

18.17: Synthesis

Disconnection of bonds

Having chosen the TARGET molecule for synthesis, the next exercise is to draw out synthetic plans that would summarize all reasonable routes for its synthesis. During the past few decades, chemists have been working on a process called RETROSYNTHESIS. Retrosynthesis could be described as a logical Disconnection at strategic bonds in such a way that the process would progressively lead to easily available starting material(s) through several synthetic plans. Each plan thus evolved, describes a 'ROUTE' based on a retrosynthesis. Each disconnection leads to a simplified structure. The logic of such disconnections forms the basis for the retroanalysis of a given target molecule. Natural products have provided chemists with a large variety of structures, having complex functionalities and stereochemistry. This area has provided several challenging targets for development of these concepts. The underlining principle in devising logical approaches for synthetic routes is very much akin to the following simple problem. Let us have a look of the following big block, which is made by assembling several small blocks (**Fig 1.4.2.1**). You could easily see that the large block could be broken down in different ways and then reassembled to give the same original block.



Fig 1.4.2.1

Now let us try and extend the same approach for the synthesis of a simple molecule. Let us look into three possible 'disconnections' for a cyclohexane ring as shown in **Fig 1.4.2.2**.



Fig 1.4.2.2

In the above analysis we have attempted to develop three ways of disconnecting the six membered ring. Have we thus created three pathways for the synthesis of cyclohexane ring? Do such disconnections make chemical sense? The background of an organic chemist should enable him to read the process as a chemical reaction in the reverse (or 'retro-') direction. The dots in the above structures could represent a carbonium ion, a carbanion, a free radical or a more complex reaction (such as a pericyclic reaction or a rearrangement). Applying such chemical thinking could open up several plausible reactions. Let us look into path b, which resulted from cleavage of one sigma bond. An anionic cyclisation route alone exposes several candidates as suitable intermediates for the formation of this linkage. The above analysis describes only three paths out of the large number of alternate cleavage routes that are available. An extended analysis shown below indicates more such possibilities (**Fig 1.4.2.3**). Each such intermediate could be subjected to further disconnection process and the process continued until we reach a reasonably small, easily available starting materials. Thus, a complete 'SYNTHETIC TREE' could be constructed that would summarize all possible routes for the given target molecule.



Fig 1.4.2.3

1.4.3 Efficiency of a route

A route is said to be efficient when the 'overall yield' of the total process is the best amongst all routes investigated. This would depend not only on the number of steps involved in the synthesis, but also on the type of strategy followed. The strategy could involve a 'linear syntheses' involving only consequential steps or a 'convergent syntheses' involving fewer consequential steps. Fig 1.4.3.1 shown below depicts a few patterns that could be recognized in such synthetic trees. When each disconnection process leads to only one feasible intermediate and the process proceeds in this fashion



Fig 1.4.3.1

all the way to one set of starting materials (SM), the process is called a Linear Synthesis. On the other hand, when an intermediate could be disconnected in two or more ways leading to different intermediates, branching occurs in the plan. The processes could be continued all the way to SMs. In such routes different branches of the synthetic pathways converge towards an intermediate. Such schemes are called Convergent Syntheses.

The flow charts shown below (Fig 1.4.3.2) depicts a hypothetical 5-step synthesis by the above two strategies. Assuming a very good yield (90%) at each step (this is rarely seen in real projects), a linear synthesis gives 59% overall yield, whereas a convergent synthesis gives 73% overall yield for the same number of steps..



Fig 1.4.3.2

1.4.4 Problem of substituents and stereoisomers

The situation becomes more complex when you consider the possibility of unwanted isomers generated at different steps of the synthesis. The overall yield drops down considerably for the synthesis of the right isomer. Reactions that yield single isomers (Diastereospecific reactions) in good yields are therefore preferred. Some reactions like the Diels Alder Reaction generate several stereopoints (points at which stereoisomers are generated) simultaneously in one step in a highly predictable manner. Such reactions are highly valued in planning synthetic strategies because several desirable structural features are introduced in one step. Where one pure enantiomer is the target, the situation is again complex. A pure compound in the final step could still have 50% unwanted enantiomer, thus leading to a drastic drop in the efficiency of the route. In such cases, it is desirable to separate the optical isomers as early

in the route as possible, along the synthetic route. This is the main merit of the Chiron Approach, in which the right starting material is chosen from an easily available, cheap 'chiral pool'. We would discuss this aspect after we have understood the logic of planning syntheses. Given these parameters, you could now decide on the most efficient route for any given target.

Molecules of interest are often more complex than the plain cyclohexane ring discussed above. They may have substituents and functional groups at specified points and even specific stereochemical points. Construction of a synthetic tree should ideally accommodate all these parameters to give efficient routes. Let us look into a slightly more complex example shown in Fig 1.4.4.1. The ketone 1.4.4.1A is required as an intermediate in a synthesis. Unlike the plain cyclohexane discussed above, the substitution pattern and the keto- group in this molecule impose some restrictions on disconnection processes.



Fig 1.4.4.1

Cleavage a: This route implies attack of an anion of methylisopropylketone on a bromo-component. *Cleavage b:* This route implies simple regioselective methylation of a larger ketone that bears all remaining structural elements. *Cleavage c:* This route implies three different possibilities. Route C-1 envisages an acylium unit, which could come from an acid halide or an ester. Route C-2 implies an umpolung reaction at the acyl unit. Route C-3 suggests an oxidation of a secondary alcohol, which could be obtained through a Grignard-type reaction. *Cleavage d:* This implies a Michael addition.

Each of these routes could be further developed backwards to complete the synthetic tree. These are just a few plausible routes to illustrate an important point that the details on the structure would restrict the possible cleavages to some strategic points. Notable contributions towards planning organic syntheses came from E.J. Corey's school. These developments have been compiled by Corey in a book by the title LOGIC OF CHEMICAL SYNTHESIS. These and several related presentations on this topic should be taken as guidelines. They are devised after analyzing most of the known approaches published in the literature and identifying a pattern in the logic. They need not restrict the scope for new possibilities. Some of the important strategies are outlined below.

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