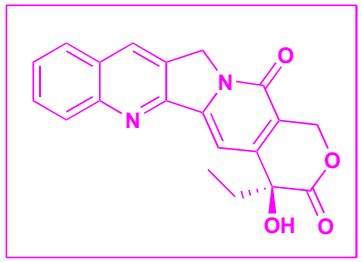
Reviewing Camptothecin

Ke Chen



Name	**Camptothecin**
IUPAC name	**4-ethyl-4-hydroxy-1H-pyrano[3',4':6,7] indolizino[1,2-b]quinoline-3,14-(4H,12H)-dione**
CAS number	**7689-03-4**
Formula	$C_{20}H_{16}N_2O_4$
Mol. mass	**348.352 g/mol**

This quinoline based alkaloid was found in the bark of the Chinese camptotheca tree.

Camptotheca goes by many names in China, including "happy tree", "dragon tree" and "fine tree".

Chinese have used the "happy tree" in traditional medicine for thousands of years. It has been used for psoriasis, leukemia and diseases of liver, gallbladder, spleen, and stomach.

During the last half century, scientists have discovered its potential as a selective anticancer drug.

The unique mode of action for this potent cytotoxic compound was found to act via inhibition of an enzyme known as DNA topoisomerase I.

In Fig 1, normally, topoisomerases I introduces a nick in the DNA backbone allowing the rotation of one strand around another. This releases the torsional strain which otherwise accumulates in front of the advancing replication fork (the large arrow). The DNA break is extremely transient and is religated as it release the other strand.

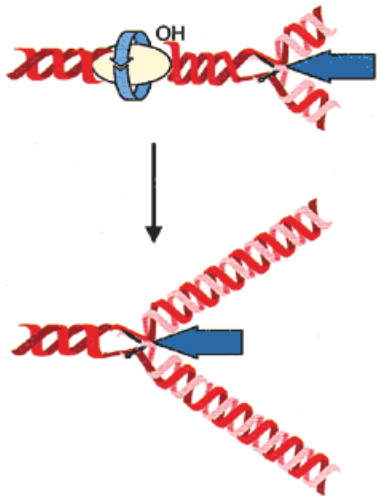


Fig 1

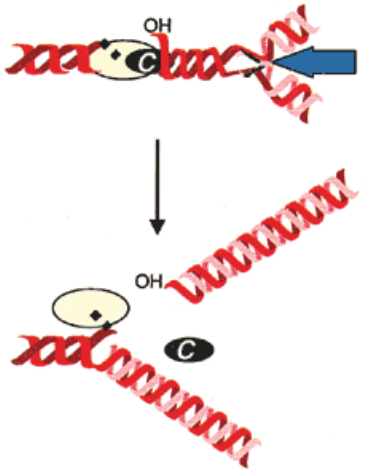


Fig 2

In Fig 2, when camptothecin is present(black oval with C), it binds to the topoisomerase I-nicked DNA complex. This prevents the religation of the nicked strand and the release of the enzyme. Eventually, the replication fork collides with the complex, causing the formation of a double-strand break.

Hsiang, Y.H. *Cancer Res.* **1989**, *49*, 5077.

Discovering Camptothecin

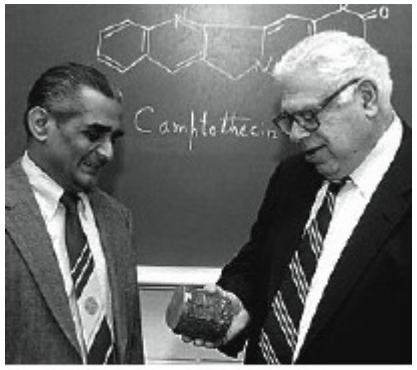
Ke Chen

Monroe Wall (left) and Mansukh Wani (right) observe a beaker of Camptothecin dissolved in chloroform and methanol as it fluoresces in UV light.

Monroe E. Wall (1916–2002)

Born in 1916 in Newark, NJ, Dr. Wall received his B.S., M.S., and Ph.D. degrees from Rutgers University. In 1941, he joined the United States Department of Agriculture. From 1941 to 1960, Dr. Wall gained national recognition as a government scientist in steroid chemistry. In 1960, Dr. Wall joined the Research Triangle Institute (RTI) to start a chemistry research group. He became RTI Vice President of Chemistry and Life Sciences in 1971. Among numerous contributions to the field of natural product research, he is best known for the discovery and development of taxol and camptothecin. In 1981 He retired from administration and devoted his time to research until two weeks before his death at 85.

Monroe Doctrine: "Get good people, support them with good facilities, do good science, work hard, and keep doing it."



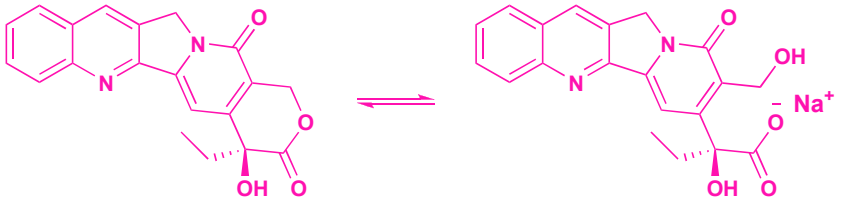
Mansukh Wani (left) and Monroe Wall (right).

Mansukh C. Wani

Born in Nandurbar, India, Dr. Wani received his B.S. and M.S. degrees from the University of Bombay. He came to the United States and finished his Ph.D in chemistry at Indiana University under the instruction of Professor Ernest Campaign. After a postdoctoral fellowship at the University of Wisconsin-Madison, he accepted a position at RTI from Dr. Wall in 1962. Together they developed two of the most promising anticancer agents, taxol and camptothecin., which are benefiting millions of people all over the world. Dr. Wani is still active at RTI, supervising junior researchers.

Timeline of Camptothecin:

1960-1966 **Isolation of active compound from amptotheca acuminata; determination of structure of camptothecin**



low solubility in water **water-soluable but inactive**

Clinical trials started in the 1960s but were abandoned shortly thereafter.

1985 **Determination of mechanism of action of camptothecin**

After Camptothecin returned, like " the phoenix from the ashes", it rekindled interest in developing analogs of camptothecin that were both water soluble and retained anticancer activity

1996 **FDA approval of two analogs of camptothecin for treatment of ovarian, lung, breast and colon cancer.**

Some numbers and facts...

11729 publications regarding "camptothecin".

114 publications involving total or formal synthese of camptothecin and its derivatives.

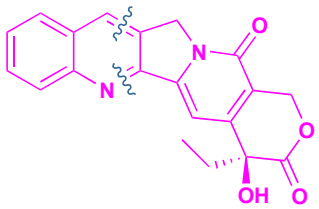
By 2001, the analogs developed included Pharmacia's Camptosar and GlaxoSmithKline's Hycamtin, collectively reporting worldwide sales approaching $ 800 million.

Synthetic chemists embrace practility and perfection.

