An Enantioselective Total Synthesis of (+)-Peloruside A

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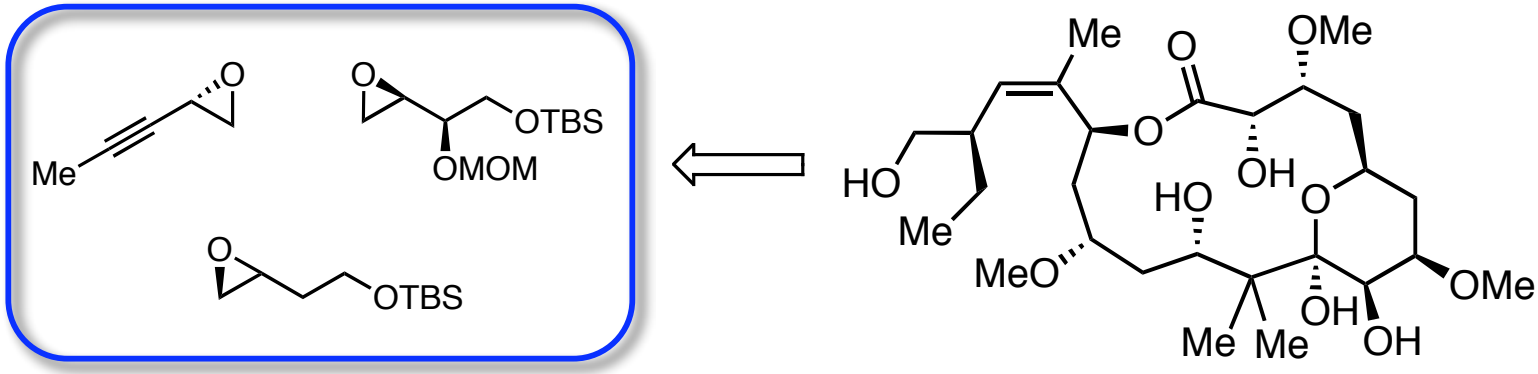
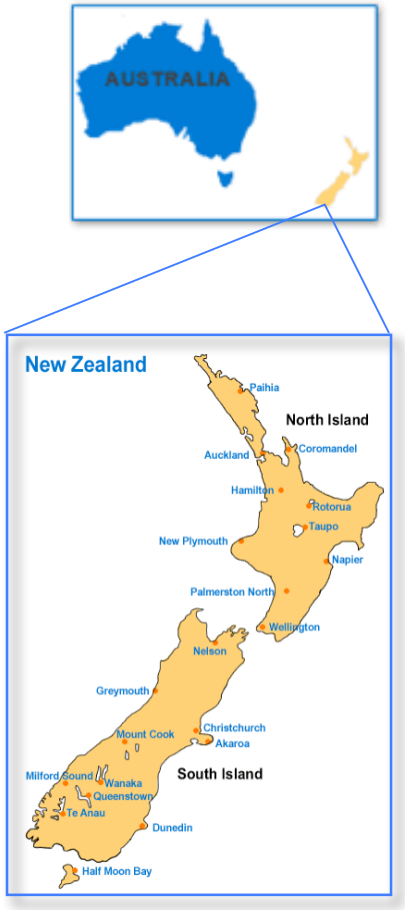
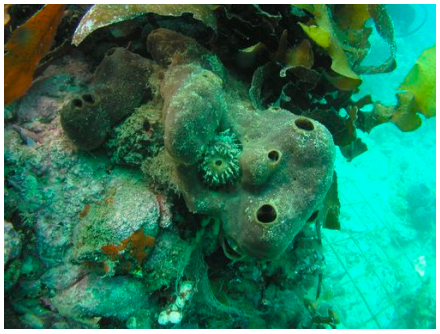


Kara George
Wipf Group - Current Literature
July 10, 2010

Peloruside A: Isolation and Biological Activity

- Isolated in 2000 by Northcote and co-workers from the marine sponge *Mycale hentscheli* collected in Pelorus Sound, New Zealand
- Found to be cytotoxic to P388 murine leukemia cells with an IC_{50}=10 nM
- Exhibits potent paclitaxel-like microtubule stabilizing activity
- Arrests cells in the G_2-M phase of the cell cycle and induces apoptosis
- Less susceptible than paclitaxel to multidrug resistance arising from overexpression of the P-glycoprotein efflux pump (P-gp)
- Not affected by mutations that affect the taxoid binding site of β-tubulin





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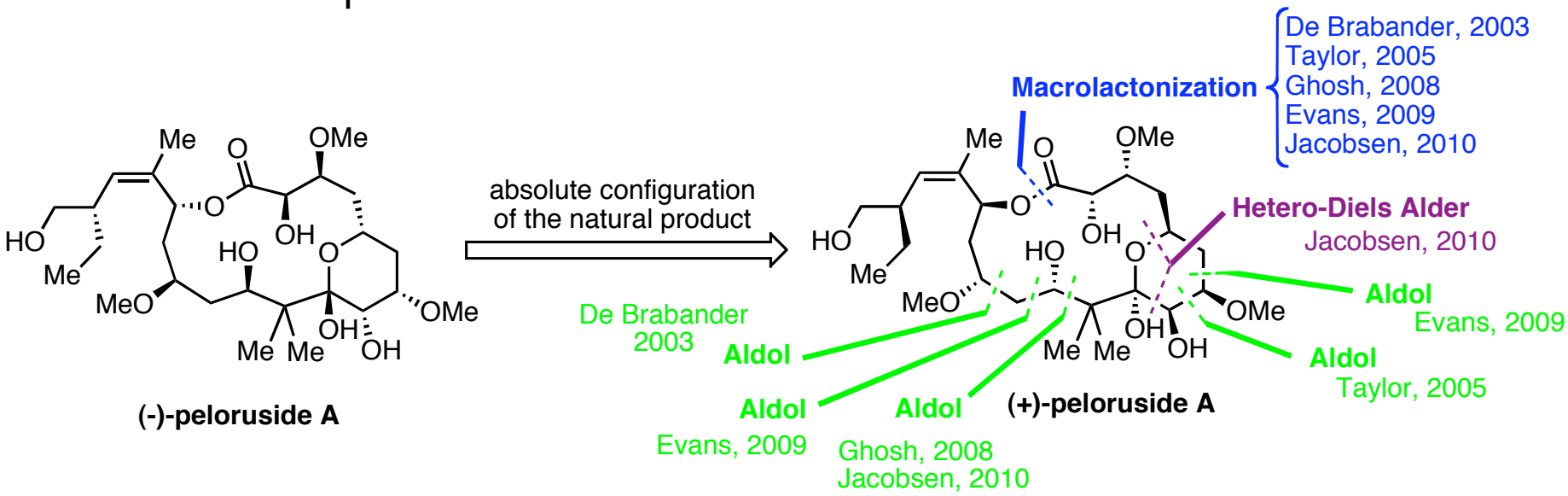
Peloruside A: Structural Determination & Total Synthesis

- Early NMR studies by Northcote and co-workers provided the relative sterochemistry of the 10 stereogenic centers
- First total synthesis of (-)-peloruside A was achieved by De Brabander and co-workers in 2003 and established the of absolute configuration of the natural product to be (+)-peloruside A
- Since the initial total synthesis in 2003, four other total syntheses of (+)-peloruside A have been reported



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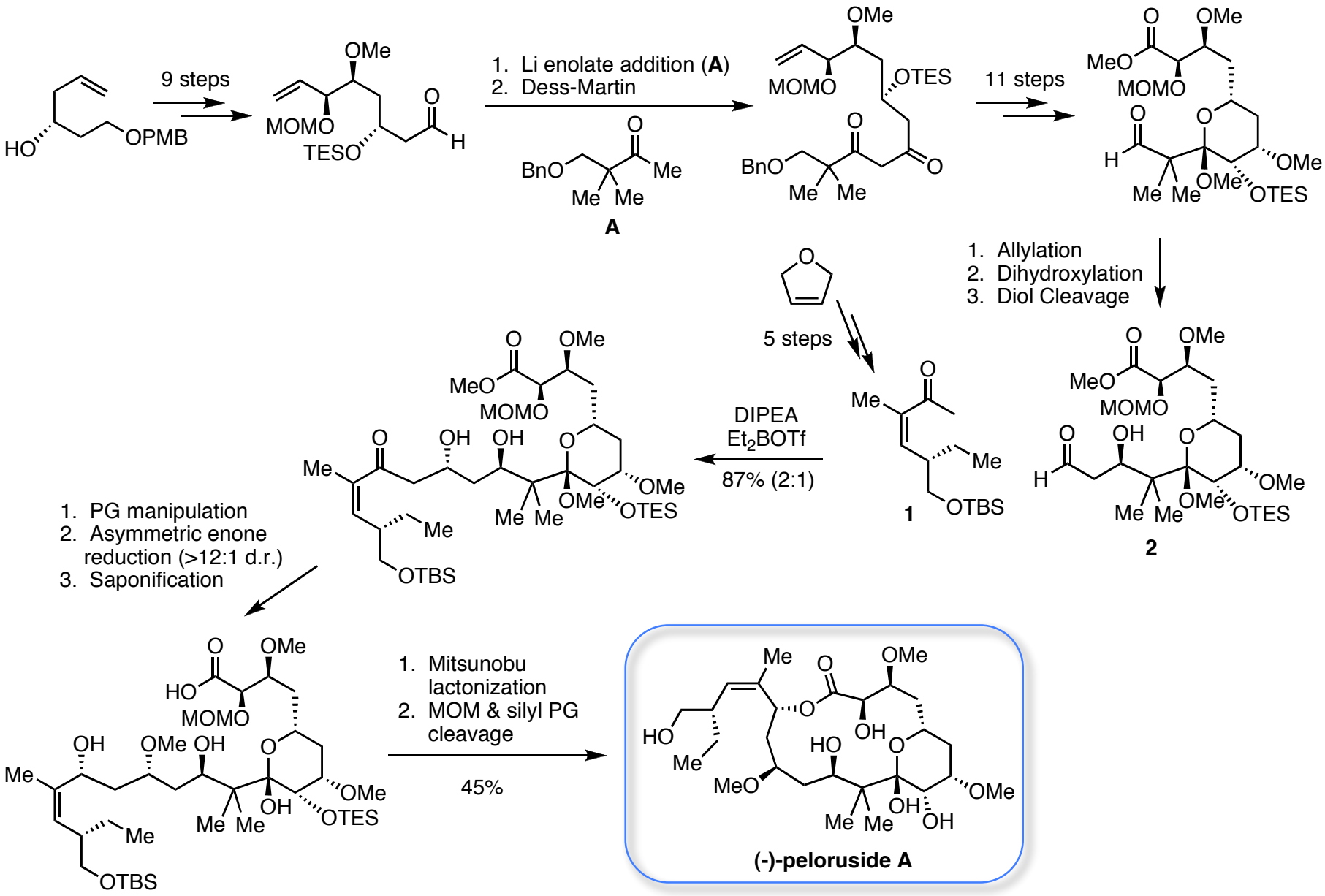
(-)-Peloruside A: First Total Synthesis



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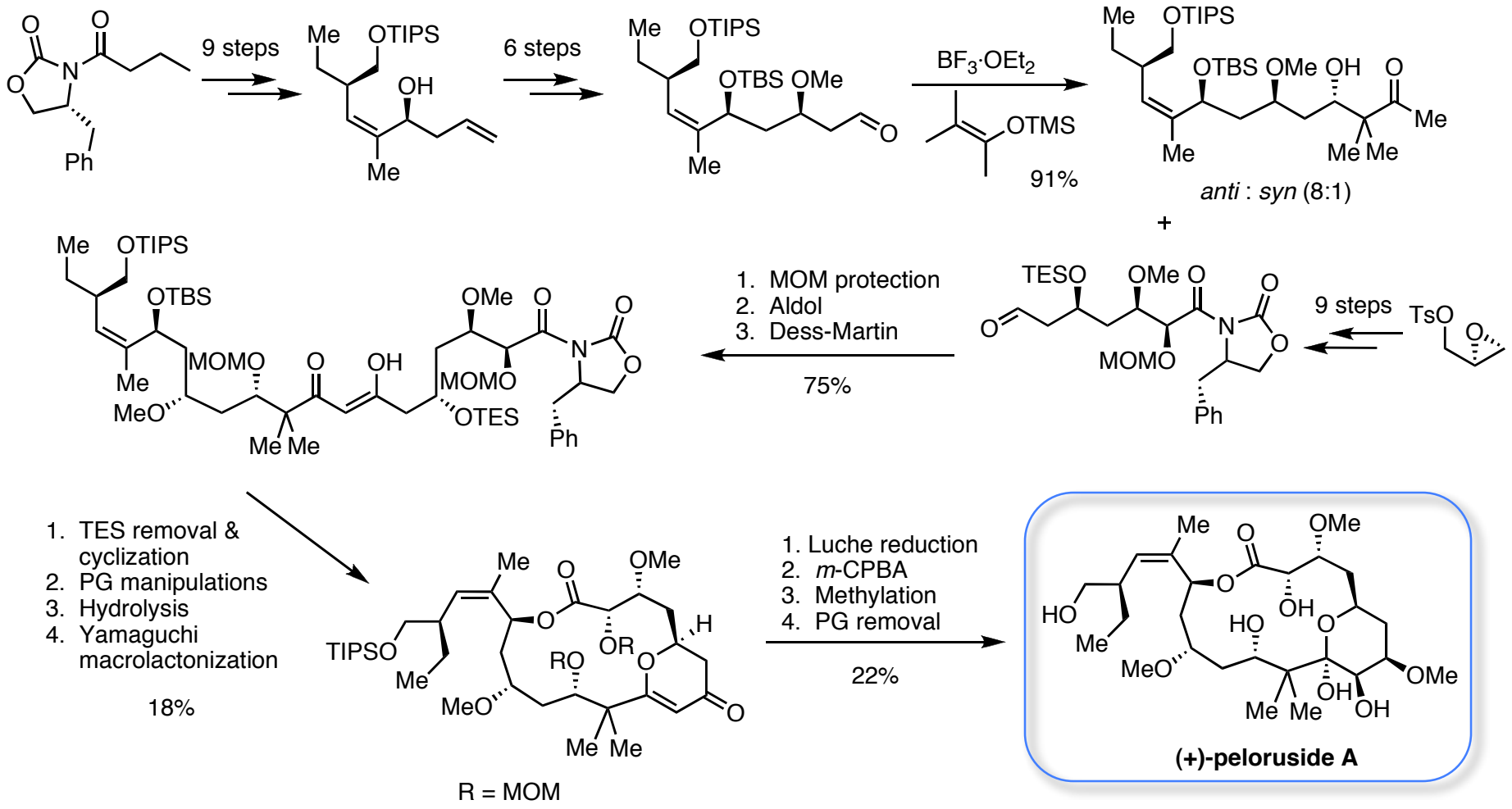
(+)-Peloruside A: Taylor's Synthesis, 2005



