1. **Goals:** after you attend this series of lectures and access the referenced literature you should be able to answer the following questions do the following skills
   a) What is a functional group?
   b) What is the definition defunctionalization?
   c) What are the elements of retrosynthetic analysis?
   d) What is the main task of retrosynthetic analysis?
   e) What are the elements of molecular complexity?
   f) How do I present a retrosynthesis on paper?
   g) How do I access the literature to aid in retrosynthesis?
   h) What do I need to know to do retrosynthetic analysis?
   i) Define synthon.
   j) What is convergency?
   k) Why are convergent syntheses desirable?
   l) What do organic chemists mean by oxidation state.
   m) Read a published synthesis to understand the logic of the synthetic approach. We will consider a synthesis cubane.

2. Before we talk about retrosynthesis we need to get a few other ideas about molecular structure down first. These are oxidation number and functional group.

3. Functional groups in organic molecules are molecular substructures that react similarly under various conditions.
   a) We can talk about the chemistry of ketones because ketones tend to behave like ketones from molecule to molecule.
   b) For example, cholestene and 2-methyl-2-butene are expected to behave similarly. They both have the alkene functionality.
      i) For example they should both react with Br_2
      ii) Divergent reactivity could be explained by differences within alkene reactivity.
      a) cis versus trans, cyclic versus noncyclic
   c) Likewise alcohols primary, secondary, and tertiary make up functional groups.
      i) We would expect to be able to tosylate all primary alcohols.
      ii) However we would not expect to be able to oxidize tertiary alcohols to ketones in the same way secondary alcohols are oxidized to ketones
      iii) Therefore with respect to oxidation the secondary alcohols and the tertiary alcohols need to be separate functional groups
      iv) The above is just language

4. Ox/Red in organic chemistry is an important concept.
   a) It is linked to the concept of the functional group.
   b) The concept of Oxidation and Reduction in organic chemistry is not as straightforward as it is in other branches of chemistry that deal more frequently with metal centers.
      i) In other branches of chem, oxidation is defined as the taking of electrons. The oxidant gets reduced. In so doing it takes electrons.
      ii) Likewise the reducing agent gives up electrons and gets oxidized.
      iii) These reactions always have both partners, oxidant and reducing agent.
   c) Organic chemists are a bit more challenged when speaking of oxidation and reduction and oxidation numbers.
      i) The principles still apply, but they are a little more difficult to apply.
ii) Most mechanisms we write in organic chemistry do not involve the direct transfer of electrons from one molecule to another.

iii) We could get real picky and talk about oxidation states of different carbons in molecules and assign increasing oxidation states to carbons bonded to more electronegative atoms.

d) Organic chemist over the years have set up functional groups in a qualitative way to reflect their oxidation number.

e) Carbons that do not make π bonds to other C atoms are easy.

i) The alkane oxidation state. A C atom in this oxidation state makes only single bonds and only to C and H atoms. Alkanes are the only functional group in this oxidation state.


iii) The aldehyde oxidation state. A C atom in this oxidation state makes two bonds to one or two heteroatoms. Examples: aldehydes and ketones, imines, acetals.

iv) The carboxylic acid oxidation state. A C atom in this oxidation state makes three bonds to heteroatoms; usually a double bond to one heteroatom and a single bond to another. Examples: carboxylic acids, carboxylic esters, carboxylic amides, acyl chlorides, nitriles, guanidines, orthoesters.


f) Alkenes and alkynes are a little more complicated. The two atoms making up the π bond must be considered together.

g) Use the H₂O trick for carbons with both heteroatoms and π bonds to C.

i) Enols → ketones is not a redox change.

5. Synthons
a) A synthon is a reactive species that can be converted into some functional group. We speak of a synthon for a ketone, or a synthon for a carboxylic acid.

b) Synthons can be further classified according to the $d^n$ or $a^n$ nomenclature:
   i) $d$ are electron donors, i.e. nucleophiles
   ii) $a$ are electron acceptors, i.e. electrophiles
   iii) The superscript indicates the number of atoms between where bond-making takes place and a polarizing heteroatom or a $\pi$ bond that can be converted into a polarizing heteroatom (ozonolysis).

\[
\begin{align*}
 &\begin{aligned}
 &\text{C} &\equiv &\text{N} \\
 &\text{H}_2\text{C} &\equiv &\text{NO}_2 \\
 &\text{CH}_3\text{CH}_2 &\equiv &\text{MgBr} \\
 &\begin{array}{c}
 \text{S} \\
 \text{S}
 \end{array} &\equiv &\text{Br} \\
 &\text{H}_2\text{C} &\equiv &\text{NMMe}_2 \\
 &\text{CH}_3\text{CH}_2 &\equiv &\text{Br}
\end{aligned} \\
\end{align*}
\]

\[
\begin{align*}
 &\begin{aligned}
 &\text{O} &\equiv &\text{C} &\equiv &\text{O} \\
 &\text{H}_2\text{C} &\equiv &\text{NMMe}_2 \\
 &\text{CH}_3\text{CH}_2 &\equiv &\text{Br}
\end{aligned} \\
\end{align*}
\]

c) Because much of organic chemistry centers around the carbonyl group, the $a^1$, $d^2$, and $a^3$ synthons are considered "natural"; the $d^1$, $a^2$, and $d^3$ synthons are "unnatural" and require considerably more synthetic expertise.

