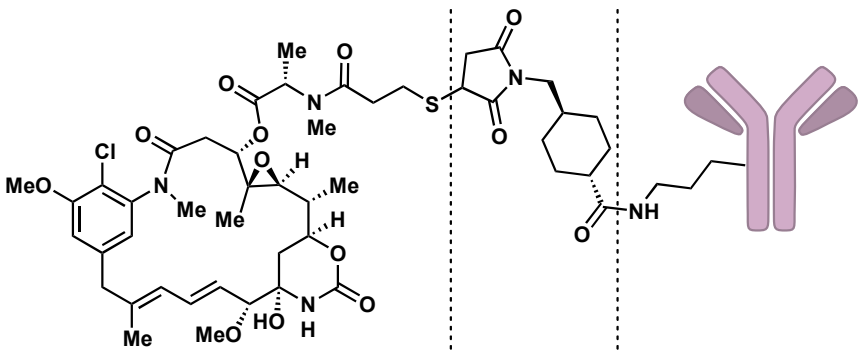
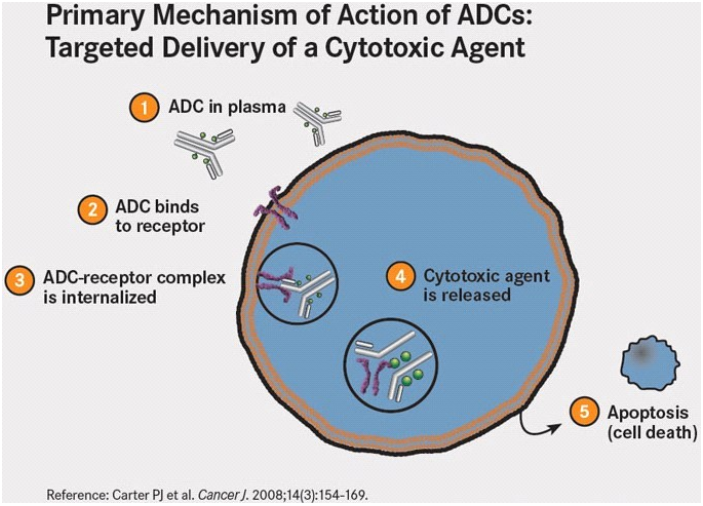
Drug of the Week: Trastuzumab emtansine (Kadcyla®)

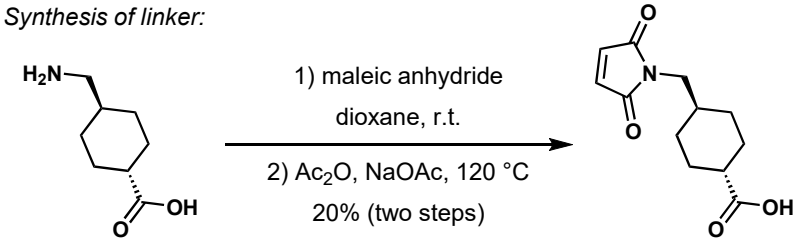


- Antibody-drug conjugate (ADC) used fo treatment of metastatic breast cancer
- Binds tubulin and inhibits microtubule assembly
- Emtansine is derived from the natural product maytansine, which alone reached phase II clinical trials but was discontinued due to its narrow therapeutic window.
- Developed by Genentech and manufactured by Lonza
- Treatment is $9,800/month or $94,000/treatment

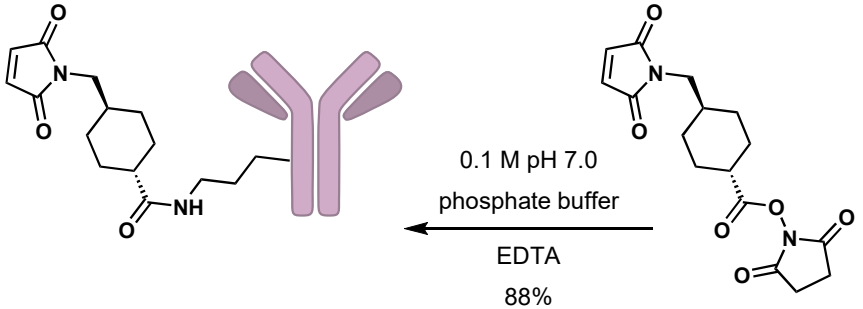


- Trastuzumab binds specifically to tumor cells and releases emtansine inside of the cell.
- Though binding concentration of trastuzuab is low, the IC_{50} of emtansine is much lower (< 10^{-9} M)
- Delivery of the emtansine as an ADC allows for a wider therapeutic window and longer half-life.

Synthesis of linker:

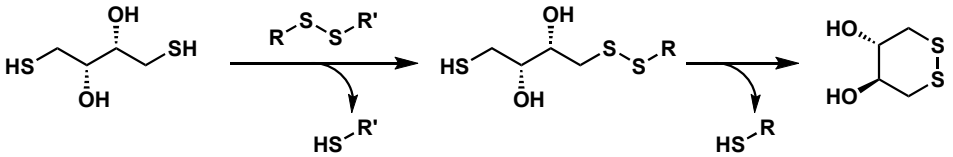


NHS, EDC
DCM, r.t.
39%



Cleland's Reagent

- Reduces disulfides to thiols



Widdison, W. C., *et al. J. Med. Chem.*, **2006**, *49*, 4392–4408.

