Topic #8: Ranking of Synthesis Plans
Spring 2019
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Evaluating Synthesis Plans

- There are many different ways to evaluate a synthesis plan, depending on one’s priorities:
  - In a medicinal chemistry lab, the top priority might be to make a target quickly so that it is available for small scale in vitro testing.
  - In a process lab or factory, the top priority might be to make a target in a cost-effective manner.
  - In an academic lab, the top priority might be to make a compound using an interesting and novel enough route to be published in a high impact journal.

- A perfect synthesis plan would meet all these goals and more - but there is no such thing as a perfect synthesis plan.
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- Hoffmann presents a few different ideas of the “ideal synthesis”:
  - Turner and Wedner suggest that an ideal synthesis is “a one-pot reaction in which all starting materials are mixed, leading directly to the final product”.\(^1\) This is reminiscent of how biological systems produce natural products; however, it is not realistic for a chemical synthesis.*
  - Hendrickson suggests that an ideal synthesis “creates a complex molecule … in a sequence of only construction reactions involving no intermediary refunctionalizations, leading directly to the target, not only its skeleton but also its correctly placed functionality.”\(^1\)

\(^*\) Some drugs are manufactured biologically. E.g. When penicillin was first marketed, its synthesis was perceived to be too difficult to achieve chemically. Penicillin G is still made from phenylacetic acid by *Penicillium chrysogenum*. Semisynthetic penicillins can now be made from 6-aminopenicillanic acid (derived from penicillin G). The semisynthetic penicillins have a different R group on the 2° amide (R = benzyl in penicillin G).

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- So, Turner and Wedner’s definition is currently unrealistic (except when using microorganisms or similar to make a drug).

- Hendrickson’s definition is somewhat more reasonable, but could be used in very misleading ways. Consider two hypothetical syntheses of a molecule containing 20 carbon atoms:
  - One synthesis involves 19 steps, each of which attaches one carbon atom to the skeleton. There are no refunctionalization steps (functional group interchanges, protections, deprotections, etc.). This gives a ratio of skeletal bond-forming steps to refunctionalization steps of $19/0 = \infty$
  - One synthesis involves 8 steps, four of which form the skeleton while four are refunctionalization steps. This gives a ratio of skeletal bond-forming steps to refunctionalization steps of $4/4 = 1$.

The numbers suggest that the first synthesis plan is superior, but which one would you rather do?
Hoffmann’s suggestion elaborates Hendrickson’s definition with a little common sense. An ideal synthesis is:

- Short. The bond-set contains a relative small number of bonds (i.e. relatively few disconnections in the retrosyntheses) and, ideally, forming more than one skeletal bond in a single step.

- Straightforward. There aren’t many refunctionalization steps (functional group interchanges, protections, deprotections, etc.)

- Simple. Keep the complexity of intermediates low until late in the synthesis. This is because chemists with significant lab experience know that even simple reactions tend to give lower yields when the reactants have complex structures. (Oxidation of 2-propanol to propanone will tend to proceed with higher yields than oxidation of a large polycyclic secondary alcohol to the corresponding ketone.)

- Robust. If one reaction doesn’t work as planned, there is a “plan B” for that step of the synthesis.

- Convergent. Smaller quantities of the initial reagents are therefore needed to produce the same mass of target. See next page.
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- Why is convergence important in a synthesis? Let’s do the math. When making an eight-part molecule, if each step has 80% yield, the overall yield of a linear synthesis will be \((0.80)^7 = 0.21 = 21\%:\)

To make 1 mole of the target will therefore require:
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- If we use a convergent approach to make the same eight-part molecule (still assuming 80% yield per step), the overall yield of a completely convergent synthesis will be $(0.80)^3 = 0.51 = 51\%$:

To make 1 mole of the target will therefore require:

- Convergent syntheses also tend to keep the complexity of synthetic intermediates low until late in the synthesis.
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Finally, in today’s world, we also need to consider how green a synthesis is - particularly if it is to be performed on a large scale. Recall the 12 principles of green chemistry: