Total Synthesis of the *Cephalotaxus* Norditerpenoids (±)-Cephanolides A−D

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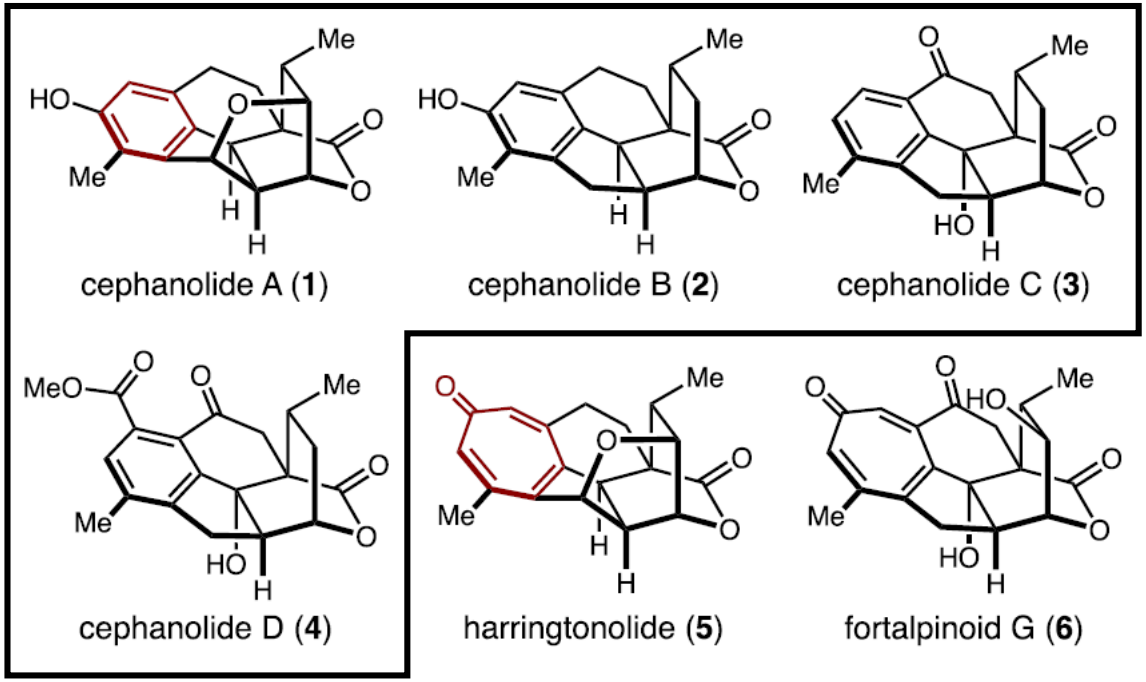
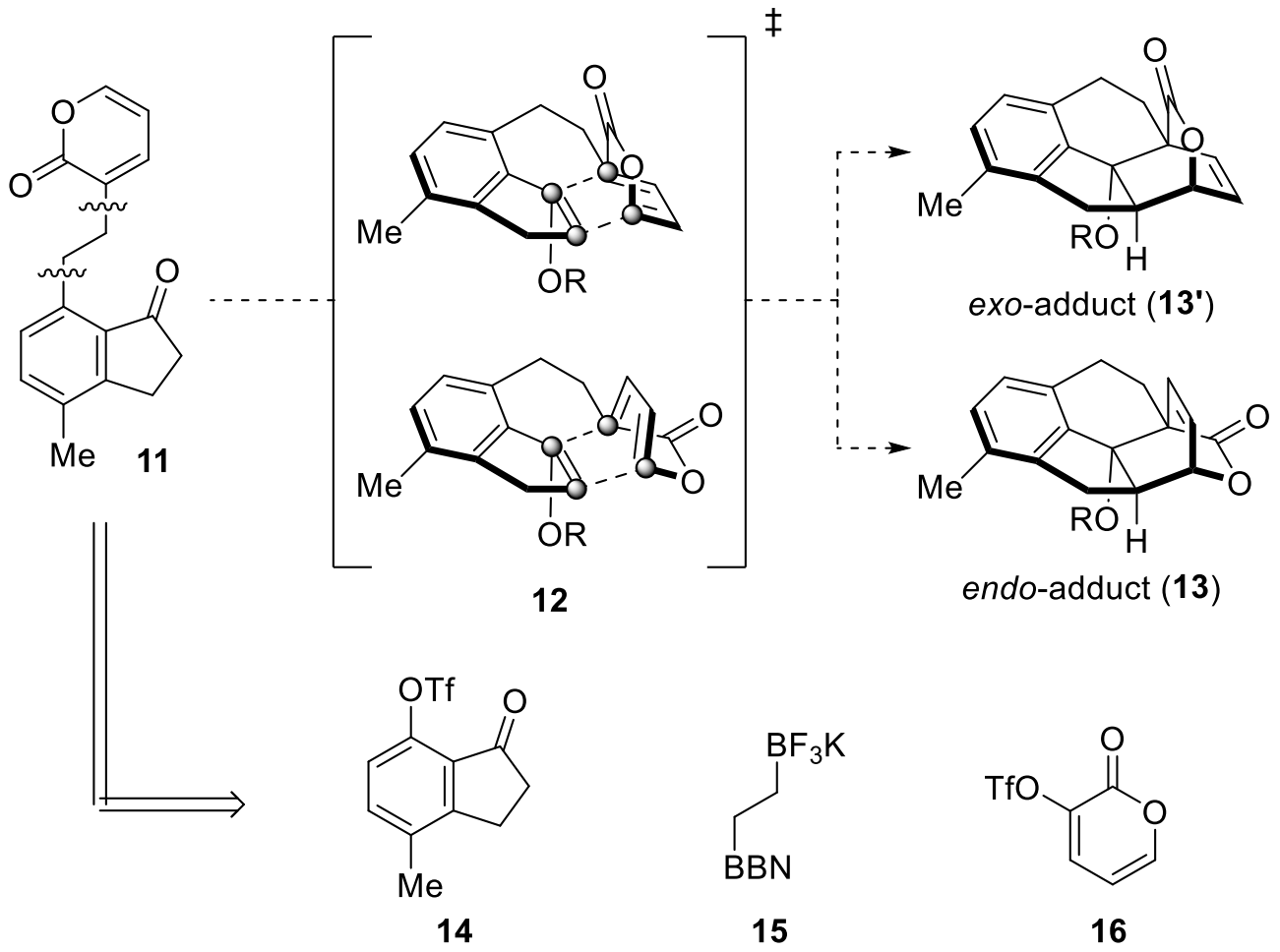
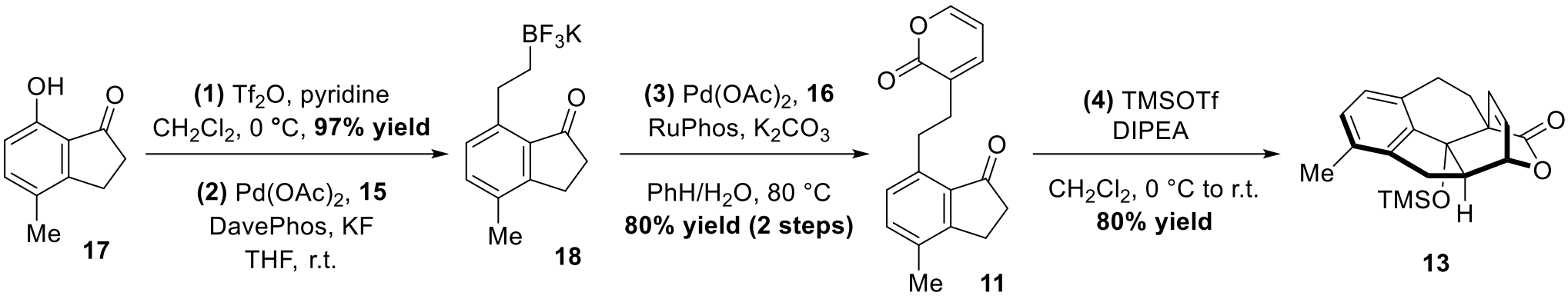
- The larger family of Cephalotaxus diterpenoids have shown a broad range of bioactivity that includes plant growth inhibition as well as antineoplastic, antiviral, and antitumor properties.
- Construction of the carbon framework through: iterative Csp2−Csp3 cross-coupling, intramolecular inverse-demand Diels−Alder cycloaddition, strategic late-stage oxidations, facilitated access to all congeners of the benzenoid cephanolides isolated to date.

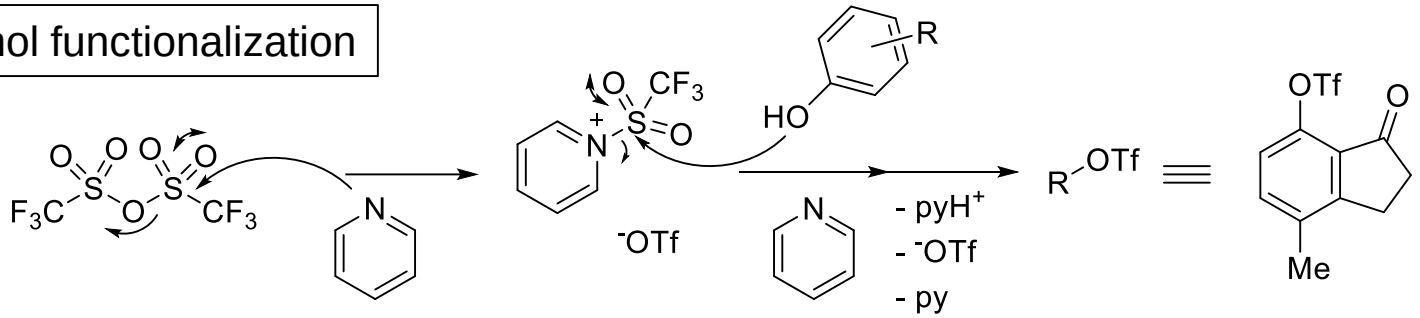


Retrosynthesis

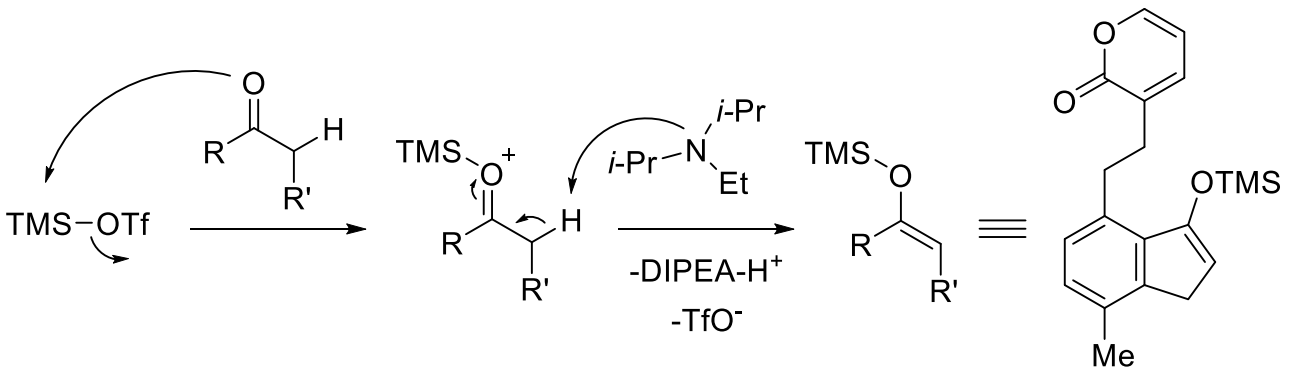




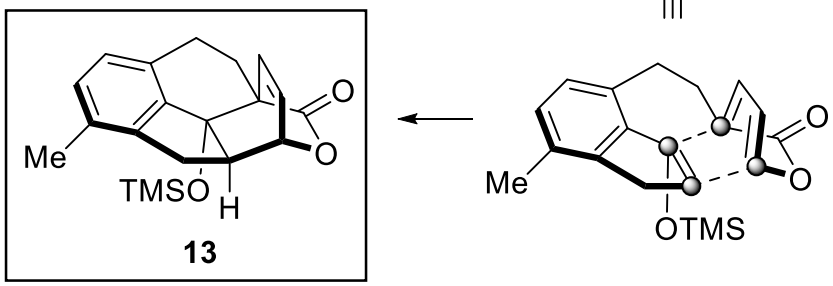
Alcohol functionalization

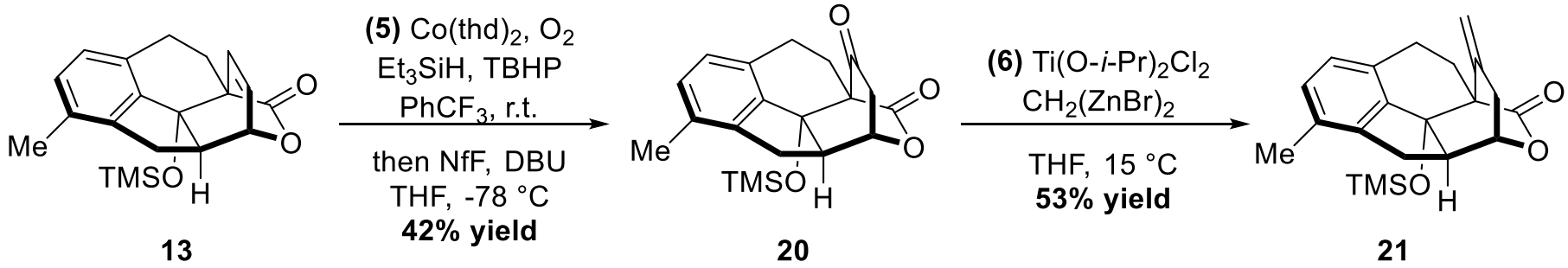


Selective [4+2] cycloaddition



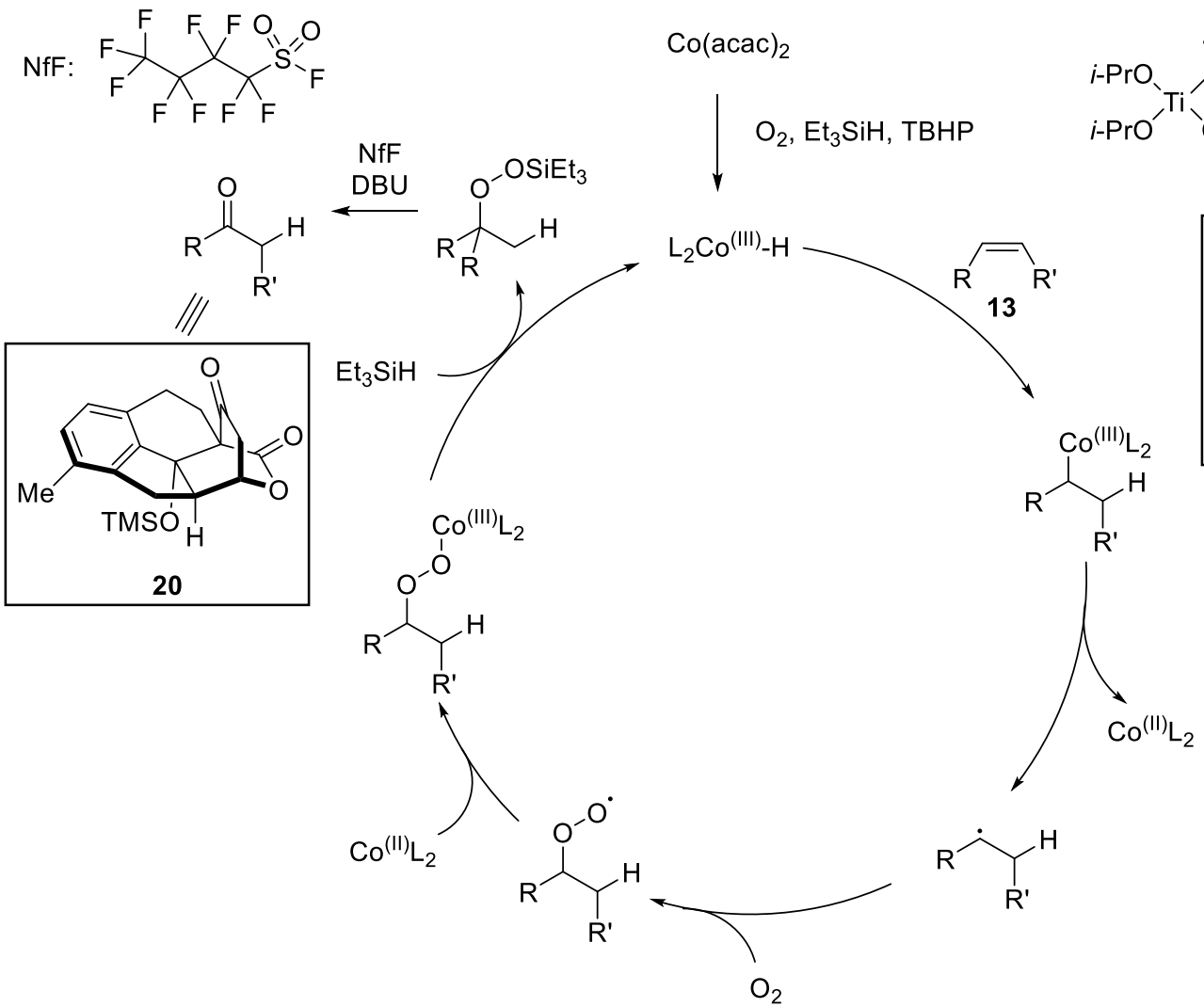
as a single diastereomer

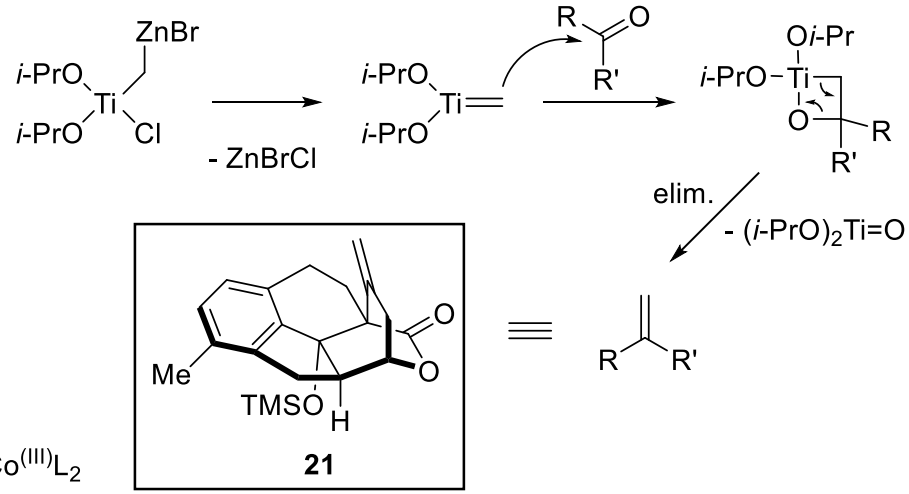


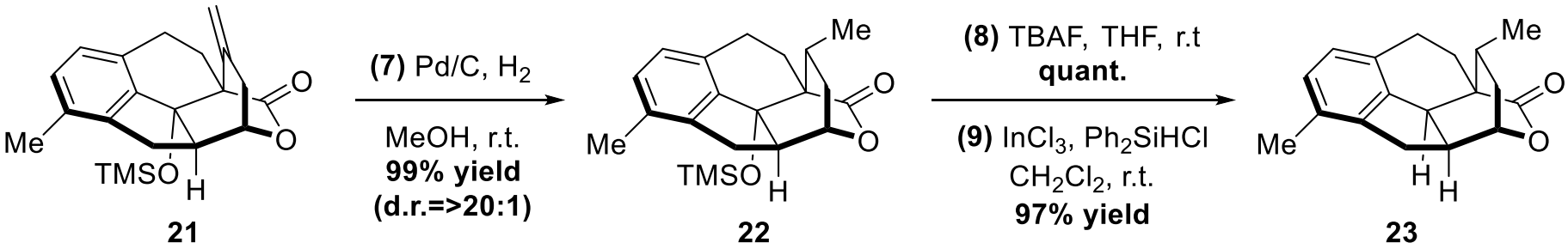


Mukaiyama hydration, then base elimination

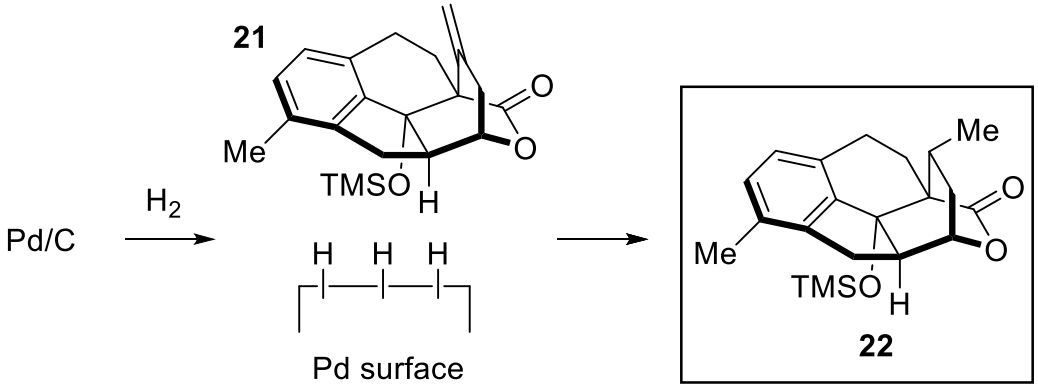
Olefination using a modified protocol



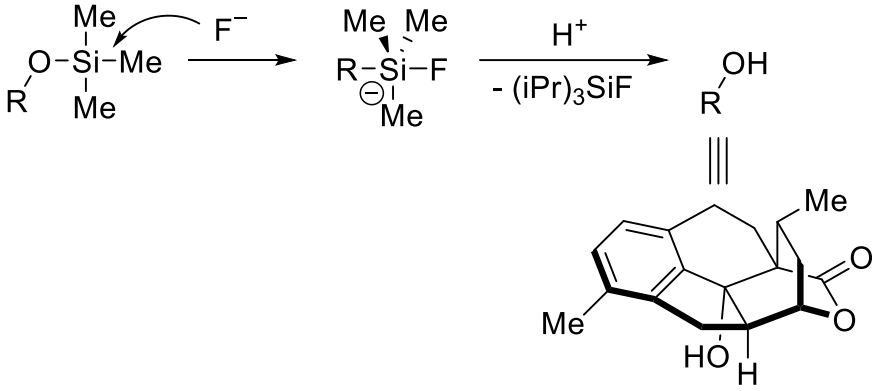




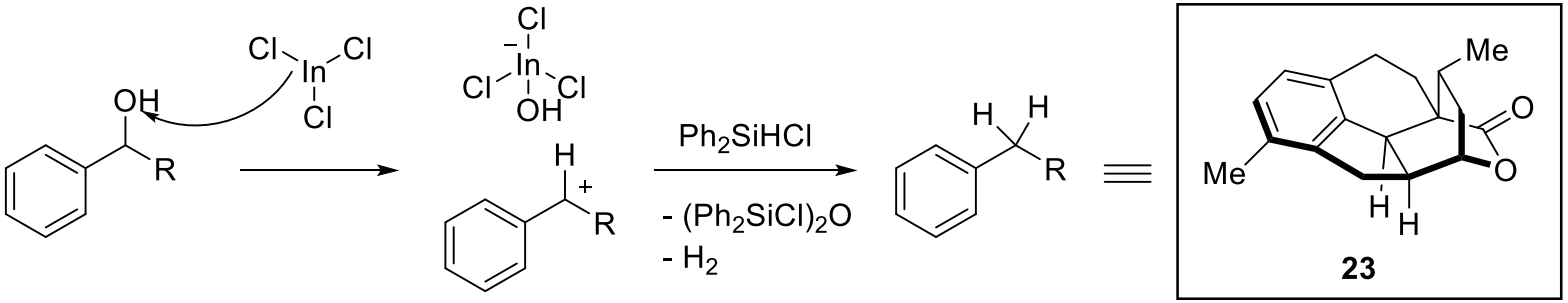
Heterogeneous Pd-catalyzed hydrogenation

