Total synthesis of marine natural products without using protecting groups

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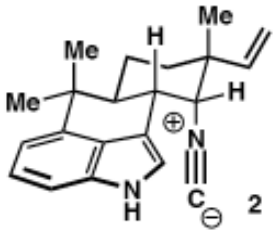
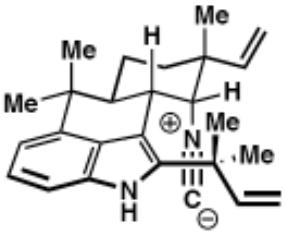
Introduction



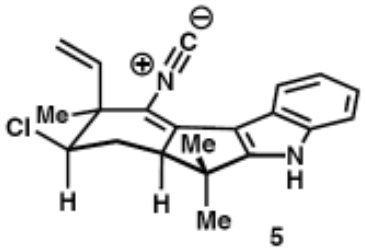
2

(-)-hapalindole U



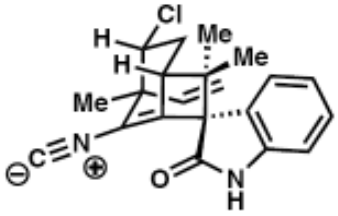
1

(+)-ambiguine H



5

(-)-fischerindole I



4

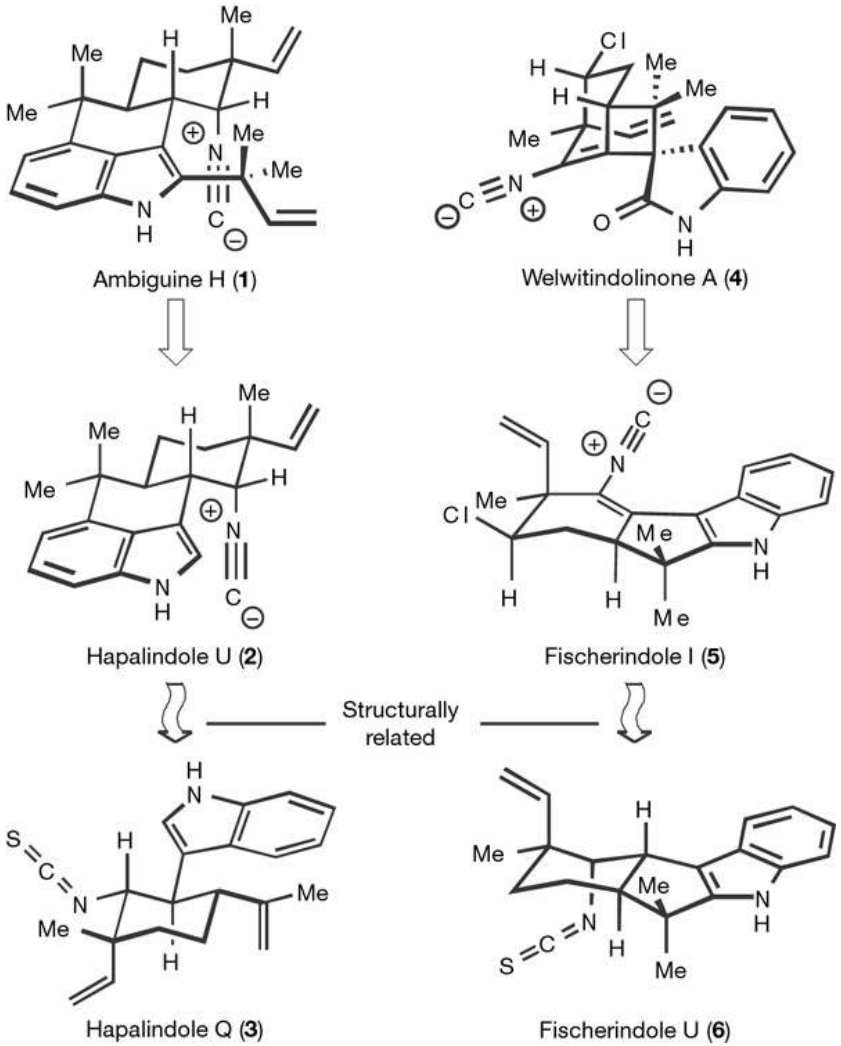
(+)-welwitindolinone A

Blue-green algae-cyanobacteria

- ♫ Moore and co-workers' isolated hapalindole, fischerindole, ambiguine and welwitindolinone indole alkaloides form marine blue-green algae (cyanobacteria)
- ♫ They exhibit a broad range of bioactivities including antifungal, antibacterial, antimycotic and anticancer properties
- ♫ Further studies of these agents is restricted because of cyanobacteria produce complex mixtures of these natural products in low yield
- ♫ Small quantities (~5mg) of all four natural products have been isolated in yields ranging from 0.00671% to 0.0213% following tedious purification and HPLC separation

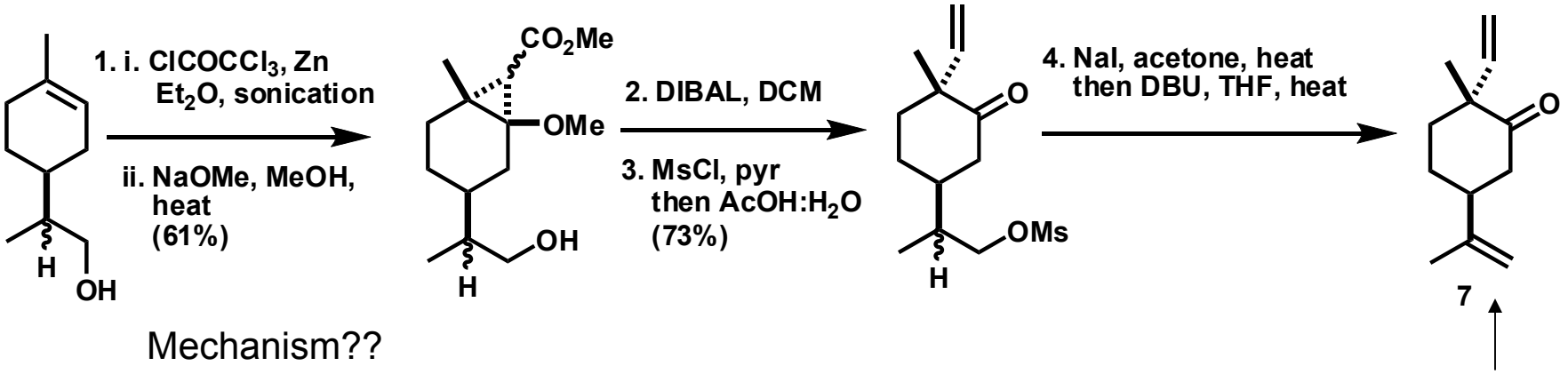
- Moore *et al.* JACS 116, 9935-9942, **1994**

Introduction



♫ Proposed biosynthetic relationships of ambiguine, fischerindole, hapalindole and welwitindolinone

Synthesis of starting material



Mechanism??

-Starting material for (-)-hapalindole U and (+)-ambiguine H synthesis

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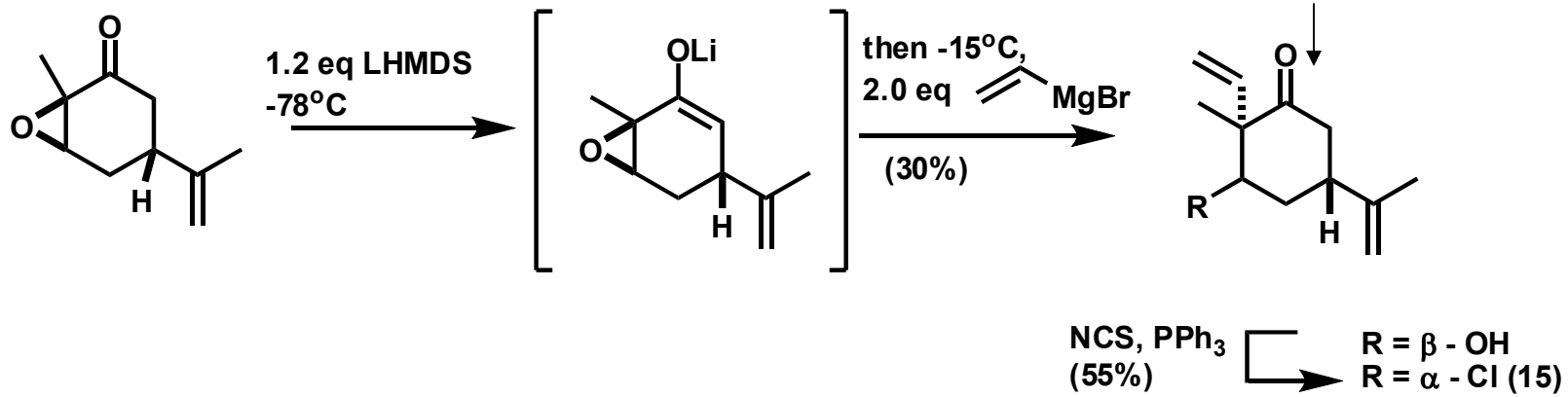
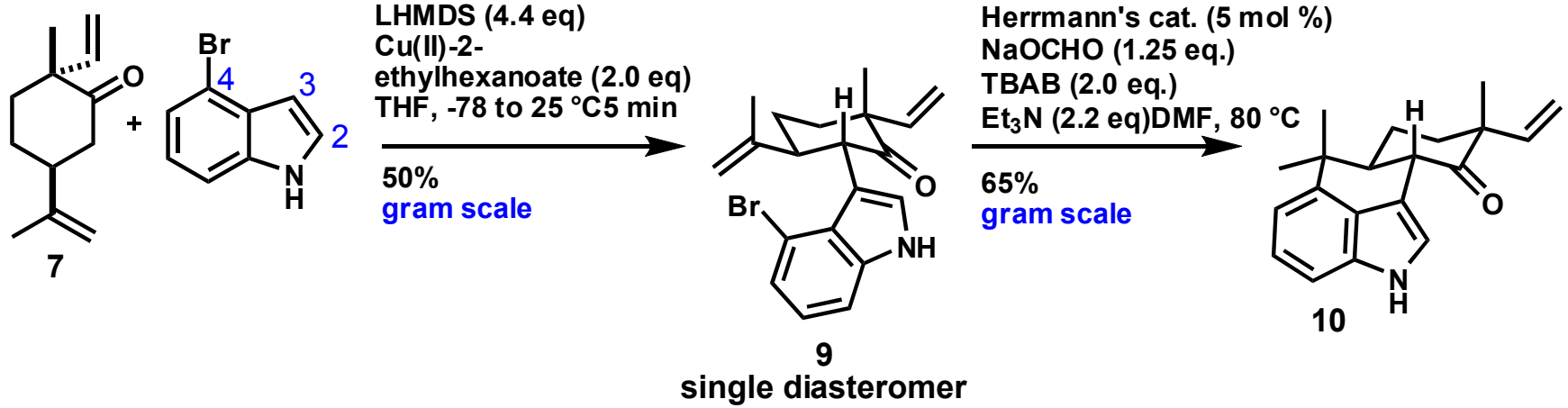
-Starting material for (-)-fischerindole I and (+)-welwitindolinone A synthesis