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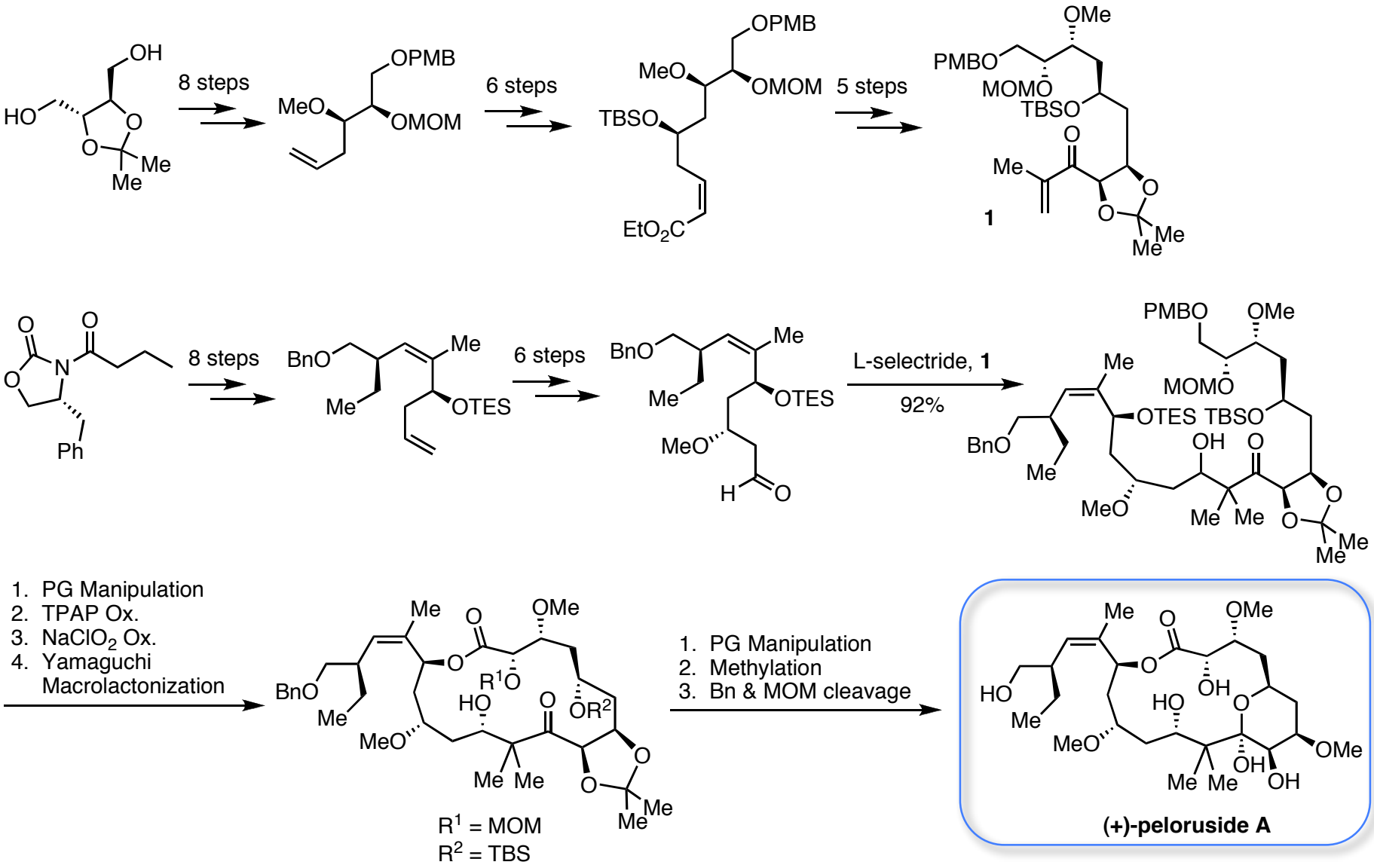
(+)-Peloruside A: Ghosh's Synthesis, 2008



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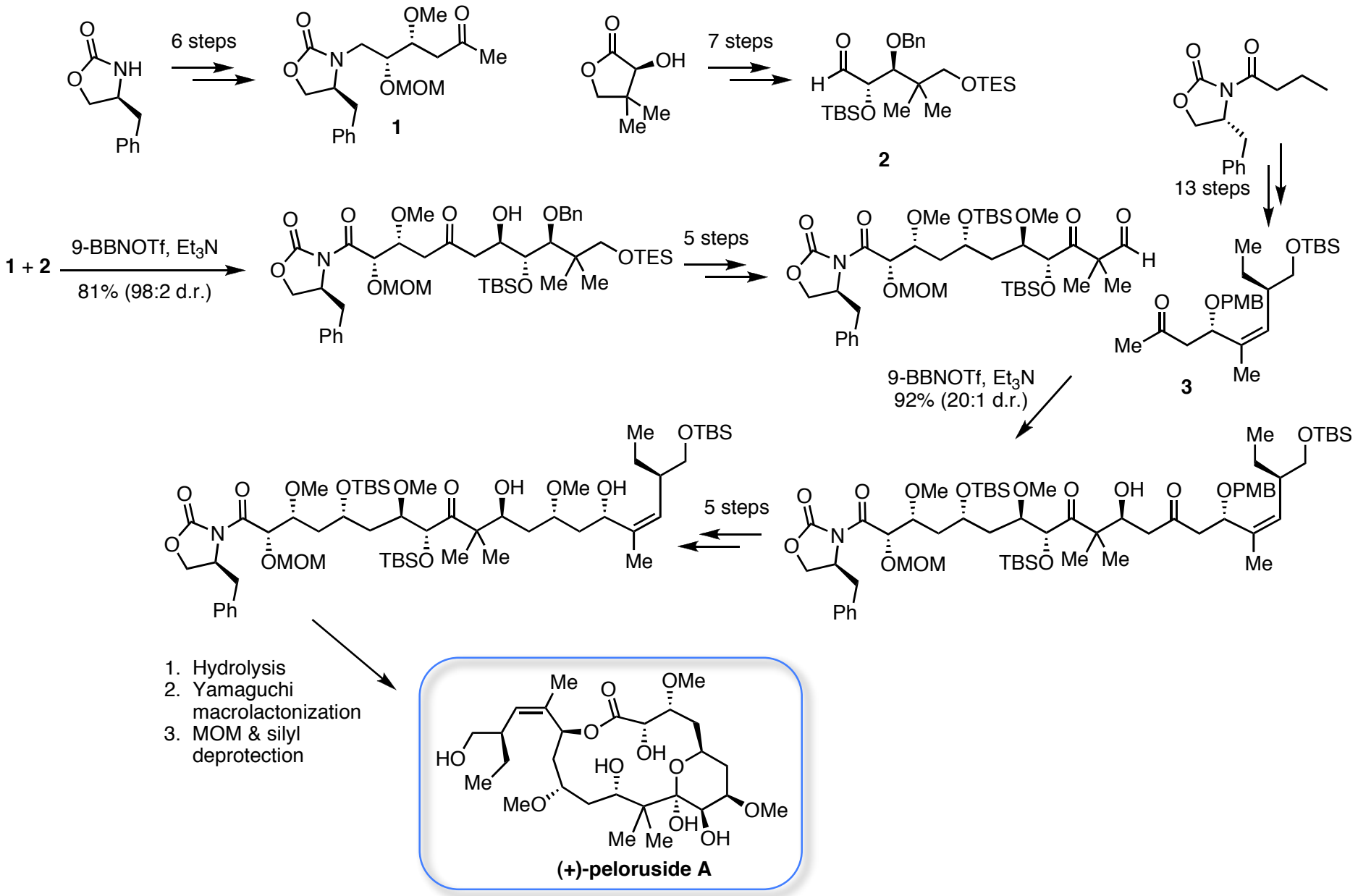
(+)-Peloruside A: Evans' Synthesis, 2009