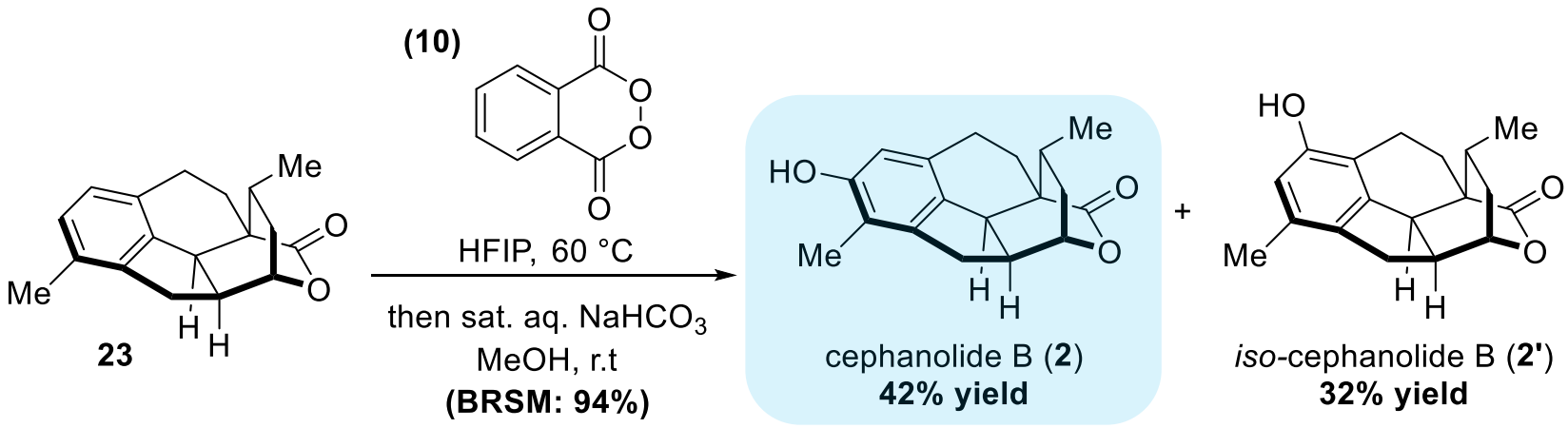


Silyl deprotection with fluoride

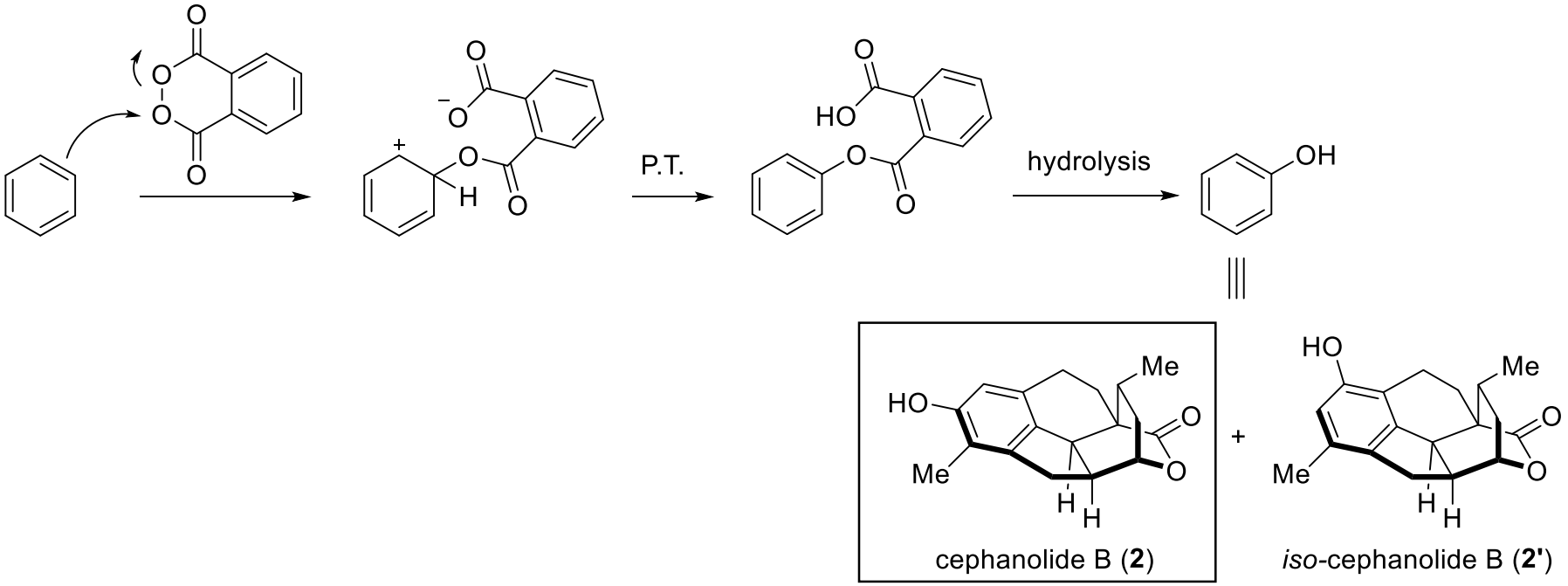


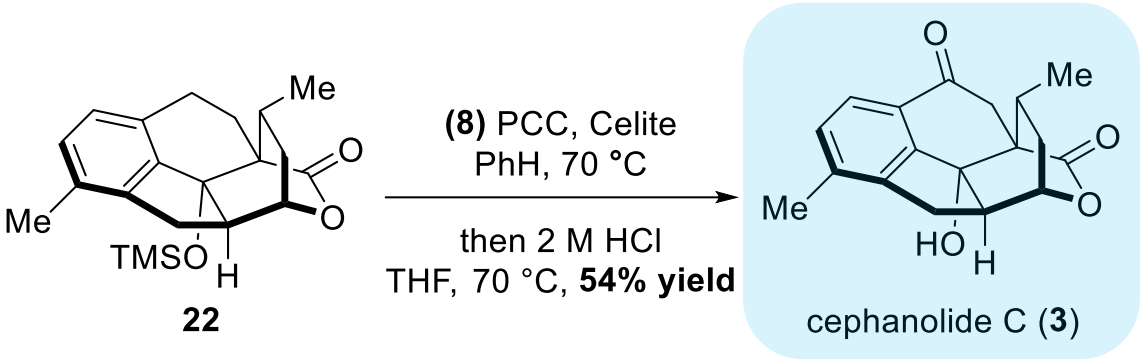
Ionic deoxygenation

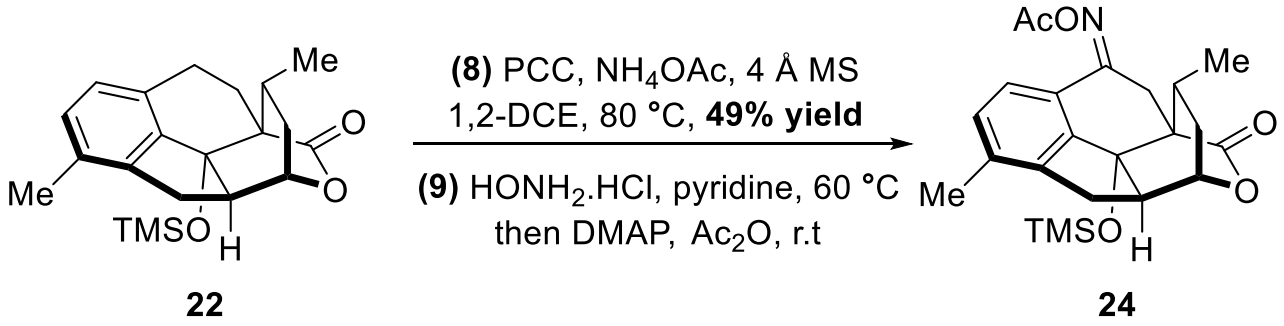




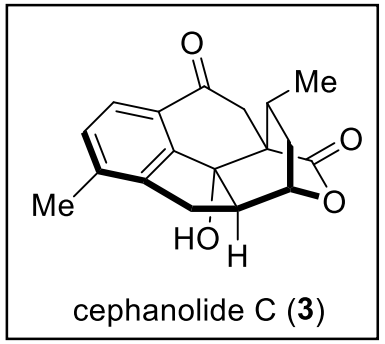
Arene oxidation with phthaloyl peroxide

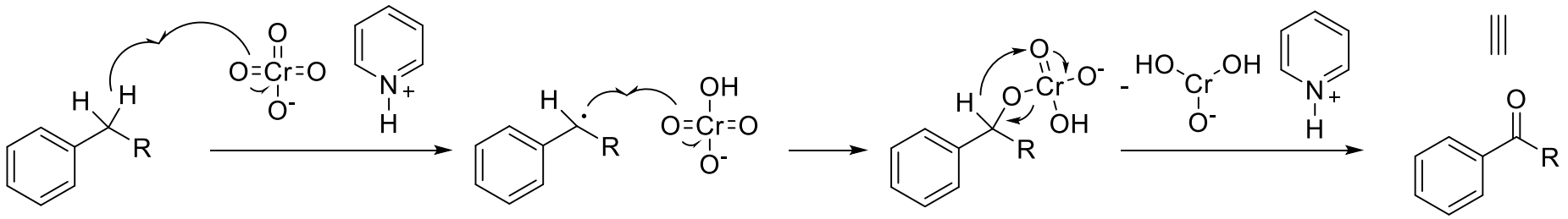






Benzylic oxidation





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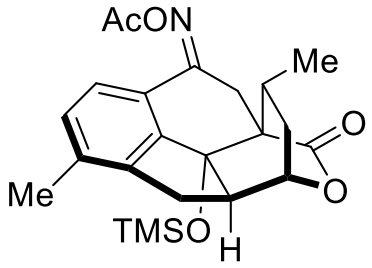
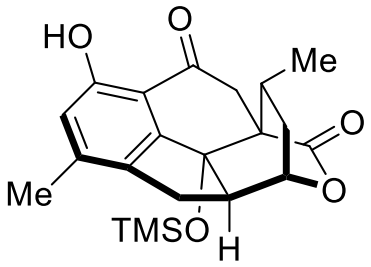
