the desired natural product is often low and the extraction process can be time-consuming and complicated. Bacteria and fungi on the other hand are more adaptable for industrial production of natural products, but either proper cultivation protocols for the strains must be known or the biosynthesis of the compound of interest must be understood to allow for metabolic engineering or heterologous expression into strains which are easier to cultivate and manage. For marine life, their submersed environment allows for better compatibility with bioreactors and fermenters, but marine life sources have the same disadvantages as bacteria and fungi.

2.1 Recent Examples of Natural Products in Drug Discovery

As stated earlier, many big companies in the pharmaceutical industry have either downscaled or shut down their natural product research divisions, but what does this mean for the role that natural products play in current drug research? In an ambitious attempt to map out the effect natural product research has had on drug development, Newman and Cragg have written a series of extensive reviews where they investigate what percentage of all approved drugs from 1981 to 2010 are either natural products, natural product derivatives, or synthetic mimics of natural products (Newman and Cragg 2007, 2012). Although their research shows that the percentage of drugs with natural product origins to be approved indeed undergoes a steep decline from 40% in 1994 to 12% in 1997, they also show that in the following years, this percentage steadily increases again, varying between 24 and 45%, with a peak at 50% in 2010.

Because much has already been written on well-known natural product drugs like Taxol and the β-lactams, we will only focus on more recent examples. For an extensive overview, the reader is directed to the books, e.g., "Molecules that changed the World" (Nicolaou and Montagnon 2008).

2.1.1 Plants

Ingenol Mebutate (Picato®)

Ingenol mebutate (**3**, Fig. 2) is a new small-molecule (430.5 Da) diterpene ester which has been approved in 2012 for the treatment of actinic keratosis. Ingenol mebutate is an unmodified natural product isolated from the plant species *Euphorbia peplus*. This plant has a long history of being used in traditional herbal remedies to a variety of ailments, including skin cancers and keratosis (Weedon and Chick 1976). Component extraction research of this plant resulted in the identification of a number of diterpene esters which all were capable of producing an inflammation reaction, of which ingenol mebutate was identified as the cytotoxic compound (Rizk et al. 1985). It exerts its mechanism of action by targeting mitochondria. It was demonstrated that mitochondria begin to swell after exposure to ingenol mebutate. Due to this swelling, the mitochondrial membrane potential is lost, effectively shutting down the available energy within the cell due to a depletion