Total Synthesis of Taxol



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Pathway to Discovery in Cancer Chemotherapy

In the second half of the 20th century, researchers realized the need for systemic treatments, such as chemotherapy and hormone therapy, to destroy cancer cells that had spread from the site of the original tumor to other parts of the body.

As Dr Wani describes it, "There was a lot of public pressure on NCI (National Cancer Institute, USA) that they should evaluate the natural products for the discovery of anticancer compounds, and they would always cite examples of countries like India, China, Latin America, Africa, where for centuries herbal products have been used as medicine.

However, the officers at the National Cancer Institute (NCI) were not too excited about exploring the potential of natural products for anticancer agents because maybe they were prejudice, and they said, yeah, nothing is going to come out of it. It's a waste of money.

But because of the public pressure, they decided to start the evaluation of natural products as potential anticancer agents but on a limited basis with limited funding and therefore initially they decided to evaluate the natural products from US flora."

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Taxol from Taxus Brevifolia

1962: Botanist Arthur Barclay collected bark from *Taxus brevifolia* in Washington State and send it to NCI.

The sample was one of approximately 114,000 plant specimens collected under the NCI program between 1960 and 1981.



Mansukh Wani in late 1960's

Initial cytotoxicity screening indicated promising activity.

1964: Additional bark (30 pounds) was collected to support isolation studies.

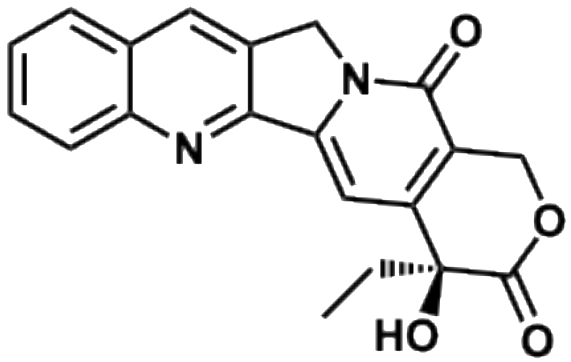
Initially it was sent to Dr. Morris Kupchan's lab as he was more prominent than Dr. Wall of RTI.

However, Dr. Kupchan was not interested as the sample showed high cytotoxicity

It was believed that anticancer compounds should be cytotoxic but not too cytotoxic

NCI to RTI for Screening

Dr. Wall wrote to NCI that his group is interested in working on this active compound because they were working on another interesting anticancer compound called camptothecin.



Camptothecin

Thus Wall and Wani of RTI undertook the challenging task of isolating the active compound.

Initially, the Pacific yew bark extract that showed cytotoxicity *in vitro* against KB cells but was found to be inactive *in vivo*

Had it not been for Dr Wall, this might have been the end of the studies with Pacific yew tree bark extracts

Despite the initial disappointing *in vivo results* with the complex *T. brevifolia* extract, fractions of the extract showed *in vivo* activity against P-534 leukemia,

This demonstrated the importance of investigating individual fractions rather than relying only on results obtained with a crude extract.

Promising Lead to Fear of Commercial Scale Up

Isolation was only the first challenge; determining the molecular structure proved even more difficult.

The researchers faced limitations in the analytical and chromatographic techniques available at the time.

Important questions remained regarding the molecular weight, elemental composition, and arrangement of functional groups.

In honor of the genus Taxus, and as the compound appeared to contain a hydroxy group, Dr Wall named the material that Dr Wani and his colleagues isolated as “taxol”

One day Dr. Wall called Dr. Wani into his office and said “We have been trying to characterize the taxol for a year and half but still couldn’t successfully achieve it. We don’t have unlimited money. As you know, we have to show progress every quarter, and NCI is not really interested in pursuing it further. This is because with bark being the only source, commercial synthesis would be difficult

Persistence and Hard Work Led to Discovery of Taxol

Dr. Wall told Dr Wani that 'forget about taxol'

But Dr Wani didn't want to give up and asked Dr. Wall whether he can work on low priority

Low priority means working during late evenings and weekends. Dr. Wall readily agreed for this.

Mansukh Wani used methanolysis to divide taxol into two fragments suitable for structural investigation.



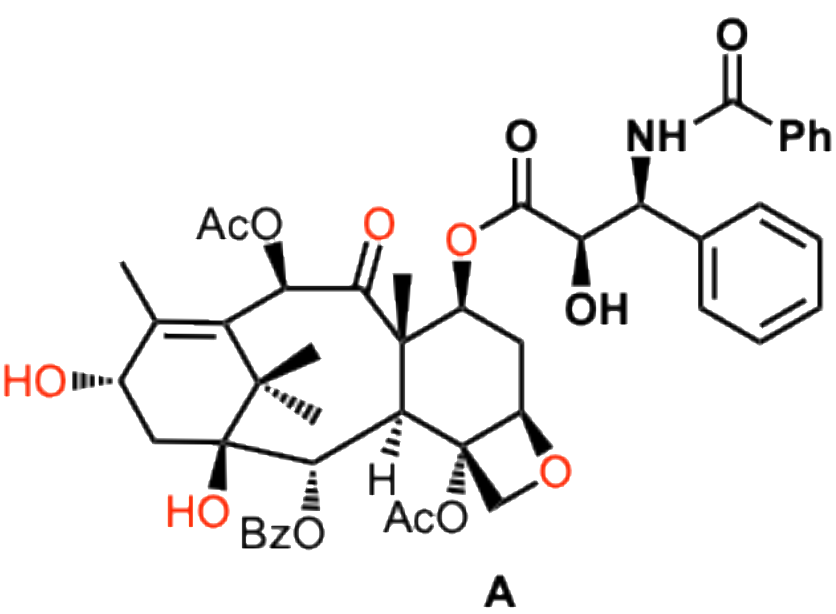
Dr. Monroe Wall and Dr Mansukh Wani

X-ray crystallography provided structural information, while chemical evidence helped establish how the fragments were connected.

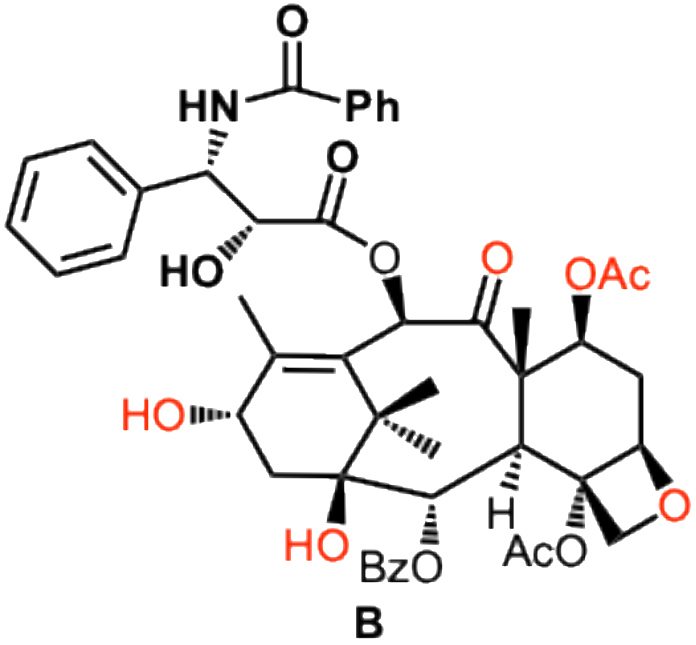
M. E. Wall, M. C. Wani, C. E. Cook, K. H. Palmer, A. T. McPhail and G. A. Sim, *J. Am. Chem. Soc.*, **1966**, *88*, 3888–3890.

Structure elucidation: Five years of persistence

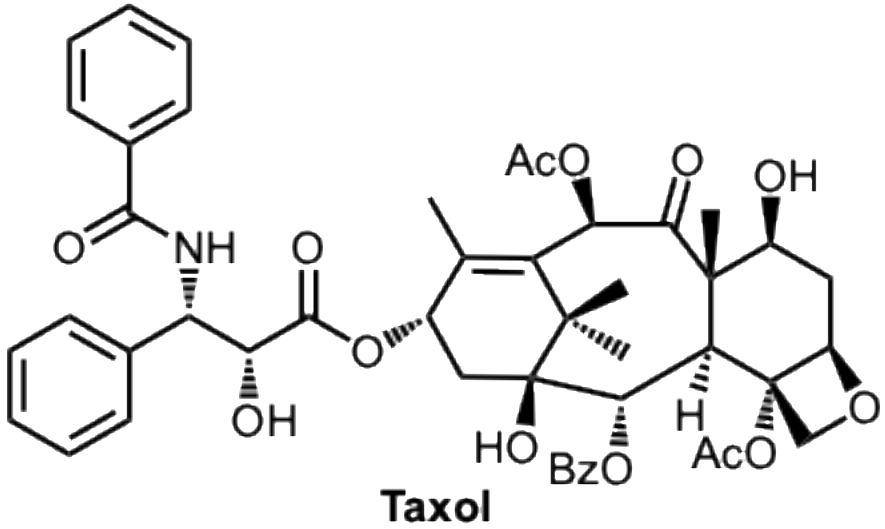
Wani proposed two structures 'A and B' based on methanolysis and crystal structure



A



B

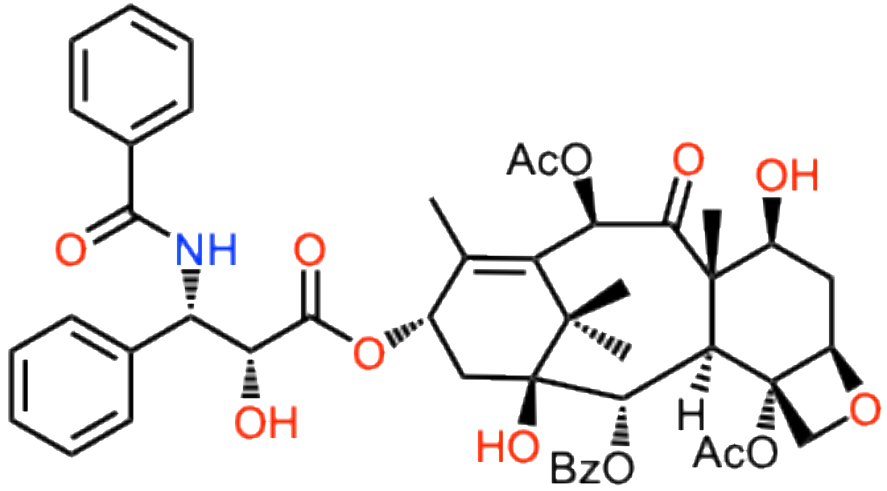


Taxol

Wani then agreed that structure A is the correct one and Dr. Wall agreed and wanted to send the publication

Wani then wanted to confirm it through one more reaction. If it has allylic alcohol, then upon oxidation, it should give α,β-unsaturated ketone. But taxol didn't undergo oxidation. That's how he proposed the correct structure

Why was Taxol Structurally Remarkable?





Seeds and bark of *Taxus brevifolia*

Taxol possesses a complex, highly oxygenated taxane framework.

Its structure contains a compact polycyclic carbon skeleton, multiple functional groups, and numerous stereogenic centres.

The molecule contains an unusual four-membered oxetane ring, which contributes to its distinctive structural architecture.

Its complex three-dimensional structure presents substantial challenges for stereoselective synthesis.

The reported structure contains 11 stereogenic centres, making stereochemical verification especially important

From Structural Discovery to Chemical Synthesis

Although paclitaxel could be found in different parts of pacific yew tree, highest concentration was found in the bark. Still the yield was very poor (0.025% from the plant material

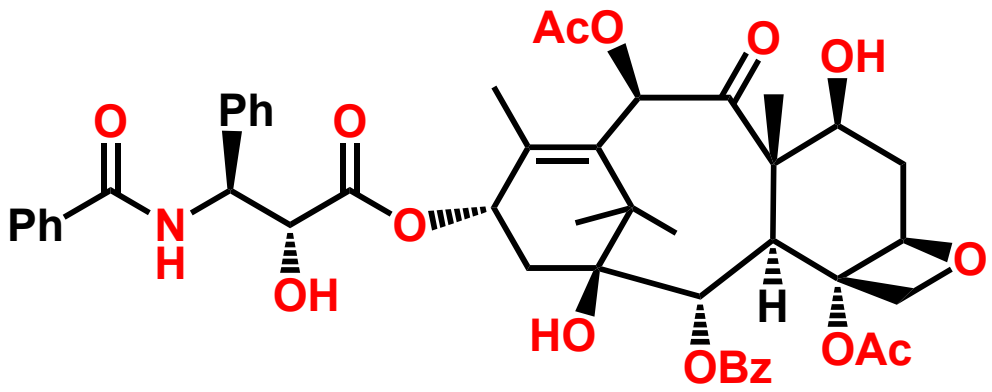
Worse, removing the bark means killing the tree. A single patient would require several trees. It is almost impossible to kill all the trees, which is also a very slow growing tree.

Total synthesis provided powerful evidence supporting the assigned molecular structure and stereochemistry but didn't provide solution to the commercial supply due to too many steps to synthesize

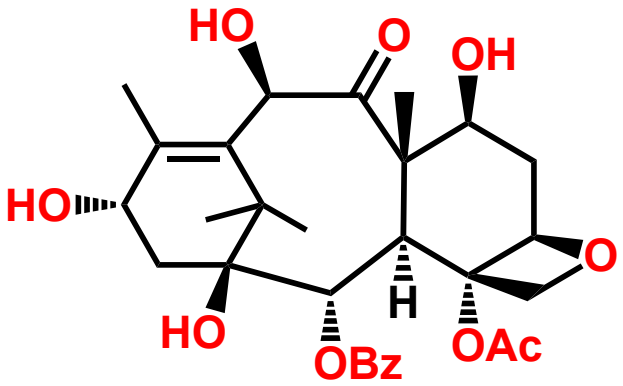
Fortunately, 10-Deacetylbaccatin (having the complete core structure of taxol) was found in the leaves of yew trees. Further these leaves are fast growing and so one need not cut the tree.

Robert Holton from Florida State University followed a semisynthetic approach to synthesize taxol from 10-DAB by attaching the side chain to meet its clinical demand.

Total & Semi-Synthesis of Taxol



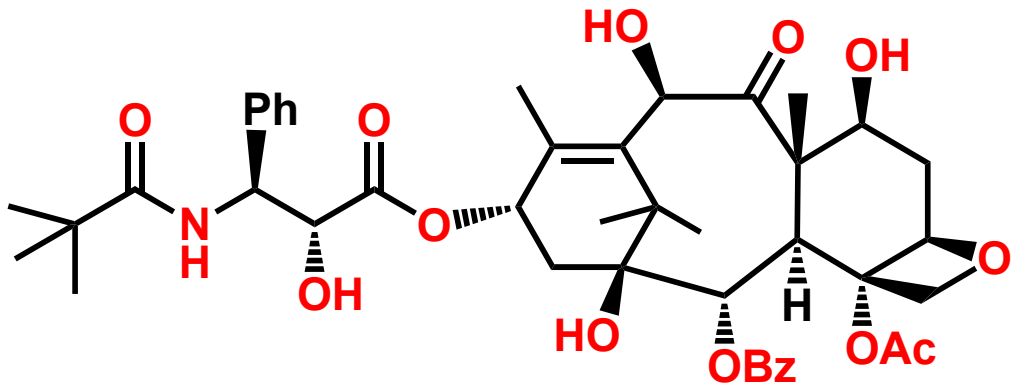
- **Isolation:** It was isolated from the bark of pacific yew tree in 1962 and the structure was elucidated in 1971 by Wall & Wani through X-ray
- Has attracted the attention of many synthetic chemists over the last three decades
- Has been successfully used for the ovarian and breast cancer treatment
- Over 200 groups started this journey towards the synthesis of taxol. So far 11 groups have reached the shore.



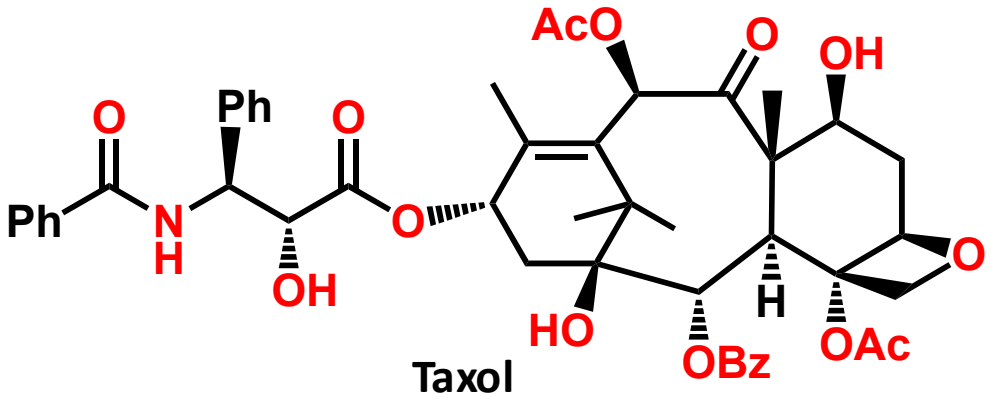
10-Deacetyl Baccatin-III

- 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

Analogues of Taxol



Taxotere/docetaxel

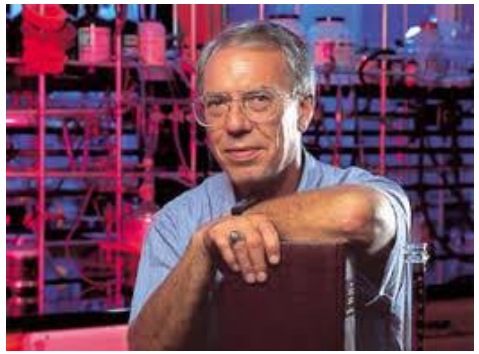


Taxol

- 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

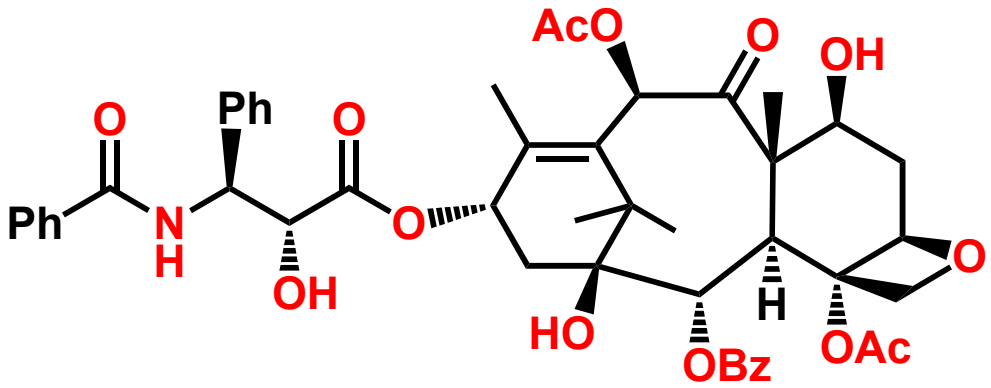
1. Robert A. Holton-1994 (SM- Patchulol)
2. K. C. Nicolaou-1994 (SM-Mucic acid)
3. S. J. Danishefsky-1996 (SM-Weiland Micher Ketone)
4. Paul Wender-1997 (SM-Verbenone)
5. Isao Kuwajima-1998
6. Teruaki Mukayama-1998 (SM-L-Serine)
7. T. Takahashi-2006 (SM-Geraniol)
8. Sato-Chida-1996 (Formal Synthesis)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



Holton's Total Synthesis of Taxol

Holton's Total Synthesis of Taxol

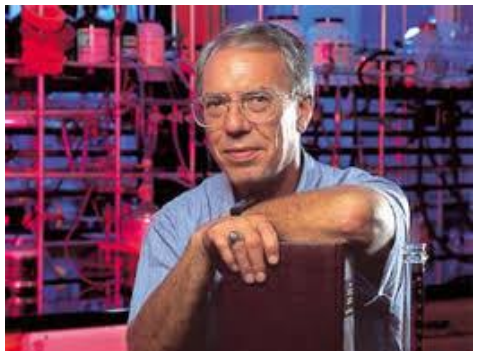
Synthetic Challenges



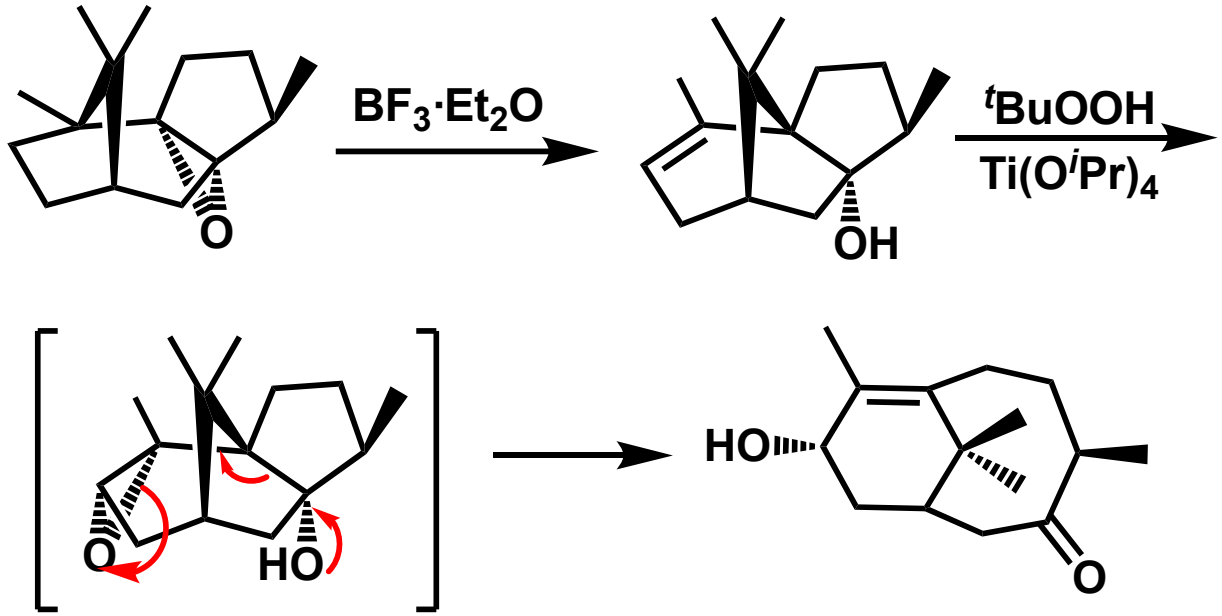
Highly congested C-ring with many chiral centers

8-Membered B-ring

6-8-6 Carbocyclic system

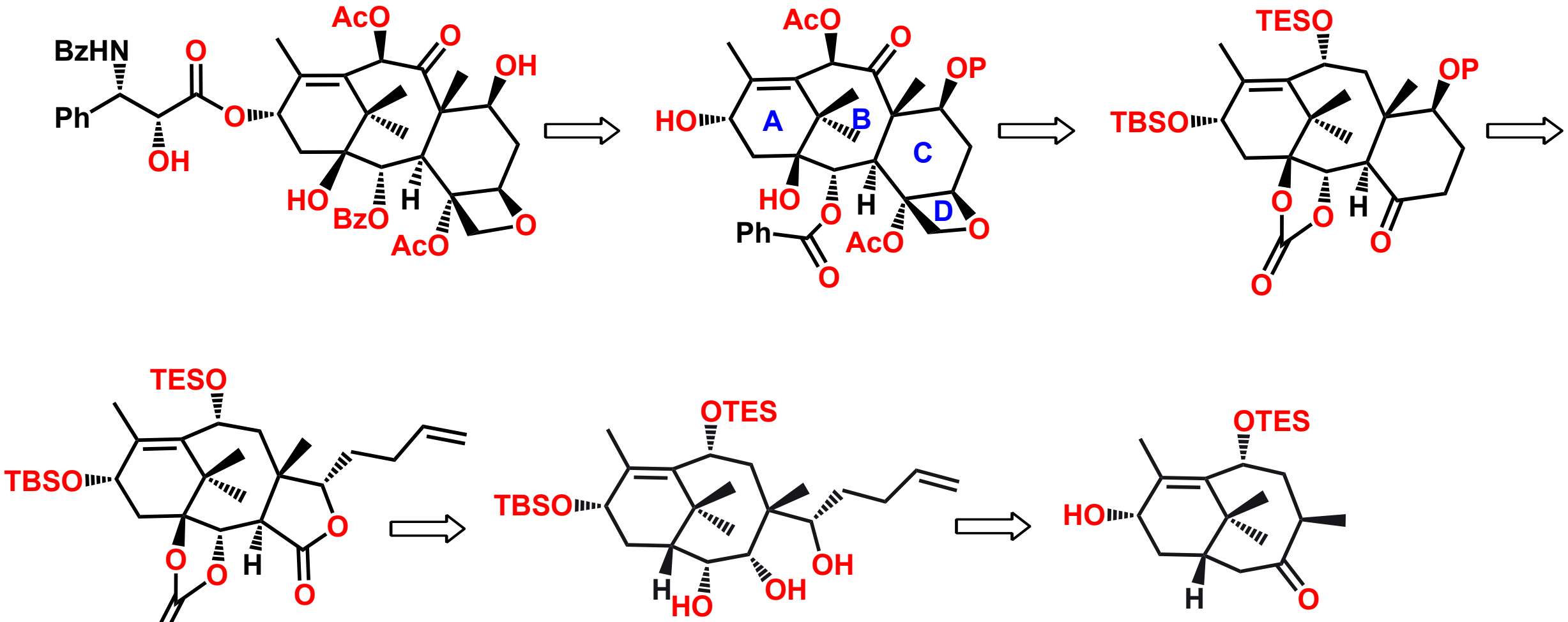


Key Reactions



- 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

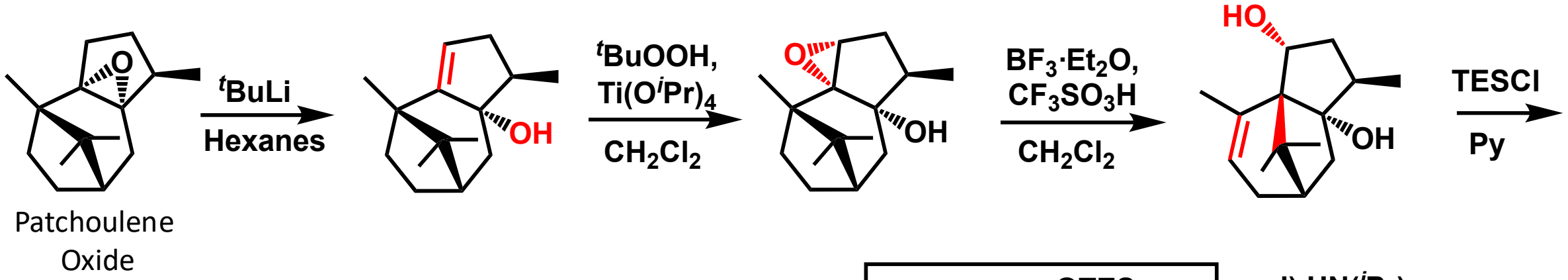
Holton's Retrosynthesis

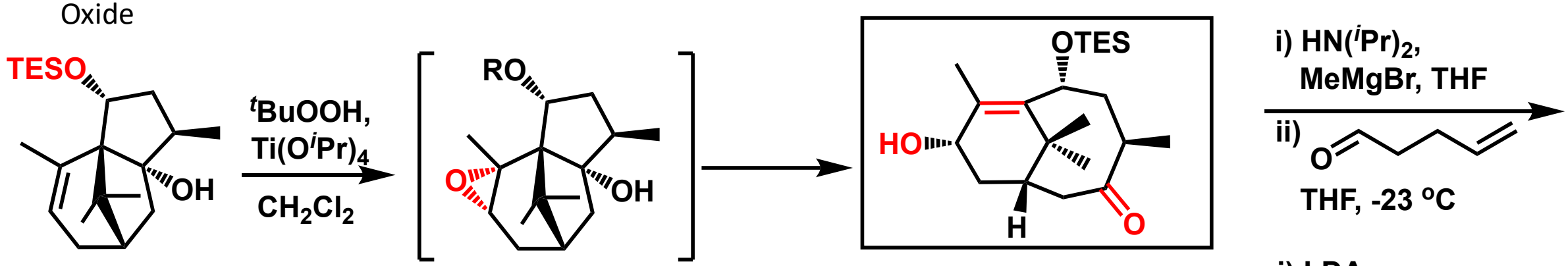


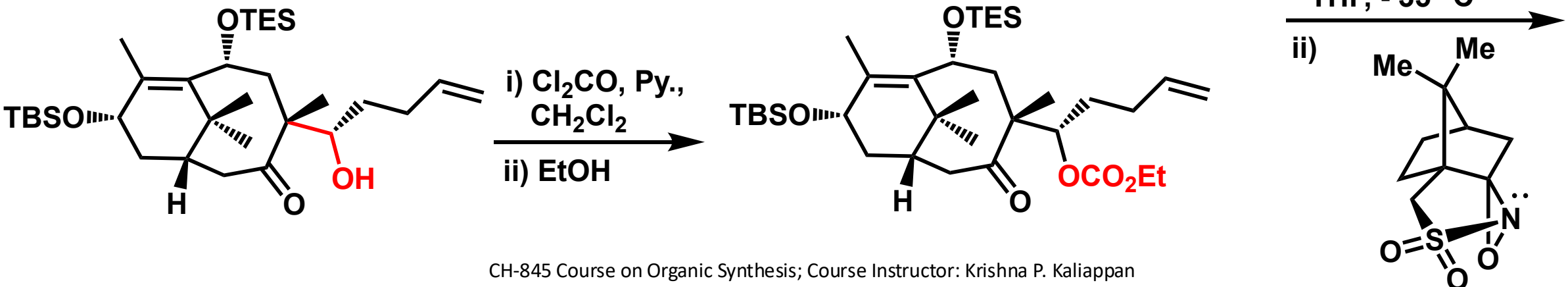
Holton, R. A.; *et al. J. Am. Chem. Soc.* **1994**, *116*, 1597-1598

