Wöhler synthesis of Urea in 1828 heralded the birth of modern chemistry. The Art of synthesis is as old as Organic chemistry itself. Natural product chemistry is firmly rooted in the science of degrading a molecule to known smaller molecules using known chemical reactions and conforming the assigned structure by chemical synthesis from small, well known molecules using well established synthetic chemistry techniques. Once this art of synthesizing a molecule was mastered, chemists attempted to modify bioactive molecules in an attempt to develop new drugs and also to unravel the mystery of biomolecular interactions. Until the middle of the 20th Century, organic chemists approached the task of synthesis of molecules as independent tailor made projects, guided mainly by chemical intuition and a sound knowledge of chemical reactions. During this period, a strong foundation was laid for the development of mechanistic principles of organic reactions, new reactions and reagents. More than a century of such intensive studies on the chemistry of carbohydrates, alkaloids, terpenes and steroids laid the foundation for the development of logical approaches for the synthesis of molecules.

The job of a synthetic chemist is akin to that of an architect (or civil engineer). While the architect could actually see the building he is constructing, a molecular architect called Chemist is handicapped by the fact that the molecule he is synthesizing is too small to be seen even through the most powerful microscope developed to date. With such a limitation, how does he ‘see’ the developing structure? For this purpose, a chemist makes use of spectroscopic tools. How does he cut, tailor and glue the components on a molecule that he cannot see? For this purpose chemists have developed molecular level tools called Reagents and Reactions. How does he clean the debris and produce pure molecules? This feat is achieved by crystallization, distillation and extensive use of Chromatography techniques. A mastery over several such techniques enables the molecular architect (popularly known as organic chemist) to achieve the challenging task of synthesizing the miracle molecular structures encountered in Natural Products Chemistry, Drug Chemistry and modern Molecular Materials. In this task, he is further guided by several ‘thumb rules’ that chemists have evolved over the past two centuries. The discussions on the topics Name Reactions, Reagents for synthesis, Spectroscopy and Chromatography are beyond the scope of this write-up. Let us begin with a brief look at some of the important ‘Rules’ in organic chemistry that guide us in planning organic synthesis. We would then discuss Protection and Deprotection of some important functional groups. We could then move on to the Logic of planning Organic Synthesis.

Modern Synthesis

A multi-step synthesis of any organic compound requires the chemist to accomplish three related tasks:

1. Constructing the carbon framework or skeleton of the desired molecule.
2. Introducing, removing or transforming functional groups in a fashion that achieves the functionality of the desired compound.
3. Exercising selective stereocontrol at all stages in which centers of stereoisomerism are created or influenced. These are not discrete independent tasks to be attacked and solved in turn, but must be integrated and correlated in an overall plan. Thus, the assembly of the molecular framework will depend in part on the structure and functionality of available starting materials, the selectivity (regio and stereo) of the various reactions that may be used to stitch them together, and the loss or relocation of functional groups in the intermediate compounds formed on the way to the final product.

Other factors must also be considered, always in context with those listed above:

4. Since a successful synthesis must produce the desired product in reasonable amount, it should be as short and
efficient as possible. A two or three-step sequence is usually better than a six or seven step procedure, even if the individual step yields are better in the longer route. Most reactions do not proceed in 100% yield, and the losses are multiplied with each additional step. Furthermore, a long multi-step synthesis requires many hours of effort by the chemists conducting the reactions.

5. The format of a synthesis is important. Assuming a constant yield for each step, a linear sequence of reactions gives a poorer overall yield than the same number of convergent reactions, as shown in the following diagram.

6. If numerous functional groups are present at intermediate stages, some of these may require protection from unwanted reaction. Since the use of a protective group requires its introduction and later removal, such operations can add many steps to a synthesis. A similar cost is attached to the use of blocking and activating groups.

7. The starting compounds and reagents for a synthesis must be purchased, so economic considerations are often significant. Recovery or recycling of expensive reagents and catalysts is often desirable. Also, if large amounts of useless by-products are formed in the synthesis, the expense of their disposal is a factor. The term atom efficiency has been coined to reflect the latter point.

8. For a given target molecule, several different reaction sequences may serve to accomplish its synthesis. Indeed, new synthetic routes to known compounds continue to be reported, particularly as new reactions are developed and applied to difficult transformations. Evaluating the quality and efficacy of these diverse procedures involves consideration of all the above. Over the course of the past hundred years, a very large number of syntheses for a wide variety of compounds have been recorded. For all but the simplest of these, a majority of the reactions in the synthesis involve functional group modification, preceding or following a smaller number of carbon-carbon bond forming reactions. Because functional group chemistry consists of such a vast number of addition, elimination and substitution interconversions, it is not possible to identify a general pattern in their application to synthesis. Instead, an example from the synthesis of reserpine by the R. B. Woodward group (Harvard), displayed in the following diagram, will serve to illustrate the importance of regio and stereo-control in the course of functional group modification.

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