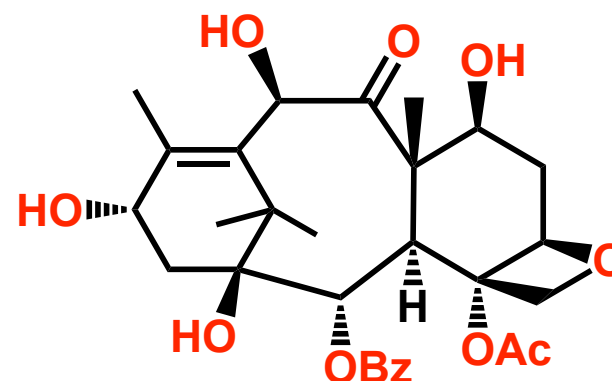
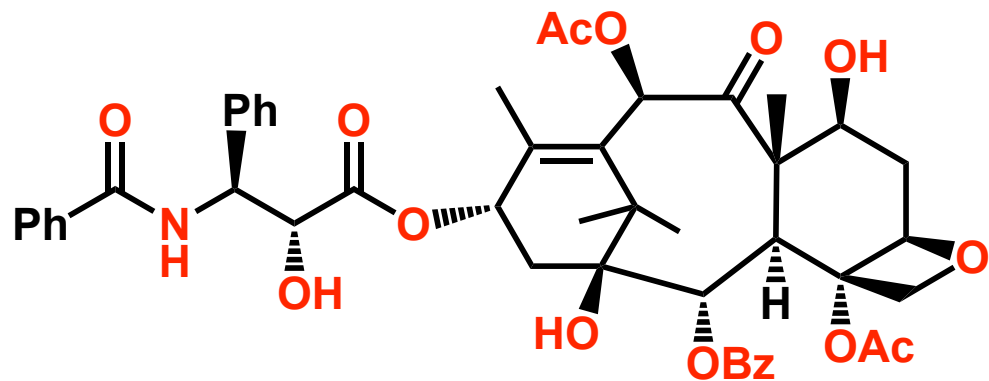




Krishna P Kaliappan
Professor of Chemistry, IIT Bombay

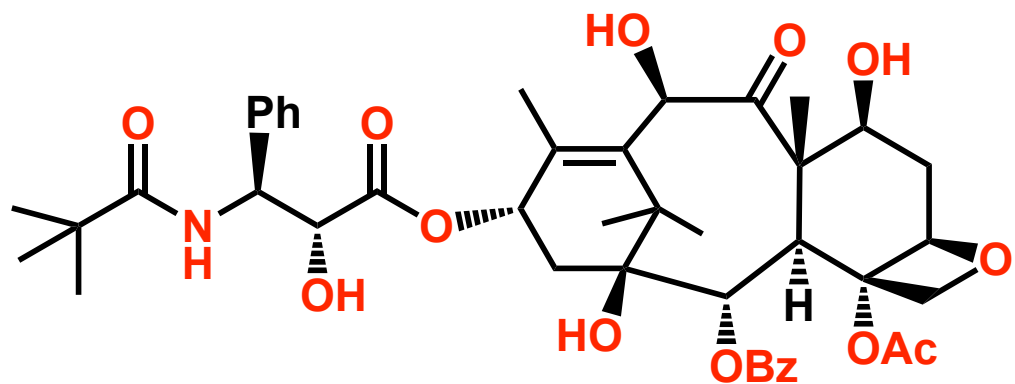
CH-588 Course on Organic Synthesis



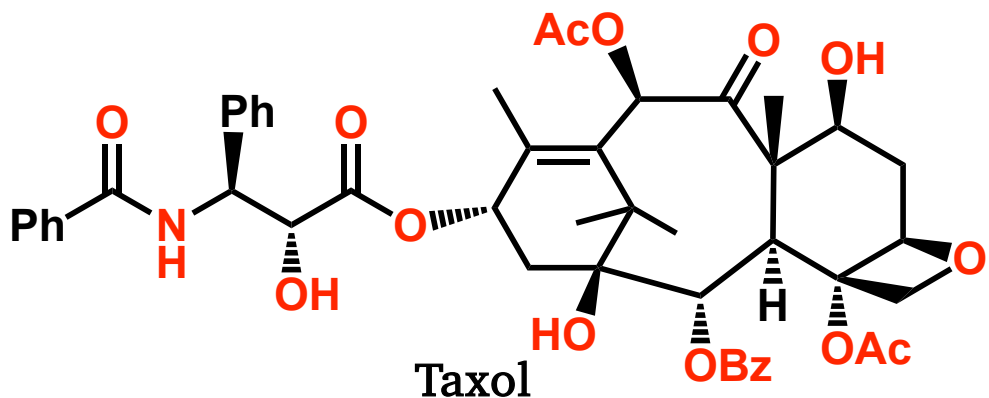
10-Deacetyl Baccatin-III

- **Isolation:** It was isolated from the bark of pacific yew tree in 1962 and the structure was elucidated in 1971 by Wall & Wani through X-ray
- Has attracted the attention of many synthetic chemists over the last two decades
- Has been successfully used for the ovarian and breast cancer treatment
- Over 200 groups started this journey towards the synthesis of taxol. So far 10 groups have reached the shore.

- A single 100 year old tree will result in 300 mg of taxol. This is just sufficient for one single dose for a cancer patient
- Fortunately, in early 90's it was found that 10-deacetyl baccatin-III (10-DAB), a precursor to taxol lacking the C-10 acetoxy group and the C-13 side chain in the needles and twigs of *Taxus baccata*, the European Yew tree



Taxotere/docetaxel



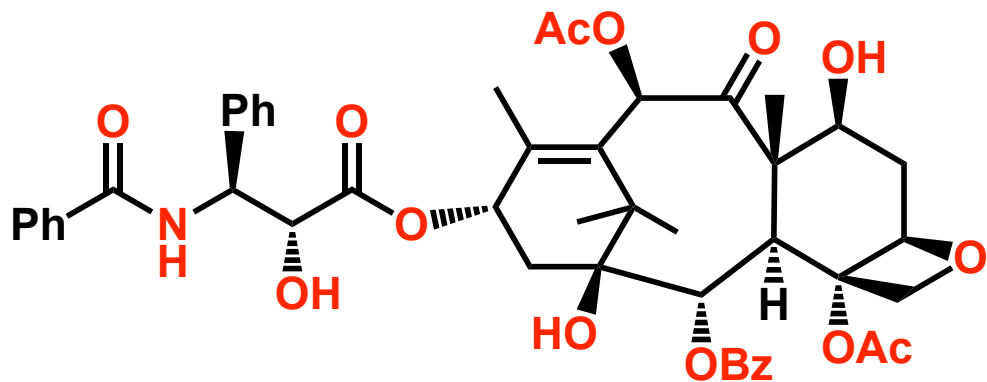
Taxol

- Reported by **Pierre Potier** at CNRS at Gif-sur-Yvette
- Developed by Rhône-Poulenc Rorer (now **Sanofi-Aventis**)
- **Twice as active** as Taxol

Total Synthesis

1. Robert A. Holton-1994 (**SM- Patchulol**)
2. K. C. Nicolaou-1994 (**SM-Mucic acid**)
3. S. J. Danishefsky-1996 (**SM-Weiland Micher Ketone**)
4. Paul Wender-1997 (**SM-Verbenone**)
5. Isao Kuwajima-1998
6. Teruaki Mukayama-1998 (**SM-L-Serine**)
7. T. Takahashi-2006 (**SM-Geraniol**)
8. Sato-Chida-1996 (**Formal Synthesis**)
9. Nakada-2015 (**Formal Synthesis**)
10. Phil Baran-2020 (**Two phase synthesis**)

Synthetic Challenges

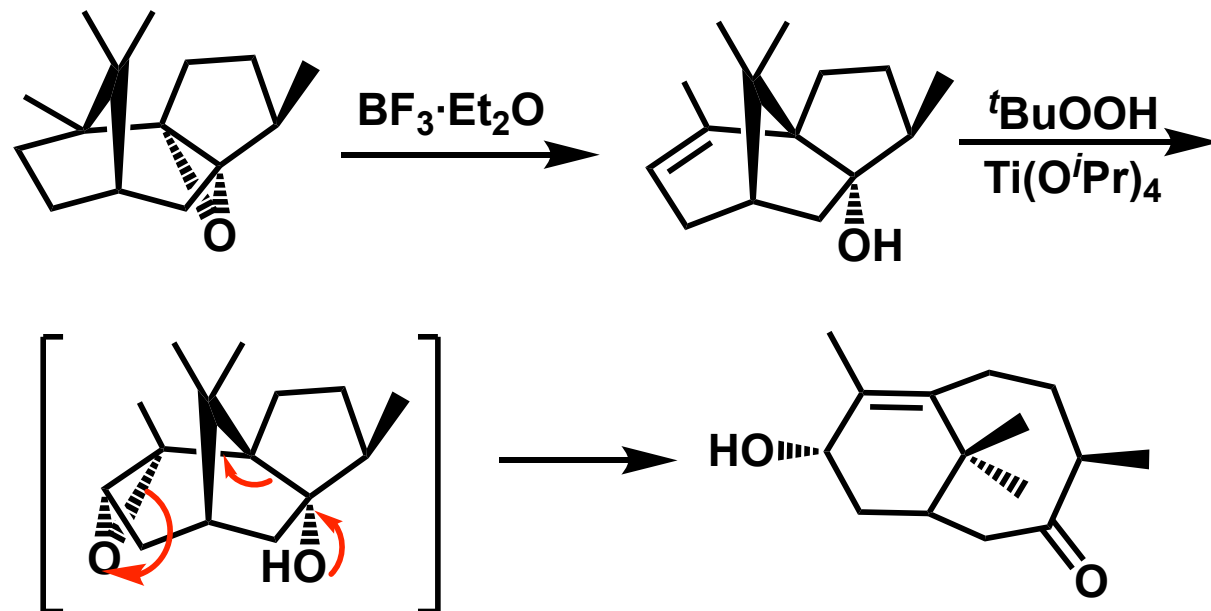


Highly congested C-ring with many chiral centers

8-Membered B-ring

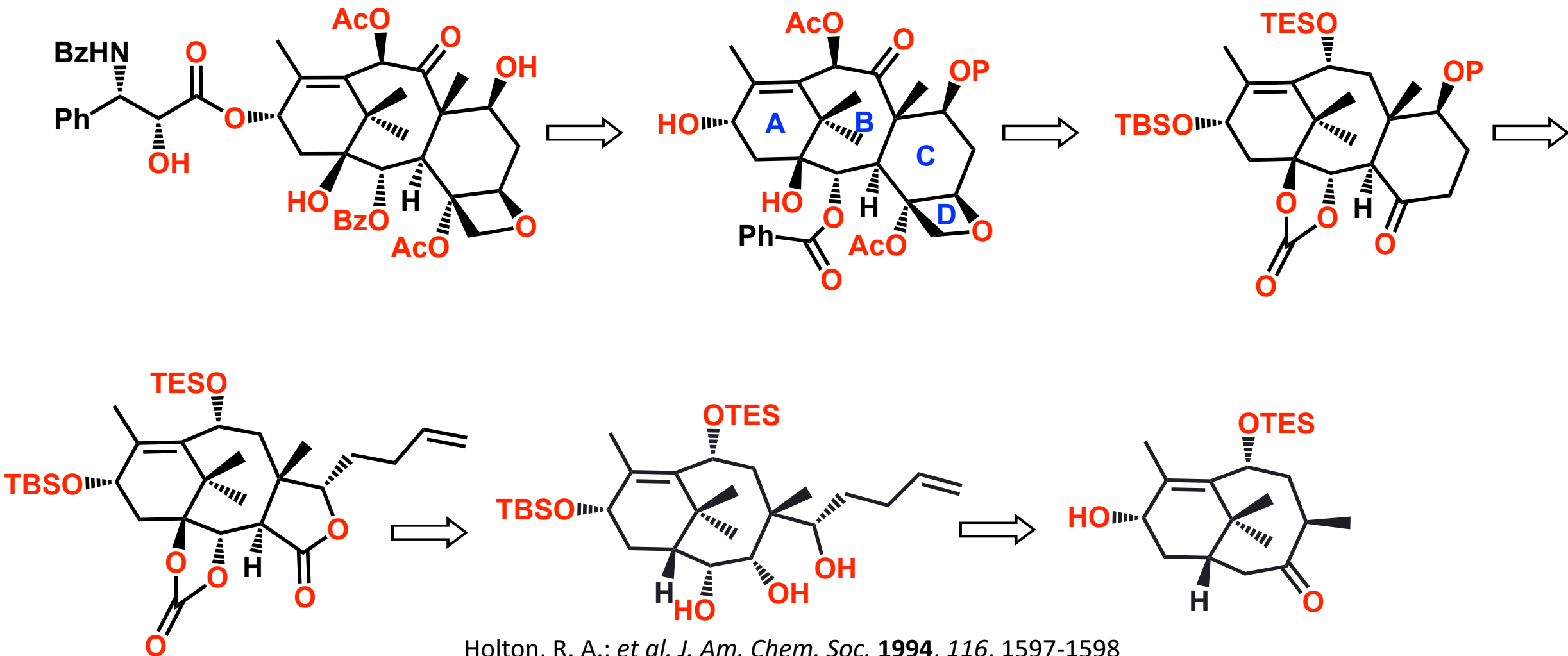
6-8-6 Carbocyclic system

Key Reactions



- Hydroxyl-directed epoxidation gave an unstable substance that underwent fragmentation *in situ* to provide the keto alcohol
- The ease of this fragmentation is surprising since the breaking bonds have a *syn* periplanar relationship

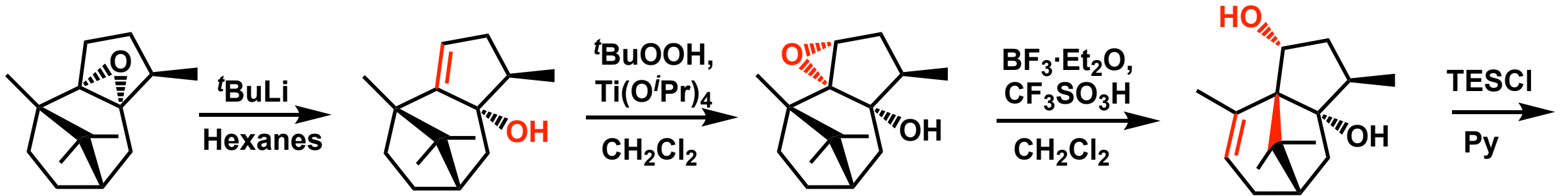
Holton's Retrosynthesis



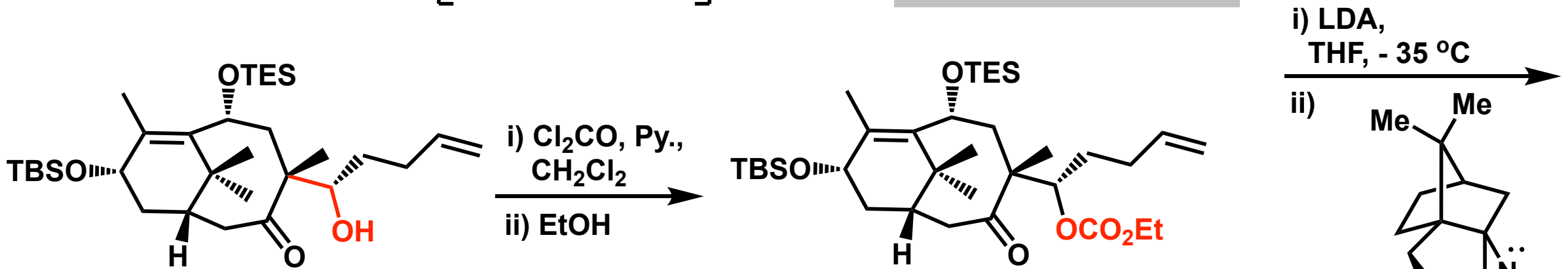
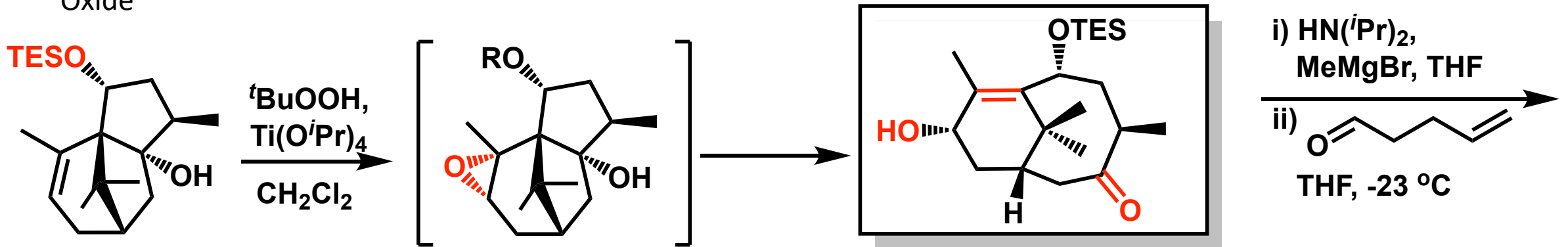
Holton, R. A.; *et al.* *J. Am. Chem. Soc.* **1994**, *116*, 1597-1598

Holton, R. A.; *et al.* *J. Am. Chem. Soc.* **1994**, *116*, 1599-1600

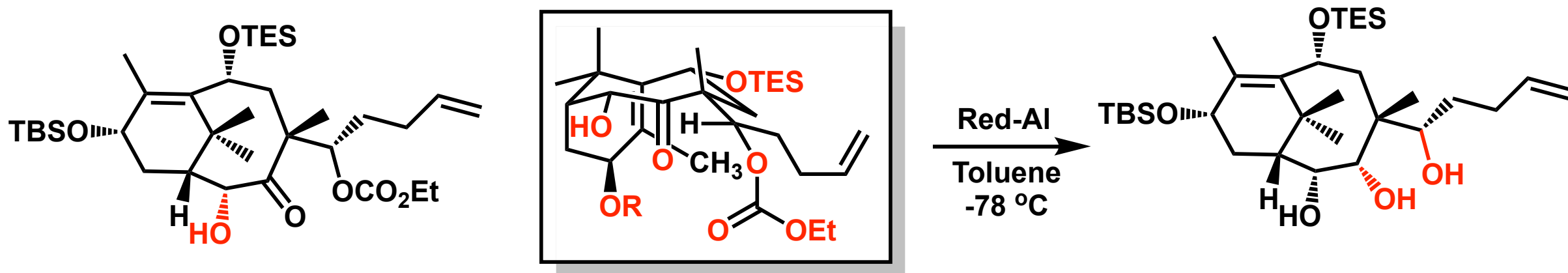
Holton's Total Synthesis



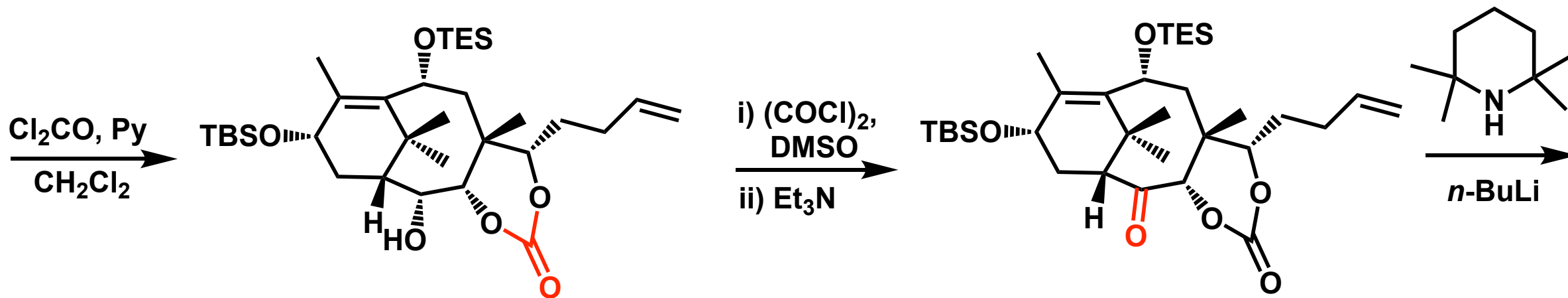
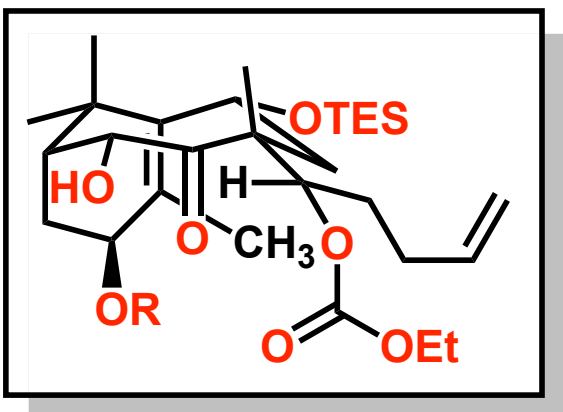
Patchoulene Oxide