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

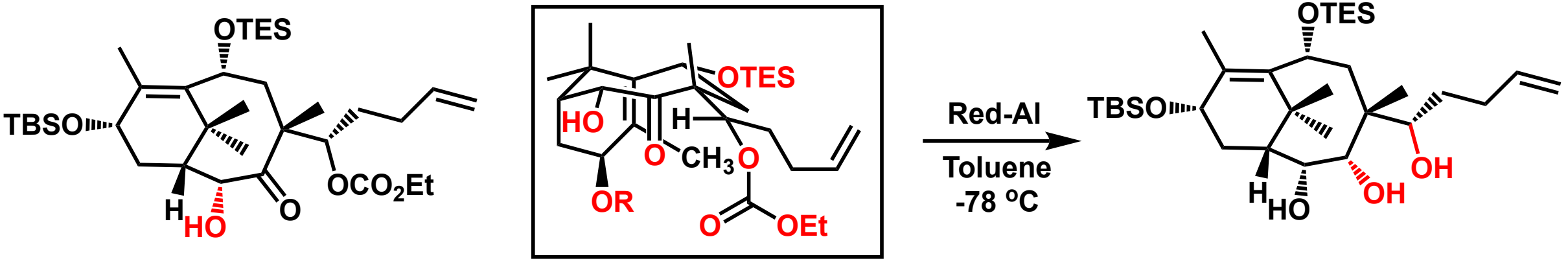
Holton's Total Synthesis



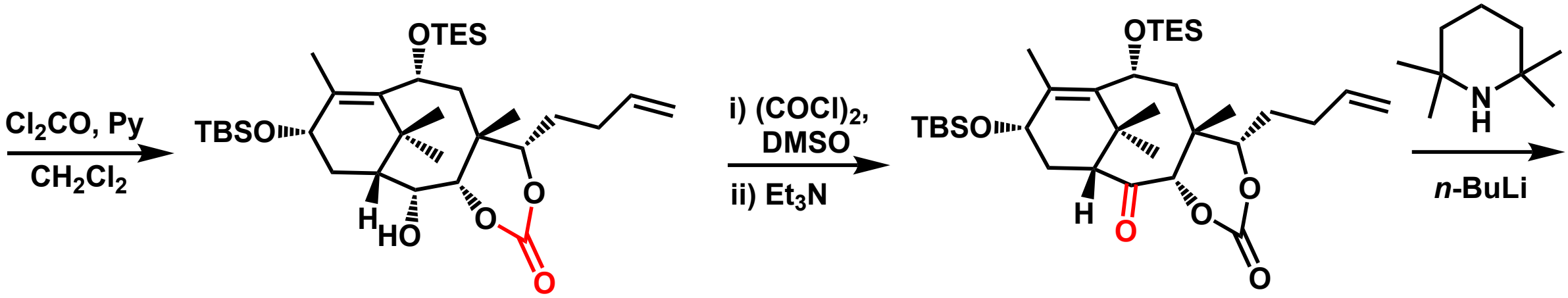




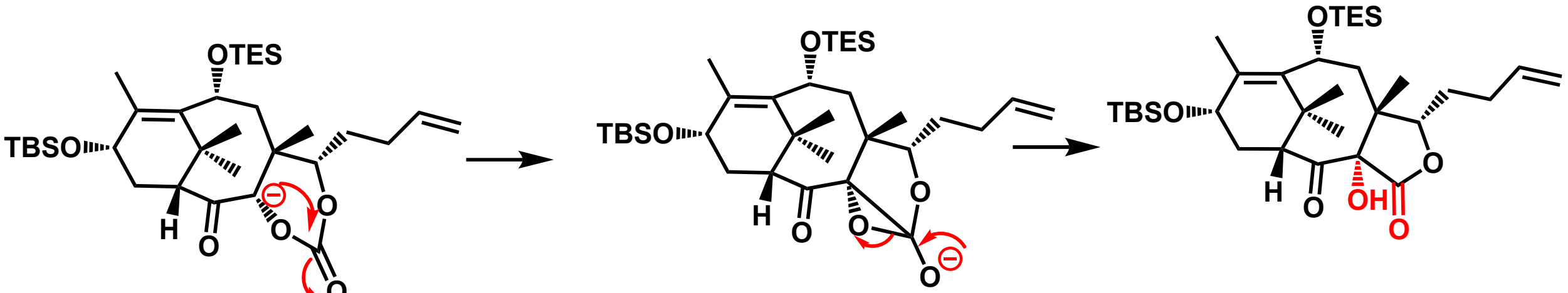
Holton's Total Synthesis



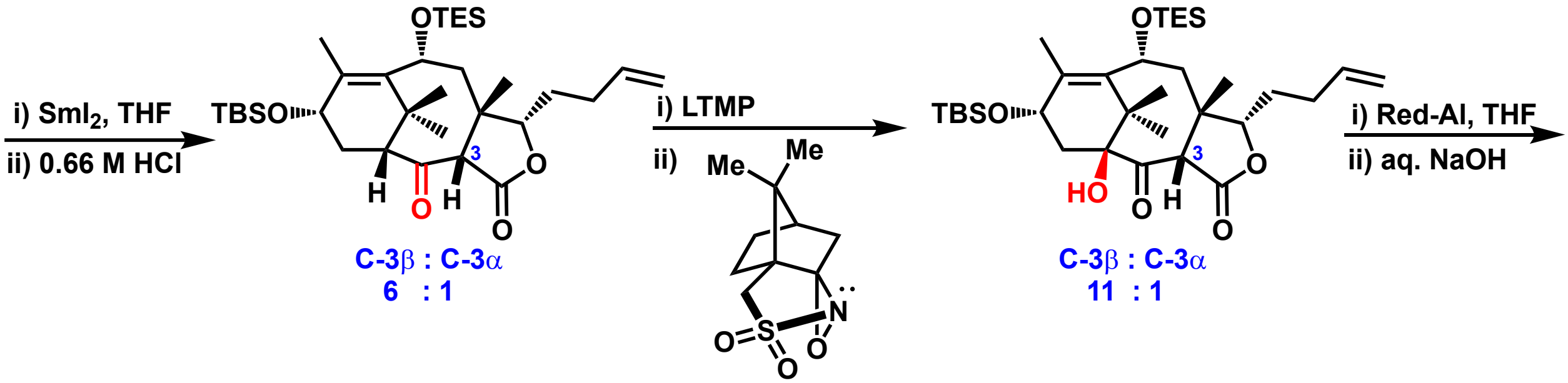
Boat-Chair Conformation



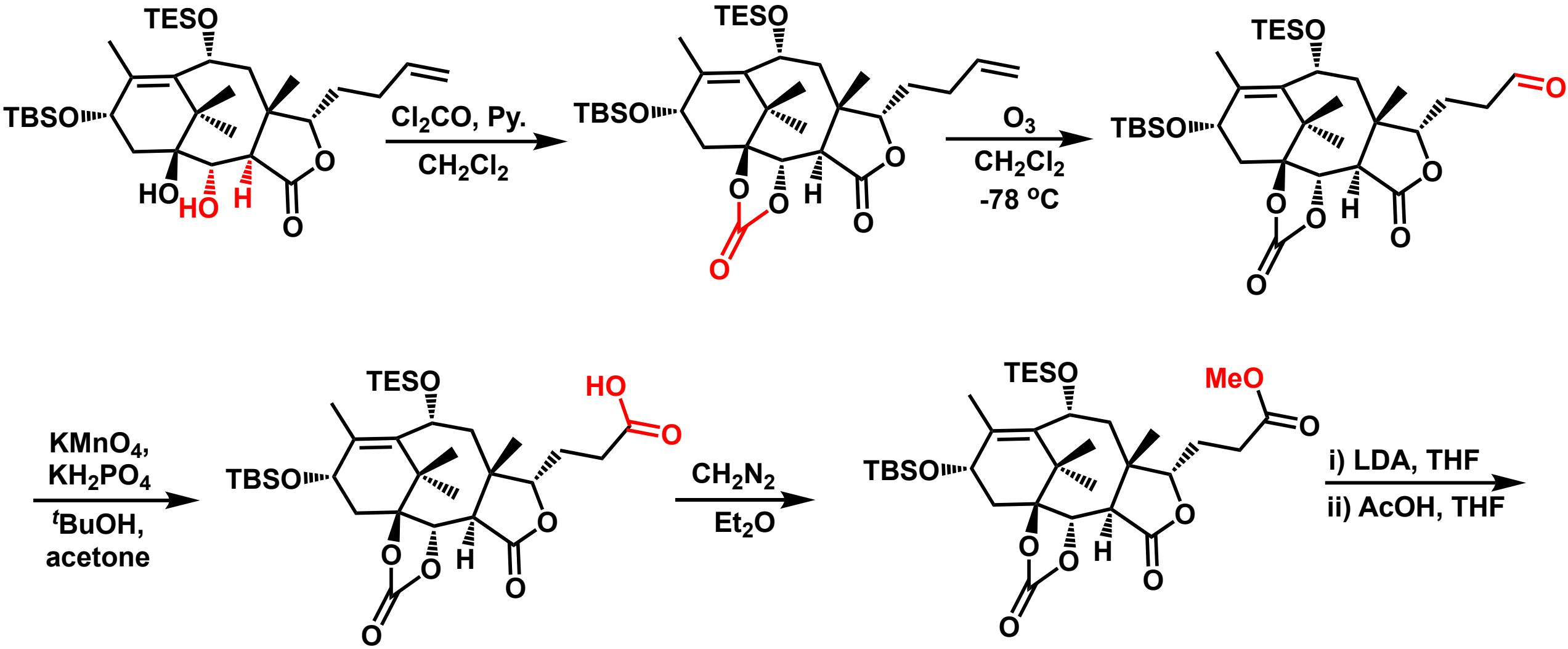
Holton's Total Synthesis



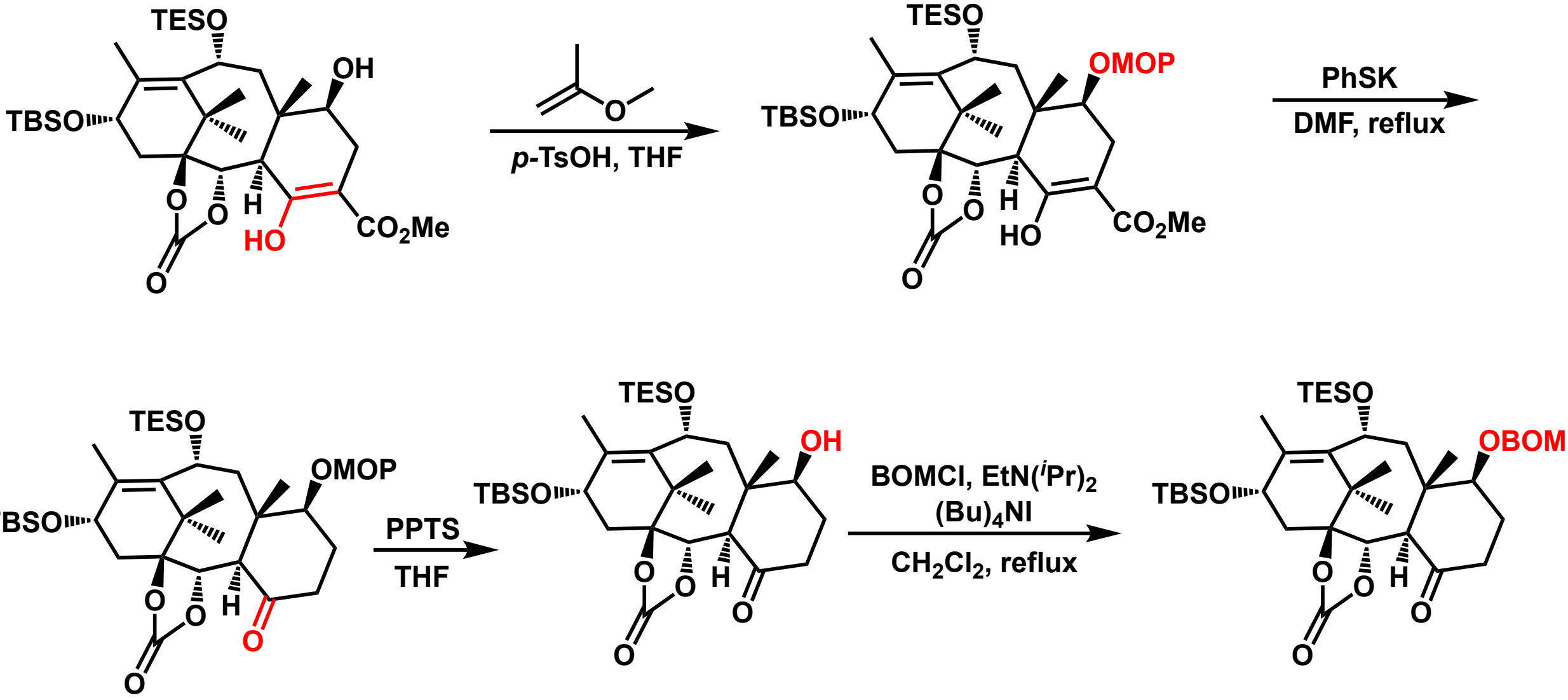
Chan, T. H. & *co-workers. Tetrahedron Lett.* **1984**, *25*, 3399-3402



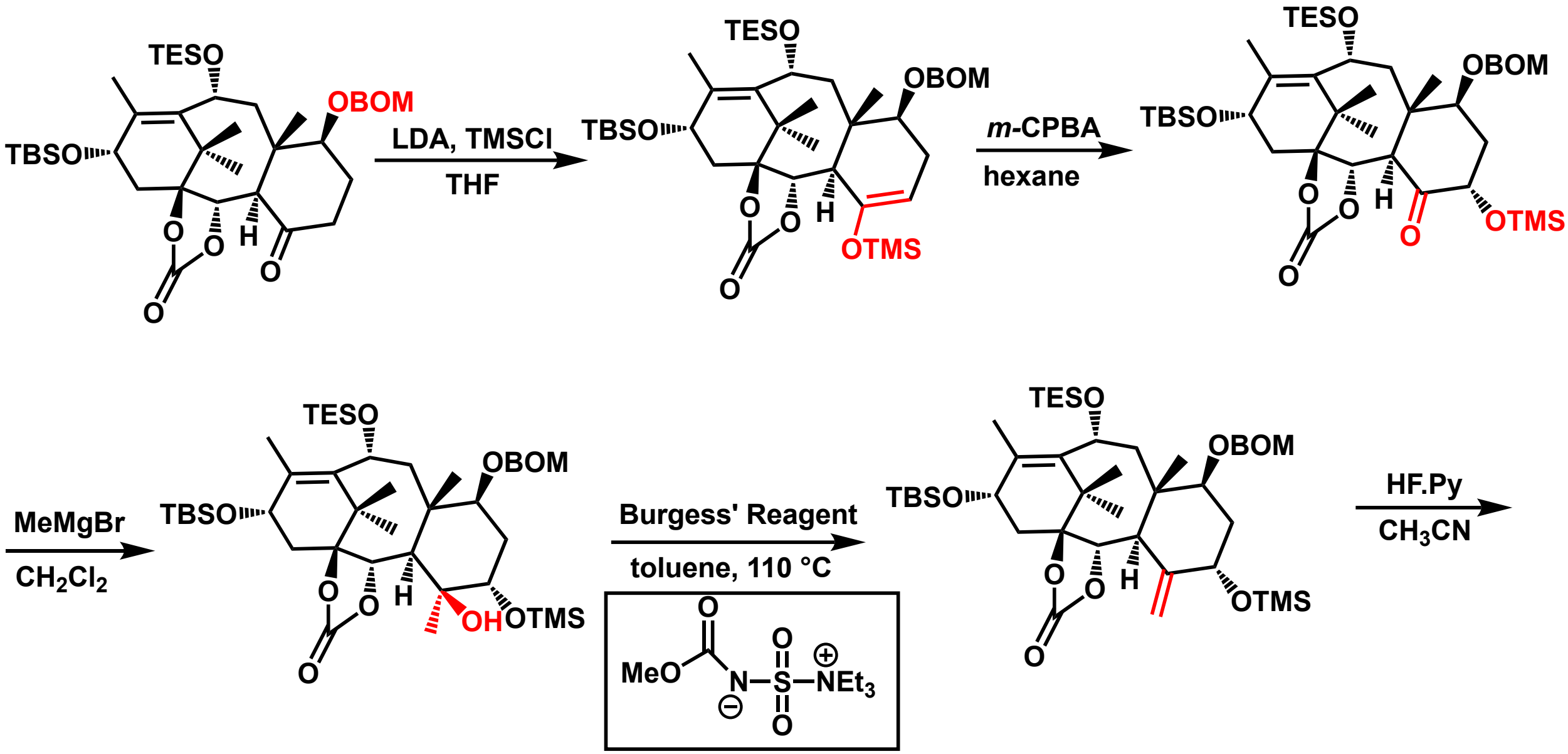
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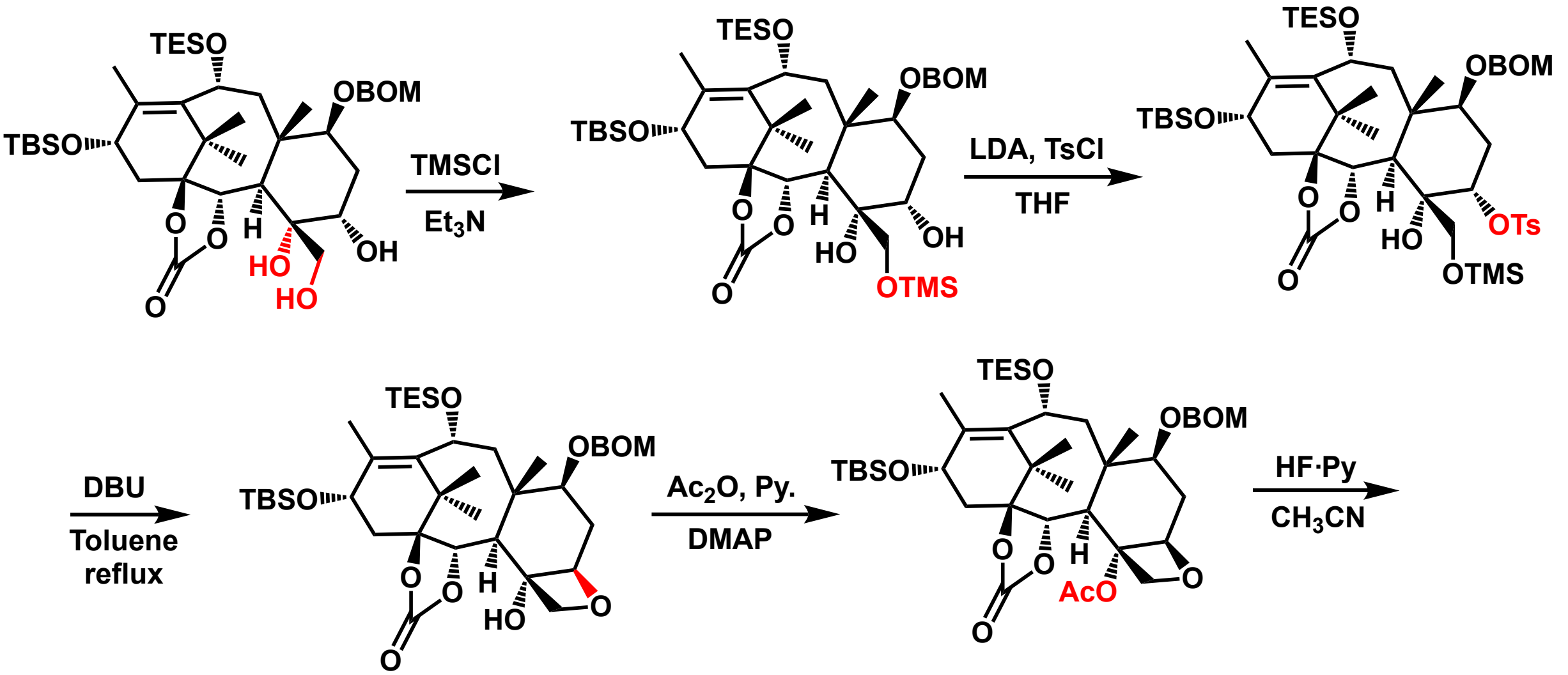
Holton's Total Synthesis



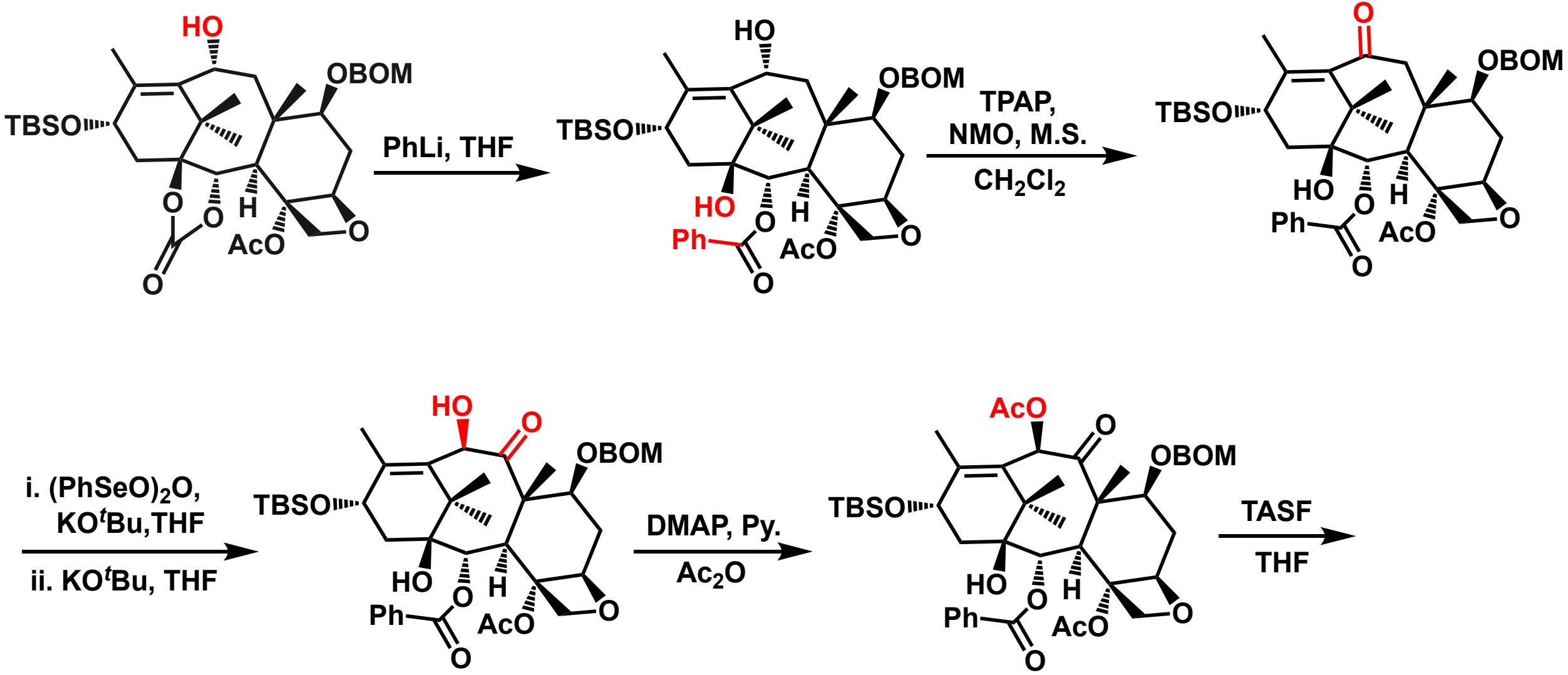
Holton's Total Synthesis



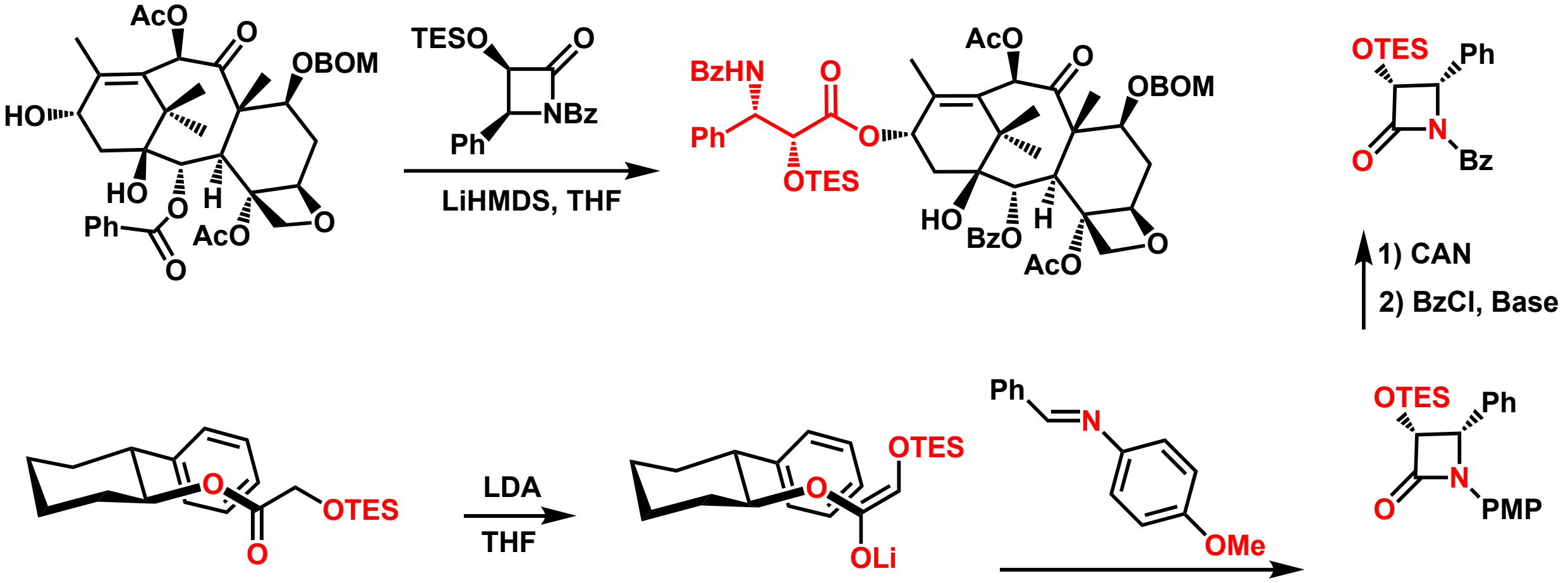
Holton's Total Synthesis



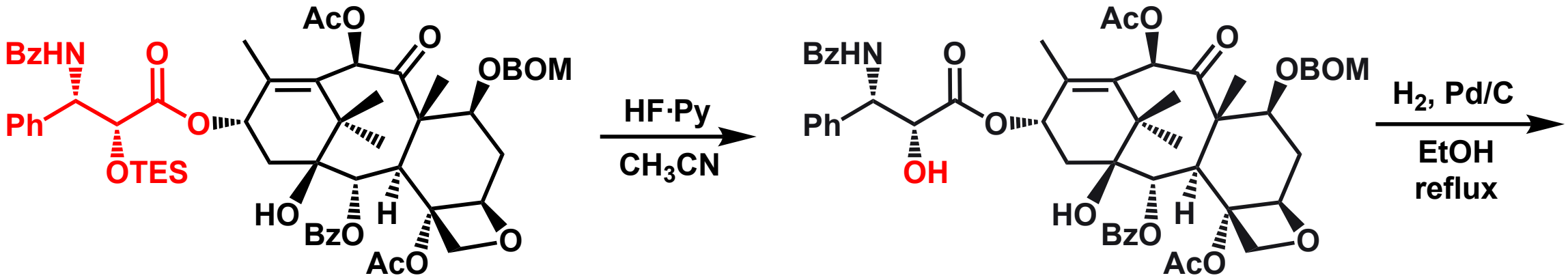
Holton's Total Synthesis

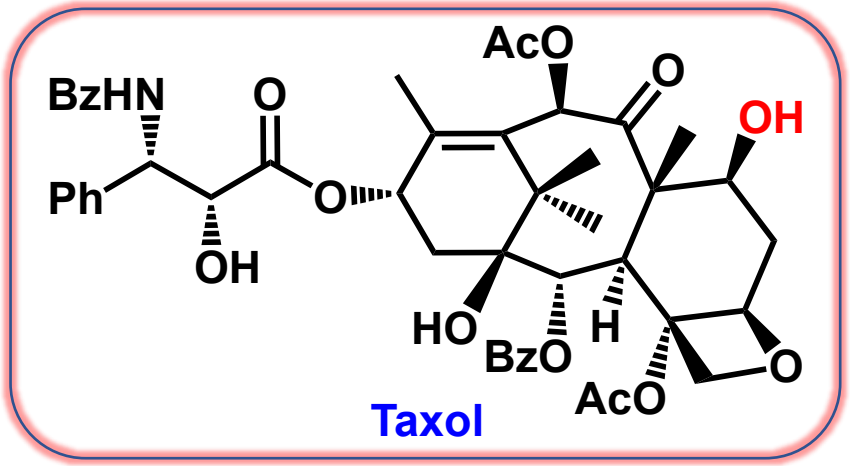


Holton's Total Synthesis

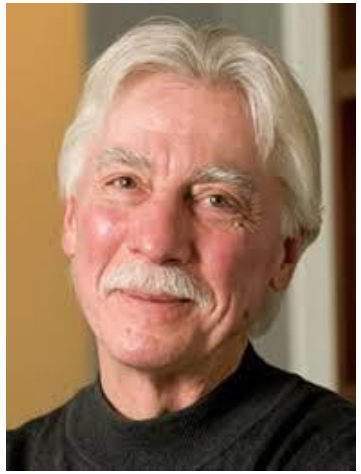


Holton's Total Synthesis



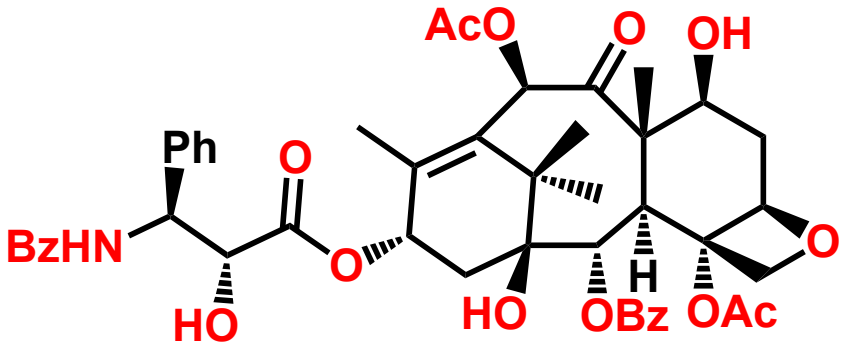


- The first total synthesis of Taxol was accomplished by Holton *et al.* in 1994
- The synthesis starts from patchino, a commercially available natural compound
- The key chemical transformations in this synthesis involve, Chan rearrangement, epoxy alcohol fragmentation and Dieckmann cyclization
- Their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



