Compton telescopes

A COMPTON telescope consists of two separate layers of scintillator material. The upper layer is a converter and tracker made from a low-atomic-weight material; the lower is an imager and calorimeter made from a high-atomic-weight material.

An incoming γ-ray Compton-scatters off one of the atomic electrons in the upper layer, changing its energy and direction. An energetic electron results from the process, and its energy is measured in the upper layer. The γ-ray goes on to the lower layer, where, ideally, it is absorbed, kicking out an even more energetic electron. The energy of the initial γ-ray is then the sum of the two electron energies, and their relative energies also constrain the source of the initial γ-ray to a circle on the sky. Measuring the track of the electron in the upper layer would reduce this circle to a point, tremendously improving the telescope's sensitivity and simplifying the overall analysis.

The next generation of Compton telescopes should be a least an order of magnitude better in sensitivity, angular resolution and energy resolution than anything flown in space before. P. L.

of the Galaxy can be measured by observing wavelength shifts in bright ^{26}Al sources.

One new satellite is already planned: INTEGRAL will be launched in the year 2001 on a two- to five-year mission (J. Matteson, Univ. California, San Diego). It will carry out high-resolution spectroscopy and imaging in the 15-keV to 10-MeV range. The coded-aperture-mask instruments on INTEGRAL are just about as sensitive as such instruments can be at these energies, but on the aforementioned questions many feel that they will only tease us.

At the meeting, there was a consensus that we should build a large Compton telescope (see box) at least ten times more sensitive than COMPTEL or INTEGRAL, and somehow squeeze it into a Medium-class Explorer (MIDEX) mission to be launched in the next five years. (NASA's goal is to launch roughly one MIDEX per year, each costing less than $100 million.) This is a challenge, but the new technologies presented at the meeting have the potential to meet it. □

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DRUG DEVELOPMENT

Myxobacterial bounty

John Mann

THE pre-eminence of taxol* as the cytotoxic drug sensation[1,2] of the 1990s is about to be challenged by a new natural product — epothilone A. The structure of this novel compound from the myxobacterium *Sorangium cellulosum* was only reported[3] in July last year, but already two groups have completed total syntheses[4,5].

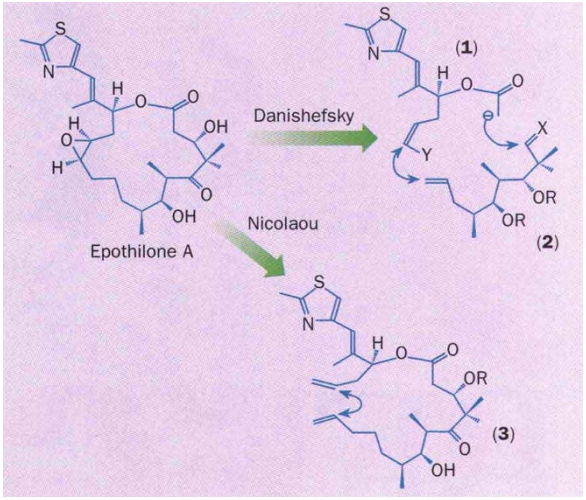
The alacrity of the response to this synthetic target was prompted by the intriguing similarity between the biological activities of taxol and epothilone A — they both stabilize microtubule assemblies and thus inhibit cell division. They apparently share a common receptor on microtubules, and at least *in vitro* have almost identical cytotoxic activities. In addition, the structure of epothilone is much simpler than that of taxol, because it has seven stereogenic centres altogether (taxol has eleven), and only one macrocyclic ring (four separate rings in taxol).

The two new synthetic strategies are entirely different, but both involve ambitious chemistry. Danishefsky and colleagues[4] prepared the two fragments **1** and **2** (see figure), then coupled the two alkenes via a Suzuki carbon–carbon-bond cross-coupling reaction. They then used the enolate derived from the methyl group of the acetate of fragment **1** to react with a terminal aldehyde of fragment **2**. This macroaldolization, and the subsequent epoxidation to form epothilone A, have a remarkably high stereoselectivity.

Nicolaou and colleagues[5], in contrast, produced the large intermediate **3** from three smaller fragments, and then produced the key carbon–carbon double bond using a ruthenium-catalysed alkene metathesis process that his group had already developed[6]. Once again, epoxidation completed the sequence. Of the two routes, the latter is marginally shorter and also requires less protection of functional groups. Other research groups are also hot in pursuit of this synthetic target; for example, Schinzer *et al.*[7] have reported a concise synthesis of key intermediates that should allow access to epothilone.

So is this intense synthetic activity justified? The answer would appear to be 'yes'. Epothilone A is 2,000–5,000 times more active than taxol *in vitro* against certain cancer cell lines that have multiple drug resistance[8]. But the two real bonuses are its water solubility (about 30 times greater than taxol), and its "almost unlimited availability by fermentation of a technical culture medium"[9]. Although taxol can be obtained from the bark of the Pacific yew, the tree grows extremely slowly so this supply is not viable. A related natural product, 10-deacetyl baccatin III, can be obtained from the needles of the European yew, and converted into taxol in four chemical steps. This still means that taxol is an expensive drug. It is likely that epothilone will be produced using fermentation technology, and the chemistry discovered during the total syntheses will be used to prepare semi-synthetic analogues with, one hopes, a better spectrum of activity.

If the compound proves to have good *in vivo* activity, it will become a very important addition to the armoury of cancer chemotherapy. Further, because the myxobacteria have been poorly investigated thus far, the discovery of epothilone offers a tempting glimpse of the treats that might be available from this section of nature's medicine cabinet. □



Routes to a total synthesis of epothilone A taken by Danishefsky's[4] and Nicolaou's[5] groups.

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*Bristol-Myers Squibb has registered Taxol as a trademark and wishes the scientific community to use the name paclitaxel.

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