Synthesis of Marine Natural Product (−)-Pericosine E. *Org. Lett.* **2014**, *16*, 3760–3763.



24

(10) $Pd(OAc)_2$, PIDA
$AcOH/Ac_2O$, 100 °C
(11) K_2CO_3, MeOH, r.t.

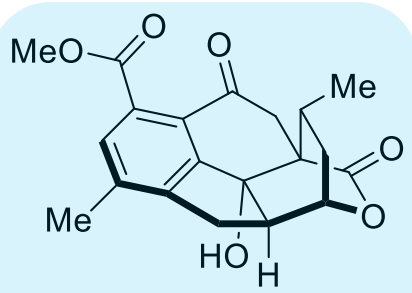
(12) $Fe(NO_3)_3.9H_2O$
O_2, PhMe, 40 °C
33% yield (4 steps)



25

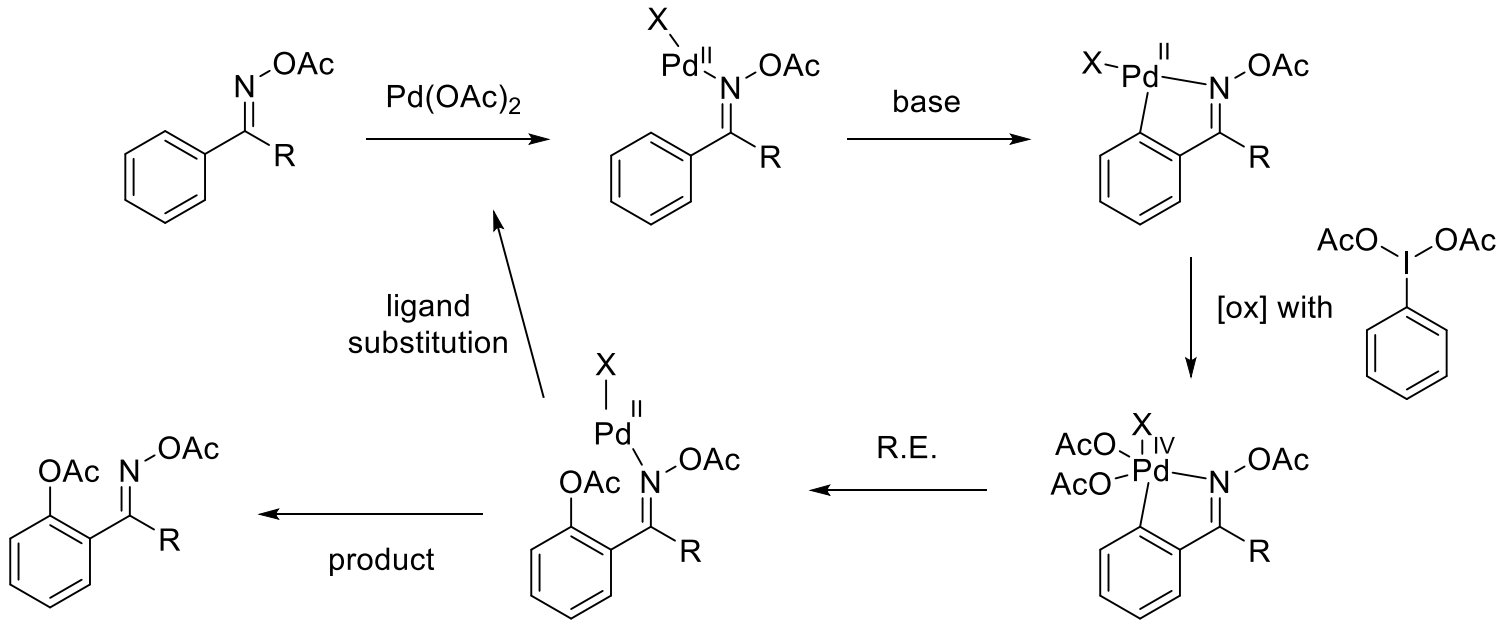
(13) Tf_2O
pyridine, 40 °C
84% yield

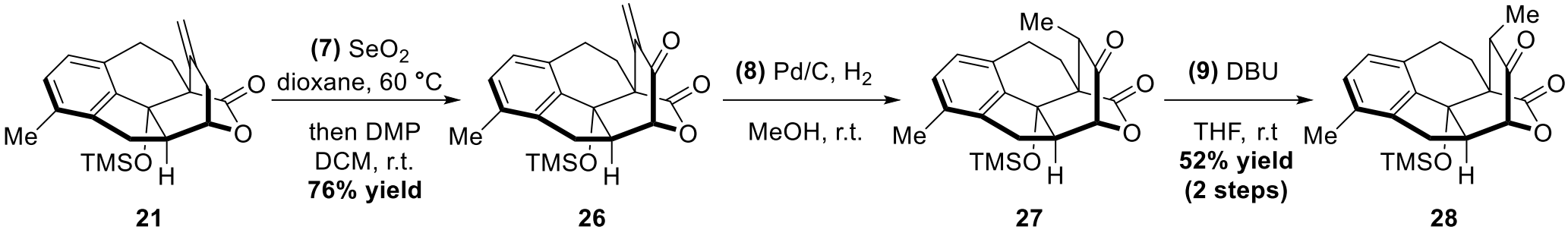
(14) $Pd(dppf)Cl_2$
Et_3N, CO
PhMe/MeOH, 60 °C
then TBAF, r.t.
93% yield