Wender's Total Synthesis of Taxol

Wender's Total Synthesis



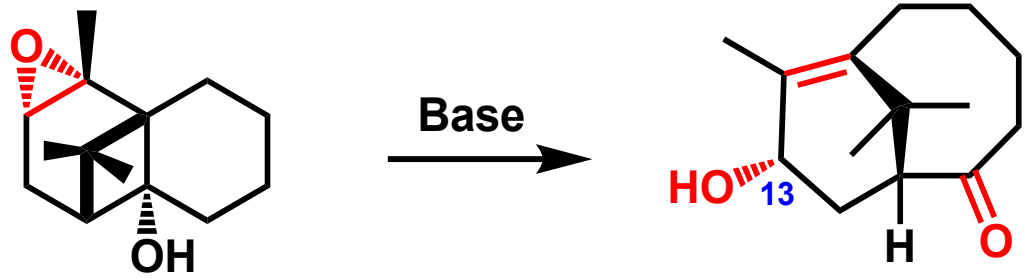
Taxol

- 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

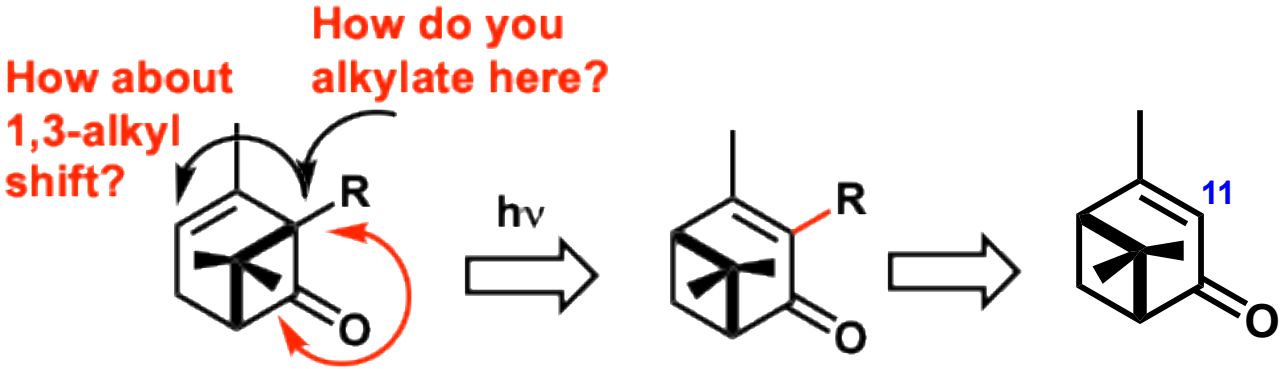
Wender, P. A.; *et al. J. Am. Chem. Soc.* **1997,** 119, 2755-2756

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

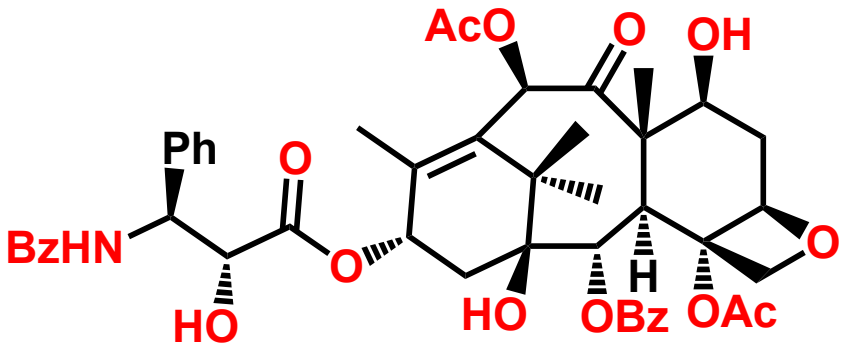
Basic Idea





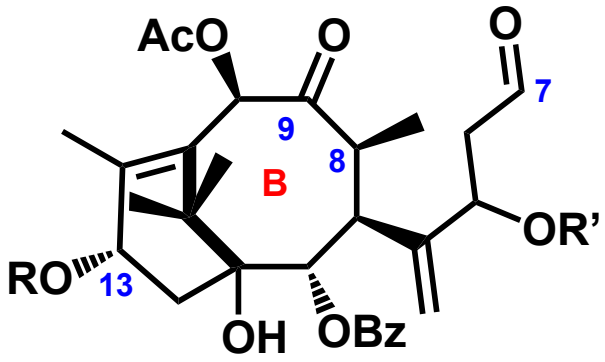


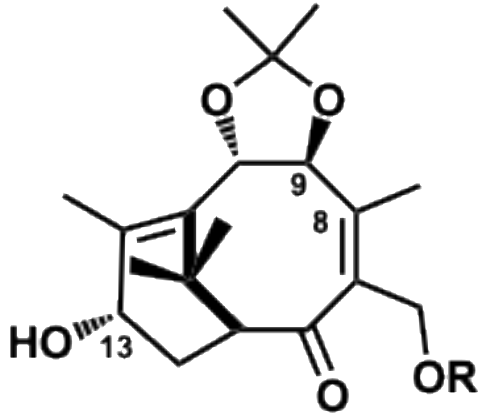
Wender's Retrosynthesis



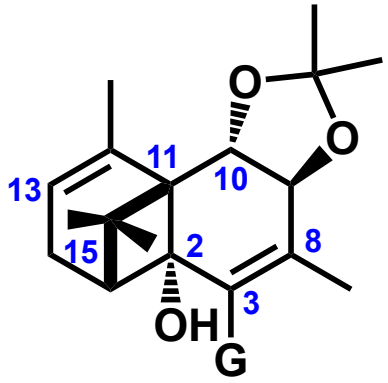
Taxol

Aldol

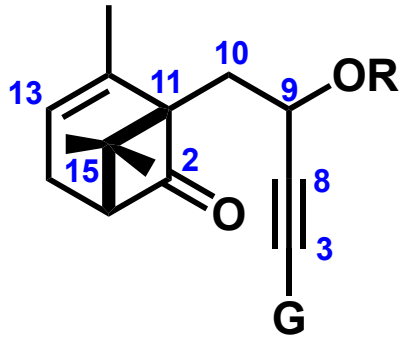




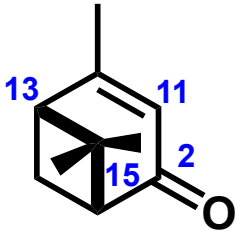
fragmentation



C2-C3

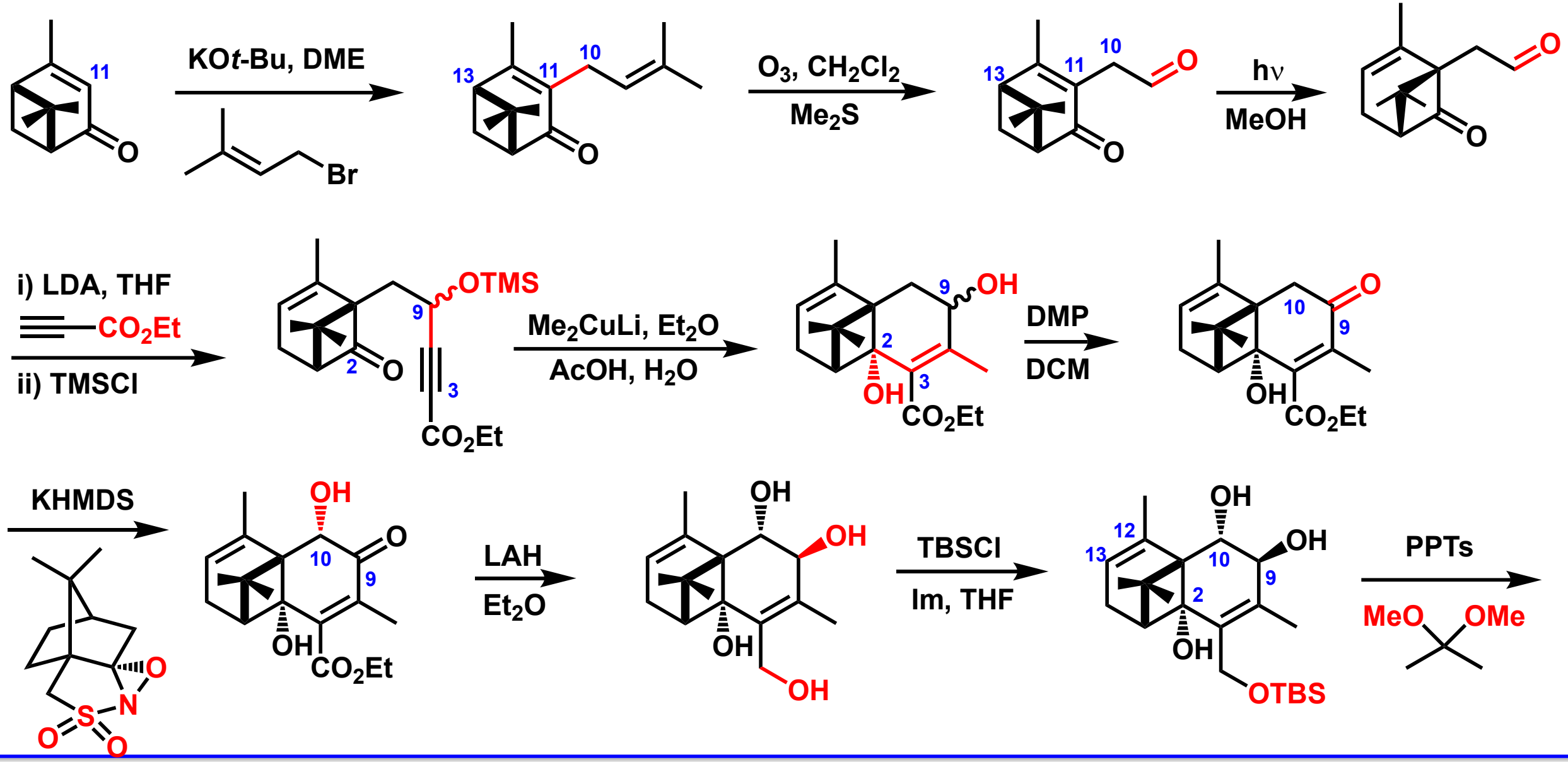


C11-C10

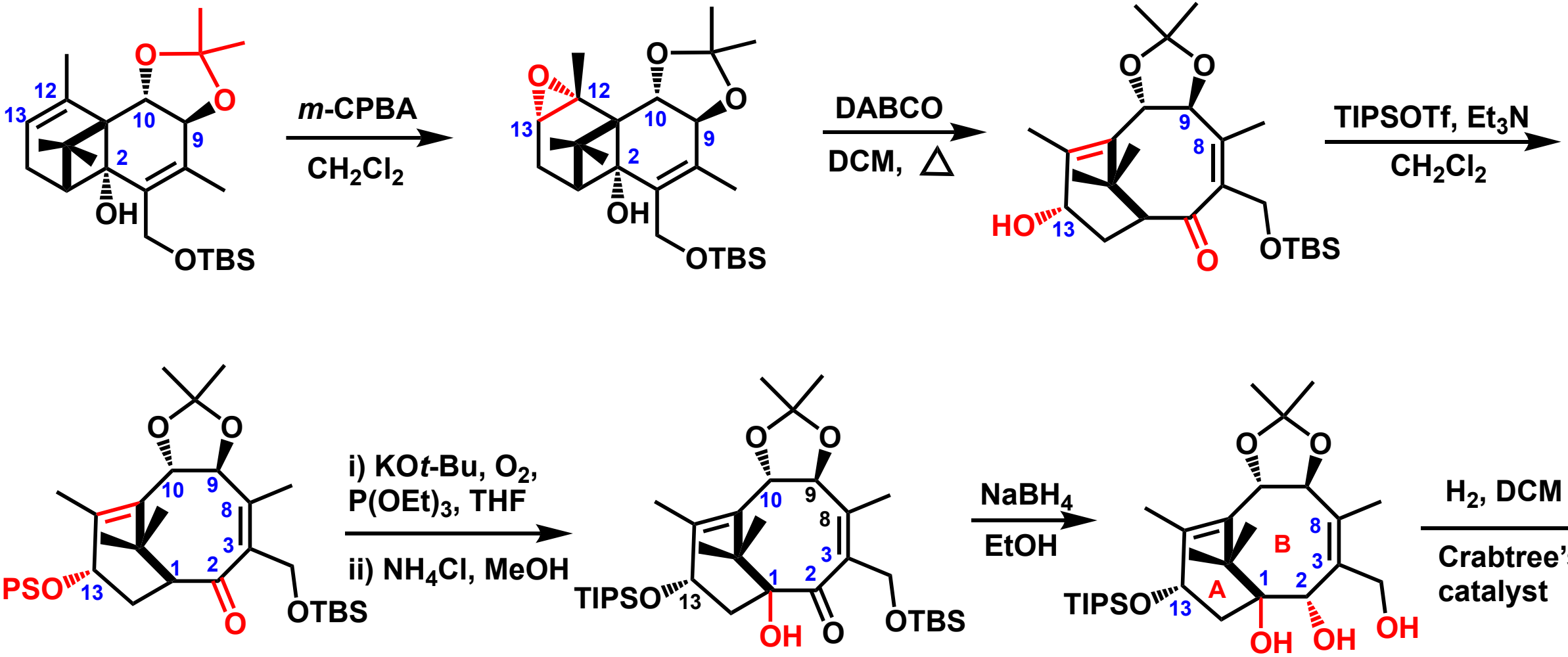


Verbenone

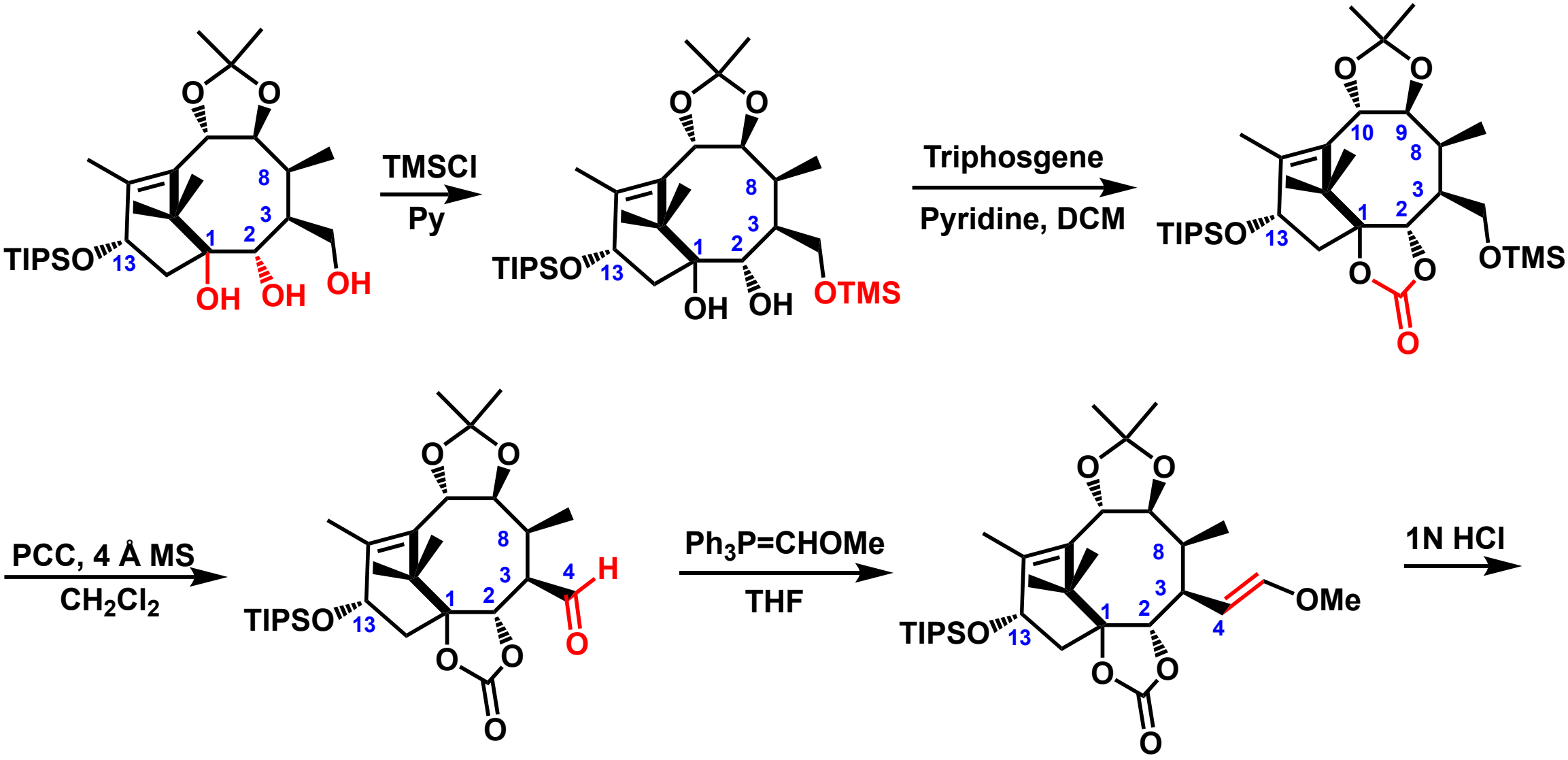
Wender's Total Synthesis



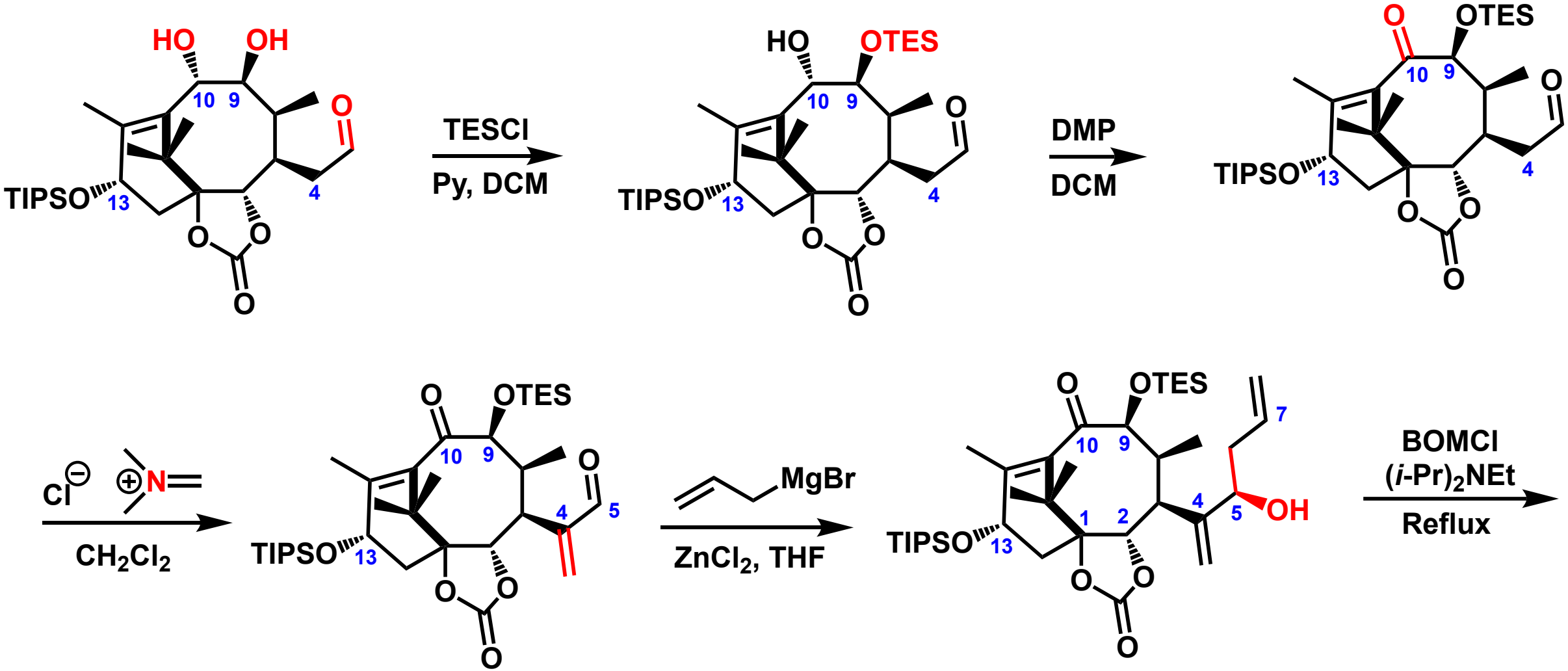
Wender's Total Synthesis



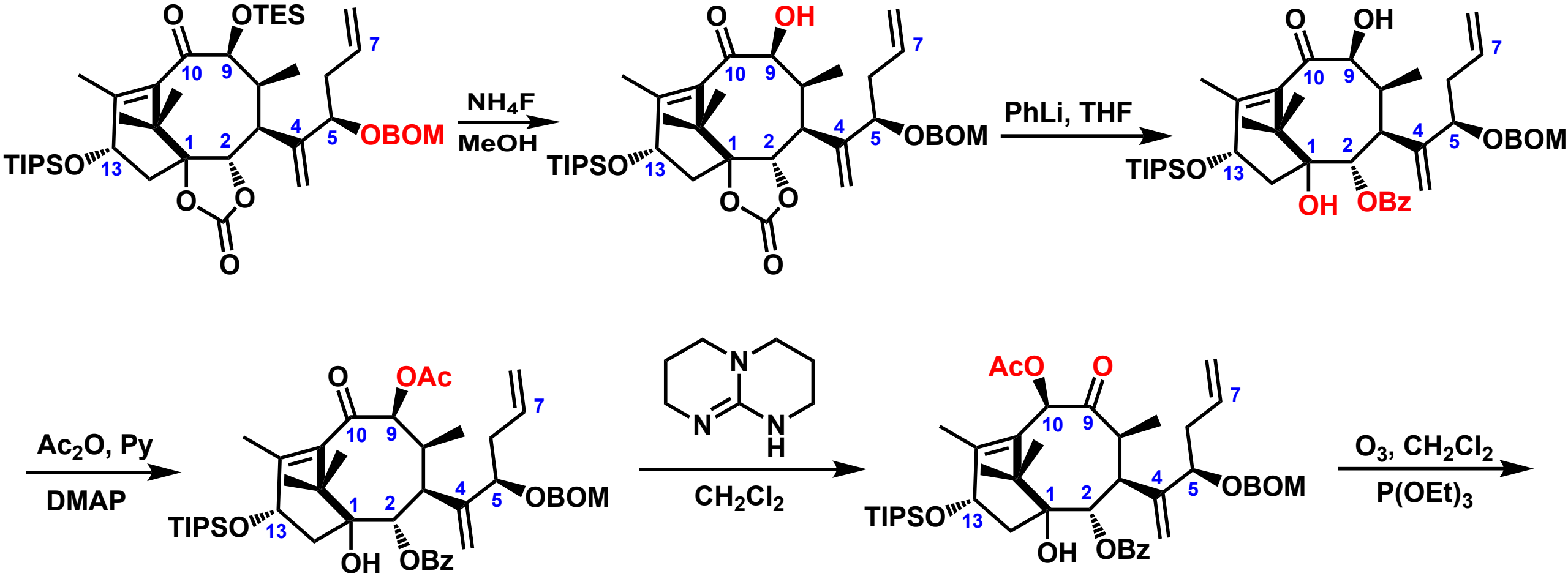
Wender's Total Synthesis



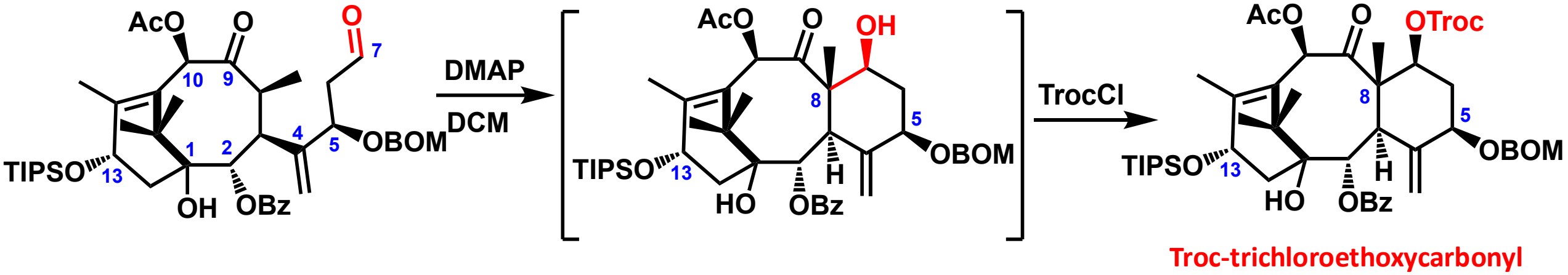
