# Putting the Pieces Together

*Outdoing Nature takes some skill, but with logic and creativity, Chemists have found a way to beat Nature at its own game.* *By Victoria A M Atkinson*

Nature is indisputably the world's greatest chemist: the efficiency with which even simple organisms are able to produce highly complex molecules is something that still cannot be rivalled synthetically. Many species produce compounds with useful biological properties in humans, quite distinct from the intended role of the chemical in the host organism, and this fact has been exploited throughout history. Plant-based medicines have been used in human societies for millennia, and a large number of these 'traditional medicines' have now been developed into modern day drugs. Perhaps the most celebrated example is that of the journey from willow bark, used by the Ancient Egyptians for pain relief, to aspirin, one of the world's most-used drugs (**Figure 1**).


***Figure 1:*** *Structure of aspirin.*

Unfortunately, Nature alone is rarely able to keep up with society's demand for these natural products. These compounds are usually only produced in small quantities, either because not much is required by the organism in question, or because it is an unnecessary by-product from another process. In the case of aspirin, the former is true, and the active ingredient is used by the willow tree as a phytohormone – a plant hormone which regulates growth, development, and immune response within the tree. As such, the concentration of this chemical within the bark is very low, meaning extraction from the plant source is incredibly inefficient, and making a synthetic means of producing the compound necessary. As aspirin has a simple structure, chemical synthesis is straightforward and a one-step procedure (an esterification reaction) readily converts commercially available salicylic acid into aspirin in quantitative yield (**Figure 2**).

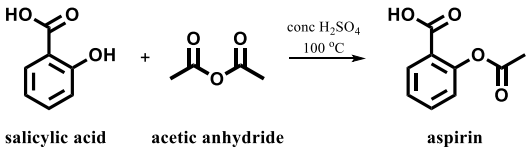


***Figure 2:*** *Chemical synthesis of aspirin via esterification of salicylic acid.*

Accessing sufficient quantities of these natural products becomes much more challenging as the compounds become more complex. Taxol (**Figure 3**) is a potent chemotherapy medication used to treat a number of human cancers, often where other treatments have failed.

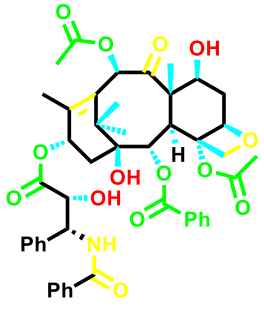


***Figure 3:*** *Structure of Taxol with stereocentres and functional groups indicated. Blue: stereocentre (stereocentre at carbon adjacent to blue bond), green: ester, red: alcohol, yellow: other functional group.*

The compound was first isolated from the bark of the Pacific Yew tree in just 0.014% yield (corresponding to roughly

10 g of Taxol from 1.2 tonnes of bark) and by the mid-70s, over 360, 000 of these slow-growing trees were felled annually in an attempt to meet the increasing demand for this powerful drug. Chemical methods to produce Taxol were investigated but with eleven stereocentres (blue), four esters (green), three alcohols (red), and a handful of other reactive functional groups (yellow), this complex target presented a stern synthetic challenge. In the decades since, although modern industrial production is still *via* semi-synthesis (in which a naturally sourced intermediate provides the starting point for chemical synthesis), numerous chemical syntheses have been reported, often requiring 40 or 50 individual steps.

Completing the synthesis of a natural product is like doing a jigsaw: many small and simple pieces are connected together very specifically to ultimately form a finished picture. But prior to assembly, it is necessary to determine which 'pieces' are actually required for a new total synthesis. Planning, or retrosynthesis as it's known by chemists, is an incredibly important process in which hypothetical pieces are removed from the natural product (disconnection), gradually simplifying the structure until suitable starting pieces can be identified (**Figure 4**).

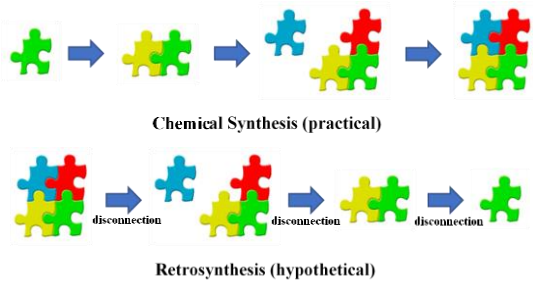


***Figure 4:*** *Chemical synthesis and retrosynthesis.*

Throughout this process, it is important to analyse the feasibility and potential problems of each disconnection step as not all reactions are possible and some may produce mixtures of products. For example, where multiple functional groups are present, it is necessary to consider how all of those functional groups will react under the chosen conditions. Reactions occurring in the wrong place or occurring in too many places are both common obstacles in synthesis, usually requiring either modification of the chosen conditions, or protection of one of the functional groups (**Figure 5**).

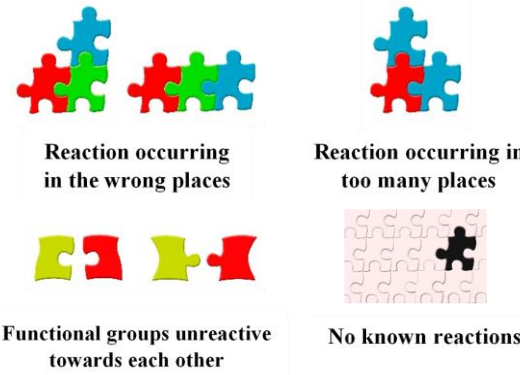


***Figure 5:*** *Limitations of Chemistry.*

Choice of suitable reaction substrates is another important consideration: much like jigsaw pieces, some functional groups are simply not reactive towards each other and creative solutions must be found to circumvent this. In a few cases, no conditions exist at all to achieve certain transformations and an alternative synthetic route must be found. These are the missing pieces of Chemistry and extensive research is seeking to fill these gaps and provide more tools for synthesis.

Yet despite these challenges, chemists are successfully able to design intricate total syntheses of complex natural products such as Taxol. Using logic and creativity during the retrosynthetic process, it is possible to plan the synthesis of any natural product. So, whilst Nature provides the inspiration, it's our turn to do the Chemistry!