Total Synthesis of Periplanone



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CH-845 Course on Organic Synthesis

What are Pheromones?

Substances which are secreted to the outside by an individual and received by a second individual of the same species, in which they release a specific reaction, for example, a definite behavior or a developmental process

There are four types of pheromones

1. Releaser
2. Signaler
3. Modulator
4. Primer

Pheromones

1. Releaser

- Releaser pheromones often prompt an immediate behavioral reaction, and have received the greatest attention in animals.

2. Signaler

- Signaler pheromones are mainly social chemosignals: they provide information on the hierarchy and the animal's place in it, and on the type of food recently consumed by other animals and thus the nearby availability of food.

3. Modulator

- Modulator pheromones influence neuropsychological parameters. While these effects are difficult to gauge in animals, they are the focus of most human studies.

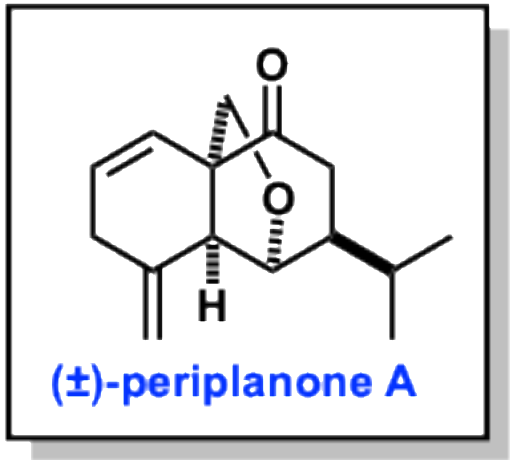
4. Primer

- Primer pheromones affect (neuro)-endocrine parameters, including the menstrual cycle

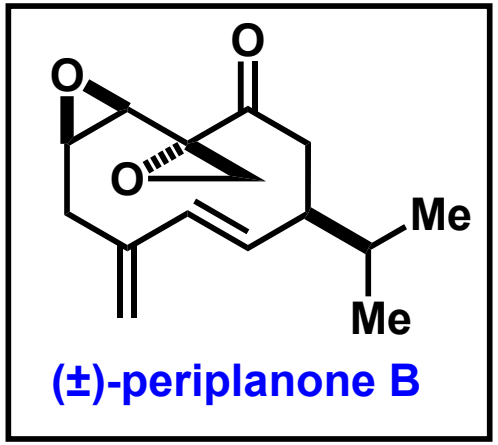
75,000 Cockroaches, One Molecule: The Periplanone B Mystery



1952 – Discovery of the pheromone



(±)-periplanone A



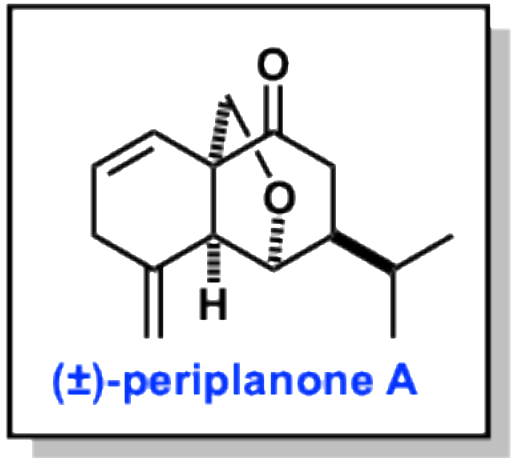
(±)-periplanone B

- Roth and Willis discovered a highly potent sex pheromone from female *Periplaneta americana (American Cockroach)*
- An astonishingly small amount ($<10^{-12}$ g) triggered a response in males.
- Even trace impurities could produce a positive bioassay → identification was extremely difficult

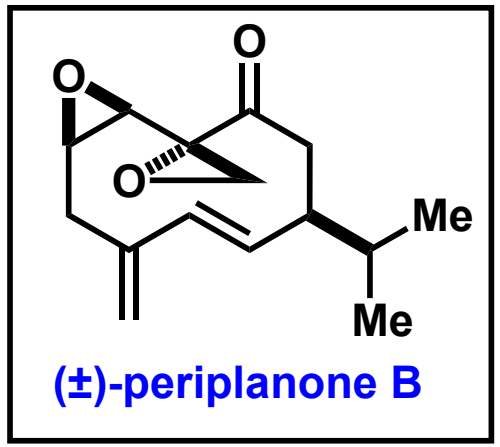
The Major Challenge

- Female cockroaches contained $<10^{-6}$ g of pheromone
- Repeated separation and purification failed because every fraction showed biological activity
- The extremely small quantity made isolation exceptionally challenging

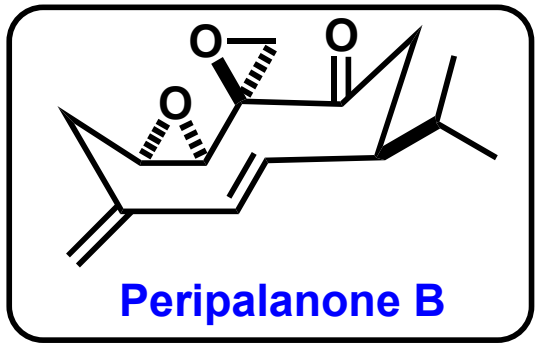
From Cockroach Pheromone to Structure



(±)-periplanone A



(±)-periplanone B



Peripalanone B

1976 – Isolation of the Active Compounds

After nearly 25 years of investigation and extraction of approximately 75,000 female cockroaches:

Persoons *et al*. isolated two active pheromones: Periplanone A and Periplanone B

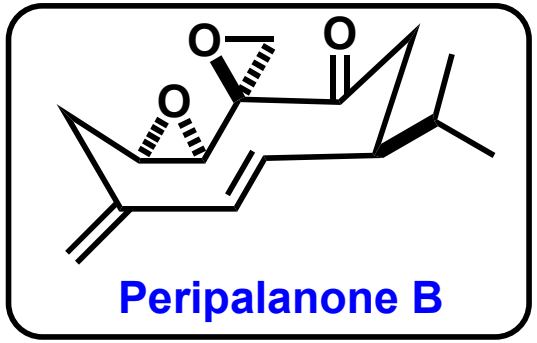
Spectroscopic studies led to the tentative structure of periplanone B. However, its relative stereochemistry remained unknown.

Persoons, C.J., *et al. Tetrahedron Lett.* **1976**, 2055

Still's Total Synthesis of Periplanone



W. Clark Still



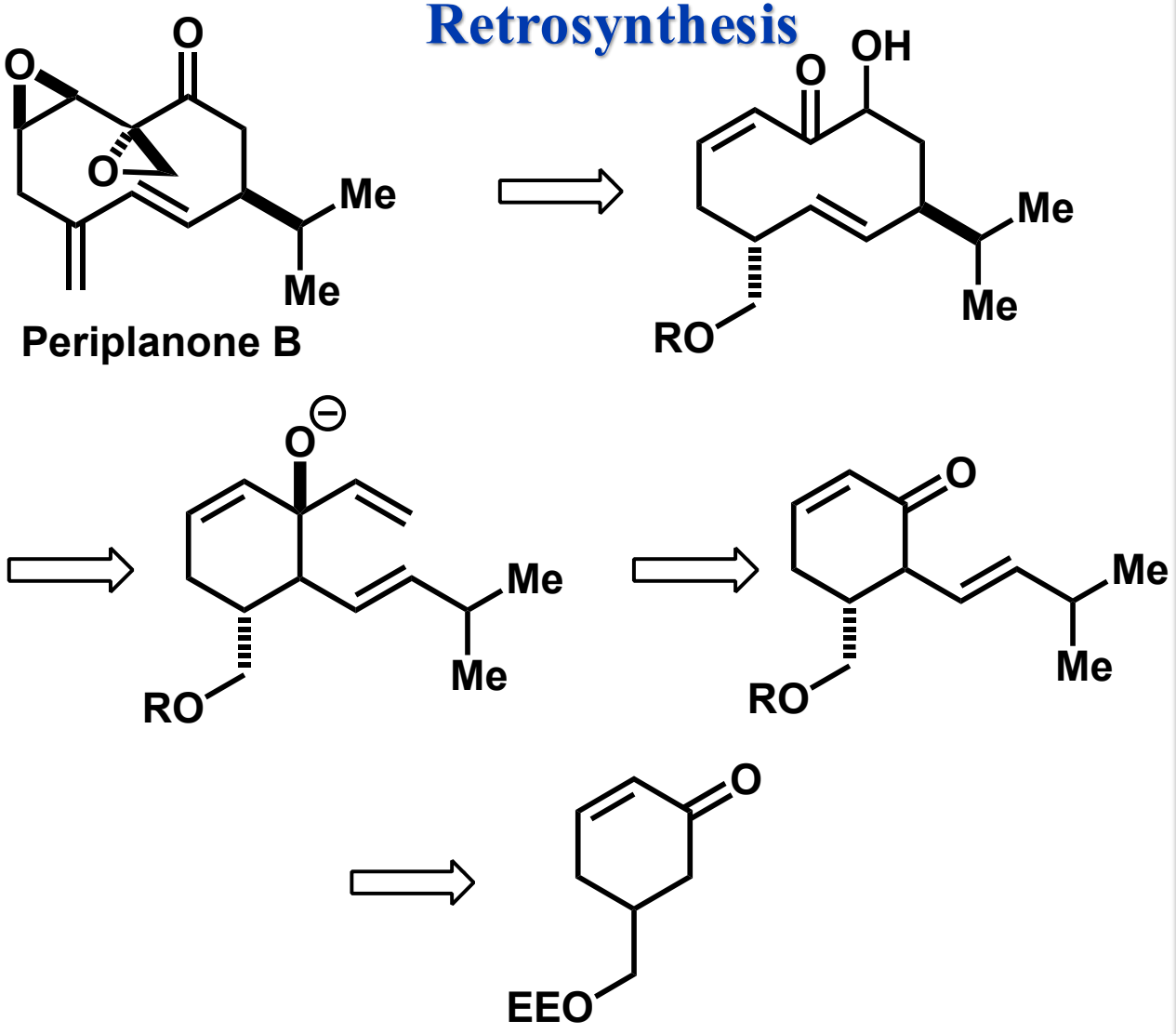
Peripalanone B

- Still's periplanone B synthesis provides a striking demonstration of the power of the anionic oxy-Cope rearrangement for the synthesis of cyclodecanoid frameworks

- The flexibility of this organic synthesis allowed the preparation of three different diastereomers of periplanone B and conclusively established the structure and relative stereochemistry of this molecule

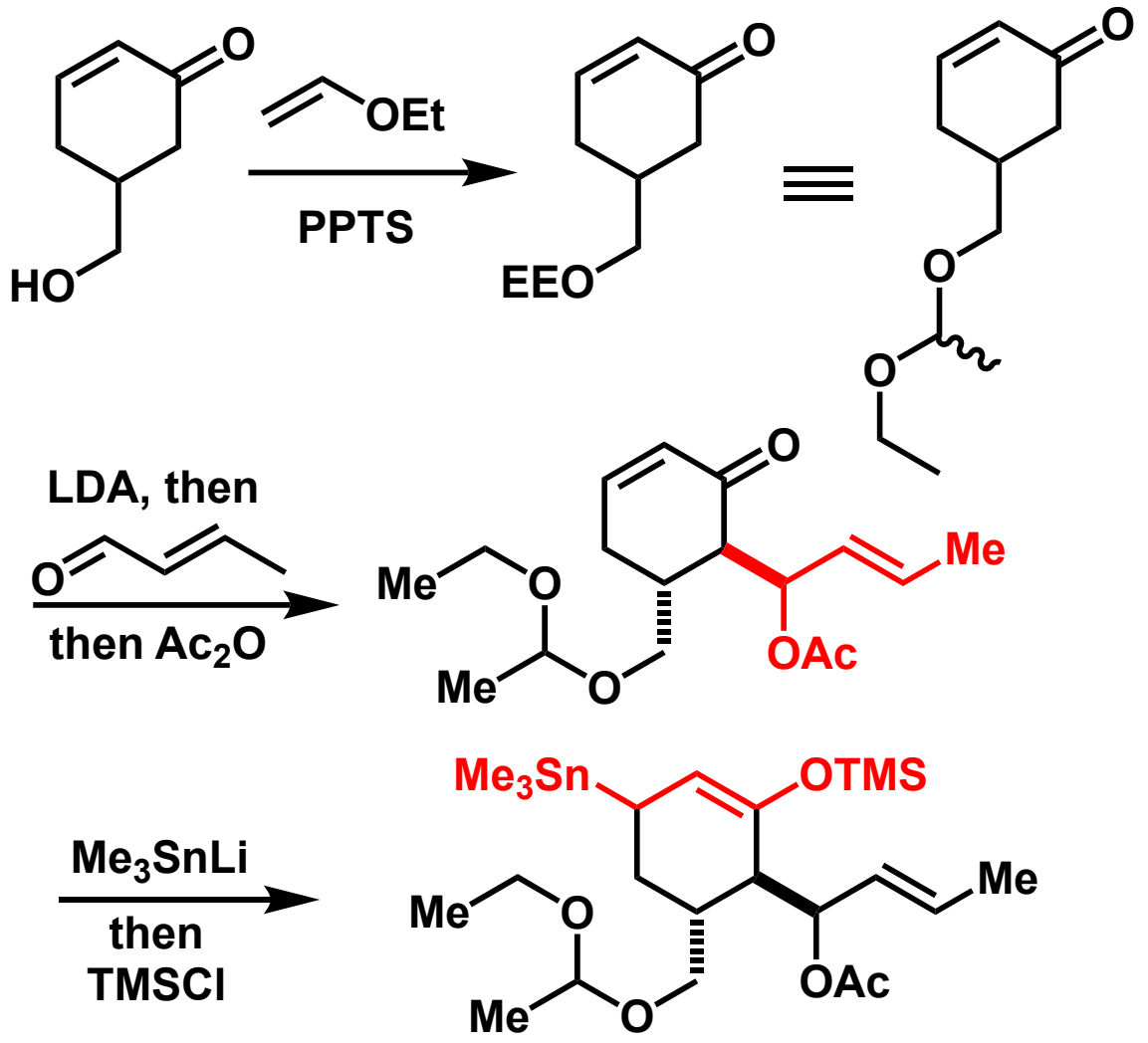
Still's Total Synthesis of Periplanone

Retrosynthesis

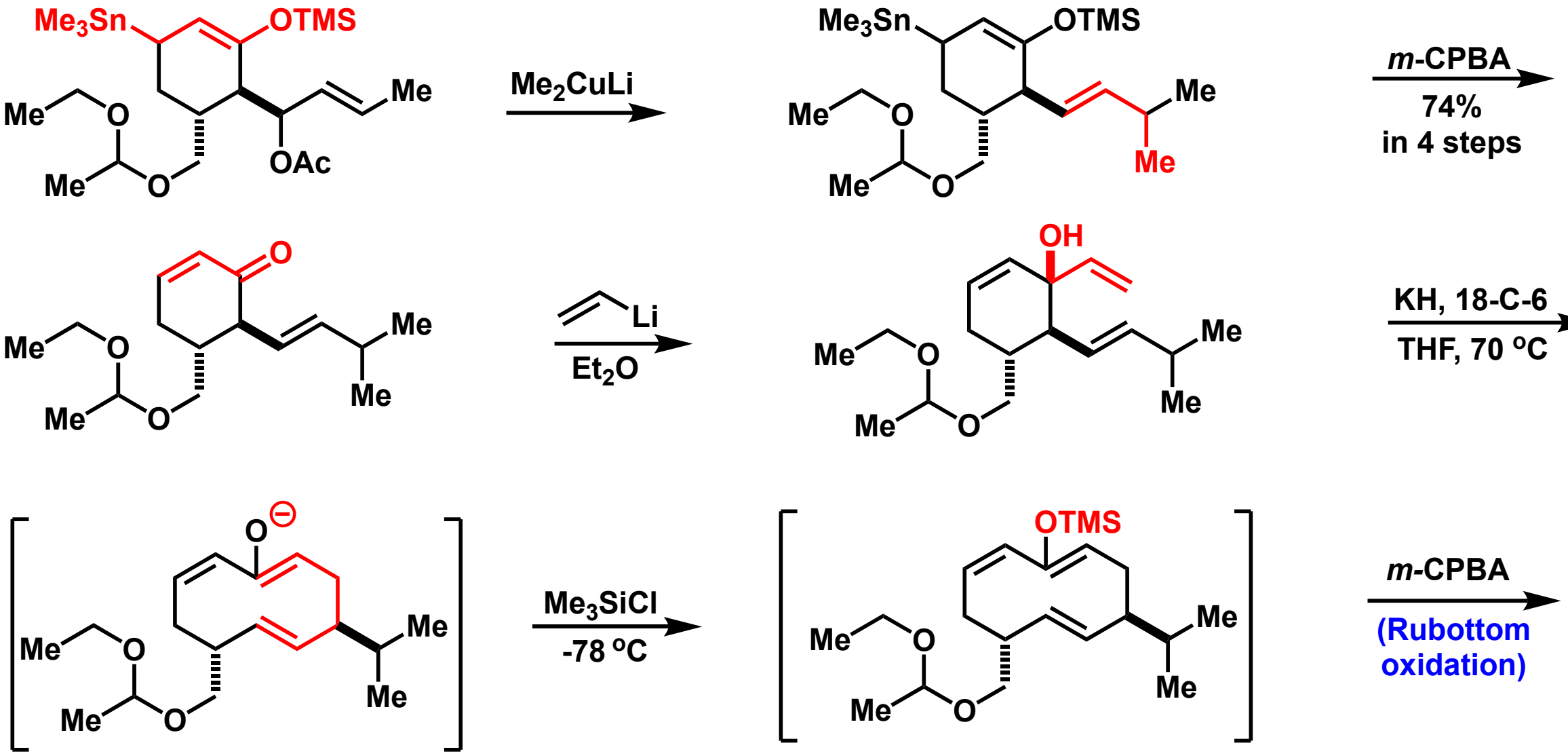


Still, W. C. *J. Am. Chem. Soc.* **1979**, *101*, 2493

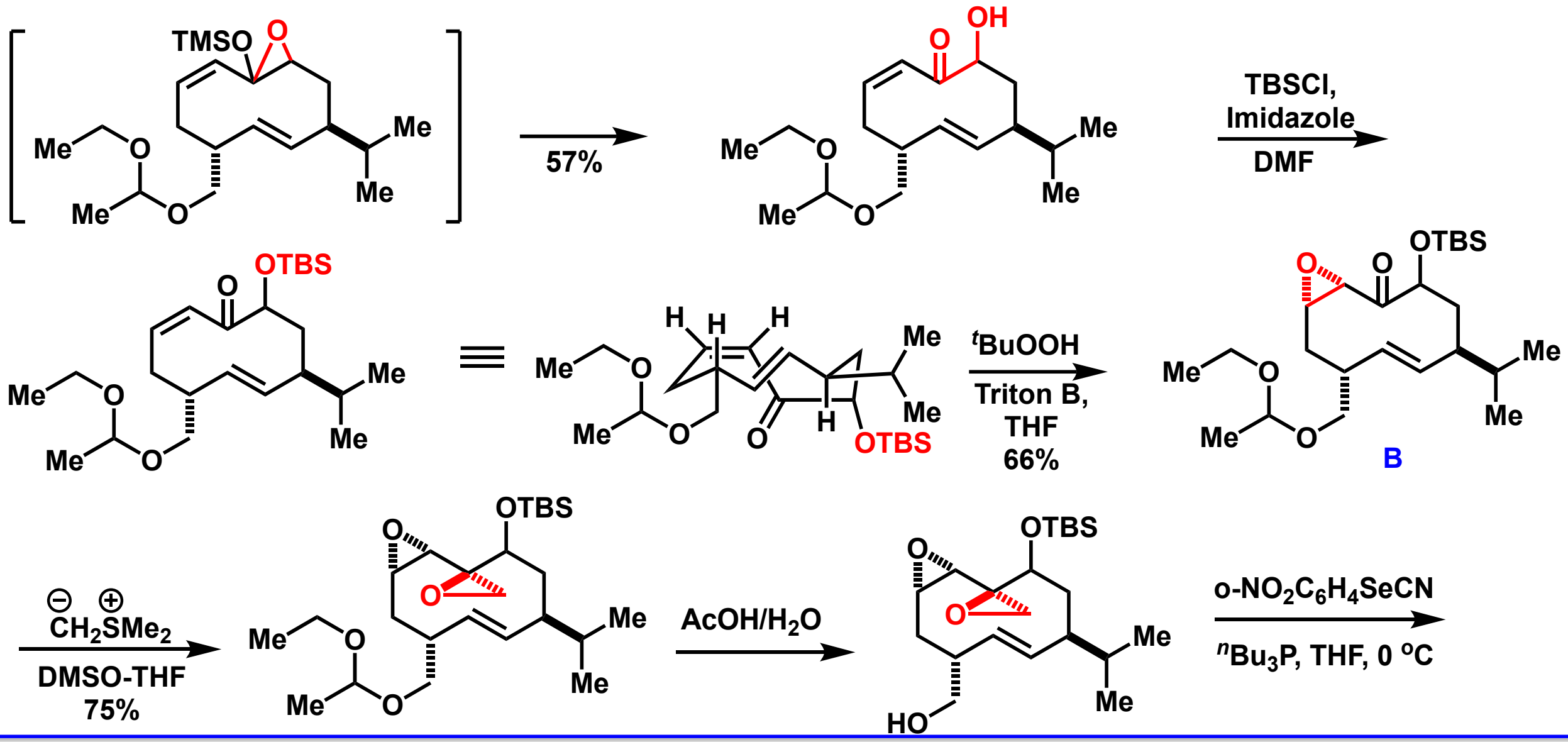
Total Synthesis



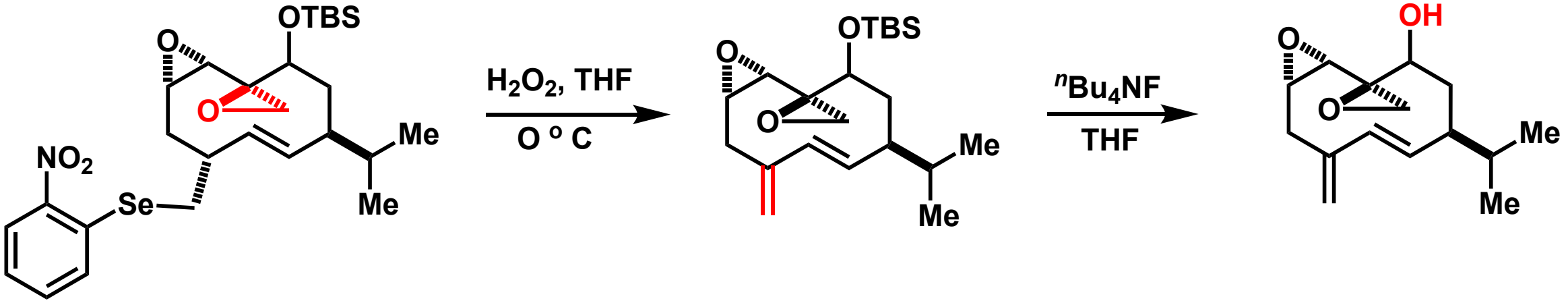
Still's Total Synthesis of Periplanone

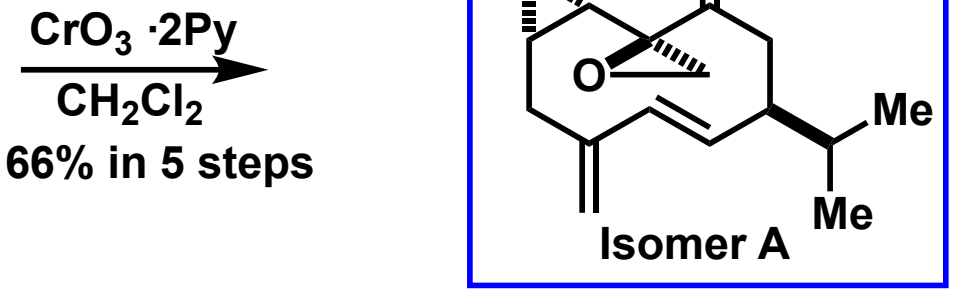


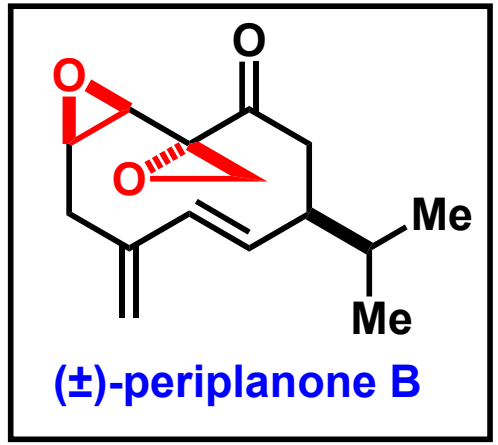
