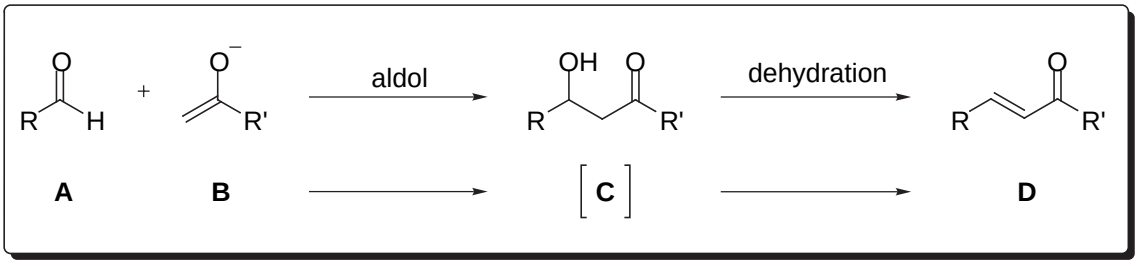
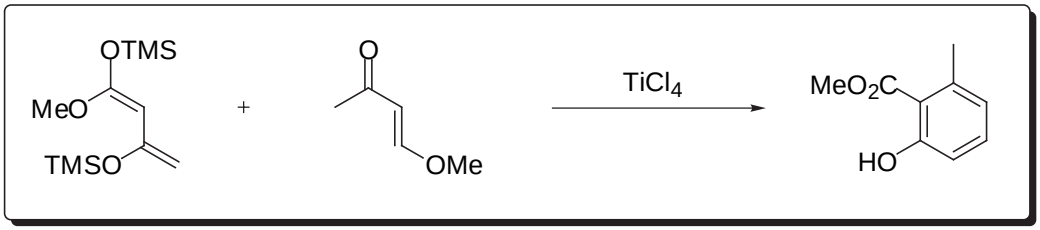
VII Tandem Reactions / Cascade Processes

One method for increasing the efficiency of a synthetic sequence is to carry out more than one transformation in a 'one-pot' process without isolating any of the intermediates. Such *tandem* or *cascade* reaction processes must be carefully planned to ensure the correct sequence of events is followed in the right order. This is most important for reactions that are under kinetic control; it is less of a problem when the desired product is also the thermodynamic product and intermediate steps are reversible. There are many examples of tandem processes in the total syntheses of natural products; we saw some good examples in the two lycopodine syntheses we examined earlier. This commonly used strategy is best illustrated by some more examples:

Example 1. Aldol-Dehydration.

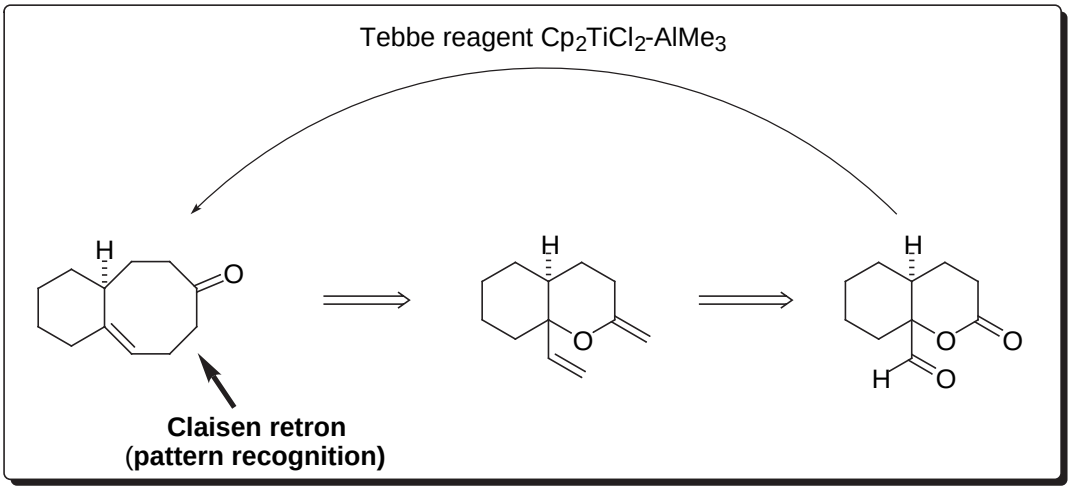


Example 2. Tandem Michael-Aldol



Make sure you can draw the mechanism for this tandem process. Hint: there are two C-C bond-forming reactions, a Michael reaction and then an aldol reaction. These are followed by several elimination steps.

Example 3. Tandem Olefination-Claisen



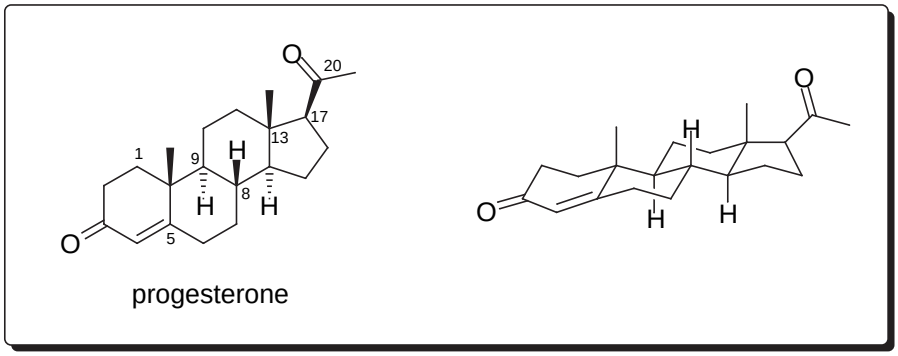
Notes:

- The [3,3]-sigmatropic rearrangement reaction is a very powerful method for inducing major skeletal changes.
- In the example in the Scheme above, it provides an elegant method for constructing eight-membered rings which are generally difficult to form.
- Starting from the aldehyde-lactone, bis-olefination using the Tebbe reagent provides the rearrangement precursor.

You may not have met the Tebbe reagent before. It operates via a metathesis-type reaction mechanism using $Cp_2Ti{=}CH_2$. Draw a mechanism for this methylenation reaction. Why is a more standard Wittig reaction unsuitable for forming the bis-olefin intermediate?

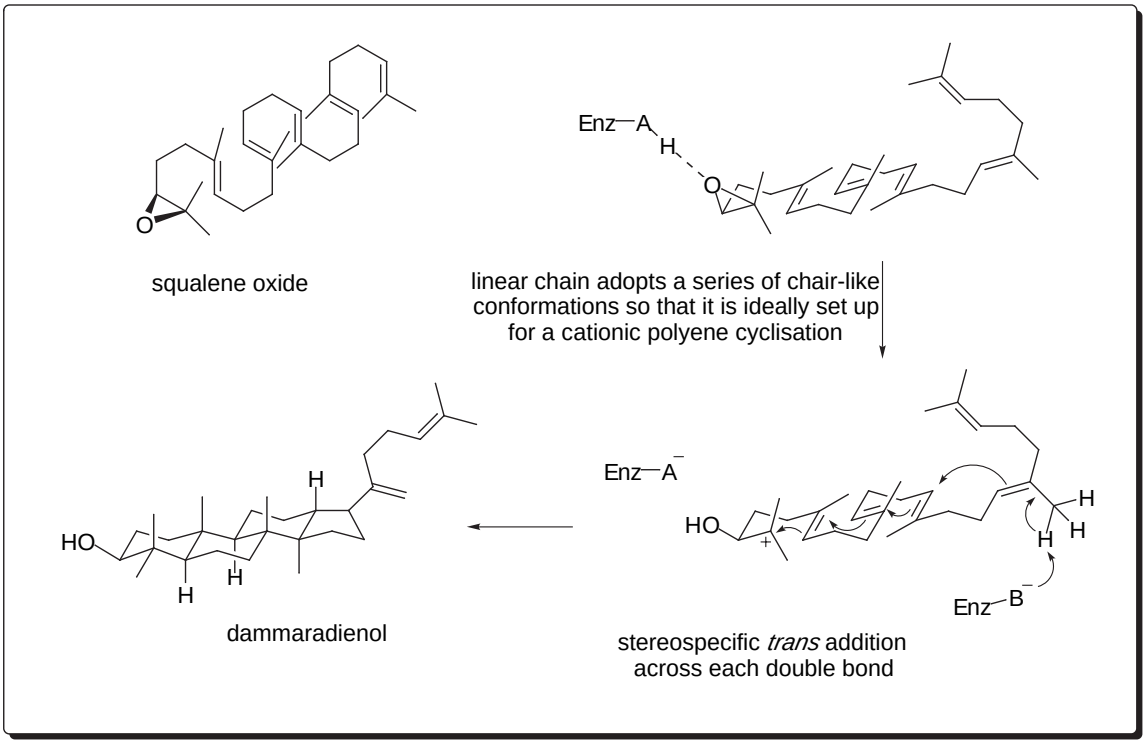
VII.A Johnson's Synthesis of Progesterone

For an excellent discussion of this synthesis: K. C. Nicolaou and E. J. Sorensen, *Classics in Total Synthesis*, Wiley-VCH, Weinheim, 1996, Chapter 6, pp 83-94.

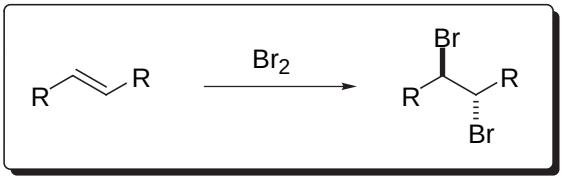


Progesterone is an important hormone. It is a member of the steroid class of natural products and is therefore derived from squalene oxide, which is the biogenetic precursor of all steroids and many polycyclic triterpenoids.

Consider the formation of the triterpenoid dammaradienol from squalene oxide. This polyene-cyclisation reaction proceeds in a *concerted* fashion and is completely stereospecific:

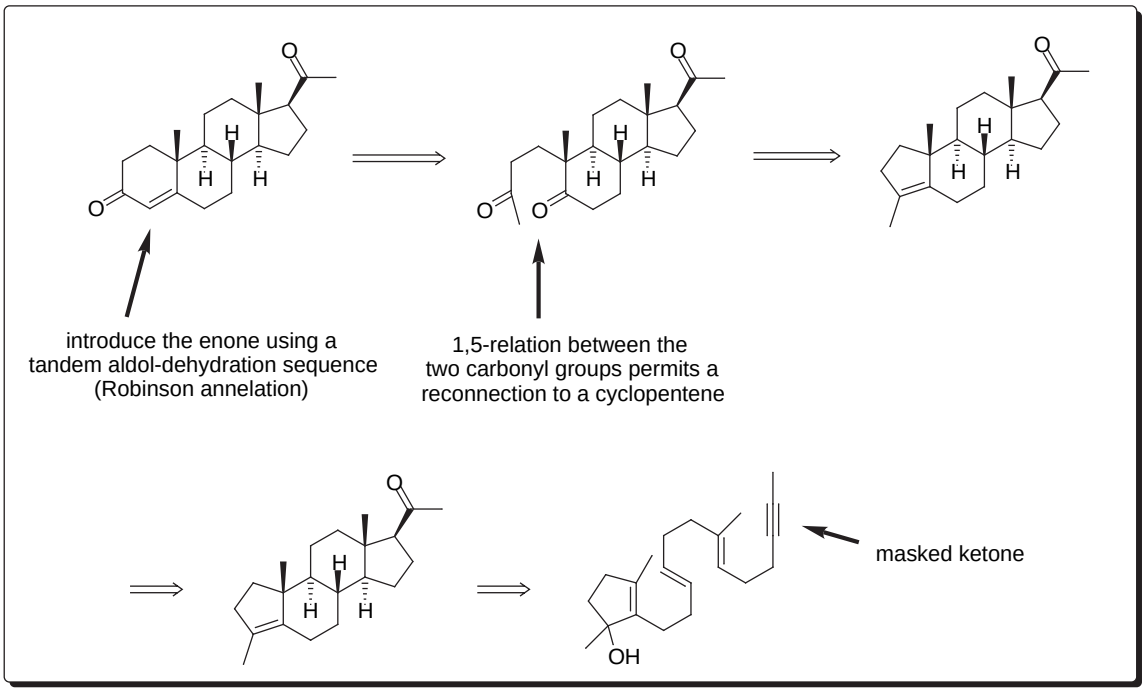


- The reaction is initiated by a general acid which regioselectively opens the epoxide to present the tertiary (most stable) carbocation to the proximal double bond.
- This C(6)-C(7) double bond traps this carbocation in a 6-*endo* fashion reacting through a chair-like conformation to generate a second tertiary carbocation.
- This is trapped by the proximal C(10)-C(11) double bond to form a second six-membered ring.
- The cascade of reactions continues until loss of a proton using a proximal general base traps the fifth carbocation and terminates the sequence.
- The geometry of the double bonds is crucial for forming the *trans-anti-trans* ring fusion found in this class of molecules. The reaction is stereospecific and is analogous to the *trans* addition of bromine across a double bond.

