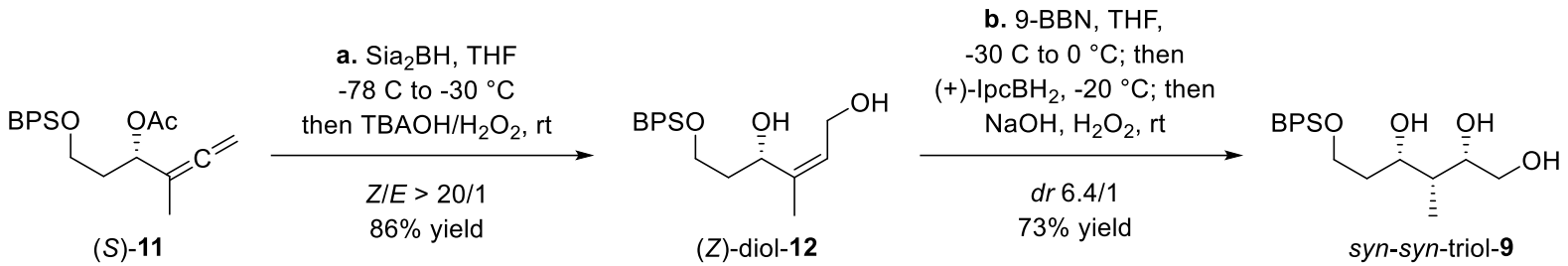
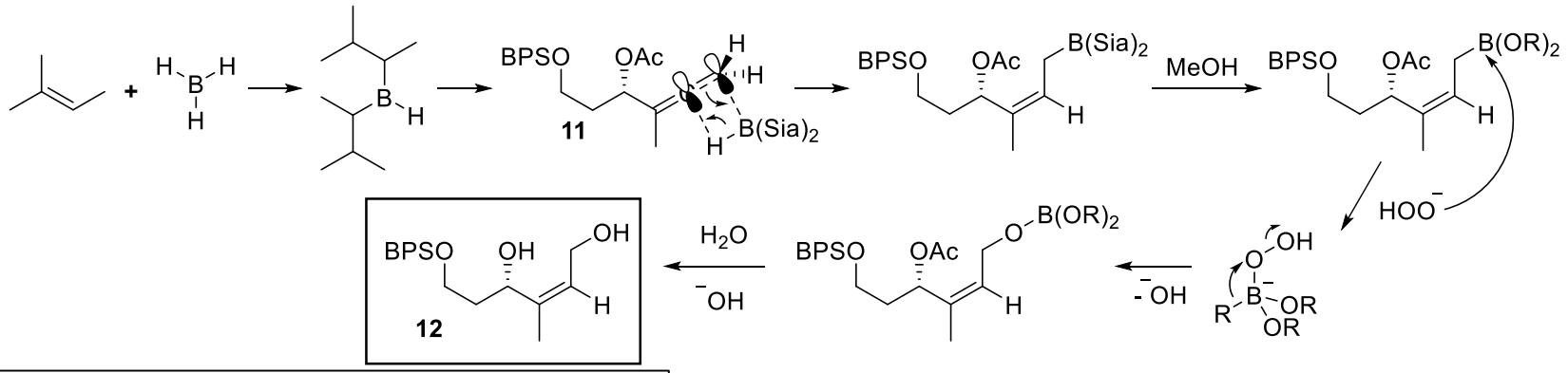
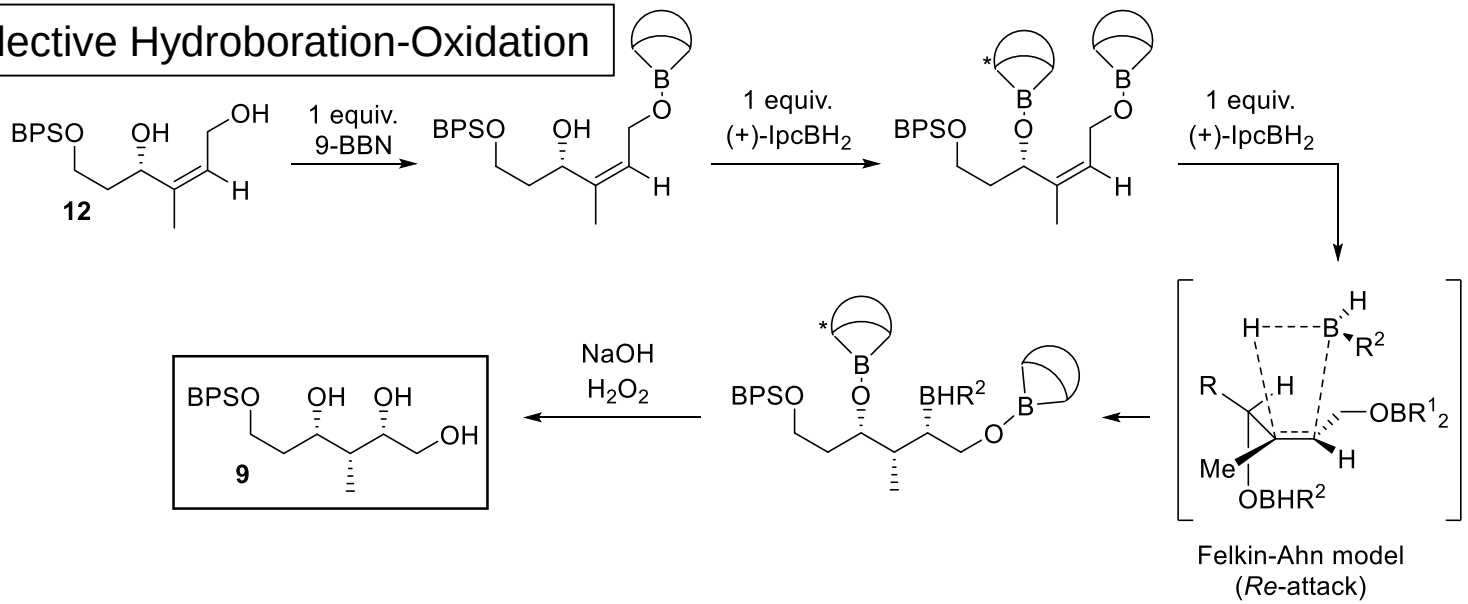
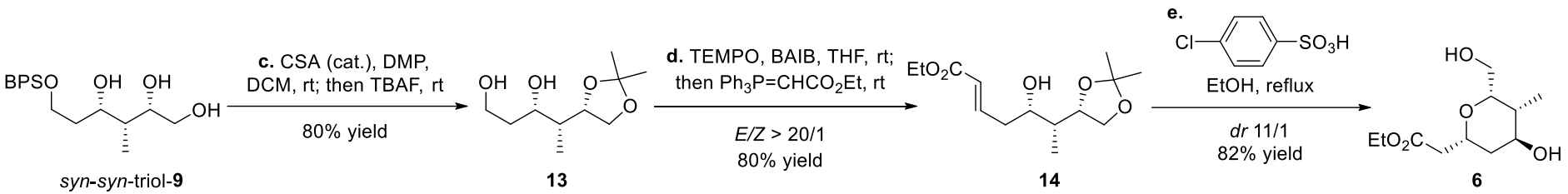


Hydroboration-Oxidation

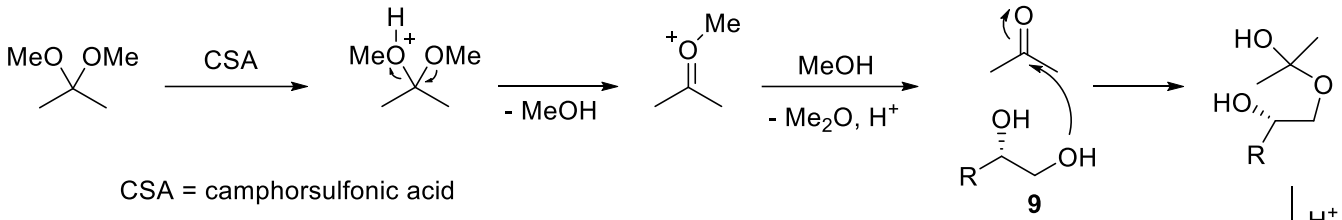


Stereoselective Hydroboration-Oxidation

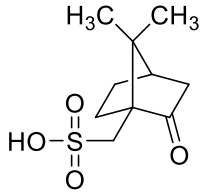




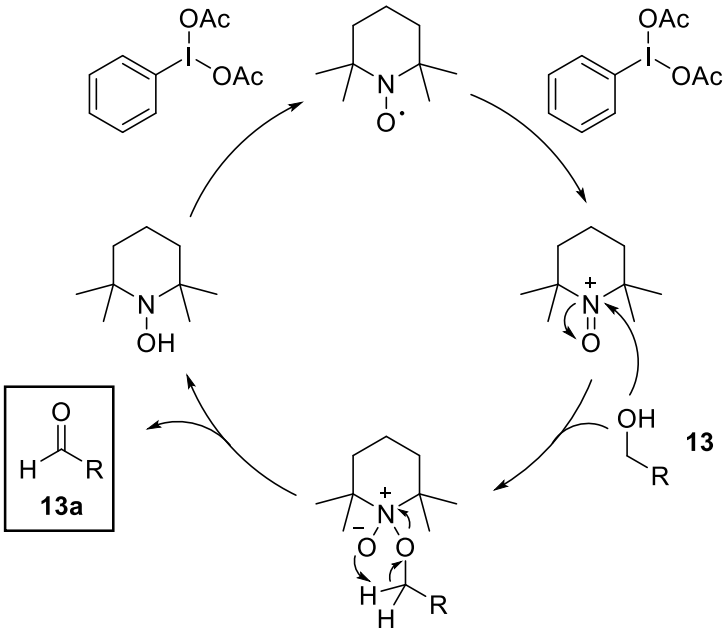
Acetal formation

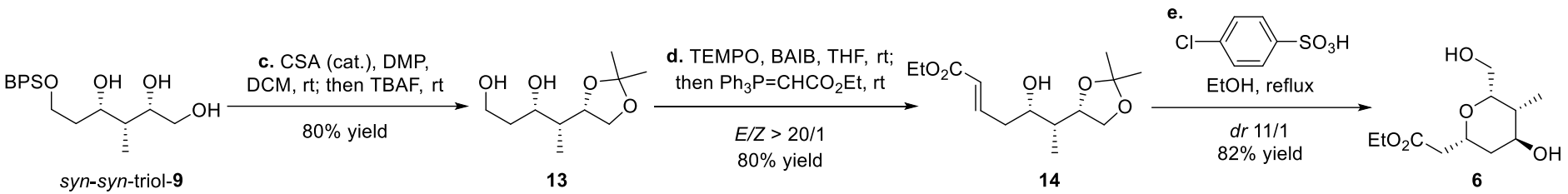


