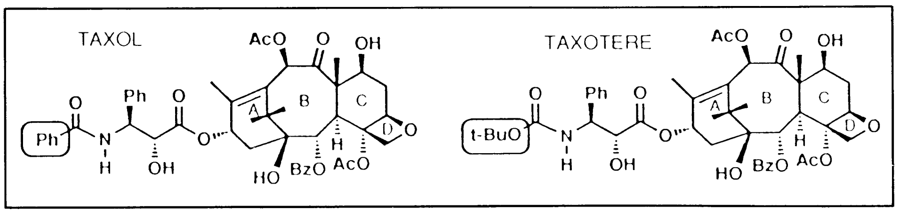
# Beyond Yew: Chemists Boost Taxol Yield




Wender/Stanford

*Chemical-structure diagrams show the similarity between taxol and Taxotere.*

Several research groups have overcome significant barriers to produce a promising new anticancer drug now derived from the bark of the Pacific yew tree. The drug, taxol, has drawn great interest because of its success as an experimental treatment for ovarian tumors and, more recently, lung and breast cancers (SN: 2/22/92, p.124). It has also sparked controversy because it exists in minute quantities in the yew's bark, whose collection results in the death of the century-old trees.

But soon taxol may come, either directly or indirectly, from much less precious sources: cedar wood oil, the leaves of a yew common in Europe, the major ingredient of turpentine or even vats of living plant cells. Scientists reported on these developments last week at the American Chemical Society spring meeting in San Francisco.

"The key message is, we're ending the dependency on the Pacific yew," says Matthew Suffness, a medicinal chemist with the National Cancer Institute in Bethesda, Md. "We're moving to other areas in which other processes are viable."

Already, these advances have led to new, possibly better drugs based on taxol.

Years before taxol's supply became an issue, its synthesis intrigued chemists. This complex compound's core contains 20 carbon atoms arranged in three linked rings. In addition, a chain of atoms hangs off one ring, while other atoms make a square formation, or fourth ring, off another. "You're looking at a molecule that has tested the limits of synthetic chemistry," says Paul A. Wender, an organic chemist at Stanford University.

Three years ago, Wender upped the taxol-synthesis ante by deciding to develop a synthesis technique that companies could adapt easily for commercial production.

Wender starts with pinene, an inexpensive pine extract found in turpentine. In five steps, he turns pinene into the three-ring core; then, with eight more steps, he adds the right side groups to two of the rings. He expects to learn how to complete the third ring by the end of 1992.

Jeffrey D. Winkler, a chemist at the University of Pennsylvania in Philadelphia, also makes the taxol core, having independently devised a strategy similar to Wender's. But Winkler's team starts with an extract from cedar oil.

Eight years ago, Pierre Potier, an organic chemist with the Institute of the Chemistry of Natural Substances in Gif-sur-Yvette, France, found that the leaves of the European yew contain a compound that closely resembles taxol's three-ring core. Potier came up with a series of chemical reactions for adding the side chain and converting this molecule to taxol.

Robert A. Holton, an organic chemist at Florida State University in Tallahassee, has also come up with an efficient way to join the leaf compound of the European yew with the side chain. Because the core molecule is bent like a cone around the place where the side chain attaches, the side chain has trouble getting close enough to attach. Holton and his group devised a rolled-up version of the side chain that fits easily into this cone. When it attaches, it opens up into the straight configuration needed to make the molecules active against tumors, says Holton. Moreover, he can easily modify the final molecule produced.

"He's improved that semisynthetic process tremendously," says Suffness. Bristol-Myers Squibb in New Brunswick, N.J., plans to produce taxol in this way, possibly for clinical use by next spring, Holton says.

Plant-cell cultures can also help improve the taxol supply and yield related compounds, reports Walter E. Goldstein, a chemical engineer with ESCAgenetics Corp. in San Carlos, Calif. "The taxol concentrations [from cultures] are many times the taxol concentrations one sees in the bark," he says. His company had begun producing vanilla through cell cultures but now has shifted its bioreactors to yew-cell cultures.

These scientists agree that taxol represents only a crude beginning for this new class of anticancer drugs. "Taxol is not the compound we want to use," Potier says. Aside from being hard to obtain, it does not dissolve easily, so it's difficult to inject into the body. Also, patients need high dosages.

Already Potier has found that one compound derived from the European yew, called Taxotere, is more soluble and more efficient than taxol at killing lab-grown cancer cells. Physicians in Europe and the United States are now trying this compound in patients. "We believe that clinical use of taxol is no longer justified," Potier says. Holton, too, has produced several dozen taxol-like compounds for evaluation.

And David G.I. Kingston at Virginia Polytechnic Institute and State University in Blacksburg has systematically altered side groups and the side chain of taxol. Kingston's data indicate that both the side chain and the box formation at the other end of the molecule are critical to taxol's anticancer effect. His work with some of these modified taxol molecules made him realize that he can make a soluble "prodrug," a compound that converts to taxol once in the body. A prodrug may make taxol easier to administer, he says.

"All of these technologies are going to play a role," says Suffness. — *E. Pennisi*

## Infant memory shows the power of place

Six-month-olds rely on surprisingly specific aspects of their incidental surroundings — such as the color or design of a crib liner — to retrieve memories of a simple learned task, according to ongoing research by psychologists at Rutgers University in New Brunswick, N.J.

"Place information enjoys a privileged [mental] status much earlier in development than previously thought and seems to be the first level of retrieval for memories among infants and adults," asserts project director Carolyn Rovee-Collier.

The new findings, described in the March DEVELOPMENTAL PSYCHOLOGY, challenge current neuropsychological theories that consider basic language skills a prerequisite for memory development and assume that infants younger than around 9 months cannot store information about their surroundings in a systematic way.

Rovee-Collier's group conducted a series of experiments with a total of 85 infants. Each baby reclined in a seat placed in a playpen whose sides were draped by a yellow liner with green squares. A mobile featuring seven wooden figures and four jingling bells hung over the playpen. On two successive days, experimenters tied a satin ribbon attached to the mobile around an infant's ankle for 6 minutes and an experimenter