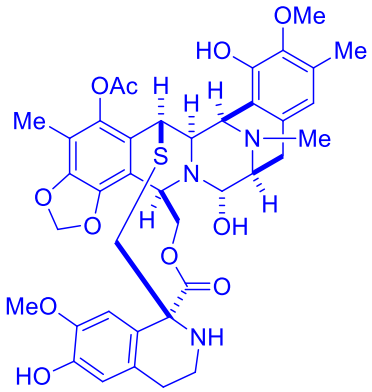
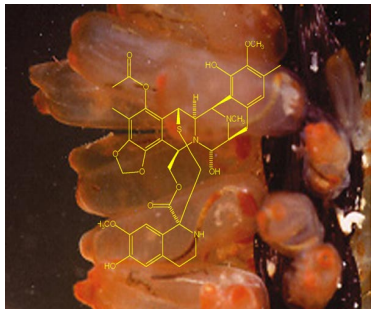
Total Synthesis of Ecteinascidin 743

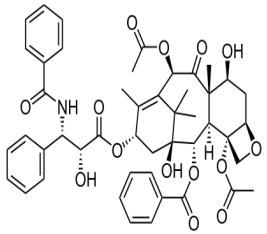


Ecteinascidin 743

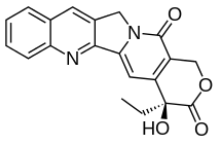
Mustafa Kazancioglu
Wipf Group
09/21/2013



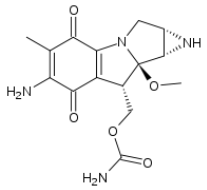
- Ecteinascidin 743 was isolated from the Caribbean tunicate Ecteinascidia turbinata by Rinehart in 1990.
- This alkaloid attracted strong interest as a potential anticancer agent because of its combination of strong cytostatic properties and antitumor activity.
- It has recently been approved for the treatment of soft tissue sarcoma and ovarian cancer.
- The antiproliferative activity of Et-743 is greater than that of paclitaxel, camptothecin, mitomycin C, and cisplatin, which are used to treat various types of cancers.