CSA = camphorsulfonic acid

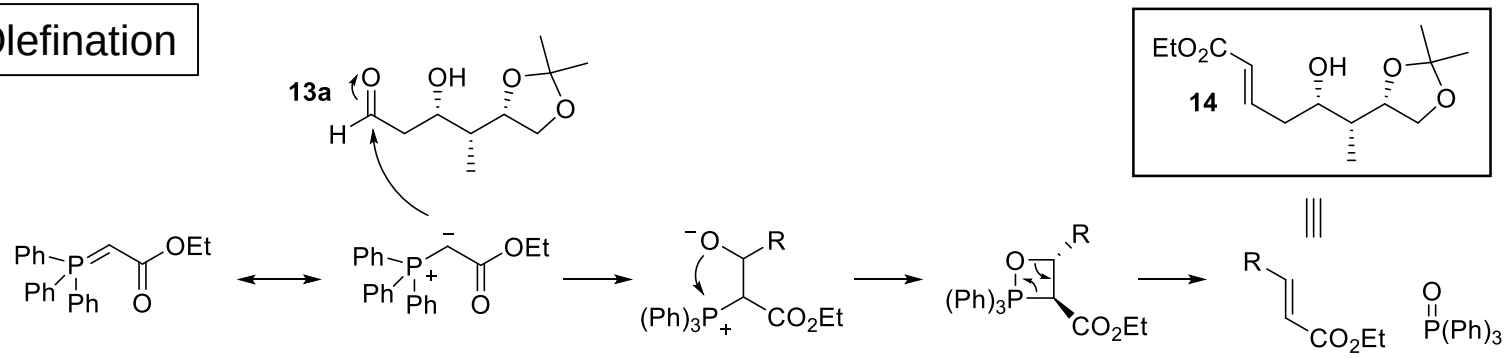


TEMPO Oxidation

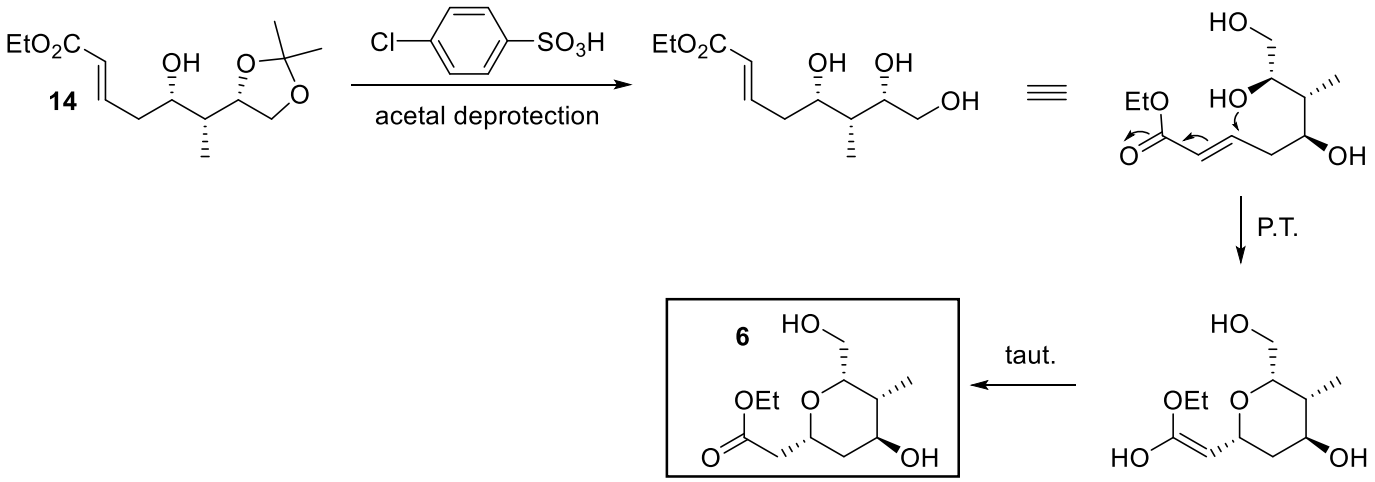


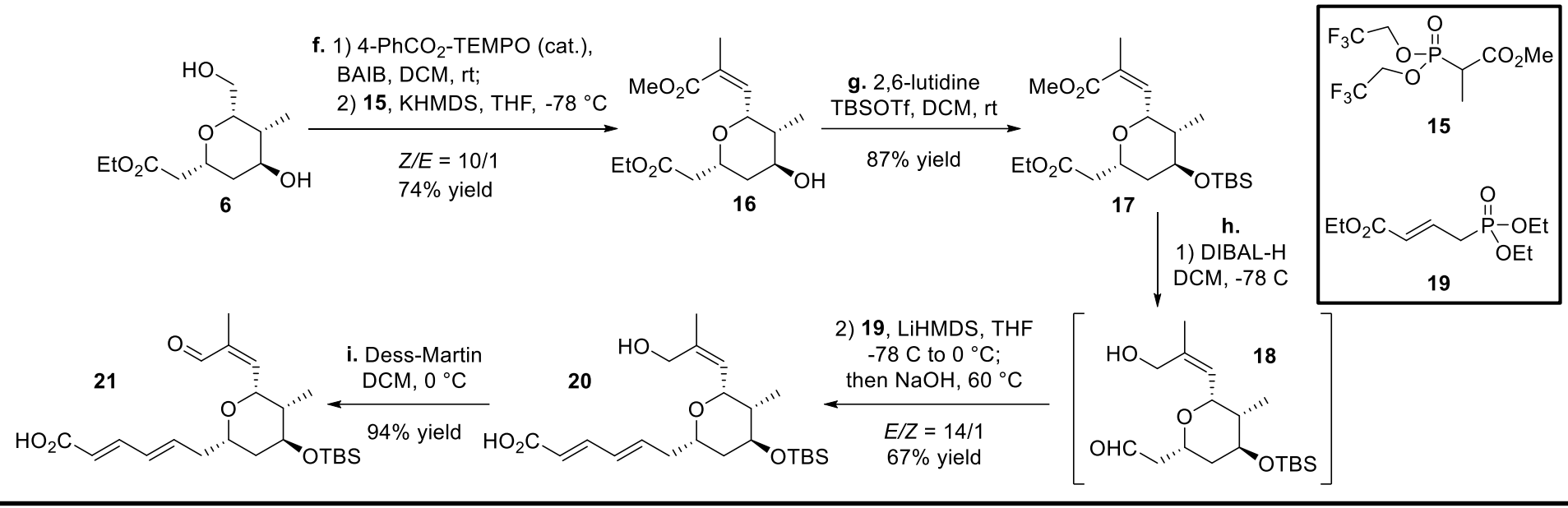


Wittig Olefination

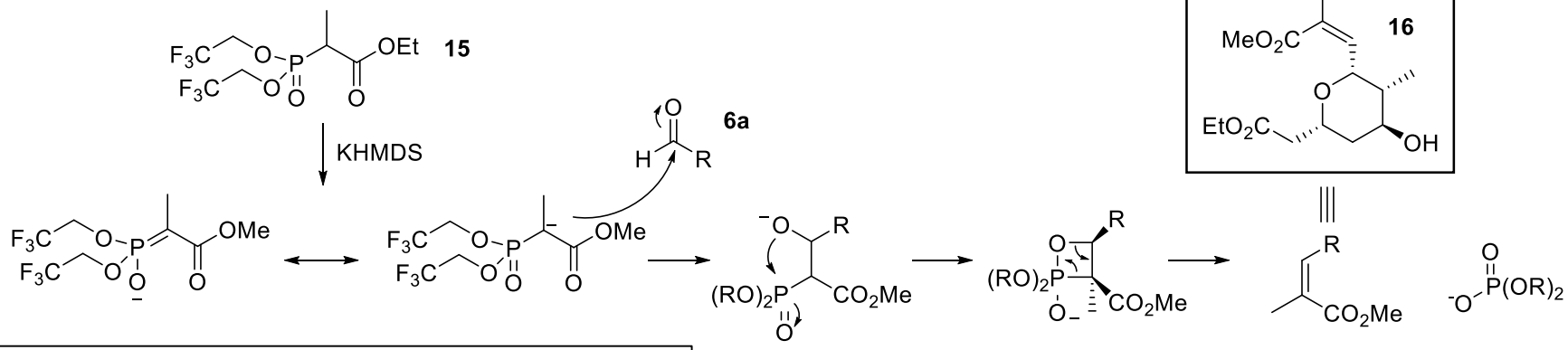


Oxy-Michael cyclization

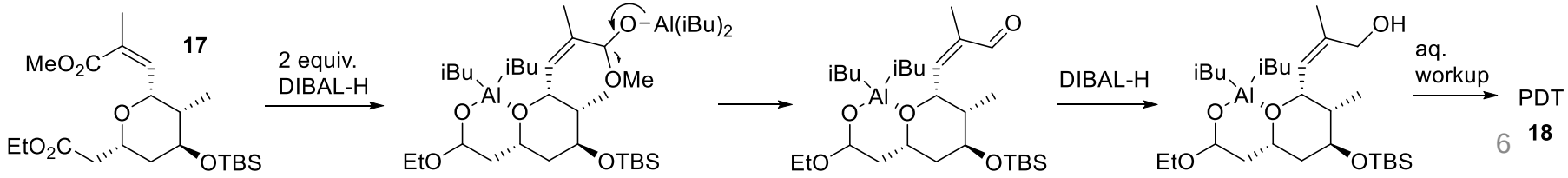


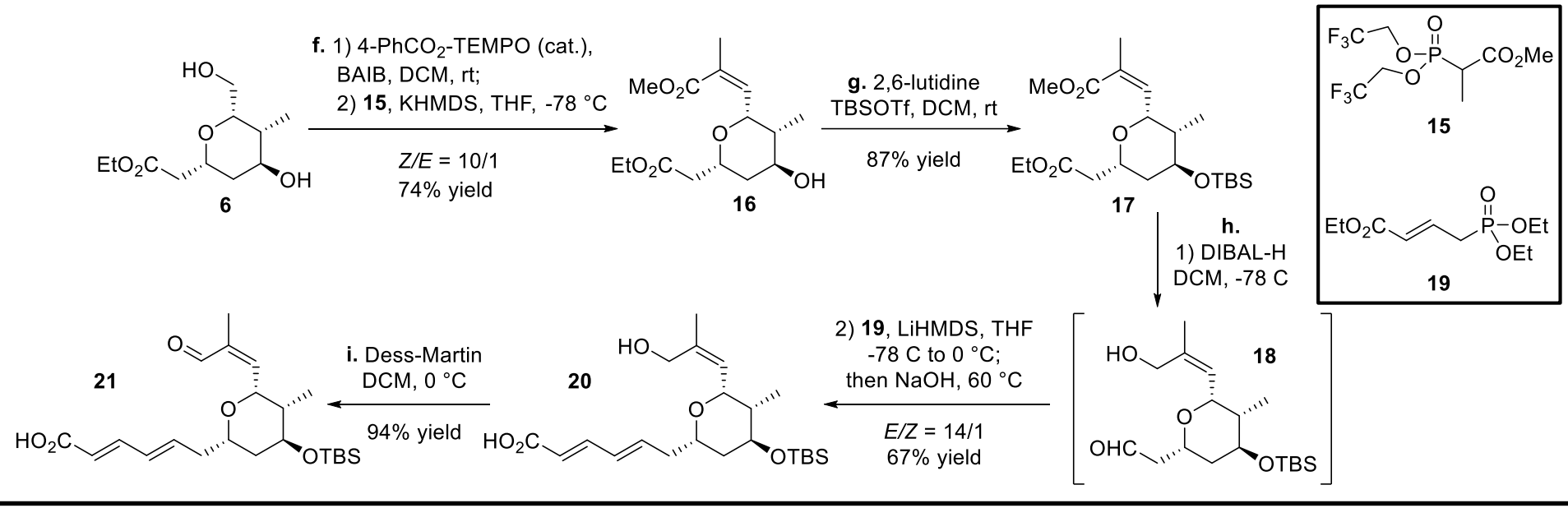


Horner-Wadsworth-Emmonds Olefination

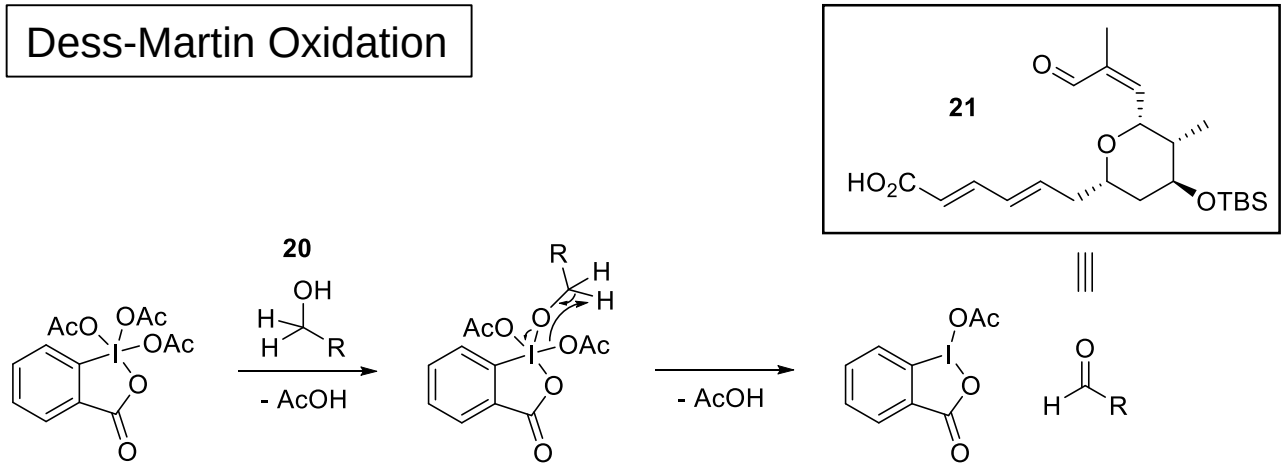


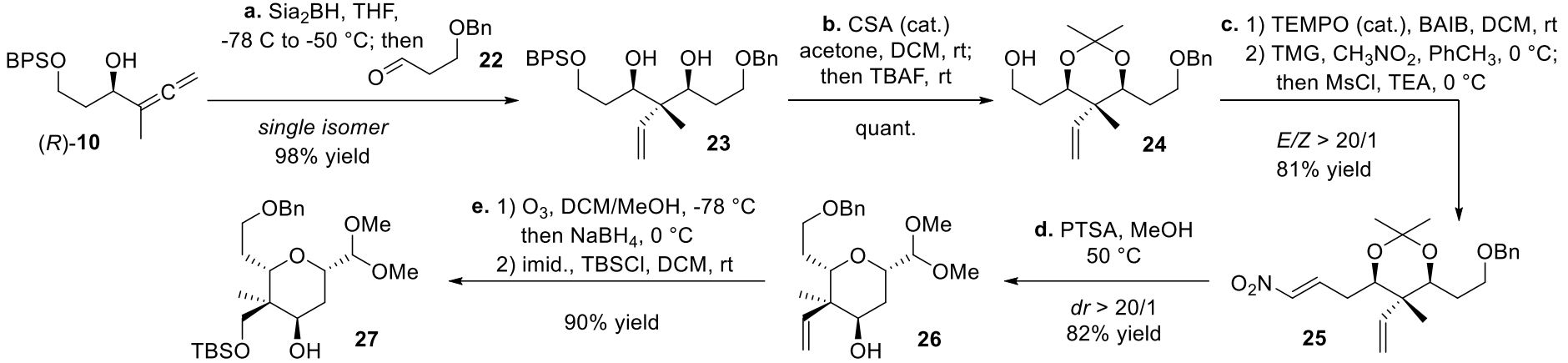
