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RETROSYNTHETIC ANALYSIS- A REVIEW

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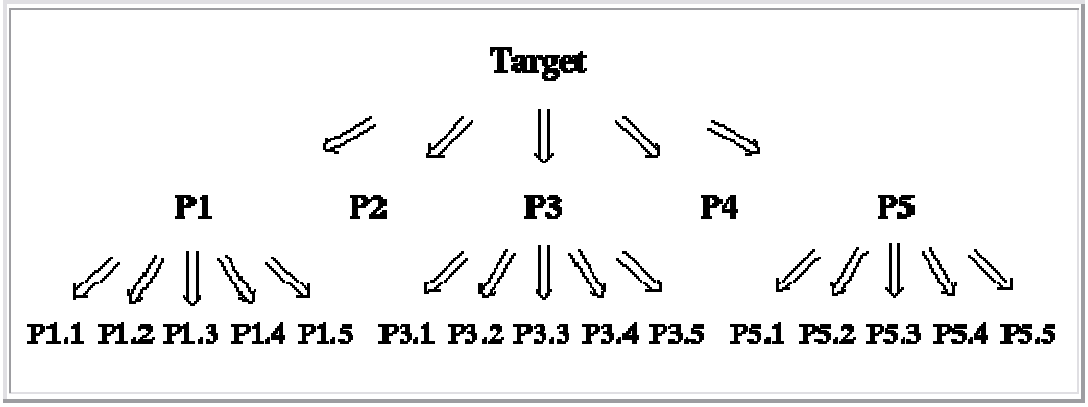
Abstract

Chemical reactions can be viewed in two directions: the synthetic direction, corresponding to laboratory operations, and the retrosynthetic (or antithetic) direction, going backwards from a target molecule to starting materials by way of retro-reactions or transforms. Retrosynthesis is often applied when a synthetic route to a target molecule has to be developed. The term retrosynthetic analysis, a synonym for retrosynthesis, expresses more clearly its `imaginary' character. This study help us to find those parent compound from which we can generate the required chemical entity.

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:



Retrosynthetic analysis is a technique for solving problems in the planning of organic syntheses. This is achieved by transforming a target molecule into simpler precursor structures without assumptions regarding starting materials. Each precursor material is examined using the same method. This procedure is repeated until simple or commercially available structures are reached.[1,2]

Key Words: Retrosynthetic analysis, Synthetic direction, Precursor, functional group.

Introduction:

"Retrosynthetic analysis is the process of working backwards from the target molecule to progressively simpler molecules by means of disconnections and/or functional group interconversions that correspond to known reactions. Then the synthetic plan is simply the reverse of the analysis. The design of a synthesis needs to take into account some important factors."

1) it has to actually work
2) in general, it should be as short as possible
3) each step should be efficient
4) side products (if formed) and impurities (there always are) should be easily separable from the desired product
5) environmental issues may be relevant

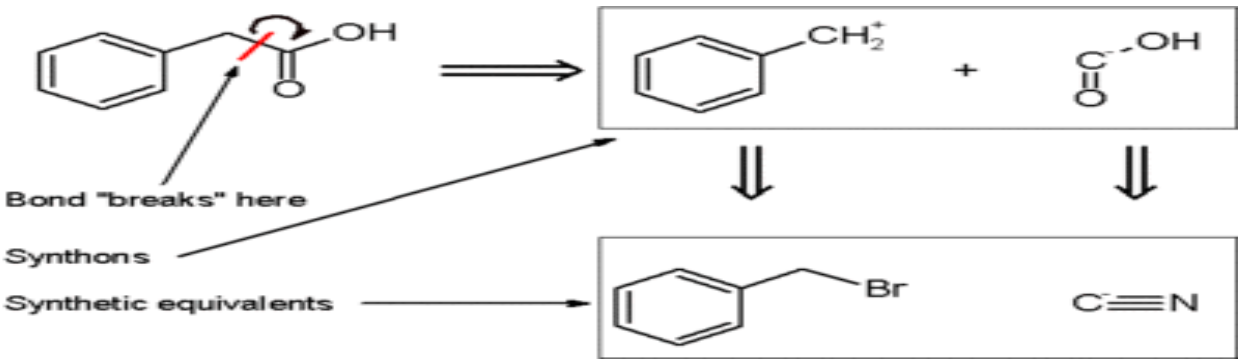
The power of retrosynthetic analysis becomes evident in the design of a synthesis. The goal of retrosynthetic analysis is structural simplification. Often, a synthesis will have more than one possible synthetic route. Retrosynthesis is well suited for discovering different synthetic routes and comparing them in a logical and straightfoward fashion. A database may be consulted at each stage of the analysis, to determine whether a component already exists in the literature. In that case, no further exploration of that compound would be required.[2]