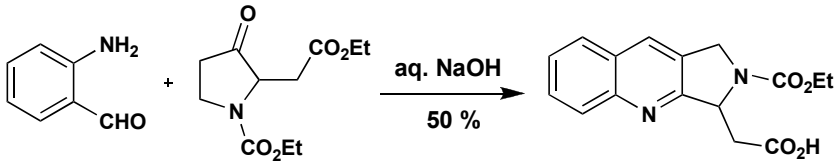
Camptothecin: From Bench to Bedside

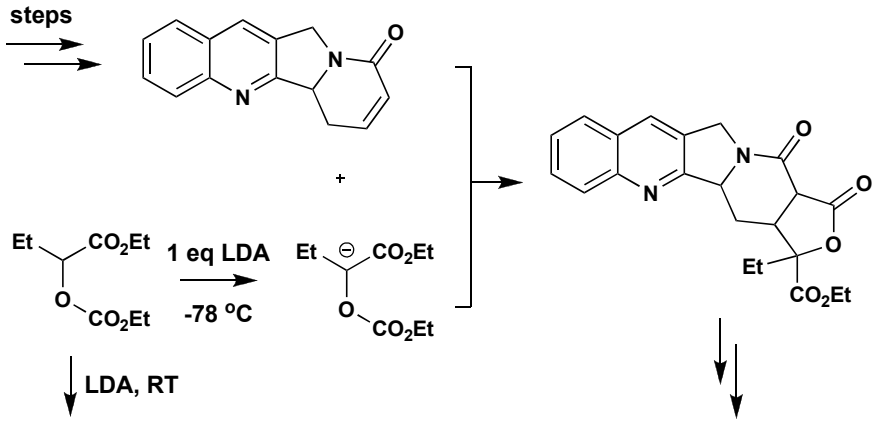
Ke Chen

Classical condensation



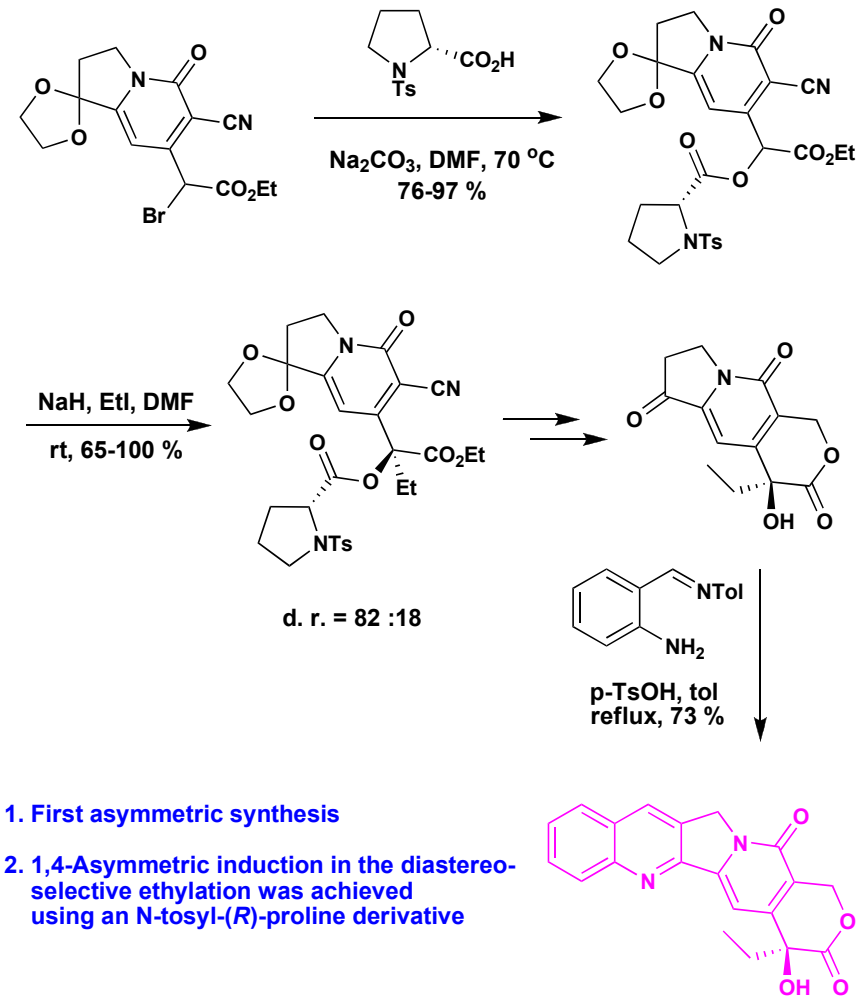
Friedlander quinoline synthesis





1. First synthesis reported
2. One of the key steps involves the annulation of an ester carbonate and unsaturated lactam

Stork G., Schultz A. G. *J. Am. Chem. Soc.* **1971**, *36*, 4074-4075.



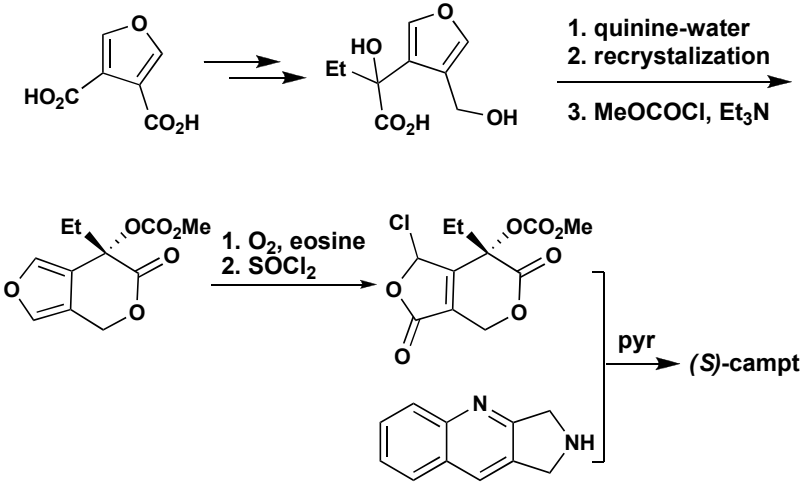
1. First asymmetric synthesis
2. 1,4-Asymmetric induction in the diastereo-selective ethylation was achieved using an N-tosyl-(*R*)-proline derivative

Tagawa H. *Tetrahedron Lett.* **1989**, *30*, 2639-2640.

Camptothecin: From Bench to Bedside

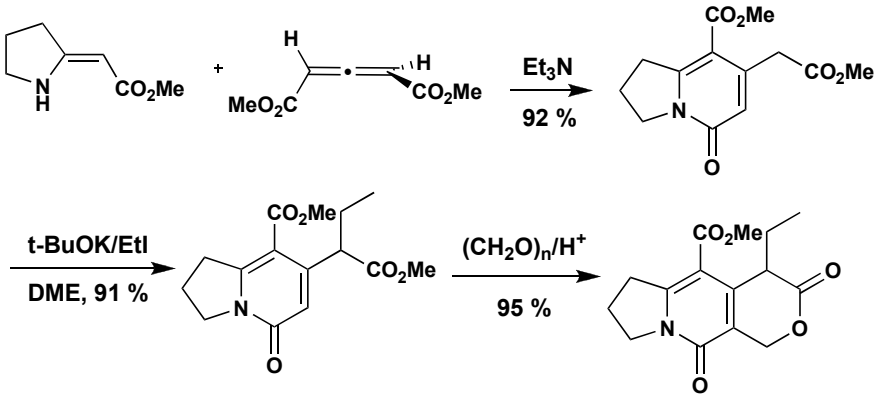
Ke Chen

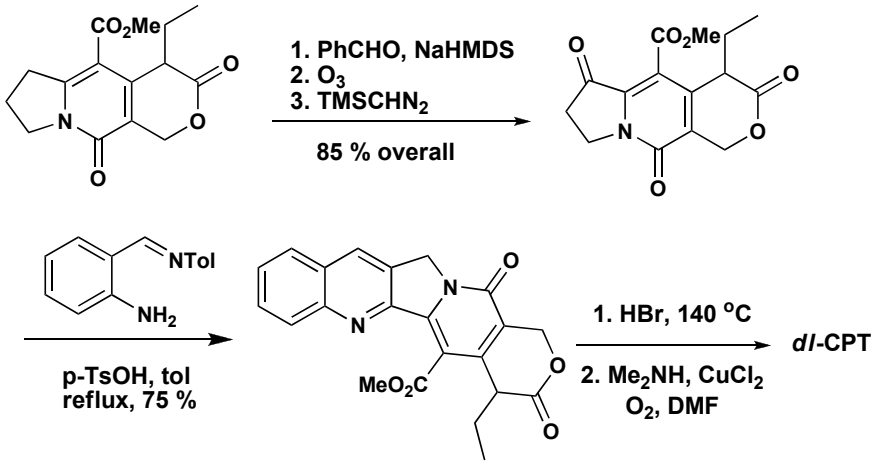
Classical condensation



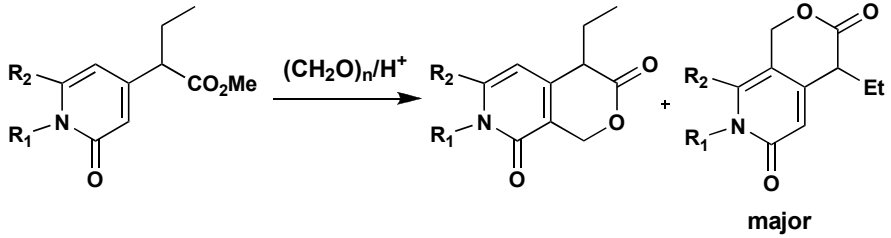
Corey E. J. *J. Org. Chem.* **1975**, *40*, 140-2141.

Friedlander quinoline synthesis

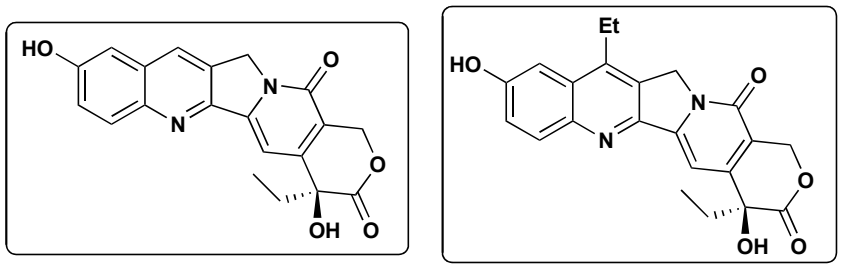




Danishefsky S. J. *J. Org. Chem.* **1993**, 58, 611-617.
Danishefsky S. J. *J. Am. Chem. Soc.* **1971**, 93, 5575.



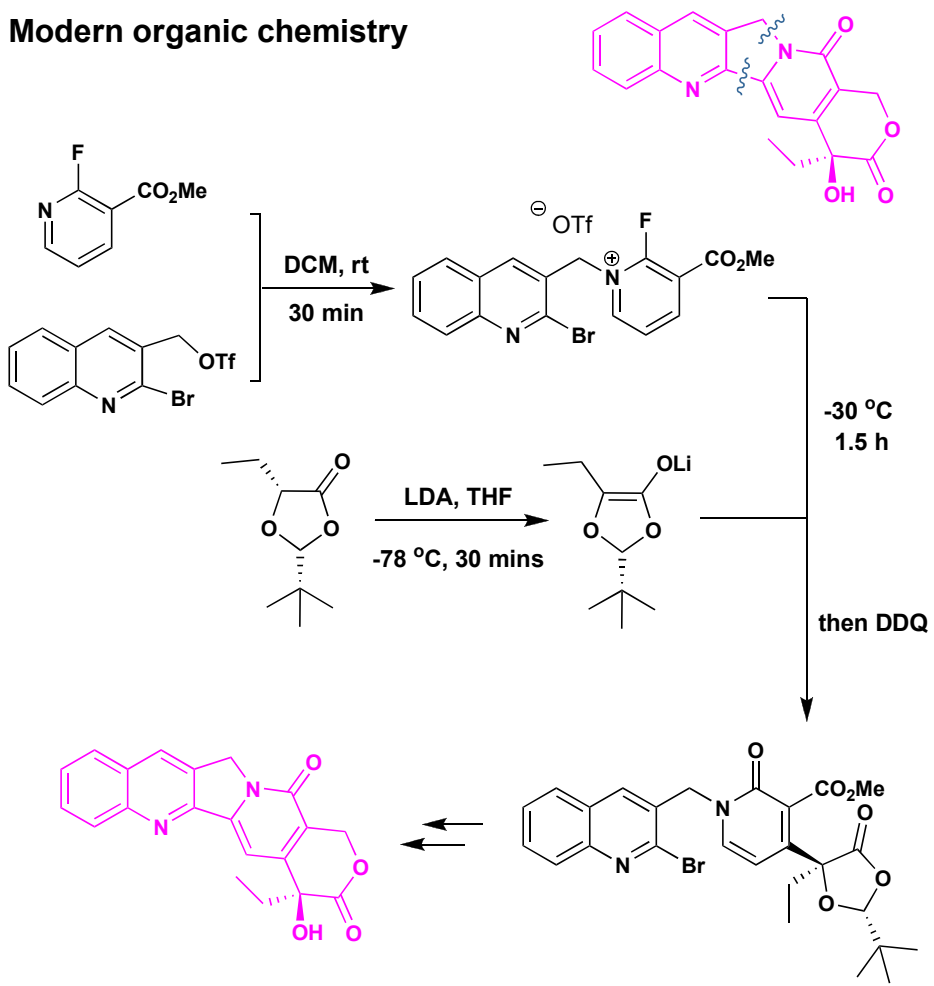
Two analogs:



Camptothecin: From Bench to Bedside

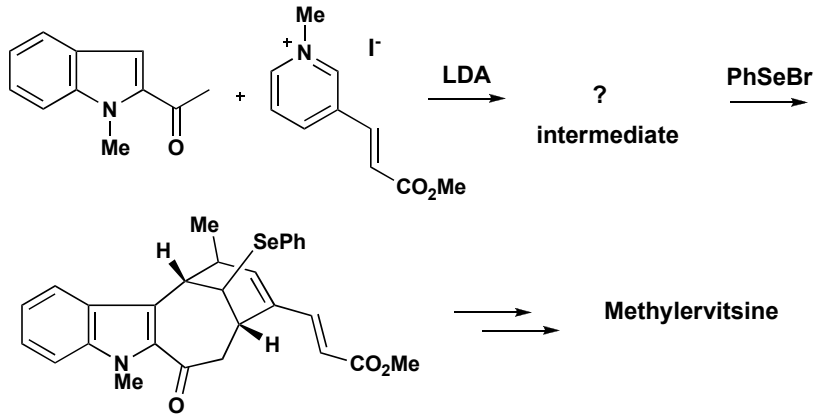
Ke Chen

Modern organic chemistry

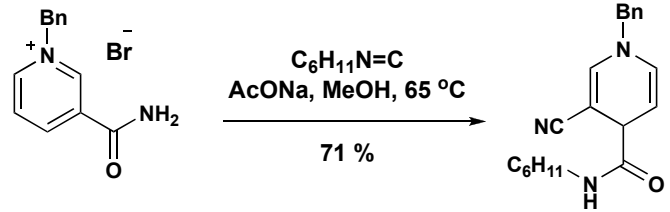


Bennasar M. L.. *J. Chem. Soc., Chem. Commun.* **2000**, 2459.
Bennasar M. L.. *J. Org. Chem.* **2002**, *67*, 7465.

Other recent applications of 1,4-addition to pyridinium salts



Bennasar M. L.. *J. Chem. Soc., Chem. Commun.* **1995**, 125.



Lavilla R. *Org. Lett* **2006**, *8*, 5789-5792.

Discovering Camptothecin

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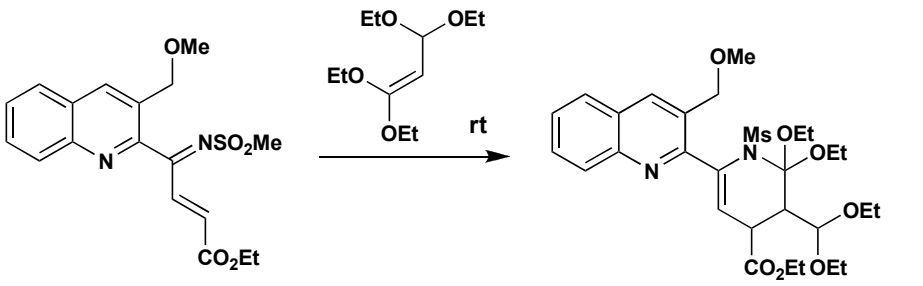
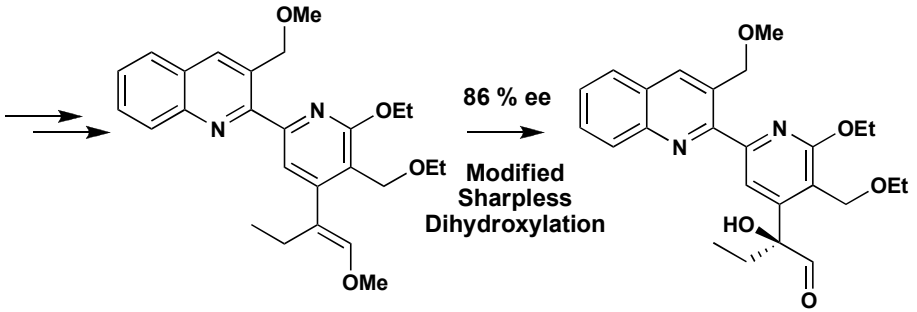
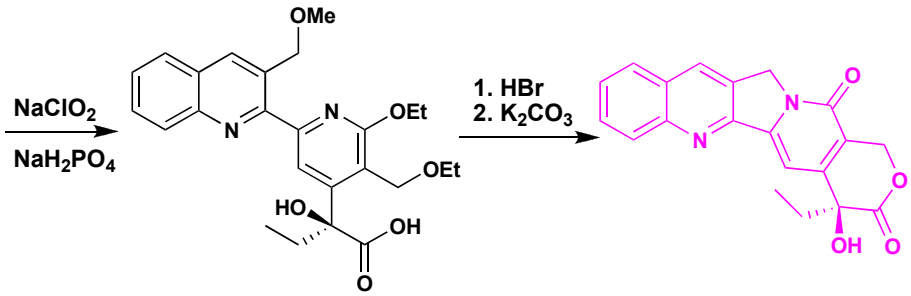
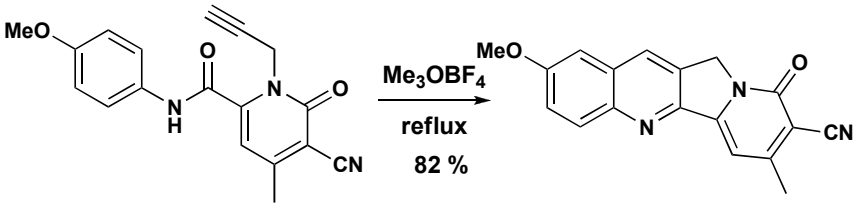
Diels-Alder Reaction:



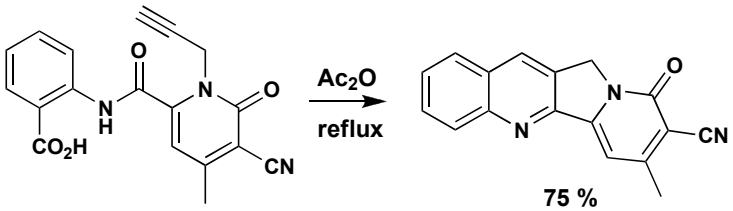


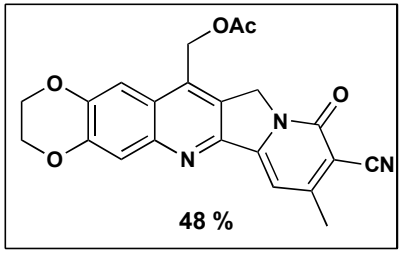


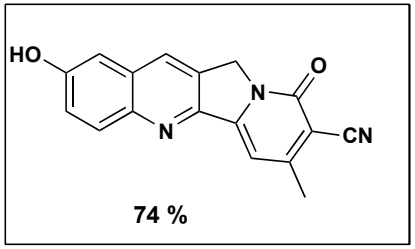
Boger, D. L.. *Tetrahedron* **2002**, *58*, 6343.



Revised alternative:





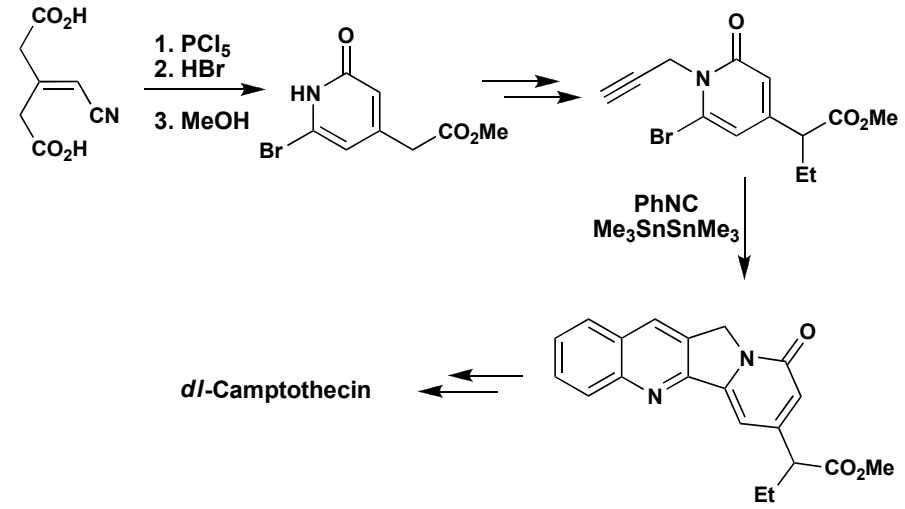


Fortunak J. *Tetrahedron Lett.* **1996**, *37*, 5679-5682.

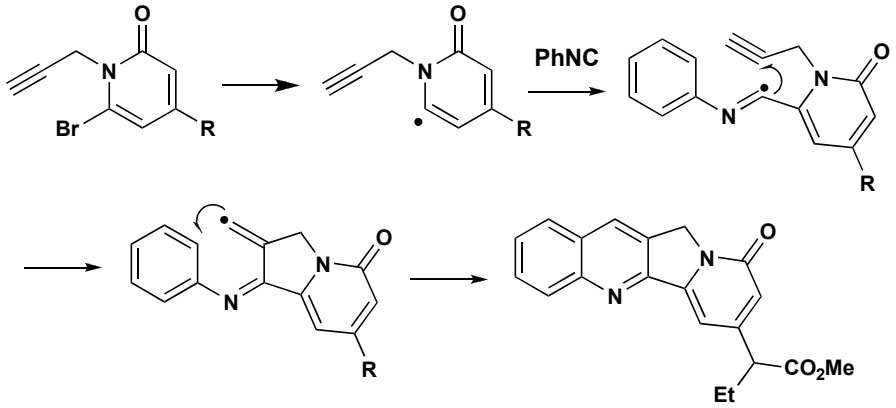
Camptothecin: From Bench to Bedside

Ke Chen

[4+1] Radical Annulation:

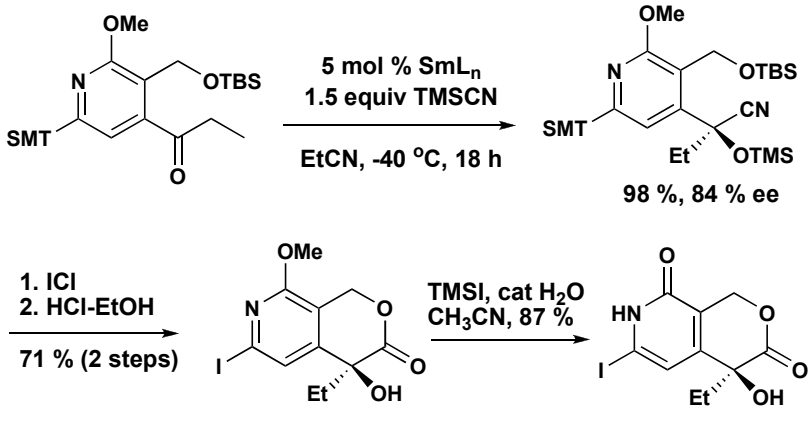


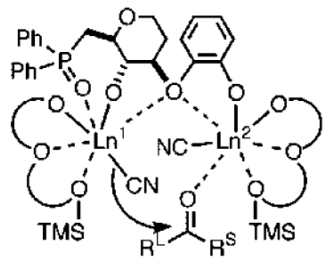
Over 100 derivatives of camptothecin have been prepared by Dr. Curran's research group utlizing this approach.



Curran D. P. *J. Am. Chem. Soc.* **1992**, *114*, 5863-5864.

Curran and Shibasaki:

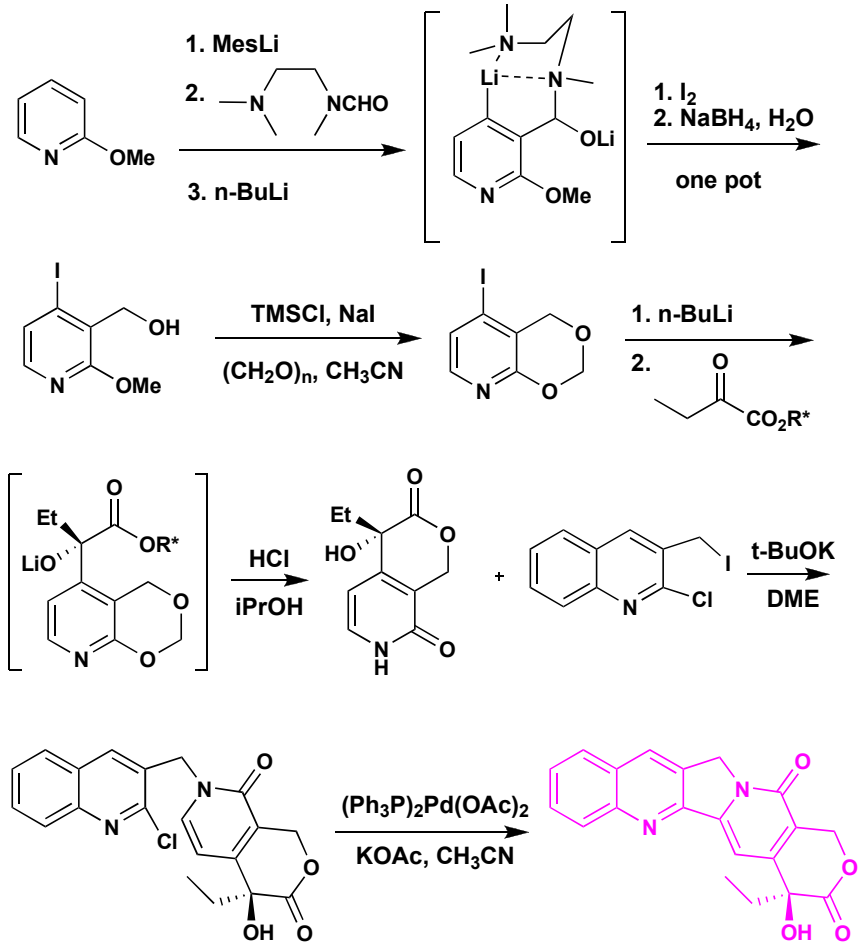




Shibasaki M.; Curran D. P. *J. Am. Chem. Soc.* **2001**, *123*, 9908-9909.
Shibasaki M. *J. Am. Chem. Soc.* **2000**, *122*, 7412-7413.

Camptothecin: the Future

Ke Chen

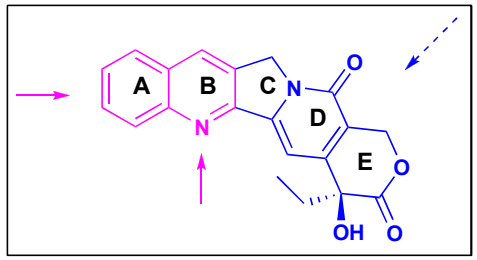


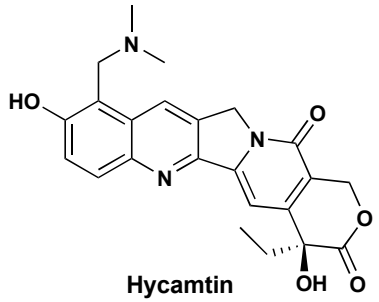
This remains the most efficient route reported (six steps, 12.5 % overall yield).

Scientists from GSK are utilizing this approach to synthesize analogs of CPT.

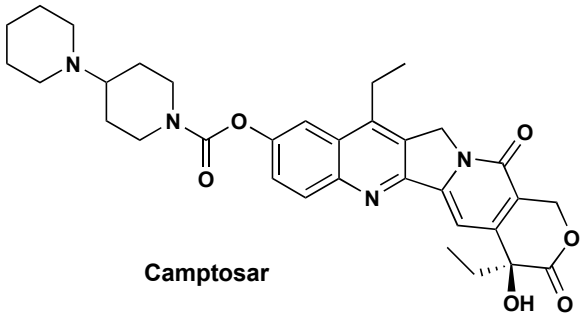
Comins D. L. *Org. Lett* **2001**, 3, 4255-4257.

Structure-Activity Relationships:





Hycamtin



Camptosar

10 additional CPT derivatives in various stages of clinical trials

"Trees hold the answer to saving the planet. Scientists are discovering more remarkable facts about trees, forests and animal interactions than ever before. The work of these scientists is immeasurably protecting humanity and all life, now and into the future."

Reese Halter