Christopher Bemis, August 19, 2016

Sarlah Group

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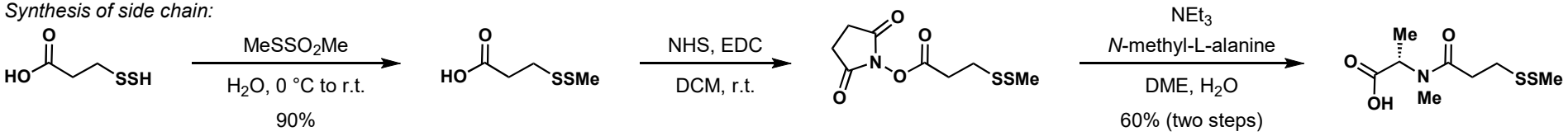
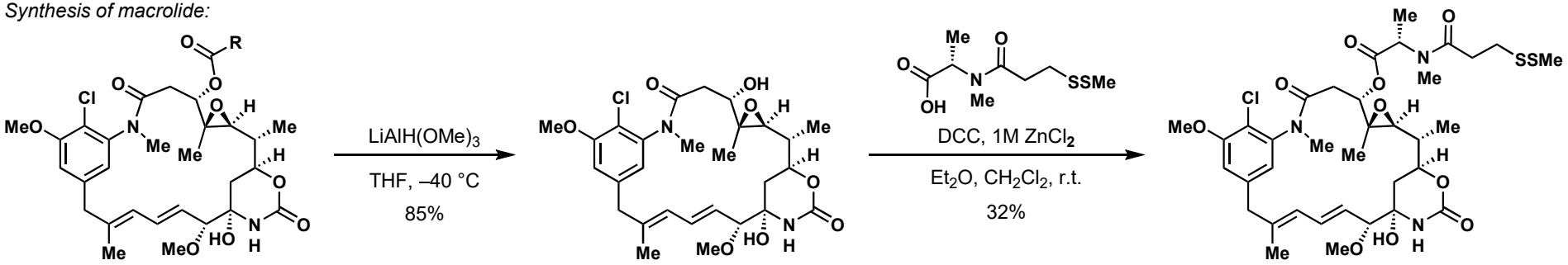
Synthesis of side chain:

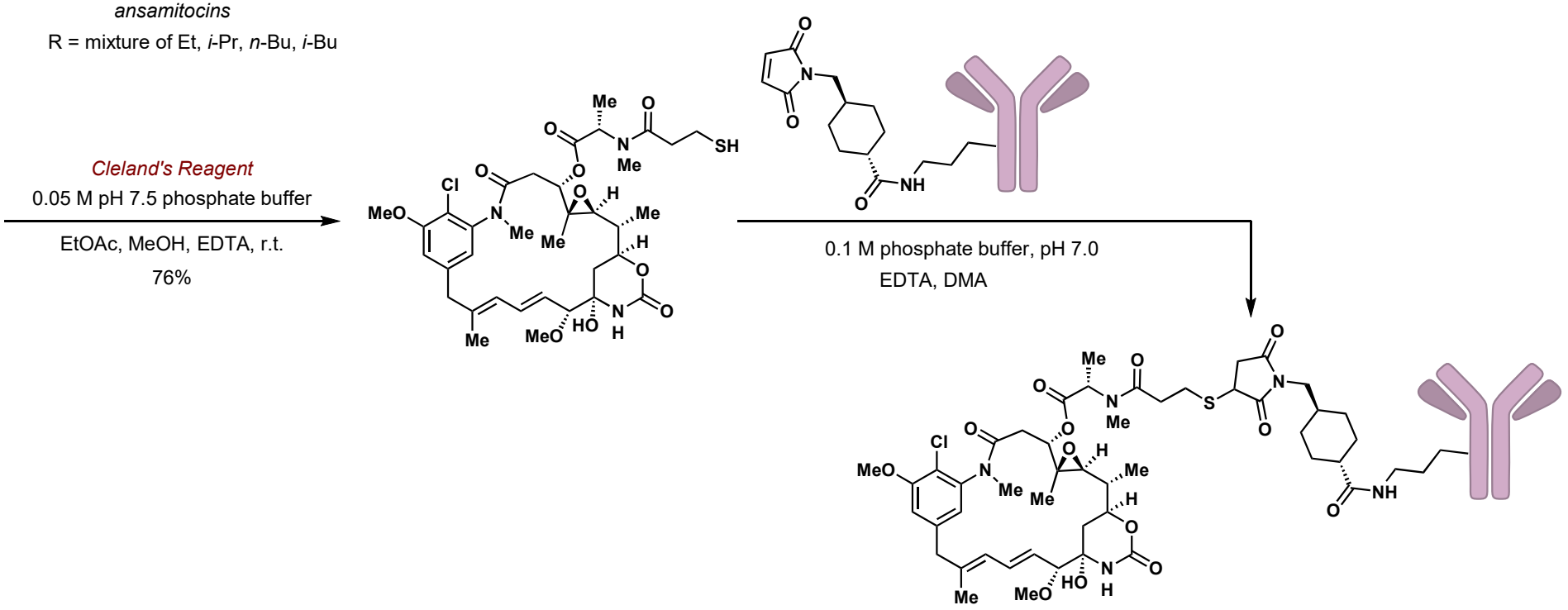


Synthesis of macrolide:



ansamitocins

R = mixture of Et, *i*-Pr, *n*-Bu, *i*-Bu



Trastuzumab emtansine

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