



High Performance Discovery Software

Technical Data

October 2006

Technical Data and Definitions of Retrosynthesis

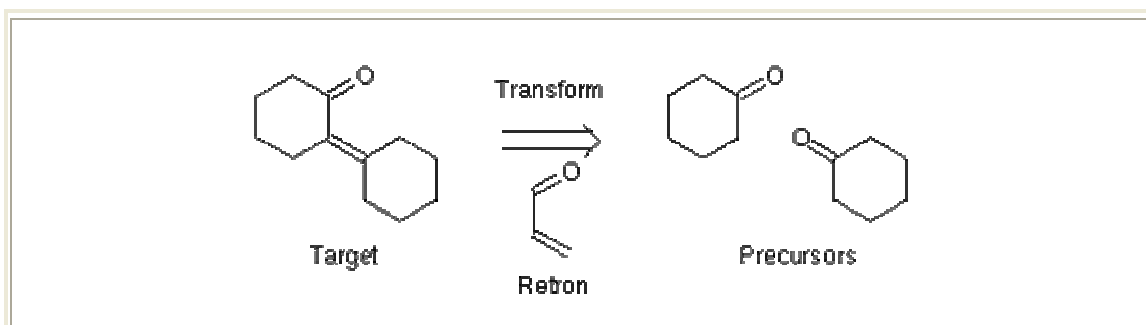
Information from www.organicworldwide.net:

Retrosynthetic analysis or *retrosynthesis* is a technique for solving problems in synthesis planning, especially those presented by complex structures. The retrosynthetic approach to synthesis planning was formulated explicitly for the first time by Corey. The purpose of retrosynthetic analysis (RA) is to transform the structure of a synthetic target molecule to simpler molecules. Hence, in RA reactions are viewed in the retrosynthetic direction, starting with the product of the reaction and going backwards to the reactants. The terminology used with RA, as opposed to synthesis, is summarized below.

Direction	Synthetic	Retrosynthetic or Antithetic
Step	Reaction	Transform or Retro-reaction
Arrow used in graphical depiction	----->	=====>
`Starting' structure	Reactant	Target
`Resulting' structure	Product	Precursor
Substructure required for operation	Reacting functionality	Retron

Synthetic versus retrosynthetic analysis

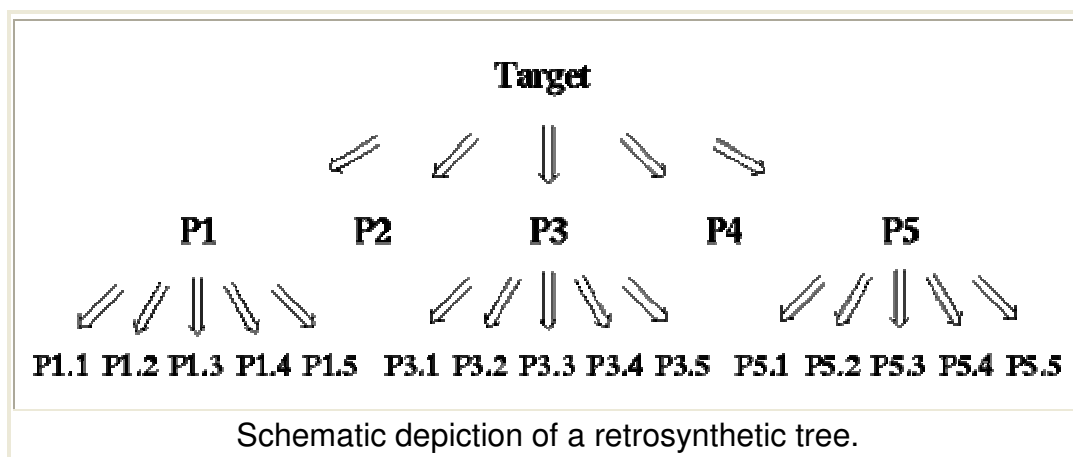
Transforms or retro-reactions, are the imaginary counterparts of reactions. Each transform corresponds to a reaction, and vice versa, but of course it cannot be carried out in the laboratory; it is purely a thought process:



A transform, in this case the retrosynthetic counterpart of the aldol condensation.

Each reaction generates a characteristic structural element in the product, such as the enone resulting from the above Aldol condensation. This substructure, called the *retron*, must be present in a target to be able to apply the corresponding transform to that target.

Retrosynthetic analysis, then, consists of applying transforms to a given target, thereby generating all precursors from which that target can be made in a single step. The analysis can be repeated for each precursor, generating a second level of precursors:



It is possible that a transform generates a precursor actually consisting of two or more fragments, as in the case of a convergent step; these fragments can each be treated in the same way as single precursors. For clarity, multiple fragments are not shown. Further analysis can generate deeper levels of precursors. Each precursor generated can then be checked for availability, thus defining an endpoint for that line of analysis. The final result, a complete retrosynthetic tree, will contain all possible syntheses of the given target, reasonable and unreasonable, efficient and cumbersome ones. Of course, such a tree would be unmanageably large both for man and computer, even when the number of precursor levels is limited. The 'combinatorial explosion', as this phenomenon is called, effectively prohibits the use of retrosynthetic analysis in such an unconstrained way. To keep the size of the retrosynthetic tree under control, a selection of transforms to be considered must be made. The guiding principles for this selection are called *strategies*.

