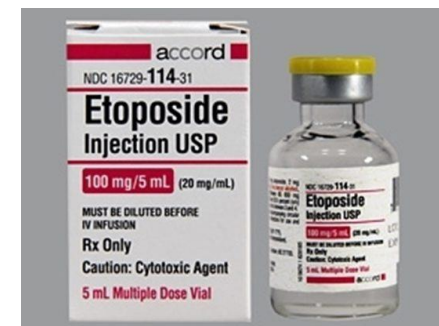
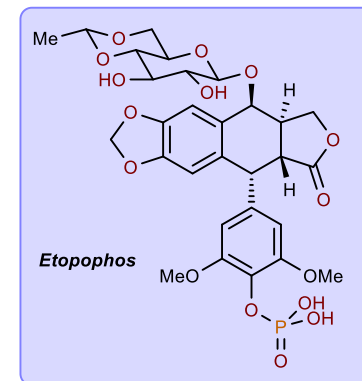
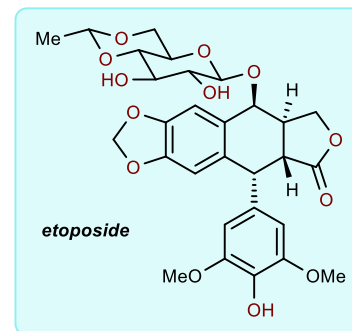
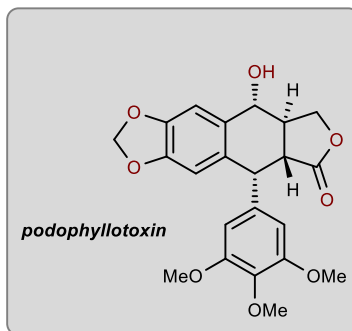
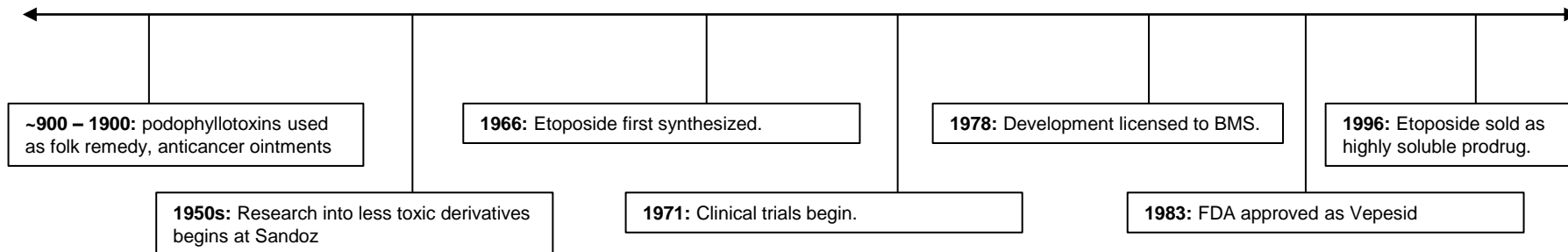


## Introduction

- A decades-old chemotherapeutic lignan glycoside
- Derived from podophyllotoxin, isolated from the roots of the wild mandrake
- Used to treat leukemia, lymphoma, lung cancer, ovarian cancer, and testicular cancer
- Poor water solubility causes large IV volumes, spurred prodrug development of Etopophos
- Side effects may include:
  - Hair loss
  - Low blood pressure
  - Diarrhea
- Low isolation yields and increasing global demand has led to shortages, concise synthesis needed!