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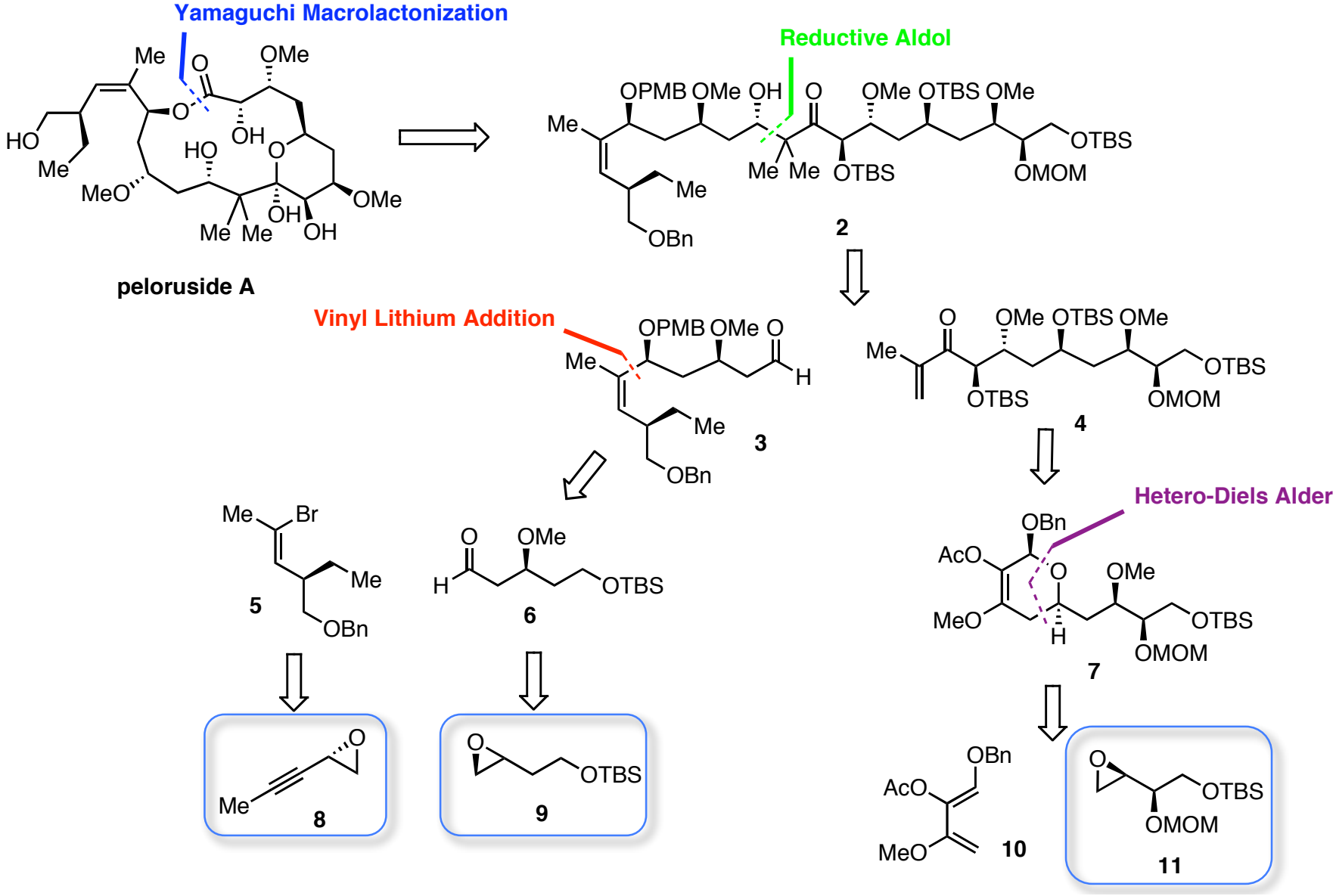

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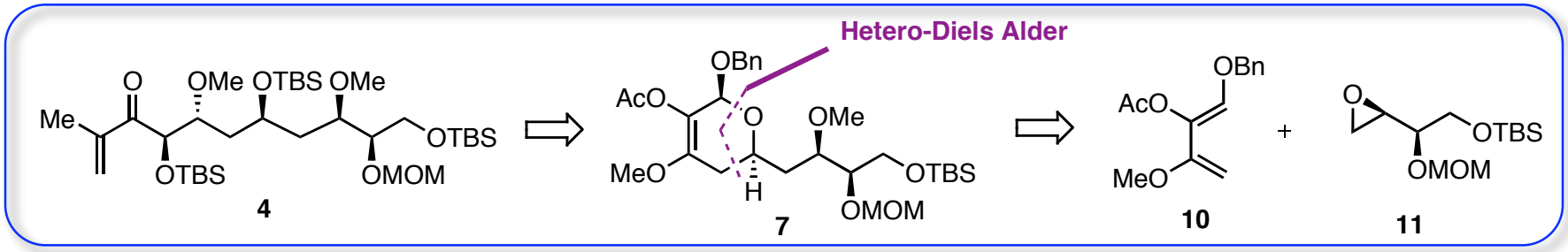