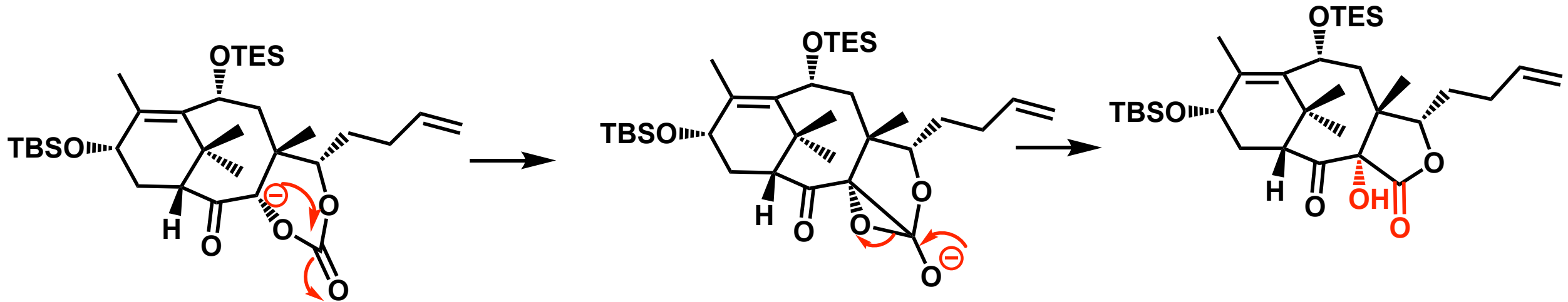


Holton's Total Synthesis

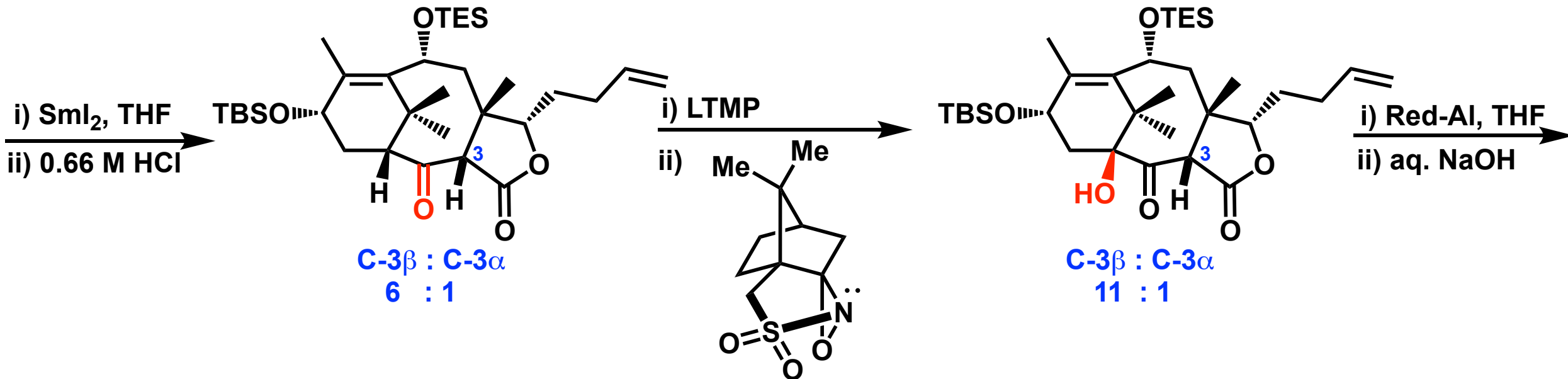


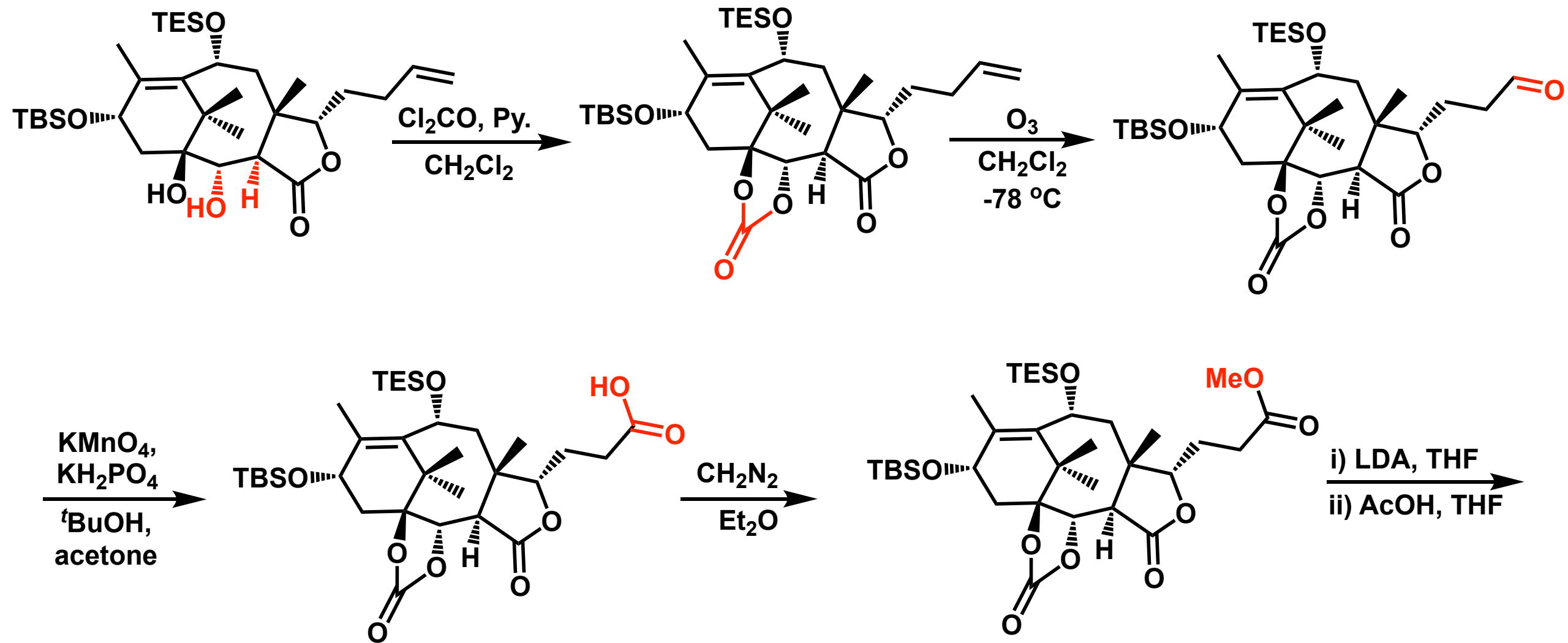
Boat-Chair Conformation

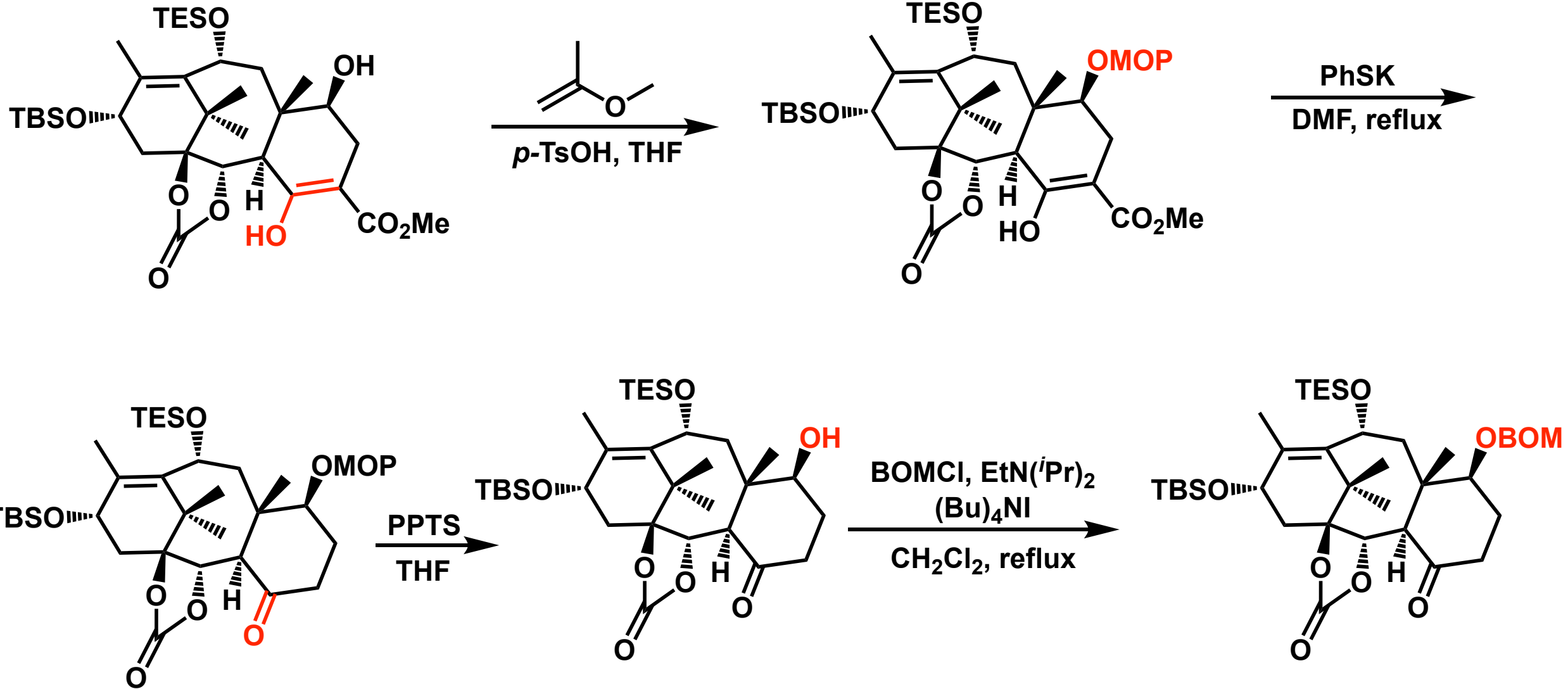


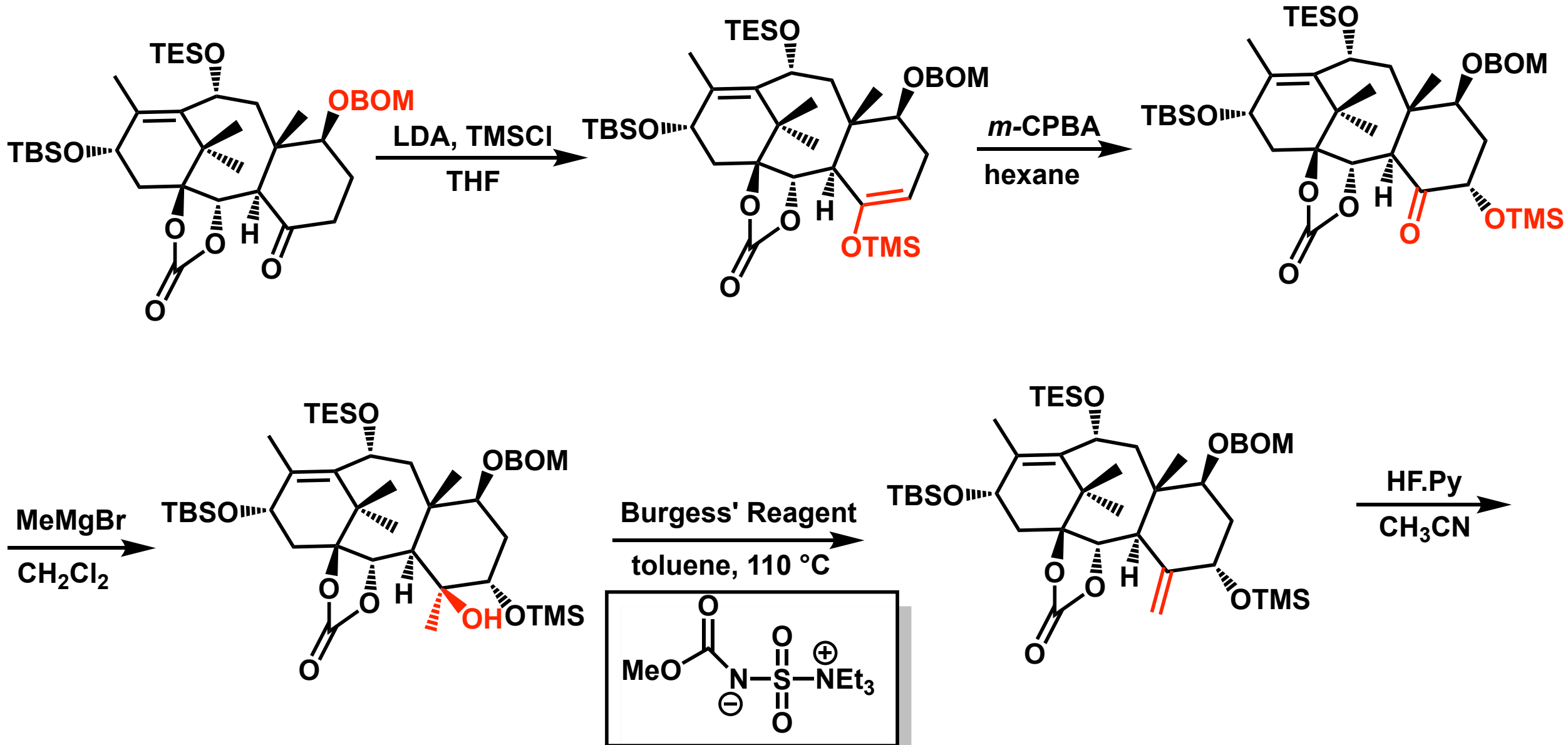


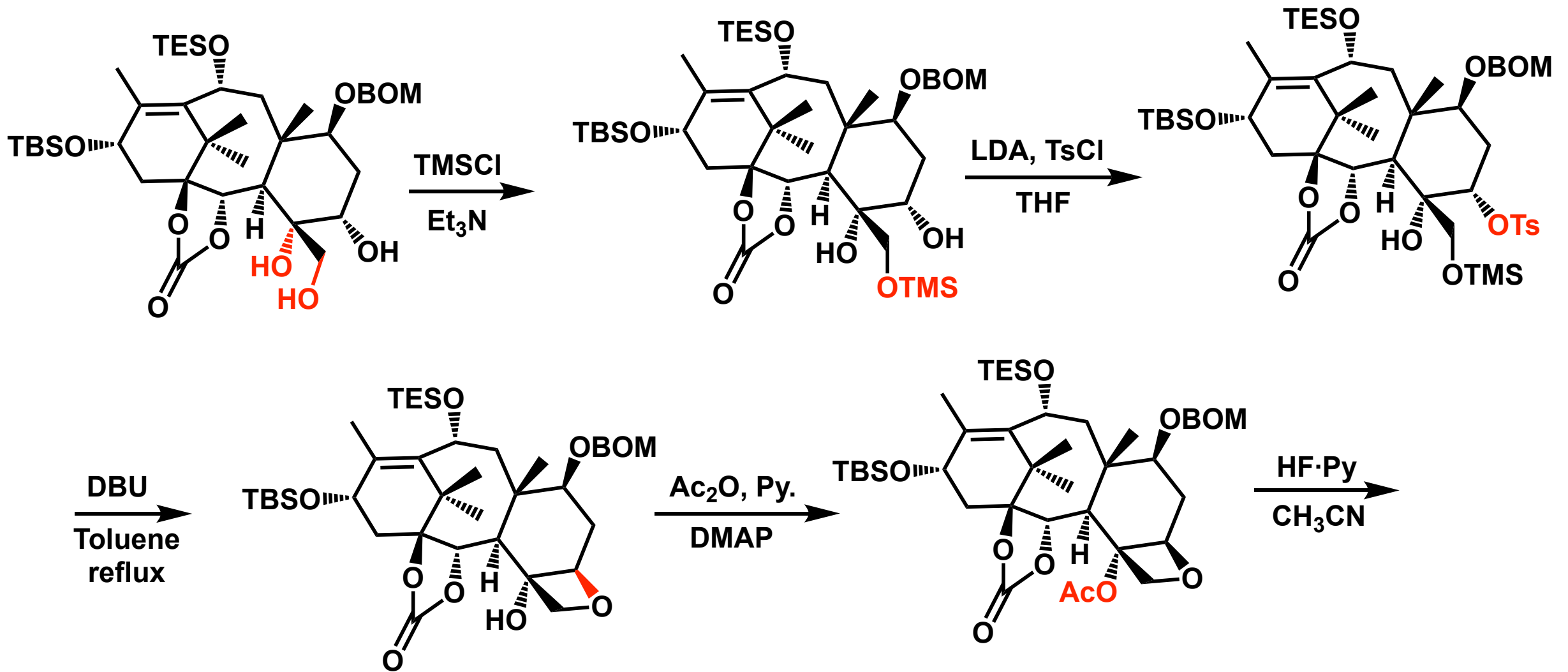
Chan, T. H. & co-workers. *Tetrahedron Lett.* **1984**, *25*, 3399-3402

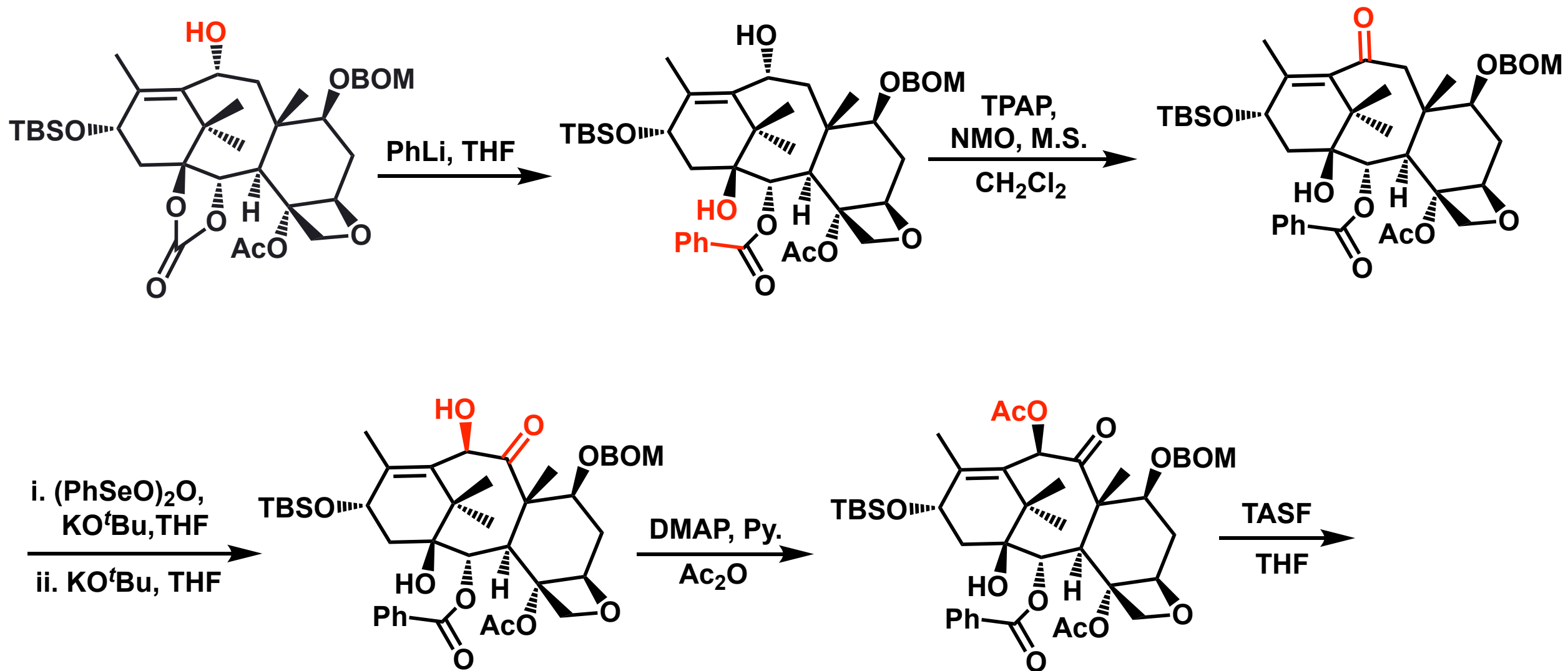


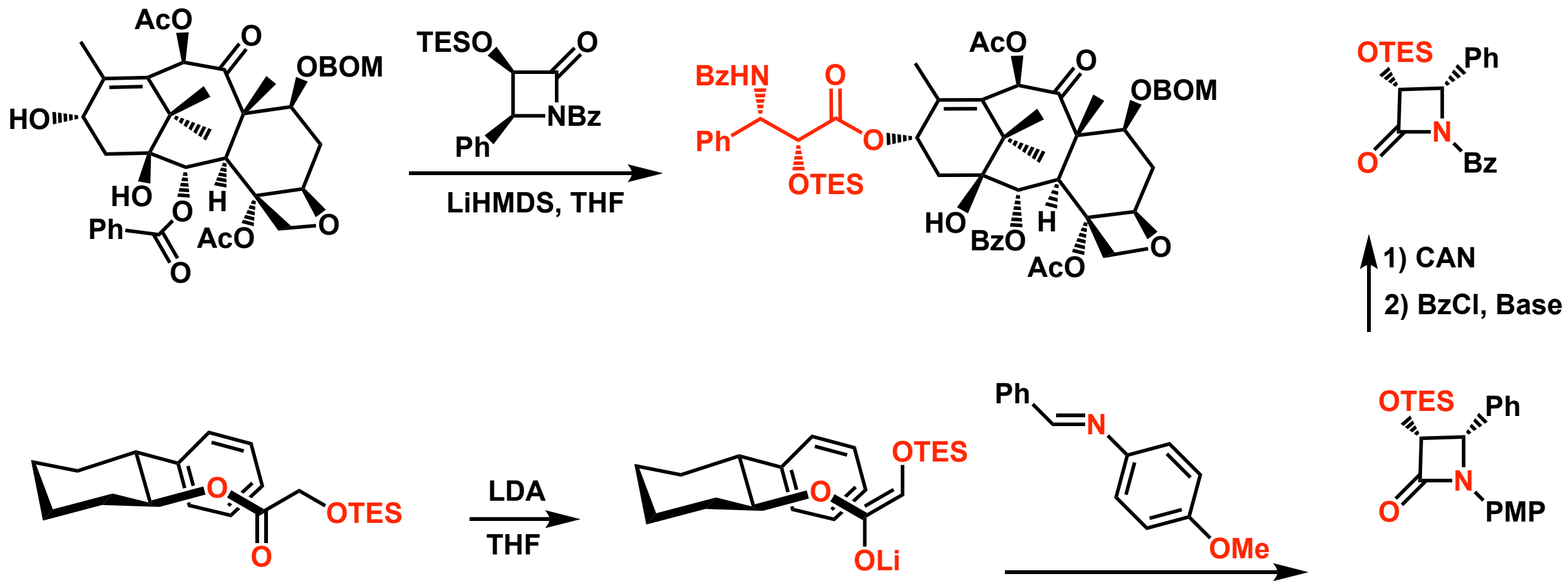




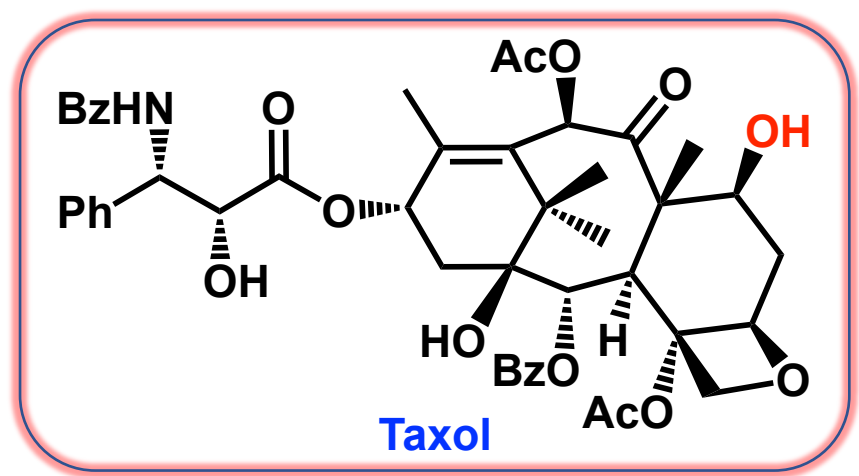
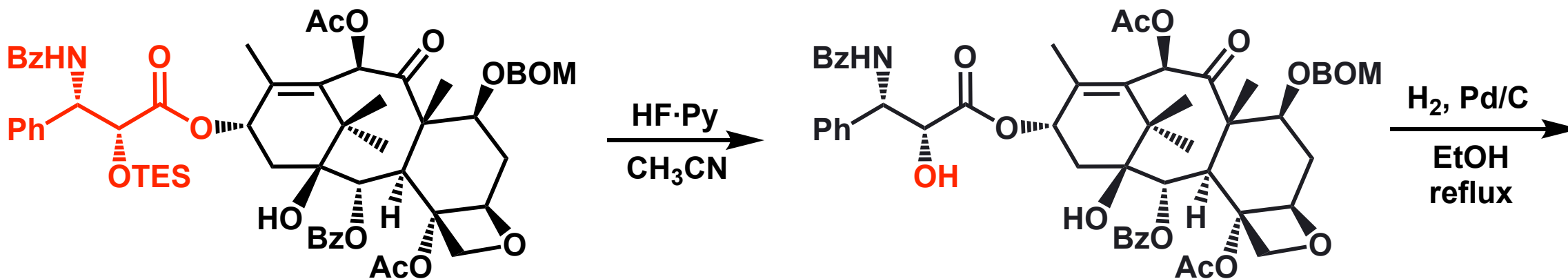






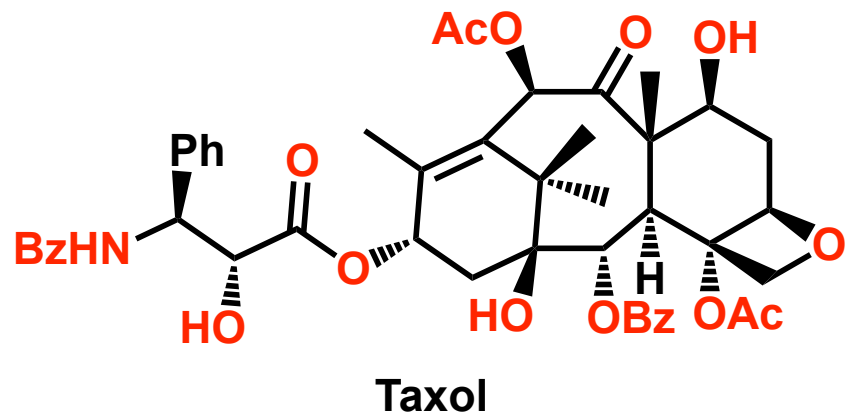


Holton's Total Synthesis



- The first total synthesis of Taxol was accomplished by Holton *et al.* in 1994
- The synthesis starts from patchino, a commercially available natural compound
- The key chemical transformations in this synthesis involve, Chan rearrangement, epoxy alcohol fragmentation and Dieckmann cyclization
- Their total synthesis was completed in 46 linear steps starting from patchoulene oxide

Wender's Total Synthesis

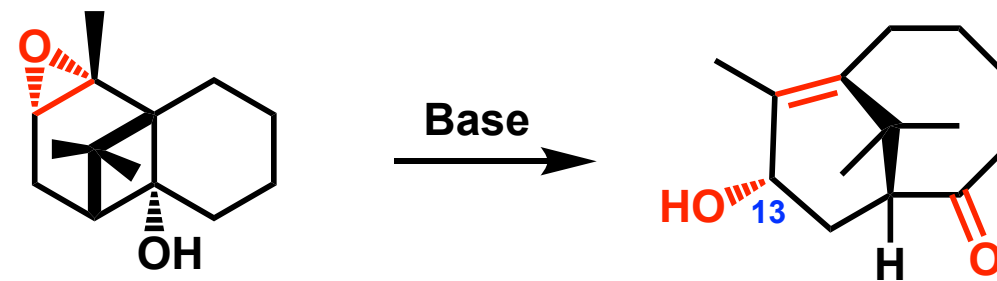
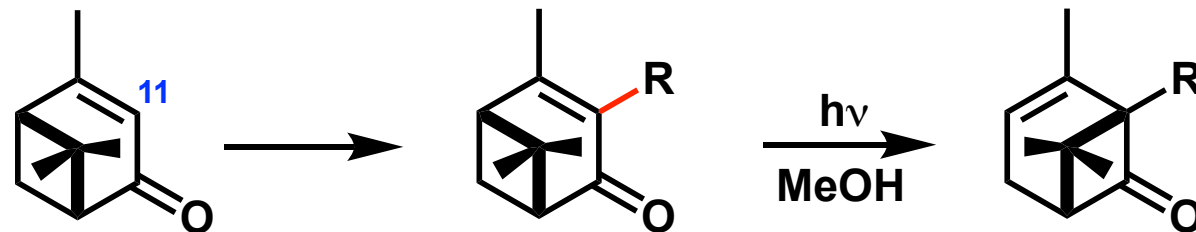


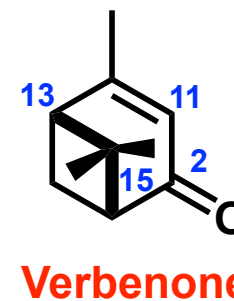
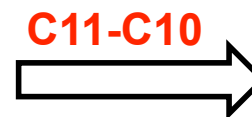
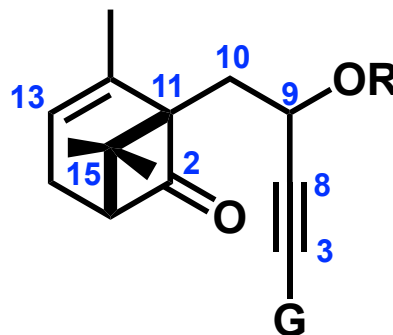
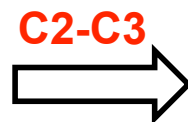
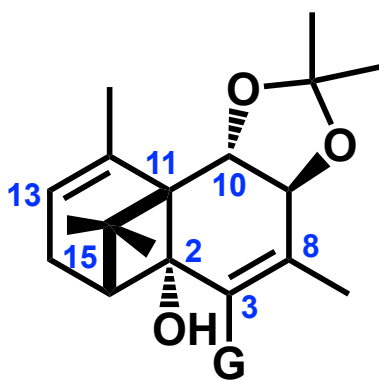
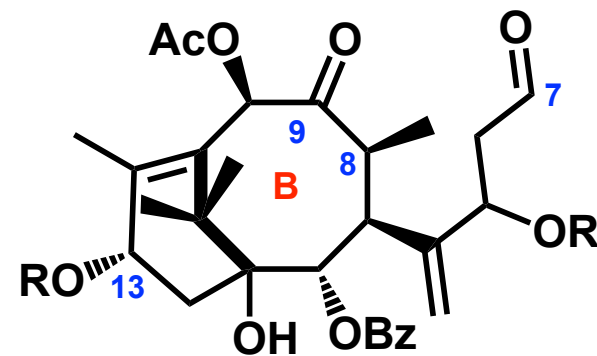
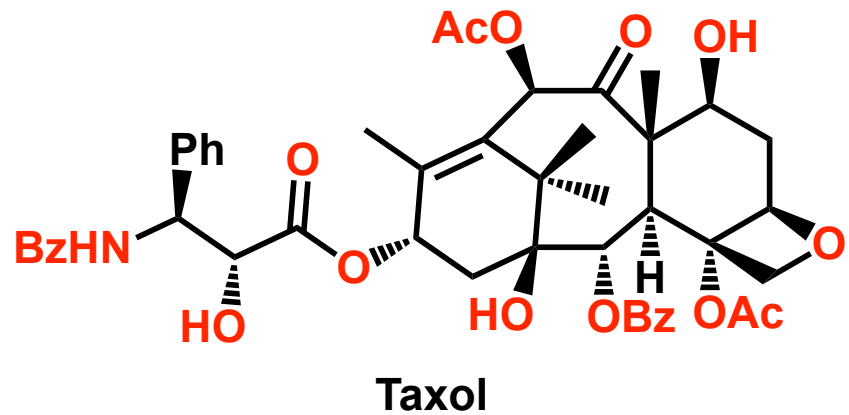
- An efficient stereocontrolled synthesis of a highly versatile taxane precursor which provides concise access to **Taxol**
- This strategy provides **Taxol** in the correct enantiomeric form in 37 steps from verbenone, the air-oxidation product of pinene

Wender, P. A.; *et al.* *J. Am. Chem. Soc.* **1997**, 119, 2755-2756

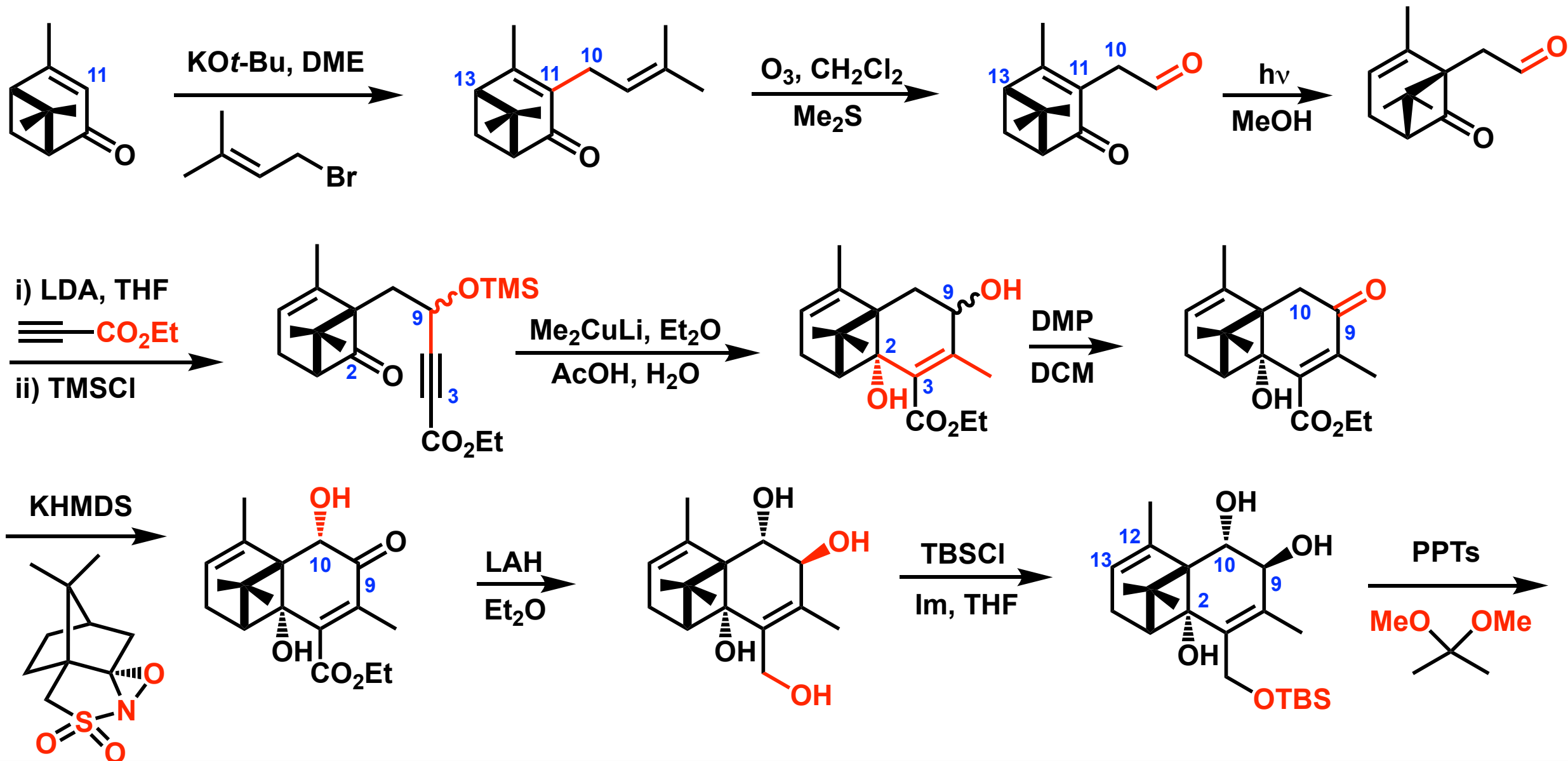
Wender, P. A.; *et al.* *J. Am. Chem. Soc.* **1997**, 119, 2757-2758

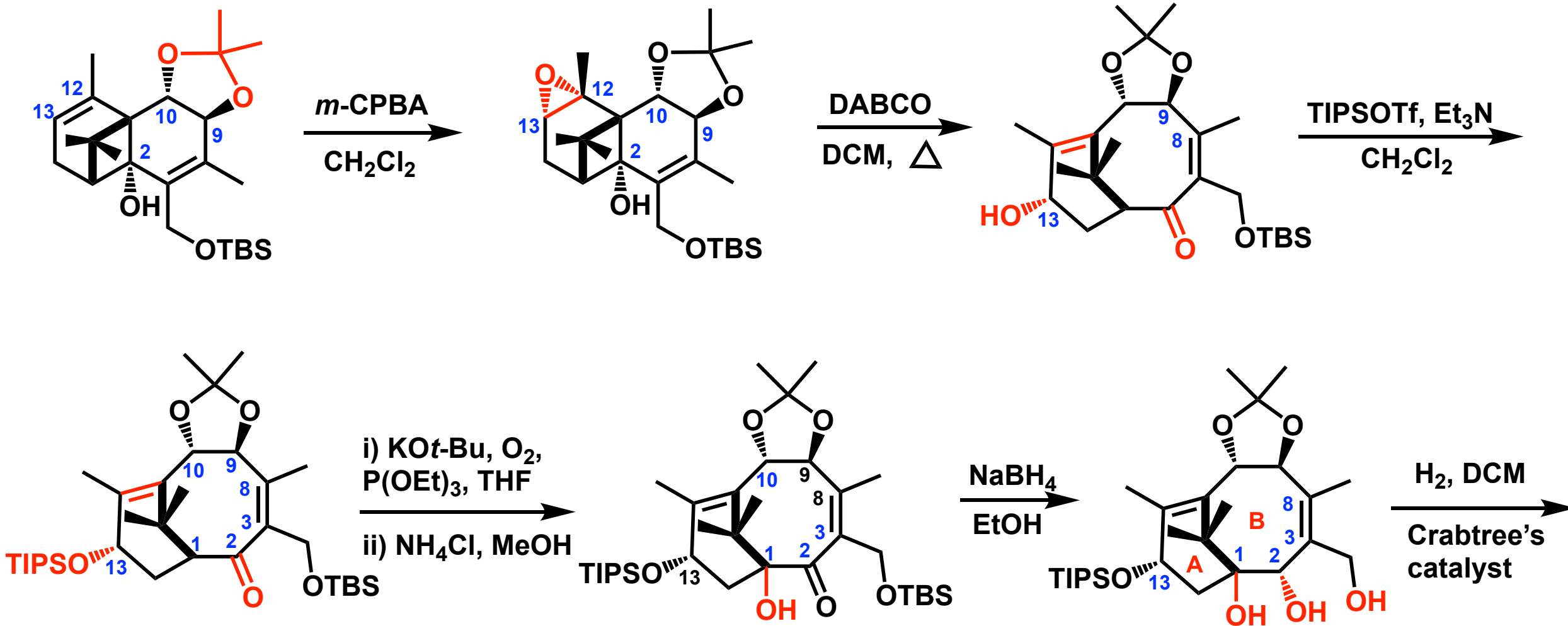
Key Reactions

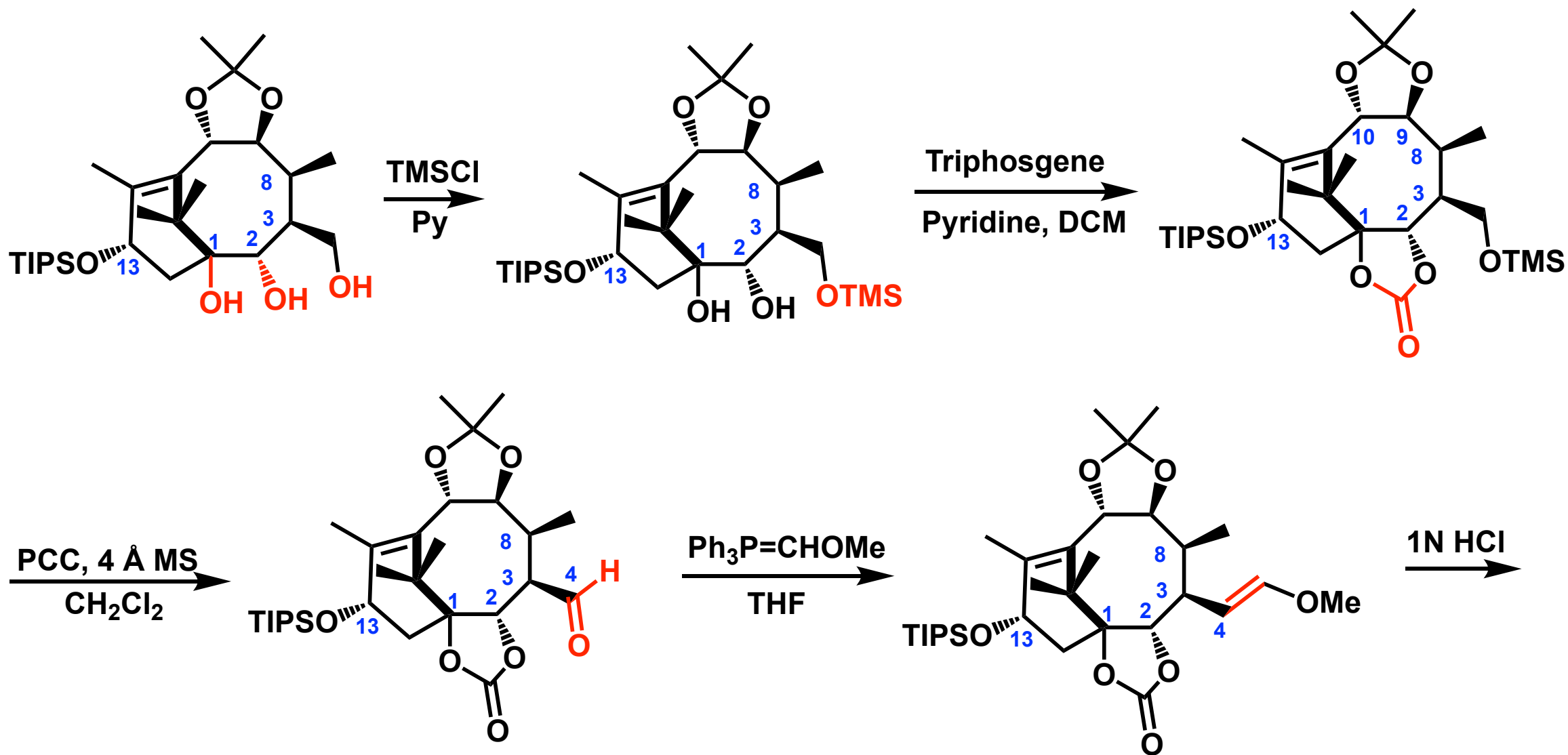


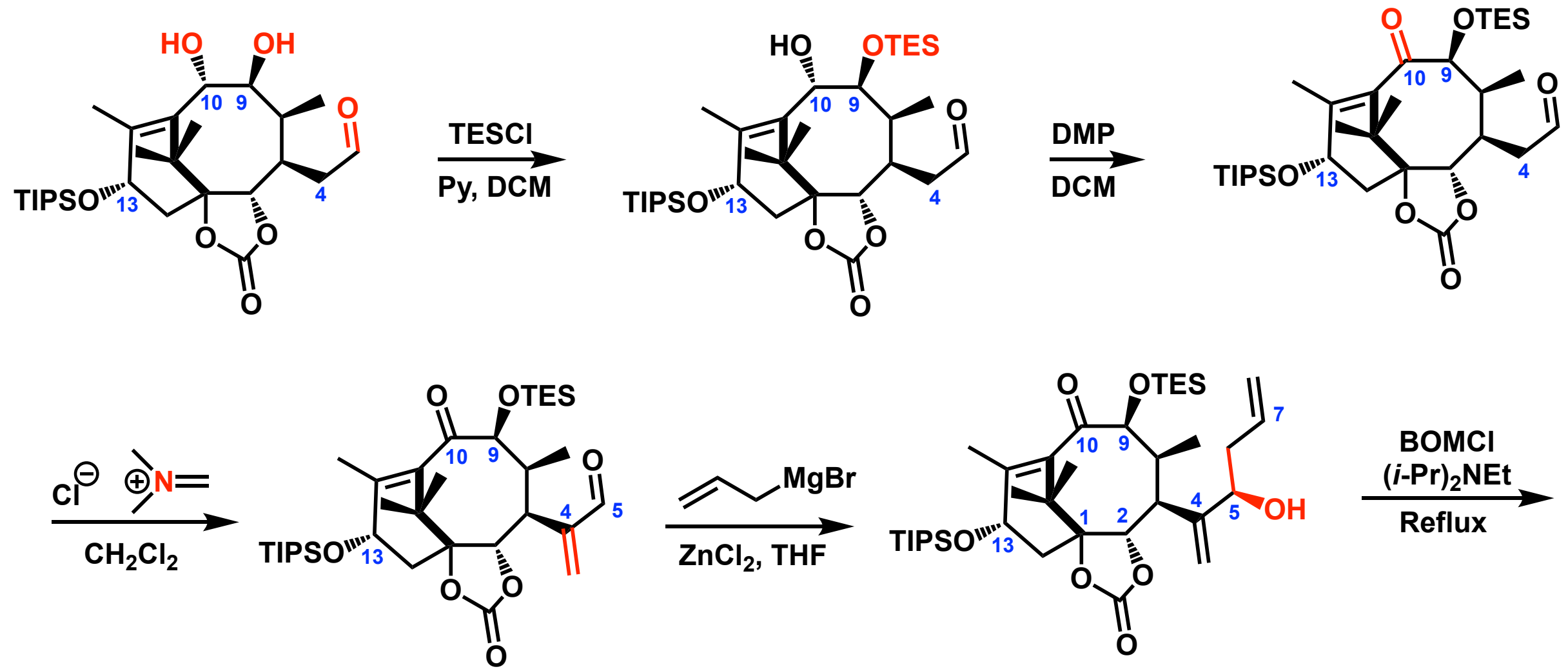


Wender's Total Synthesis

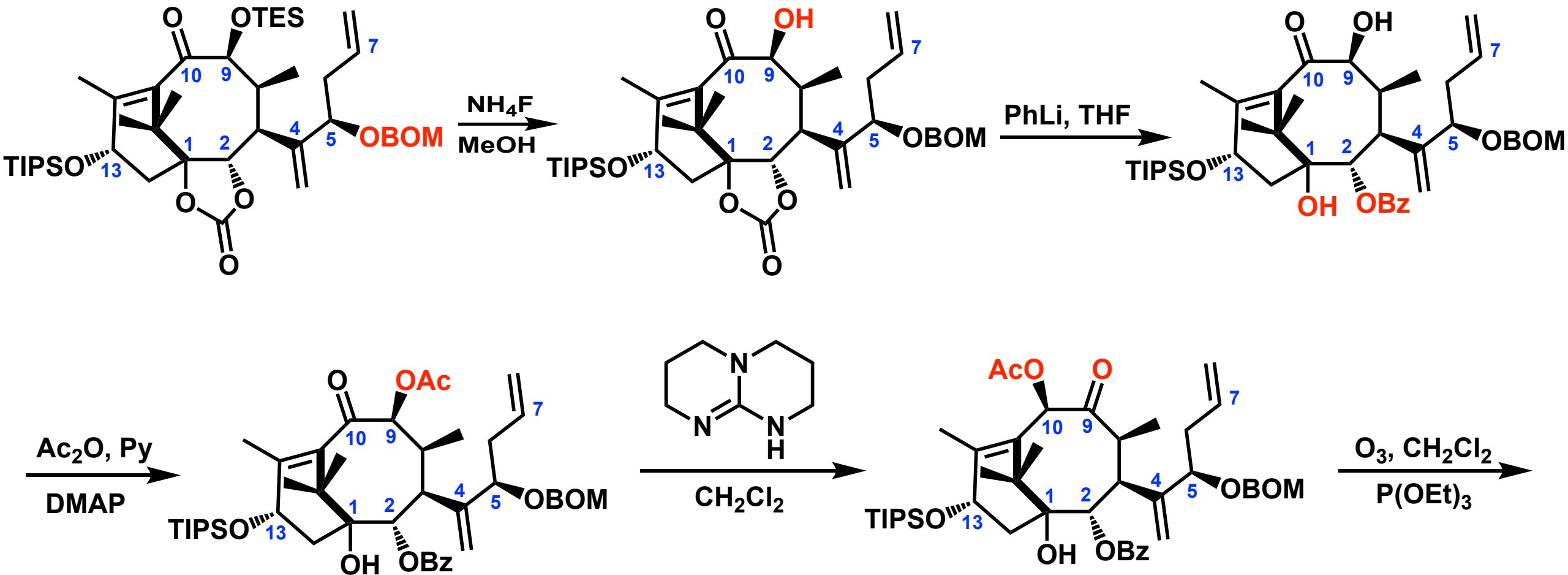




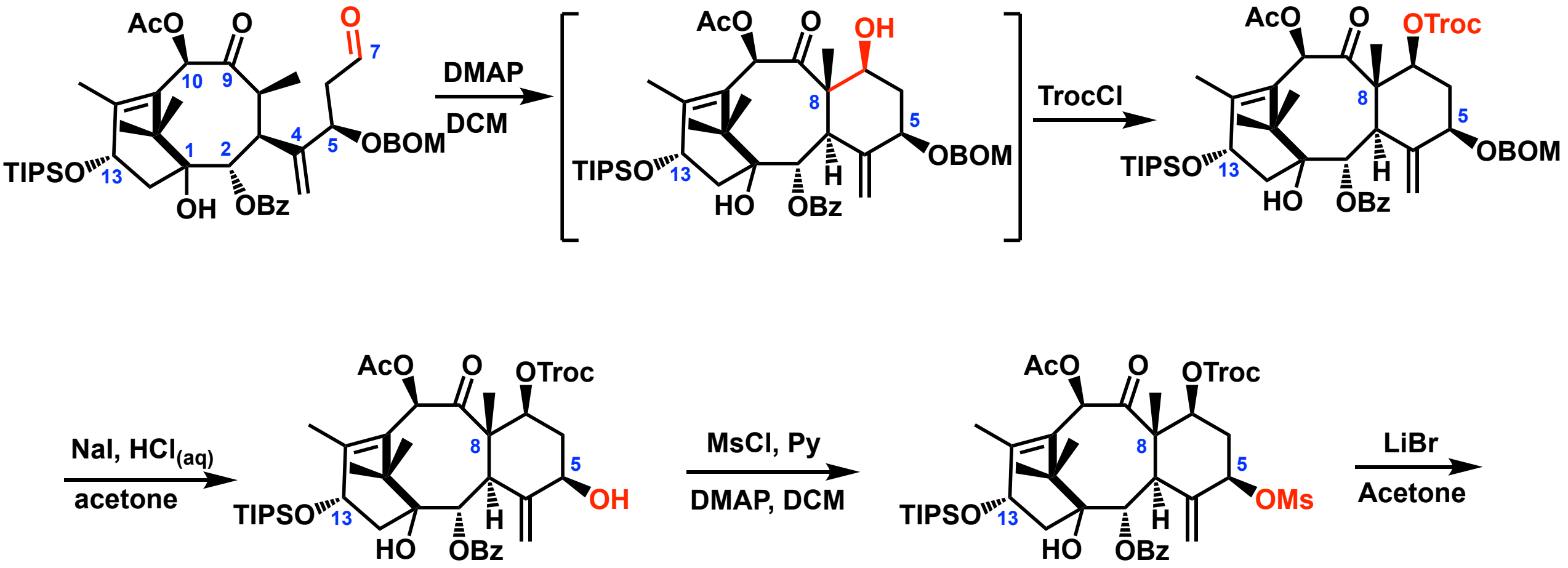




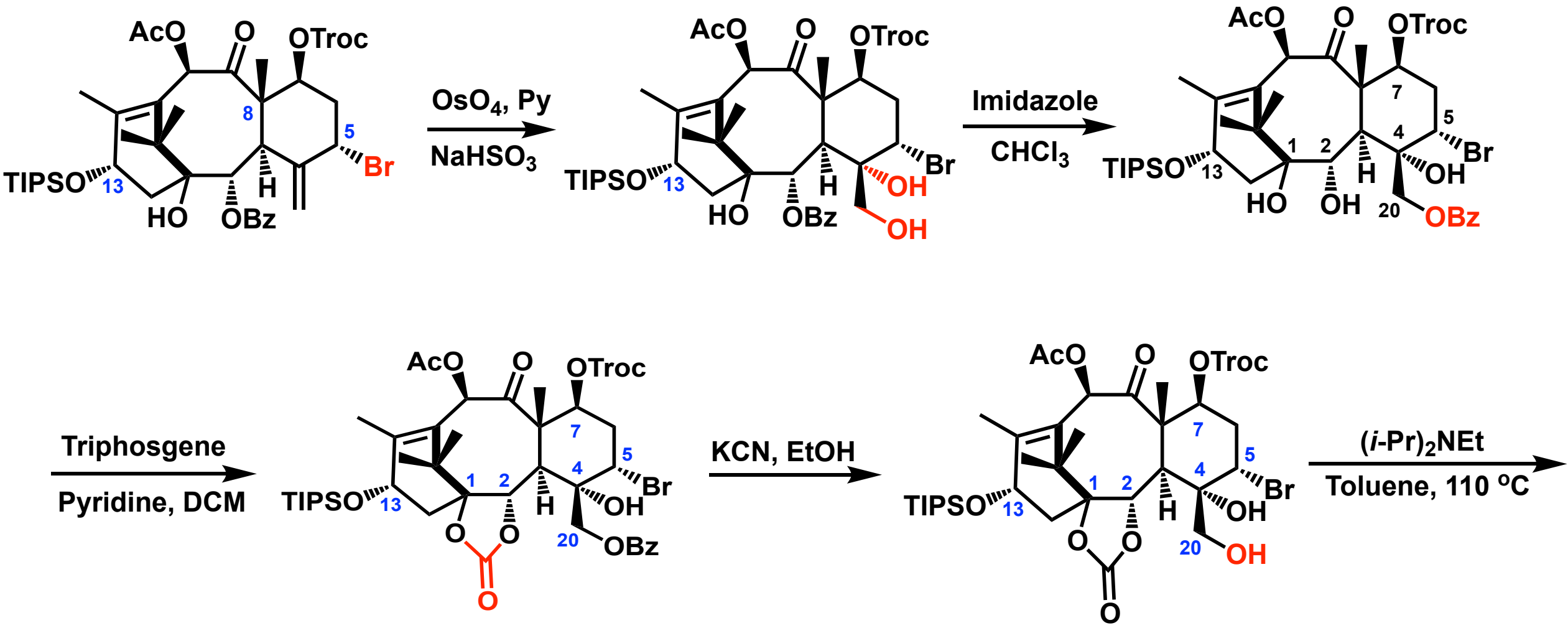
Wender's Total Synthesis



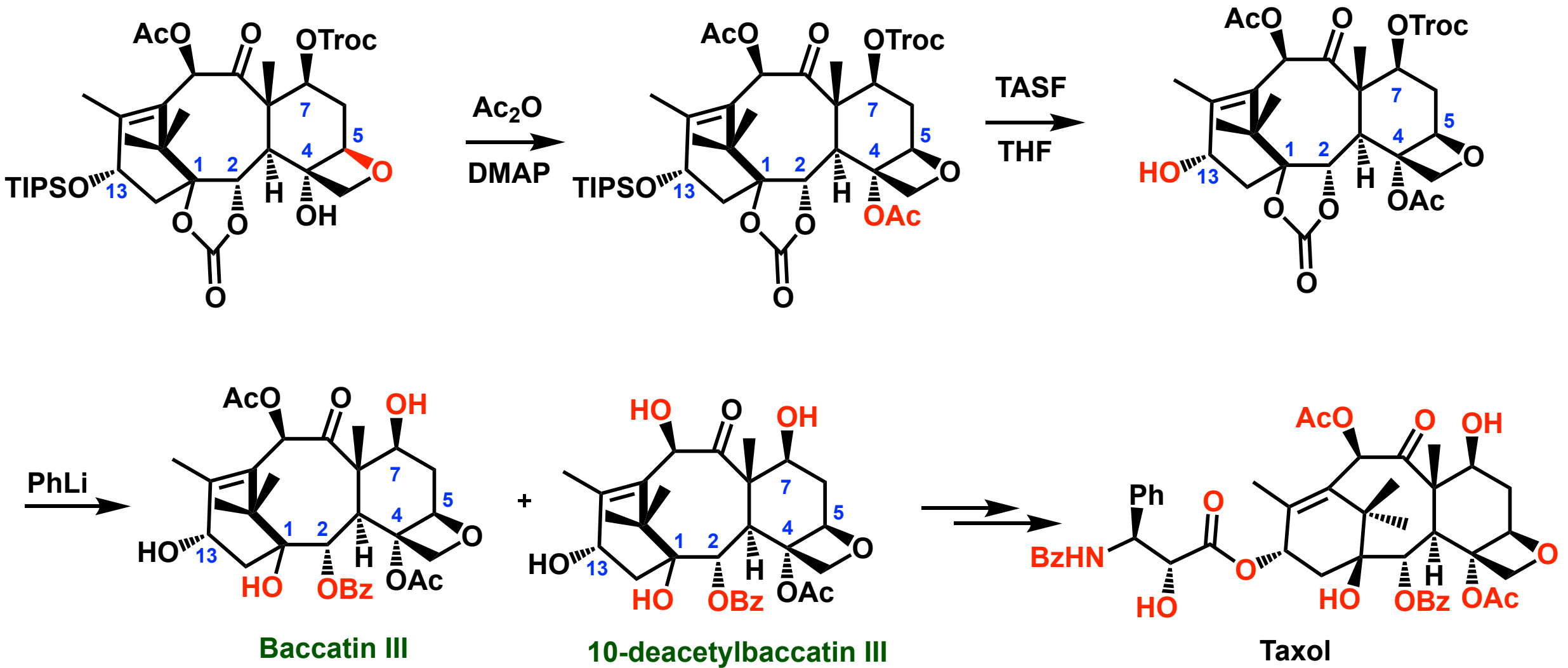
Wender's Total Synthesis



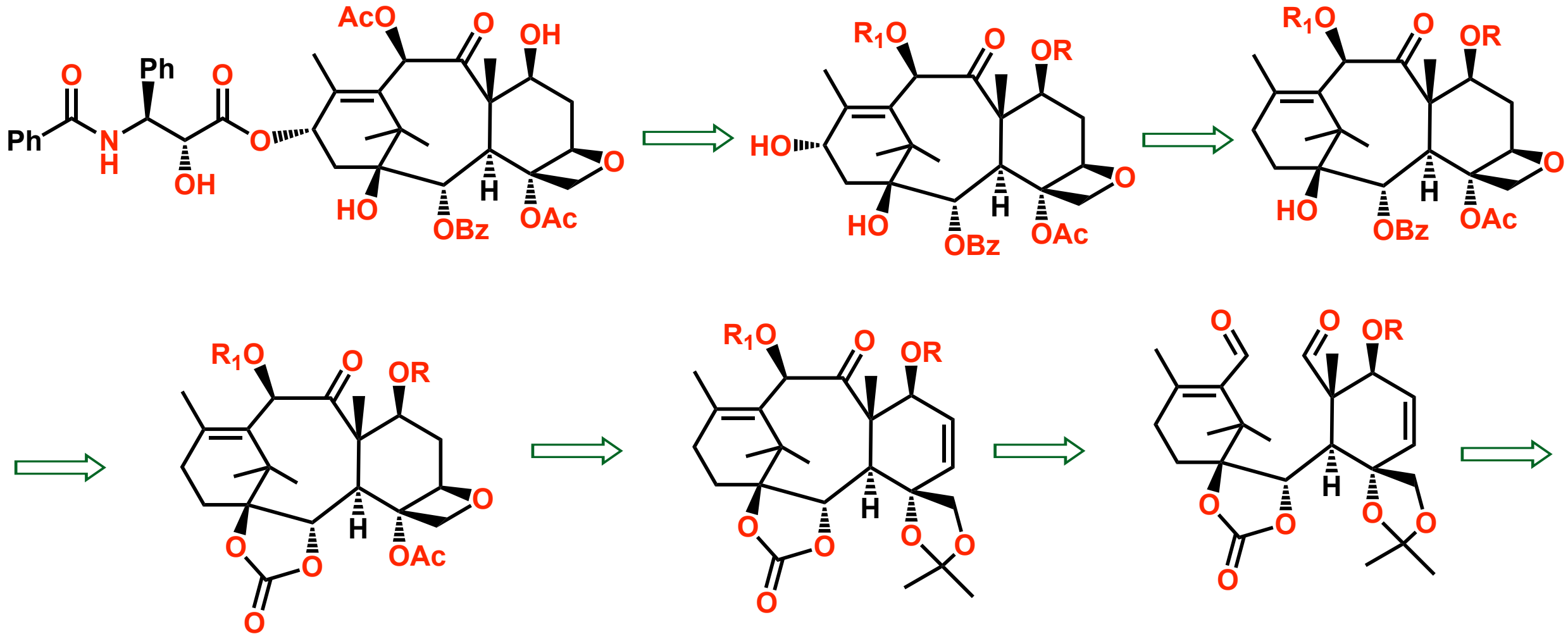
Wender's Total Synthesis

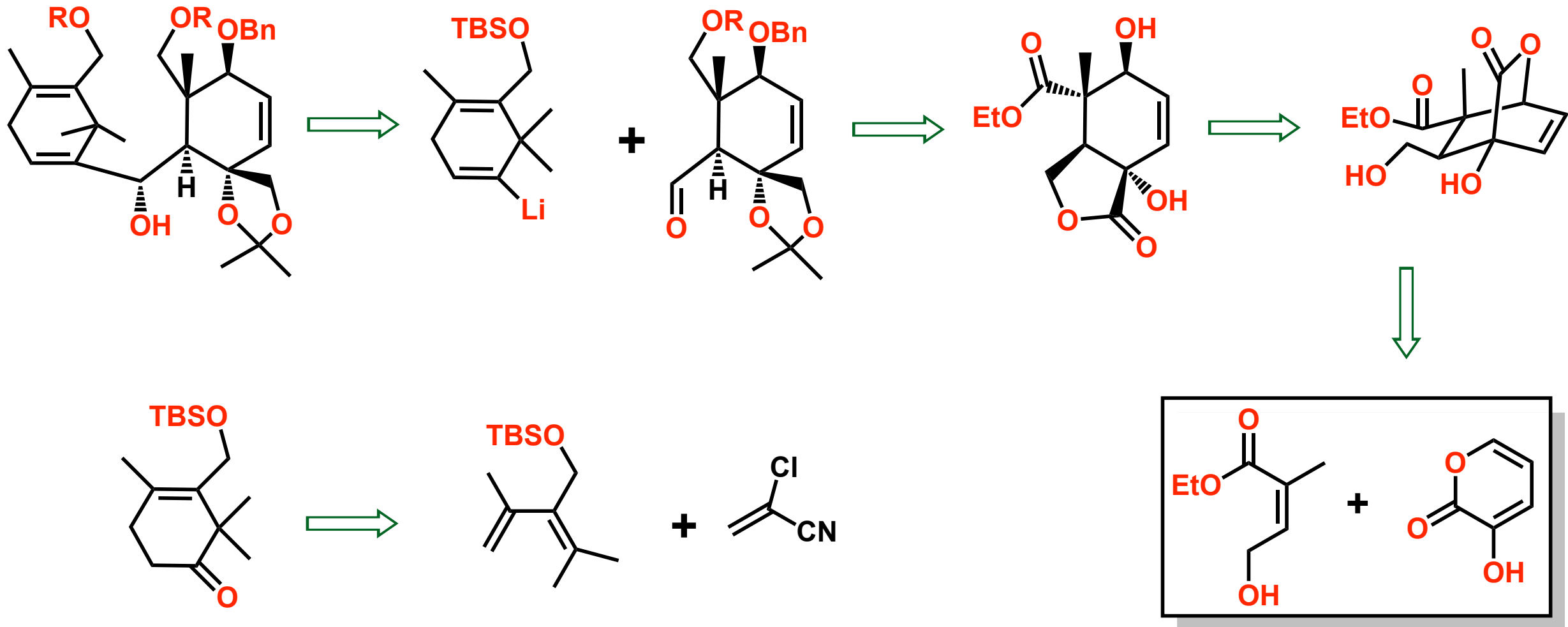


Wender's Total Synthesis



Retrosynthesis





Nicolaou's Total Synthesis

