IV Lycopodine

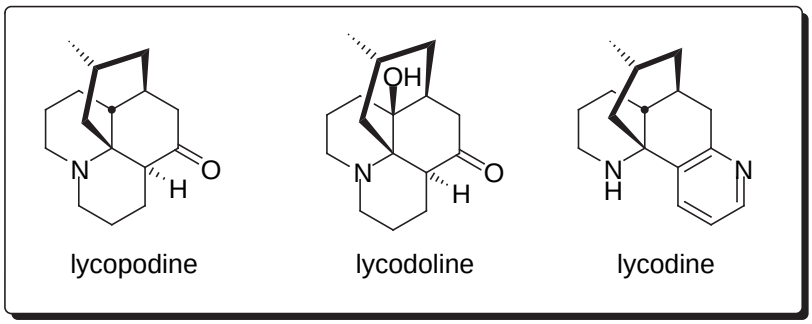
Objectives

By the end of this section you will:

- have seen two synthetic approaches to a complex alkaloid natural product.
- be able to contrast the two synthetic approaches highlighting the pros and cons of each route.

Introduction

Lycopodine is the commonest alkaloid in its class (~100 members of biogenetically related molecules). It is found in club mosses of the genus *Lycopodium*.



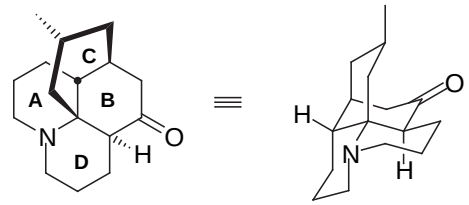
There have been a few syntheses of lycopodine. We will take two which are particularly noteworthy and analyse the strategies employed in constructing this (fairly) complex polycyclic molecule.

V.A Heathcock Synthesis

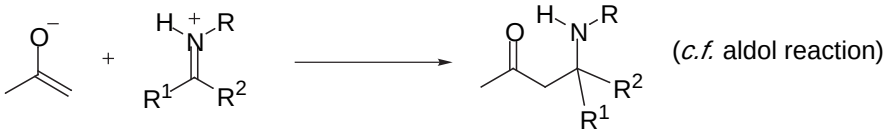
i) C. H. Heathcock, E. Kleinman, E. S. Binkley, *J. Am. Chem. Soc.*, 1978, **100**, 8036-8037.

ii) C. H. Heathcock, E. F. Kleinman, E. S. Binkley, *J. Am. Chem. Soc.*, 1982, **104**, 1054-1068.

V.A.1 Analysis

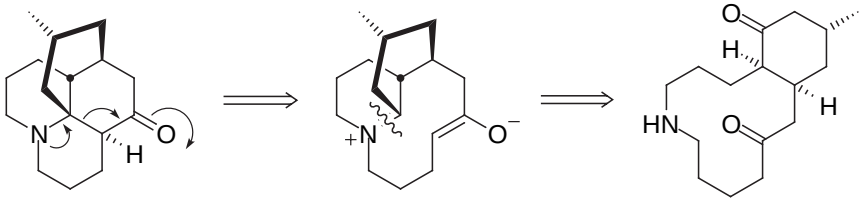


pattern recognition: β-amino ketone ⟹ Mannich condensation



(*c.f.* aldol reaction)

Can we use this disconnection to simplify the molecule?



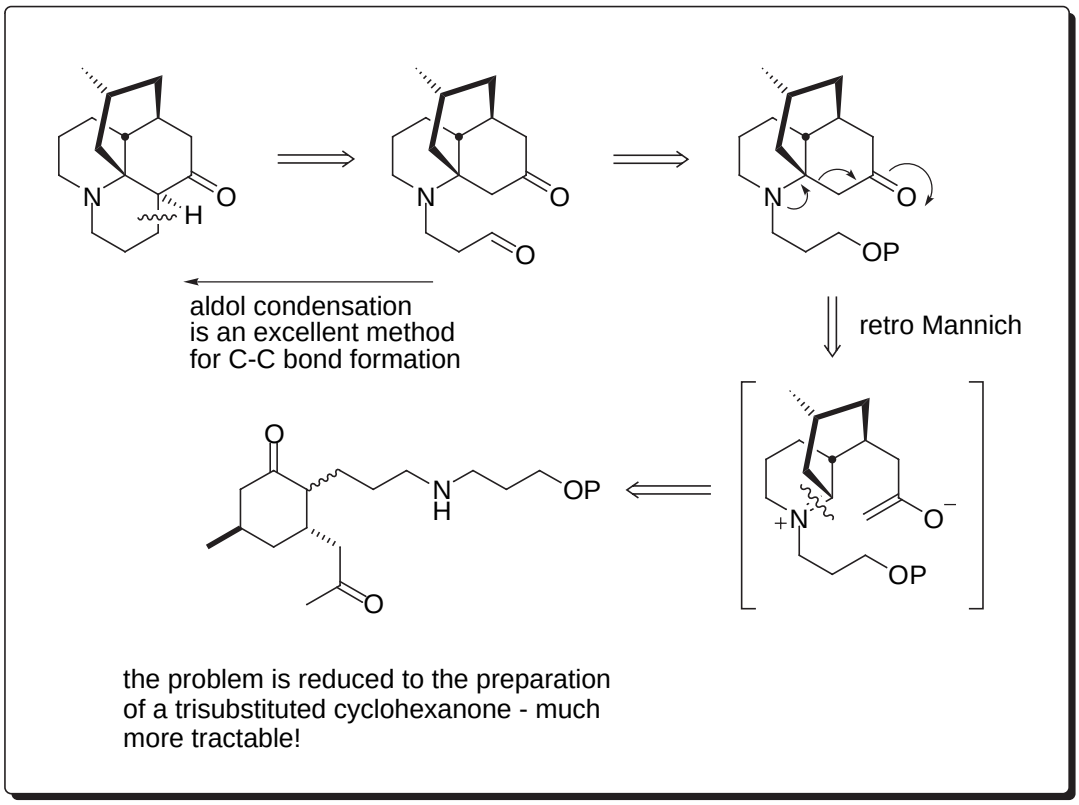
problem reduced to a bicycle although now we have a 12-membered ring to prepare

The retro-Mannich disconnection greatly simplifies the problem but can we simplify the problem even further?

Observe that if we use the Mannich approach to construct rings **A**, **B** and **C**, then we can prepare ring **D** at a late stage:

- six-membered rings are easy to form
- the ketone functionality provides a good handle for forming ring **D**

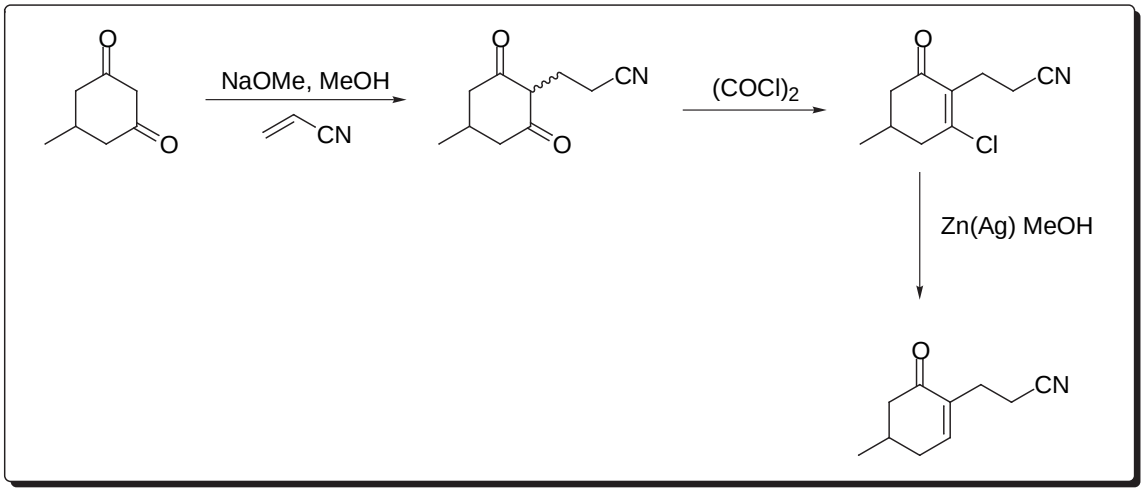
Modify the retrosynthetic analysis:



Our analysis is complete. By exploiting a Mannich condensation as the key step, a viable synthetic approach has been developed.

Outline a retrosynthesis for the preparation of the trisubstituted cyclohexanone. (Make use of 1,4-addition reactions for forming the strategic bonds and a C=C group to mask one of the ketones)

