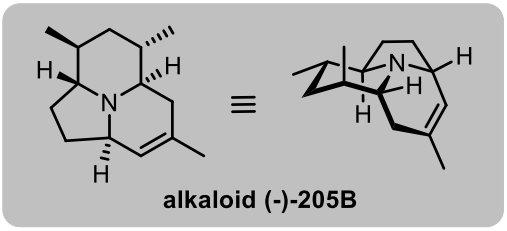
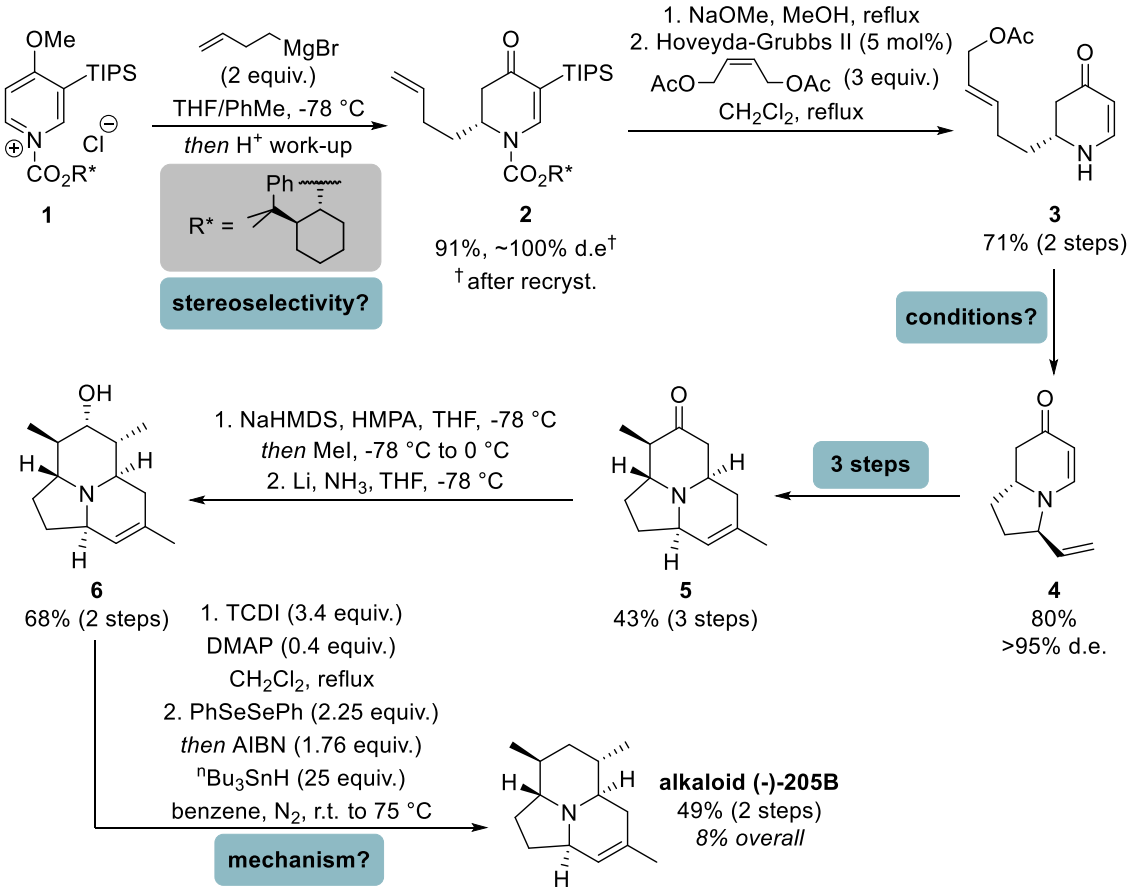
Approaches to Alkaloid (-)-205B



J. Nat. Prod., **2005**, *68*, 1556

1. Fundamental aspects of alkaloid (-)-205B
   a. Briefly discuss the likely biological origins of (-)-205B.
   b. Outline the key pieces of spectroscopic evidence you would use to confirm that the structure and relative stereochemistry of this compound are as shown above, assuming that its molecular formula has already been established.
   c. The absolute stereochemistry of alkaloid (-)-205B was actually determined by the total synthesis of its antipode, (+)-205B. This enantiomer was found to be a potent and selective non-competitive inhibitor of α7 nicotinic receptors (nAChRs). Explain the potential value of non-competitive inhibitors in the context of drug discovery.