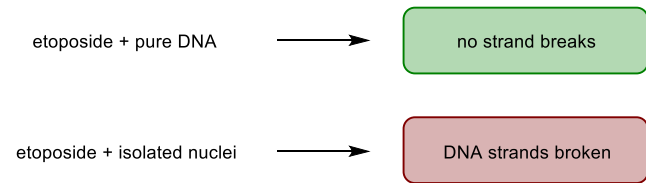


## Historical Development

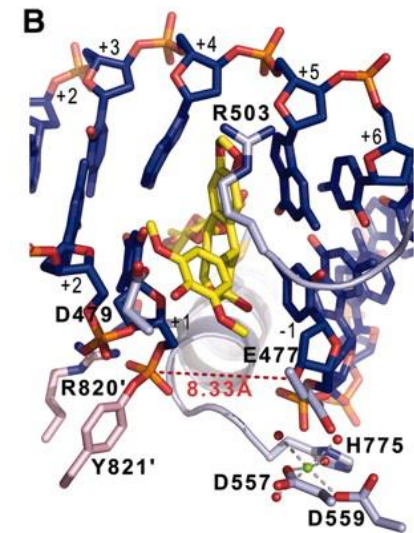
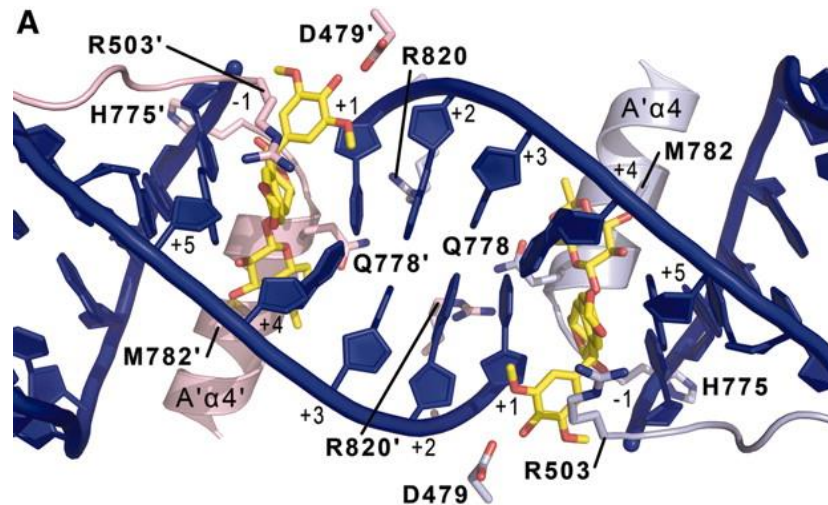
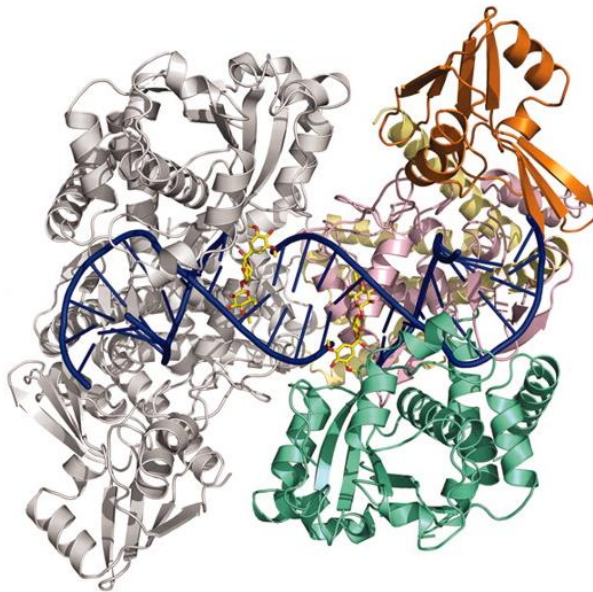


## Mechanism of Action

- A non-intercalating Topoisomerase II (TopII) poison
- Interferes with DNA organization by forming a ternary complex with TopII and DNA, preventing reassembly
- “Holds open” DNA strands and makes TopII enzymes cause more DNA breaks than they can repair
- As broken DNA dissociates and accumulates, apoptosis results
- Related intercalating TopII poisons include anthracyclines like doxorubicin and idarubicin



