Captothecin 1 was first isolated by Wall and Wani in 1966. Captothecin and its derivatives have been identified as promising agents for the treatment of solid tumors by chemotherapy. They act by interfering with the enzyme topoisomerase I, which is over expressed in malignant cells and is involved in the unwinding of supercoiled DNA. A ternary complex is formed with topoisomerase I, DNA and camptothecin, triggering a cascade of events leading to apoptosis and programmed death.

In 1999, Curran et al. published a synthesis of captothecin 1 which allowed for the synthesis of a range analogues via a common late stage intermediate. It is Curran’s synthesis which we will discuss today.

**Question 1.** Follow the synthesis of captothecin 1 filling in the blanks for the intermediates and reagents. Give mechanisms for each step and discuss any issues of selectivity.
From intermediate 10, a range of analogues were synthesised. One of them was (+)-irinotecan 12, a derivative of camptothecin 1. Irinotecan 12 shows higher water solubility than camptothecin 1 and is used in several countries for cancer therapy.

**Question 2.** Fragment 13 is used in the synthesis of irinotecan 12. Again, fill in the blanks in the scheme shown below.

**References**