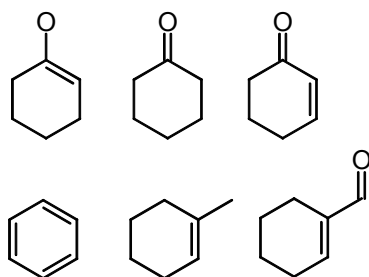


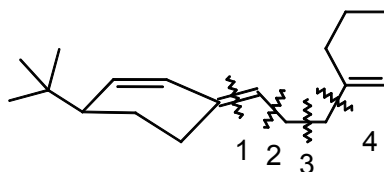
Chem 535-Synthetic Organic Chemistry**Disconnections with topological Molecular complexity in mind.**

Some of the following discussion is taken from "The Logic of Chemical Synthesis" E. J. Corey and Xue-Min Cheng. J. Wiley & Sons 1989.

1. There are arguments to be made for preserving four, five, six, and even seven-membered rings.
 - 1.1. Especially in the five and six-ring families of structures, stereocontrol at the carbon atoms in these systems is well understood and often very selective.
 - 1.2. Rings can be incorporated in the growing structure at reactive centers.
 - 1.3. For example



- 1.4.
- 1.5. At this point your imagination regarding how to use these substructures in synthesis should run wild.
 - 1.5.1. The ring-growing utility of the cyclic enolate and ketone is obvious.
 - 1.5.1.1. Especially in the light of our previous discussions this semester.
 - 1.5.2. The enone gives an added option of Michael addition.
 - 1.5.3. Benzenoid derivatives and alkenes open doors to electrophilic aromatic substitution.
- 1.6. Disconnections that preserve rings also tend to be convergent strategies.
- 1.7. So retrosynthetic analyses that preserve ring structure are often preferred.
 - 1.7.1.1. as in the following example.



- 1.7.1.2.
 - 1.7.1.3. Hopefully you can see some problems with disconnection 1.
 - 1.7.1.4. What is it?
2. There are some bonds which one would want to break in a disconnection even if

these bonds form part of ring systems.

2.1. C-N, C-O, C-S.

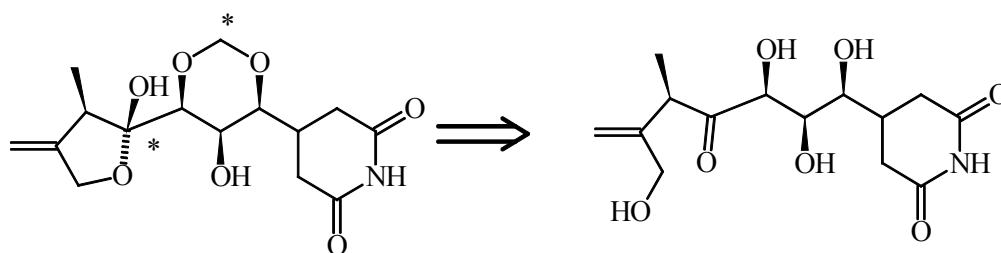
2.2. As you have learned, extra attention should be paid to facile cleavages such as O-CR₂-O which is really simply a masked ketone.

3. The synthetic advantages of disconnecting labile bonds trump the advantages of ring preservation.

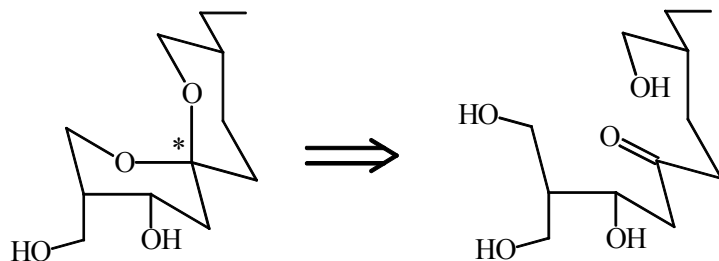
3.1.1. Why?

3.2. Look at the following example. With an eye open for labile bonds; the centers marked with * should be your first disconnection in the following molecules.

3.2.1. Why?



(+)-Sesbanimide A



Talaromycin A

3.3. One would expect to make the target acetals above in the presence of other alcohol functionality.

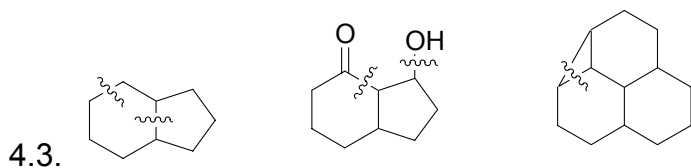
3.3.1. Why?

3.4. Although the supposition that the thermodynamic labile connection is the natural product has led to difficulty in rare cases, by far in the majority of cases the thermodynamic acetal is the natural product.

4. Strategic cyclic C-C disconnections.

4.1. When the topology in the structure is polycyclic and complex, one has to think very carefully about how to retroanalyze the structure, similar to undoing a knot.

4.2. You will need to disconnect a cyclic substructure in this case. There is no way to avoid it.



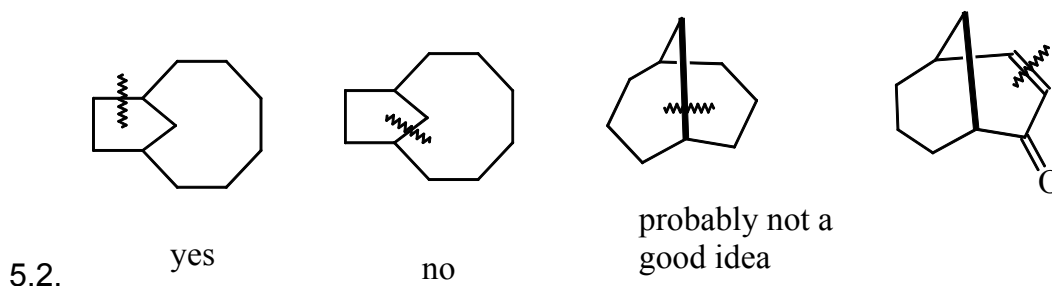
4.4. Diels-Alder

1,3-dipolar addition cyclopropanation

4.4.1. Quick analyses above brings to mind some name reactions.

5. Disconnections of Bridged-Ring Systems.

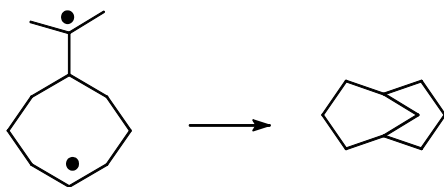
5.1. Disconnections that generate rings bigger than 7 members are not usually advantageous.



5.2.1. Applying this axiom to the above structures in deciding how to retroanalyze them leads to the above rough guides.

5.3. The cyclization of the [3.3.1] bicyclic system is difficult due both to strain and poor ΔS^\ddagger of the cyclization.

5.3.1. imagine



5.3.2. There is quite a bit of torsional energy in bringing these two ends together.

5.3.3. Wiberg, K. B. "The Concept of Strain in Organic Chemistry." *Angew. Chem., Int. Ed. Engl.* **1986**, 25: 312.

6. Medium sized rings are strained due to transannular interactions.

6.1. See: Mandolini and Illuminati *Accts. Chem. Res.*, **1981** 14, 95.

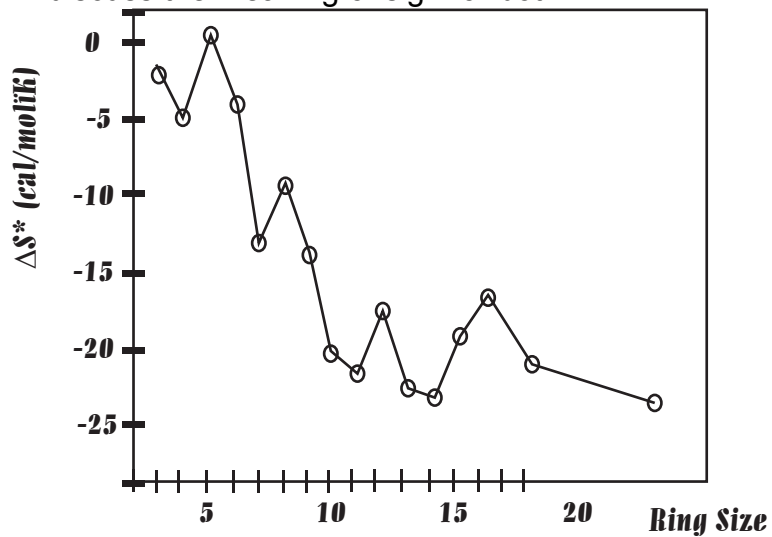
6.2. the ground state thermodynamics of ring size are reflected in the transition state energies of the formation of rings. Medium sized rings are strained on enthalpic grounds and are difficult to form entropically