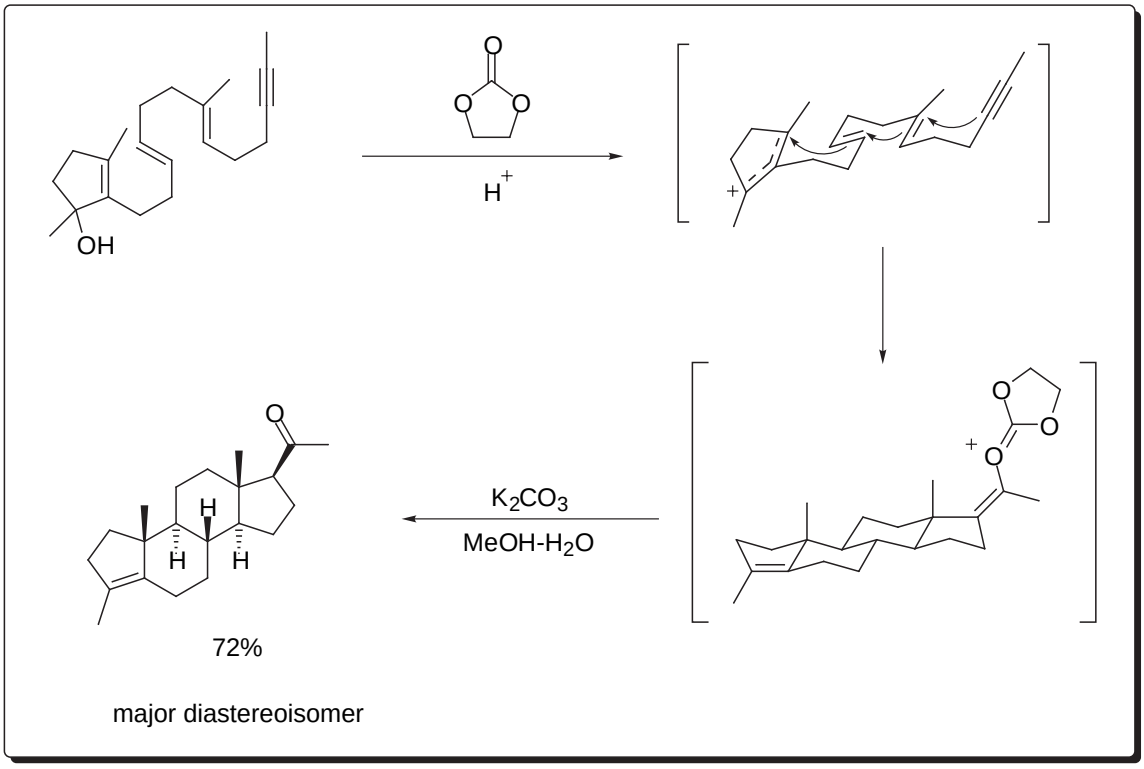


Make sure you can draw a mechanism for this electrophilic addition reaction and transition states which account for the trans addition.

Johnson recognised that the steroid framework of progesterone could be constructed using a similar polyene cascade strategy. Part of his retrosynthesis is presented in the scheme below:



The acyclic precursor is readily made (see above reference). Treatment of the tertiary allylic alcohol with a Lewis acid or Brønsted acid would be expected to induce heterolysis of the C-O bond and form an allylic carbocation that would then initiate the cascade of cyclisation steps.



72%

major diastereoisomer

In just one step, 3 new rings and 6 contiguous stereogenic centres are formed in a highly efficient manner.

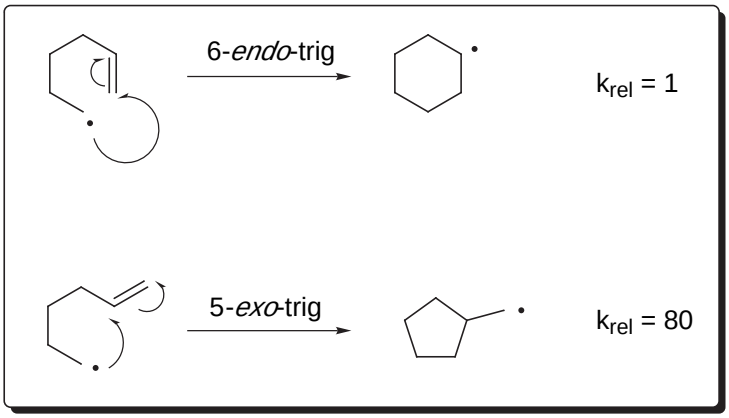
There are numerous other examples of similar polyene cascade cyclisation reactions. All operate in a similar manner. This strategy provides one of the best routes to polycyclic frameworks of this type.

VII.B Curran's Synthesis of Hirsutene

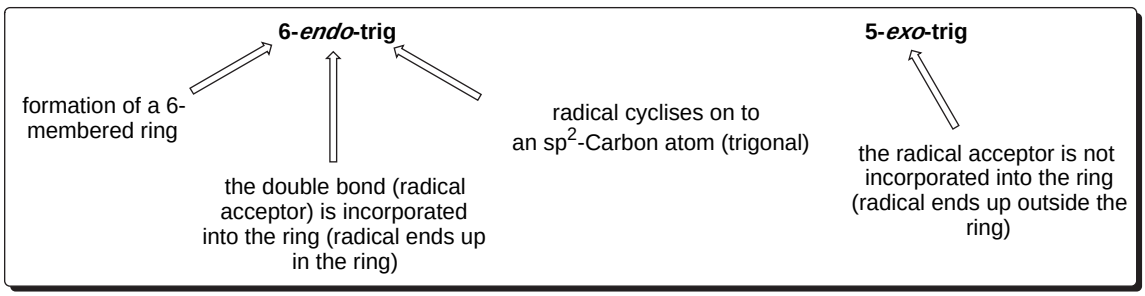
It used to be thought that free radicals were too reactive to be of any use in synthesis. Thankfully, this myth has now been dispelled. Although free radicals are reactive species, if they are generated under the right circumstances, they can be very useful for bond formation. Free radicals can be used in intermolecular reactions, however they find much more widespread application in intramolecular processes. The rates of ring formation using radical cyclisation processes have been investigated in great detail.

VII.B.1 5-*exo*-trig *versus* 6-*endo*-trig Cyclisation Processes

Consider the various modes of cyclisation available to the 5-hexenyl radical:



- Radical reactions are usually *kinetically controlled*.
- In the case of the 5-hexenyl radical, cyclisation to form the five-membered ring (and the less stable radical) is much more rapid than formation of the six-membered ring.
  What are the possible reasons for this rate difference?
- The radical cyclisation is described in the following way:



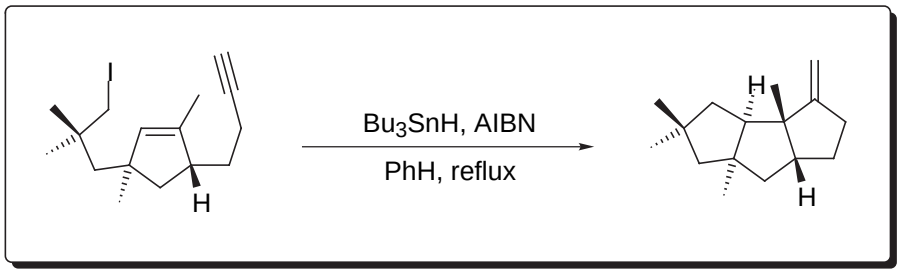
- Baldwin has provided a series of simple rules which can be used to predict the relative ease of ring formation when a carbon-centred radical adds to a double (trig process) or triple (dig process) bond, which is connected to the radical through a carbon chain - **Baldwin's rules**.
  - For example 5-*endo*-trig processes are not allowed whereas 5-*endo*-dig processes are.
  - *You should be able to rationalise this observation. Hint: consider the accessibility of the LUMO (π^*) for the radical in each case.*

VII.B.2 Analysis of Hirsutene

From the analysis it can be seen that the tricyclic ring skeleton might be constructed *via* a tandem radical cyclisation sequence starting from a substituted cyclopentene that will become the middle ring.

VII.B.3 Tandem Cyclisation

The radical cyclisation precursor was readily prepared and when treated with Bu_3SnH in the presence of a sub-stoichiometric amount of AIBN (radical initiator), provided hirsutene in excellent yield:



Draw a mechanism for this reaction sequence.

- In both cases a *cis* ring junction is formed: five-membered rings are relatively small; the transition state leading to the *cis* ring junction is relatively free from strain in allowing the SOMO (Singly Occupied Molecular Orbital) to overlap efficiently with the π^* LUMO. Such efficient overlap of these important frontier orbitals is not possible in the T.S. leading to a *trans* ring junction.

Make a model to convince yourself that cis ring junctions are easier to form.

- The *trans*-substituted cyclopentene ensures the desired *cis-anti-cis* ring fusion is obtained.

Summary

Tandem reaction cascades have been widely exploited in synthesis for decreasing the number of steps along a synthetic pathway; they often – but not always – lead to increased overall efficiencies. The key to success in this – and for that matter any – strategy is a good understanding of reaction mechanism, and for kinetically controlled reactions, a knowledge of relative rates; this then allows the order of the reactions in the sequence to be predicted. Many reactions have been used in this approach although the cationic polyene cyclisations and tandem radical cyclisation sequences described in the last two sections constitute some of the most impressive and elegant examples.