Wender's Total Synthesis



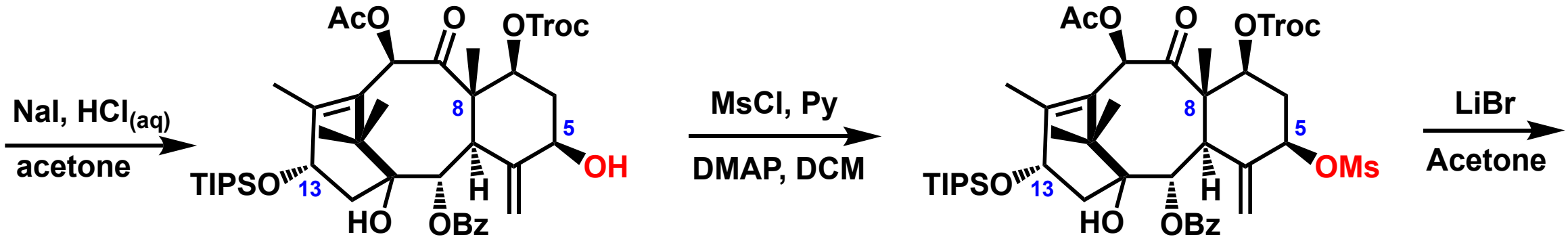
Wender's Total Synthesis



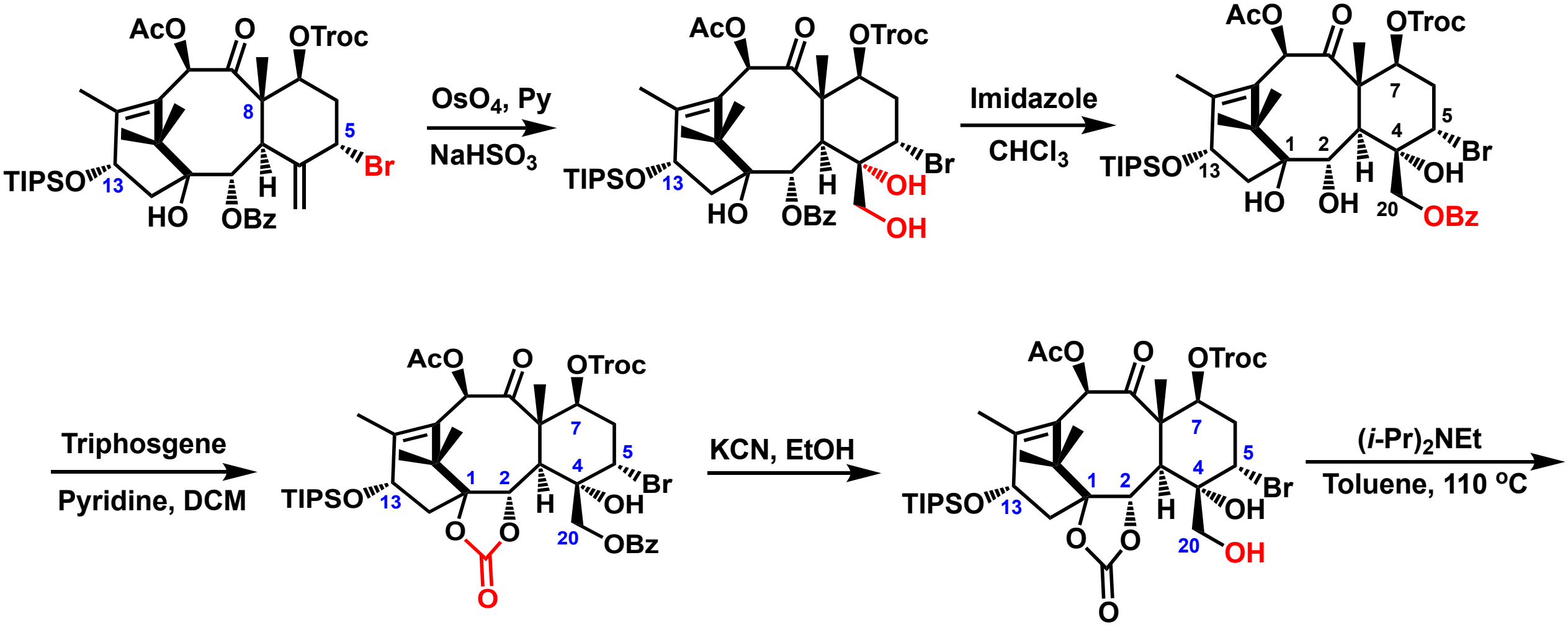
Wender's Total Synthesis



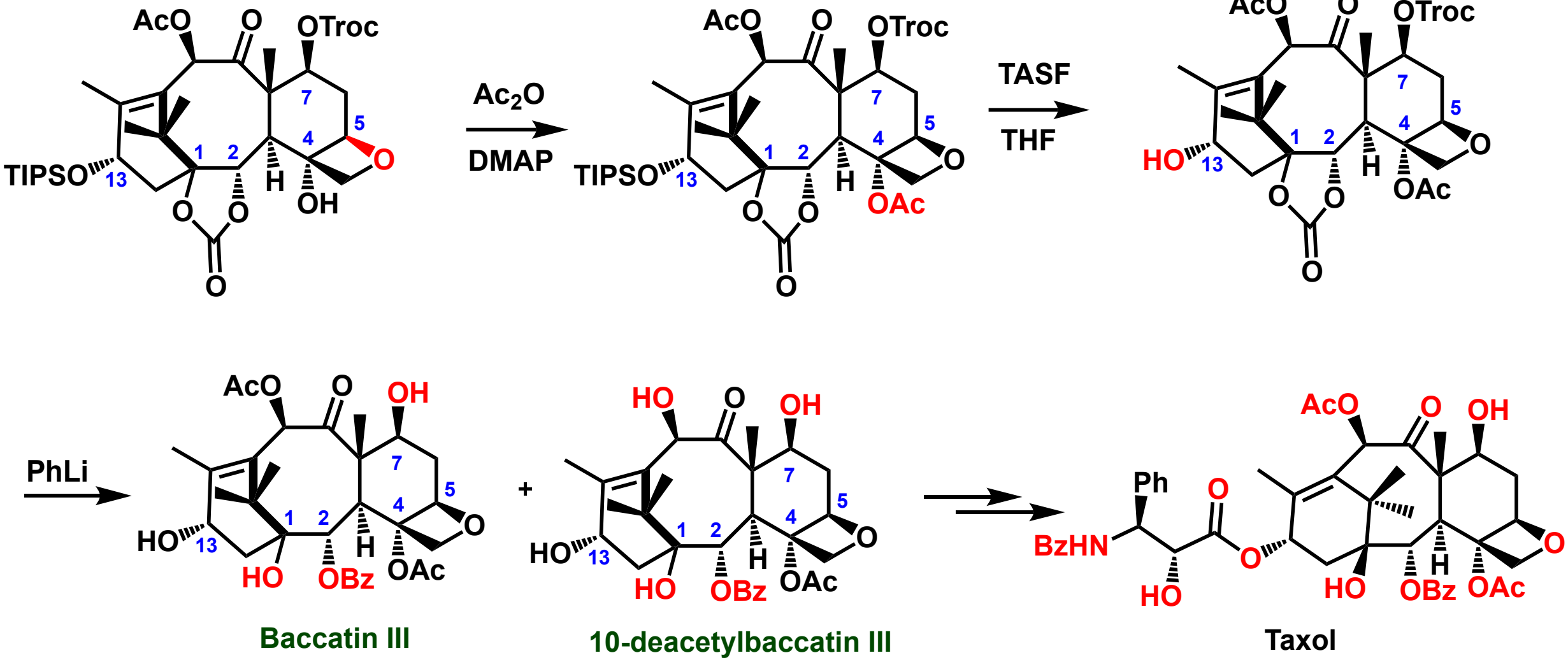
Troc-trichloroethoxycarbonyl



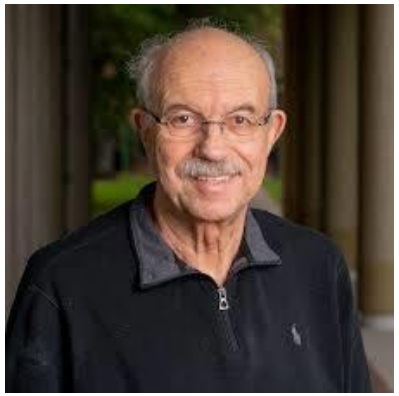
Wender's Total Synthesis



Wender's Total Synthesis



Taxol



Nicolaou's Total Synthesis of Taxol

KC's Visit to IIT Bombay









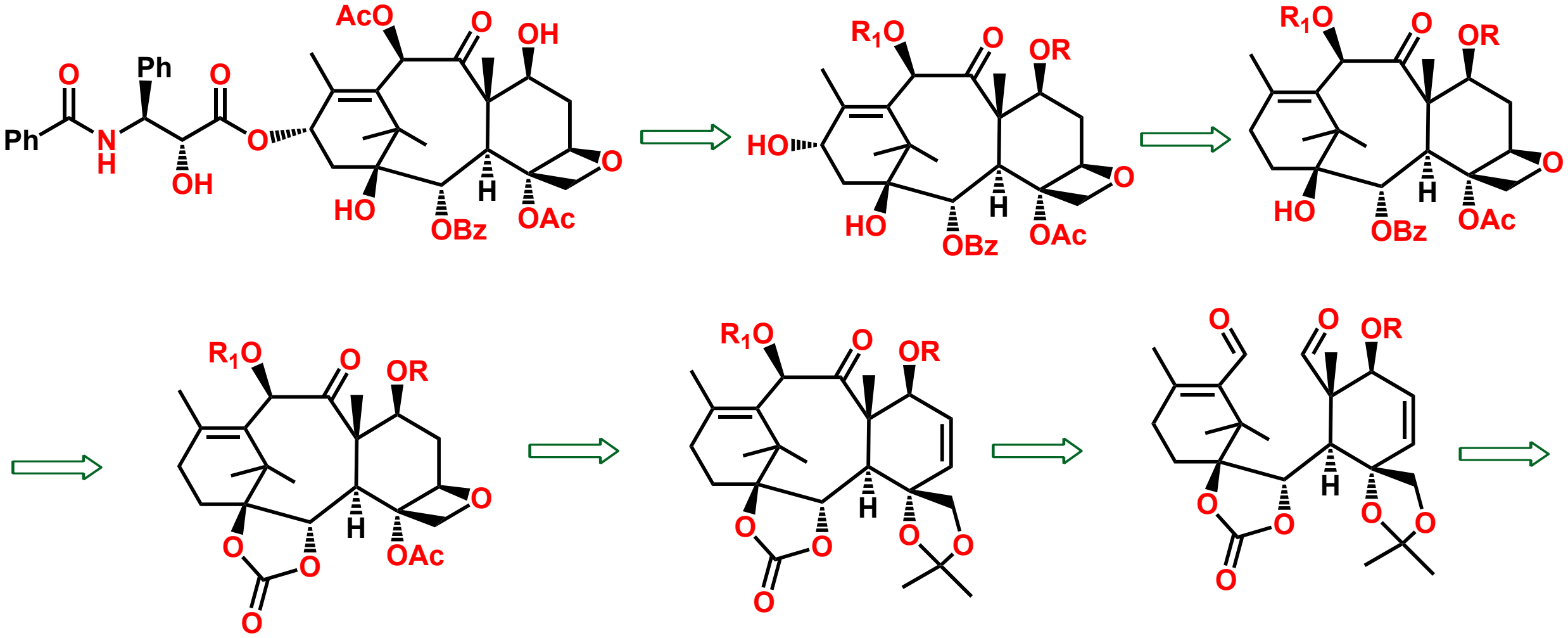




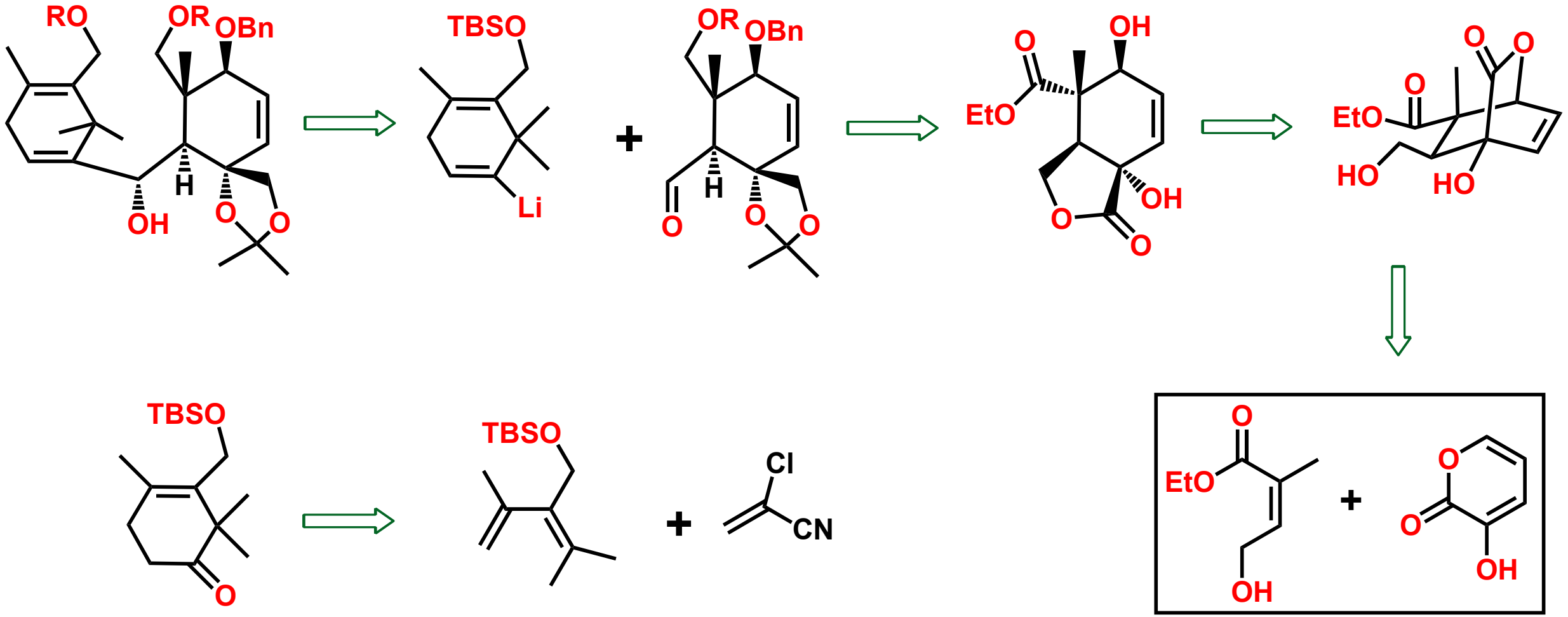


Nicolaou's Total Synthesis

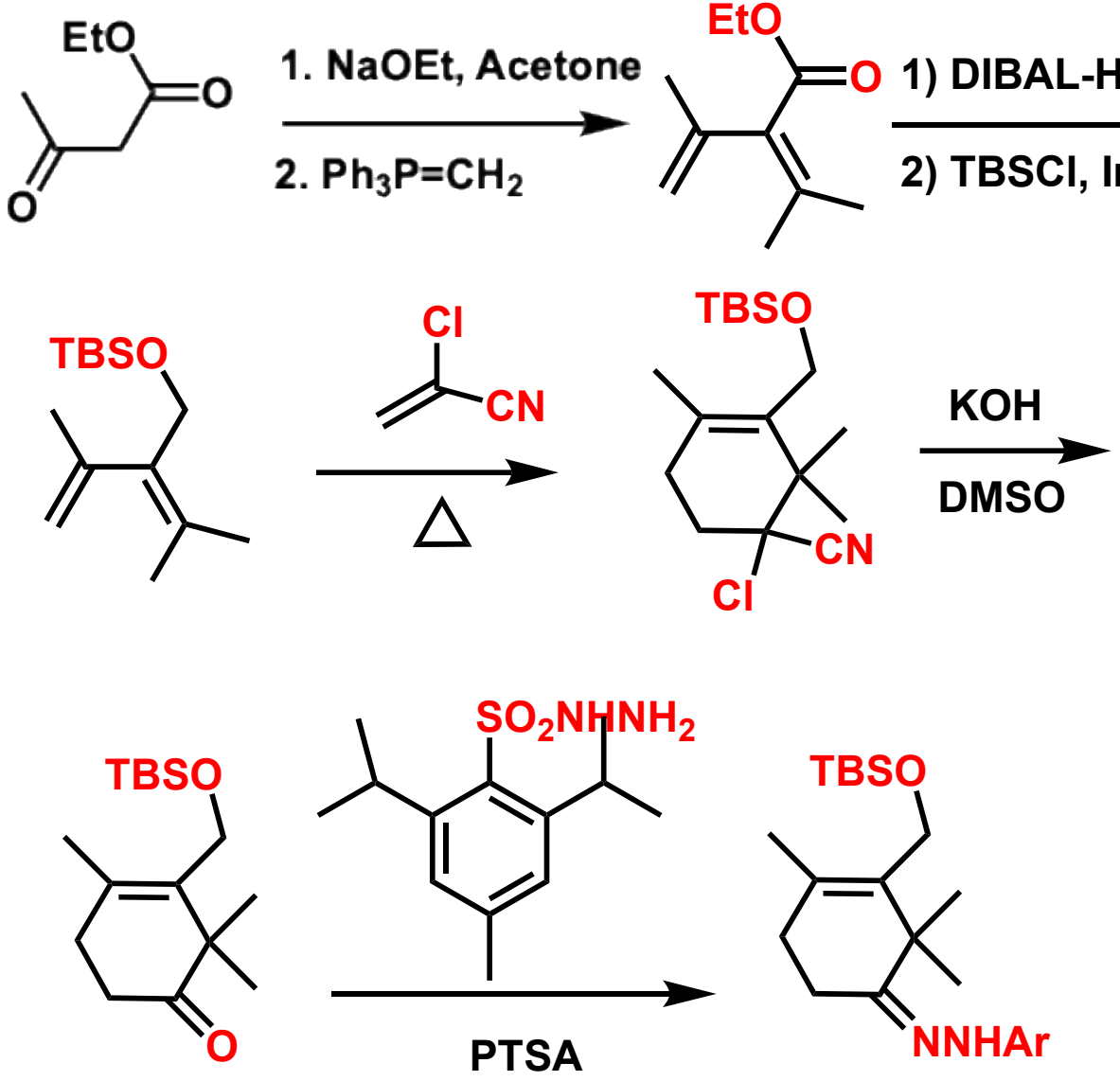
Retrosynthesis

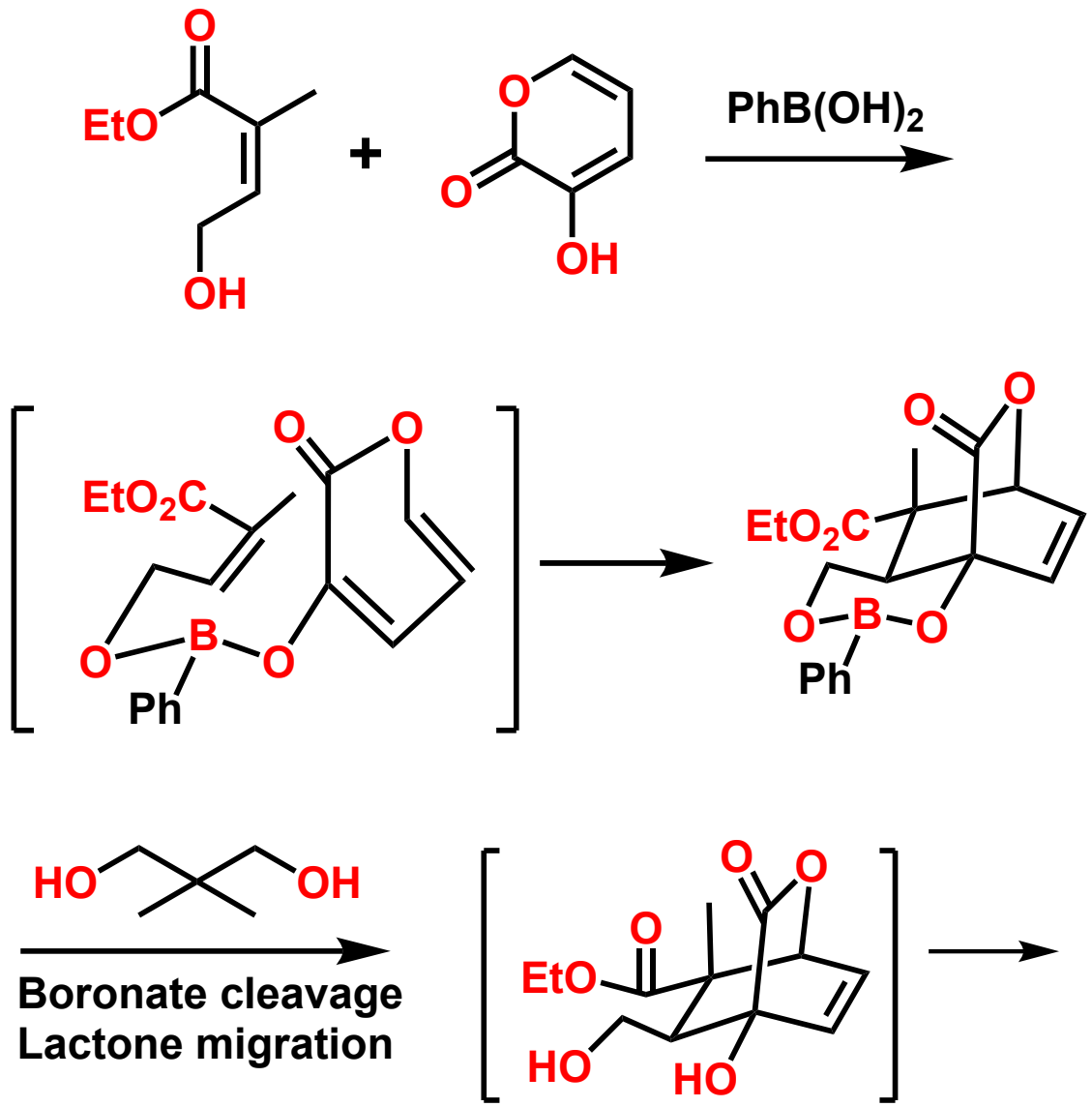


Nicolaou's Total Synthesis

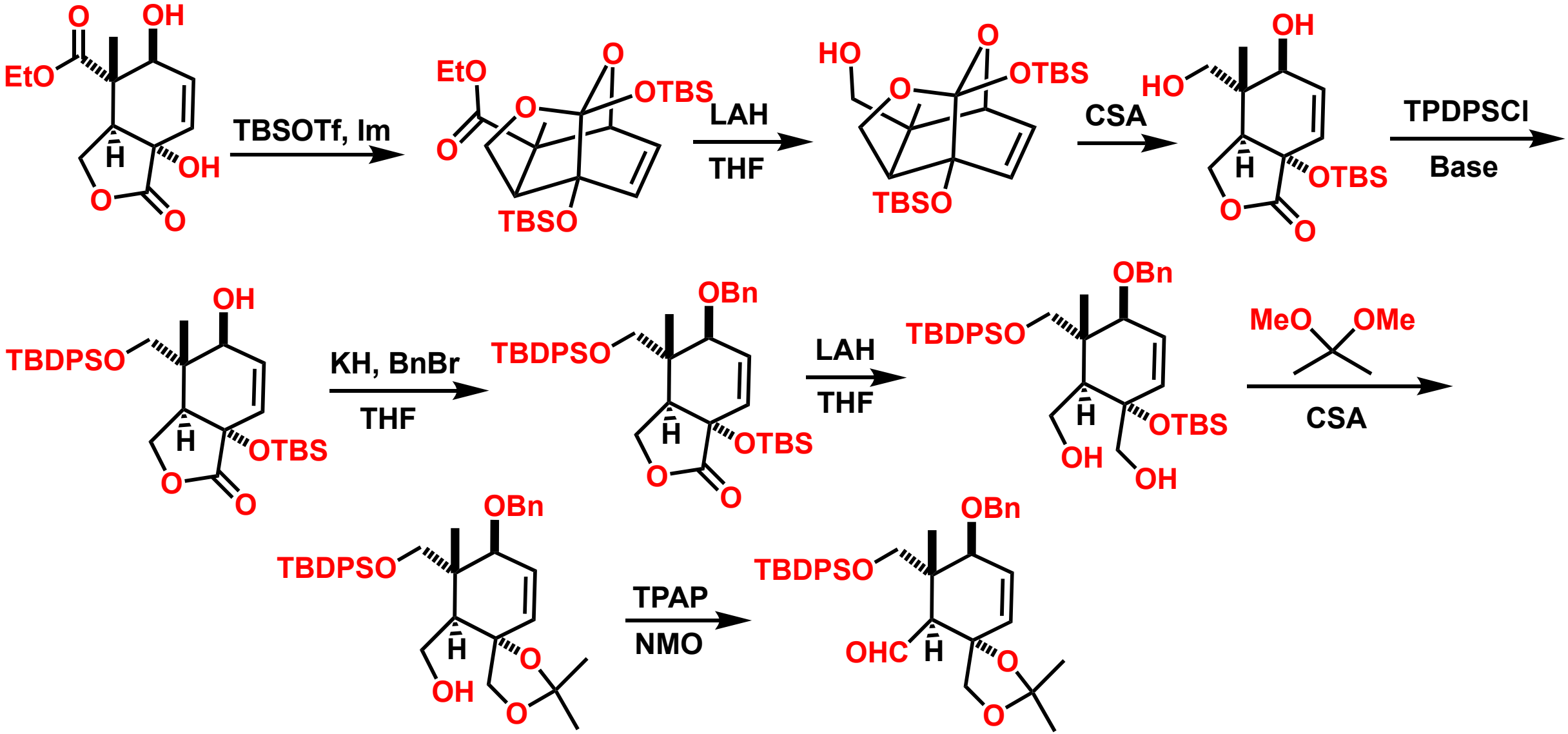


Nicolaou's Total Synthesis

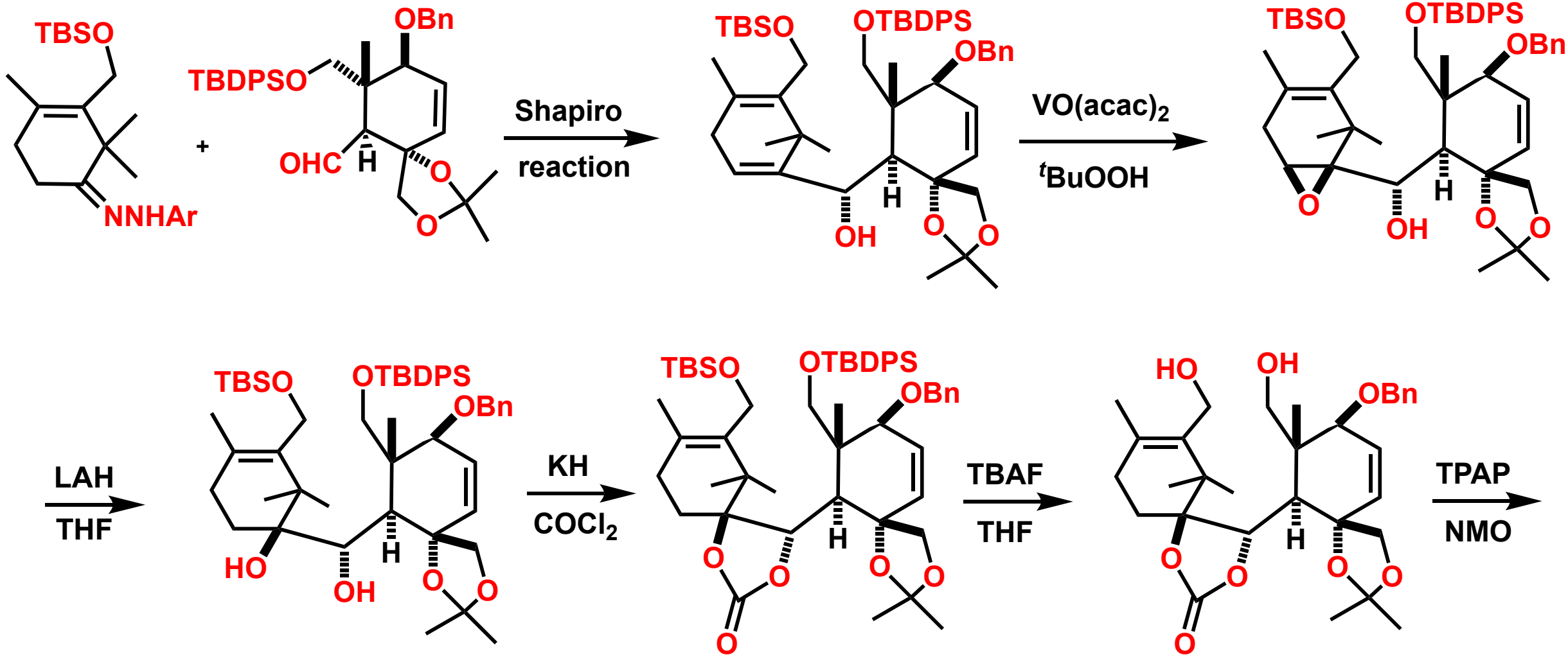




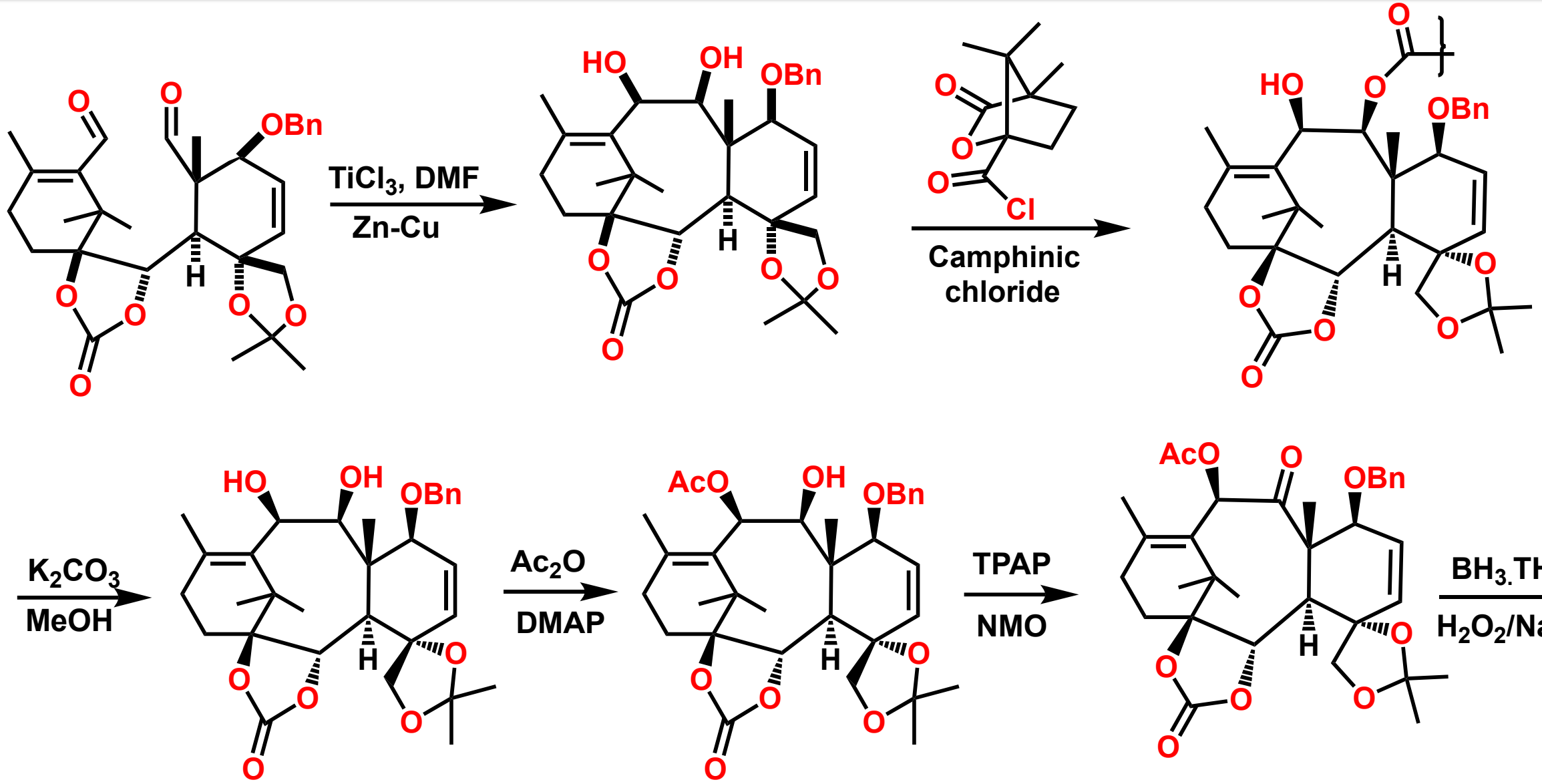
Nicolaou's Total Synthesis



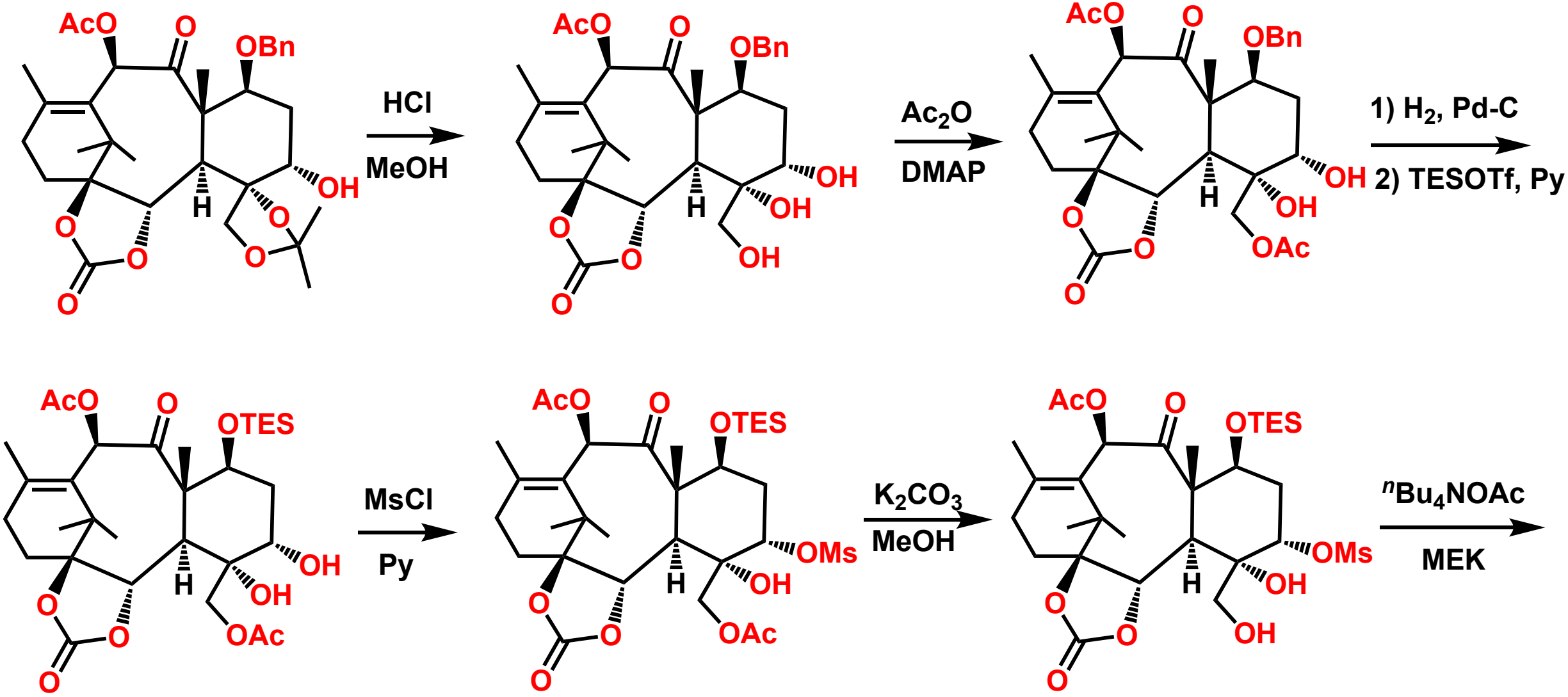
Nicolaou's Total Synthesis



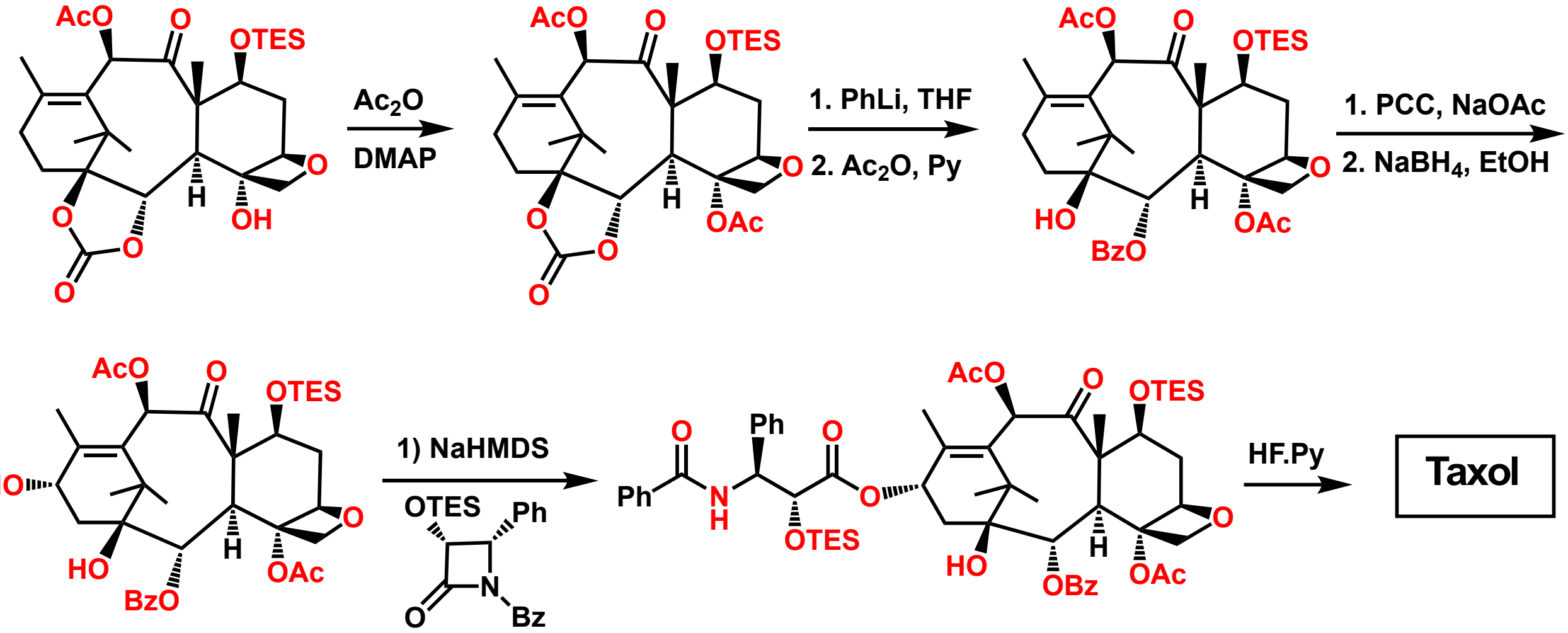
Nicolaou's Total Synthesis



Nicolaou's Total Synthesis



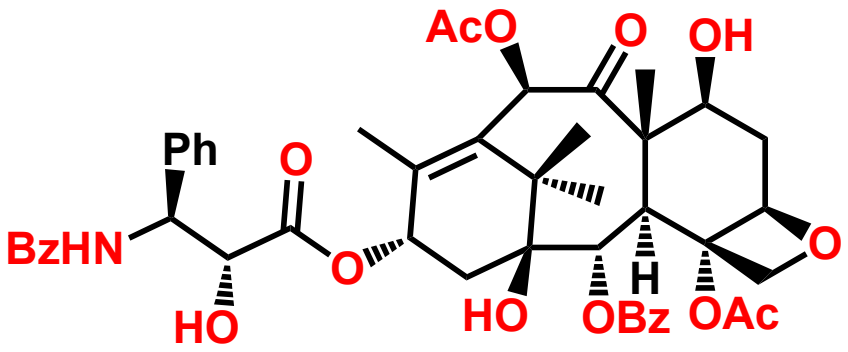
Nicolaou's Total Synthesis





Danishefsky's Total Synthesis of Taxol

Danishefsky's Total Synthesis

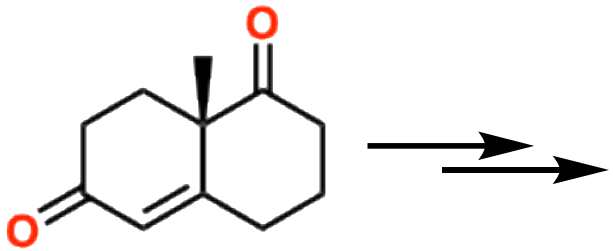


Taxol

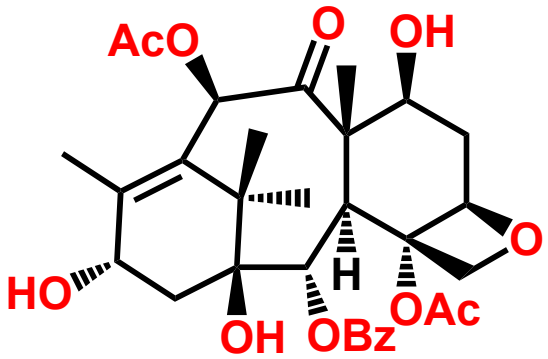
- The total synthesis of baccatin III has been achieved by Danishefsky *et al.* in 1996
- The most rewarding aspect of the synthesis was the ability to start with Wieland-Miescher ketone

Danishefsky, S. J.; *et al. J. Am. Chem. Soc.* **1996**, *118*, 2843-2859

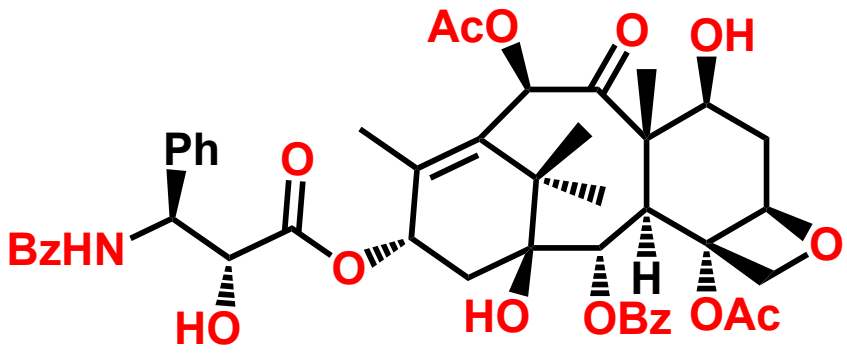
Short Synthetic Overview



Wieland-Miescher ketone

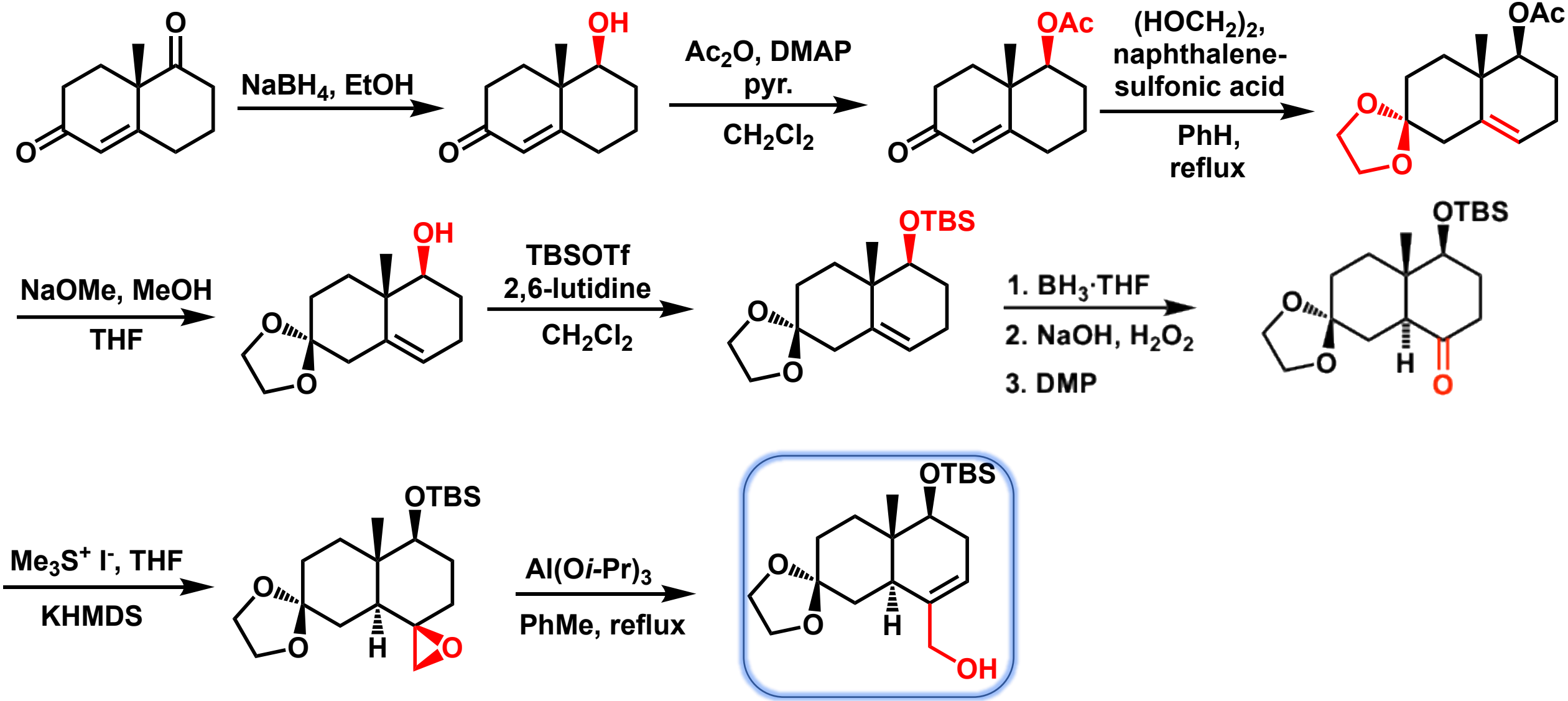


Baccattin III

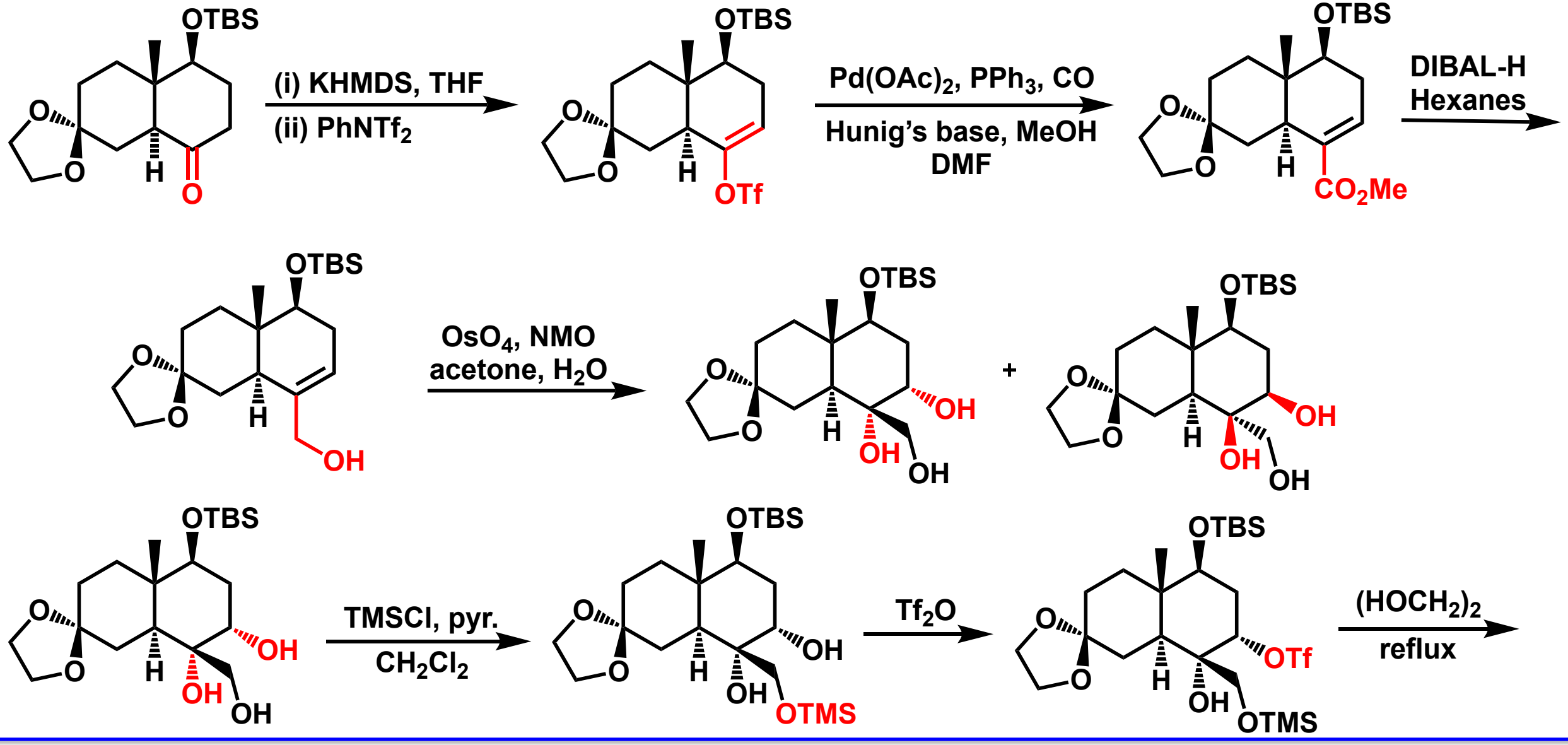


Taxol

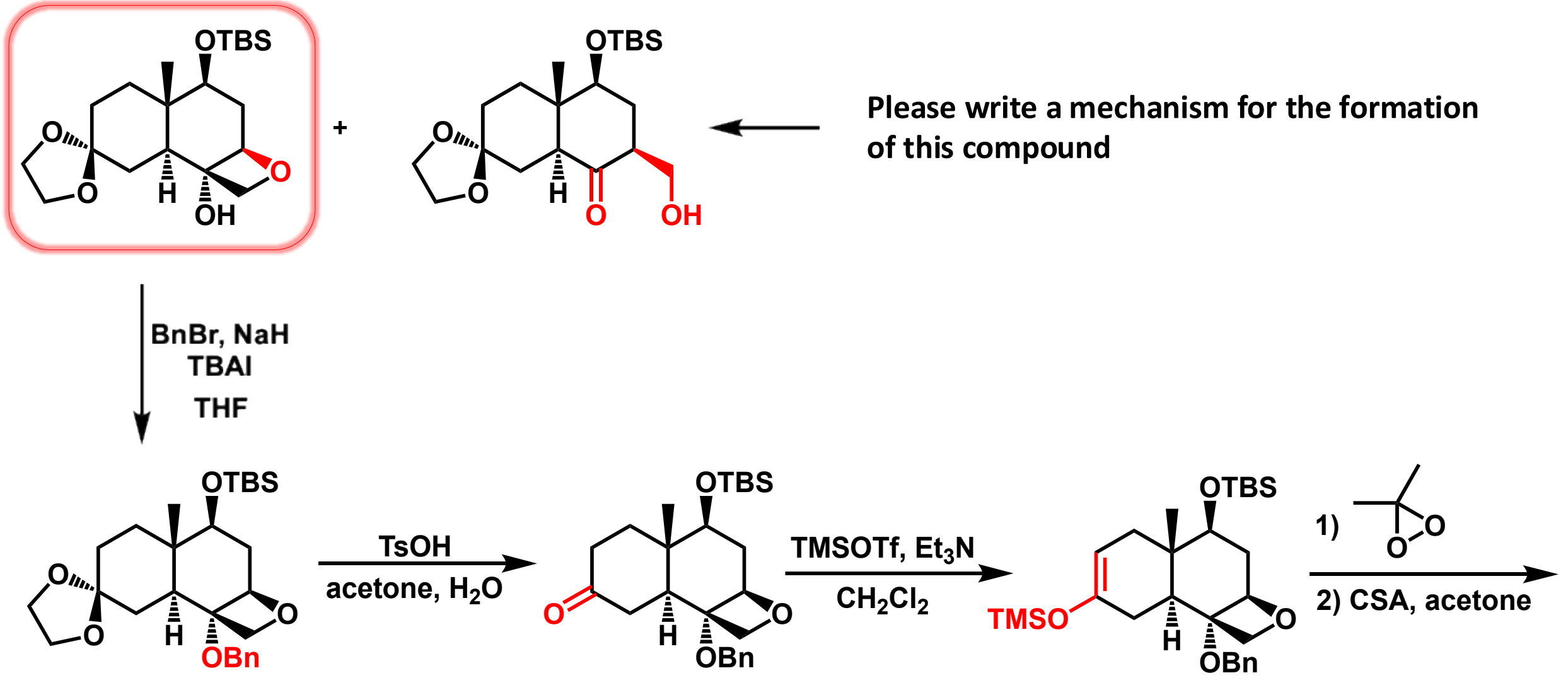
Construction of CD-ring of Taxol



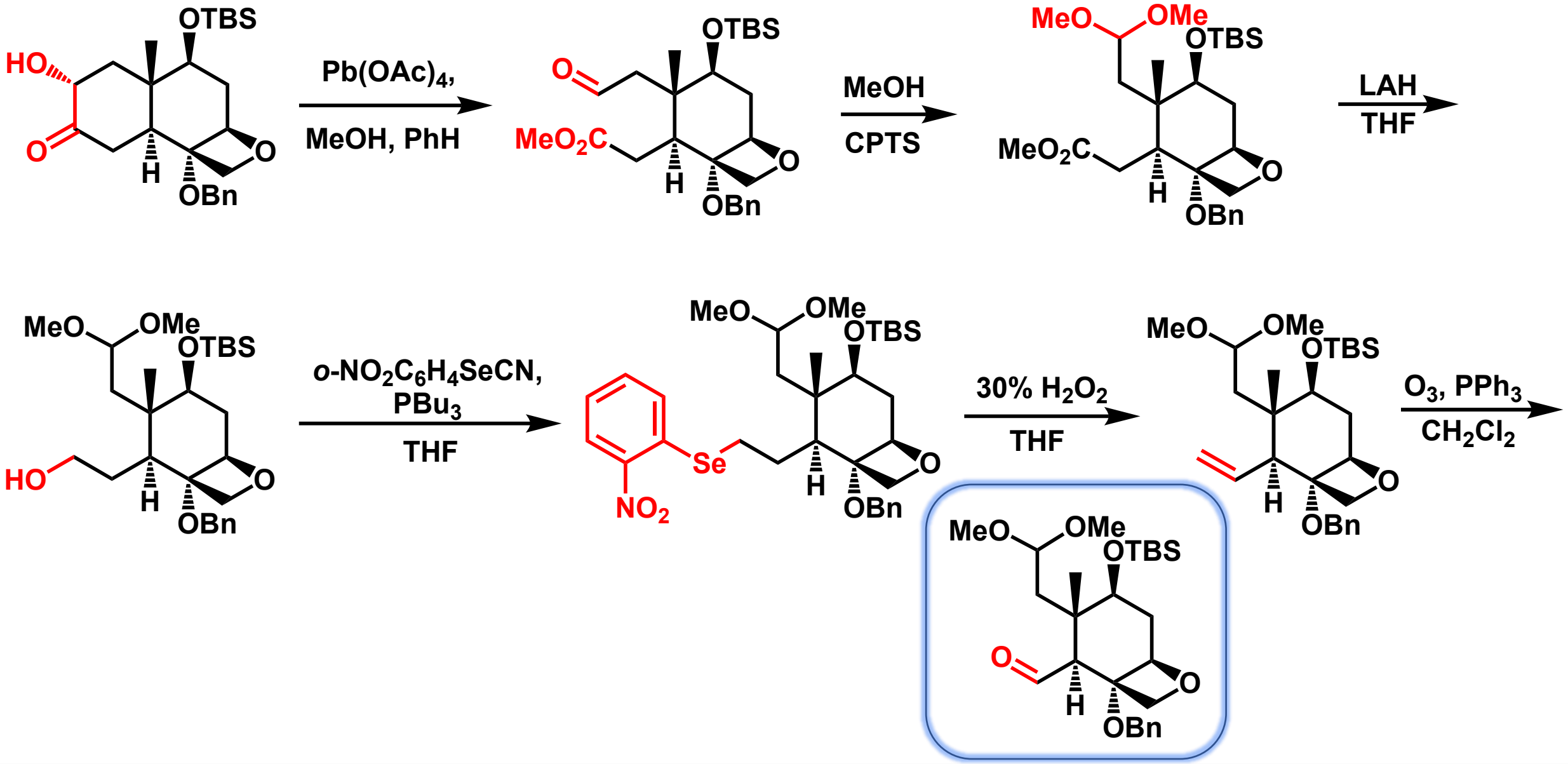
Alternate Route to CD-ring of Taxol



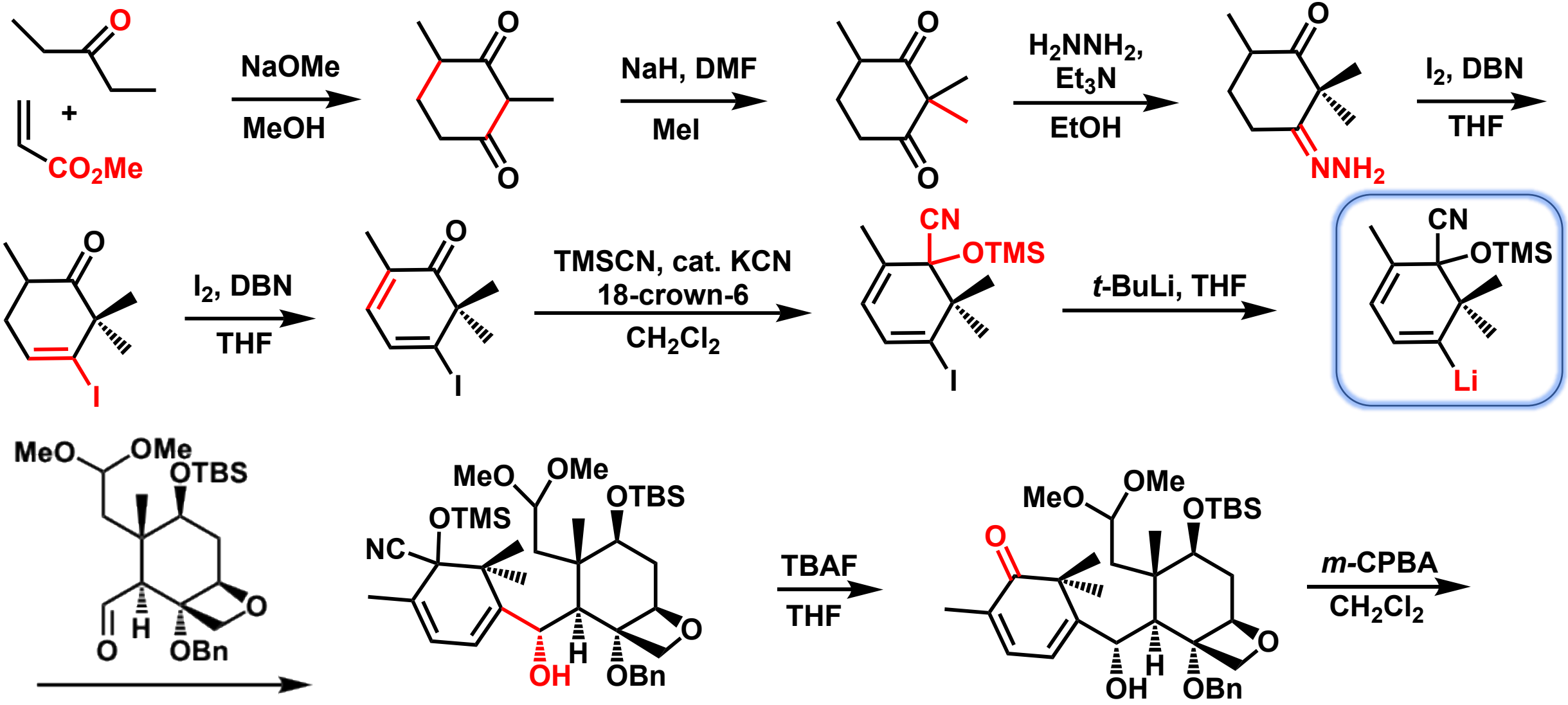
Danishefsky's Total Synthesis



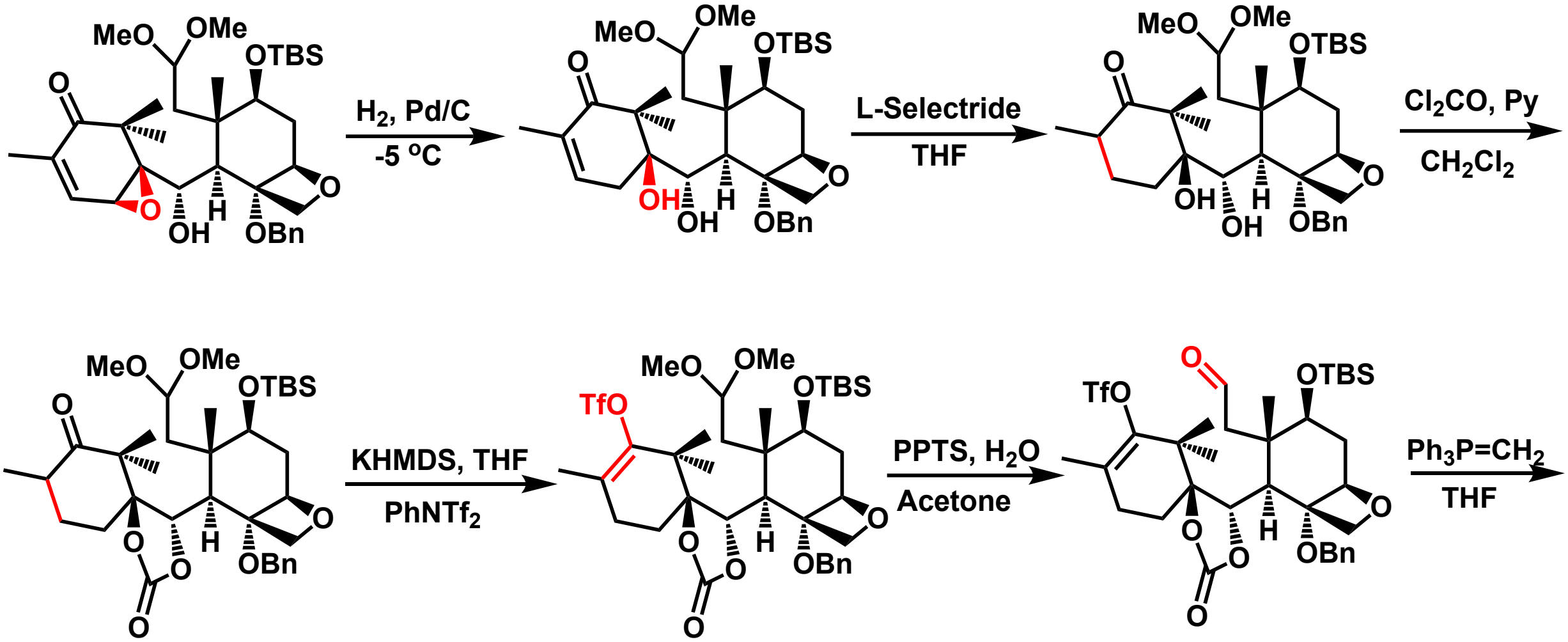
Danishefsky's Total Synthesis



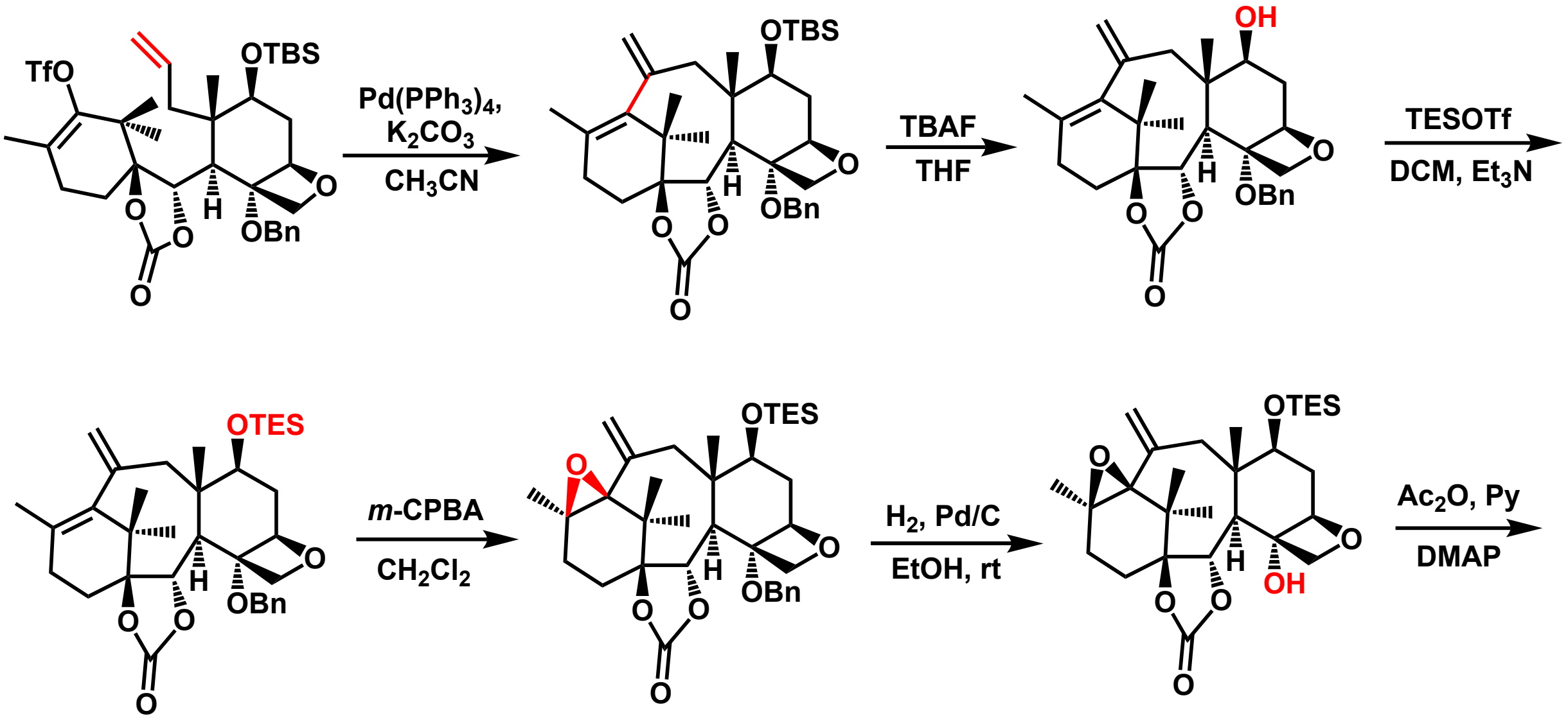
Construction of A-Ring of Taxol



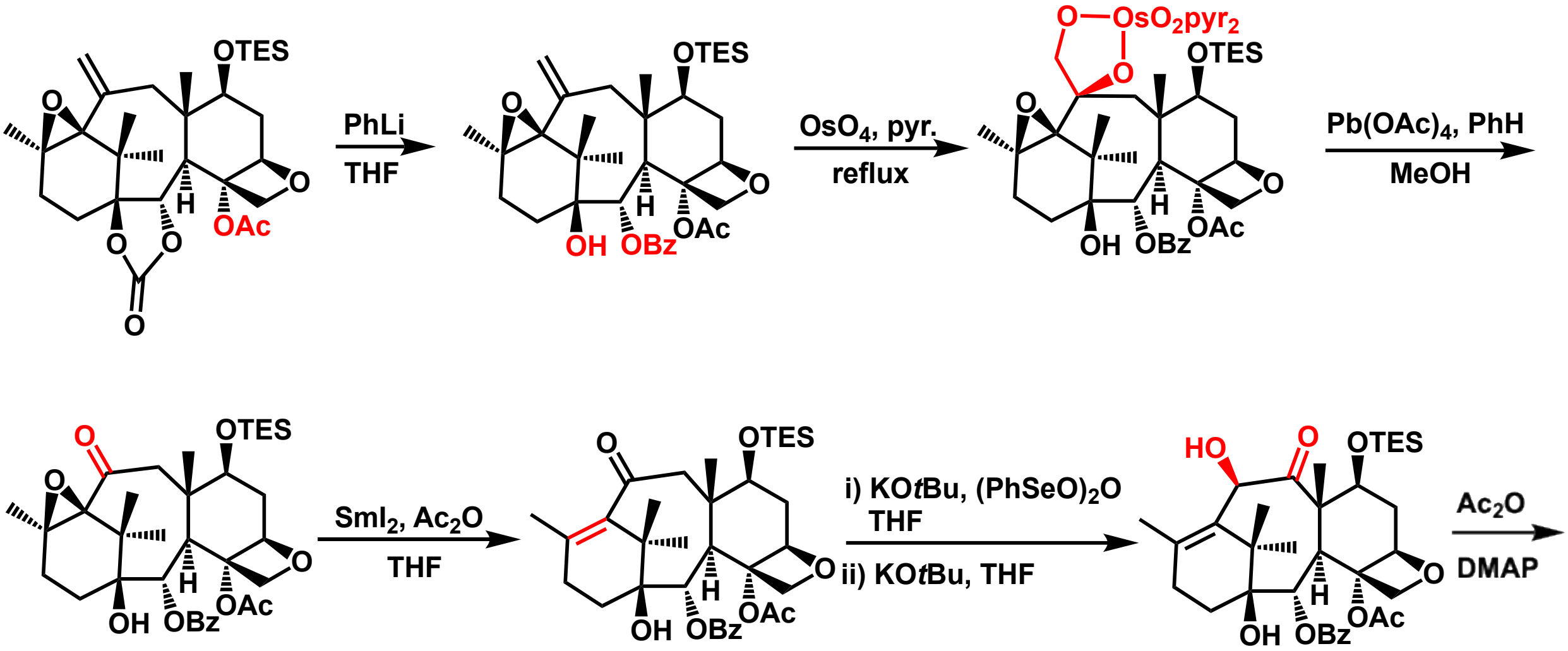
Danishefsky's Total Synthesis



Danishefsky's Total Synthesis



Danishefsky's Total Synthesis



Danishefsky's Total Synthesis