Chemoselective reductions with DIBAL-H



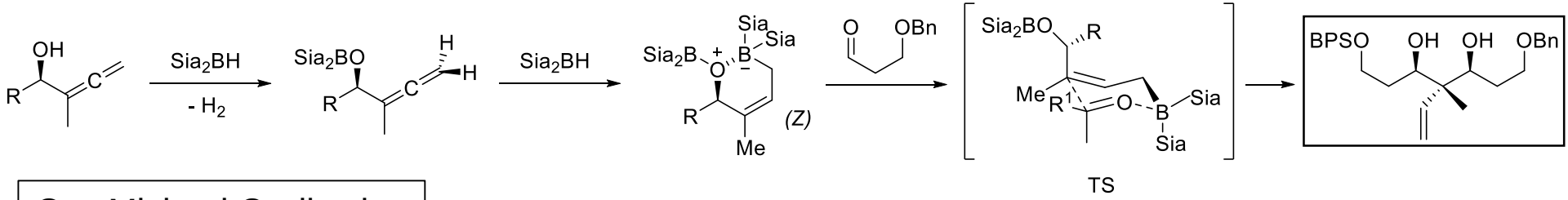


Dess-Martin Oxidation

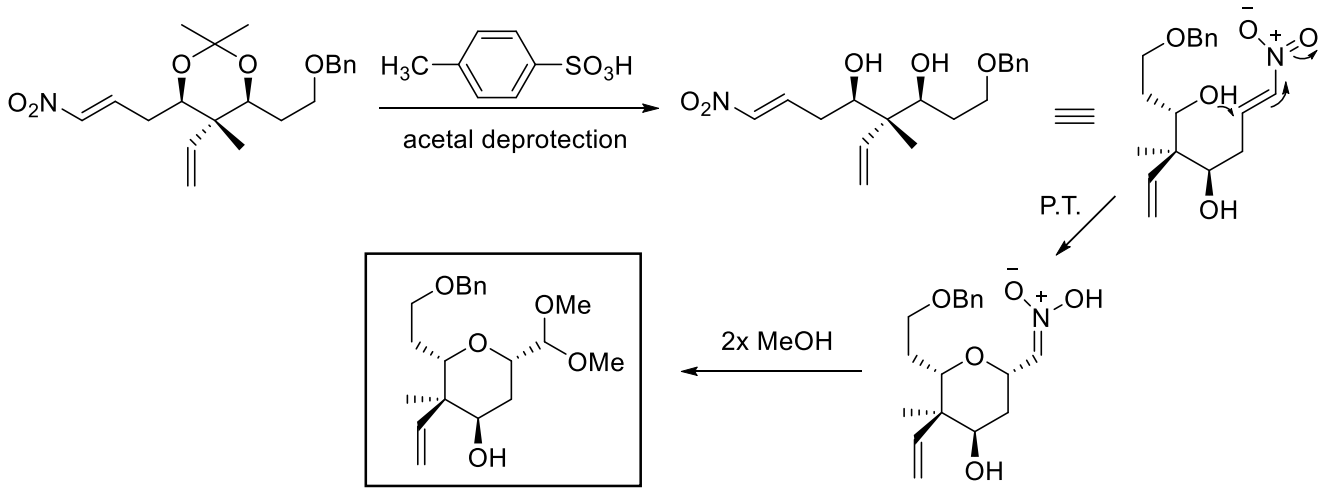


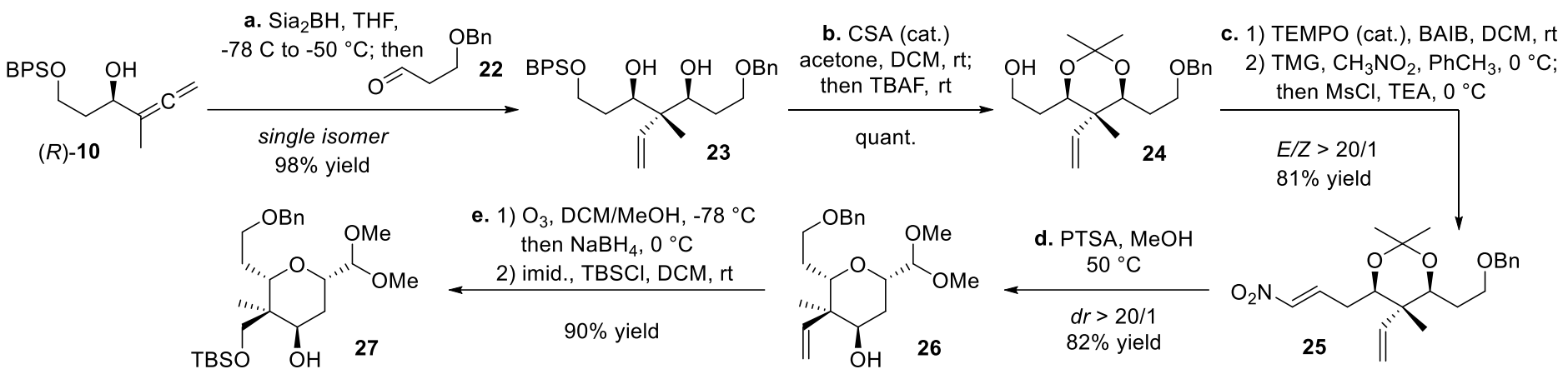


Stereoselective Hydroboration-Allylation

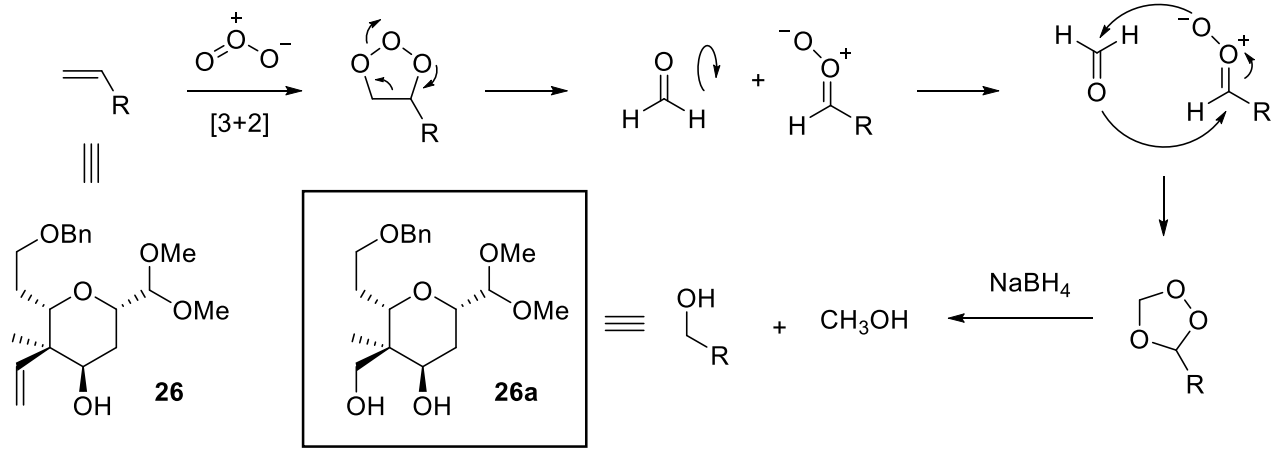


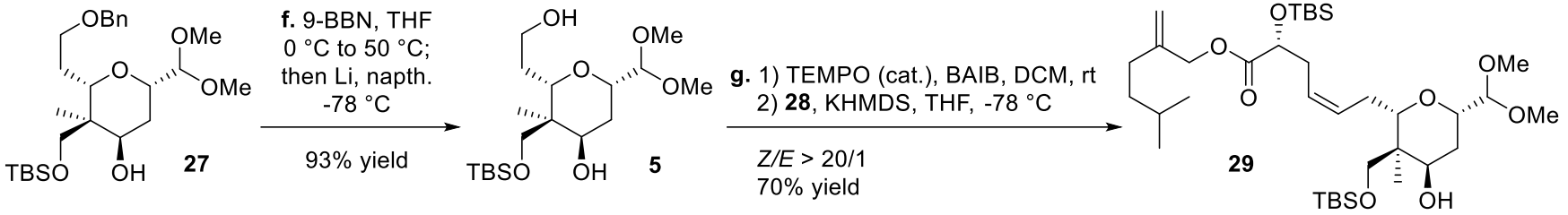
Oxy-Michael Cyclization

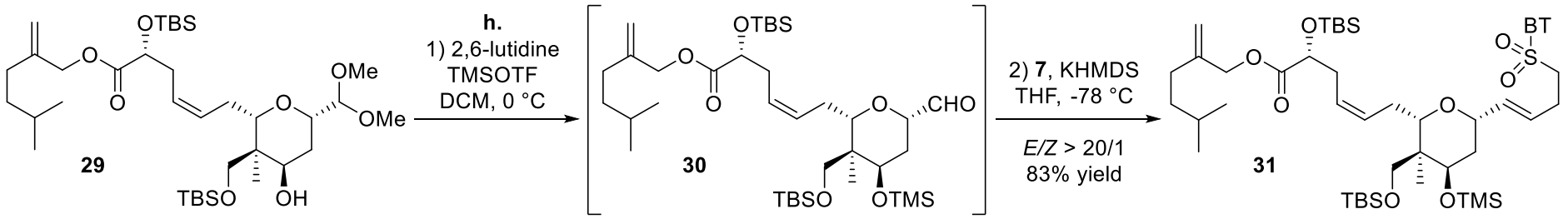



(R)-10
a. Sia2BH, THF, -78 C to -50 °C; then
22
single isomer
98% yield
23
b. CSA (cat.) acetone, DCM, rt; then TBAF, rt
quant.
24
c. 1) TEMPO (cat.), BAIB, DCM, rt
2) TMG, CH3NO2, PhCH3, 0 °C; then MsCl, TEA, 0 °C
E/Z > 20/1
81% yield
25
d. PTSA, MeOH 50 °C
dr > 20/1
82% yield
26
e. 1) O3, DCM/MeOH, -78 °C then NaBH4, 0 °C
2) imid., TBSCl, DCM, rt
90% yield
27