Synthesis of hapalindole



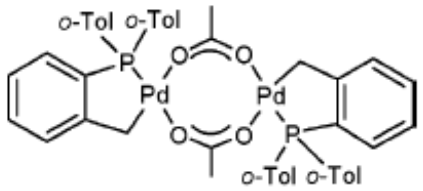
reductive Heck-type annulation

9 → 10

10 mol. % Pd, Et_3N (2.2 equiv), HCO_2Na (1.25 equiv), DMF, 80 °C

Entry	Pd-source, additives, time	Yield (%)[a]
1	$Pd(OAc)_2$, TBAC (1.0 equiv), Et_3N (2.5 equiv), 15 h	18[b]
2	$Pd(OAc)_2$, Ph_3P (0.2 equiv), 15 h	39[c]
3	$Pd_2(dba)_3$, TBAB (2.0 equiv), Et_3N (2.2 equiv), 15 h	22
4	$Pd(PPh_3)_4$, TBAB (2.0 equiv), Et_3N (2.2 equiv), 15 h	42
5	Herrmann's catalyst, TBAB (2.0 equiv), 15 h	50
6	$Pd(OAc)_2$, TBAB (2.0 equiv), Et_3N (2.2 equiv), *added over 5 h*	<10[d]
7	Herrmann's catalyst, TBAB (2.0 equiv), Et_3N (2.2 equiv), *added over 5 h*	65[d]

[a] isolated yield after chromatography; [b] conditions from ref. 26; [c] conditions from ref. 25; [d] isolated yield after 5 h (syringe pump) addition complete



