Synthesis of the Death-Cap Mushroom Toxin α-Amanitin

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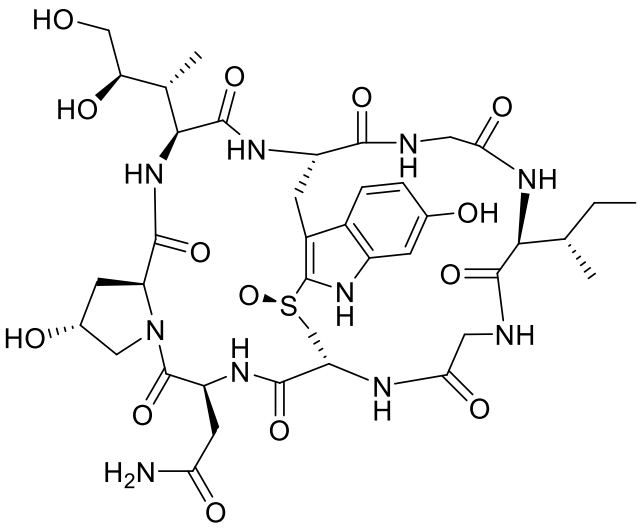
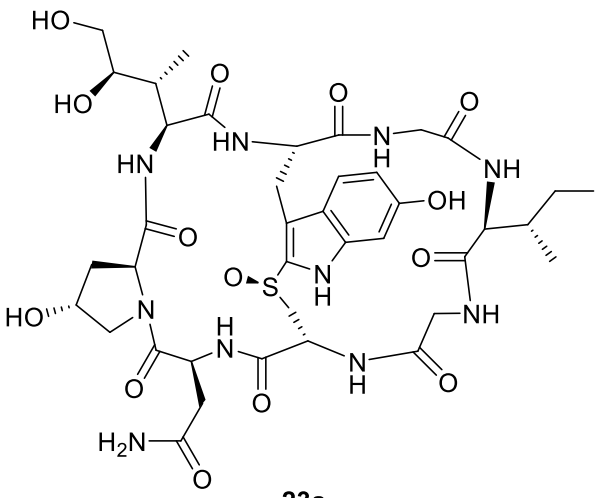
- One of the deadliest toxins known to humankind (LD50 = 50-100 ug/kg). Principal toxin of the amatoxin family of peptides produced by *Amanita phalloides*, the notorious death cap mushroom.
- A potent, orally available, highly selective allosteric inhibitor of RNA polymerase II.
- A bicyclic octapeptide structure containing two oxidized amino acids, which are key to its toxicity: *trans*-4-hydroxyproline (Hyp) and (2S,3R,4R)-4.5-dihydroxyisoleucine. Also contains a cross-linking 6-hydroxyl-tryptathionine-(R)-sulfoxide that is unique among natural products.
- Recently, it was shown that α-amanitin when injected at sublethal doses, prevents cancer relapse in mice bearing tumor xenografts that are resistant to common chemotherapeutics.
- Antibody-drug conjugates of α-amanitin have also been shown to cure mice of pancreatic cancer xenografts, and this is advancing towards human trials.



α-Amanitin (**23a**)

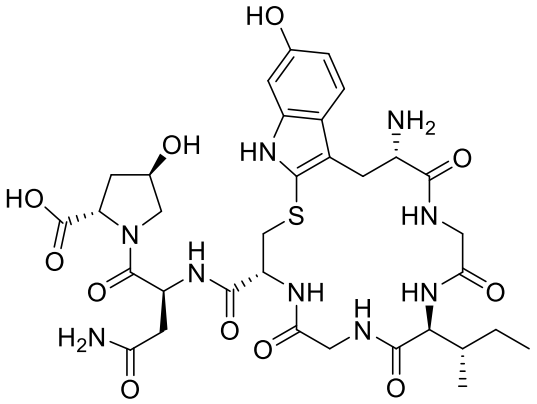
Ricky Alvarado
June 20th, 2018
Liu Group