6.3. Both ΔH^\ddagger and ΔS^\ddagger oppose each other in medium sized and small ring synthesis (cyclizations).

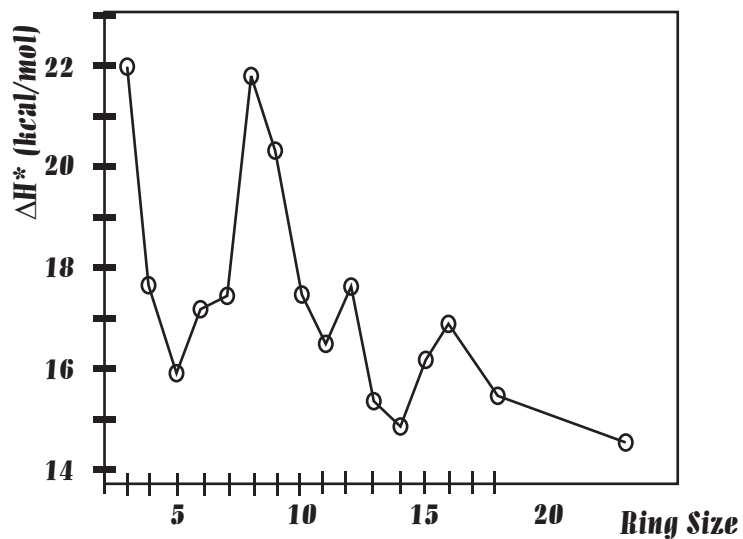
6.3.1. interpretation of activation H and S with respect to transition state structure

6.3.1.1. bond making versus bond breaking

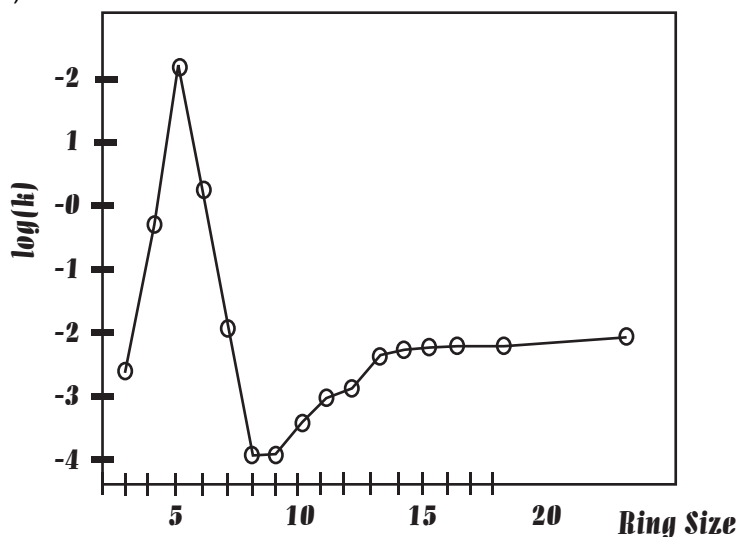
6.3.1.2. discuss the meaning of sign for both



6.3.2.



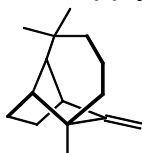
6.3.3.



6.3.4.

- 6.3.4.1. Sometimes transannular closures work extremely well.
- 6.3.4.2. Keep an open mind when you are creating synthetic approaches to systems like these.
- 6.3.4.3. Always make a model even when you are not in doubt!
- 6.3.4.4. All of this can get too prescriptive. There is no substitute for thinking and thorough literature searching.