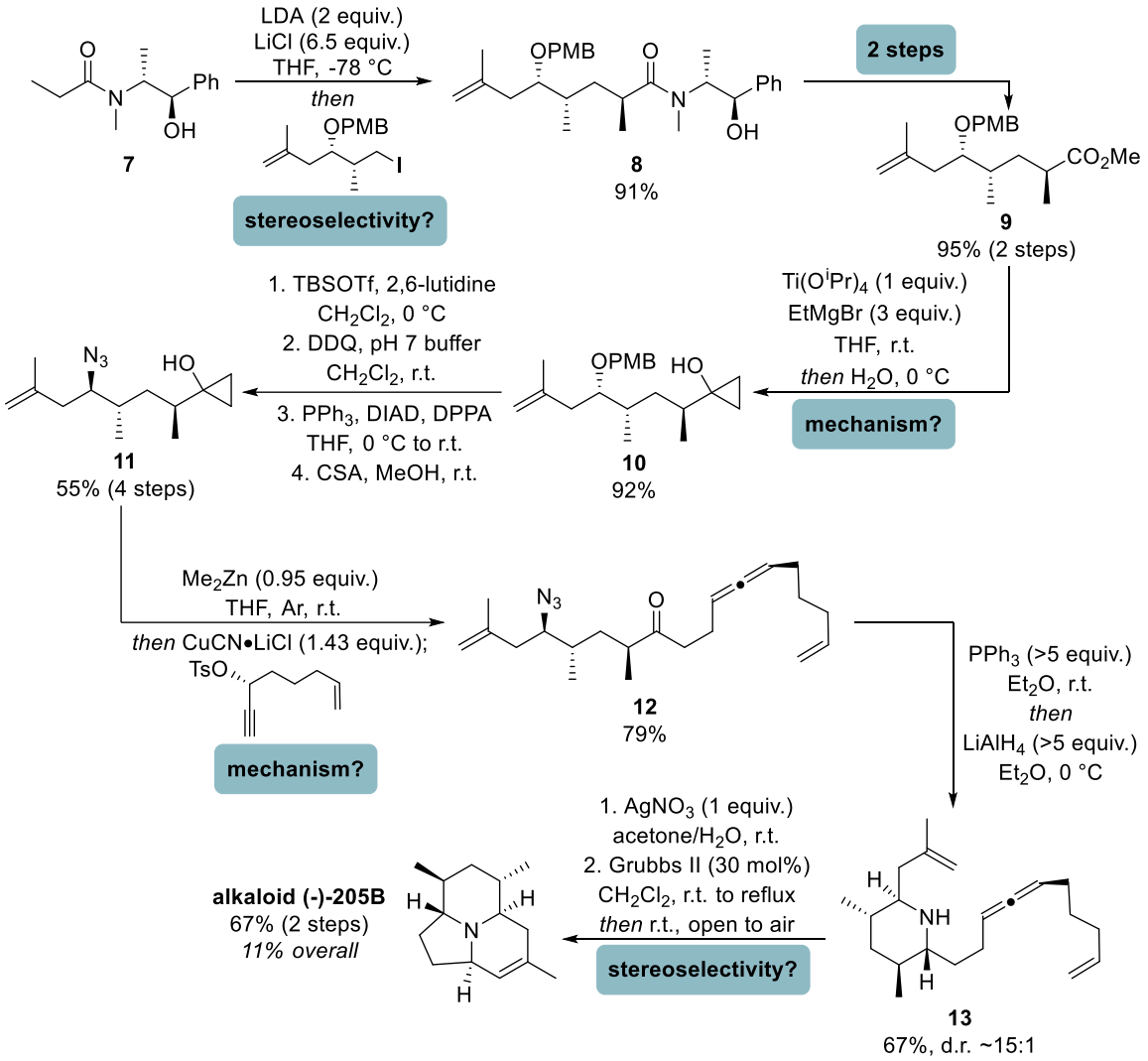
2. The Comins synthesis



   a. Rationalise the sense of asymmetric induction in the formation of dihydropyridone **2** from pyridinium **1**.
   b. Suggest conditions for the cyclisation of **3** to give bicycle **4**.
   c. Outline the steps required for the conversion of **4** to tricycle **5**.