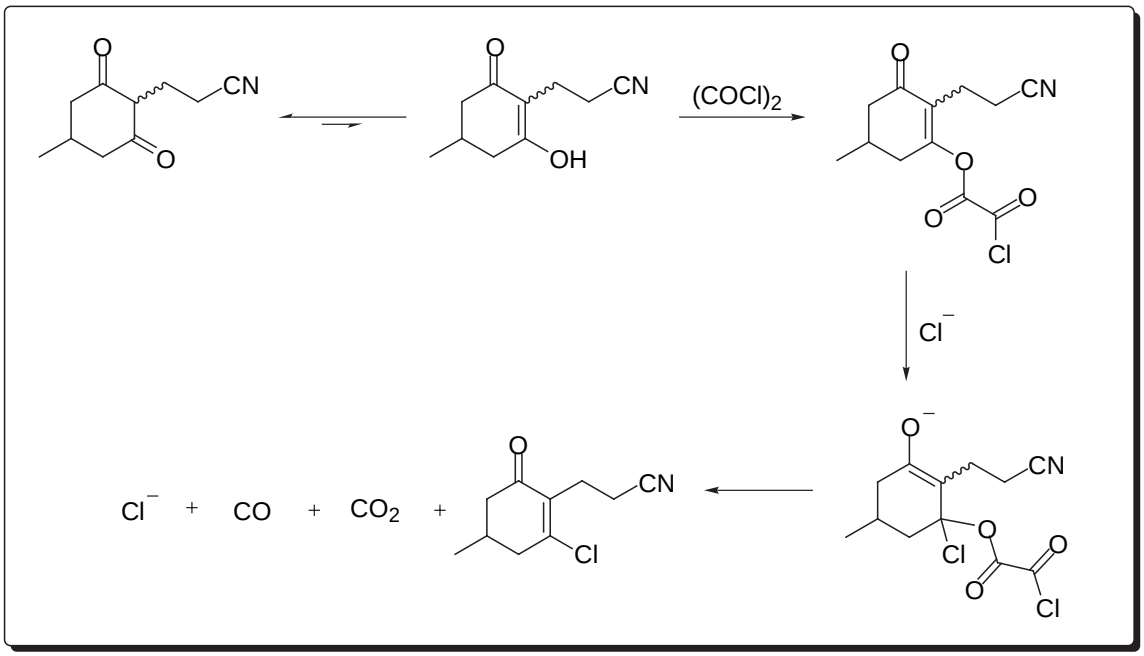
V.A.2 Forward synthesis



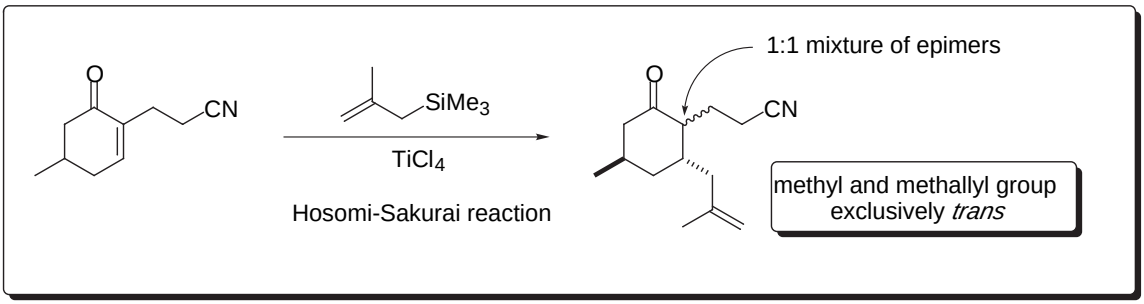
Notes:

1. The Michael addition with acrylamide is a good method for adding the three-carbon linkage.
2. Why do we use the β-diketone as a nucleophile and not one derived from 3-methylcyclohexanone?
   - α,β-unsaturated carbonyl groups (and related compounds including α,β-unsaturated nitriles) are ambident electrophiles
   - we require regioselective enolate formation - pK_as

Mechanism of enone formation



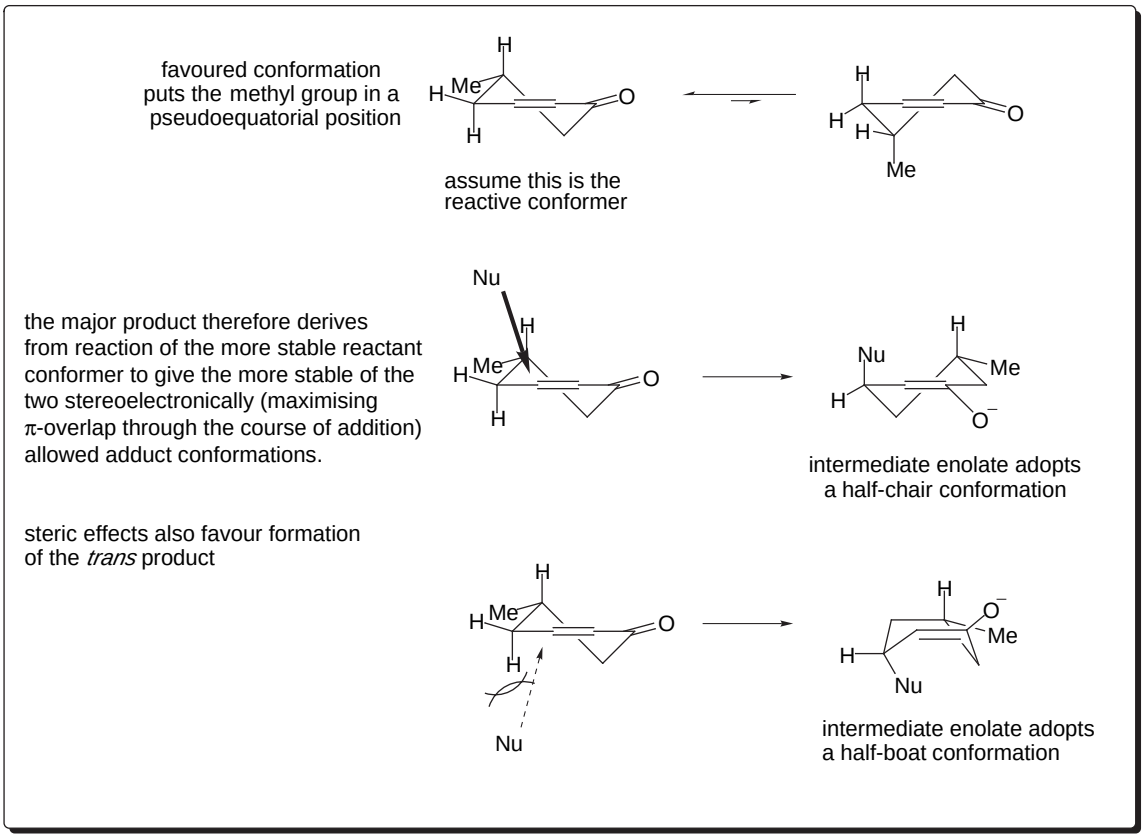
Continuing with the forward synthesis; the second Michael addition must be stereoselective.



A number of methods were investigated to instal the four-carbon unit. The Hosomi-Sakurai reaction was the most efficient and provided two diastereoisomers (epimeric at C(2)) with the desired *trans* relationship between the methallyl and methyl substituents on the ring.

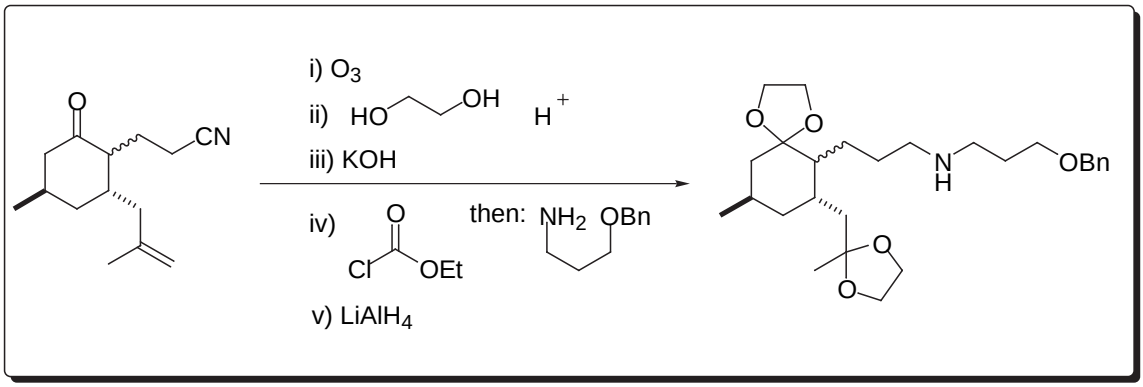
Allylsilanes are relatively poor nucleophiles. What might be the role of the titanium tetrachloride?

Accounting for the observed stereochemical outcome of the Michael addition.



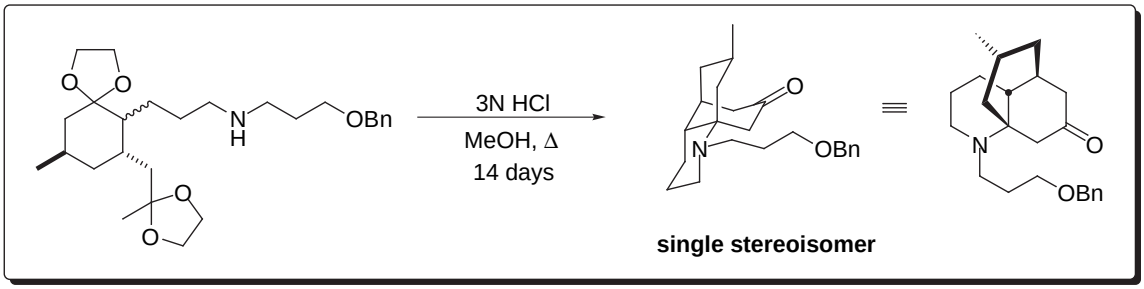
The enolate intermediate is quenched equally well from either stereoface (the electrophile here is only a proton) leading to – as we shall see later – an inconsequential mixture of epimers at C(2).

Elaboration to the Mannich cyclisation precursor is easy:



Make sure you can write mechanisms for each of these transformations.

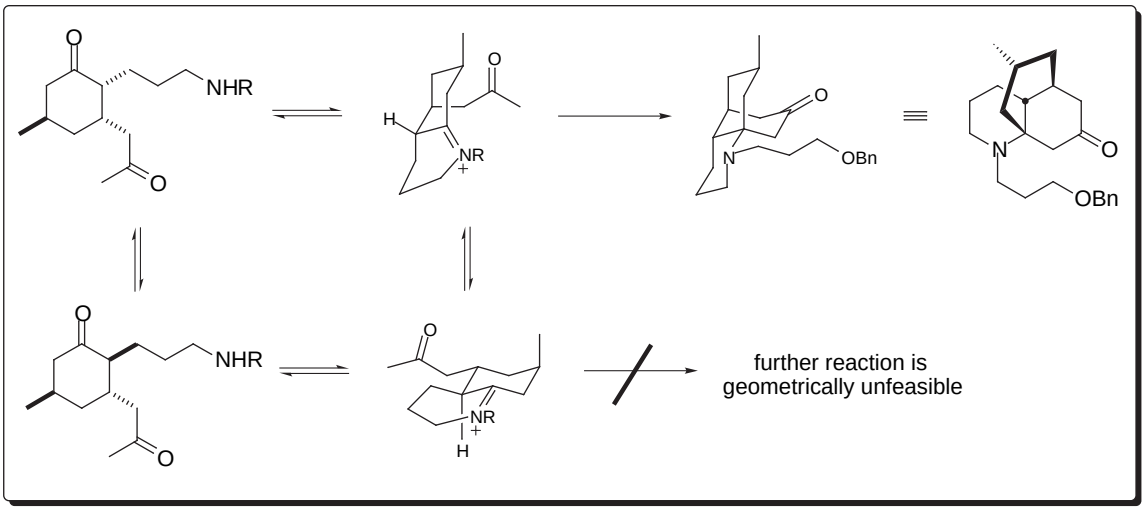
Key Mannich Cyclisation



single stereoisomer

The crucial Mannich reaction provided exclusively the desired product. It is important to note that this reaction is carried out under conditions that provide the *thermodynamic product*.