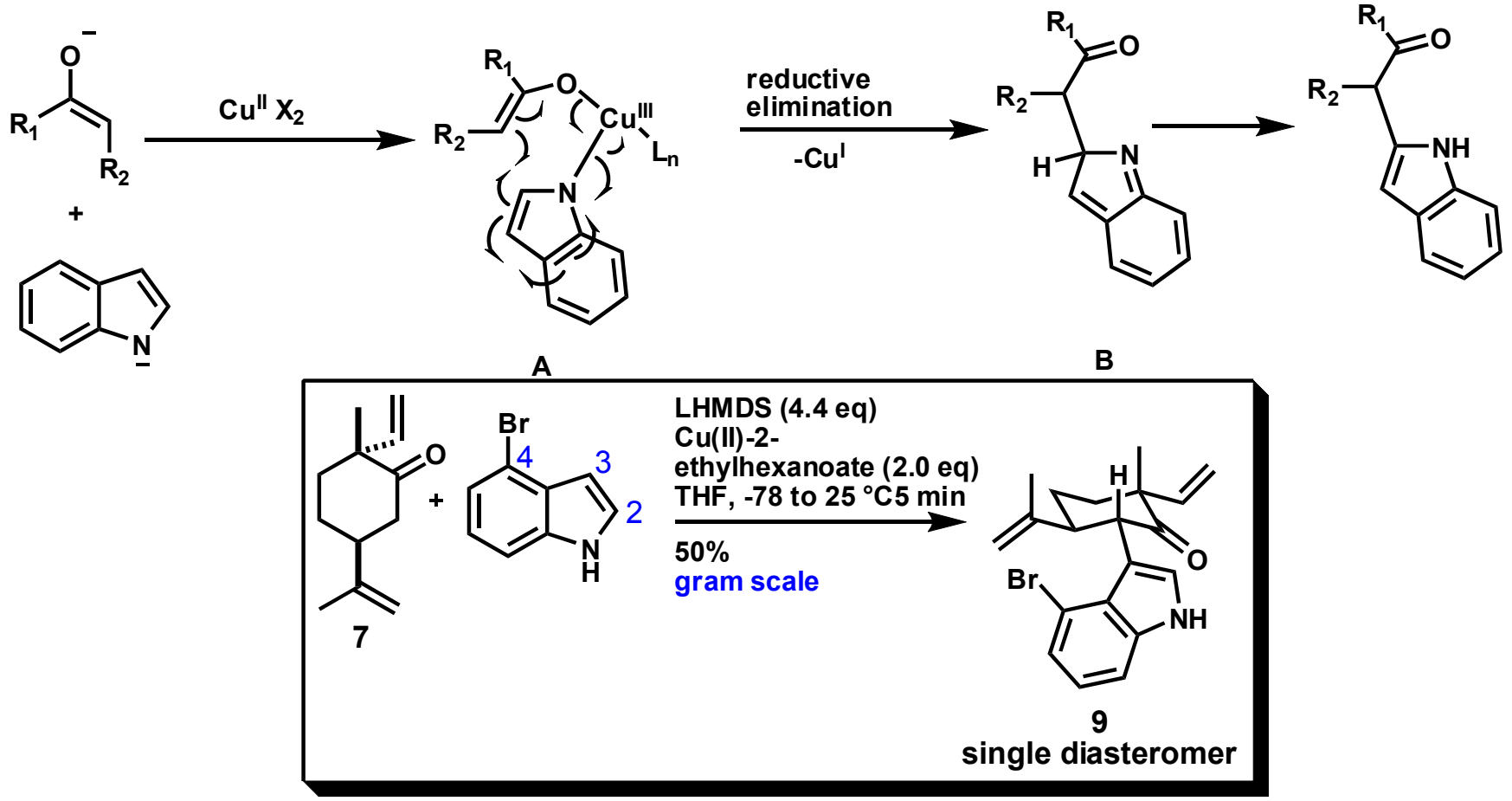
1

Structure of Herrmann–Beller phosphapalladacycle

♫ Friedel-Crafts annulation from 9 to 10 failed; leading to cyclization at C2 rather than C4, with decomposition

♫ Radical cyclization lead to 7-*endo*-trig, rather than 6-*exo*-trig

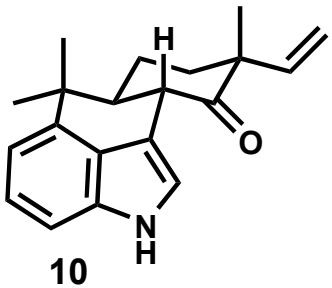
Synthesis of hapalindole



- Observations that support this mechanistic model:
  - dimerization never observed
  - N-protected indoles (& pyroles) do not react
  - only 1 equiv. of oxidant is necessary; although use of 1.5 equiv gives higher yield
  - characteristic red-brown colour of copper(I) salts is observed at the end of rxn

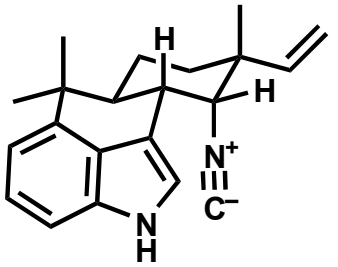
- Baran *et al. Angew. Chem. Int. Ed.* **2005**, 44, 609-612

Synthesis of hapalindole



10

1) NH_4OAc, $NaCNBH_3$ μw 150 °C, MeOH/THF
2) HCO_2H (2 eq.) CDMT(2.2 eq) DMAP (5 mol %) NMM (2.2 eq) CH_2Cl_2
3) $COCl_2$ (2 eq) Et_3N (17.5 eq) CH_2Cl_2 (60% overall)

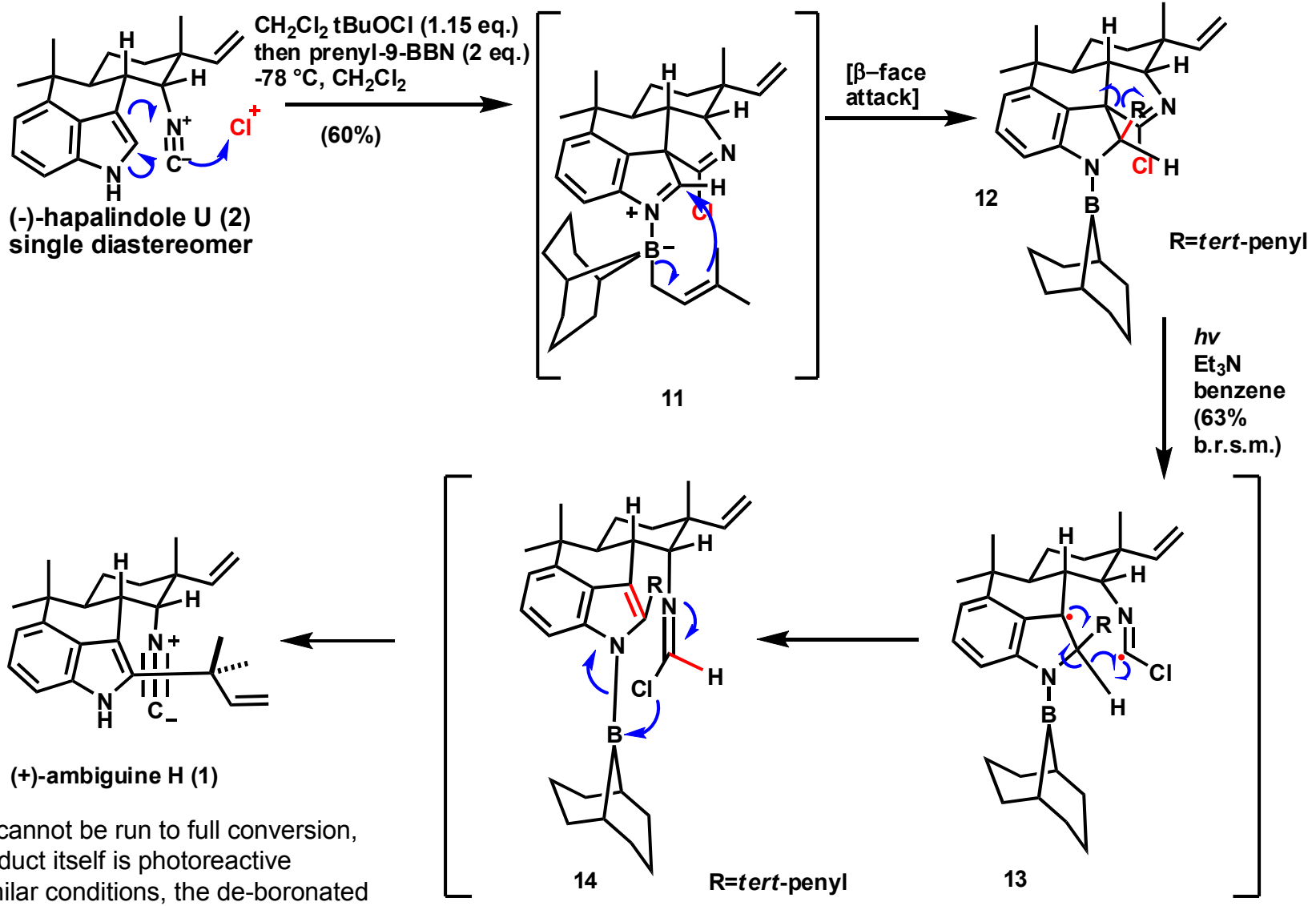


(-)-hapalindole U (2) single diastereomer

♫ Previous synthesis of hapalindole U made in 20 steps, racemic; by non-stereocontrolled sequence.

♫ Sythetic **2**, prepared in four steps from ketone **7**, 20% isolated yield, >1g prepared.

Synthesis of ambiguine

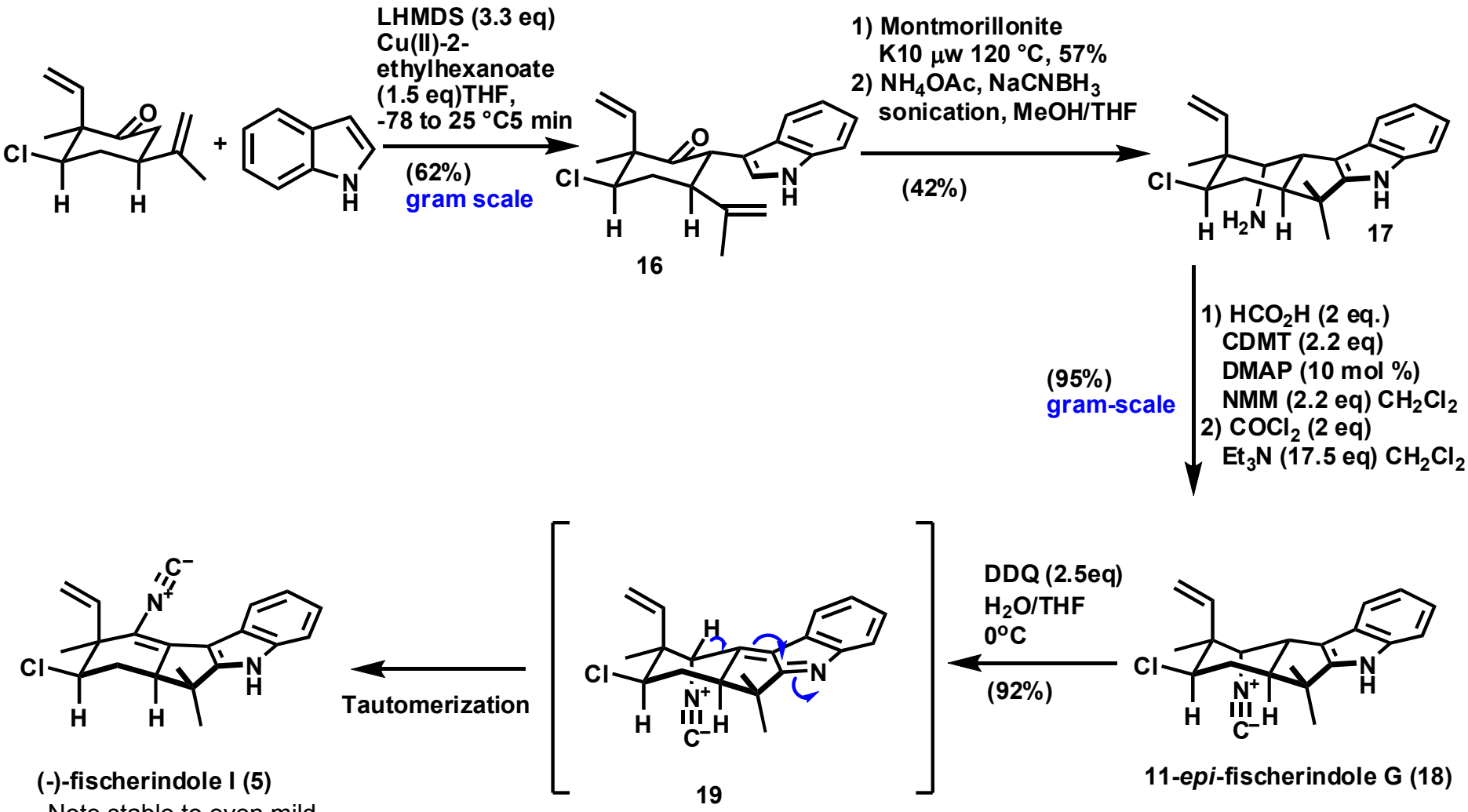


-Reaction cannot be run to full conversion, since product itself is photoreactive

