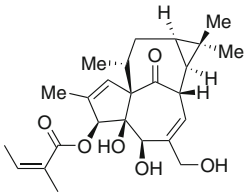

3

Fig. 2 Structure of cytotoxic natural product ingenol mebutate (**3**)

of ATP. This then ultimately leads to necrosis of the cell (Ogbourne et al. 2004). Because of this mechanism, the chances of tumors developing resistance are low since most tumor drug-resistance genes expressed are apoptose-resistant genes (Ivanov et al. 2003). Besides mitochondrial swelling, ingenol mebutate also binds to protein kinase C, activating the associated signaling pathway. This activation triggers an inflammation reaction and subsequent elimination of residual tumor cells by antibodies (Kedei et al. 2004).

It is possible that in the near future, ingenol mebutate will be approved for other types of skin cancer, as the drug is also under clinical evaluation for superficial basal cell carcinoma (Siller et al. 2010). While the first total synthesis was published in 2002 (Winkler et al. 2002), a highly efficient total synthesis was published recently, which could possibly be more favorable than the current biotechnological production methods (McKerrall et al. 2014).

2.1.2 Terrestrial Fungi

Statins: Mevastatin and Lovastatin

An important and almost classical group of medication from fungal origin is the statins (Fig. 3). The statins originate from two natural compounds: mevastatin (**4**) and lovastatin (**5**). Mevastatin was isolated from *Penicillium citrinum* (Endo et al. 1976), and lovastatin was isolated from *Monascus ruber* (Endo and Monacolin 1979). Although mevastatin and lovastatin are structurally very similar, clinical development of mevastatin was discarded (Endo 2004), while clinical development of lovastatin continued and as a consequence lovastatin was the first statin to be approved. Soon thereafter, the semisynthetic derivatives simvastatin (**6**) and pravastatin (**7**) were developed and approved. Their introduction has had an enormous impact on treatment of cardiovascular diseases, and the statins are among the most-prescribed drugs worldwide. The statins exert their mechanism of action through the inhibition of hydroxyl-methylglutaryl coenzyme A (HMG-CoA) reductase. The inhibition of this enzyme prevents the conversion of HMG-CoA into mevalonic acid, thereby disrupting the mevalonate pathway which is responsible for the biosynthesis of cholesterol (Alberts 1988). As high cholesterol levels are associated with coronary heart disease (Lewington et al. 2007), the reduction of cholesterol levels significantly reduces the chances of a heart attack or stroke (Law et al. 2003).