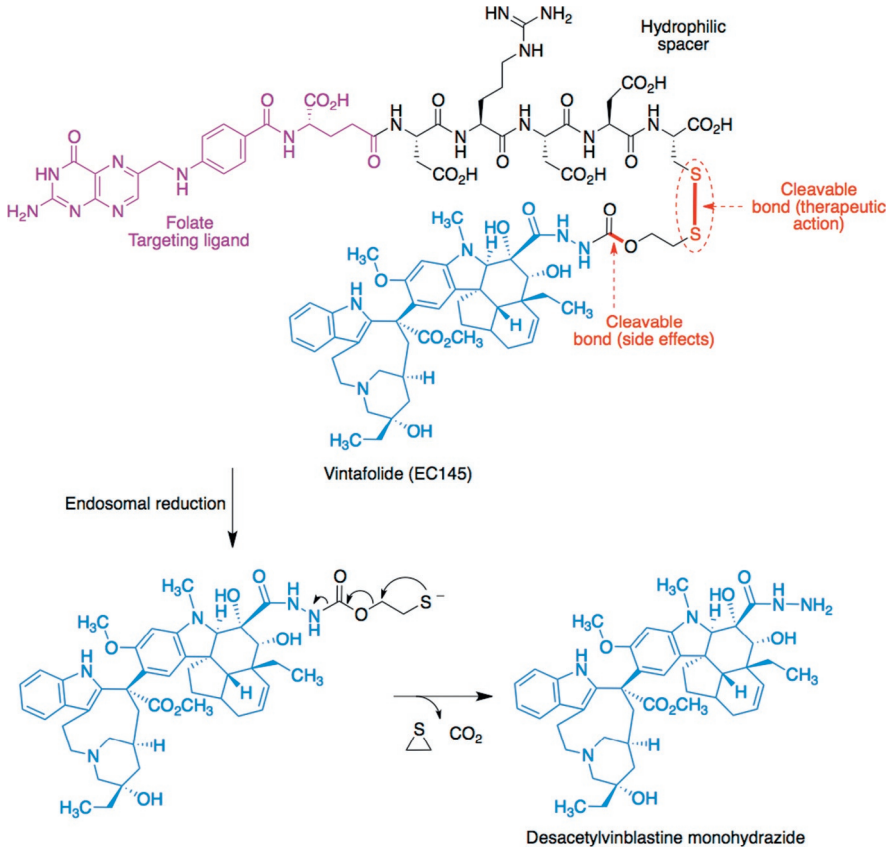

FIGURE 13.38

Structure and bioactivation of vintafolide.

Among folate–drug conjugates that have reached clinical trials vintafolide (EC-145) is a water-soluble, folate-targeted conjugate of a *Vinca* alkaloid developed as a treatment for patients with FR^+ cancers, such as platinum-resistant ovarian cancer.[81] The bioactivation of this compound is initiated by reduction of the disulfide bond between the cysteine units of the spacer and the linker, which takes place in the endosome formed in the endocytosis process through a mechanism that is not completely understood. The release of the active species occurs via a self-immolative process that transforms the linker into a molecule of thiirane (which is later hydrolyzed to 2-mercaptoathanol) and another of carbon dioxide (Figure 13.38).[82]

Constipation was identified as the dose-limiting toxicity of vintafolide during a phase I trial. The origin of this problem was the release of unconjugated vinca alkaloid to the bile following hepatic hydrolysis of the carbamate moiety that connects the alkaloid to the spacer, which led to the development of analogs with an increased hydrolytic stability (see the discussion of EC0489 below).