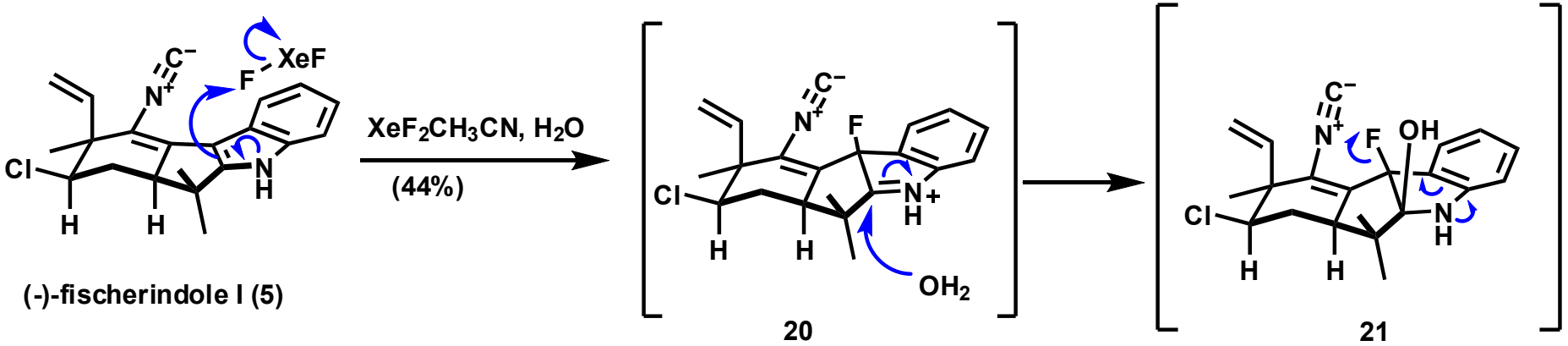
-Under similar conditions, the de-boronated product cleanly forms (+)-ambiguine H in >70%

- **1** unstable under prolonged storage

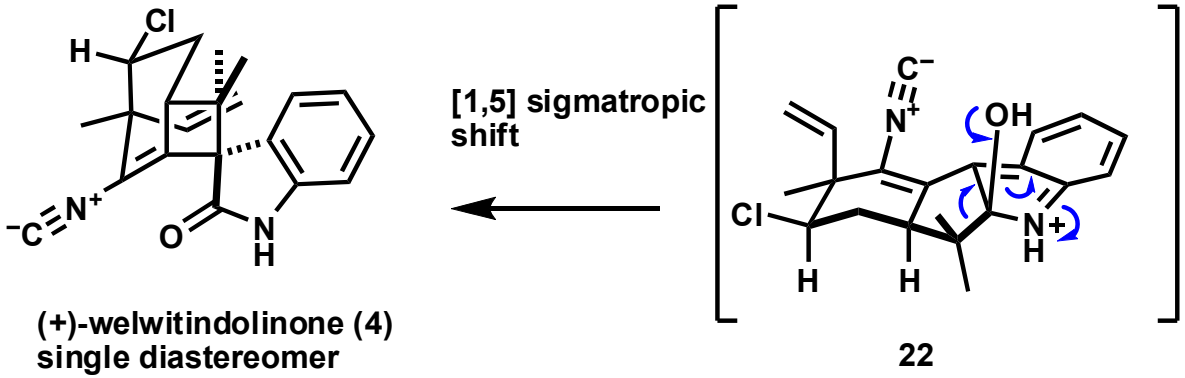
Synthesis of fischerindole



Synthesis of welwitindolinone



-Rxn from **5** to **4** run at room temp. for 5 mins
- Is it uphill or downhill? driving force??



♫ The only reported previous synthesis of **4** requires 25 steps with six protecting groups, to give **4** as racemic material.

Summary

- Enantioselective synthesis of ambiguine H, hapalindole U, welwitindolinone A and fischerindole I require seven to ten steps form commerically available materials
- These natural products can easily be prepared on a preparative scale using inexpensive reagents
- Exclusion of protecting groups from overall synthesis
- Exclusion of protecting groups aided in the development and discovery of new chemical reactions by exploiting the natural reactivity of functional groups