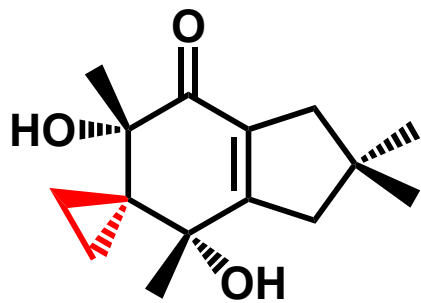


Total Synthesis of Illudins

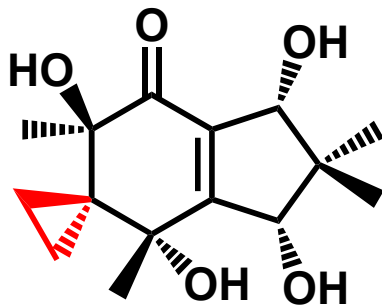


Krishna P Kaliappan
Professor of Chemistry, IIT Bombay

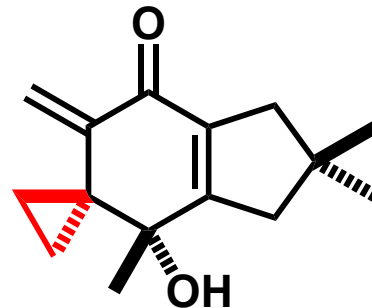
CH-845 Course on Organic Synthesis



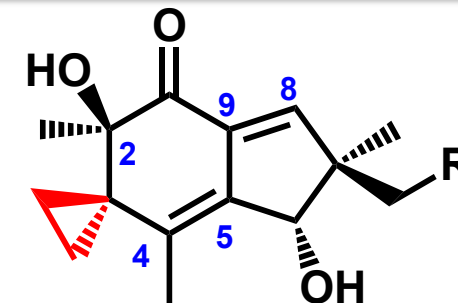
Illudin A



Illudin B

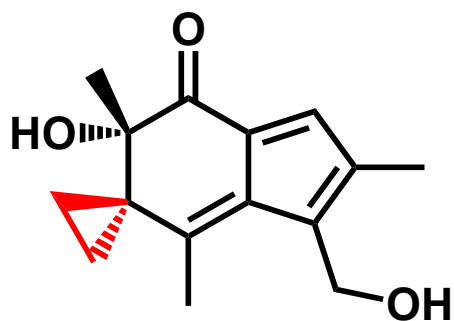


Illudin C

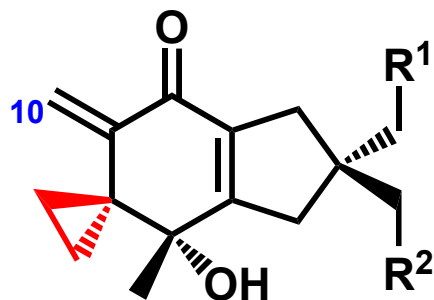


R=H Illudin M
R=OH Illudin S

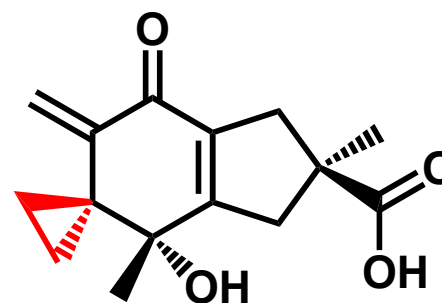
- The **illudins** are an intriguing class of **sesquiterpenes** isolated from several fungi
- These natural products can be structurally categorized according to the **degree and position of unsaturation** in the **unusual tricyclic ring system** and the site of tertiary hydroxyl substituents
- Illudin M and S are **sesquiterpenes** produced by the fungus *Omphalotus illudens*
- Kelner, McMorris, and Taetle have recently reported that the illudins demonstrated ***in vitro* selective toxicity** for tumor cells compared to normal cells
- The **oxidized analog of illudin M** was shown to be **less toxic** to mice than illudin M



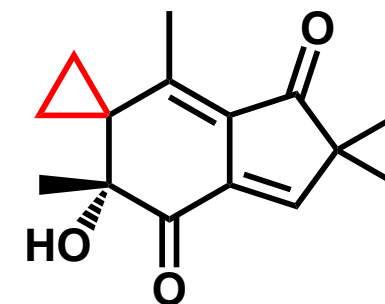
6-Hydroxymethyl-
acylfulvene



$R^1, R^2 = H$ **Illudin C**
 $R^1 = OH, R^2 = H$ **Illudin C₂**
 $R^1 = H, R^2 = OH$ **Illudin C₃**



Illudinic Acid



Dehydroilludin M

Isolation of Illudin M and S: Anchel, M. *et al. Proc. Natl. Acad. Sci. U.S.A.* 2399, **1950**, 36, 300

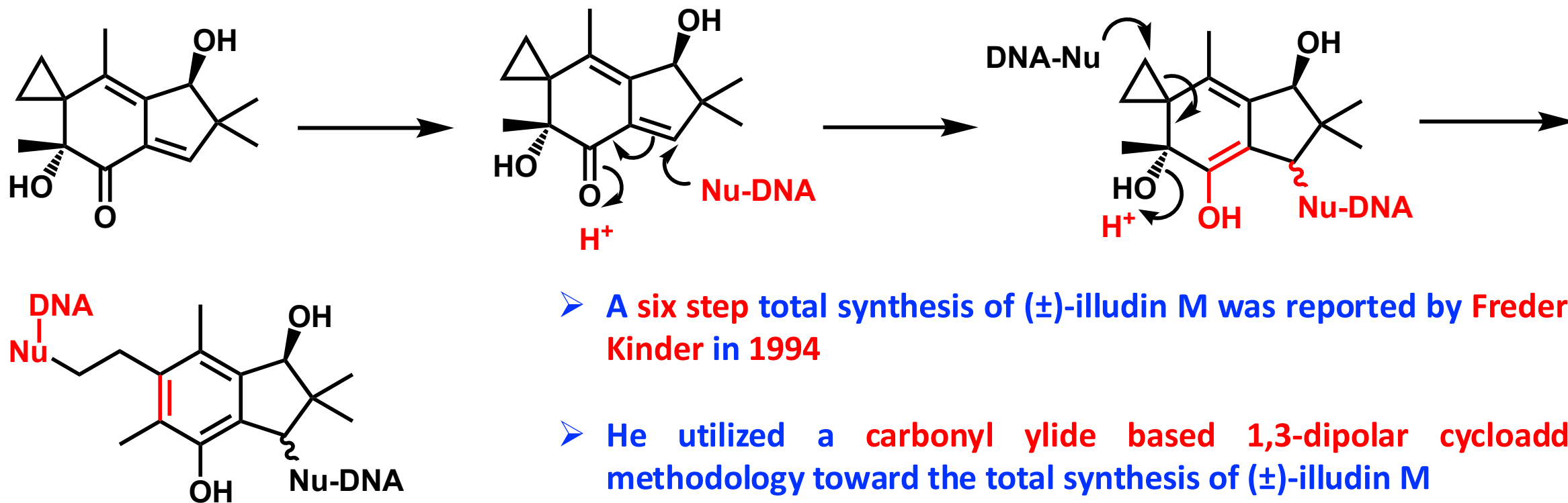
Isolation of Illudin A and B: Arnone, A. *et al. J. Chem. Soc., Perkin Trans. 1*, **1991**, 733-737

Isolation of Illudin C₂, C₃: Lee, I. K.; *et al. J. Antibiot.* **1996**, 49, 821

Isolation of Illudinic acid: Dufresne, C.; *et al. J. Nat. Prod.* **1997**, **60**, 188-190

Mechanism of Action of Illudins & Total Synthesis

- The mechanism of action for the illudins has been proposed as an **acid catalyzed dialkylation of DNA**



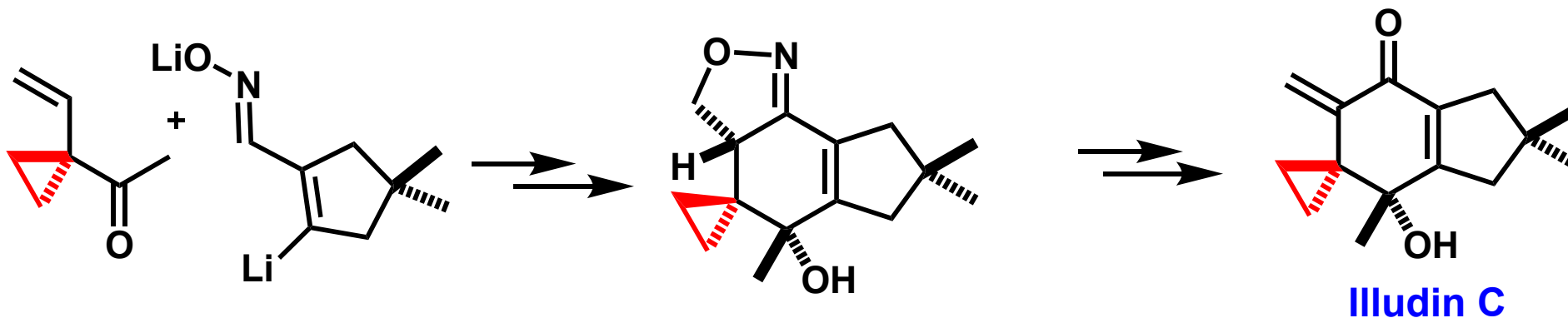
- A **six step** total synthesis of ($\pm$)-illudin M was reported by **Frederick R Kinder** in **1994**
- He utilized a **carbonyl ylide based 1,3-dipolar cycloaddition** methodology toward the total synthesis of ($\pm$)-illudin M
- The total synthesis of illudin M was accomplished from a **diazo ketone** and **bromocyclopentenone**

McMorris, T. C.; Kelner, M. J.; Wang, W.; Estes, L. A *J. Org. Chem.* **1992**, 57, 6876

Kinder, F. R.; Bair, K. W. *J. Org. Chem.* **1994**, 59, 23, 6965–6967

Total Synthesis of Illudin C

- **Raymond L. Funk and co-workers** accomplished the first total synthesis of **illudin C** in **10 steps** with an overall yield of **8.2 %**
- The tricyclic ring system of the natural product was quickly assembled from cyclopropane and cyclopentene precursors via an **intramolecular nitrile oxide-olefin cycloaddition**

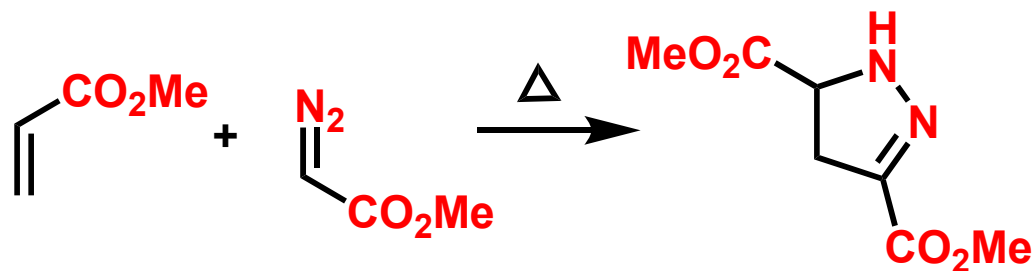


Aungst, R. A. Jr.; Chan, C.; Funk, R. L. *Org. Lett.* **2001**, 3, 2611

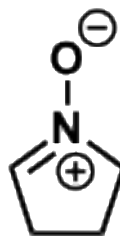
- **1,3-dipolar cycloaddition reaction**
- **Carbonyl Ylide**
- **Nitrile Oxide-Olefin 1,3-Dipolar Cycloaddition**
- **Dirhodium tetracetate**

1,3-Dipolar Cycloaddition

- The addition of a **1,3-dipole** to an **alkene (dipolarophile)** is called **1,3-dipolar cycloaddition reaction** and it forms a new **5-membered ring**
- In 1888, **Buchner** reported the first 1,3-dipolar cycloaddition between **diazoacetic ester** and α,β -unsaturated ester to form **1-pyrazoline**



- In 1898, **Beckmann** discovered “**Nitrones**”

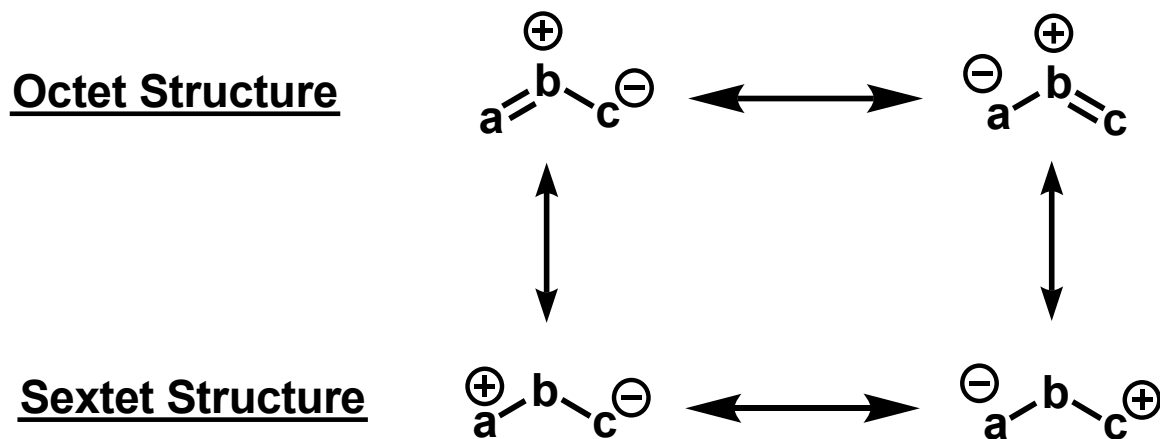


- In 1903, **Werner and Buss** discovered “**Nitrile Oxides**”

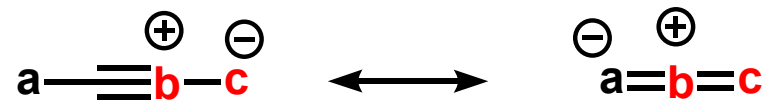


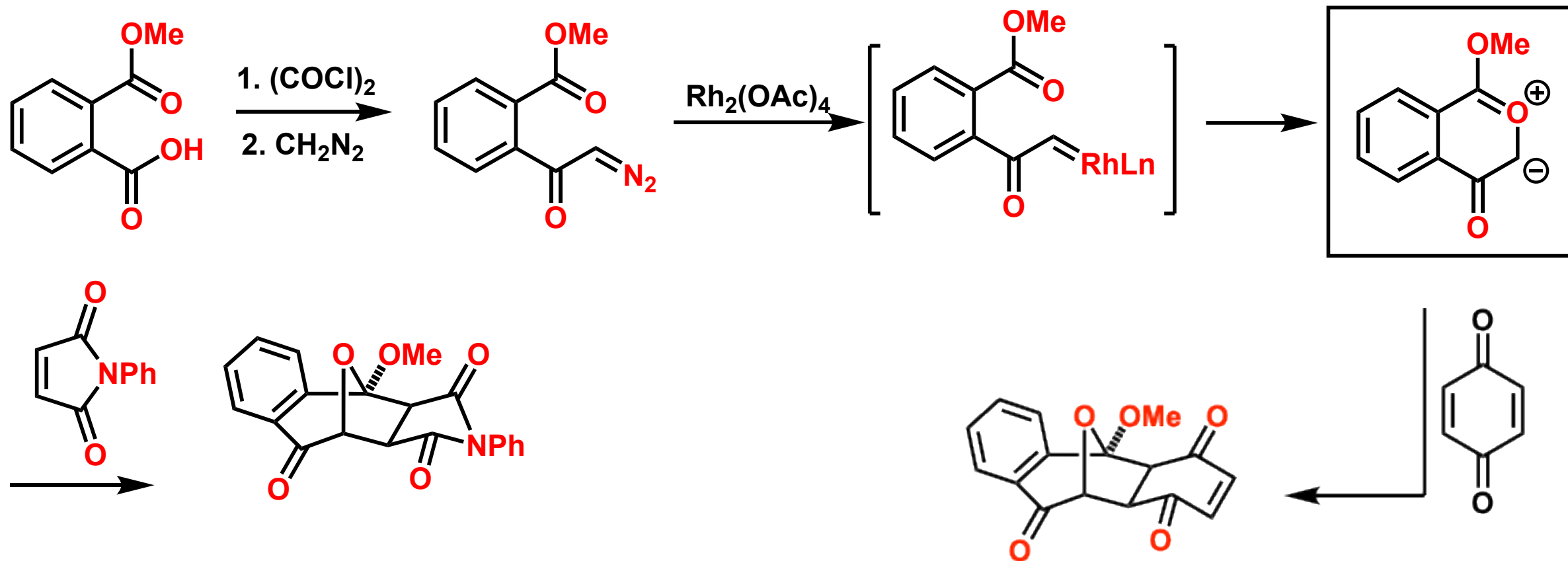
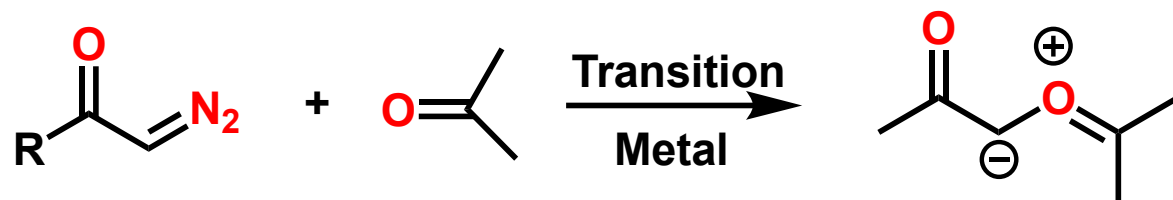
1,3-Dipolar Cycloaddition

