

## Thinking backwards

1. Many problems are best solved thinking backwards. This is certainly true in many fields of chemistry besides synthetic organic chemistry.
  - 1.1. Analyzing the problem in reverse especially comes in handy when you know where you need to go but there are many steps that might take you there.
  - 1.2. Think about people being stuck in a maze. If you can see the exit. You can tell them all how to get out (or suggest the best of many routes to get out) or for example, if you are lost and you have a map and you know where you need to go on the map you will trace steps back to where you are.

## 2. Retrosyntheses.

- 2.1. Are sketchier than their forward counterparts, retrosyntheses are only an outline of the plan.

### 2.2. Vocabulary

2.2.1. **Synthon**: a representation of a set of real molecules/ reactive molecule(s) or conditions that transforms a functional group in “trusted” ways into a new desired functional group.

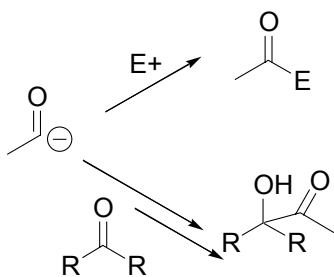
2.2.1.1. A synthon is not necessarily a real molecule.

2.2.1.2. EXAMPLE

2.2.1.3. The acyl anion is represented by the synthon.



2.2.1.4. This ‘synthon’ stands for or represents a plethora of different specific ways to accomplish the synthetic equivalent of these two procedures. There are many ways to get either one of these products.



2.2.1.5. When would you use a synthon?

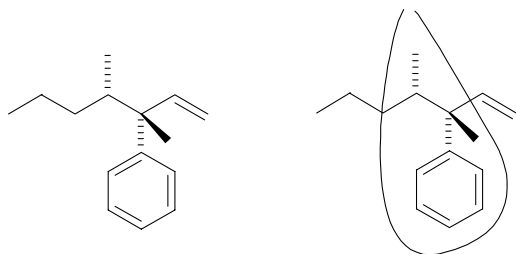
2.2.1.5.1. You might use a synthon to represent a series of steps that you are not sure about in a retrosynthesis.

2.2.1.5.2. You would do some digging later in the library for the specific conditions to carry out your plan to include in the stepwise description in the forward synthesis.

2.2.2. **Retron**: a functional group or substructure of a target molecule that signals the facile application of a method or a reagent trusted to give rise to the desired functional group or substructure.

2.2.2.1. Sometimes seeing a retron versus not can be a matter of opinion.

2.2.2.2. Sometimes applying a retron to a specific synthetic problem is like shoving a round peg into a square hole.



2.3. The above target structure contains the retron for a 3,3-sigmatropic rearrangement, why?

2.3.1. These reactions can make 3° to 4° C-C bonds.

2.3.1.1. Sigmatropic shifts put the two termini in bonding distance in the transition state.

2.3.1.2. The two 'reactive ends' are tethered.

2.3.2. The alkene group also hints at a 3,3-sigmatropic rearrangement.

2.3.3. Read the references below and devise a retrosynthesis of the molecule above. Think about today's lecture and decide what challenges there are in the synthesis. Be prepared to discuss this problem next time.

#### **2.4. ASSIGNMENT FOR NEXT LECTURE! READ THE FOLLOWING**

#### **2.5. REVIEWS!**

2.5.1. Ziegler, F. E. "The Thermal Aliphatic Claisen Rearrangement." *Chem. Rev.***1988**, 88, 1423.

2.5.2. Bennett, G. B. "The Claisen Rearrangement in Organic Synthesis." *Synthesis***1977**, 589.

2.5.3. Blechert, S. "The Hetero-Cope Rearrangement in Organic Synthesis." *Synthesis***1989**, 71.

2.6. Retrosynthesis is hypothetical, stepwise and systematic simplification of a target structure.

2.6.1. Start with the product!

2.6.2. Hypothetical – You don't know if you can really do it. You can hopefully make a strong argument for your ability to carry out the plan.

2.6.3. Systematic-

2.6.3.1. You are confined by the laws of nature. You must work within earthly parameters.

2.6.3.2. Thermodynamics

2.6.3.3. Kinetics

2.6.3.4. Steric effects

2.6.3.5. Literature precedent

2.6.3.6. Don't plan to carry reactive groups through many steps.

2.6.3.7. Minimize the steps.

#### 2.6.4. Stepwise-

2.6.4.1. Make your simplifying changes in the structure easily followed by others

2.6.4.2. Don't make more than 1 key disconnection at a time.

2.6.4.2.1. Key disconnections usually break critical C-C bonds.

2.6.4.2.2. Establish critical stereochemistry

#### 2.6.5. simplification

2.6.5.1. Each step must take you down a molecular complexity gradient.

2.6.5.2. You don't want to invent a sub-target molecule that is more difficult to make than the desired final product for example.

### 3. Molecular complexity

3.1. Since we are trying to simplify the structure we need to know what make structures complex

3.1.1. Size, solubility

3.1.2. Diversity of Elemental content

3.1.3. Diversity of functional groups

3.1.4. Strain

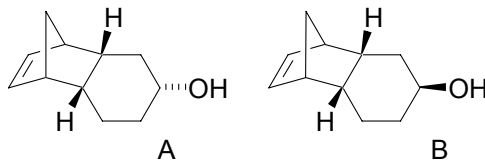
3.1.5. Stereocenter content

3.1.6. Ease of epimerization

3.1.7. Chemical reactivity

3.1.8. Structural instability

3.1.9. Topology, Cyclic connectivity



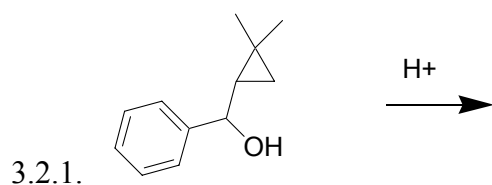
The carbon skeleton has a plane of symmetry. Topological complexity means that the two hydroxyl groups are going to have very different reactivity.

3.1.9.2. I don't think you could even make molecule A.

3.1.9.2.1. What do you think might happen to molecule A?

3.1.10. Related previous synthetic experience (literature precedent)

3.2. The above elements of complexity geometrically expand the difficulty of the synthesis. Example



3.2.2. Consider how these two functional groups might make reactivity toward a proton donor a complex issue.

**3.3. Which facet of Molecular complexity does one attack first retrosynthetically and why?**

3.3.1. The answer here is complex.

3.3.1.1. Likely the question is answered by trial and error. Develop a few routes and see which one minimizes the effort, has the most precedent, has least complex synthetic intermediates, etc.

3.3.2. The timing of synthetic events depends on the structure and what you want to accomplish.

3.3.3. For small polycyclic structures topological thinking may be the most important in when trying to avoid painting oneself in a corner you may have to install functionality at some stage in the synthesis wherein the topology of the molecule prevents reactivity at that site.

3.3.4. For straight chain molecules with many stereocenters you might have to focus on transformations that faithfully pass stereochemical information from center to center

3.3.5. For larger molecules the prime simplifying criterion may be the junction of two pieces of approximately equal size.

3.3.5.1. 99% of all molecular transformation is done in solution--you have to dissolve the material

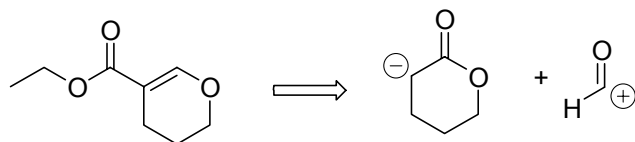
3.3.5.2. large molecules tend to be insoluble

### 3.4. PRESENTING RETROSYNTHESES

3.5. Synthons are important in retrosynthesis

3.5.1. A representation functional group that can be transformed in a known manner to give a desired functional group.

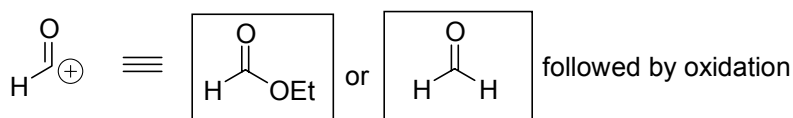
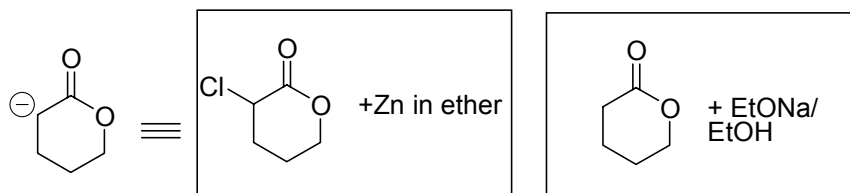
3.5.2. Synthons are general.



