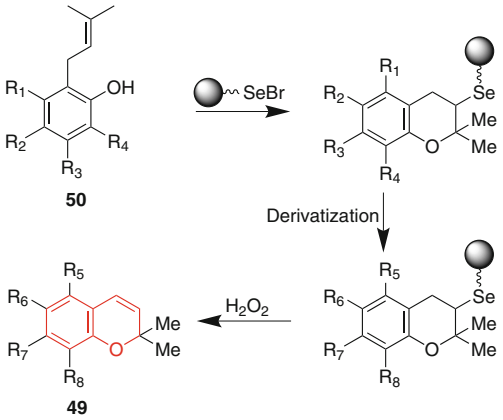

Fig. 27 Combinatorial approach to build a large library of natural-product-like compounds. Starting from butylenephenol **50**, the immobilized privileged scaffold are constructed on solid support and allow for the rapid generation of a large amount of variants containing the benzopyran moiety (indicated in *red*), which could be isolated by oxidative cleavage of the selenium-containing resin

By constructing privileged scaffolds on a solid support and then using combinatorial chemistry, various research groups have successfully built up libraries. Due to the large amount of research interest this topic has generated over the years, only a couple of examples will be discussed here.

A tremendous effort has been made by the Nicolaou group, who decided to build a library around the 2,2-dimethylbenzopyran (**49**) moiety. By attaching butylenephenol **50** to an oxidation-labile solid support, the privileged scaffold could be constructed, after which the residual groups were modified by exchanging functional groups or coupling additional fragments. This approach ultimately led to the construction of a library consisting of more than 10,000 different natural product-like compounds (Fig. 27) (Nicolaou et al. 2000).

In another example, privileged scaffolds were used by the Hergenrother group as starting point for a DOS approach, using so-called ring distortion reactions to generate new natural product-like scaffolds, in a concept they named "complexity to diversity" (CtB) approach (Huigens III et al. 2013). This idea is illustrated in Fig. 28. Starting from the natural steroid adrenosterone (**51**), five different scaffolds were synthesized in three to five stereoselective reactions in solution. These scaffolds were in turn further derivatized to yield a small library of structurally diverse and complex molecules. Using the same approach starting from the natural products gibberellic acid, quinine and abietic acid (Rafferty et al. 2014), a highly diverse and structurally complex library was attained.