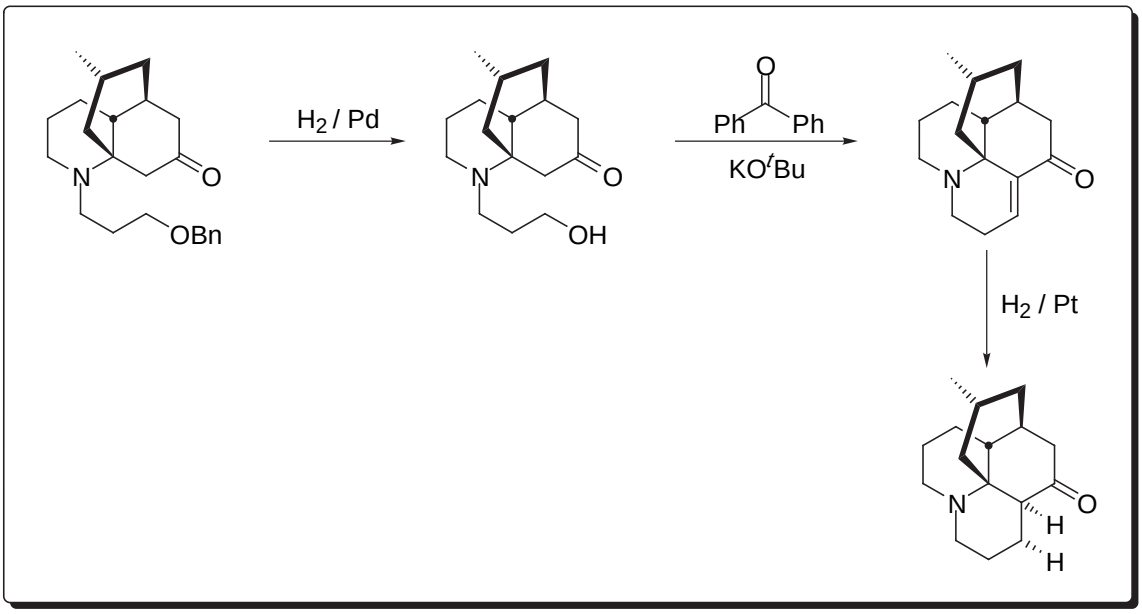
We can account for the stereochemical outcome of the reaction:



Notes:

- stereogenic centres α to carbonyl groups (this includes iminium ions) are readily epimerised under these acidic reaction conditions.
  - *you should be able to draw a mechanism for the epimerisation reaction*
- 6-membered rings form faster than 8-membered rings and are also usually thermodynamically more stable; this determines the first cyclisation and the intermediate iminium species.

With the tricycle in place, further elaboration to the product is easy.



Notes:

- The penultimate step is an example of a *tandem process*. Oppenauer oxidation (the reverse reaction of the Meerwein-Ponndorf-Verley reduction - see notes on reduction) provides the aldehdye. In the presence of a base, aldol condensation followed by dehydration provides the enone. This all occurs in one pot.

- The final step introduces the final stereogenic centre. Hydrogenation of the double bond proceeds with complete stereoselectivity and is under *substrate control*. Make a model of the enone to determine which is the less hindered diastereoface.

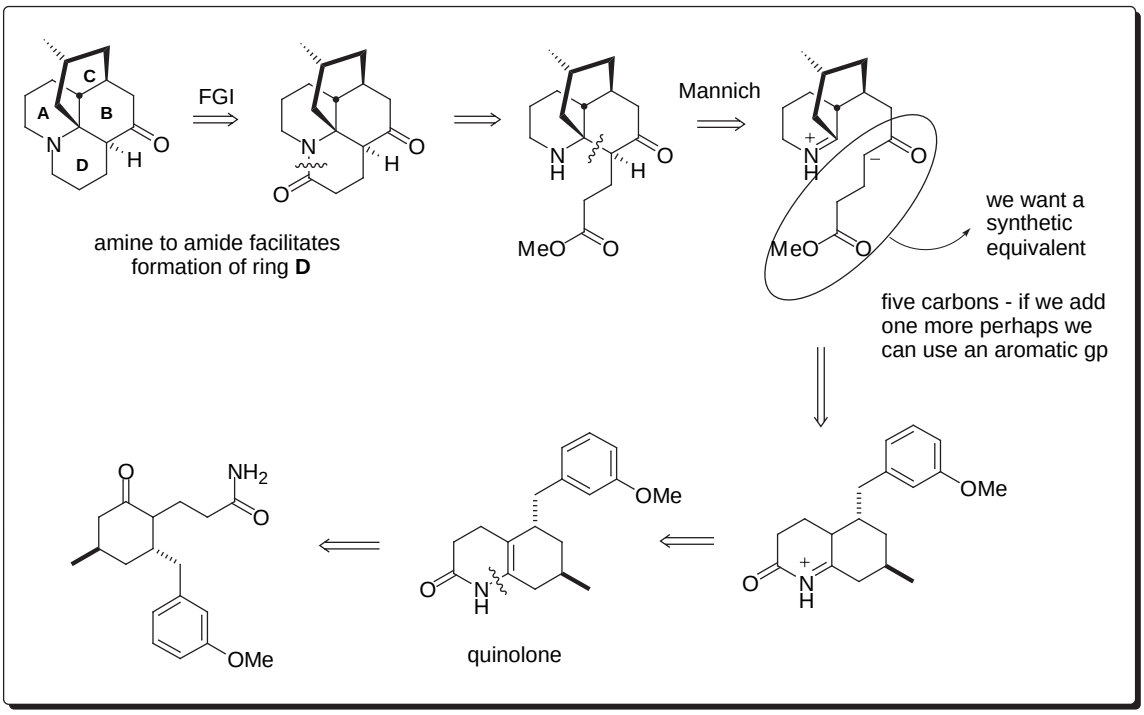
Lycopodine was produced *via* this highly efficient route in only 13 steps and in an overall yield of 16.6 %.