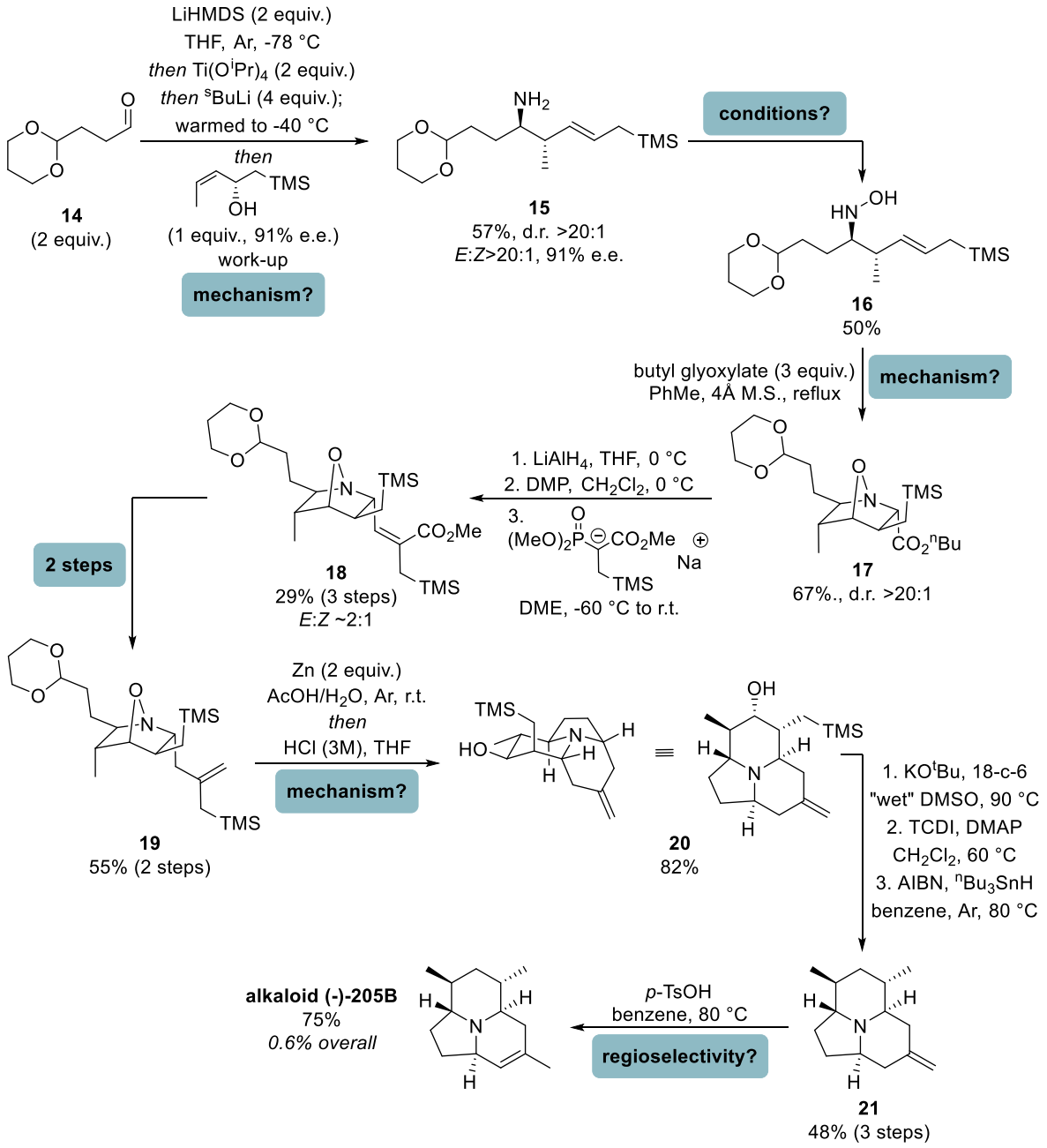
d. Propose a mechanism for the completion of the target by deoxygenation of **6** under the conditions shown.