- **1. Allyl anion**, characterized by “four electrons in parallel *p* orbitals” perpendicular to the plane of the dipole and the dipole is ‘bent’

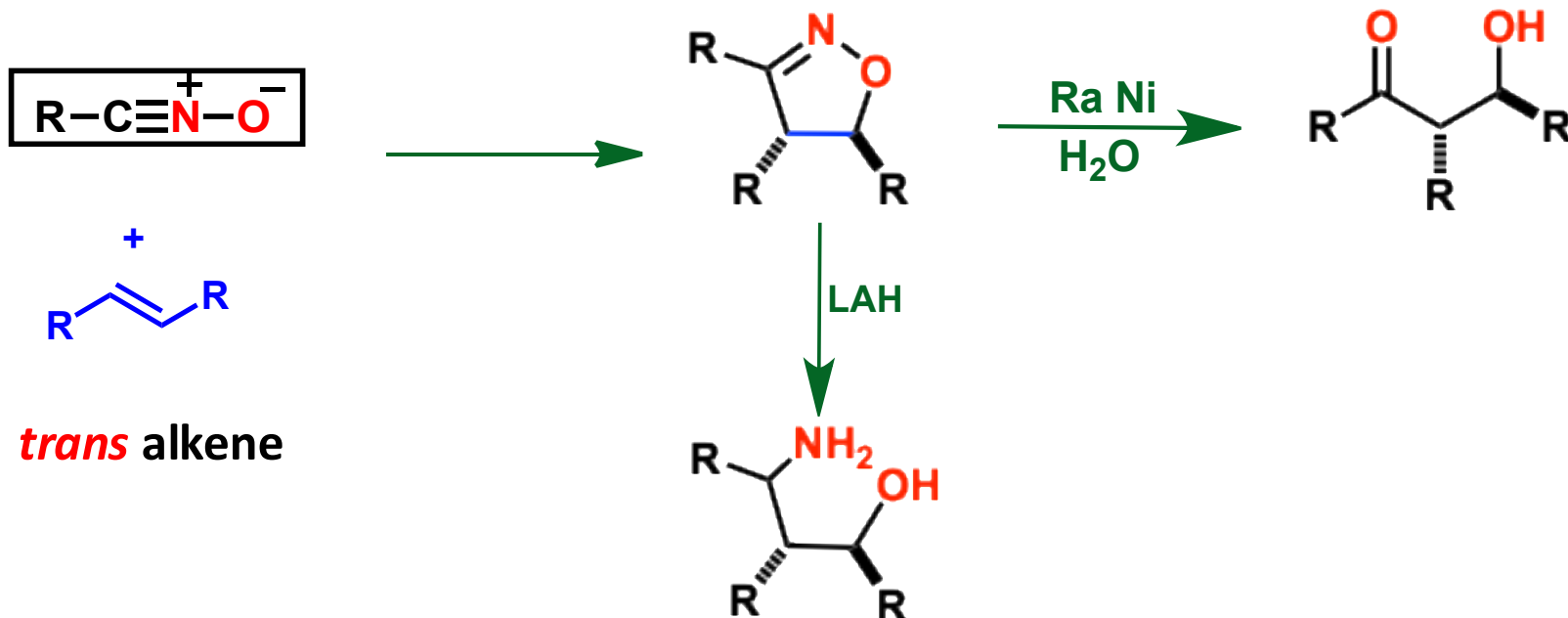
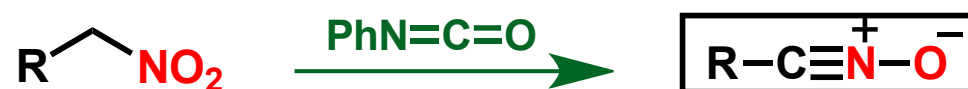
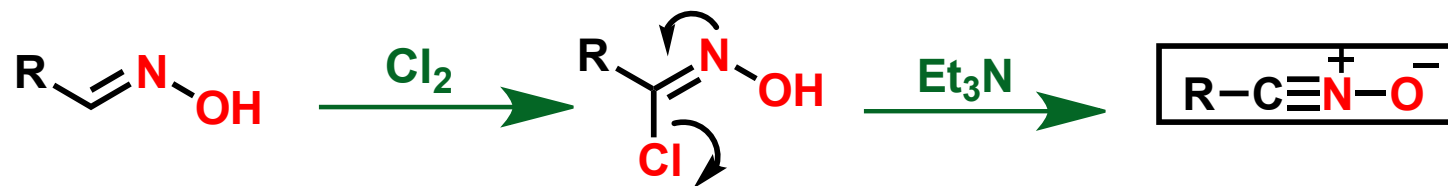


- **2. Propargyl or allenyl anions** characterized by an “extra π orbital” orthogonal to the allenyl anion MO. The dipole is ‘linear’

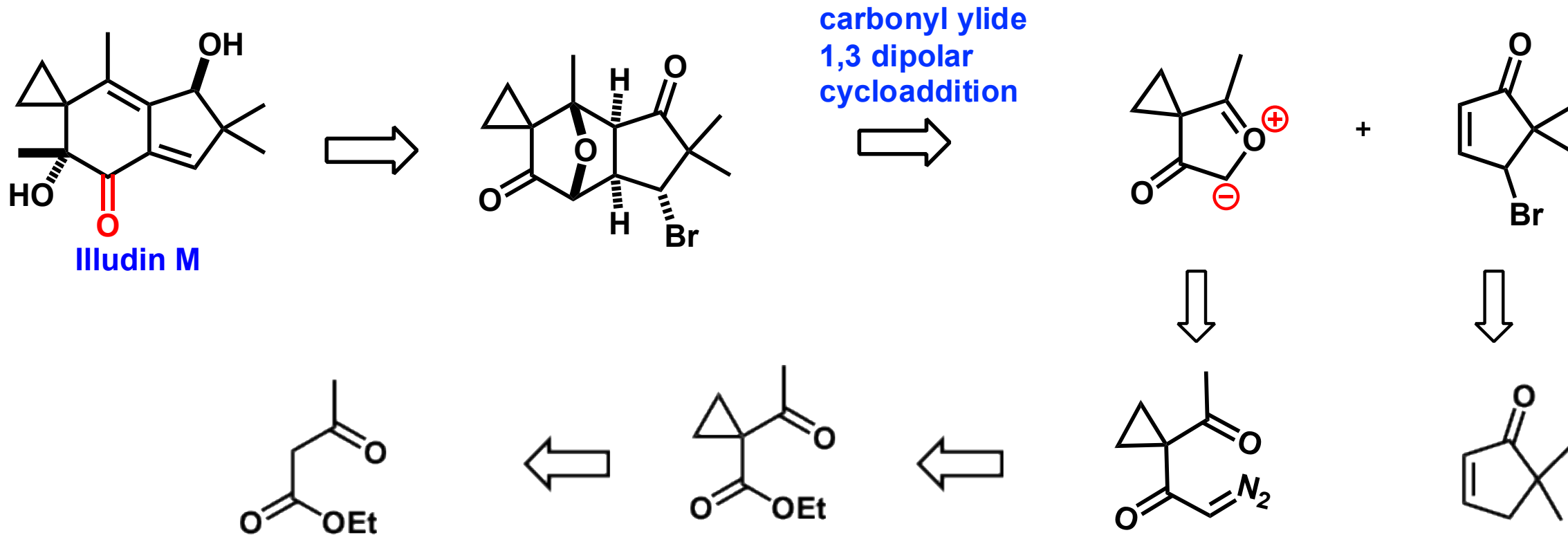




Nitrile Oxides

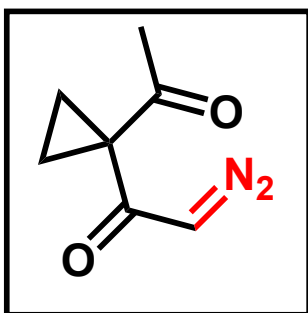
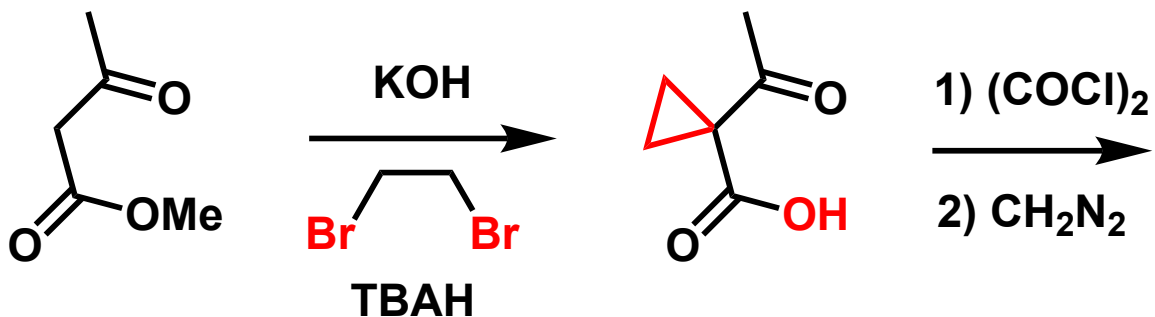


