‘There could be ART in Organic Synthesis’ declared the inimitable monarch of organic synthesis, Professor R.B. Woodward. His school unveiled several elegant approaches covering a variety of complex structures and broke new grounds to define the art of organic synthesis. ‘If organic synthesis is a branch of science, what is the LOGIC of organic synthesis?’ marveled several others. The development of the concept of logical approaches towards synthesis has been evolving over the past several decades. A few stalwarts focused their attention on this theme and attempted to evolve a pattern to define this logic. There is no doubt that all of us who dabble with synthesis contribute our small bit in the magnificent direction. A few names stand out in our minds for their outstanding contributions. Notable contributions came from the schools of J.A. Marshal, E.J. Wenkert, G. Stork, S Hanessian, E.E. van Tamalen, S. Masamune, R.B. Woodward, E.J. Corey and several others. More focused on this theme were the contributions from the school of E.J. Corey.

The period 1960 – 1990 witnessed the evolution of this thought and the concept bloomed into a full-fledged topic that now merits a separate space in college curriculum. Earlier developments focused on the idea of ANTITHETIC APPROACHES and perfected the art of DISCONNECTION via RETROSYNTHESIS. This led to logical approaches for the construction of SYNTHETIC TREES that summarized various possible approaches for the proposed Target structure. All disconnections may not lead to good routes for synthesis. Once the synthetic tree was constructed, the individual branches were analyzed critically. The reactions involved were looked into, to study their feasibility in the laboratory, their mechanistic pathways were analyzed to understand the conformational and stereochemical implications on the outcome of each step involved and the time / cost factors of the proposed routes were also estimated. The possible areas of pitfall were identified and the literature was critically scanned to make sure that the steps contemplated were already known or feasible on the basis of known chemistry. In some cases, model compounds were first constructed to study the feasibility of the particular reaction, before embarking on the synthesis of the complex molecular architecture. Thus a long process of logical planning is now put in place before the start of the actual synthetic project. In spite of all these careful and lengthy preparations, an experienced chemist is still weary of the Damocles Sword of synthesis viz., the likely failure of a critical step in the proposed route(s), resulting in total failure of the entire project. All achievements are 10% inspiration and 90% perspiration. For these brave molecular engineers, sometimes also called chemists, these long-drawn programs and possible perils of failures are still worth, for the perspiration is enough reward.

A sound knowledge of mechanistic organic chemistry, detailed information on the art and science of functional group transformations, bond formation and cleavage reactions, mastery over separation and purification techniques and a sound knowledge of spectroscopic analysis are all essential basics for the synthesis of molecules. A synthetic chemist should also be aware of developments in synthetic strategies generated over the years for different groups of compounds, which include Rules and guidelines governing synthesis. Since organic chemistry has a strong impact on the development of other sister disciplines like pharmacy, biochemistry and material science, an ability to understand one or more of these areas and interact with them using their terminologies is also an added virtue for a synthetic chemist. With achievements from synthesis of strained molecules (once considered difficult (if not impossible) to synthesize, to the synthesis of complex, highly functionalized and unstable molecules, an organic chemist could now confidently say that he could synthesize any molecule that is theoretically feasible. This is the current status of the power of organic synthesis. Based
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.
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.
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
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.
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