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.
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...
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.
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 regiospecific methylation of a larger ketone that bears all remaining structural elements. *Cleavage c:* This route implies three different possibilities. Route C-1 envisages an acylonium 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 Micheal 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 compiles 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.
When a synthetic chemist looks at the given Target, he should first ponder on some preliminary steps to simplify the problem on hand. Is the molecule polymeric? See whether the whole molecule could be split into monomeric units, which could be coupled by a known reaction. This is easily seen in the case of peptides, nucleotides and organic polymers. This could also be true to other natural products. In molecules like C-Toxiferin 1 (1.4.5.1A) (Fig 1.4.5.1), the point of dimerisation is obvious. In several other cases, a deeper insight is required to identify the monomeric units, as is the case with Usnic acid (1.4.5.1B). In the case of the macrolide antibiotic Nonactin (1.4.5.1C), this strategy reduces the possibilities to the synthesis of a monomeric unit (1.4.5.1D). The overall structure has S4 symmetry and is achiral even though assembled from chiral precursors. Both (+)-nonactic acid and (−)-nonactic acid (1.4.5.1D) are needed to construct the macrocycle and they are joined head-to-tail in an alternating (+)-(−)-(+)−(−) pattern. (see J. Am. Chem. Soc., 131, 17155 (2009) and references cited therein).
Is a part of the structure already solved? Critical study of the literature may often reveal that the same molecule or a closely related one has been solved. R.B. Woodward synthesized (1.4.5.2C) as a key intermediate in an elegant synthesis of Reserpine (1.4.5.2A). The same intermediate compound (1.4.5.2C) became the key starting compound for Velluz et.al., in the synthesis of Deserpidine (1.4.5.2B) (Fig 1.4.5.2).

Such strategies reduce the time taken for the synthesis of new drug candidates. These strategies are often used in natural product chemistry and drug chemistry. Once the preliminary scan is complete, the target molecule could be disconnected at Strategic Bonds.

1.4.6 Strategic Bonds, Retrons and Transforms
STRATEGIC BONDS are the bonds that are cleaved to arrive at suitable Starting Materials (SM) or SYNTHONS. For the purpose of bond disconnection, Corey has suggested that the structure could be classified according to the sub-structures generated by known chemical reactions. He called the sub-structures RETRONS and the chemical transformations that generate these Retrons were called TRANSFORMS. A short list of Transforms and Retrons are given below (TABLE 1.4.6.1). Note that when Transforms generate Retrons, the product may have new STEREOPOINTS (stereochemical details) generated that may need critical appraisal.

Fig 1.4.6.1

The structure of the target could be such that the Retron and the corresponding Transforms could be easily visualized.
and directly applied. In some cases, the Transforms or the Retrons may not be obvious. In several syntheses, transformations do not simplify the molecule, but they facilitate the process of synthesis. For example, a keto-group could be generated through modification of a -CH-NO$_2$ unit through a Nef reaction. This generates a new set of Retron / transforms pair. A few such transforms are listed below, along with the nomenclature suggested by Corey (Fig 1.4.6.2).

**Fig 1.4.6.2**

A Rearrangement Reaction could be a powerful method for generating suitable new sub-structures. In the following example, a suitable Pinacol Retron, needed for the rearrangement is obtained through an acyloin transform (Fig 1.4.6.3). Such rearrangement Retrons are often not obvious to inexperienced eyes.
Some transforms may be necessary to protect (acetals for ketones), modify (reduction of a ketone to alcohol to avoid an Aldol condensation during a Claisen condensation) or transpose a structural element such as a stereopoint (e.g. $S_N2$ inversion, epimerization etc..) or shifting a functional group. Such transforms do not simplify the given structural unit. At times, activation at specific points on the structure may be introduced to bring about a C-C bond formation and later the extra group may be removed. For example, consider the following retrosynthesis in which an extra ester group has been introduced to facilitate a Dieckmann Retron. In complex targets, combinations of such strategies could prove to be a very productive strategy in planning retrosynthesis. Witness the chemical modification strategy shown below for an efficient stereospecific synthesis of a trisubstituted olefin (Fig 1.4.6.4)
Amongst the molecular architectures, the bridged-rings pose a complex challenge in Structure-Based disconnection procedures. Corey has suggested guidelines for efficient disconnections of strategic bonds.

A bond cleavage for retrosynthesis should lead to simplified structures, preferably bearing five- or six-membered rings. The medium and large rings are difficult to synthesize stereospecifically. Amongst the common rings, a six-membered ring is easily approached and manipulated to large and small rings. Simultaneous cleavage of two bonds, suggesting cycloaddition – retrons are often more efficient. Some cleavages of strategic bonds are shown in Fig 1.4.6.5, suggesting good and poor cleavage strategies based on this approach. However, these guidelines are not restrictive.
Some cleavages at strategic bonds on bridged-ring systems.

Identifying Retron – Transform sets in a given target molecule is therefore a critical component in retrosynthesis. Such an approach could often generate several synthetic routes. The merit of this approach is that starting materials do not prejudice this logic. Retrosyntheses thus developed could throw open several routes that need further critical scrutiny on the basis of known facts.

Identification of Retrons / Transforms sets provided the prerequisite for computer assisted programs designed for generating retrosynthetic routes. A list of Retrons and the corresponding transforms were interlinked and the data was stored in the computer. All known reactions were thus analyzed for their Retron / Transform characteristics and documented. The appropriate literature citations were also documented and linked. Based on these inputs, computer programs were designed to generate retrosynthetic routes for any given structure. Several such programs are now available in the market to help chemists generate synthetic strategies. Given any structure, these programs generate several routes. Once the scientist identifies the specific routes of interest for further analysis, the program generates detailed synthetic steps, reagents required and the appropriate citations. In spite of such powerful artificial intelligence, the intelligence and intuitive genius of a chemist is still capable of generating a new strategy, not yet programmed. Again, human intelligence is still a critical input for the analysis the routes generated using a computer. Based on the experience of the chemists’ team, their projected aim of the project and facilities available, the routes are further
screened.

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