7. Let's apply some of these principles in a consideration of some syntheses of

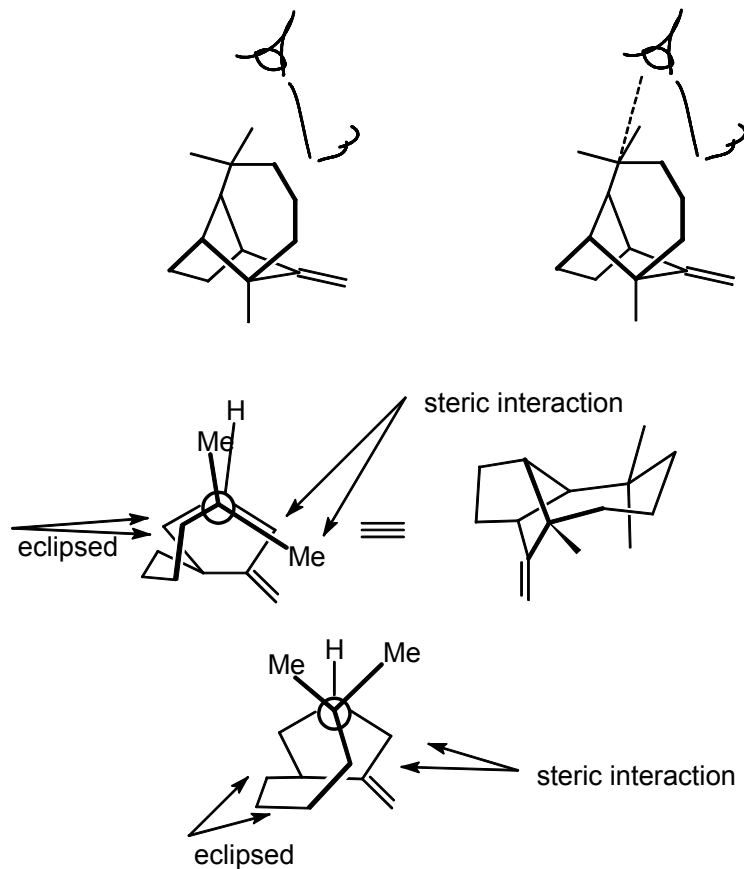


longifolene.

- 7.1. McMurry, J.E.; Isser, S.J. *J. Am. Chem. Soc.* **1972**, 94, 7132.
 - 7.2. Oppolzer, W.; Godel, T. *J. Am. Chem. Soc.* **1978**, 100, 2584.
 - 7.3. Johnson, W.S.; Andrews, G.C.; Volkmann, R.A. *J. Am. Chem. Soc.* **1975**, 97, 4777.
 - 7.4. Schultz, A.G. *et. al. J. Org. Chem.* **1985**, 50, 916.
 - 7.5. Let's consider the last one first, but first let's take a good hard look at longifolene and see what we can find in the way of molecular complexity.
8. Where do you think the synthetic challenges are in the structure?
- 8.1. Four asymmetric carbon atoms.
 - 8.2. Medium sized ring—well almost.
 - 8.3. [2.2.1]-bicyclo systems are strained.

8.4. Pull out model and discuss it.

8.4.1. There is extra strain in the large ring from the gem methyls. We would not have seen this without having built a model.



8.4.2.

8.4.3. A tangential approach to the medium-sized ring is probably best.

8.4.4. ie. don't plan on making the bond that we are sighting down with all the groups present.

8.4.5. This substructure is an element of complexity that entails both topological, strain and stereochemical content.

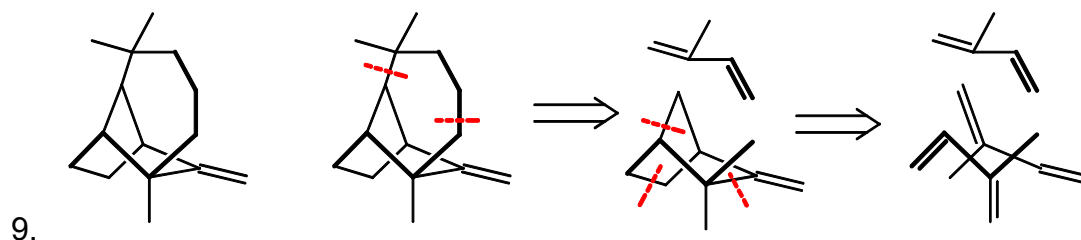
8.4.6. Schultz, A.G. *et. al. J. Org. Chem.* **1985**, 50, 916.

8.4.7. Synthesis of the **sesquiterpine**, longifolene.

8.4.7.1. A natural analysis based on units of Isoprene (2-methy-1,3-butadiene). The building block composes many natural hydrocarbons.