3. The Cha synthesis



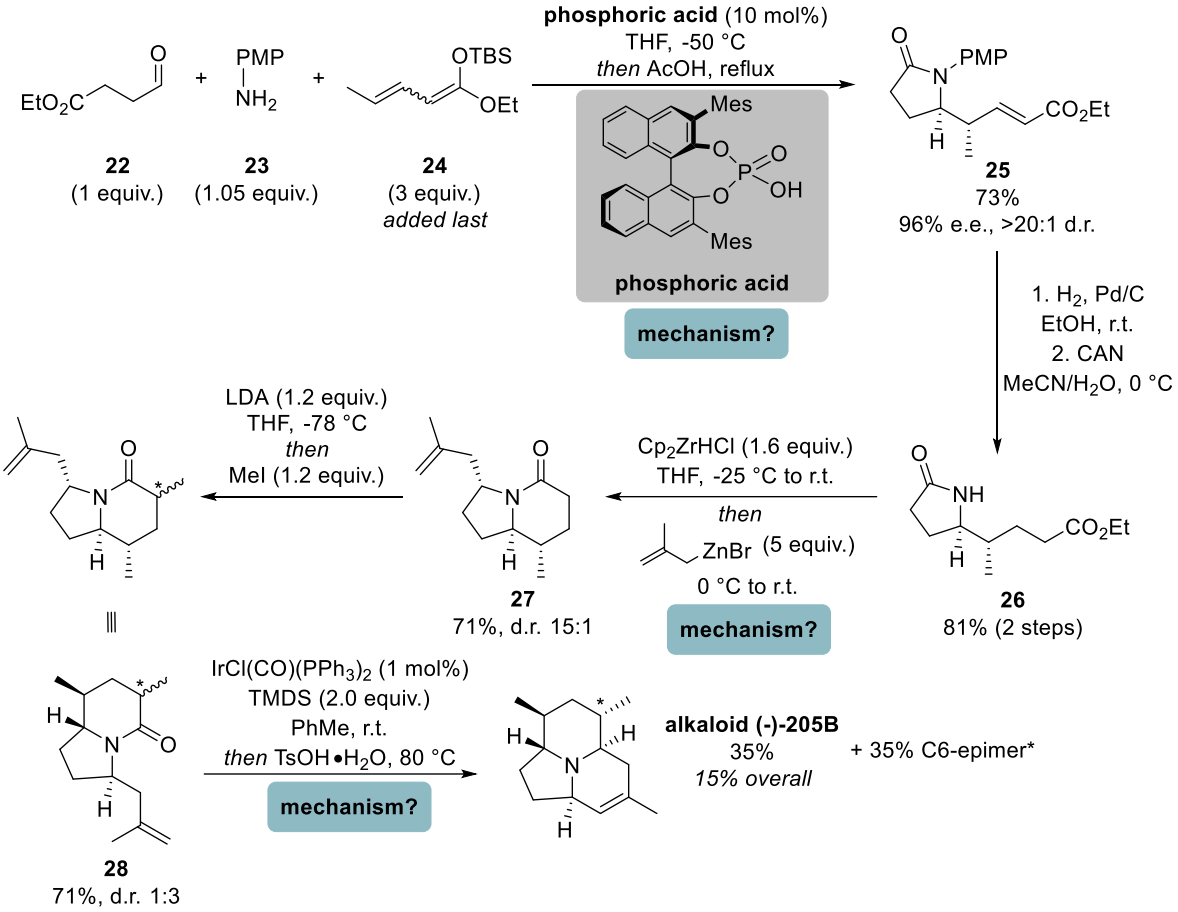
a. Rationalise the sense of asymmetric induction in the alkylation of **7** to give **8**. What are the advantages of using the chiral auxiliary shown?
b. Suggest conditions for the conversion of amide **8** to ester **9**.
c. Provide a mechanism for the formation of cyclopropanol **10** from ester **9**. How could this chemistry be adapted to allow for the formation of cyclopropylamines or substituted cyclopropanols?
d. Provide a mechanism for the coupling of **11** with the electrophile shown to give ketoallene **12**, accounting for the stereochemistry shown.
e. Give the product of the silver-mediated step and propose a reasonable model to account for the stereochemical outcome of this step.
f. Suggest a practical reason for the exposure of the reaction mixture to the air in the final step.

4. The Micalizio synthesis



a. Propose a mechanism for the formation of amine **15** from aldehyde **14**, accounting for the stereochemistry shown.
b. Suggest conditions for the oxidation of amine **15** to give hydroxylamine **16**.
c. Provide a mechanism for the formation of [2.2.1] bicycle **17** under the conditions shown.
d. Suggest conditions for the conversion of ester **18** to allylsilane **19**.
e. Provide a mechanism for the formation of tricycle **20** from [2.2.1] bicycle **19**.
f. Outline the issues associated with the use of tributyltin hydride. Suggest an alternative reagent that could replace tributyltin hydride in this sequence.
g. Consider the isomerisation of **21** to give alkaloid (-)-205B. Why is the natural product favoured over regioisomer **21**?

5. The Schneider synthesis



a. Provide a mechanism for the three-component coupling to give lactam **25**.
b. Provide a mechanism for the formation of bicycle **27** from lactam **26**. Explain the chemoselectivity of the organometallic addition step.
c. Consider the Ir complex shown in the final step. Give the name and d-electron count of this complex, and briefly explain its reactivity.
d. Propose a reasonable mechanism for the final step. Explain why, following treatment with TsOH, the desired compound is accessed in a 1:1 ratio with its C6-epimer (the epimeric position is highlighted with an asterisk), given that the methylation step delivered a 1:3 mixture, with the undesired epimer as the major component.