6. Disconnections
   a) Two types of problems
      i) Those in which the starting materials are provided
      ii) Those in which the starting materials are not provided
      iii) First kind is much easier
   b) Example of first kind of problem

\[
\begin{align*}
 &\begin{aligned}
 &\begin{array}{c}
 \text{CH}_3
 \end{array} &\equiv &\begin{array}{c}
 \text{CH}_2
 \end{array} &\equiv &\begin{array}{c}
 \text{CH}_3
 \end{array} &\equiv &\begin{array}{c}
 \text{O}
 \end{array}
\end{aligned} \\
\end{align*}
\]

   i) Find the starting material in the product.

\[
\begin{align*}
 &\begin{aligned}
 &\begin{array}{c}
 \text{CH}_3
 \end{array} &\equiv &\begin{array}{c}
 \text{CH}_2
 \end{array} &\equiv &\begin{array}{c}
 \text{CH}_3
 \end{array} &\equiv &\begin{array}{c}
 \text{O}
 \end{array} \\
 &\begin{array}{c}
 \text{CHO}
 \end{array} &\equiv &\begin{array}{c}
 \text{CHO}
 \end{array} &\equiv &\begin{array}{c}
 \text{CHO}
 \end{array}
\end{aligned} \\
\end{align*}
\]

   a) The arrow ⇒ indicates a disconnection, a backwards thought process, not an actual real chemical change. It allows us to break up a compound into smaller pieces.
b) When we do disconnections, we don't worry about what chemistry we will use to put the molecule back together.

ii) 90% of the chemistry we do is ionic, so either of these disconnections can done in two ways: the left half can be nucleophilic and the right electrophilic, or vice versa.

iii) The best disconnections are those that lead to the most natural synthons, i.e., disconnections (1) and (4).

iv) Now we think of real compounds that have the desired reactivities.

v) Finally we describe the specific reactions and reagents that will be used to accomplish the transformation.

c) The second kind of problem is more difficult

i) requires a knowledge of available starting materials

ii) requires literature searches (usually)

iii) many, many solutions are possible

d) Particular sorts of molecular structures suggest particular types of disconnections and the reactions that make them.

i) β-Hydroxycarbonyl compounds and 1,3-diols suggest an aldol reaction

ii) 1,5-dicarbonyl suggests a Michael reaction

iii) Two contiguous stereocenters suggests a pericyclic reaction — Diels–Alder, Cope or Claisen rearrangement, etc.

iv) We will discuss these as we move along through the course.

7. Molecular complexity

a) Since we are trying to simplify a structure we need to know what makes structures complex

i) Size

ii) Diversity of elemental content

iii) Diversity of functional groups

iv) Cyclic connectivity

a) strain

b) fused, bridged, spiro

v) Stereocenter content

a) Number of stereocenters

b) Spatial relationship: 1,2-, 1,3-, or 1,8?

c) On a ring or acyclic?

d) Racemic or enantiopure?
e) ease of epimerization  
vi) Chemical reactivity  
vii) Structural instability  
viii) Relative previous synthetic experience (literature precedent)  

8. **Retrosynthetic analysis** in organic chemistry  
a) Working backwards  
b) Hypothetical, stepwise and systematic simplification of a target structure.  
i) Start with product!  
ii) Hypothetical  
iii) Systematical — you are confined by the laws of nature  
   a) thermodynamics  
   b) kinetics  
   c) steric effects  
   d) be ready to refer to the closest literature precedent  
iv) Stepwise —  
   a) make your simplifying changes in the structure easily followed by others  
   b) don’t do too much at once  
   c) consider the logic of when in the synthesis these steps are done  
v) Simplification — attack molecular complexity on its many levels  

9. **Which facet of molecular complexity does one attack first?**  
a) the answer here is complex  
b) depends on the structure  
i) for small polycyclic structures topological thinking may be the most important in  
   when trying to avoid painting oneself in a corner  
   a) you may have to install functionality at some stage in the synthesis wherein the  
      topology of the molecule prevents reactivity at that sight.  
ii) for straight chain molecules with many stereocenters you will have to focus on  
   transformations that faithfully pass stereochemically information from center to  
   center  
iii) for larger molecules the prime simplifying criterion may be the junction of two pieces  
   of approximately equal size.  
   a) As we mentioned yesterday--99% of all molecular transformation is done in  
      solution  
   b) You have to dissolve the material  

10. **Convergency**  
a) Consider a seven step linear synthesis, $S \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow P$  
i) hypothetically let’s say you get 70% yield/step.  
ii) the total yield is $0.7^7 = 0.082\%$  
b) Now consider a seven step convergent synthesis:  
   $P \Rightarrow I_1 + I_2$  
   $I_1 \rightarrow \rightarrow S_1$ and $I_2 \rightarrow \rightarrow S_2$  
i) combination of two linear sequences  
ii) with the same hypothetical 70% yield/step, the total yield is $0.7^3 \times 0.7 = 24\%$  
c) in practice the philosophy of convergency is more powerful than the above math seems to  
   indicate
i) your chances of mishandling a step decreases the amount of material you can safely
carry through the synthesis

ii) retrosynthesis is hypothetical — greater possibility of introducing an Achilles heal in
the linear synthesis — an impasse

iii) increase your chances of having good yields because the pieces you have to carry
though x amount of steps are less complex.