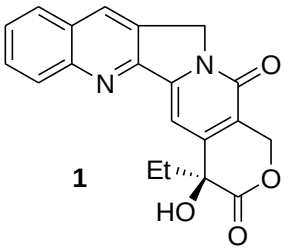
Problem Session – 27/09/2009 – Set by Sarah Warren

D. P. Curran's Synthesis of Captothecin

Captothecin **1** was first isolated by Wall and Wani in 1966[1]. Captothecin and its derivatives have been identified as promising agents for the treatment of solid tumors by chemotherapy[2]. 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[3]. 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[4]. It is Curran's synthesis which we will discuss today.



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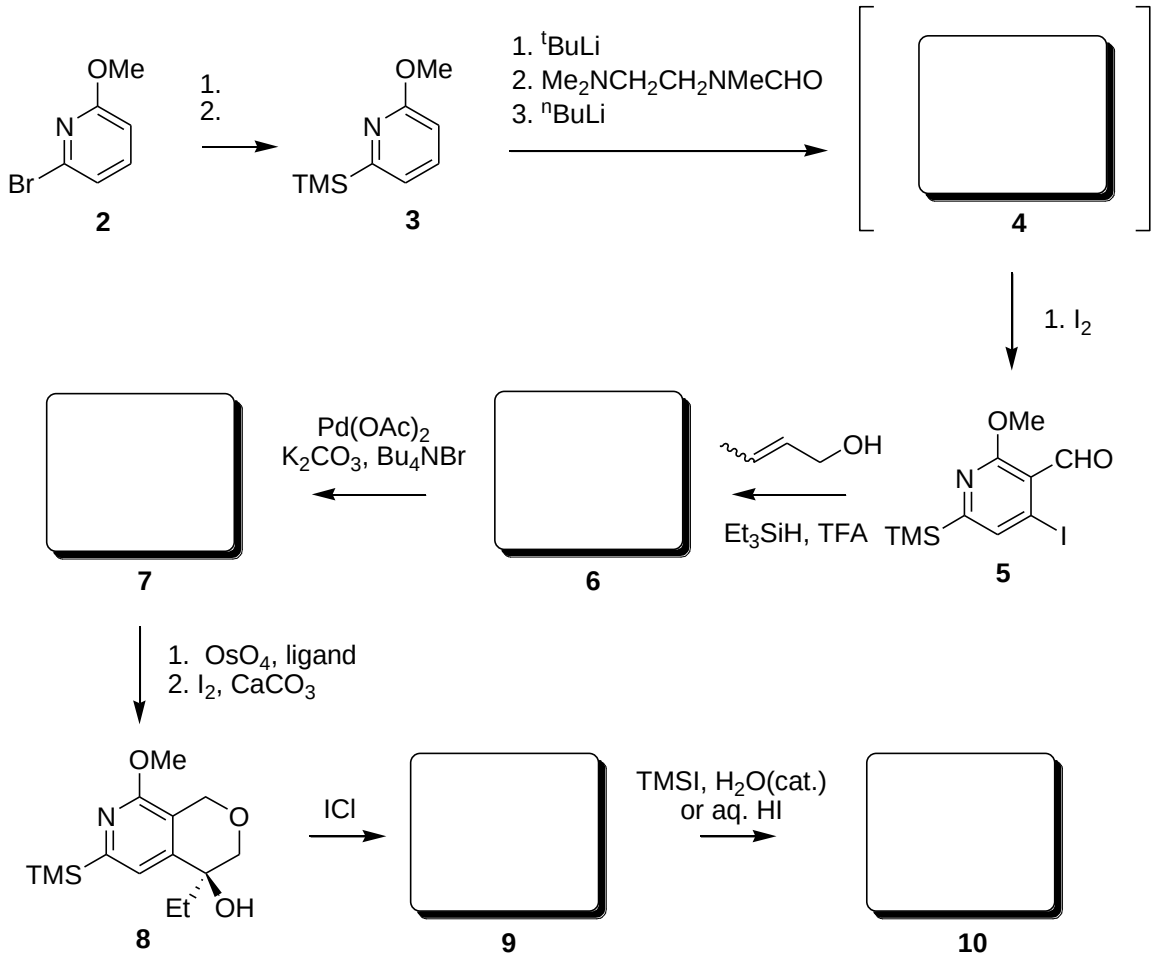
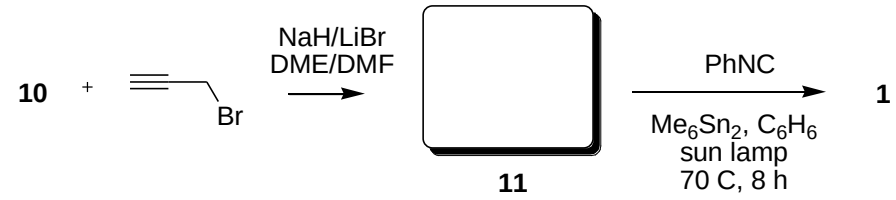
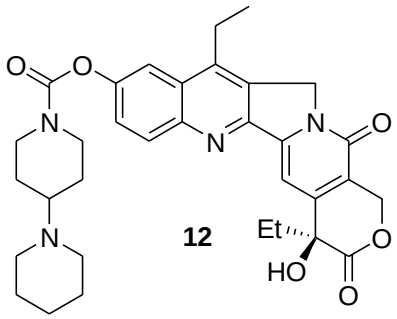
Question 1. Follow the synthesis of captothecin **1** filling in the blanks for the intermediates and reagents. Give mechanisms for each step and discuss any issues of selectivity.

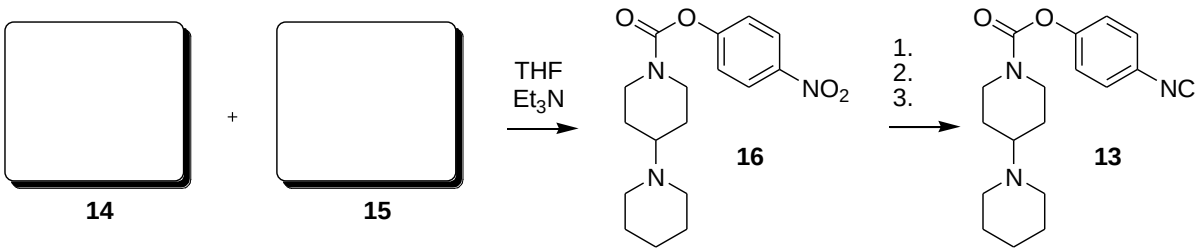




From intermediate **10**, a range of analogues were synthesised. One of them was (+)-irinotecan **12**, a derivative of camptothecin **1**. Irinotecan **12** shows higher water solubility than camptothecin **1** and is used in several countries for cancer therapy.



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



References

1. M. E. Wall, M. C. Wani, *J. Ethnopharmacol*., **1996**, *51*, 239.
2. J. Bonneterre, *Bull. Cancer*, **1995**, *270*, 21429.
3. Y. Pommier, G. Kohlhagen, K. W. Kohn, F. Leteurtre, M. C. Wani, M. E. Wall, *Proc. Natl. Acad. Sci. USA*, **1995**, *92*, 8861.
4. H. Josien, S.-B. Ko, D. Bom, D. P. Curran, *Chem. Eur. J*., **1998**, *4*, 67-83.