Retrosynthesis of Illudin M

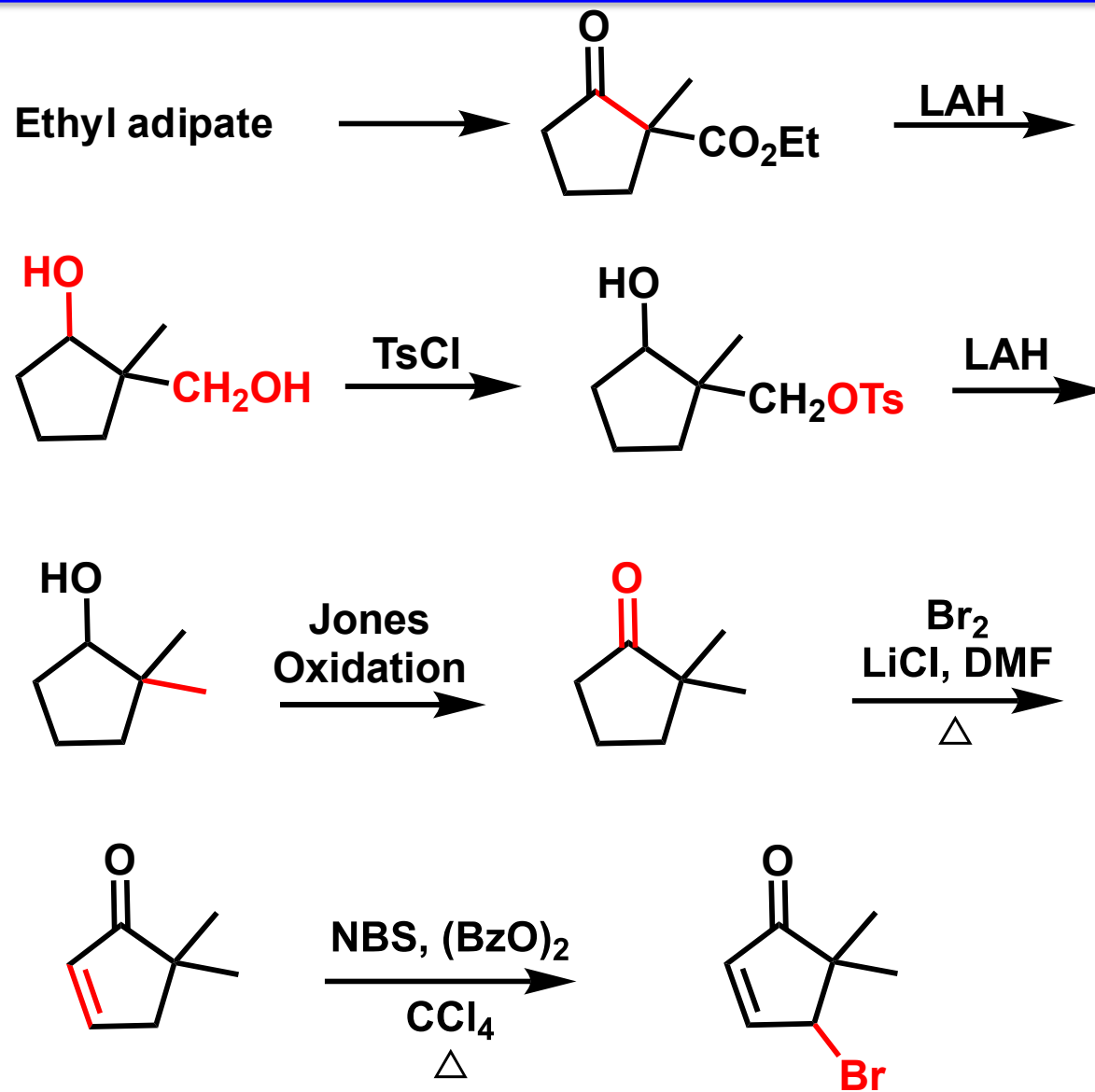


Kinder, F. R.; Bair, K. W. *J. Org. Chem.* **1994**, 59, 23, 6965–6967

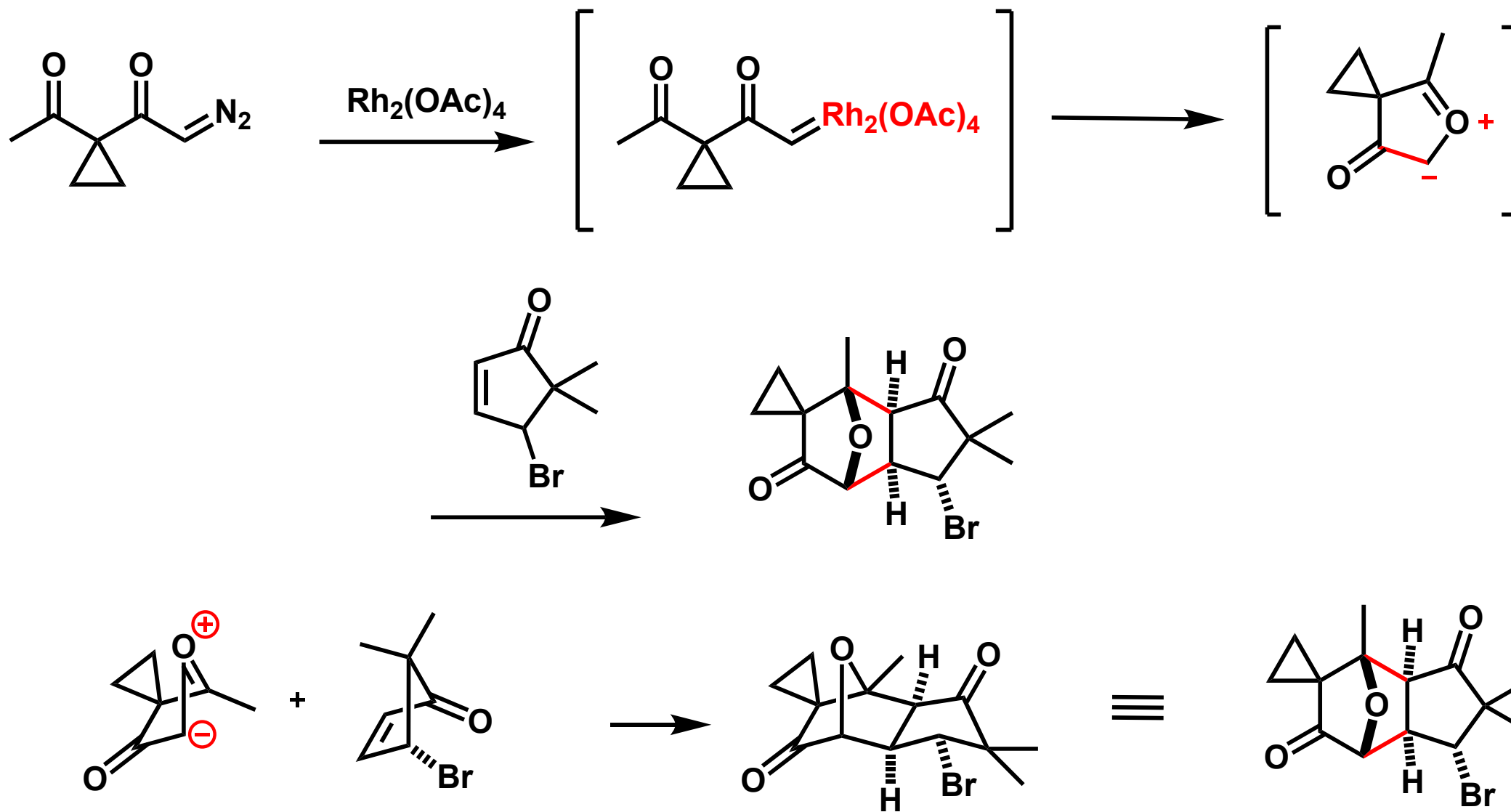
Preparation of Starting Materials



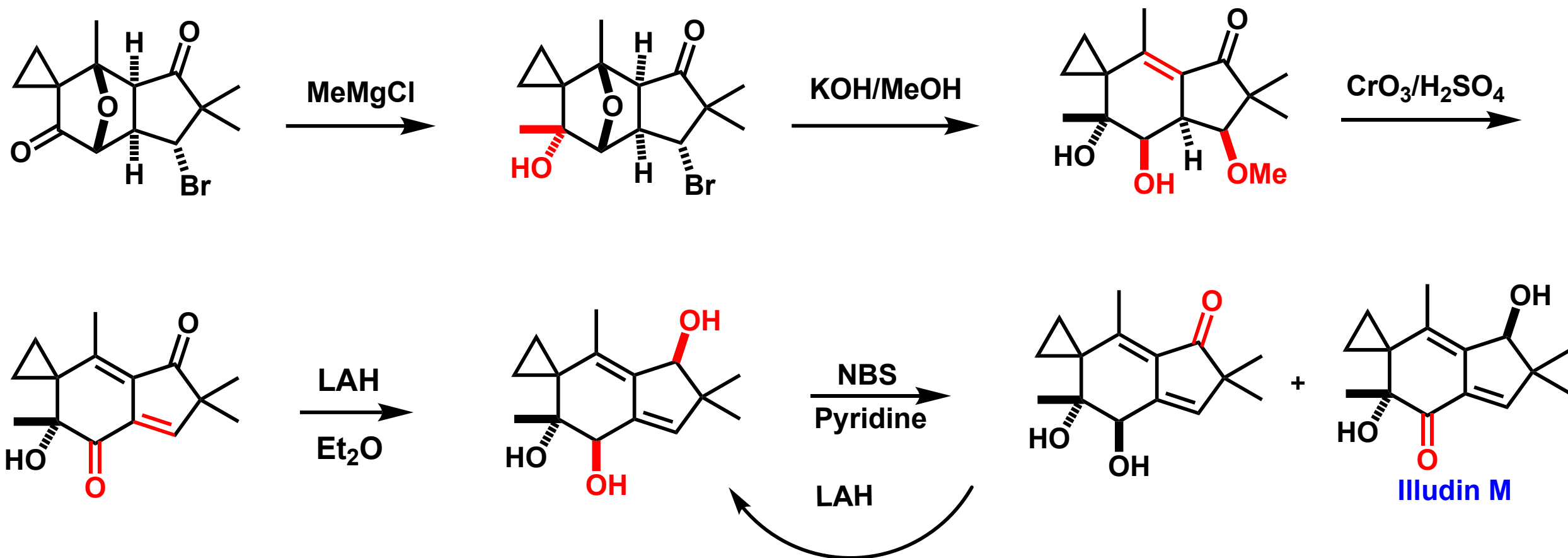
Padwa, A.; Chinn, R. L; Hombuckle, S. F.;
Zhang, Z. J. *J. Org. Chem.* **1991**, 56, 3271



Total Synthesis of Illudin M

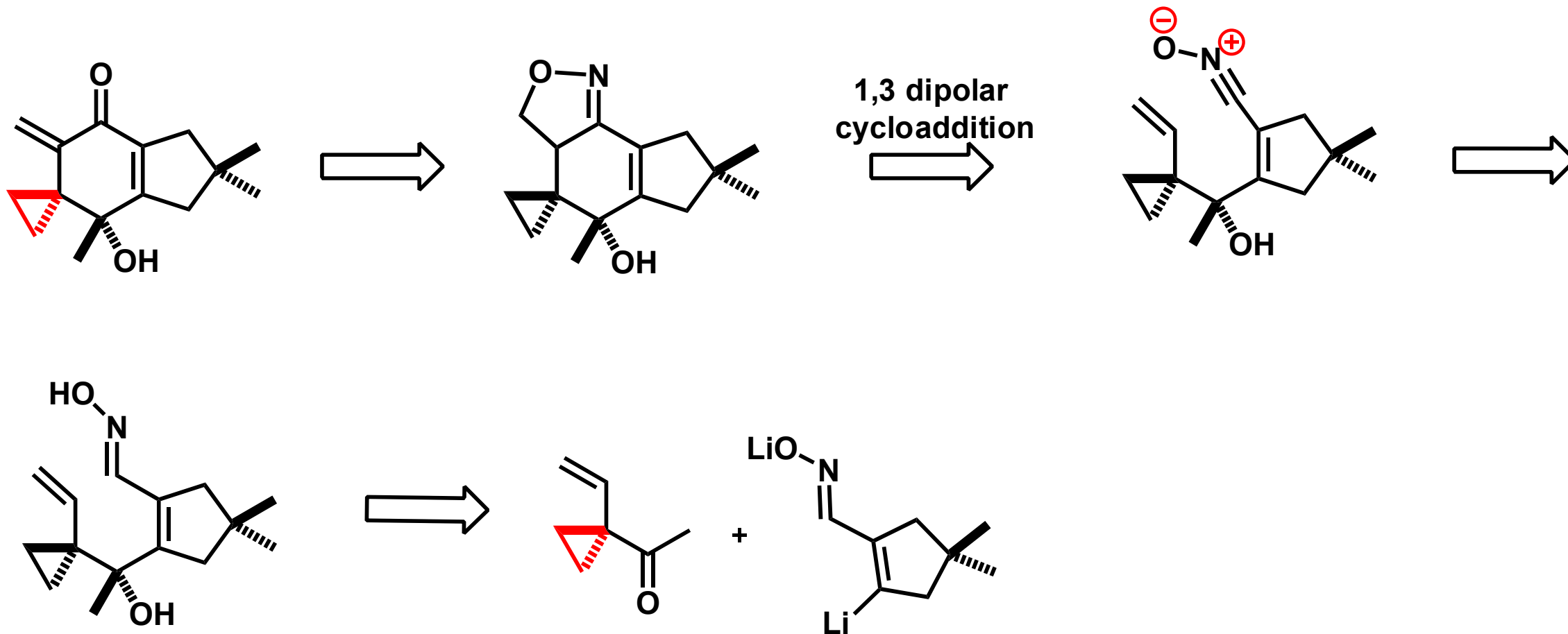


Total Synthesis of Illudin M



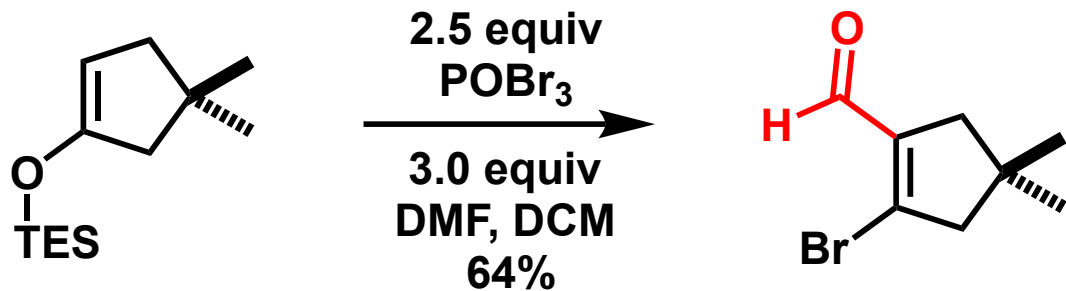
Kinder, F. R.; Bair, K. W. *J. Org. Chem.* **1994**, 59, 23, 6965–6967

Retrosynthesis of Illudin C

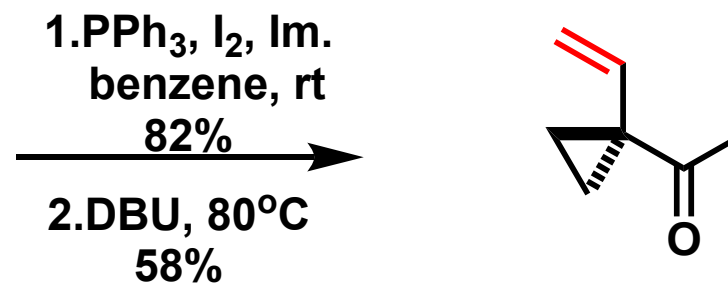
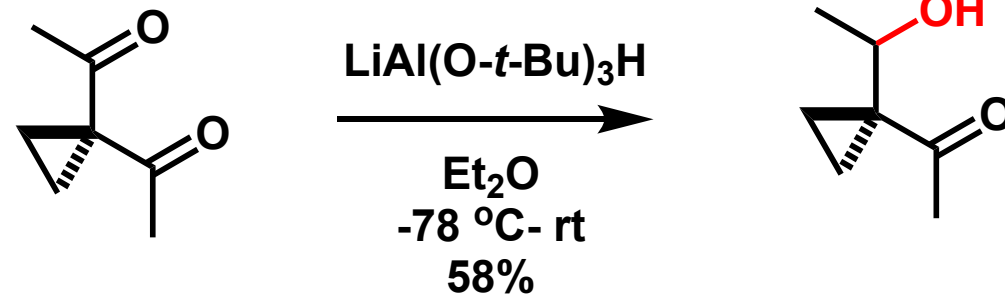
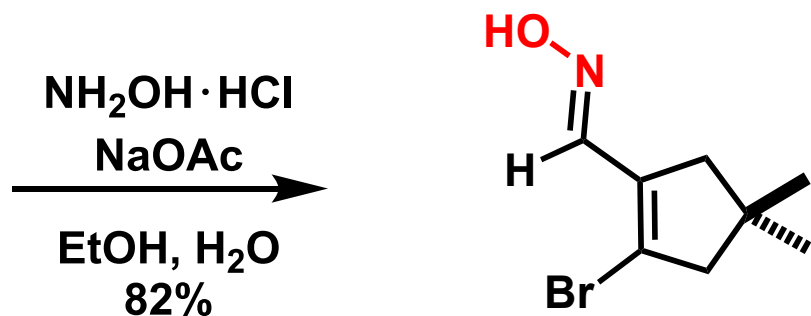


Aungst, R. A. Jr.; Chan, C.; Funk, R. L. *Org. Lett.* **2001**, 3, 2611

Total Synthesis of Illudin C



Vilsmeier-Haack Reaction



Aungst, R. A. Jr.; Chan, C.; Funk, R. L. *Org. Lett.* **2001**, 3, 2611

Total Synthesis of Illudin C