E.J Corey's definition of retrosynthetic analysis:

"It is a problem solving technique for transforming the structure of synthetic target molecule (TM) to a sequence of progressively simpler structures along the pathway which ultimately leads to simple or commercially available starting materials for a chemical synthesis."[1,3]

Example

An example will allow the concept of retrosynthetic analysis to be easily understood.

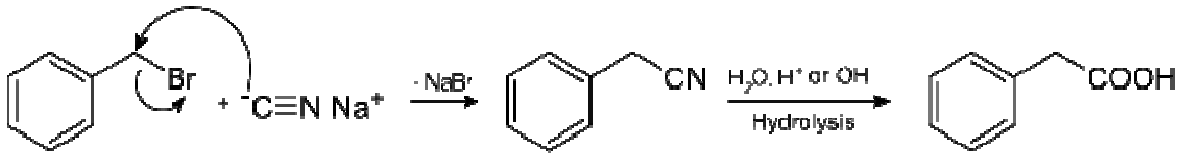


In planning the synthesis of phenylacetic acid, two synthons are identified. A nucleophilic "-COOH" group, and an electrophilic "$PhCH_2^+$" group. Of course, both synthons do not exist per se; synthetic equivalents corresponding to the synthons are reacted to produce the desired product. In this case, the cyanide anion is the synthetic equivalent for the $^-$COOH synthon, while benzyl bromide is the synthetic equivalent for the benzyl synthon.[7,8]

The synthesis of phenylacetic acid determined by retrosynthetic analysis is thus:

$PhCH_2Br + NaCN \rightarrow PhCH_2CN + NaBr$

$PhCH_2CN + 2\ H_2O \rightarrow PhCH_2COOH + NH_3$



In fact, phenylacetic acid has been synthesized from benzyl cyanide itself prepared by the analogous reaction of benzyl chloride with sodium cyanide

Some guidelines for retrosynthesis are given below

1. It is better to use convergent approach rather than divergent for many complex molecules.

2. Use only disconnections corresponding to disconnect C–C bonds and C–X bonds wherever possible.

3. Disconnect to readily recognizable synthons by using only known reactions (transform).

4. The synthesis must be short.

5. It is better to use those reactions which do not form mixtures.

6. The focus is on the removal of stereocentres under stereocontrol. Stereocontrol can be achieved through either mechanistic control or substrate control.[3,4]

RULES- Some Basic Rules of Retro synthesis is as follows:

1. Each of the major synthetic reactions generates specific structural features which act as markers for the use of the reaction in a synthesis (e.g. an alkene from a Wittig reaction, a cis ring junction from a Diels–Alder reaction).

2. The relationship between functional groups may provide the clue to a particular strategy (e.g. a β-hydroxy ketons may imply an aldol condensation). As you learn a synthetic reaction, note the relationship that is involved between: (i) the activating group that generates the reactive species, (ii) the new bond that is formed and (iii) the structural fate of the recipient group which is attacked by the reactive species.

3. The presence of electron-donating or electron-withdrawing groups may favour particular reactions at particular centers. For example, this is very important in aromatic substitution. As you learn a synthetic sequence, note the influence of the factors such as resonance that may favor regions of electron density or deficiency.

4. In dissecting a target molecule, look for competing functional groups and then either mask (protect) them or place them in a separate arm of a convergent synthesis.

5. Look for the residues of standard building blocks [e.g. a CH3CO (Ac) group from ethyl acetoacetate (ethyl 3-oxobutanoate)].

6. A helpful way of learning to dissect simple target molecules and applying synthetic methods is to consider the ways in which particular centers might be isotopically labeled for metabolic studies.[5,7]

Retrosynthesis: Expected feature

1. Evaluation of Alternative Synthesis Pathways

Sorting criteria are necessary for broad representations with many expanding paths:

- Yield
- Type of transformation (e.g. ring-closures or construction reactions preferred, etc.)

2. Support of Multistep Synthesis

Necessary to guide the synthesis from the target to all existing precursors that can be obtained from commercially available substances,

3. Organized Visualization

Allows a broad view over the different strategies, a tree view, i.e., gives an organized representation of the synthesis paths to the target.

Planning of retrosynthesis

When planning a synthesis, the most suitable starting materials should be chosen. These should be structurally and/or stereo chemically as closely related to the target as possible, to keep the synthesis brief. The first steps of a good synthesis may even be low- yielding (if the products are easy to purify), because at these early stages little work and reagents have been invested and the intermediates are still cheap. Poor yields at later stages of a multistep synthesis, however, strongly reduce its usefulness, because most steps of the synthesis will have to be run on a large scale, using large amounts of solvents and reagents, to obtain a small amount only of the final product, which will, accordingly, be rather expensive.

In a retro synthesis the easiest bonds to make are often cleaved first (i.e. these bonds will be made at the end of the synthesis), yielding several fragments which can be joined together at late stages of the synthesis, using straightforward and high-yielding chemistry. Such reactions would usually be condensations, for example acetal, amide, or ester formation, or the formation of carbon–heteroatom bonds, but might also be high-yielding C–C bond-forming reactions if the required reaction conditions are compatible with all the structural elements of the final product.

If the target contains synthetically readily accessible substructures (e.g. cyclic elements accessible by well established cycloaddition or cyclization reactions), these might be chosen as starting point of a disconnection.If

such substructures are not present, their generation by introduction of removable functional groups (e.g. by converting single bonds into double bonds or by formal oxidation of methylene groups to carbonyl groups) should be attempted.

If this approach fails to reveal readily accessible substructures, the functional groups present in the target structure which might assist the stepwise construction of the carbon framework must be identified, and the bonds on the shortest bond paths between these groups should be considered as potential sites of disconnection. Retro-aldol or Mannich reactions, optionally combined with the "Umpolung" of functional groups, have been the most common and successful tools for disconnection of intricate carbon frameworks, but any other, high-yielding C–C bond-forming reaction can also be considered.[6,8]

Some terms related to retrosynthetic analysis:

Target material	what you need to make
Retrosynthetic analysis	the process of deconstructing the TM by breaking it into simpler molecules until you get to a recognisable SM
Starting material	an available chemical that you can arrive at by retrosynthetic analysis and thus probably convert into the target molecule
Disconnections	taking apart a bond in the TM to see if it gives a pair of reagents
Functional group interconversion(FGI)	changing a group in the TM into a different one to see if it gives an accessible intermediate
Synthon	conceptual fragments that arise from disconnection

Synthetic equivalent	chemical that reacts as if it was a synthon

Basic steps of retrosynthesis

1. Analyse the Target and use FGI, if necessary, to reveal “fundamental” FGs.

In this course, we will only use reactions of oxygen-containing functional groups (Paul Murphy will discuss nitrogen-containing targets). Targets containing non-oxygen FGs will be derived from precursors containing oxygen FGs, so that the methods of forming alcohols, ketones, esters, etc can then be applied. The "Common FGIs" handout gives a summary of the most useful functional group interconversions.

2. Disconnect C–C and C=C bonds using

(i) Key reactions and synthons, e.g. carbonyl reactions, and

(ii) “Principle of maximum simplification”.

Choosing C–C bond disconnections is the key issue in most synthetic routes. The problem is that there are too many possibilities. How can you identify the “best” disconnections?

Identify key transformations,

e.g.

- substituted ketone
- enolate alkylation.

The "Key Disconnections" handout summarises the most important reactions.

- Choose disconnections that give maximum simplification: disconnect near middle of target

  (Convergent versus linear route), at branches, chains from rings, between FGs.

- Sometimes it is helpful to add a FG to the molecule (FGA) to allow use of key transformations, e.g

  –Alkyl cyclohexane

  –Alkyl cyclohexanone

  –Enolate alkylation.

3. Plan in the forward sense, evaluate each step carefully.

(i) It is vital to evaluate each step of a proposed route carefully to avoid disaster later.

- Consider the efficiency, scope, and reliability of the reaction; keep dodgy steps early.
- Check for any problems with chemoselectivity, regioselectivity, or stereoselectivity.
- If necessary, avoid problems by (i) using alternative reagents/conditions

(ii) Changing the order of the steps,

(iii) Using kinetic or thermodynamic control, or

(iv) Using protecting groups.

4. Repeat steps 1 to 3 as necessary.

Repeat until you arrive at precursors that are commercially available, the proposed synthetic route is then complete. For more complex targets it is best to devise several alternative synthetic routes.

5. Evaluate the whole synthetic plan.

Get an overall perspective; it's easy to get lost in the detailed planning.

- Consider the overall efficiency: number of steps, likely yields, costs in time/materials.
- Flexibility is important: to overcome potential problems, to allow preparation of related compounds.
- Consider safety issues and environmental impact.

Retrosynthetic schemes

1) Functional group interconversion:

In this process the functional group present in the target compound is first converted to other so as to simplify the process or for easy reaction process.

FGI can be divided into two groups:

Type 1m Isohypsic transformations with no change to the oxidation level of carbon

Type 2, Non-isohypsic transformations, where carbon atom is either reduced or oxidised

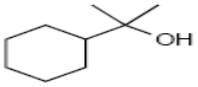
2) Disconnections:

The place to start a synthesis is with a target molecule. The term disconnection implies breaking the bond of a molecule to generate simpler fragments.

a) One group disconnections

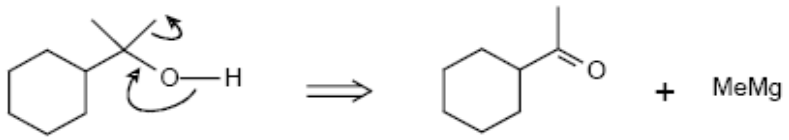
Target molecule

Eg.

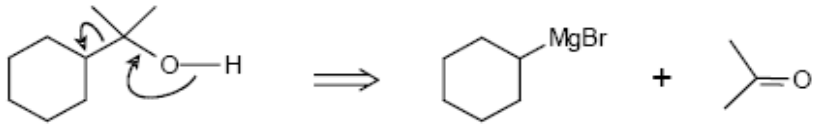


There are two possibilities:

a)



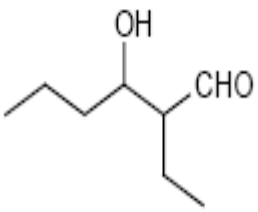
b)

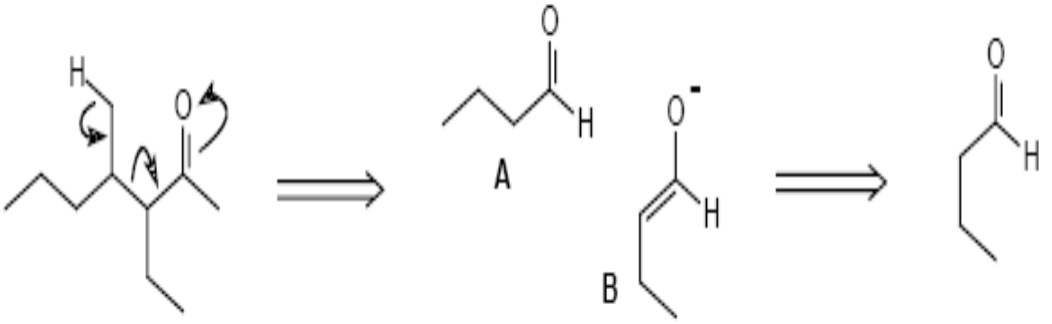


Both have reasonable mechanisms, but we prefer (b) because it introduces more simplification.

b) Two group disconnections:

When a molecule contains two functional groups, the best disconnection uses the two together. E.g. B hydroxyl carbonyl compound.





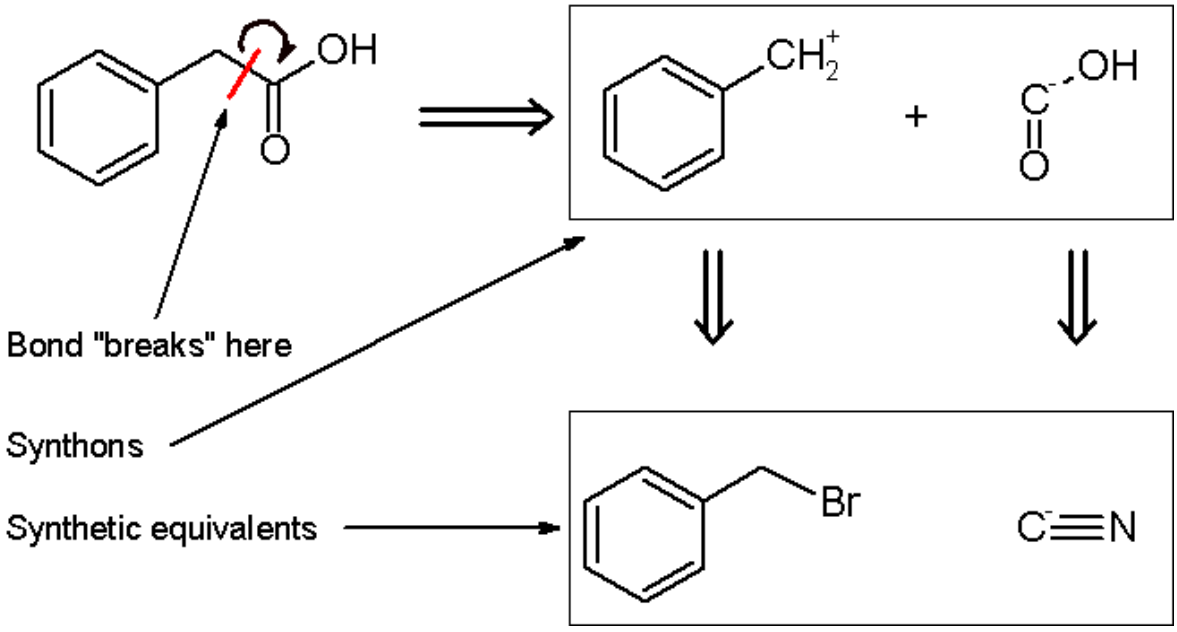
The anion B is just the enolate anion of a carbonyl compound, actually the same as A.

Applications of retrosynthesis

1. Retrosynthesis in inorganic crystal structures: application to nesosilicate and inosilicate networks

This presents the use of a retrosynthetic tool allowing one to reduce any crystalline structure to a set of two or three simple chemical "tectons" from which the whole network may be reconstituted. This reduction is performed by probing the susceptibility of any finite secondary building unit to the removal of translation symmetry operators.[8,9]

2. Structural simplification-



3. Computer-Assisted Retrosynthetic Analysis

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. The application of a computer program which can assist in retrosynthetic analysis is then of great value.

4. Recap—(Retro synthetic Combinatorial Analysis Procedure): a powerful new technique for identifying privileged molecular fragments with useful applications in combinatorial chemistry.The use of combinatorial chemistry for the generation of new lead molecules is now a well established strategy in the drug discovery process. Central to the use of combinatorial chemistry is the design and availability of high quality building blocks which are likely to afford hits from the libraries that they generate. Herein we describe "RECAP" (Retrosynthetic Combinatorial Analysis Procedure), a new computational technique designed to address this building block issue. RECAP electronically fragments molecules based on chemical knowledge.[9]

5)Analysis of Complex Synthetic Problems

The total synthesis of structurally complex compounds is a challenging undertaking, in intellectual as well as practical respects. Whereas simple compounds can usually be made by synthesis routes comprising a few reaction steps (say two to five), complicated molecules may require a lengthy sequence of reactions, not seldom more than twenty. . A more systematic and generally applicable problem-solving technique is clearly called for, and is presented by retrosynthetic analysis

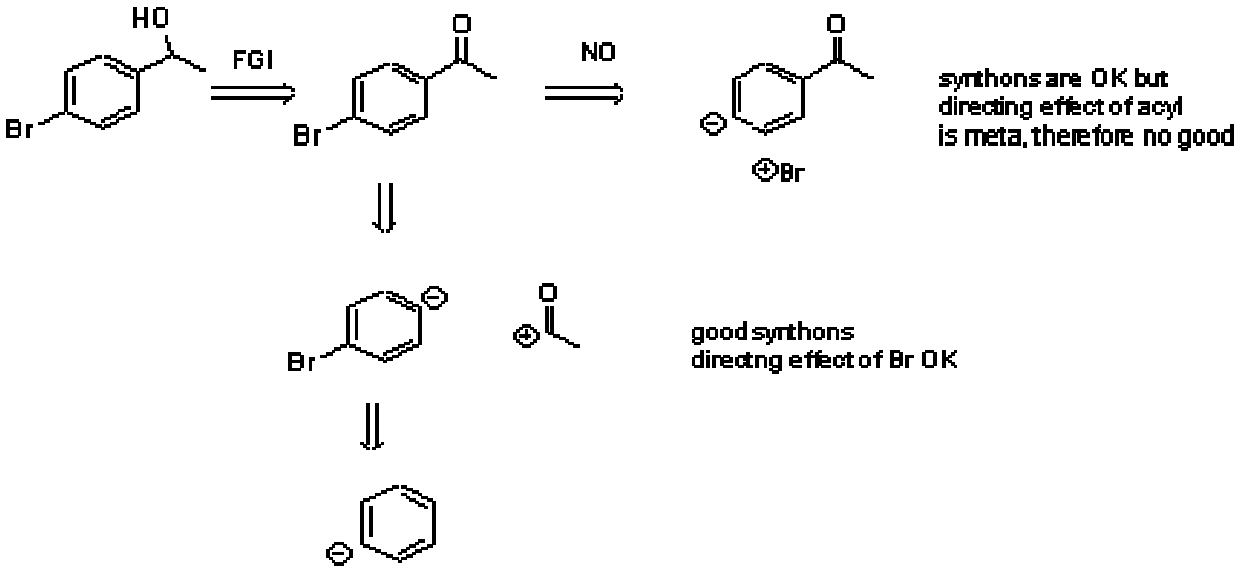
Goals and Subgoals

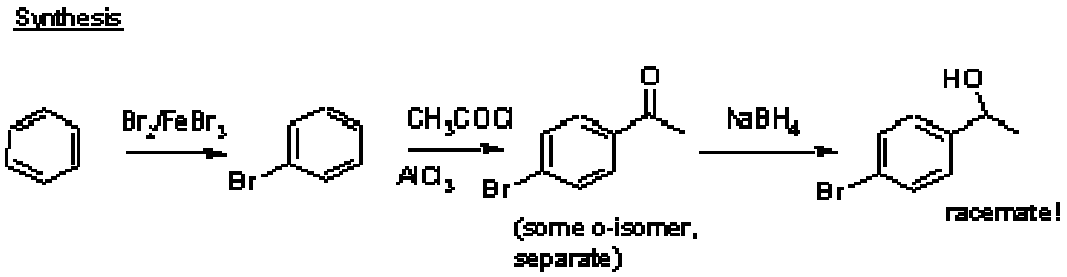
Although the general goal for RA is structural simplification, this does not mean that each step in a retrosynthesis must be, or even can be, simplifying. Certainly, if most steps are simplifying, the resulting synthesis is likely to be very efficient. Many actual syntheses, however, contain fewer construction steps than functional group manipulations which are generally non-simplifying. Because RA is a goal-driven activity, synthesis routes produced by RA tend to be quite efficient. Transforms which effect a desired simplification are called goal transforms.

The term subgoal is used because such a step is subordinate to the application of a goal transform. Without a goal transform `in mind', there is really no good reason to apply a subgoal transform. Subgoal transforms which

manipulate functional groups are very common: functional group addition (FGA), functional group removal (FGR), functional group interchange (FGI), and functional group transposition (FGT) are frequently employed. But in fact any transform which assists in `setting up' the retron for a goal transform can be thought of as a subgoal transform.

Example of retrosynthetic analysis.





Result and Discussion

Retrosynthetic analysis is very good method for building or creating a method for manufacturing or synthesis of any drug. Which is very valuable for the human wellfare, the analysis is very helping for creating a unit molecule. Which may help for the betterment of the manufacturing method and may economise the manufacturing cost.[4,6]

This analysis is found very important now a days for the finding of the parent entity, which is always help full in forming of the drug or the medicinal compound. The analysis can found those compound which are very

frequently found on the earth and from which the important compound can be creat very easily by just some simple chemical or physical methods.

It concludes that the method is very important for the finding of new sources of the drug.[5, 6]

Conclusion

Retrosynthetic analysis is a basic term used for synthesis of complex material.In this method the starting material is synthesized from target material. Retrosynthetic analysis is a problem-solving technique for transforming the structure of a synthetic target (TGT) molecule to a sequence of progressively simpler structures along a pathway which ultimately leads to simple or commercially available starting materials for a chemical synthesis. The transformation of a molecule to a synthetic precursor is accomplished by the application of a transform, the exact reverse of a synthetic reaction, to a target structure. Each structure derived antithetically from a TGT then itself becomes a TGT for further analysis.[8, 9]

In this approach the target structure is subjected to a deconstruction process which corresponds to the reverse of a synthetic reaction, so as to convert that target structure to simpler precursor structures, without any assumptions with regard to starting materials. Each of the precursors so generated is then examined in the same way, and the process is repeated until simple or commercially available structures result. This “retrosynthetic” procedure constitutes the basis of a general logic of synthetic planning which was developed and demonstrated in practice over the ensuing decade.[7]

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