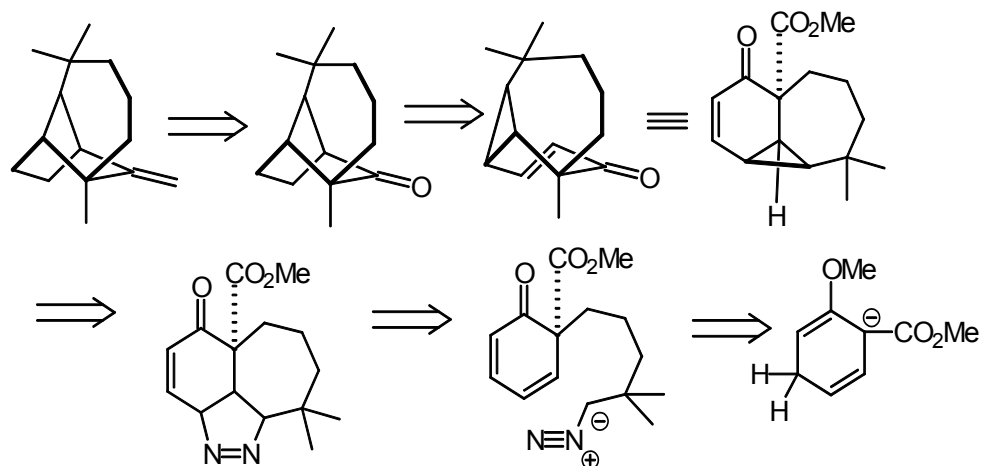
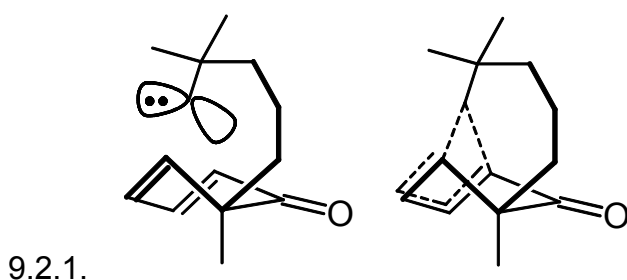
8.4.7.2. Isoprene is a five carbon unit; longifolene is a **15 carbon unit**.

8.4.7.3. You can almost see the *biological* disconnection. Mother Nature's retrosynthesis.



9.1. The above shows a hypothetical biological disconnection of longifolene into isoprene units.

9.2. The Schultz et. al. frame their approach as the 'synthetic equivalent' of Mother Nature's approach.

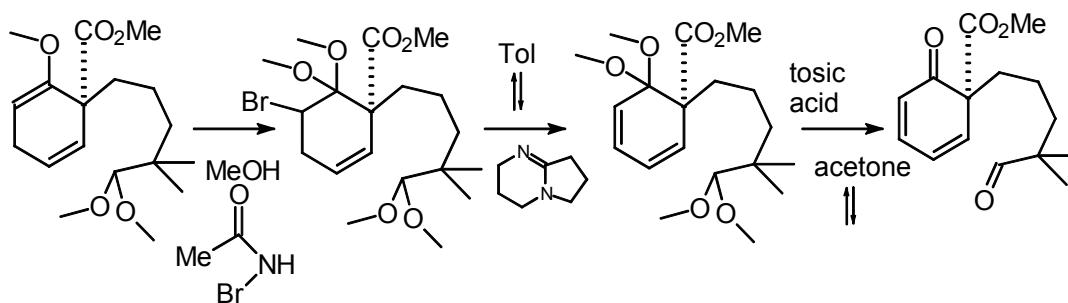


9.2.2.

Careful with six membered rings this close to aromatic

9.3. Alkylation of the Birch reduction product by the acetal bromide puts the quaternary center in place.

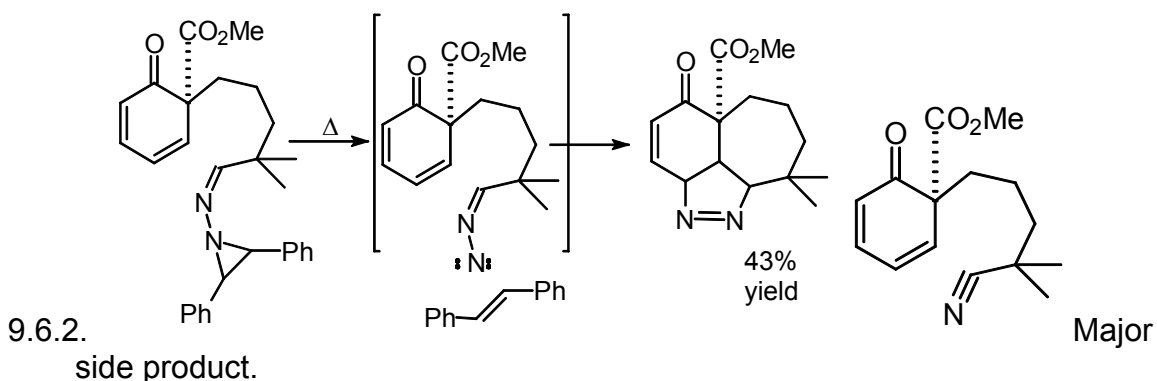
9.4. The stereochemistry of all reactions to follow is governed by this quaternary stereogenic carbon atom.



9.5. Birch reduction and alkylation runs in 95% yield.

9.6. The following three steps run in 86% yield.

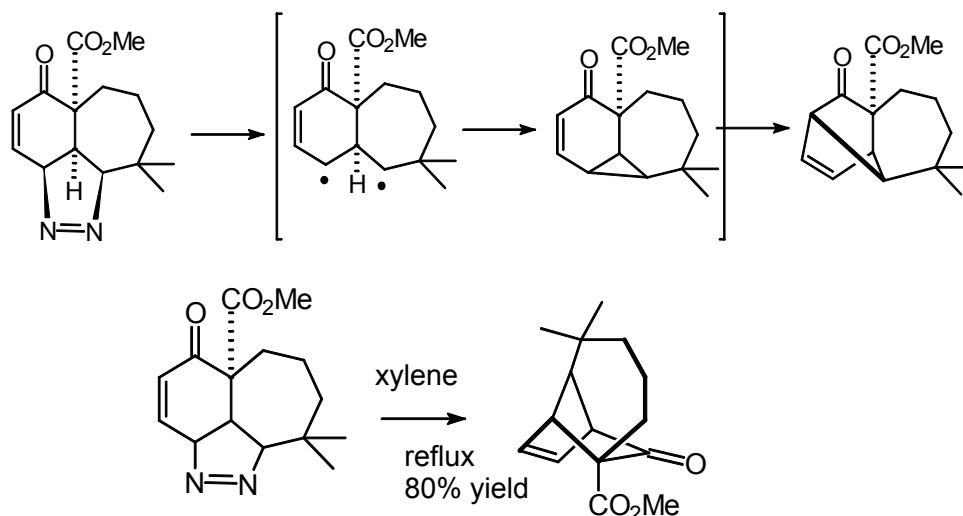
9.6.1. The bromo diacetate (second structure from the left above) is a mixture of diastereomers.



9.6.3. The authors do not describe the aziridine imine formation well. One wonders how efficient it is.

9.6.4. In general these reactions are quite good the aziridine imine is a hydrazone, a common derivative of carbonyl functionality.

9.6.4.1. In the generation of the 1,3-dipole some fragmentation results.

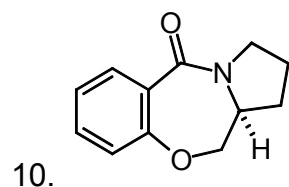


9.7. At this point what would you do?

9.7.1. Pd/H₂ reduction saturates the ring,

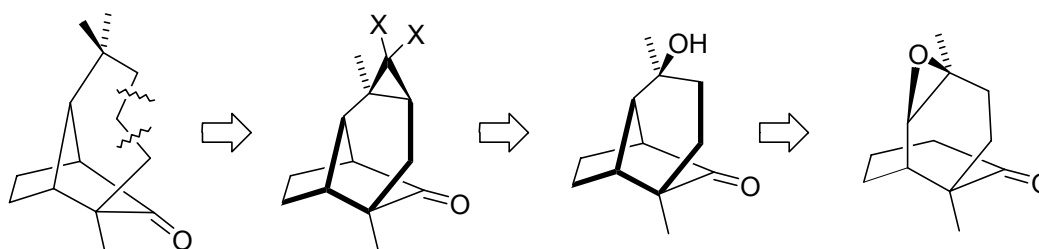
9.7.2. MeLi followed by elimination furnishes the natural product.

9.7.3. Had to go with addition elimination because the ketone is sterically hindered.



10.1.1. Birch reduction / alkylation of this proline derived amide furnished Longifolene optically pure with the route above.

11. McMurry, J.E. *JACS* **1972**, *94* 7132.



11.1.1. Wieland-Miescher ketone is the starting point

11.1.2. This ketone has been utilized in many syntheses.