Still's Total Synthesis of Periplanone



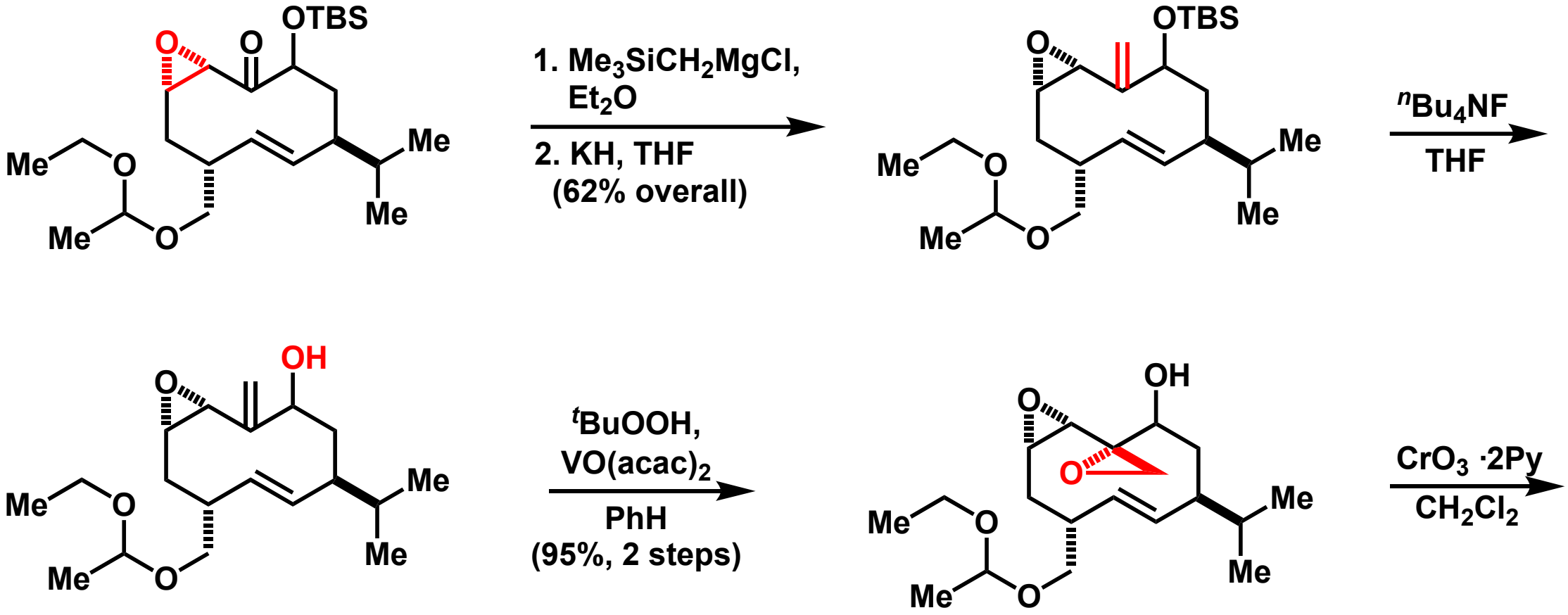
Still's Total Synthesis of Periplanone



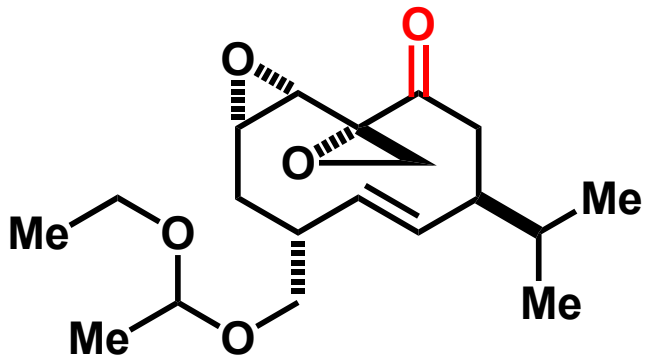




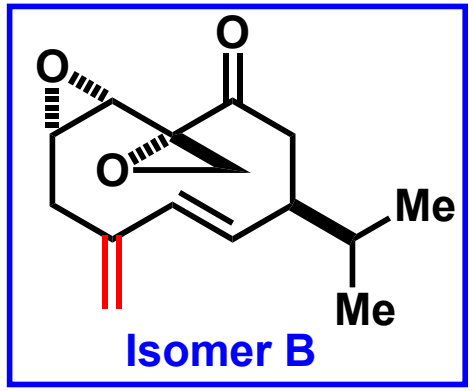
Still's Total Synthesis of Periplanone



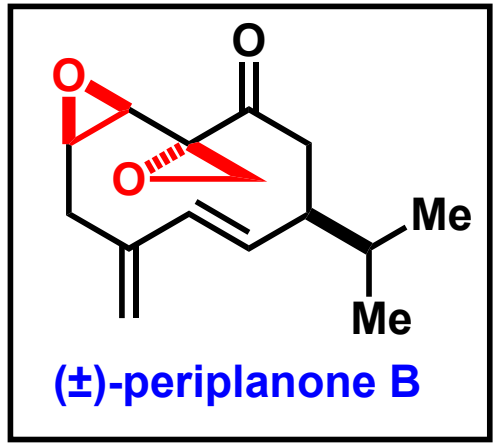
Still's Total Synthesis of Periplanone



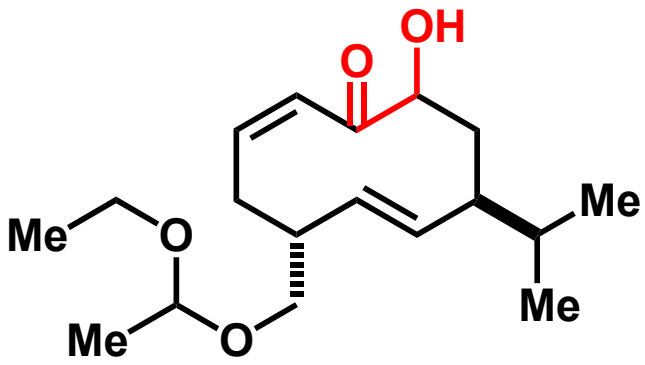
1. $AcOH\text{-}H_2O$
2. $o\text{-}NO_2C_6H_4SeCN$, $^nBu_3P$, THF
3. H_2O_2, THF