V.B Stork Synthesis

G. Stork, R. A. Kretchmer, R. H. Schlessinger, *J. Am. Chem. Soc.*, 1968, **90**, 1648-1649.

V.B.1 Analysis

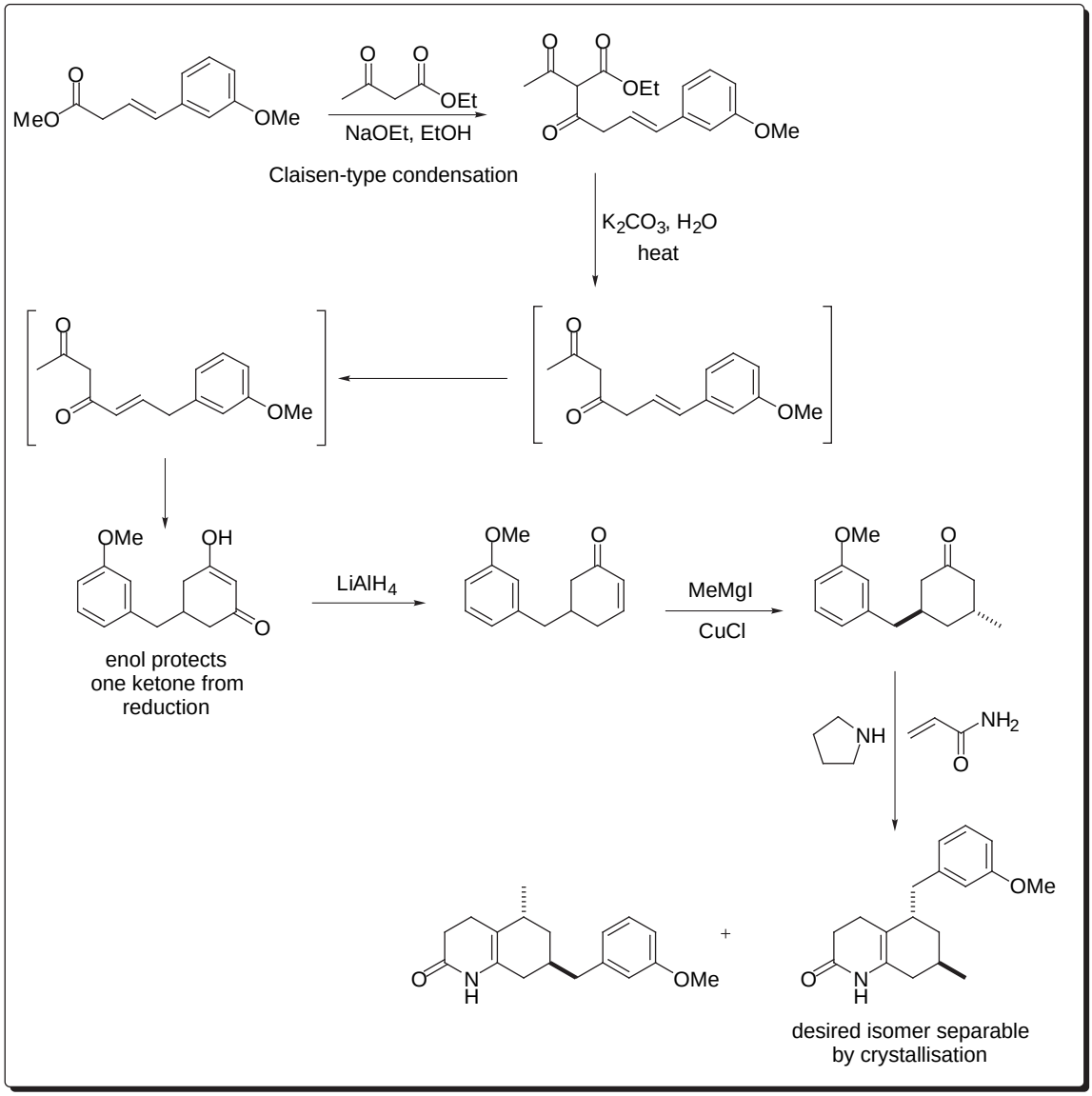
Stork also recognised that cyclisation on to an iminium ion would provide an efficient approach to preparing the polycycle. In this case he chose an electron-rich methoxyphenyl group as the nucleophile. Significantly this group also serves as a *masking group* for further functionality required later in the synthesis.



Notes:

- the **D** ring is again formed at a late stage reducing the problem to the preparation of a tricycle.
- the aryl ring provides a number of roles:
  - it is electron-rich and acts as the nucleophile for trapping the iminium ion to form ring **B**.
  - it provides, in masked form, the carbons (one too many remember) for forming ring **D**
- cyclisation is once again thermodynamically controlled.
- the problem is again reduced to the preparation of a trisubstituted cyclohexanone in which the *trans* substituent pattern between C(3) and C(5) is all that is important.

V.B.2 Formation of the quinolone.