3.5.3. The formyl(+) above, stands for all reagents capable of adding the formyl group to an anion.

3.6. Likewise in the retrosynthesis above I did not denote the type of ester enolate.

3.7. Real reagents for this synthon might look like the following:



3.8. We use retrosynthetic schemes to talk about synthesis from a problem oriented approach

4. **Convergence**, a guide to better synthetic design.

4.1. Convergent syntheses are better than linear syntheses with all other things equal.

4.2.  $S \rightarrow T_1 \rightarrow T_2 \rightarrow T_3 \rightarrow T_4 \rightarrow T_5 \rightarrow T_6 \rightarrow P$

4.2.1. A linear retrosynthetic scheme.

4.3. The scheme depicts a seven step linear synthesis

4.4. Hypothetically let's say you get 70% yield/step.

4.5. The total yield is  $0.7^7 \times 100\% = 08.2\%$

4.6. Consider the convergent alternative to the linear synthesis

4.6.1.  $T'_6 \rightarrow T'_7 \rightarrow T'_8 \rightarrow T'_2$

4.6.2.  $T'_5 \rightarrow T'_4 \rightarrow T'_3 \rightarrow T'_1$

4.6.3.  $T'_1 + T'_2 \rightarrow P$

4.6.4. The scheme above depicts a more convergent approach.

4.6.5. The above retrosynthetic scheme is a combination of two linear steps.

4.6.5.1. With the same hypothetical 70% yield/step.

4.6.5.2. The total yield is  $(0.7^3 \times 0.7)$  or  $0.7^3 \times 0.7 = 0.24$  or 24% yield.

4.6.6. In practice the philosophy of convergent syntheses is more powerful than the above math indicates

4.6.7. Your chances of mishandling a step decreases the amount of material you can safely carry through the synthesis.

4.6.7.1. You are running less risk at any point in time in the convergent process.

4.6.8. Notice how the linear steps depend on the preceding step. Convergent syntheses are more amenable to be reengineered.

4.7. Convergence increases your chances of having good yields because the pieces you have to carry through x amount of steps are less complex.

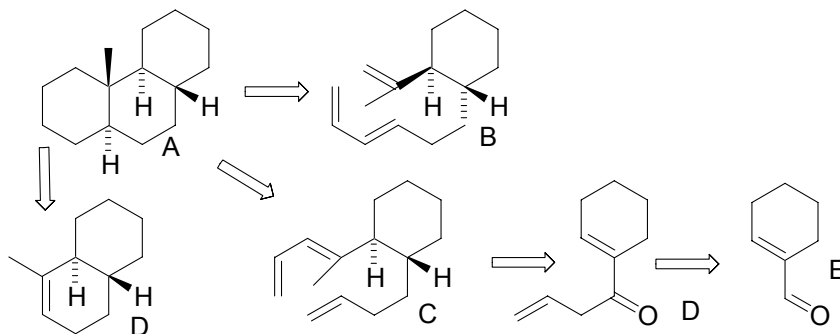
4.7.1. Here I am talking about molecular complexity with elemental content or functional group content or size as criteria.

## 5. EXAMPLES (applications of the concepts above!)

5.1. In continuing with retrosynthetic analysis I would like to consider fused six-membered rings with stereochemical issues at the fusion sites.

5.2. I am also stressing the fact that topologically complex structures (functionality-rich cycloalkanes) are derived from alkenes.

5.3. Stereocontrolled alkene (a subject for the near future) is very important in the construction of more complex structures.



## 6. Three possible Diels-Alder retrosyntheses for A

6.1. Ciganek, E. (1984). "The Intramolecular Diels-Alder Reaction." *Org. React.* (N.Y.) **32**: 1.

6.2. A is a common substructure of mammalian hormones.

6.3. Unlike the intermolecular Diels-Alder, intramolecular Diels-Alder can occur unsubstituted.

6.4. In the construction of six membered rings with Diels-Alder retrosynthesis there are three possibilities. Two of which above are intramolecular.

6.5. The D-A reaction translates the stereochemistry of the ring carbons to the nascent cyclohexene in the retrosynthesis A->B and A->C.

6.6. Retro A->D is inferior for various reasons

6.6.1. The target is trans fused and Diels-Alder gives cis fused product

6.6.2. Unsubstituted intermolecular Diels-Alder will not work.

6.6.2.1. The diene will have to be functionalized and this functionality will have to be burned away to make the product.

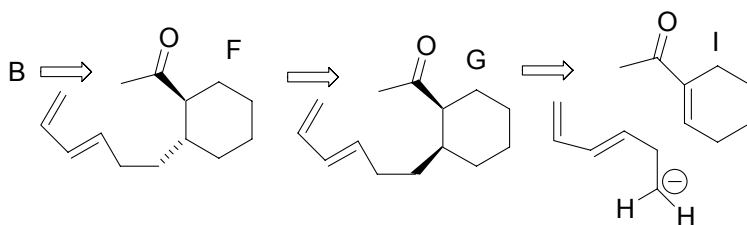
6.6.3. A->C is an undesirable synthetic transformation if it can be avoided on the principles of molecular complexity.

6.6.3.1. There is a trisubstituted olefin in C.

6.6.3.2. These are hard to synthesize purely cis or purely trans.

6.6.4. Furthermore synthetic intermediate D will be sensitive to base.

6.7. Retro A->B is the one to pick.



6.8.

6.9. A->B solves the molecular complexity issue much better.

6.10. The starting materials contain alkenes (olefins) that are easier to synthesize lacking the cis trans isomer issue.

6.11. The materials for this approach should be readily available.

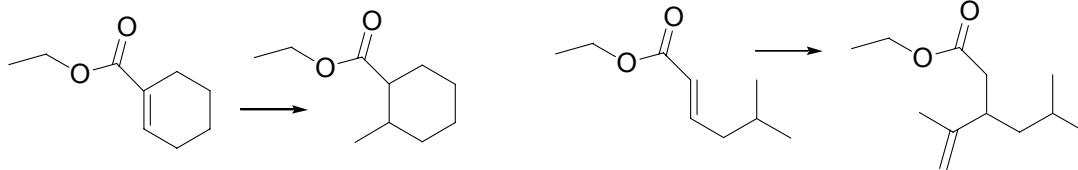
6.12. I is a commercial compound.

6.13. Supposedly the anion of H is synthetically available.

6.13.1. Use 1,4 addition.

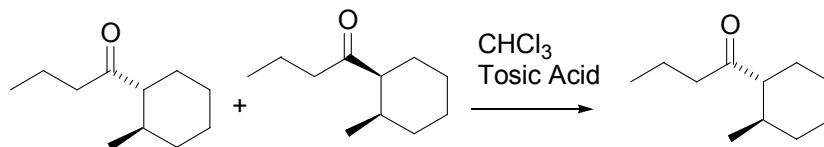
6.13.2. Erdik, E. "Copper(I)-Catalysed Reactions of Organolithiums and Grignard Reagents" *Tetrahedron* **1984**, *40*, 641.

6.13.3. Yamamoto, Y. ; Yamamoto, H.Y.; Maruyama, K.; Ishihara, Y. *J. Org. Chem.* **1982**, *47*, 119-126. CuI, (R-Li or RMgX), BF<sub>3</sub>OEt<sub>2</sub>.



6.13.4. 1,4 addition of alkyl to alpha-beta unsaturated esters is difficult but feasible

6.13.5. see: Kuwajima/Yamamoto BF<sub>3</sub> catalyzed 1,4-addition of cuprates.



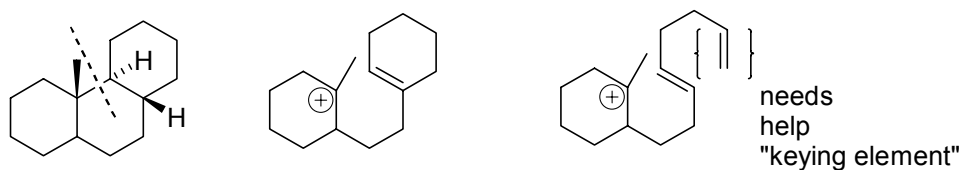
6.13.6. These products can be equilibrated (epimerized) to the thermodynamically favorable material.

7. We can think retrosynthetically using the cation as a functional group.

7.1.1. Of course chemically this is a bit rough to conceptualize.

7.1.2. The positive charge below allows you to at least think about a few different bond cleavages (different retrosyntheses).

7.1.3. Can you see them??



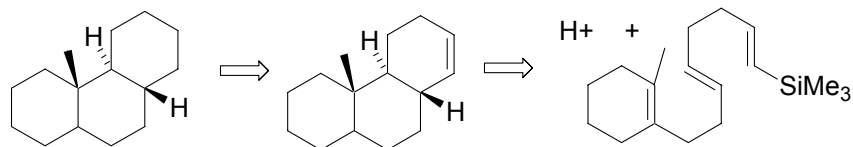
7.1.4. Six Membered rings can be synthesized efficiently by cationic cyclization.

7.1.5. You can think of this reaction Retrosynthetically by using the cation as a substituent.

7.1.6. When there are more than two double or triple bonds, the reaction is called polyene

7.1.7. cyclization.

7.1.8. See: Comprehensive Organic Chemistry, vol 3 pp. 341-375.

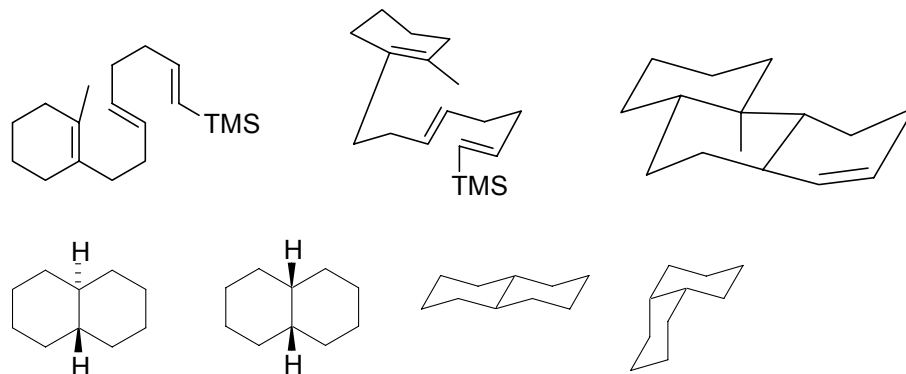


7.1.9. Primary/ secondary cations are difficult to generate.

7.1.10. Rely on the  $\beta$ -silyl effect to stabilize the intermediate cation.

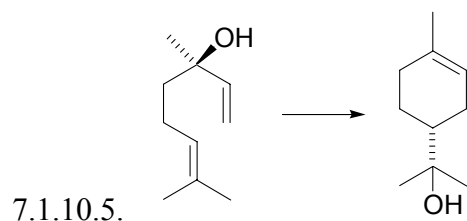
7.1.10.1. You can also rely on the silyl group to direct the cyclization.

7.1.10.2. The double bond (elimination) will terminate the zipper reaction.



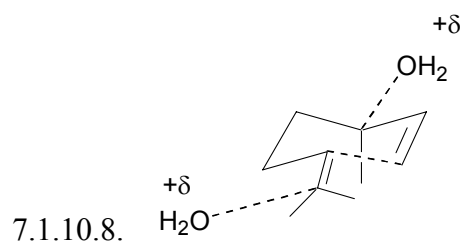
7.1.10.3. The stability of the *trans* versus *cis* decalin determines the C-C bond formation.

7.1.10.4. Examples of the kind of stereochemistry that can be effected with cation cyclization:

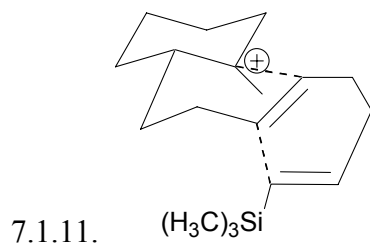


7.1.10.5. The rearrangement above occurs under the action of acid. The OH group is protonated and leaves to make a tertiary cation which rearranges to another tertiary cation.

7.1.10.7. The stereocontrol is so good that the reaction is proposed to be concerted. See below.



7.1.10.9. There are many examples of bi and tri cyclizations. The results of most of these appear to indicate chair-like transition states.



7.1.12. In the transition state structure in above figure the new bonds are forming in equatorial positions.