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Synthesis of Natural Products and its Methodological Applications

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Opinion Article

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DESCRIPTION

All natural products begin as complicated mixes of various molecules derived from the natural source in which the product must be extracted and purified. Depending on the context, the isolation of a natural product refers to either the isolation of sufficient quantities of pure chemical matter for chemical structure elucidation, derivitzation/degradation chemistry, biological testing, and other research needs (generally milligrammes to grammes, but historically, often more), or the isolation of "analytical quantities" of the substance of interest, where the focus is on identification and quantitation of the substance of interest. The ease with which the active agent can be isolated and purified is determined by the natural product's structure, stability, and quantity. The isolation methods used to achieve these two distinct scales of product are also distinct, but generally involve extraction, precipitation, adsorptions, chromatography, and, in some cases, crystallisations. In both cases, the isolated substance is purified to chemical homogeneity, i.e., specific combined separation and analytical methods, such as LC-MS methods, are chosen to be "orthogonal" achieving separations based on distinct modes of interaction between substance and isolating matrix with the goal of repeated detection of only a single species present in the putative pure sample. Early isolation is almost always followed by structure determination, especially if the purified substance has a significant pharmacologic activity. Structure determination refers to methods used to determine the chemical structure of an isolated, pure natural product, a process that involves a variety of chemical and physical methods that have evolved significantly throughout the history of natural product research; in the early days, these focused on chemical transformation of unknown substances into known substances, measurement of physical properties such as melting point and boiling point, and related methods for detection.

Modern methods emphasise mass spectrometry and nuclear magnetic resonance methods, which are frequently multidimensional, and, when possible, small molecule crystallography. Dorothy crowfoot hodgkin, for example, determined the chemical structure of penicillin in 1945, for which she later received the Nobel Prize in Chemistry (1964).

Synthesis

Many natural products have extremely complex structures. The perceived complexity of a natural product is a qualitative matter that takes into account its molecular mass, the specific arrangements of substructures (functional groups, rings, etc.) with respect to one another, the number and density of those functional groups, the stability of those groups and of the molecule as a whole, the number and type of stereo chemical elements, the physical properties of the molecule and its intermediates (which bear on the ease of use). Some natural products, particularly those that are less complex, can be easily and cheaply prepared through complete chemical synthesis from readily available, simpler chemical ingredients, a process known as total synthesis (especially when no biological agents are involved). Not all natural products, whether cost-effective or not, lend themselves to total synthesis. Those that are the most complex, in particular, are frequently not. Many are accessible, but the required routes are simply too expensive to allow for practical or industrial-scale synthesis. However, in order to be studied further, all natural products must be isolated and purified. This may be sufficient if isolation provides sufficient quantities of the natural product for the intended purpose (for example, as a drug to treat disease). Drugs like penicillin, morphine, and paclitaxel were discovered to be inexpensively obtained at required commercial scales solely through isolation procedures (with no significant synthetic chemistry contributing). In other cases, however, necessary agents are not available without synthetic chemistry manipulations.

Semi synthesis: Isolating a natural product from its source can be costly in terms of time and material expenditure, and it may jeopardise the availability of the relied-upon natural resource (or have ecological consequences for the resource). It has been estimated that to extract enough paclitaxel for a single dose of therapy, the bark of an entire yew tree (Taxus brevifolia) would have to be harvested. Furthermore, the number of structural analogues available for Structure-Activity Analysis (SAR) simply through harvest (if more than one structural analogue is present) is limited by the biology at work in the organism, and thus beyond the control of the experimentalist.

When the ultimate target is difficult to obtain or limits SAR, it may be possible to obtain a middle-to-late stage biosynthetic precursor or analogue from which the ultimate target can be prepared. Semisynthesis or partial synthesis is the term for this. The related biosynthetic intermediate is harvested and then converted to the final product using conventional chemical synthesis procedures.

Total synthesis: In general, total synthesis of natural products is a non-commercial research activity aimed at developing fundamental new synthetic methods and gaining a better understanding of the synthesis of specific natural product frameworks. Nonetheless, it is enormously commercial and societally significant. It has played an important role in the development of the field of organic chemistry, for example, by providing challenging synthetic targets. Prior to the development of analytical chemistry methods in the twentieth century, total synthesis was used to confirm the structures of natural products (so-called "structure proof by synthesis"). Early efforts in natural product synthesis focused on complex substances like cobalamin (vitamin B12), which is a necessary cofactor in cellular metabolism.

Symmetry: An examination of dimerized and trimerized natural products revealed that bilateral symmetry is frequently present. A molecule or system with bilateral symmetry has a C_2, C_s, or C_{2v} point group identity. C_2 symmetry is far more common than other types of bilateral symmetry. This discovery sheds light on how these compounds might be created mechanistically, as well as on the thermodynamic properties that make these compounds more desirable. Density Functional Theory (DFT), the Hartree-Fock method, and semi empirical calculations all show that dimerization in natural products are advantageous because it evolves more energy per bond than the equivalent trimer or tetramer.