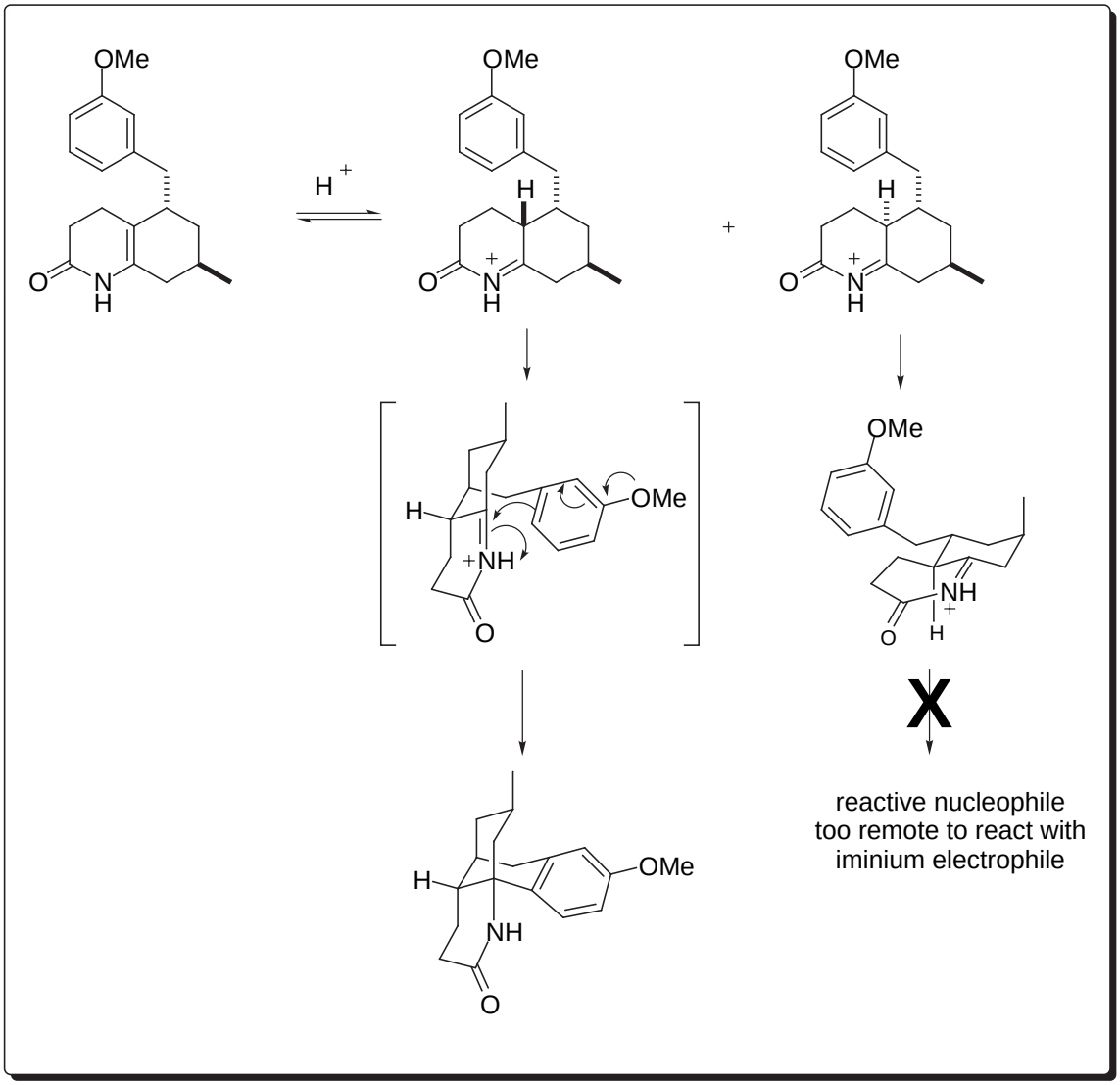
desired isomer separable by crystallisation

The synthesis of the quinolone uses very simple reagents and is prepared in a remarkably low number of steps.

- *Make sure you can draw mechanisms for the tandem sequence involved in the K_2CO_3 reaction. The intermediates should help.*
- *Why is the CuCl needed in the conjugate addition reaction?*
- The final step suffers from a lack of regioselectivity in the initial enamine formation (*make sure you can draw a mechanism for this step*) and produces two products which have to be separated. This is not ideal but the short synthetic sequence compensates for this drawback.

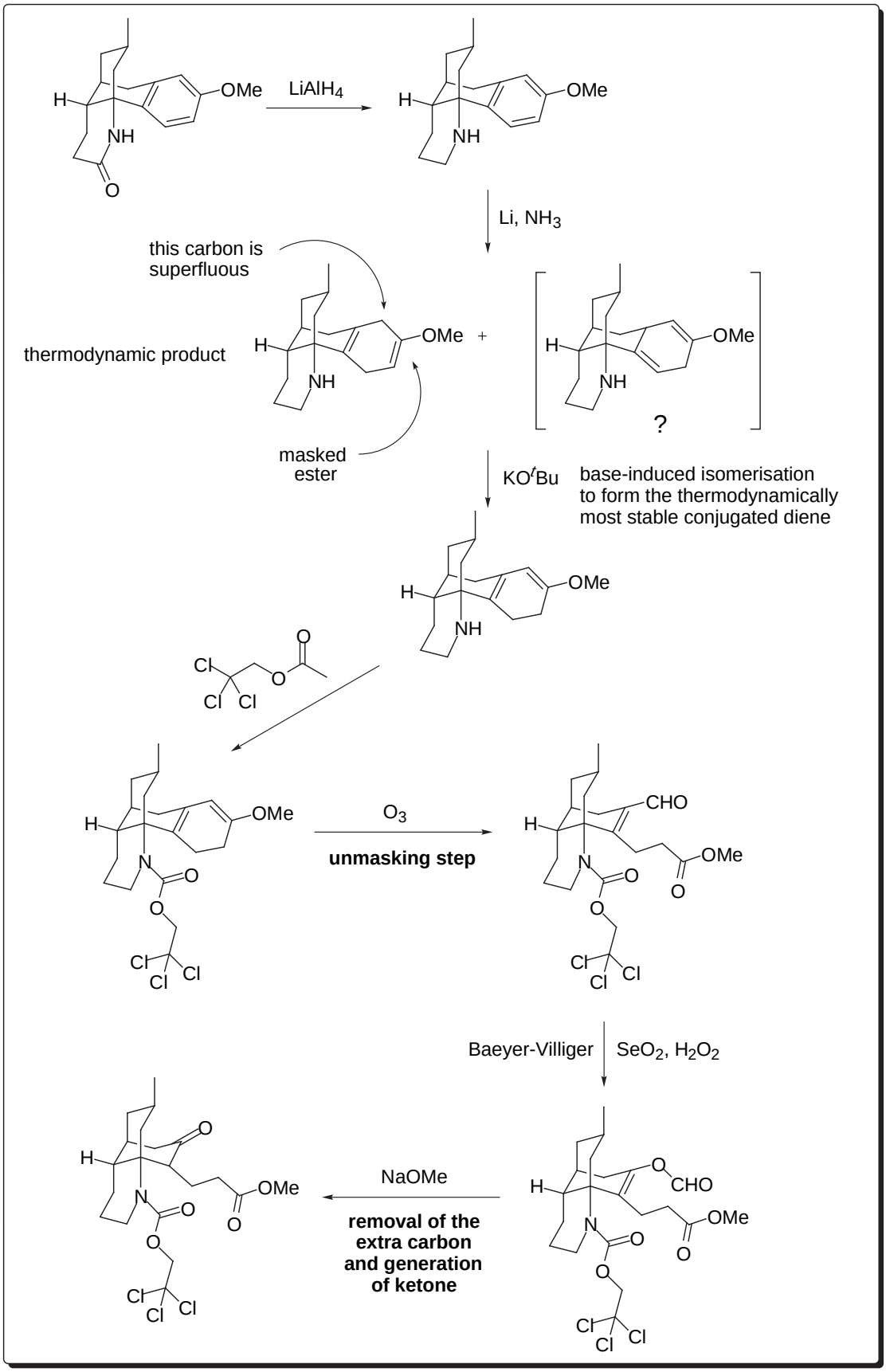
V.B.3 Formation of Ring B

This is the key step and just as in the Heathcock synthesis, Stork relies on thermodynamic control to direct the reaction along the desired pathway.



Unmasking the fuctionality in the aromatic ring

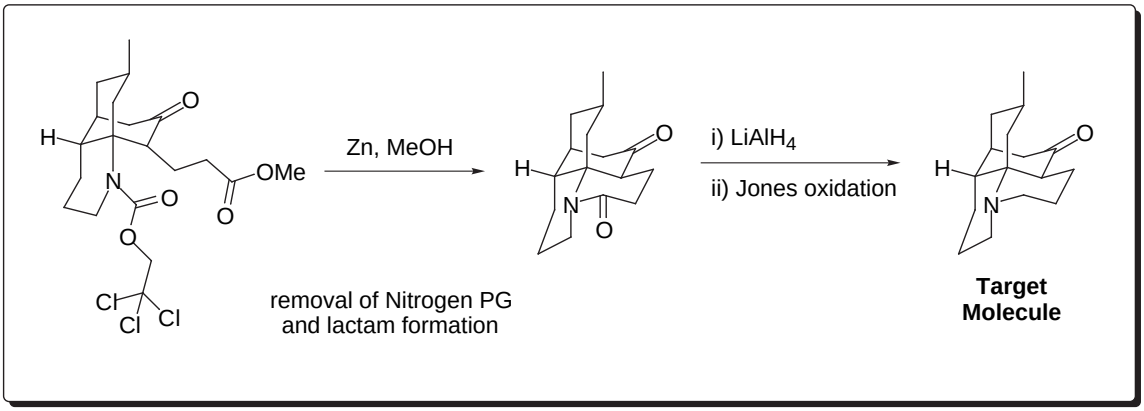
We must unmask the functionality in the aromatic group to construct the final ring (**D**):


LiAlH4
Li, NH3
this carbon is superfluous
thermodynamic product
masked ester
?
KO^{t}Bu
base-induced isomerisation to form the thermodynamically most stable conjugated diene
O3
unmasking step
Baeyer-Villiger
SeO2, H2O2
NaOMe
removal of the extra carbon and generation of ketone

In this set of steps the ester side-chain required to form ring **D** has been uncovered, the superfluous carbon atom removed and at the same time the requisite oxygenation in ring **B** installed.

- This strategy illustrates how Birch reduction is a very powerful way of elaborating aromatic rings.
- The major (exclusive ?) product is that containing the tetrasubstituted double bond (thermodynamically more stable)
  - however in this state, the superfluous carbon cannot be readily removed
  - by isomerisation to the more stable conjugated diene (the reaction conditions will also isomerise any of the minor Birch reduction product), ozonolysis can then be used to cleave the ring *regioselectively*.
  - Ozone reacts preferentially with electron-rich olefins, which in this case is the enol ether.
  - This releases the desired ester and an aldehyde.
- *Chemoselective* Baeyer-Villiger oxidation with the aldehyde generates the enol formate. This readily cleaves in the presence of sodium methoxide to provide methyl formate and the enol which tautomerises to the desired ketone

Completion of the synthesis:



In 17 steps and 1.1% overall yield, Stork provides the first total synthesis of Lycopodine.

Summary

The two elegant syntheses of Lycopodine exemplify a number of important guiding principles used widely in the synthesis of complex molecules.

1. **Clever retrosynthetic analysis simplifies the problem: in both cases late stage construction of ring D and trapping an iminium ion provides an efficient route to the ABC tricycle.**
2. **Tandem reactions are used to good effect for carrying out multiple transformations and bond-forming processes reducing the overall number of steps and increasing efficiency.**
3. **Careful analysis of reaction mechanism allows the prediction of the reaction products in the thermodynamically driven cyclisation steps.**
4. **Masking strategies can be useful.**
5. **Substrate control can be a powerful method for creating stereogenic centres.**