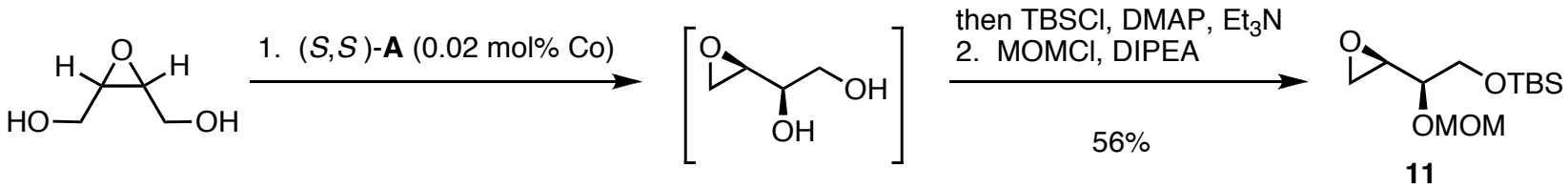

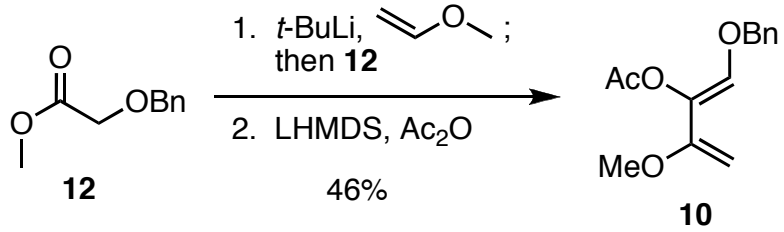

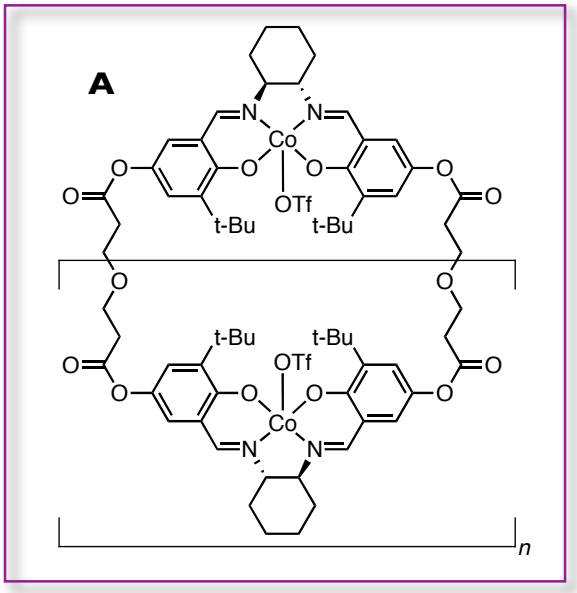

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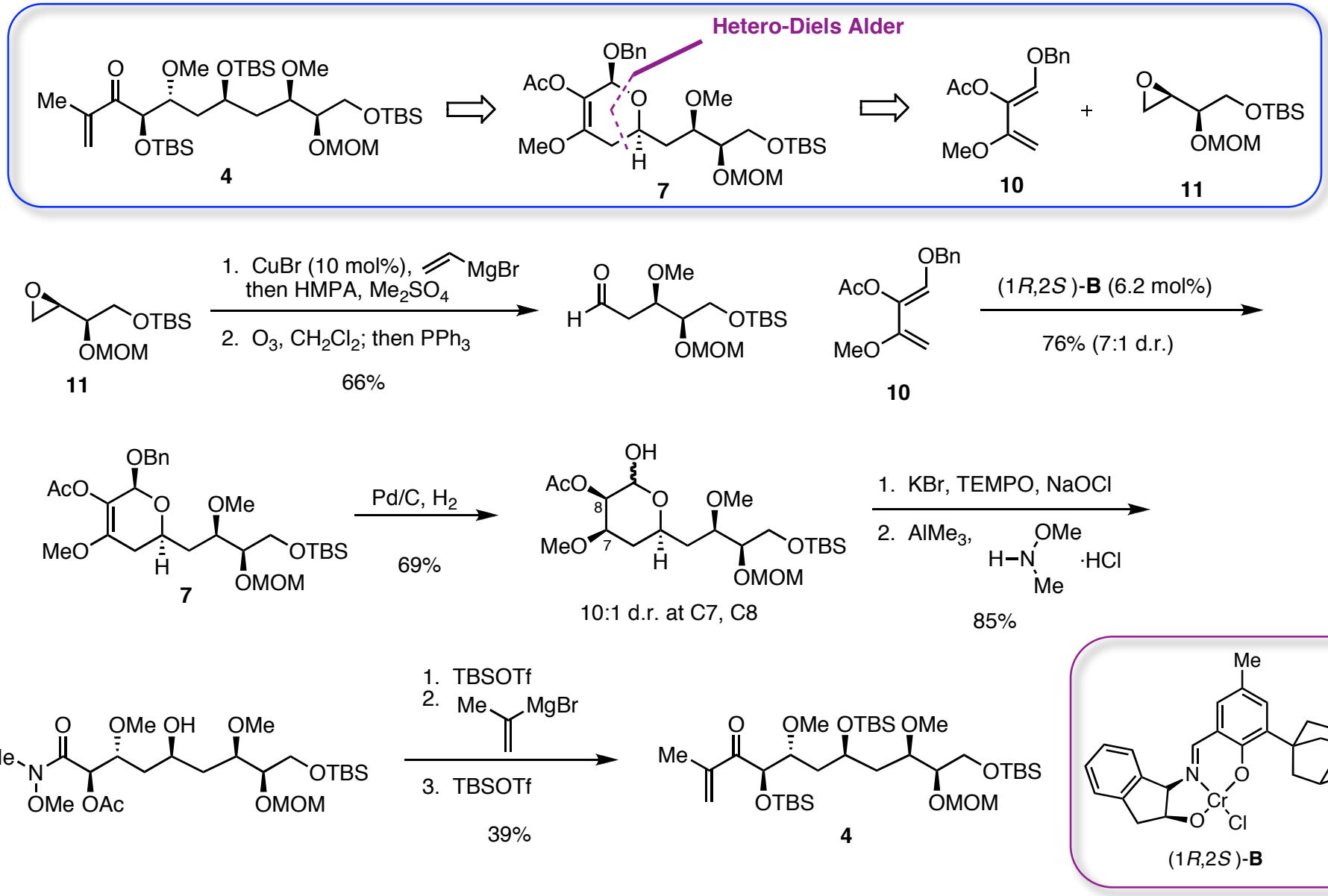