Strategies for Retrosynthesis

Retrosynthetic analysis will only lead to useful results if it is directed towards some goal. The basic goal is to generate precursors that correspond to available starting materials. However, this goal can be used as a guiding principle only when possible starting materials can be identified from the target structure. In general, obvious starting points cannot be found when it comes to complex target structures (and that is where RA is most useful). The basic goal, then, becomes

the generation of precursors that are easier to synthesize than the original target; such precursors are likely to be closer to available compounds than the original target. Stated differently, retrosynthetic analysis is directed towards molecular simplification. Corey has formulated five main types of strategies that lead to the desired simplification. These will be treated briefly, each illustrated by a sample analysis:

Functional-group based strategies

Functional groups in the target structure may direct the transform search in several ways:

- Removal of reactive and masked functionality
- Disconnection based on the location of functional groups
- Reconnection of functional groups to form rings retro-synthetically

The reconnection strategy is constrained by strategic rules. Clearly, it is not practical to attempt every possible reconnection.

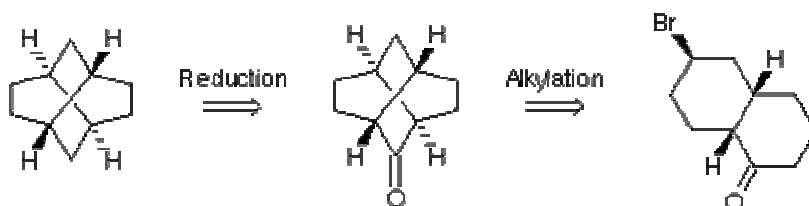


Topological strategies

The disconnection of specific, so-called 'strategic' bonds can lead to major molecular simplification. There are several types of strategic bonds:

- Bonds in (poly)cyclic ring systems
- Bonds in (poly)fused ring systems
- Pairs of bonds in ring systems (disconnection by intramolecular cycloaddition transforms)
- Bonds connecting chains to rings
- Bonds connecting chains to other chains
- Bonds connecting chains to functional groups

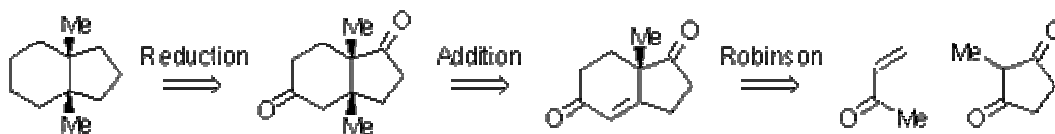
Heuristics (empirical rules) have been devised to select these types of bonds from any target structure. It is also possible to identify rings which should be disassembled early in the retrosynthetic process, or rings which should be kept intact during these stages.



Transform-based strategies

A very useful guidance for retrosynthetic analysis can be provided by the application of a powerfully simplifying transform -- corresponding to a reaction effecting a considerable increase in complexity. Very often such an application is suggested by the presence of (functionalized) rings of specific sizes in the target molecule. Some powerfully simplifying transforms are:

- Diels-Alder
- Hetero Diels-Alder
- Robinson annulation
- Birch reduction
- Internal ene reaction
- Halo-lactonization

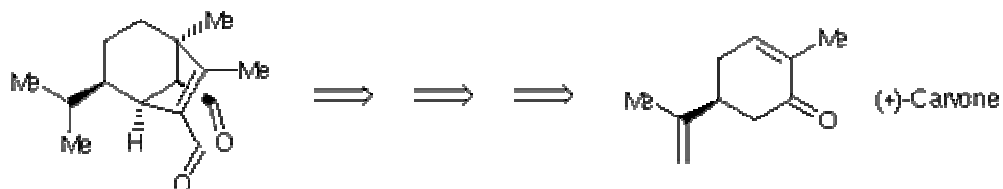


Structure-goal strategies

The analysis can also be directed towards a particular (sub)structure. Such a (sub)structure can be a:

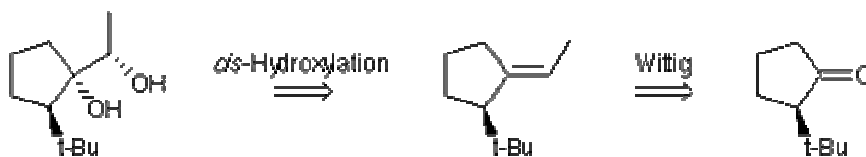
- Starting material
- Chiral building block
- Retron-containing structure

An analysis directed towards such a structure-goal does not need to be purely retrosynthetic. It can even be synthetic, but probably the most efficient search would be a bidirectional one.



Stereochemical strategies

Here the focus is on removal of stereocenters under stereocontrol. Stereocontrol can be achieved through either mechanistic control or substrate control. Reconnections that move stereocenters from chains (where they are difficult to introduce) into rings (where introduction is usually much easier) can also be considered stereochemically strategic.



Potential of Computers in Retrosynthetic Analysis

Quote from www.organicworldwide.net:

Retrosynthetic analysis in itself is already a powerful tool for the chemist. However, the enormous amount of chemical knowledge available nowadays makes it difficult to use RA efficiently and thoroughly. Most of the information is relatively inaccessible, especially the newer reactions and developments in scope of older ones. In practice, the synthetic chemist is limited by the information that is most readily available to her/him. Furthermore, there is a tendency to accept the first reasonable solution and to focus attention to that direction, whereas a more thorough analysis may result in a much better solution saving weeks or even months work in the laboratory. The required extra effort is almost always a worthwhile investment. **The application of a computer program which can assist in retrosynthetic analysis is then of great value. A computer program has no bias and, of course, has total recall.**