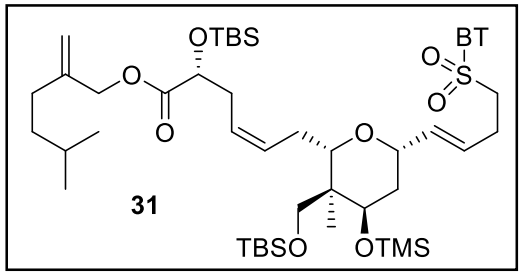
Ozonolysis

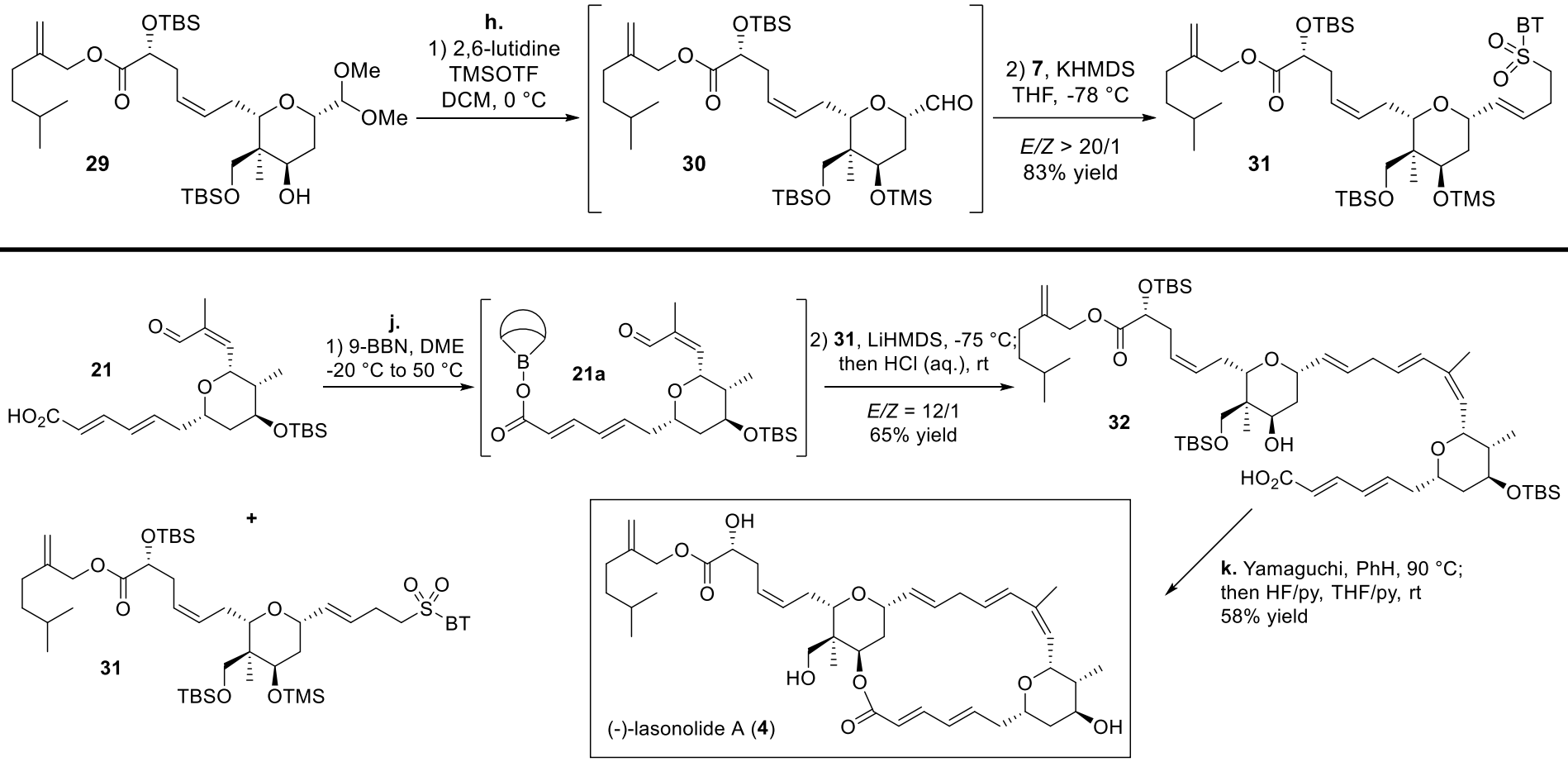

[3+2]
NaBH4
CH3OH
26
26a





Julia Olefination





Yamaguchi esterification