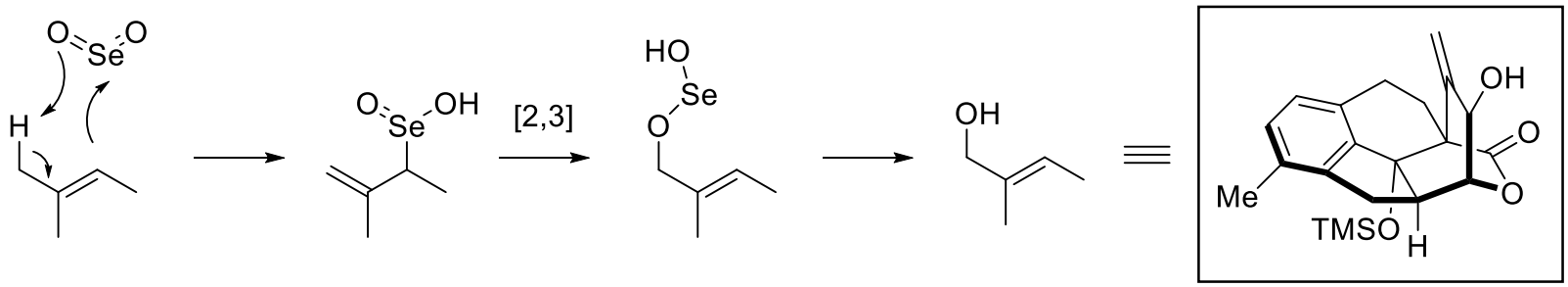
cephanolide D (**4**)

Oxime-directed arene acetylation

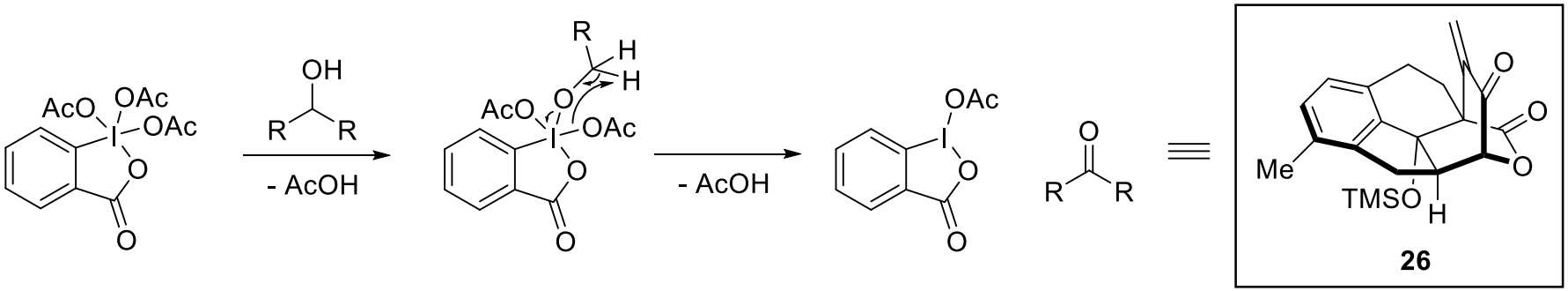


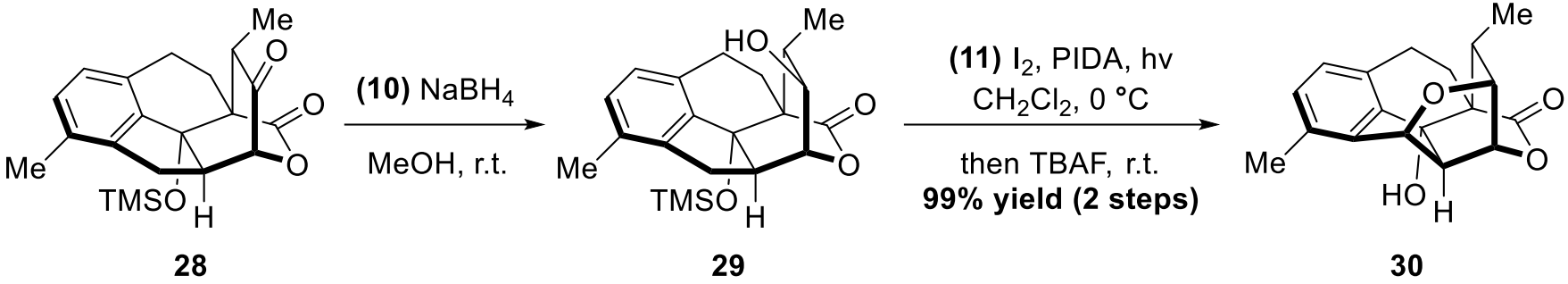


Allylic oxidation with selenium dioxide

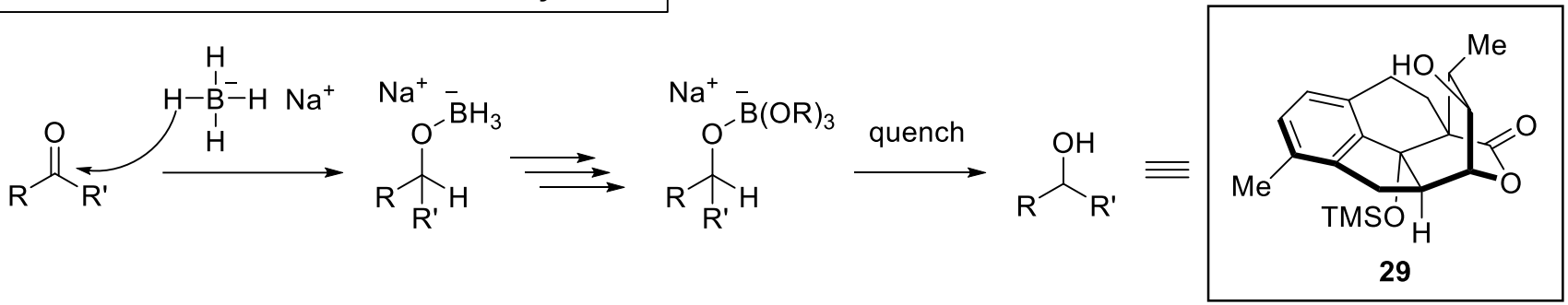


Dess-Martin Oxidation

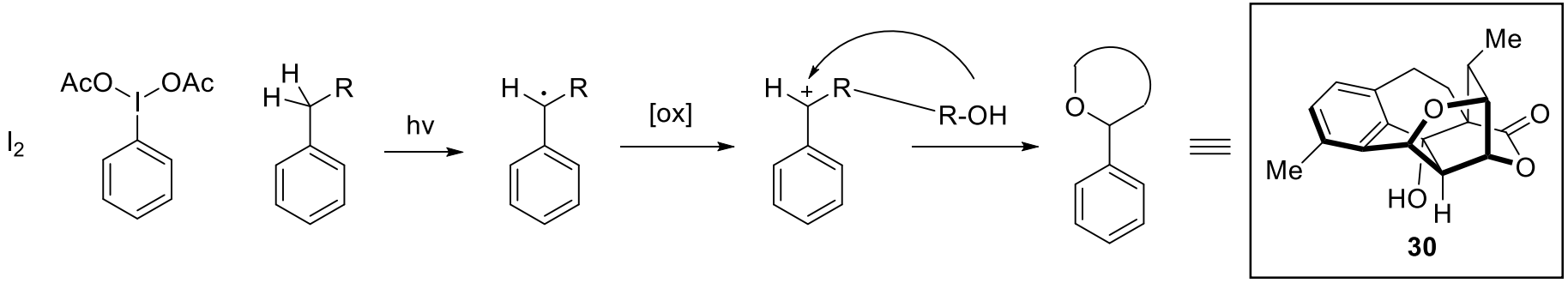


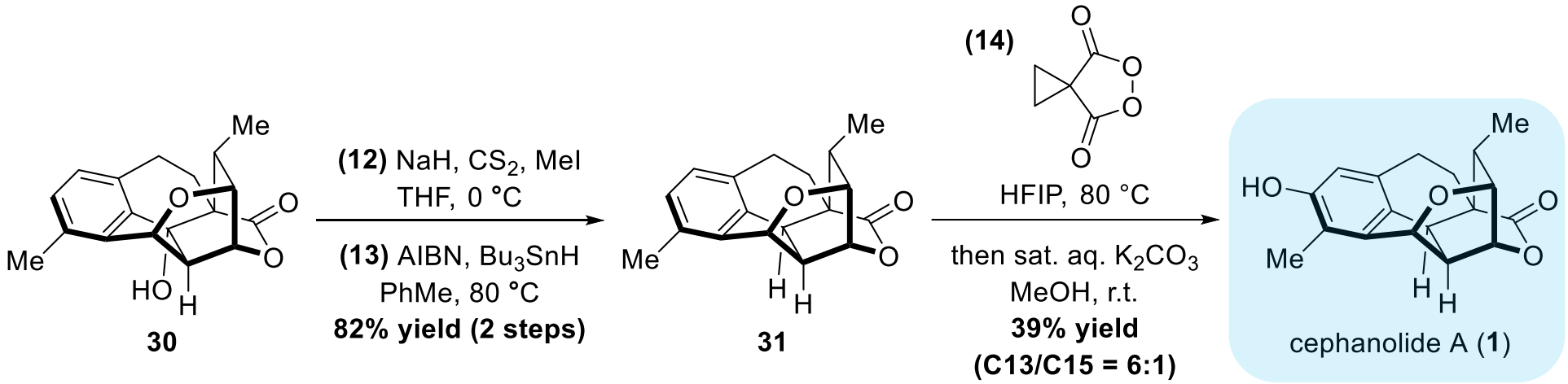


Ketone reduction with sodium borohydride

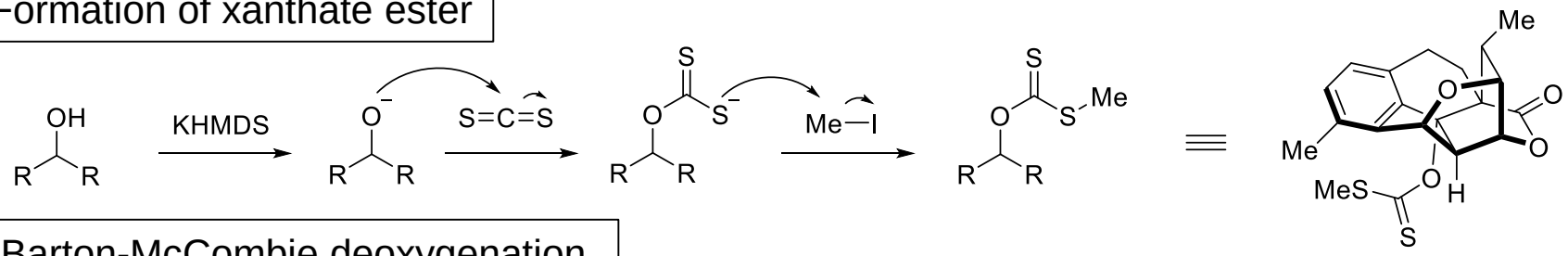


Intramolecular benzylic oxidation



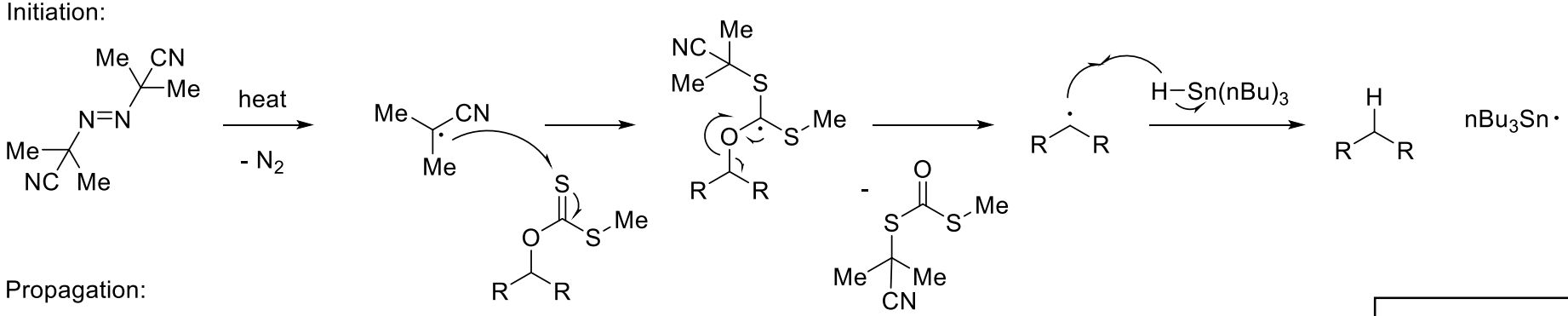


Formation of xanthate ester



Barton-McCombie deoxygenation

Initiation:



Propagation: