when taxol was first introduced into clinical trials was the high incidence of major hypersensitivity reactions that may have been related to the formulation of the drug in Cremophor EL. Although these hypersensitivity reactions have been overcome by premedication regimens and alterations in the administration of the drug, they delayed clinical trials by five years[10].

Nonetheless, taxol has become an important new cancer chemotherapeutic agent, one of the first in a number of years. It has significant activity in drug-refractory ovarian cancer[11] and was approved for this disease by the US Food and Drug Administration in 1992. Other tumours for which taxol has shown activity are cancers of the breast[12] and lung[13,14], and melanoma[15]. Although it holds uncommon promise in the treatment of various cancers, it is not a panacea or a cure for cancer; rather, it is an active drug whose true clinical potential will be realized only with time. Its effectiveness in combination chemotherapy, with radiation, with growth factors or as adjuvant chemotherapy in breast cancer remains to be seen.

The synthesis carried out by Nicolaou *et al.* opens up possibilities for the development of new active anti-tumour drugs, for compounds with greater aqueous solubility, and for others with the ability to reverse taxol-resistance. It will lead to extensive structure–activity studies that will allow an examination of interactions between different parts of the taxol molecule and the microtubule. Access to new derivatives and a second generation of taxoids will further our knowledge of microtubule structure and function, and should add impetus to the development of rationally designed anti-tumour drugs to interact with microtubules. Not least, the work of all concerned in the taxol story has focused attention on natural products as a source for drugs and has implicated the microtubule as a major target for cancer chemotherapeutic agents. □

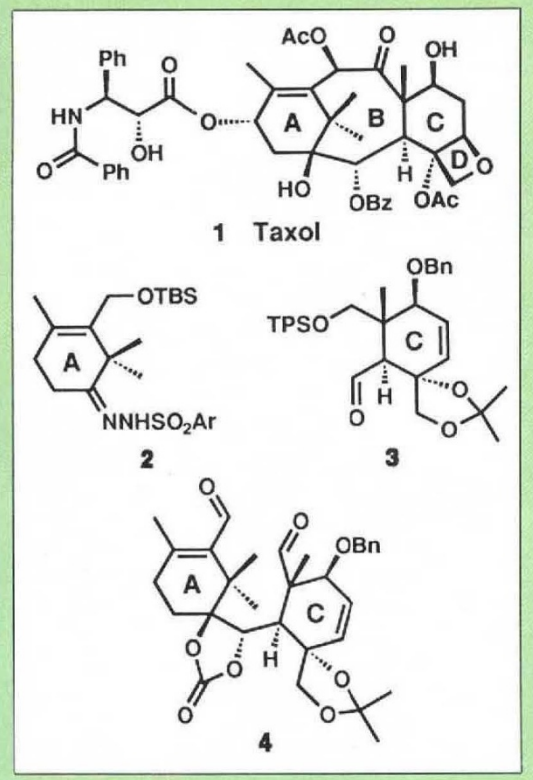
Susan Band Horwitz is in the Department of Molecular Pharmacology, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, New York 10461, USA.

Steps to a successful synthesis

In book VI of his *Gallic Wars* Caesar tells us that Catuvolcus, a chieftain of the Eburones, committed suicide by taking an extract of the yew tree. This was a common form of poisoning in ancient times, but the broad-spectrum cytotoxicity of extracts from the Pacific yew, *Taxus brevifolia*, was only discovered in 1964. Subsequent purification and structure elucidation of the major cytotoxic principle, the diterpene taxol (1), was achieved by Wani *et al.* in 1971, but clinical trials were delayed by the paucity of natural taxol available. Nonetheless, phase I trials in humans commenced in 1983 and the great promise of taxol was confirmed.

The growing interest in the anti-tumour potential of taxol, coupled with the synthetic challenge offered by a molecule of this structural complexity and rarity, attracted the attention of many of the world's leading synthetic chemists. Taxol rapidly became one of the most fashionable targets of the eighties. In a review written in early 1992, Swindell[1] provided a progress report on the work of more than 30 groups, but noted that there had been "only modest success in total synthesis". Two years on, we have the first total synthesis by Nicolaou and co-workers.

The molecule presents a formidable synthetic challenge with its eleven stereocentres and dense array of functionality. Nicolaou and colleagues' synthesis is both convergent — it employs the fully functionalized A-ring and C-ring fragments 2 and 3 (the former first prepared[2,3] in 1992) — and flexible in that it should allow the construction of numerous analogues. The first carbon–carbon bond between rings A and C was created through reaction of the carbanion generated from sulphonylhydrazone (2) and aldehyde (3) (Shapiro reaction). Subsequent manipulation of functional groups provided the dialdehyde (4), and ring B was closed using a McMurry reaction mediated by titanium trichloride and activated zinc. The yield of this step was very low (23 per cent), but the rest of the synthesis, which included oxetane formation, oxygenation of ring A and introduction of the side-chain, proceeded without major problems.



There are 28 chemical steps based on the intermediates 2 and 3 (which also have to be prepared), so the synthesis can hardly be described as commercially viable. An alternative, shorter route by Wender's group, based on α-pinene, must be nearing completion[4], and other groups are not far behind. Indeed, as these pages are finalized, a group led by Robert Holton at Florida State University has claimed, in a press release, that it has achieved a total synthesis. Details will appear in the *Journal of the American Chemical Society*.

Meanwhile, as Susan Horwitz describes, it has been shown that taxol and certain related structures, especially 10-deacetyl baccatin III, may be obtained from needles of the European yew, *Taxus baccata* (for a review, see ref. 5). And the demonstration that a fungal endophyte of the Pacific yew, *Taxomyces andreanae*, will produce taxol and other taxanes in culture[6], offers some promise for the microbial production of these molecules.

It would be wrong, however, to underestimate the importance of the elegant synthesis developed by Nicolaou *et al.* It will allow access to structures not available from natural sources, some of which may be more potent than taxol. Structure–activity studies will help to clarify the mode of action of this fascinating molecule. John Mann

John Mann is in the Department of Chemistry, University of Reading, Whiteknights, Reading, Berkshire RG6 2AD, UK.

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