Retrosynthesis



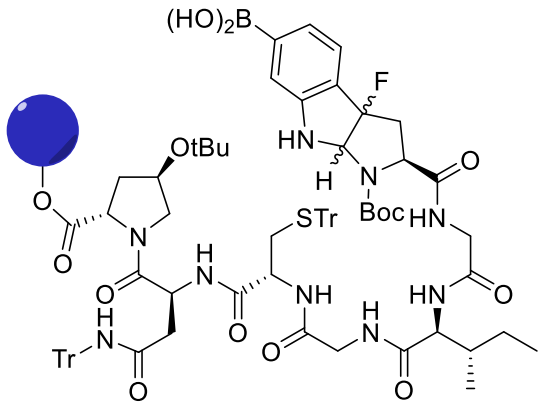
23a

DHIle Coupling
Macrolactamization
Sulfoxidation

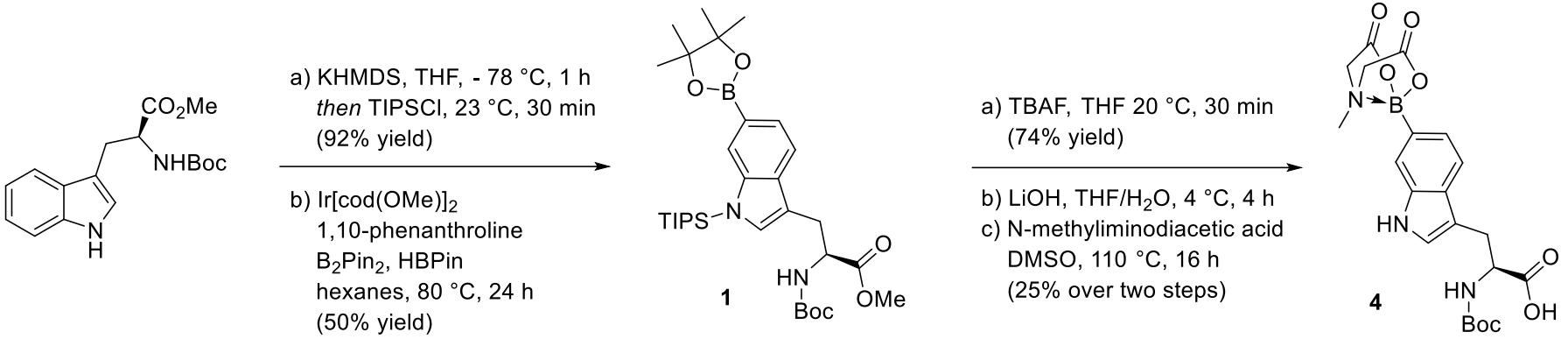


8

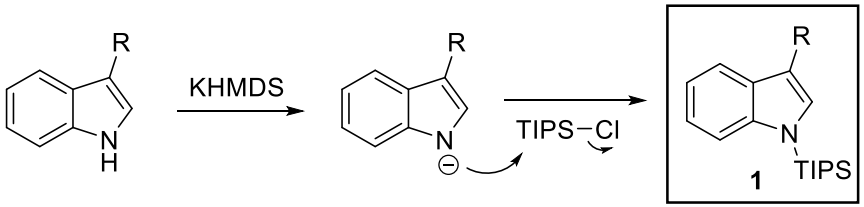
Tryptathionylation
Oxidative deborylation



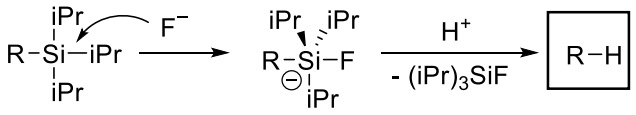
6'



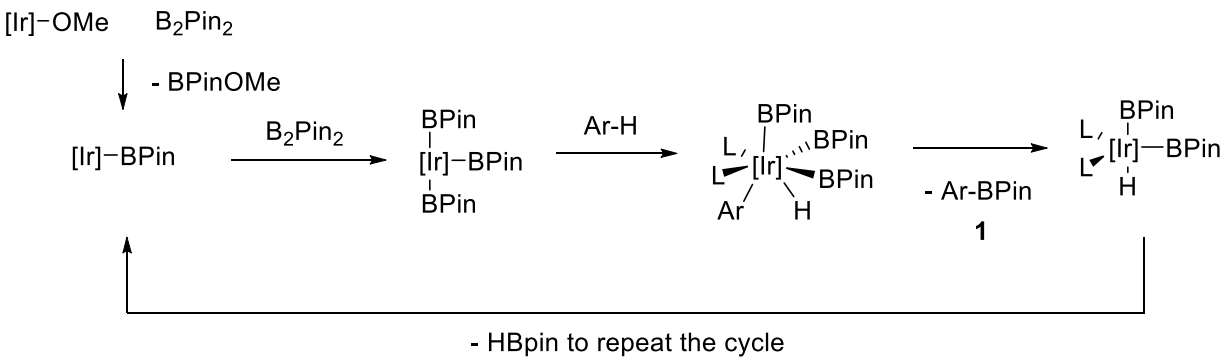
Silyl group protection

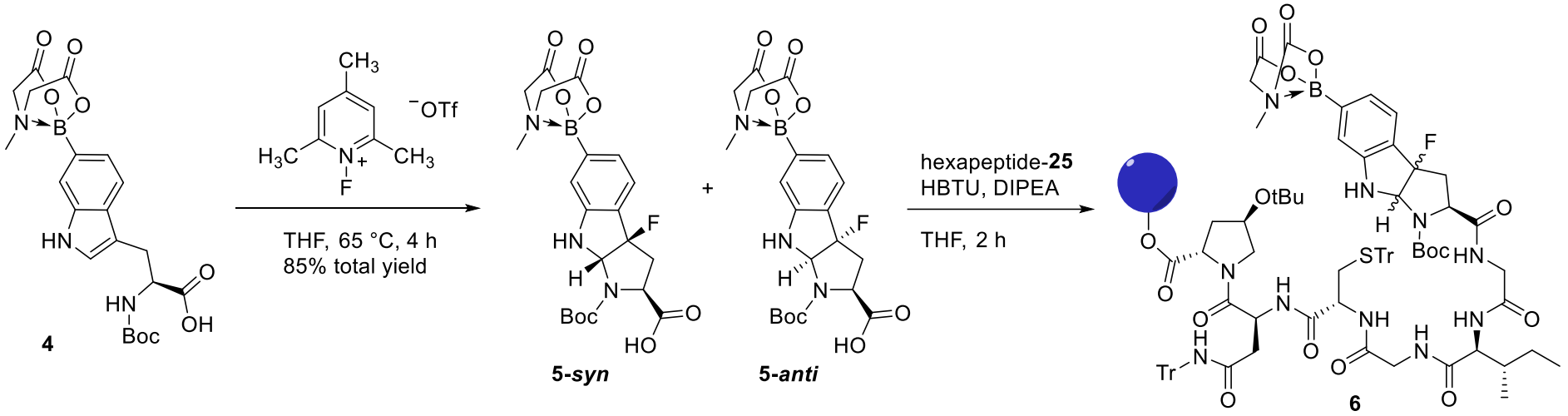


Silyl deprotection by fluorine

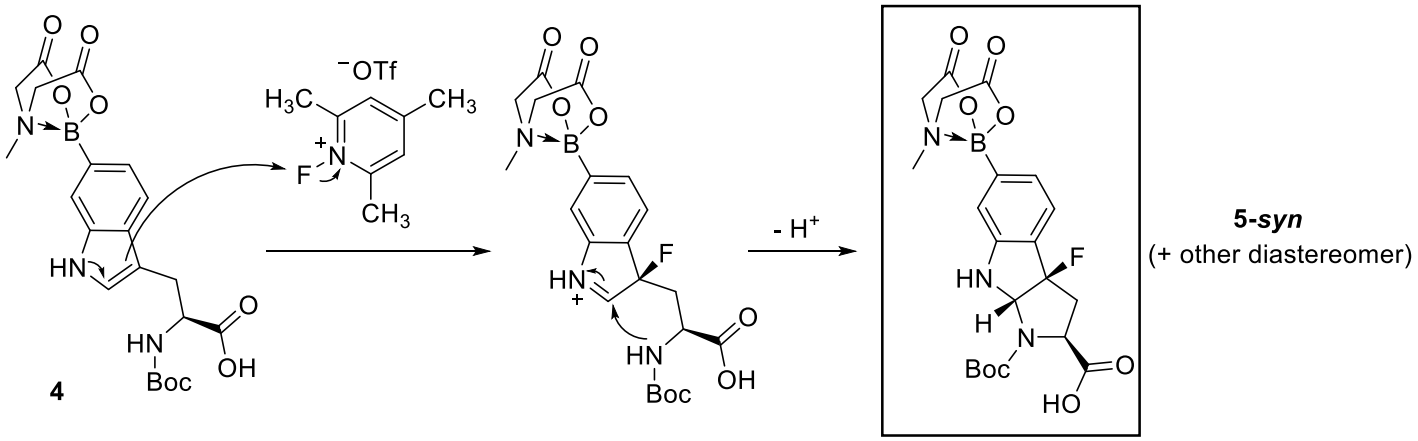


Ir-catalyzed C-H borylation



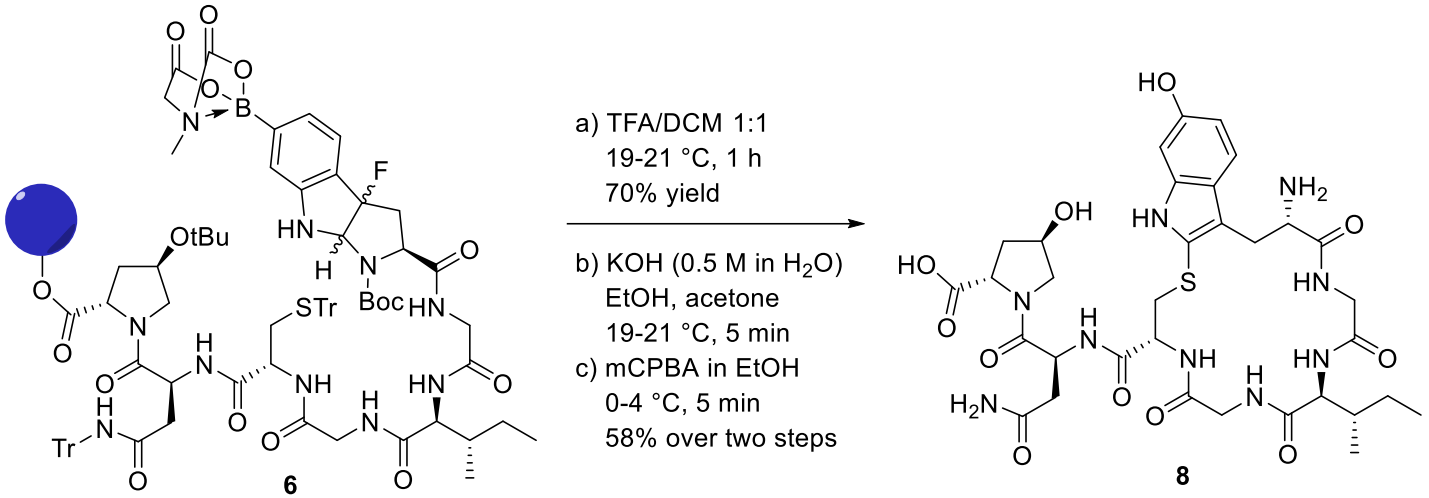


Electrophilic fluorocyclization

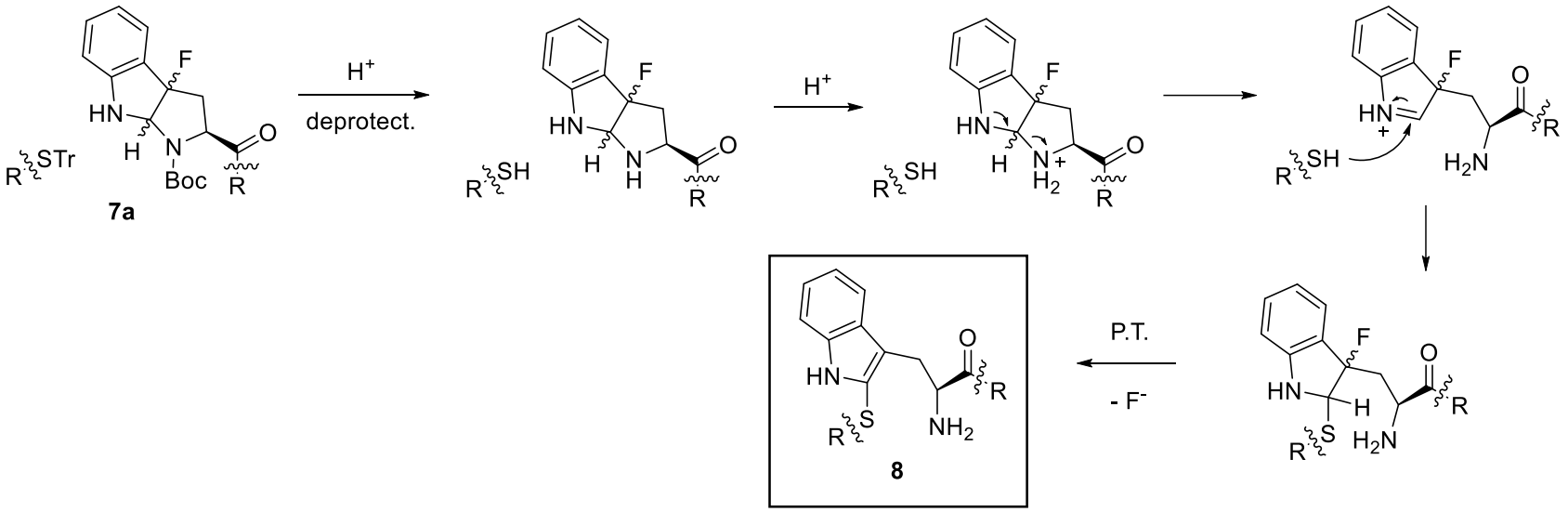


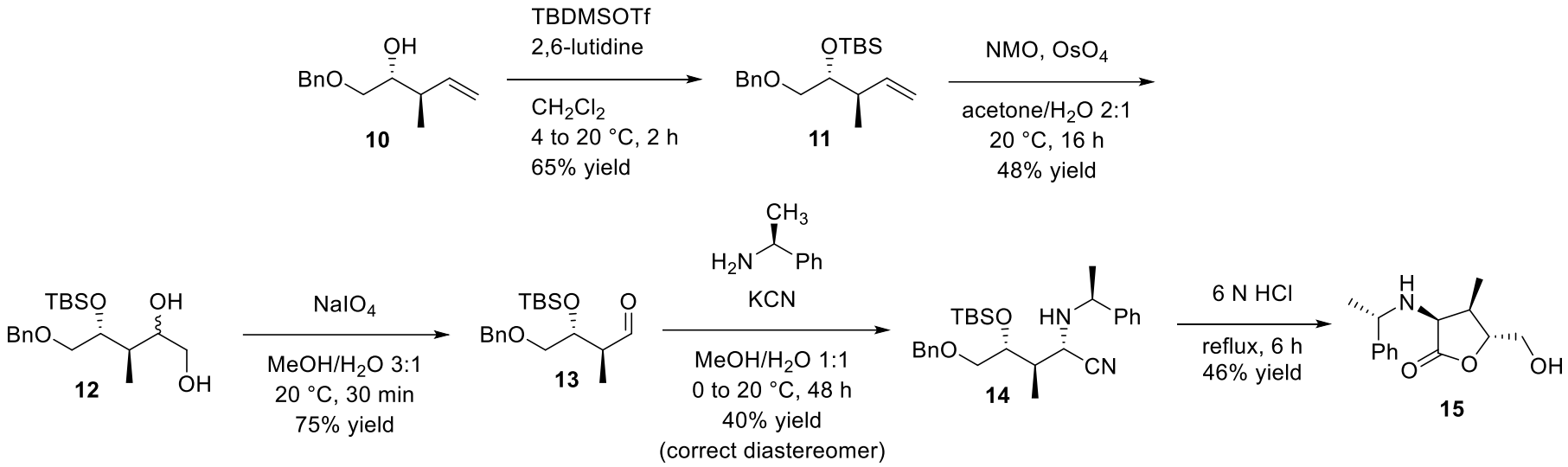
Synthesis of hexapeptide-**25**

The synthesis of hexapeptide was perfomed by loading Hyp amino acid onto a chlorotrityl resin, and sequential addition of the desired amino acids as follows: Asn(NTr), Cys(STr), Gly, Ile, Gly. These were each coupled sequentially using equivalents of HBTU/DIPEA as coupling agents. Reactions were performed at room temperature, and in DMF.