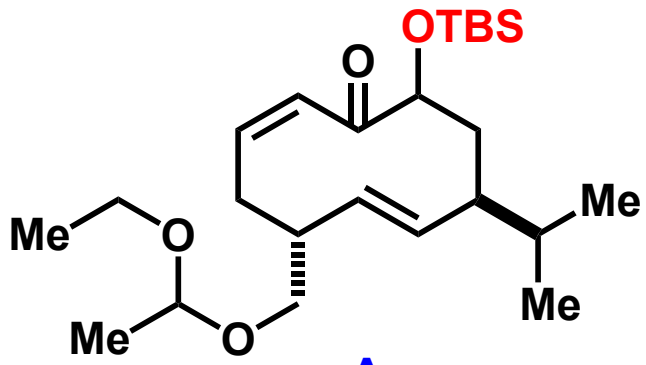
Isomer B



(±)-periplanone B

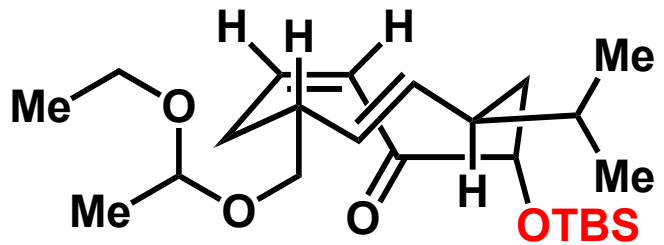


TBSCl, Imidazole, DMF

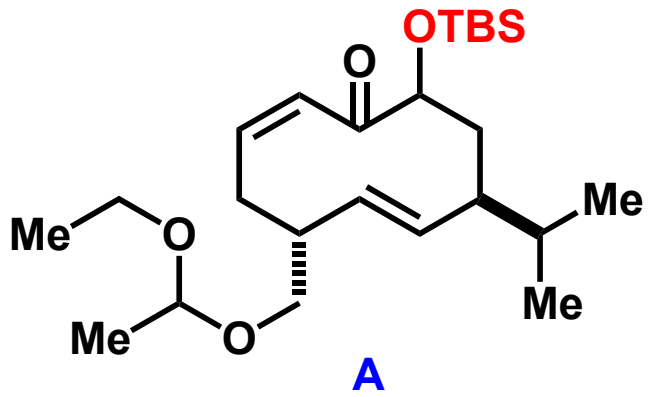


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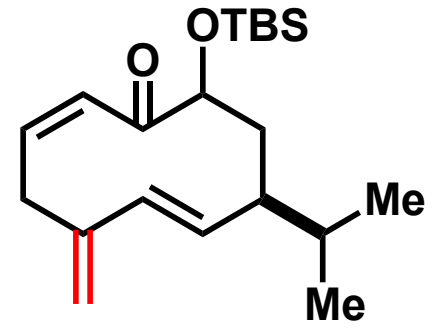


Still's Total Synthesis of Periplanone

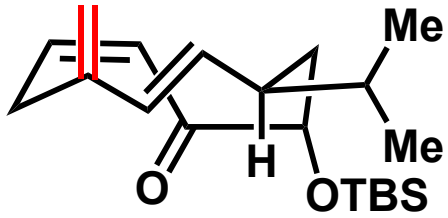


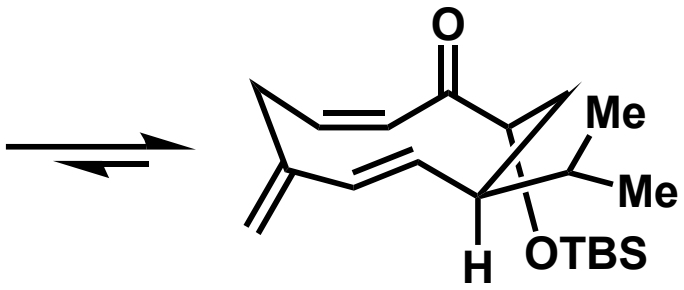
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1. AcOH-H_2O
2. o-$NO_2C_6H_4SeCN$
   $^nBu_3P$, THF
3. H_2O_2, THF

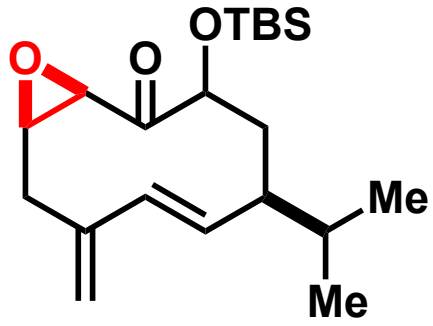


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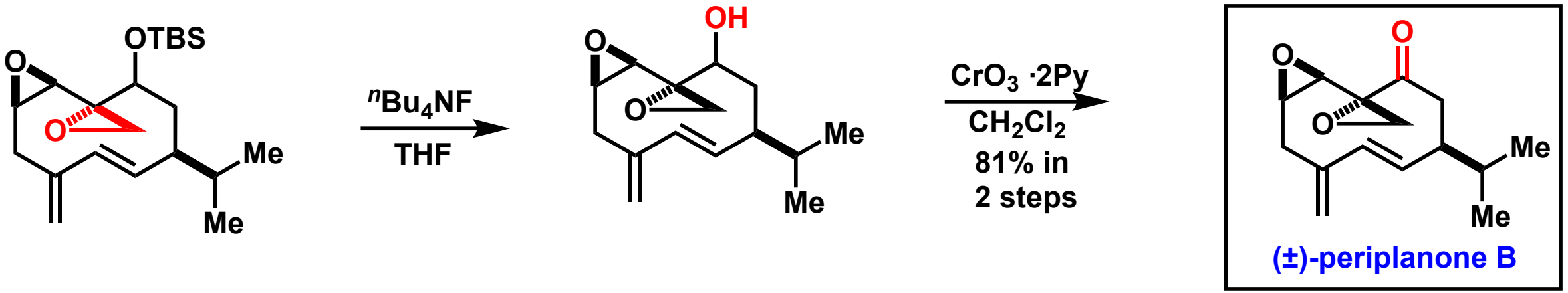
^{t}BuOOH,
KH
THF, -20 °C
74%



(4:1 mixture of
epoxide diastereomers)

$\ominus$ $\oplus$
CH_2SMe_2
DMSO-THF
69%

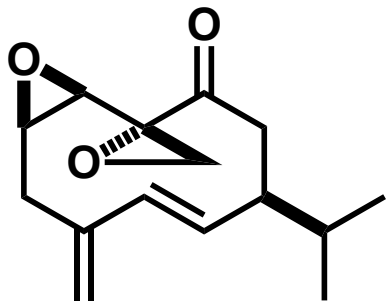
Still's Total Synthesis of Periplanone



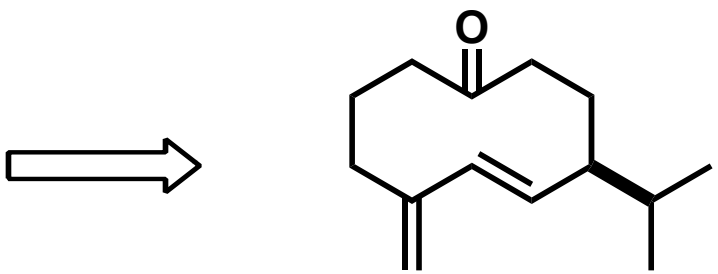
- Still's periplanone B synthesis utilizes the anionic oxy-Cope rearrangement as the key step in the synthesis of cyclodecanoid frameworks
- In this synthesis of periplanone B, Still demonstrated a classical aspect and use of total synthesis for the unambiguous establishment of the structure of the natural product.
- Their synthesis began with the ethoxyethyl ether of 5-(hydroxymethyl)cyclohexanone
- The total synthesis was accomplished in 15 steps with an overall yield of 8.92%

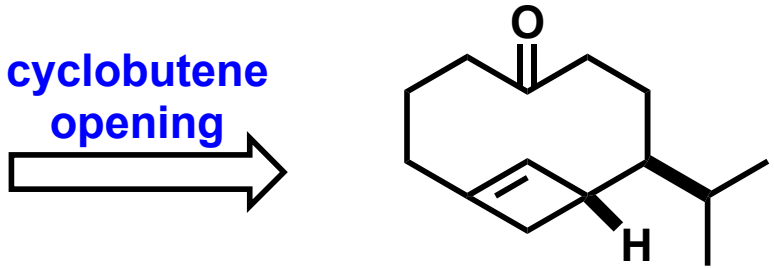
Schreiber's Total Synthesis of Periplanone

- Schreiber's approach to periplanone B takes full advantage of the facility with which functionalized 5-cyclodecen-1-one systems can be constructed via anionic oxy-Cope rearrangements of readily available divinylcyclohexanols