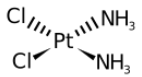
Paclitaxel



Camptothecin



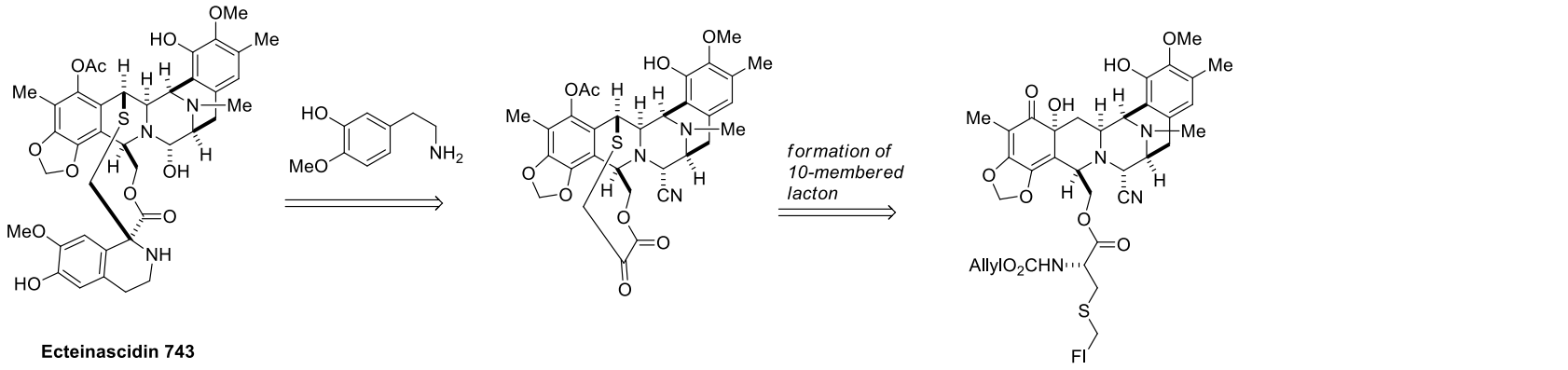
mitomycin C



Cisplatin

J. Am. Chem. Soc., **2013**, *135*, 13684–13687
J. Org. Chem. **2010**, 75, 4876-4879

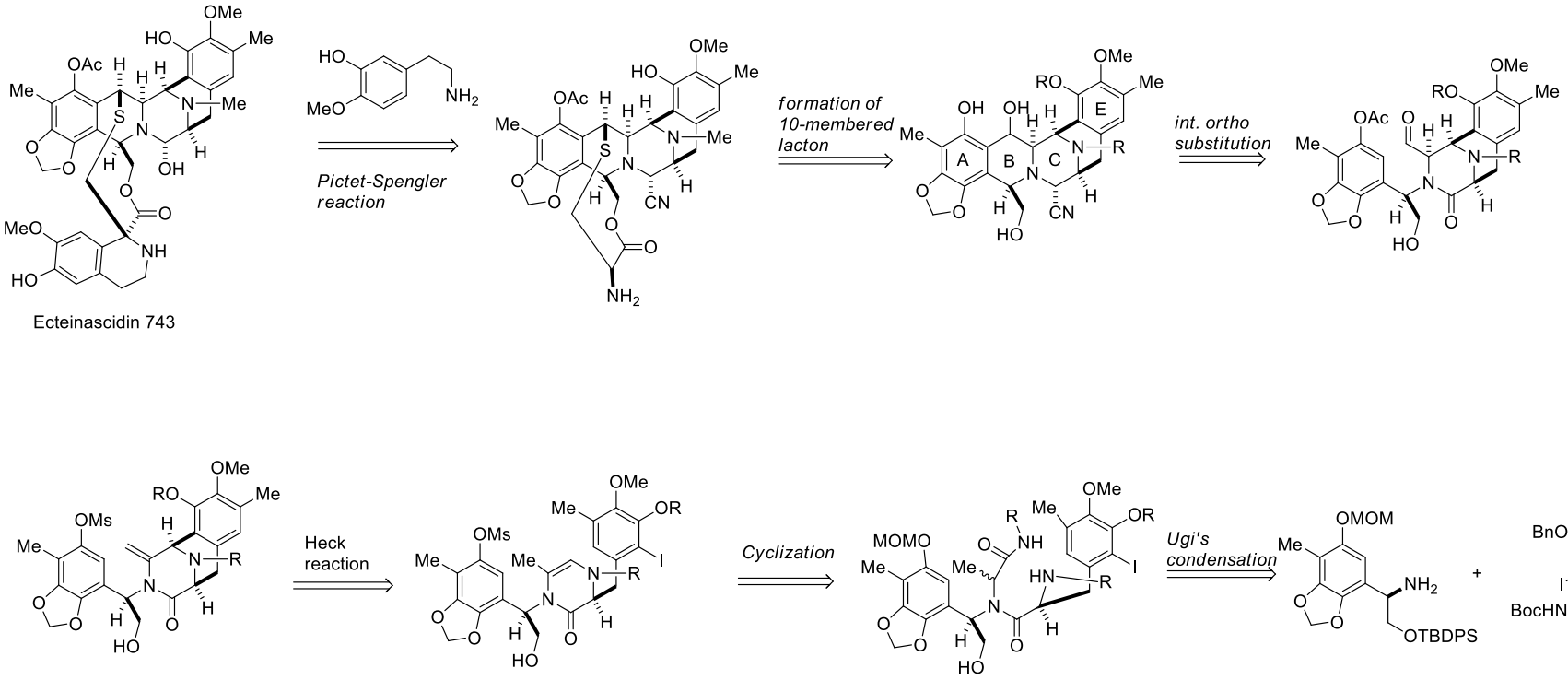
First total synthesis of Ecteinascidin 743 by Corey



- 36 steps
- **0.72%** overall yield

J. Am. Chem. Soc. **1996**, *118*, 9202-9203

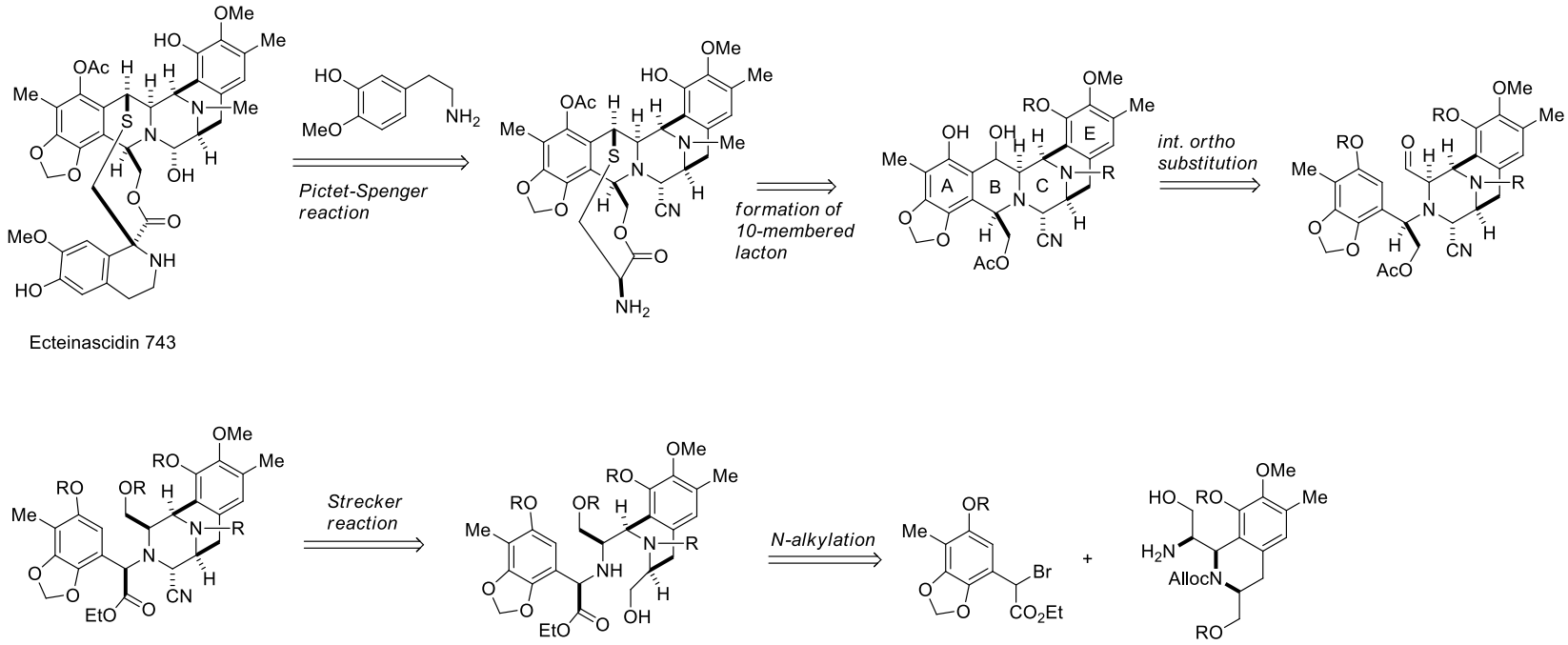
Second total synthesis of Ecteinascidin 743 by Fukuyama



- 50 steps
- **0.56%** overall yield

J. Am. Chem. Soc. **2002**, *124*, 6552-6554

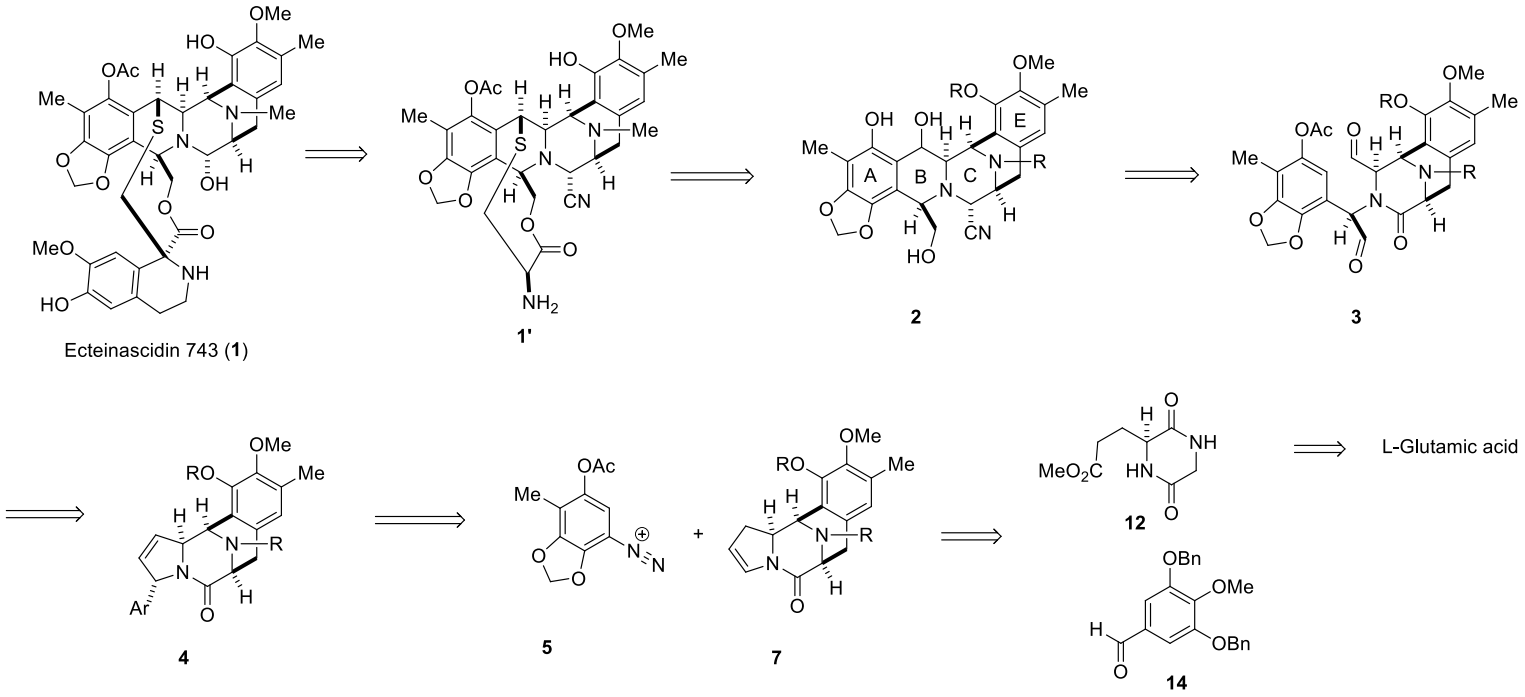
Third total synthesis of Ecteinascidin 743 by Zhu



- 31 steps
- **1.7%** overall yield

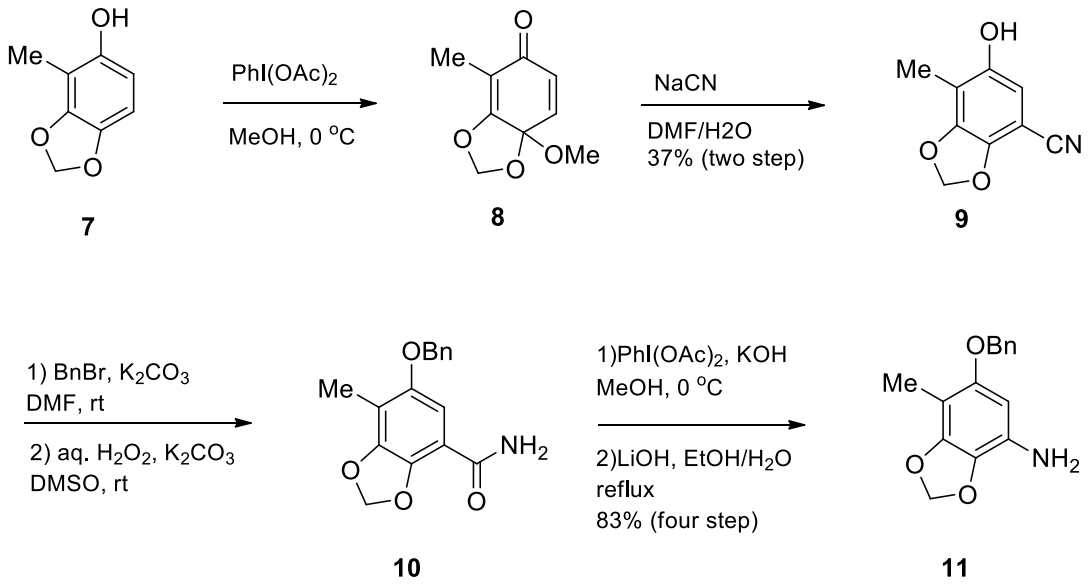
J. Am. Chem. Soc. **2006**, *128*, 87-89

Retrosynthetic Analysis for Ecteinascidin 743



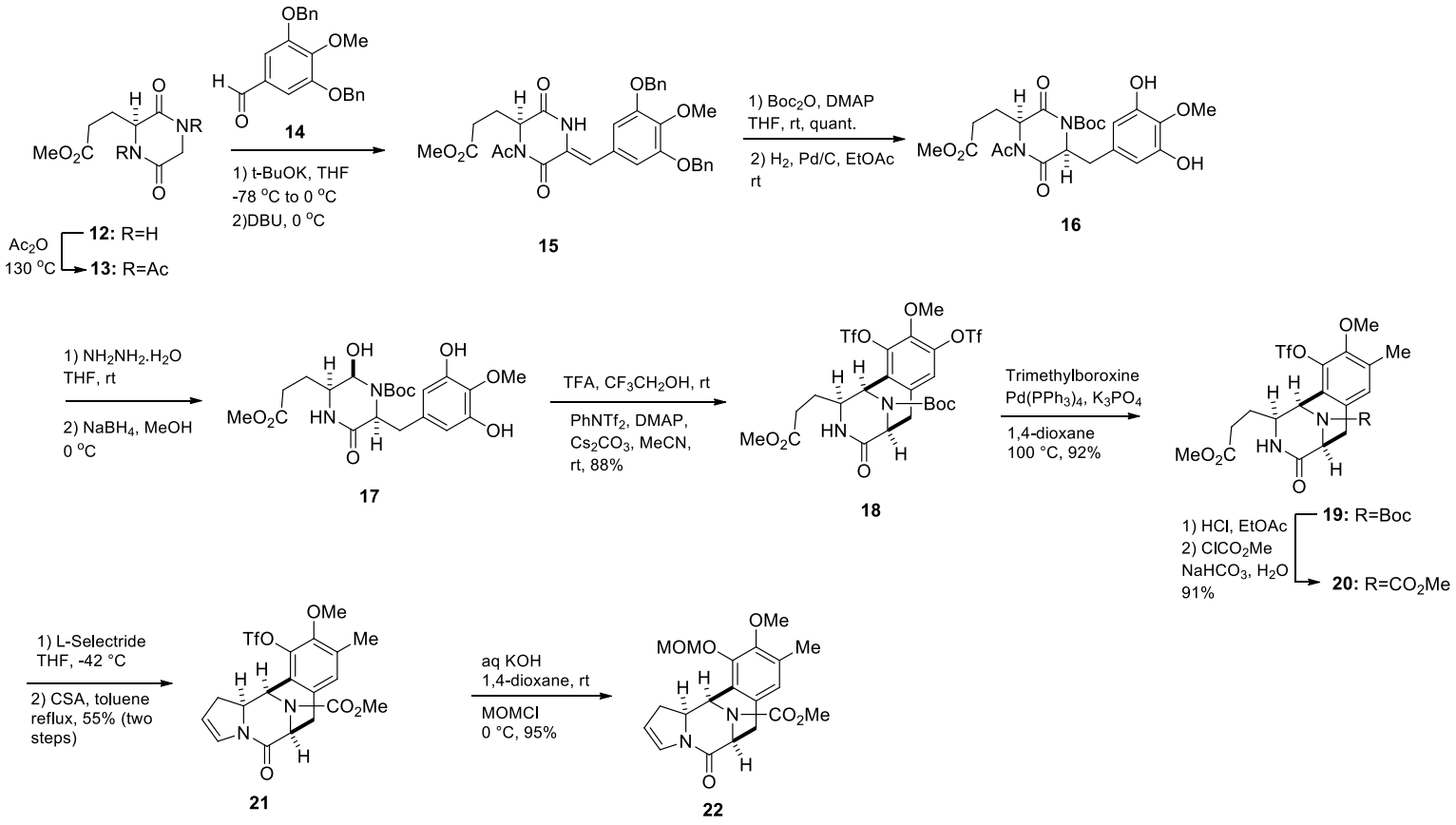
J. Am. Chem. Soc., **2013**, *135*, 13684–13687

Synthesis of amine 11 as the precursor for diazonium salt

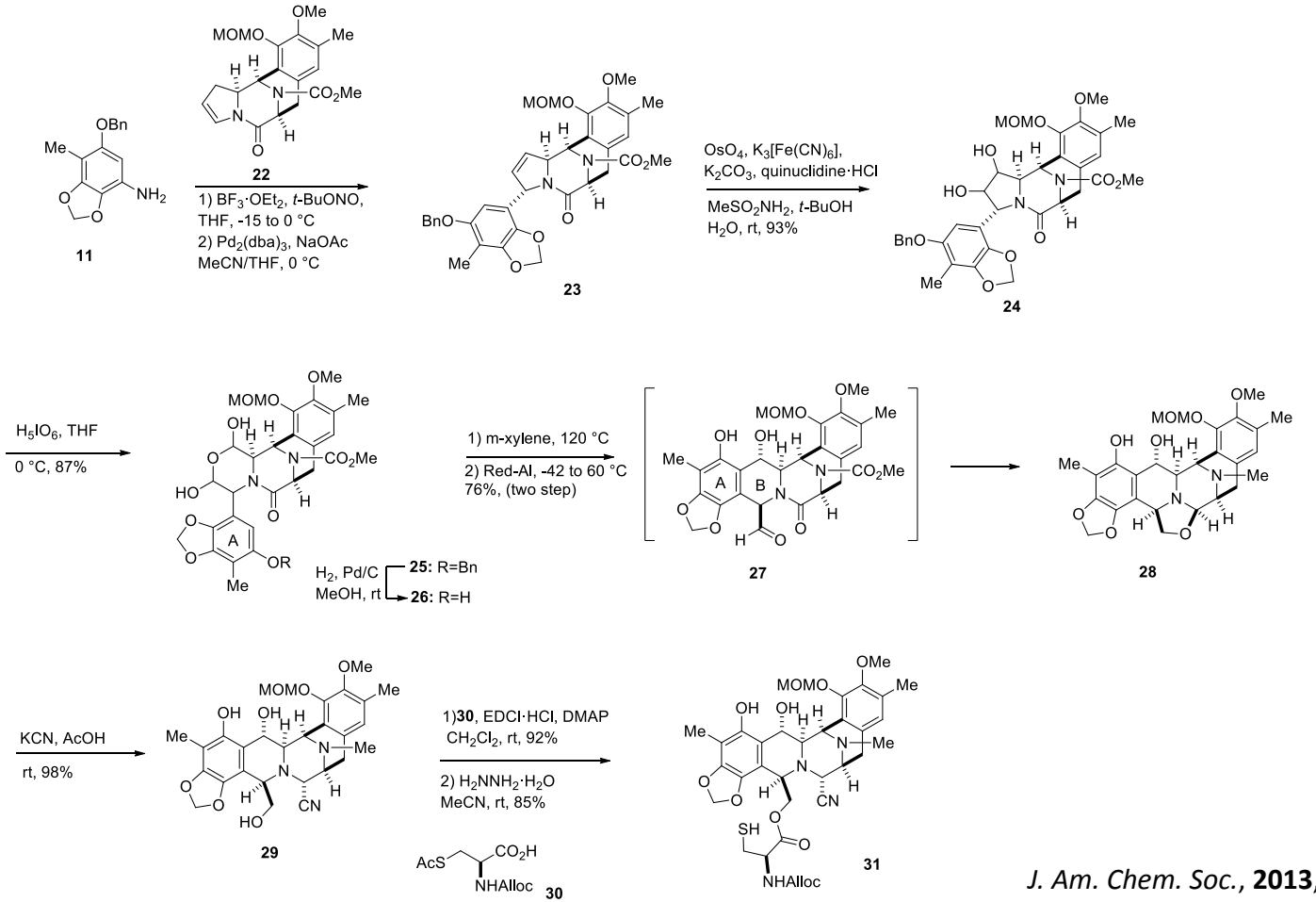


J. Am. Chem. Soc., **2013**, *135*, 13684–13687

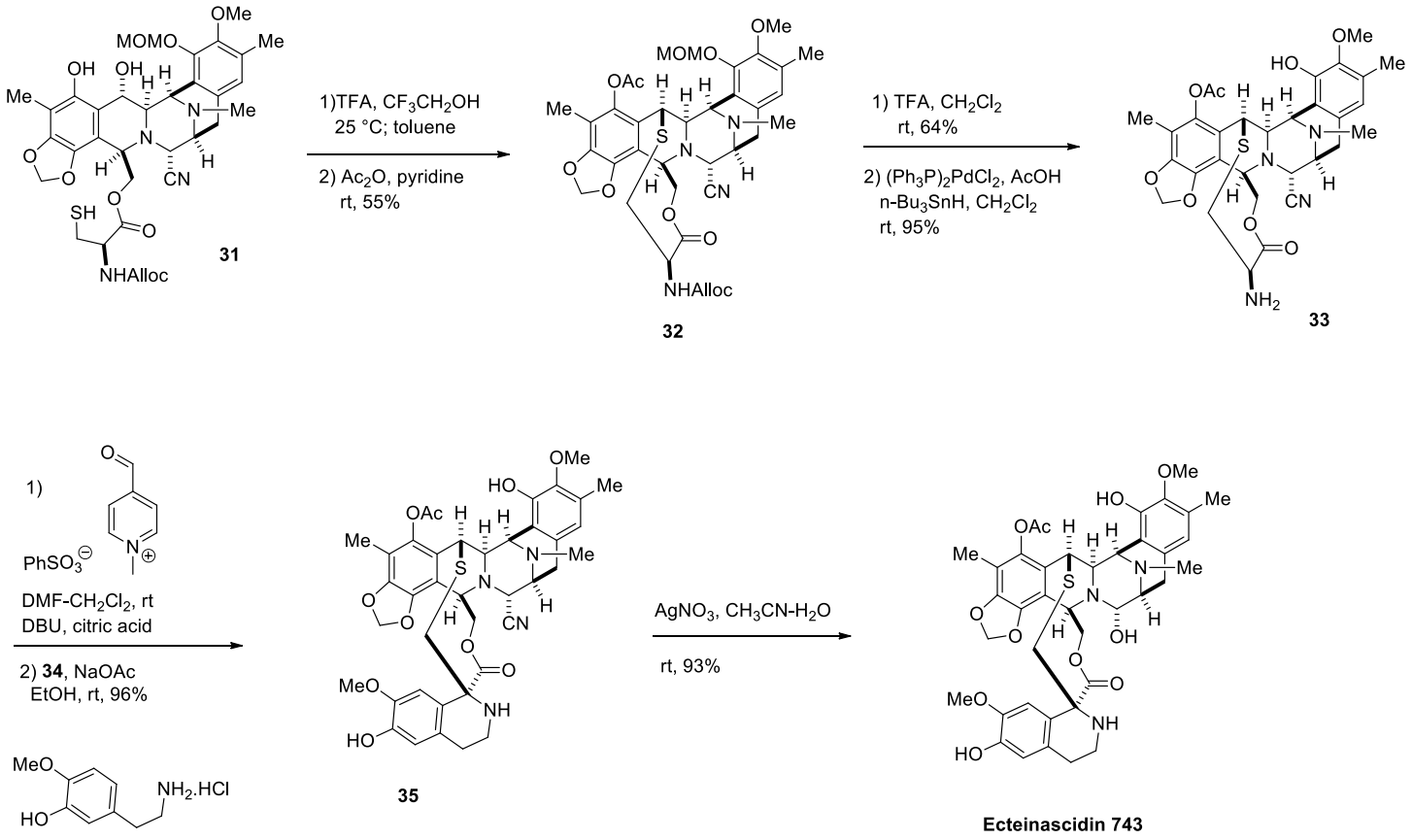
Synthesis of enamine 22



J. Am. Chem. Soc., **2013**, *135*, 13684–13687



J. Am. Chem. Soc., **2013**, *135*, 13684–13687

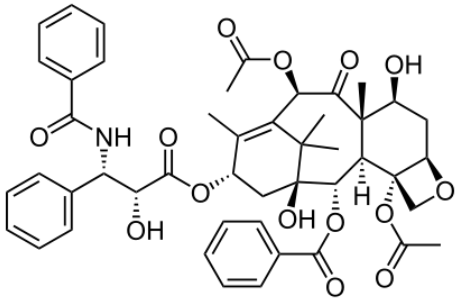


J. Am. Chem. Soc., **2013**, *135*, 13684–13687

Conclusion:

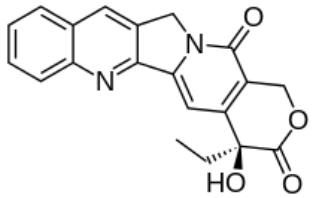
- Synthesis of ecteinascidin 743 has been accomplished in 28 steps and 1.1% overall yield from readily available L-glutamic acid as a single chiral source.
- Stereoselective Heck reaction between a diazonium salt and enamide, oxidative cleavage of the resulting alkene, and intramolecular ortho substitution of the phenol by an aldehyde give B-ring.
- Other highlights of the synthesis include a straightforward method to access a functionalized diketopiperazine by Perkin condensation, facile construction of the bicyclo[3.3.1] system by an N-acyliminium ion-mediated cyclization, and a regioselective Suzuki−Miyaura coupling.
- They are currently exploring a more practical synthetic route that could be applied on a manufacturing scale to supply ecteinascidin 743 for clinical use.

J. Am. Chem. Soc., **2013**, *135*, 13684–13687



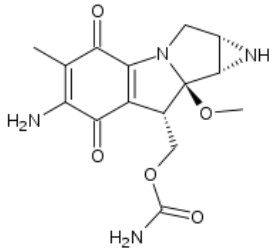
Paclitaxel

Paclitaxel is a mitotic inhibitor used in cancer chemotherapy

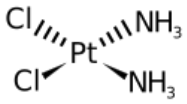


Camptothecin

used in cancer chemotherapy



mitomycin C finds use as a chemotherapeutic agent by virtue of its antitumour antibiotic activity



Cisplatin is a chemotherapy drug

Heck-Matsuda (HM) reaction