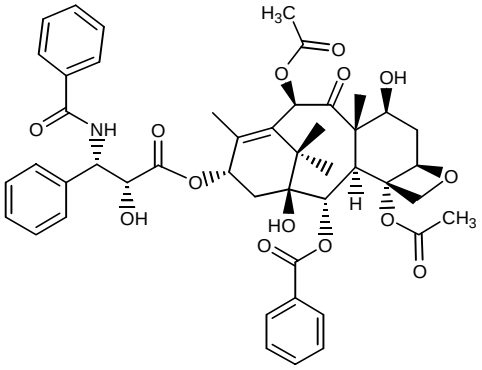
Taxol (Paclitaxel)

Taxol (paclitaxel) is a tricyclic diterpene isolated from *Taxus brevifolia*, the Pacific yew. Taxol has been in the news lately because of its very potent antineoplastic activity and its restricted availability. Taxol was originally isolated in 1963 by Wall and Wani at Research Triangle Institute, and the structure was finally elucidated in 1971. Taxol is an antimitotic agent, but acts by stabilizing microtubules and promoting microtubule assembly, rather than by depolymerizing microtubules. Phase II clinical trials of taxol have shown 30% improvement in patients with ovarian cancer and 48% improvement in patients with metastatic breast cancer which is unresponsive to other chemotherapy. Recent clinical trials involving women with advanced ovarian cancer have shown that combination chemotherapy, using taxol in combination with cisplatin, resulted in an average survival time of three years. The best previous chemotherapeutic treatment, cisplatin plus cyclophosphamide, results in a two year average survival time. Taxol is clearly one of the most important experimental antineoplastic drugs currently under investigation.

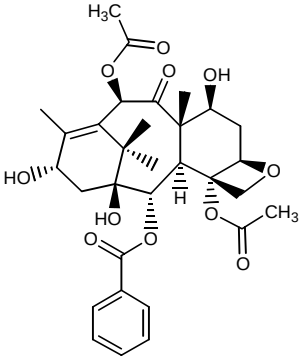


taxol

The major problem with developing taxol as a cancer chemotherapeutic agent in recent years has been supply. Taxol is only isolated in "large" amounts from the bark of the Pacific yew, a slow growing tree found only in the Pacific northwest in slow growth forests, but stripping the bark kills the tree. Originally, the Pacific yew was considered a waste tree by loggers in the Pacific northwest. Consequently, much of the inventory was destroyed in the course of logging. A December, 1992 survey estimated that there were approximately 40 million Pacific yews with diameters greater than one inch on public lands. Approximately 45% of the trees are on land where they can be harvested, but 55% are on land where harvesting is prohibited, such as spotted owl habitats and other special management areas.

The rush to produce sufficient quantities of taxol for clinical trials has raised environmental and ethical concerns which are not easy to resolve. While this is a specific case, the arguments can apply to any biologically active natural product derived from a rare resource. For example, should a species be essentially wiped out to produce a drug which can potentially help people? What is fair compensation for the use of this resource and who should get the compensation, i.e., who owns the resource? If the plant is in a foreign country which does not have the means to develop the drug, what are the ethics of the U.S. acquiring the resource? What is adequate compensation of the company or institution which develops the drug as a marketable product? In this latter case, the development process can be exceedingly costly with clincial trials and pre-clinical trial pharmacological studies. Some of these questions have been addressed in a declaration adopted by the American Society of Pharmacognosy at the Thirty-third National Meeting in August, 1992.

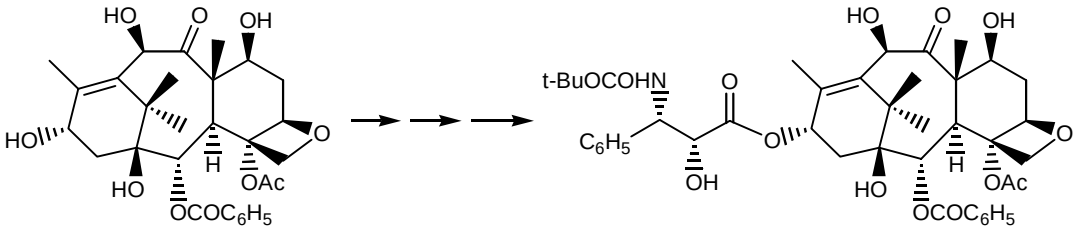
Since taxol is only available, as a natural product, at the present time in large quantities from the bark of *T. brevifollia*, other sources for taxol have been investigated, including production of taxol from plant tissue cultures. There was a report in the *Richmond Times-Dispatch* on Sunday, November 8, 1992 that researchers at Cornell have succeeded in producing taxol from *Taxus* cell cultures. The commercial production of taxol via this method appears to be several years off. Other researchers are working on improved means of extraction and isolation from the bark. There has, of course, also been significant efforts to synthesize taxol, and Dr. Robert Holton at Florida State University has recently succeeded in his efforts. However, synthesis of a complex molecule like taxol from simple precursors can rarely be used to produce large quantities of the compound, due to the large number of steps and specialized conditions. Much more viable is "semi-synthesis," synthesis from a natural precursor which can be obtained in significant amounts. Baccatin III is such a precursor which can be isolated from the needles of many different types of yews, including many of the ornamental yews sold in nurseries. Since



baccatin III

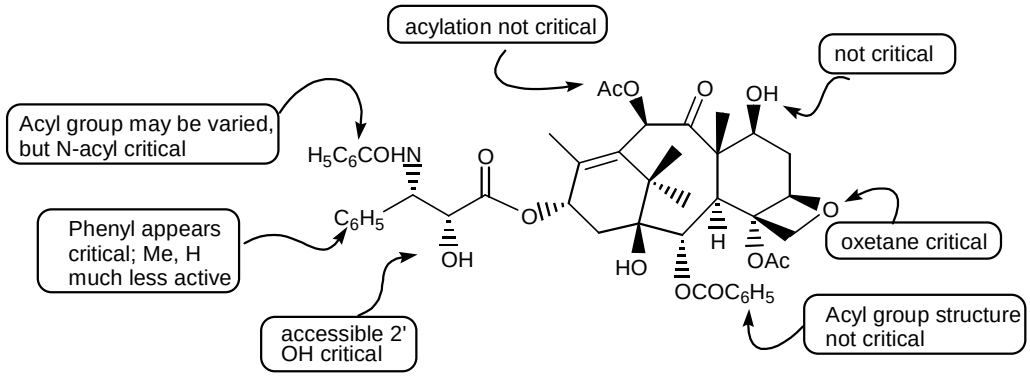
the needles are renewable, the production of baccatin III is less damaging to the yews. The key is to be able to esterify the C-13 alcohol of baccatin III with the appropriate amino acid derivative. There are now several stereoselective syntheses of the appropriate amino acid derivative, and several methods for performing the acylation of baccatin III and other homologues, making this a potentially viable method for producing the needed quantities of taxol. Unfortunately, the semi-synthetic taxol must go through its own set of rigorous tests prior to approval for use as an investigational drug, even though it is chemically identical to the natural product.

There is also an effort underway by several major drug companies, and other independent invesatigators, to produce second and third generation drugs. One of the major problems with taxol, as with many biologically active natural products, is its lipophiicity and lack of solubility in aqueous systems. This leads to the use of an emulsifier in clinical preparations. In taxol's case, significant efforts have been directed toward understanding the structure-activity relationships in order to be able to prepare second generation drugs with improved activity and/or solubility. Initial efforts determined that the C-13 ester is required for activity. Baccatin III is substantially less cytotoxic than taxol (ED_{50} 2.0 µg/ml vs. 10^{-5} µg/ml, respectively, against the KB cell culture). However, the N-acyl group on the side chain ester does not appear to significantly influence the activity. The presence of the acetyl group at C-10 also has little effect, 10-deacetyltaxol is almost as cytotoxic as taxol in certain systems. These findings led to taxotere, prepared from 10-deacetylbaccatin III by Rhone-Poulenc Rorer. Taxotere is more water soluble than taxol, giving it better bioavailability. It is also reported to be more active in clinical trials, presumably due to its increased bioavailability.

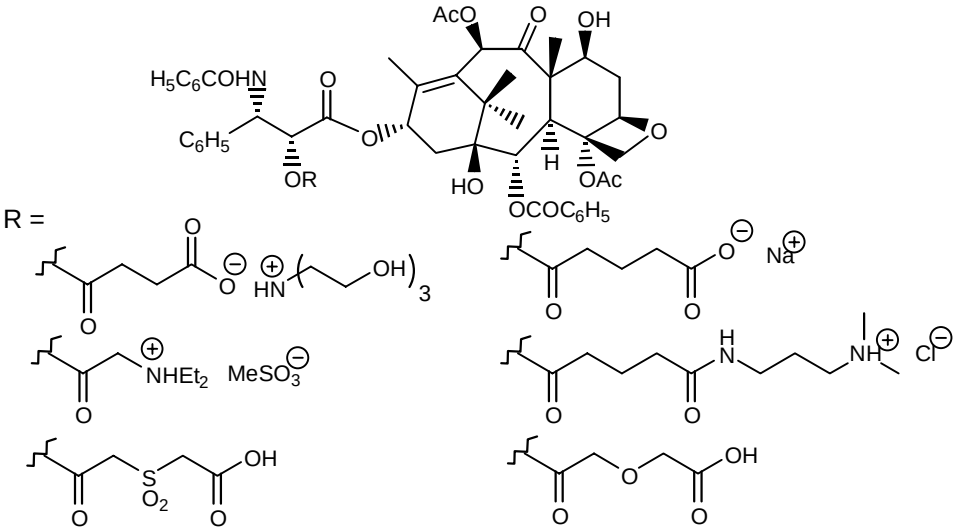


10-deacetylbaccatin III taxotere

Some of the other structure-activity relationships for taxol which have been elucidated by testing naturally-occurring and semi-synthetic homologues are illustrated below.



The finding that the 2'-hydroxyl must also be accessible was determined by preparing a series of esters of this moiety. In testing these derivatives, it was found that some esters were evidently being hydrolyzed *in vivo*. This suggested that the 2'-hydroxyl might be a good functional group to derivatize with moieties designed to improve water solubility, particularly groups containing a salt. Some of those prepared are shown below. Preliminary testing suggests that these taxol derivatives do have increased water solubility. The activity levels must still be evaluated.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