

## Advanced Chemistry 2018 : Studies in natural product synthesis: Elevenol, lodopyridone and isoquinocyclinone - Ulrich Koert

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Elevenol isolated from the roots of *Flueggea virosa* is a 7,-20-oxa-bridged dinorditerpene that exhibits anti-Hepatitis C virus activity. Lodopyridone an unprecedented pentasubstituted 4-pyridone comes from the marine bacterial strain CNQ490 which was collected near the La Jolla Canyon. Isoquinocyclinone is the common aglycone of isoquinocycline A and B. Both natural products belong to the quinocyclines, a class of anthracycline natural products with antimicrobial and cytotoxic compounds which were isolated first from *Streptomyces aureofaciens*. Here we present progress towards the total syntheses of these natural products. Key steps for the synthesis of elevenol are a stereoselective Stetter-type Michael addition, a Tishchenko reaction, and an intra-molecular lactone enolate arylation. For lodopyridone a pentasubstituted 4-pyridone is prepared from kojic acid via a regioselective bromination, a thio-Ullmann reaction and a regioselective lithiation/iodination. The anthraquinone core of isoquinocyclinone is synthesized by a Hauser annulation. The 2,4,5,6-tetrahydropyrrolo[2,3-b] pyrrole substructure can be prepared via a Ni(0)mediated cyanide addition followed by the conversion of an O,O into an N,O acetal and an intra-molecular N-alkylation.

A natural product is a chemical compound or substance produced by a living organism, that is, found in nature. In the broadest sense, natural products include any substance produced by life. Natural products can also be prepared by chemical synthesis (both semi-synthesis and total synthesis) and have a central role in the development of the field of organic chemistry by providing difficult synthesis targets. The term natural product has also been added for commercial purposes including cosmetics, food supplements and foods with no natural sources added. .

In the field of organic chemistry, the definition of natural products is generally limited to purified organic compounds that are isolated from natural sources, such as primary or secondary metabolic pathways. In the field of medicinal chemistry, the definition is often limited to secondary metabolites that are not essential

for survival, but nevertheless provide the organisms which produce them with an evolutionary advantage. Many secondary metabolites are cytotoxic and have been evolutionarily selected and optimized for use against "chemical warfare" agents.

Chemical examination of an organic extract of CNQ490, a *Saccharomonospora* sp. isolated from marine sediment off the coast of San Diego, gave lodopyridone. The low proton / carbon ratios exhibited by the structure of lodopyridone prevented elucidation by NMR spectroscopic methods, and the structure was finally determined by X-ray crystallography. Lodopyridone cancer as a mass spectrometry test in ultrafiltration, but it does not inhibit the enzymatic activity.

All natural products begin with mixtures and other naturally occurring compounds, often very complex mixtures, from which the product's interest must be isolated and purified. The isolation of a natural product refers to the context, to the degree of elucidation of the chemical content, the derivatization / degradation chemistry, the biological tests and the research requirements (usually milligrams to grams, but historically, often more), [citation needed] or to isolate "analytical quantities" of the substance of interest, where the emphasis is on the identification and quantification of the substance (for example in tissues or biological fluids)

The isolation methods applied to attend to these two separate product scales are also separate, but generally involve extraction, precipitation, adsorption, chromatography and sometimes crystallization. In both cases, the isolated substance is purified to chemical homogeneity, that is to say that specific combined separation and analysis methods such as LC-MS methods are chosen or be "- carrying out their separations on the basis of modes of interaction distinctions between the substance and the isolation matrix - with the objective being the repeated detection of a single species present in the putative

pure sample. Early isolation is almost inevitably followed by a determination of the structure,

Determination of structure refers to the methods applied to determine the chemical structure of a pure and isolated natural product, a process that involves a range of chemical and physical methods that have changed considerably over the course of natural product history; in the early days, these focused on the chemical transformation of unknown substances into known substances, and the measurement of physical properties such as melting point and boiling point, and related methods for determining molecular weight.