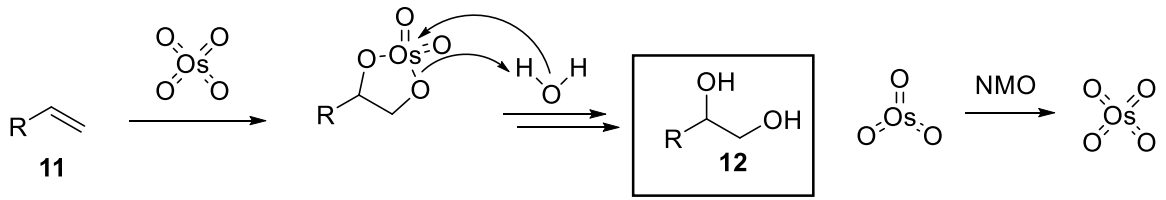


Trityl deprotection and macrocylization

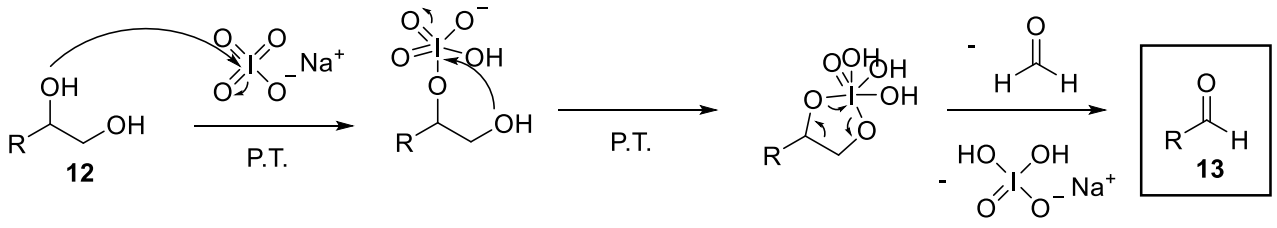


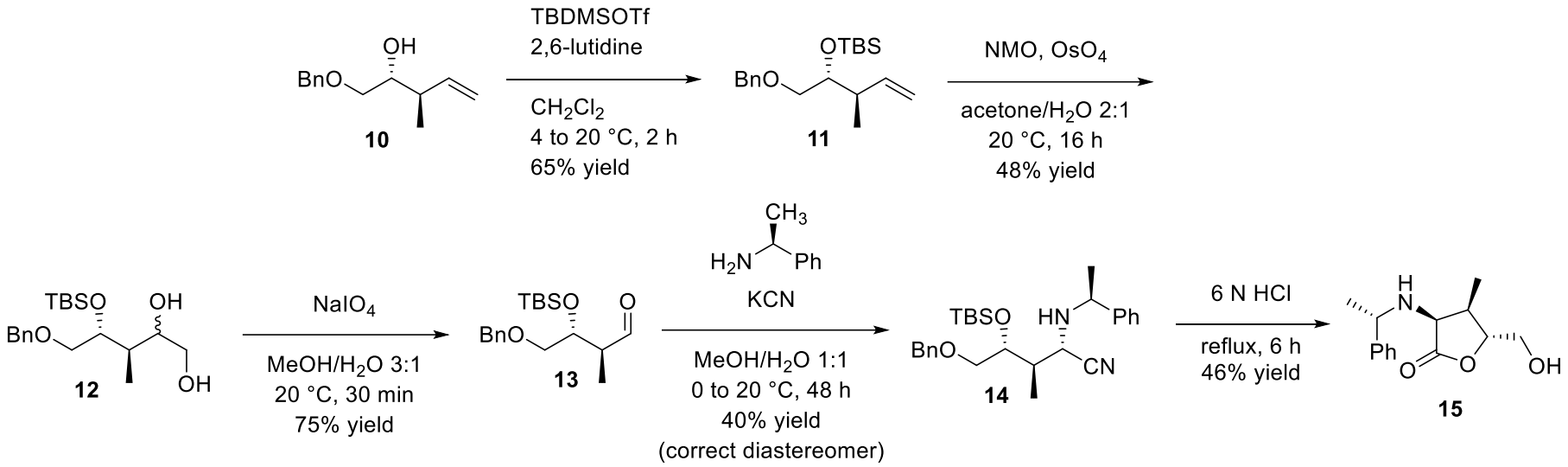


Upjohn dihydroxylation

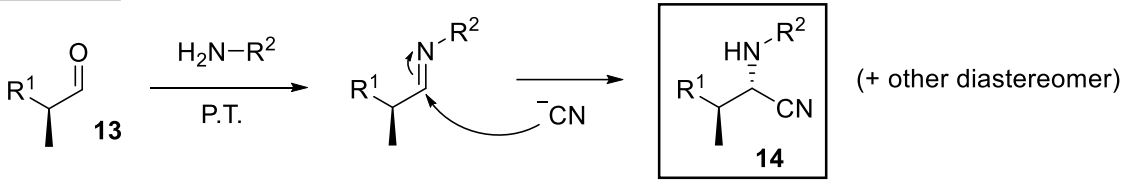


Periodate oxidative cleavage

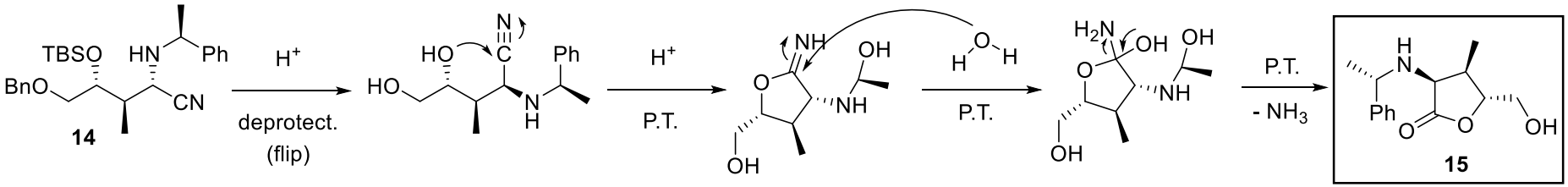


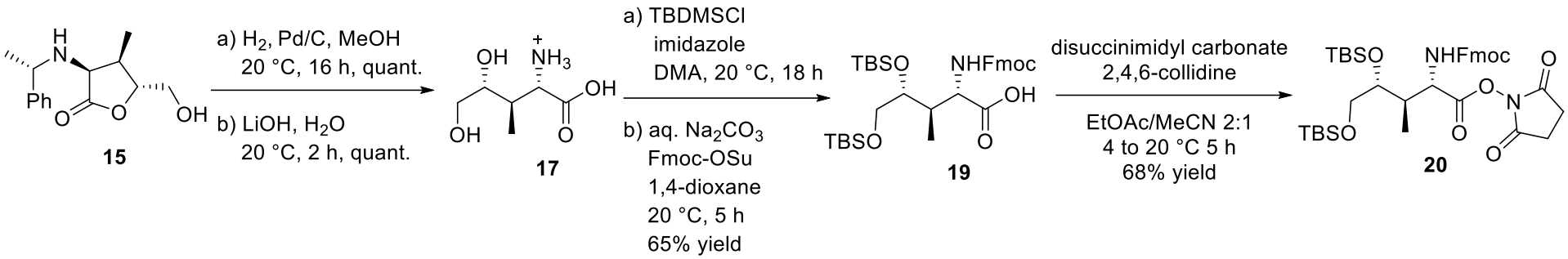


Imination-cyanation

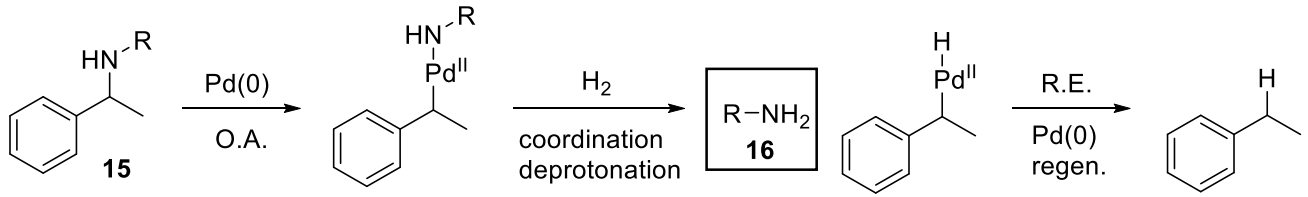


Lactonization

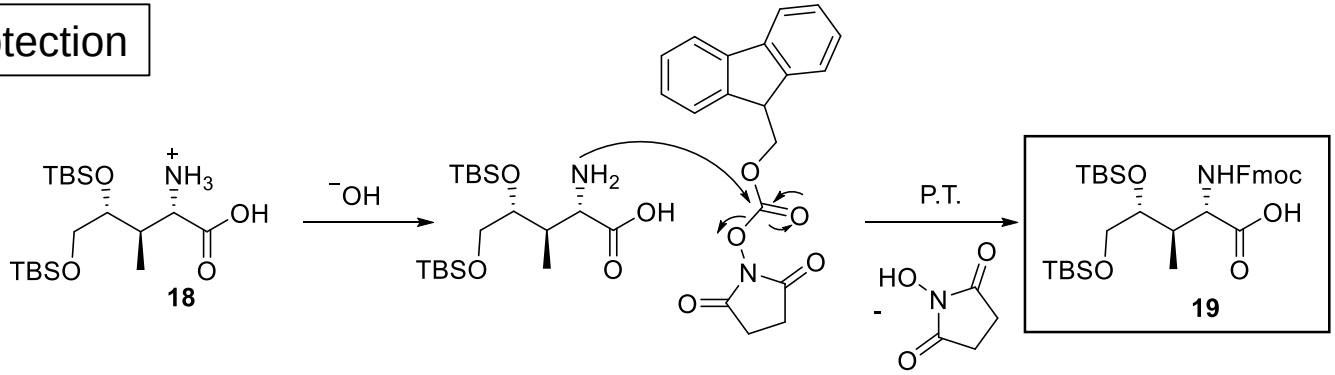




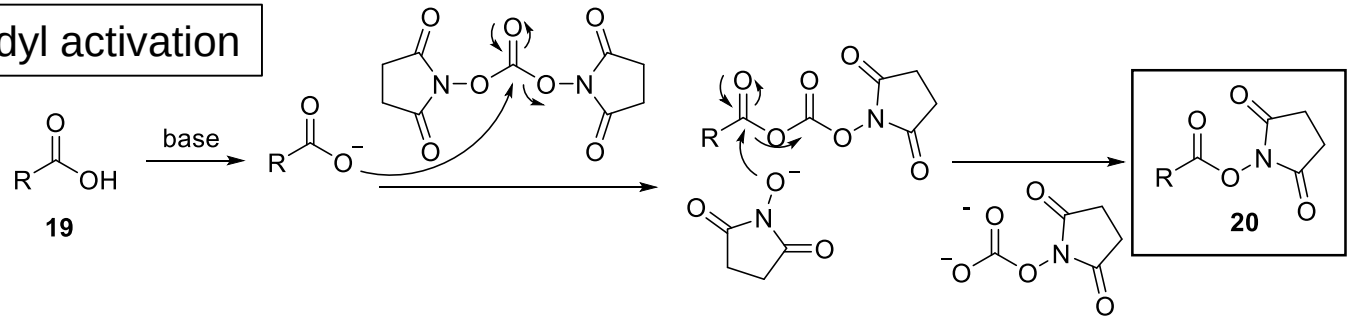
Pd-catalyzed benzylic deprotection

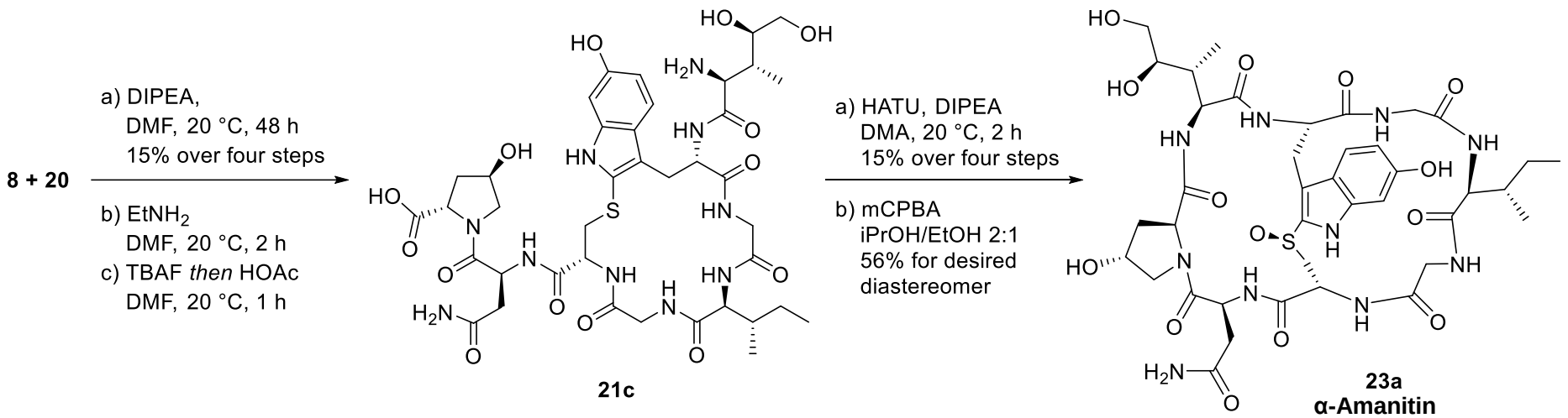


Fmoc protection

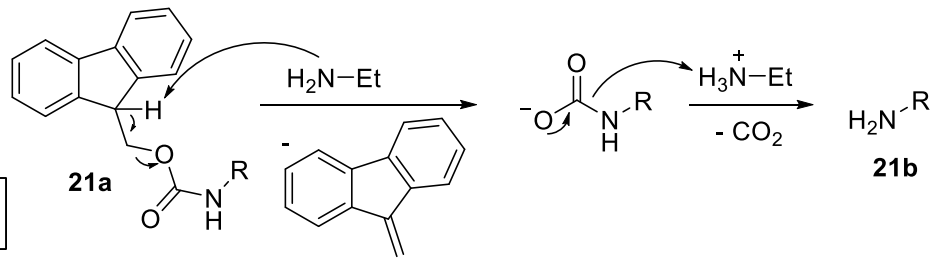


Succinimidyl activation

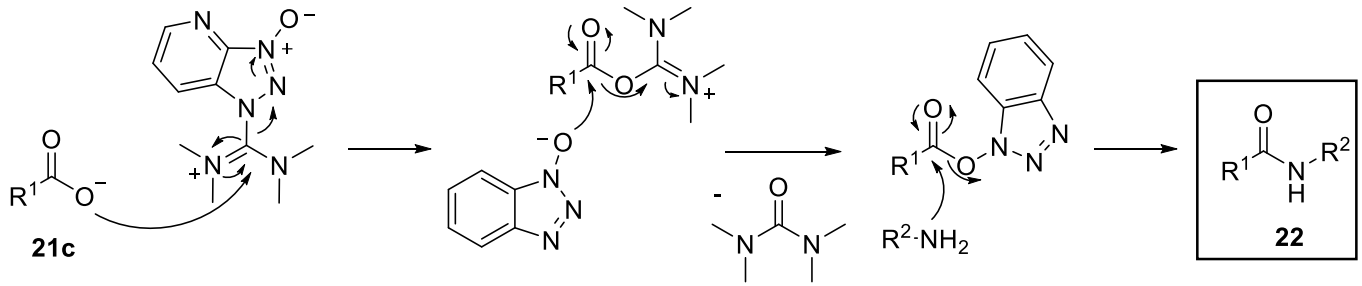


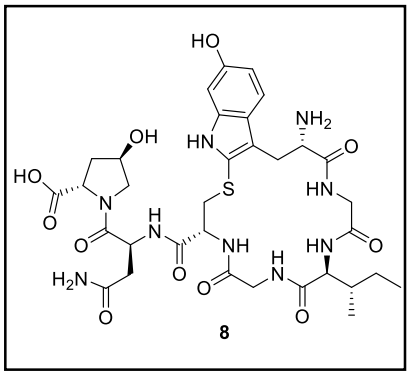


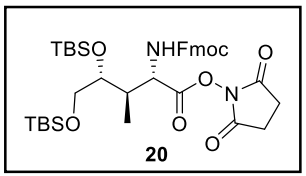
Fmoc deprotection



HATU amide coupling







mCPBA sulfoxidation