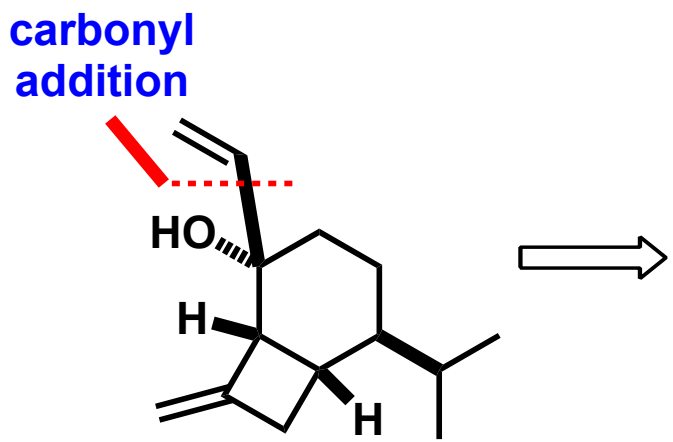
Periplanone B

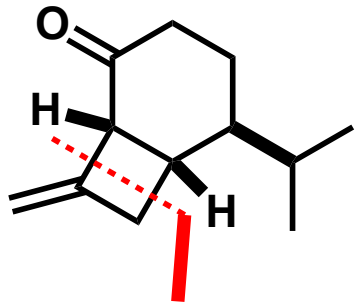


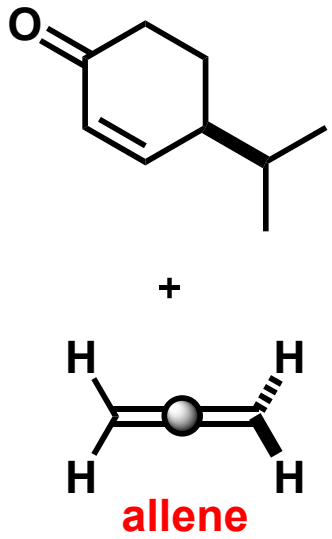




Stuart Schreiber

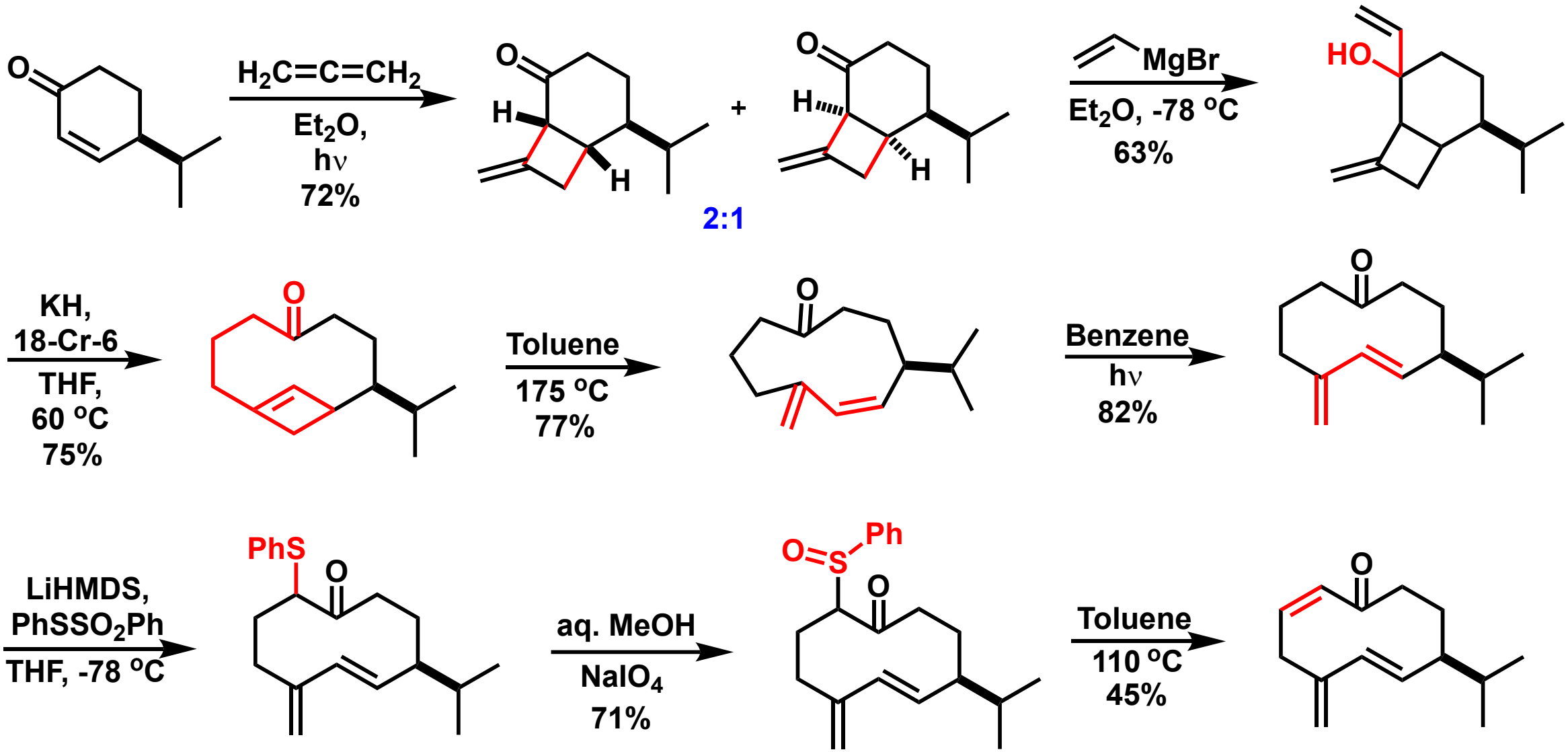




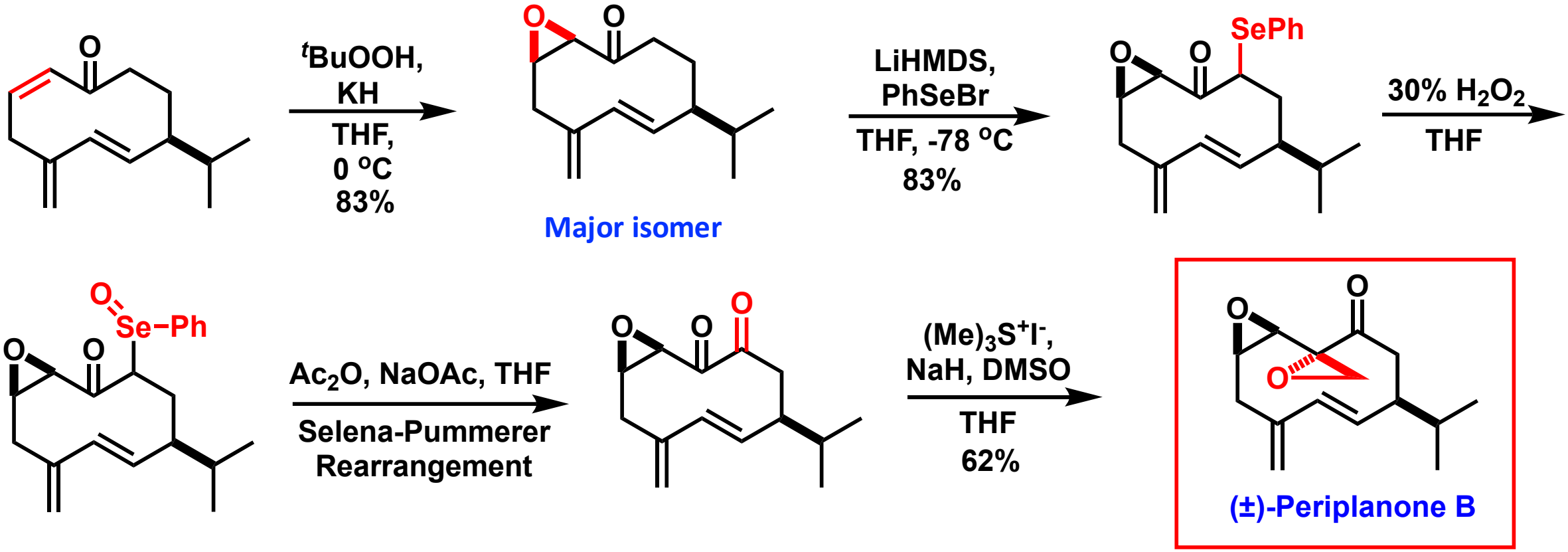


Schreiber, S. L., *et al. J. Am. Chem. Soc.* **1984**, *106*, 4038-4039

Schreiber's Total Synthesis of Periplanone



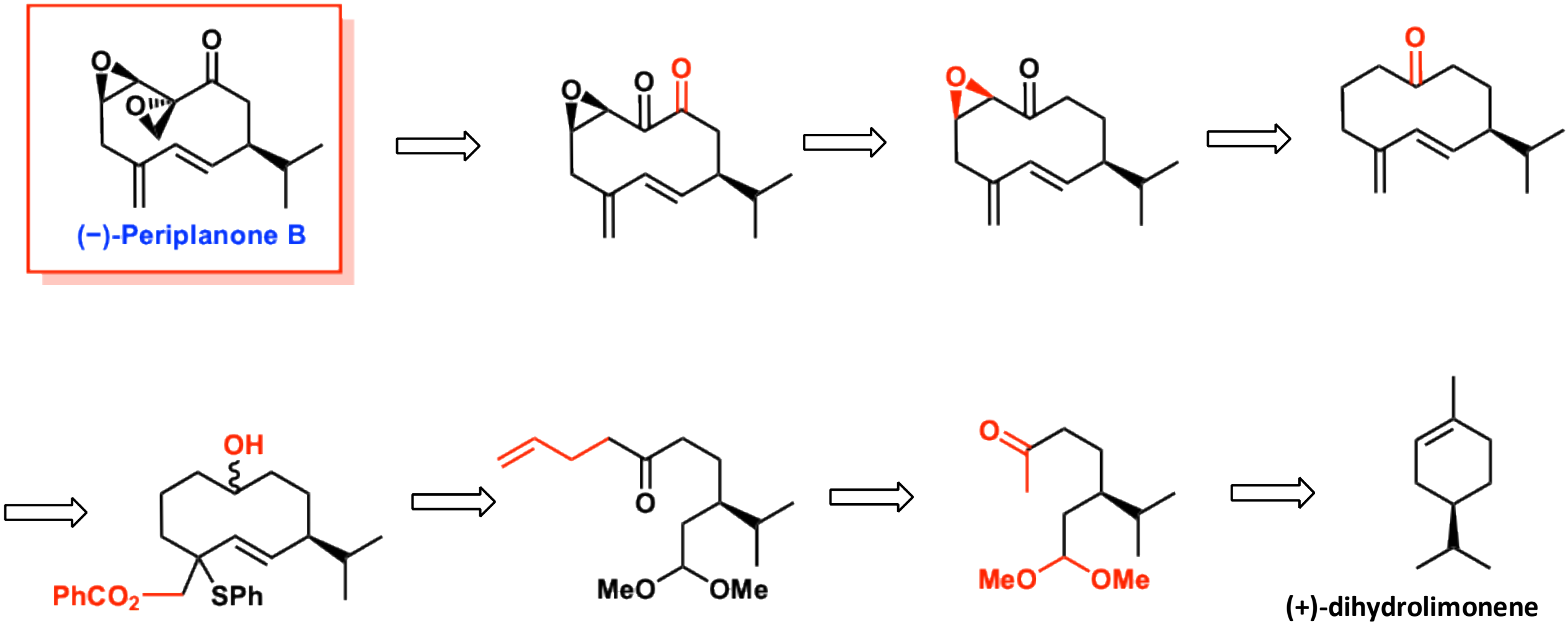
Schreiber's Total Synthesis of Periplanone



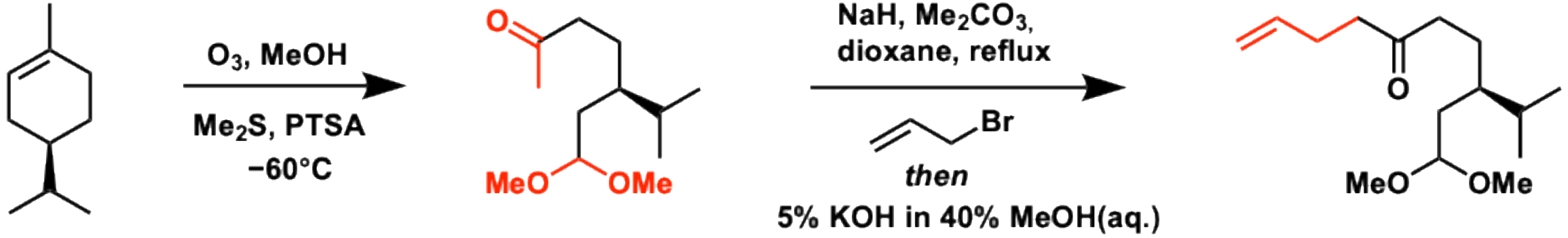
- Schreiber's approach to periplanone B takes full advantage of the facility with which functionalized 5-cyclodecen-1-one systems can be constructed via anionic oxy-Cope rearrangements of readily available divinylcyclohexanols
- Their synthesis commenced from the 4-isopropyl-2-cyclohexen-1-one
- The total synthesis was accomplished in a LLS of 13 steps with an overall yield of 1.75%

T Kitahara's Synthesis of (−)-Periplanone

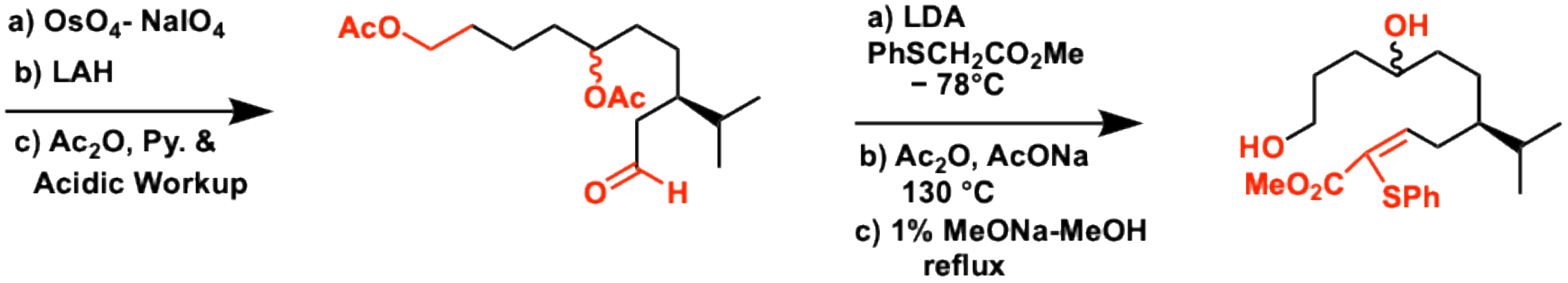
Retrosynthesis



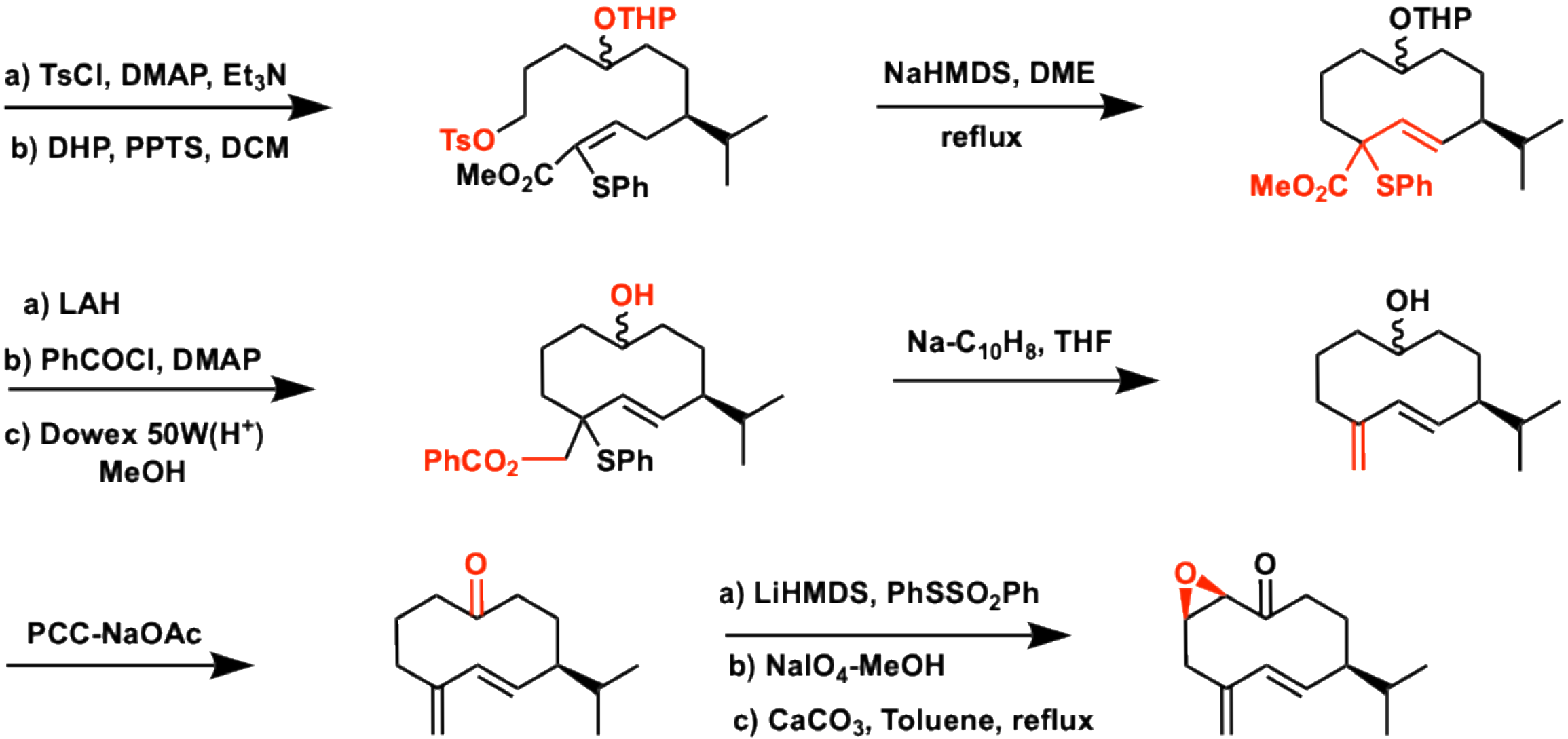
T Kitahara's Total Synthesis of (−)-Periplanone



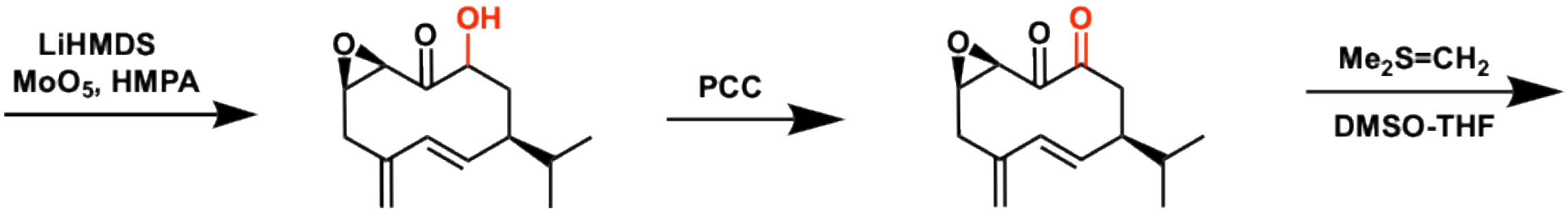
(+)-dihydrolimonene

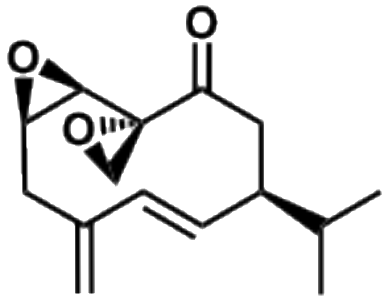


T Kitahara's Total Synthesis of (−)-Periplanone



T Kitahara's Total Synthesis of (−)-Periplanone





(−)-Periplanone B

The total synthesis of (-)-periplanone was accomplished in a LLS of 24 steps starting from (+)-dihydrolimonene

Kitahara T, *et al. Tetrahedron Lett.* **1986**, *27*, 1343–1346