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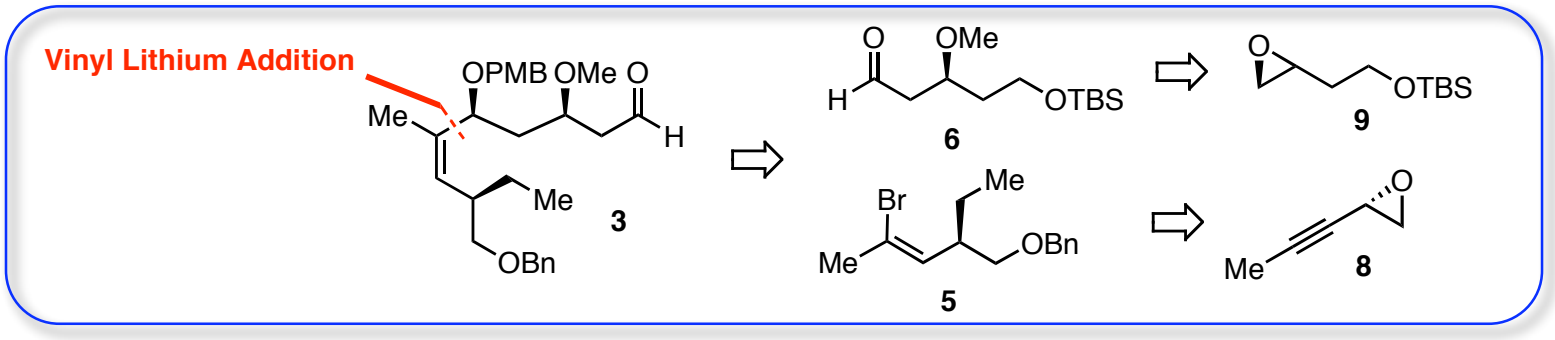

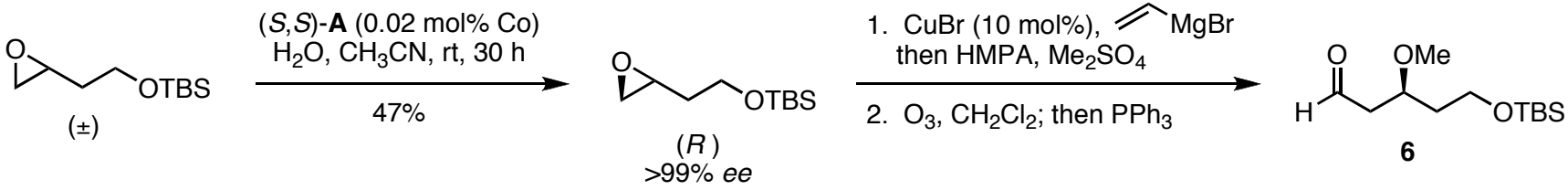

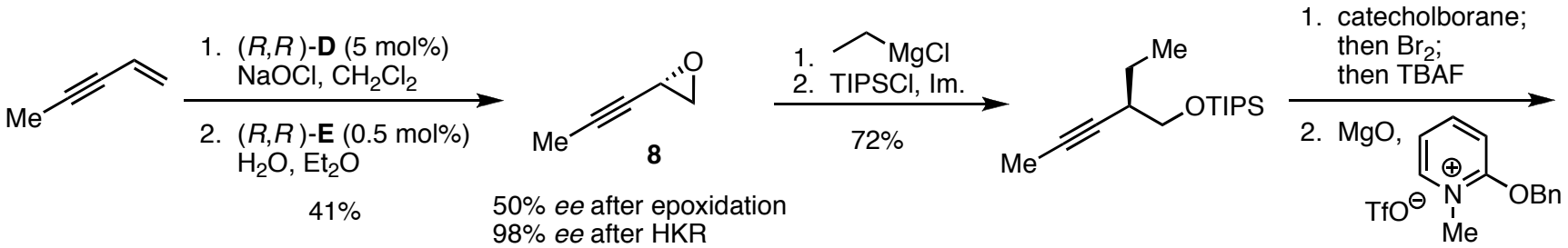

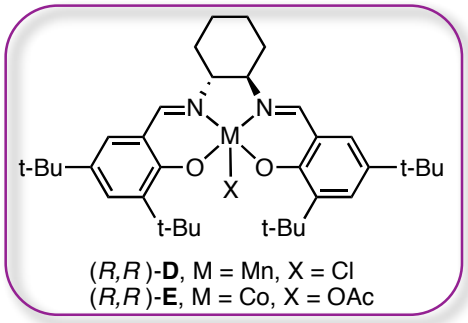

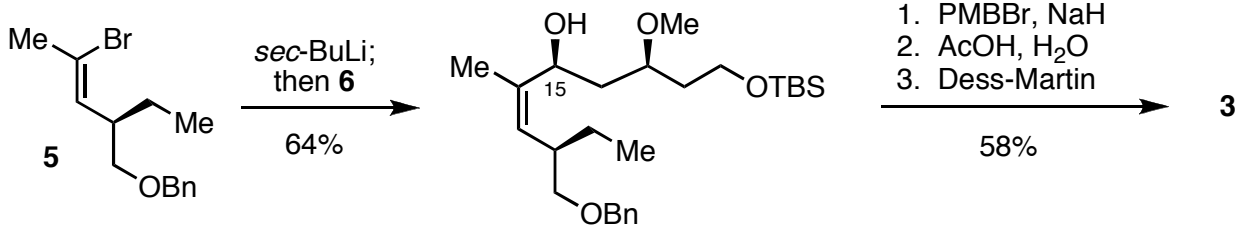

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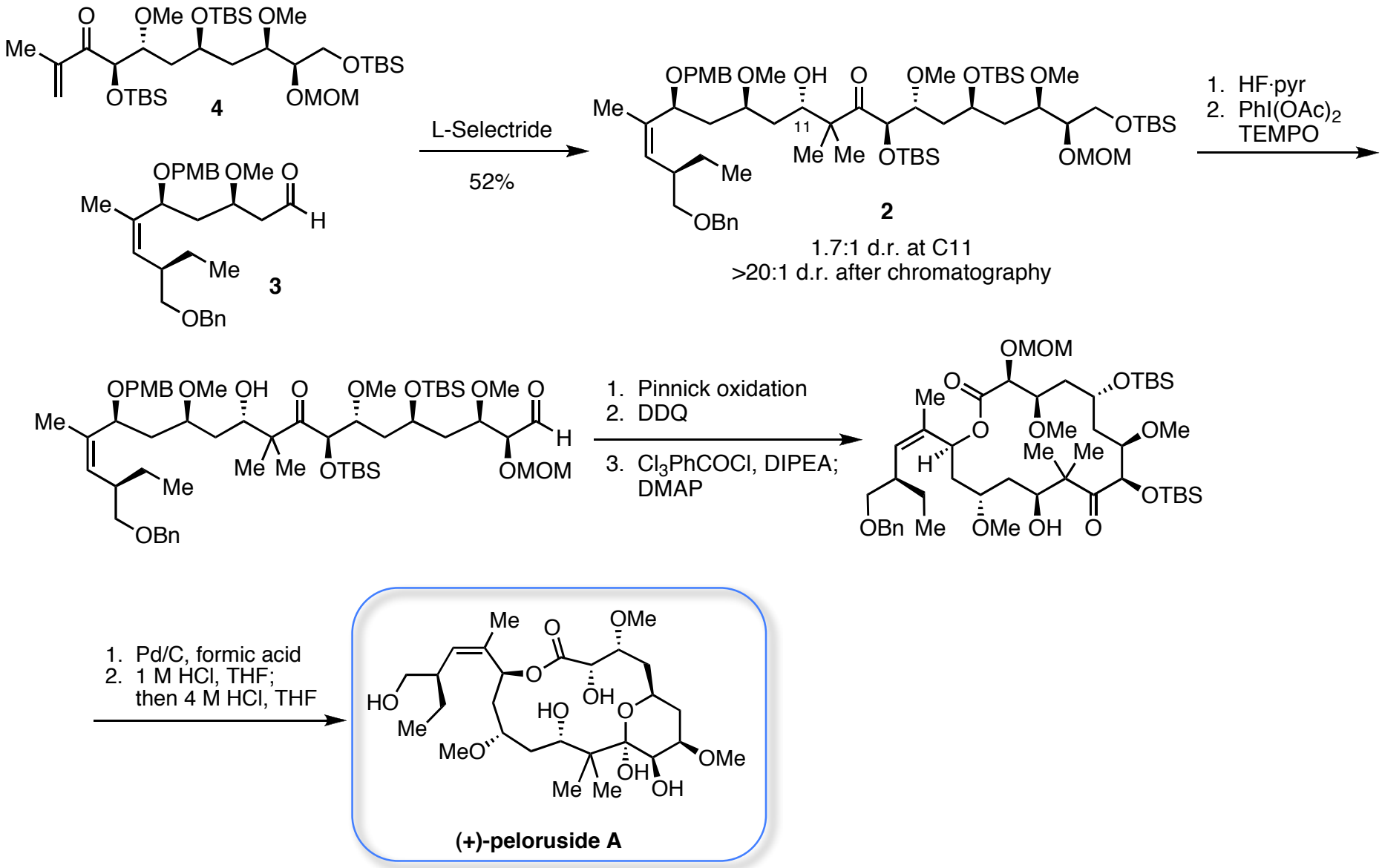

Conclusion

- Convergent total synthesis of (+)-peloruside A was achieved and required 20 steps in the longest linear sequence from commercially available materials
- Utilizes both simple and relatively complex terminal epoxides generated from (salen)Co-catalyzed ring opening reaction
- Features chiral-catalyst induced diastereocontrol in a key hetero-Diels-Alder cycloaddtion reaction between advanced intermediates