The isolation, total synthesis, and mechanism of action of neopeltolide, a cytotoxic marine macrolide.

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December 2, 2008

Marine natural products provide an important source of bioactive molecules which can serve as leads in the drug discovery process. Sponges of the order Lithistida, in particular, have proven to be a plentiful source of potential therapeutic compounds which include the calyculins, the callipeltosides, and the callipeltins. Among these compounds is neopeltolide, a marine macrolide isolated from a deep-water sponge off the coast of Jamaica. Initial biological testing revealed neopeltolide to possess highly potent antiproliferative activity in the low nanomolar range. The natural product was also shown to inhibit fungal growth. Although certainly of interest because of the cytotoxic activity, neopeltolide posed an exciting challenge to synthetic chemists due to its structurally complex skeleton which includes a 14-member macrolactone, six stereocenters, and a side chain containing a conjugated oxazole. The first total synthesis of neopeltolide was reported concurrently by Karl Scheidt and James Panek and resulted in the stereochemical reassignment of the chiral centers at C-11 and C-13. Although there were insufficient quantities of the natural extract available to conduct extensive cellular testing, synthetically generated neopeltolide was used to study the molecular mechanism of action. Neopeltolide was found to inhibit the cytochrome bc1 complex, which is a key component of the mitochondrial electron transport chain. Recently, various analogs of neopeltolide have been synthesized. While none surpass the potency of the natural product, the studies suggest that it is the side chain which is most critical for maintaining activity.

References: