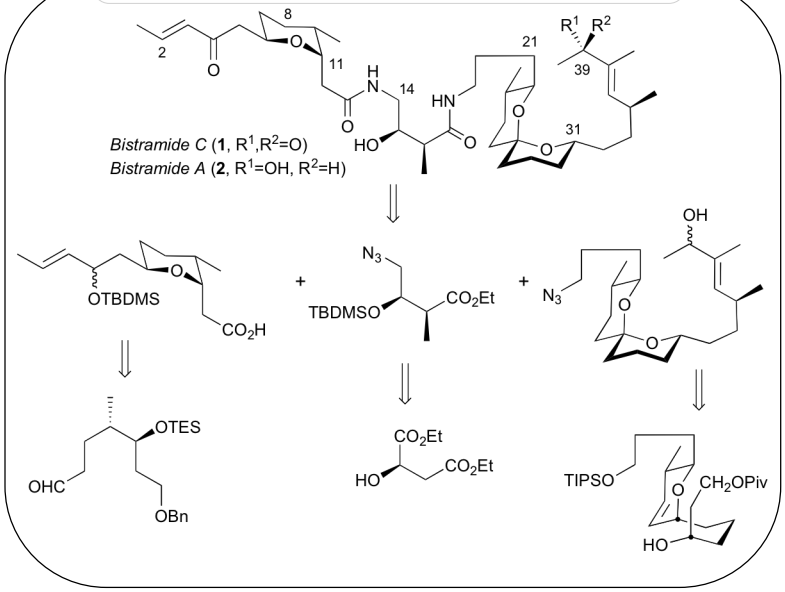
III-A. RETROSYNTHETIC ANALYSIS



Definitions

- ***Disconnection***: An analytical operation, which breaks a bond and converts a molecule into a possible starting material. The reverse of a chemical reaction. Symbol ⇒ and a curved line drawn through the bond being broken.
- ***FGI***: Functional Group Interconversion: The operation of writing one functional group for another so that disconnection becomes possible. The reverse of a chemical reaction. Symbol ⇒ with FGI written over it.
- ***Reagent***: A compound which reacts to give an intermediate in the planned synthesis or to give the target molecule itself. The synthetic equivalent of a synthon.
- ***Synthetic equivalent***: A reagent carrying out the function of a synthon which cannot itself be used, often because it is too unstable.
- ***Synthon***: A generalized fragment, usually an ion, produced by a disconnection. (some people also use synthon for a synthetic equivalent).
- ***Target Molecule***: The molecule whose synthesis is being planned.

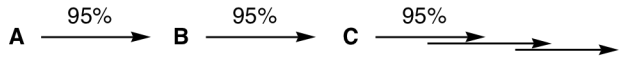
Retrosynthesis

Retrosynthesis is the process of "deconstructing" a target molecule into readily available starting materials by means of

- imaginary breaking of bonds (*disconnections*) and by the conversion of one functional group into another (*functional group interconversions*).

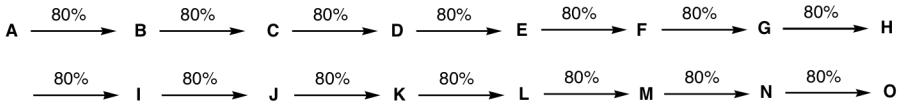
The following factors need be taken into consideration:

Efficiency, e.g. the "arithmetic demon":
"The arithmetic demon dictates one of the major axioms of synthesis: Get the most done in the fewest steps and in the highest yield." (R. E. Ireland)



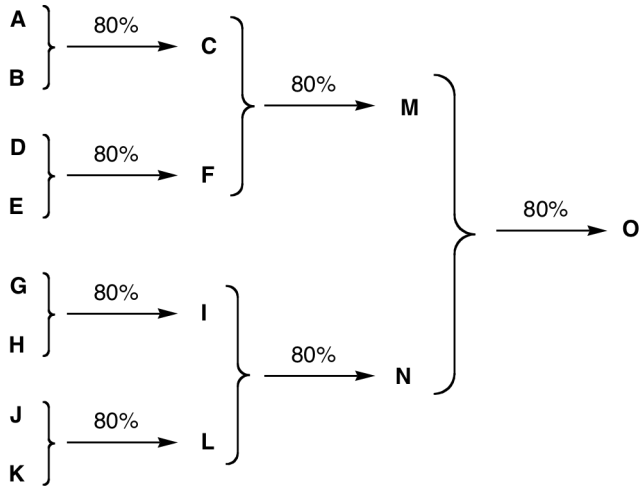
5 steps: $(0.95)^5 = 77\%$
25 steps: $(0.95)^{25} = 28\%$
100 steps: $(0.95)^{100} = 0.6\%$

A linear synthesis with 14 starting materials and intermediates:



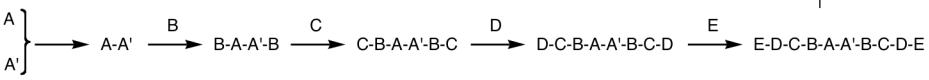
yield = $(0.8)^{14} = 4\%$

A convergent synthesis with 14 starting materials and intermediates:

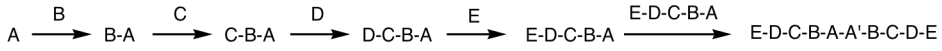


yield = $(0.8)^3$ = 51%

Question: If every reaction goes with a 60% yield, what is the more efficient strategy:



or



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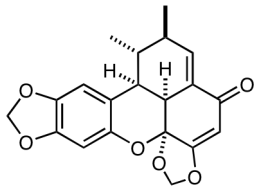
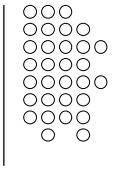
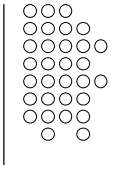
Carpanone: Chapman, O. et al. *J. Am. Chem. Soc.* **1971**, *93*, 6696.



Mechanism:

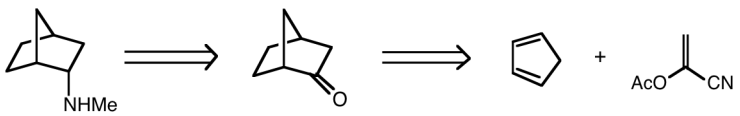


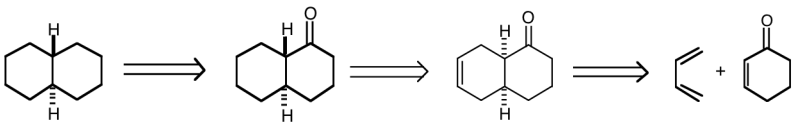


Retrosynthetic analysis

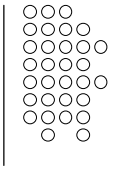
General strategy:

- Remove, add or change functional groups; FGI



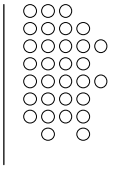


- Apply one- and two-group disconnections ("1,n-relationships), pericyclic reactions, etc.

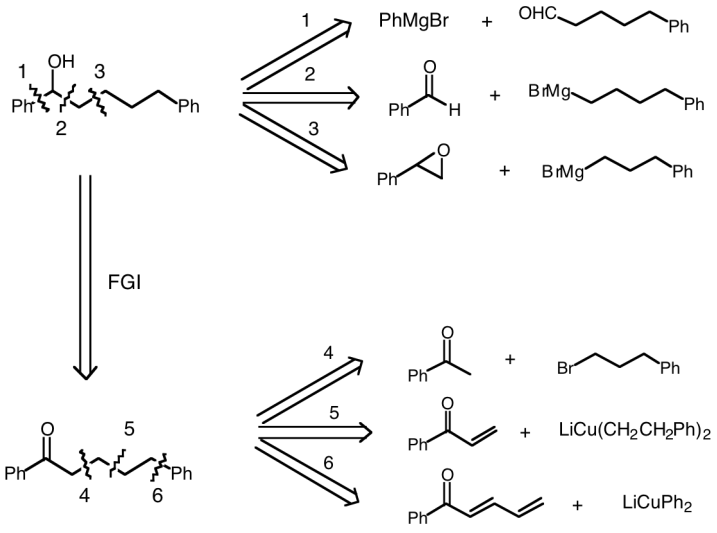


Example:

Retrosynthesis 1:



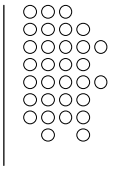
Summary of retrosynthetic approaches:



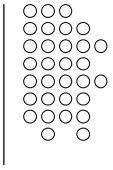
The "best" approach uses readily available starting materials in high yielding, reliable transformations. It may very often be based on personal choice.

Warren, S. *Designing Organic Synthesis*, Wiley, 1978.

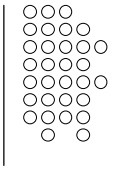
- One group disconnections:



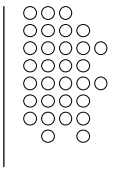
Two group disconnections:



Illogical two group disconnections:



Heteroatoms:



Corey, E. J. *J. Am. Chem. Soc.* **1975**, *97*, 430