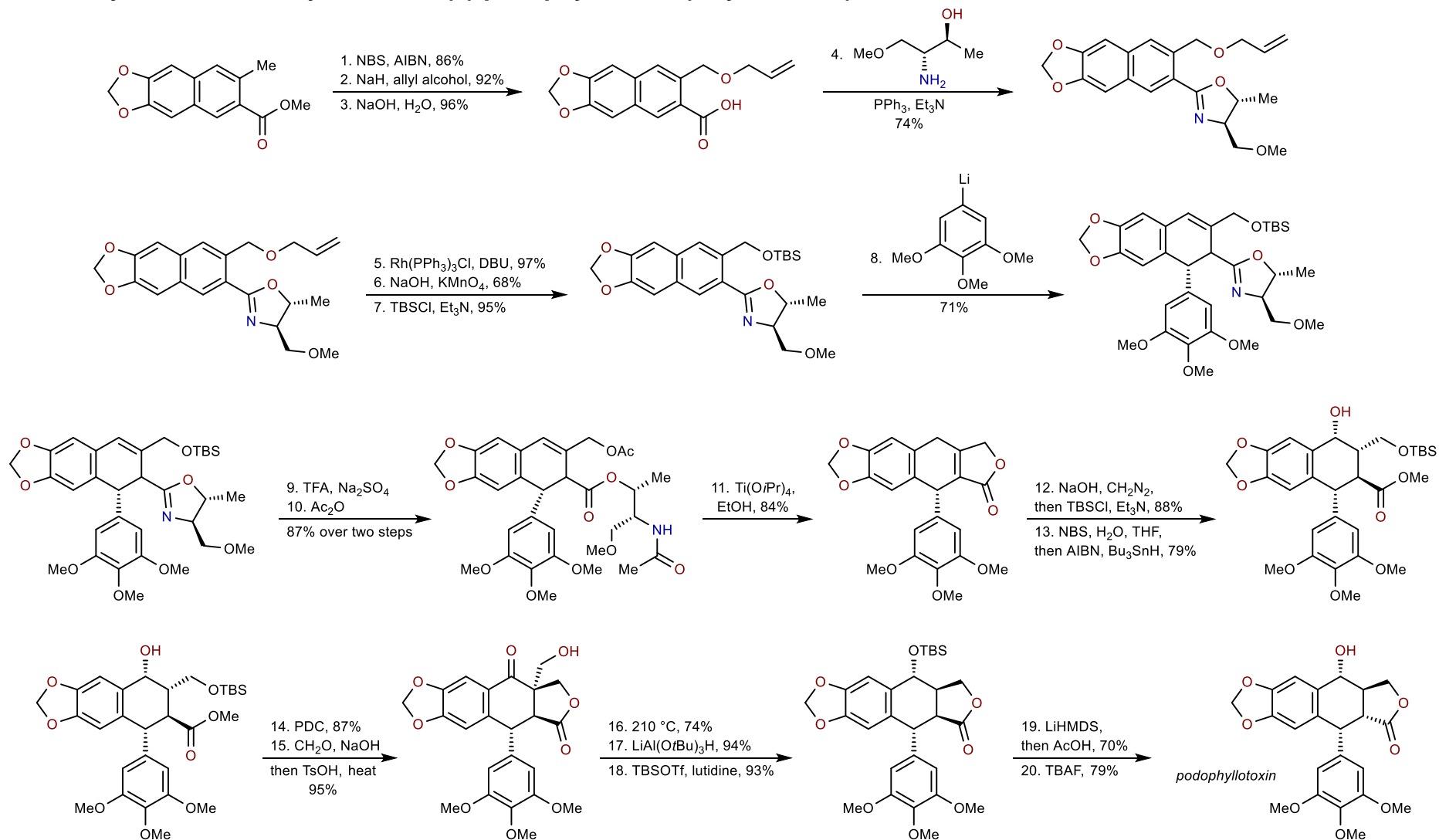
Hande, K. R. *Eur J Cancer* **1998**, *34*, 1514. [https://doi.org/10.1016/S0959-8049\(98\)00228-7](https://doi.org/10.1016/S0959-8049(98)00228-7)



- Crystal structure of a TopII – DNA cleavage complex stabilized by etoposide

Chan, N.-L. *Science* **2011**, *333*, 459. <https://doi.org/10.1126/science.1204117>

## First Asymmetric Total Synthesis of (-)-podophyllotoxin (Meyers, 1988)



5% overall yield  
poorly scalable  
inefficient

## Industrial Semisynthesis

