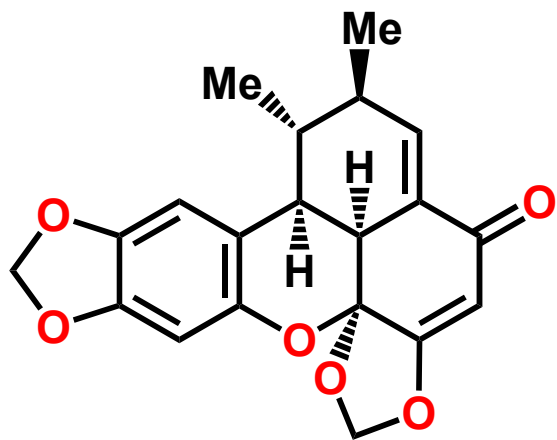


Total Synthesis of Carpanone



Krishna P Kaliappan
Professor of Chemistry, IIT Bombay

CH-845 Course on Organic Synthesis



carpanone

Isolation: Brophy, G. C.; et al. *Tetrahedron Lett.* **1969**, 59, 5159

- Carpanone, a lignan obtained from the bark of the carpano tree, poses a significant synthetic challenge
- The molecule possesses no element of symmetry and has five contiguous asymmetric centers
- The structure of carpanone was revealed by Australian scientists in 1969

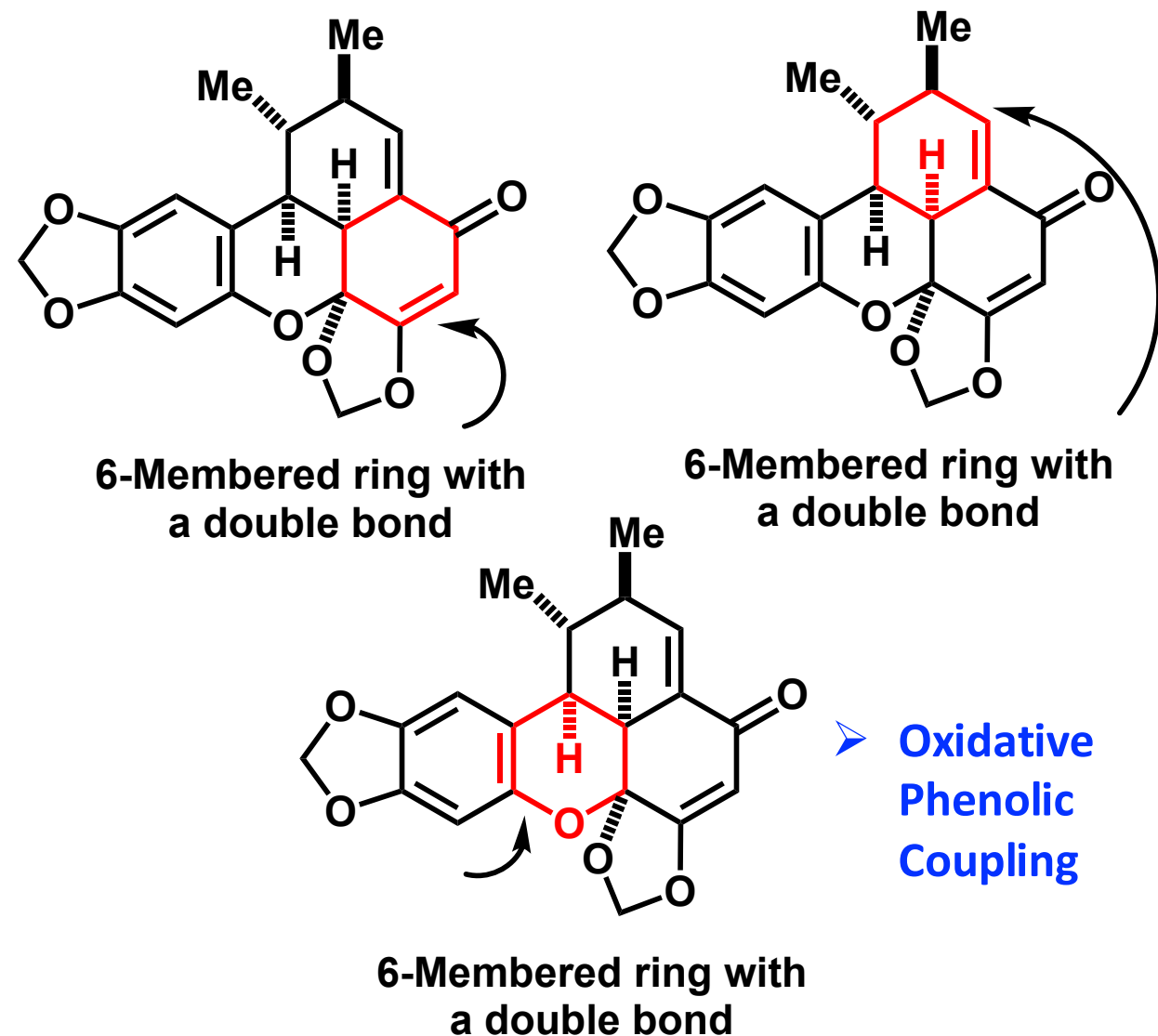
Chapman's Synthesis of Carpanone

- An elegant biomimetic synthesis of carpanone was reported by Chapman and co-workers in 1971
- This remarkable two step synthesis of carpanone involves Diels-Alder cycloaddition and oxidative phenolic coupling as the key reactions

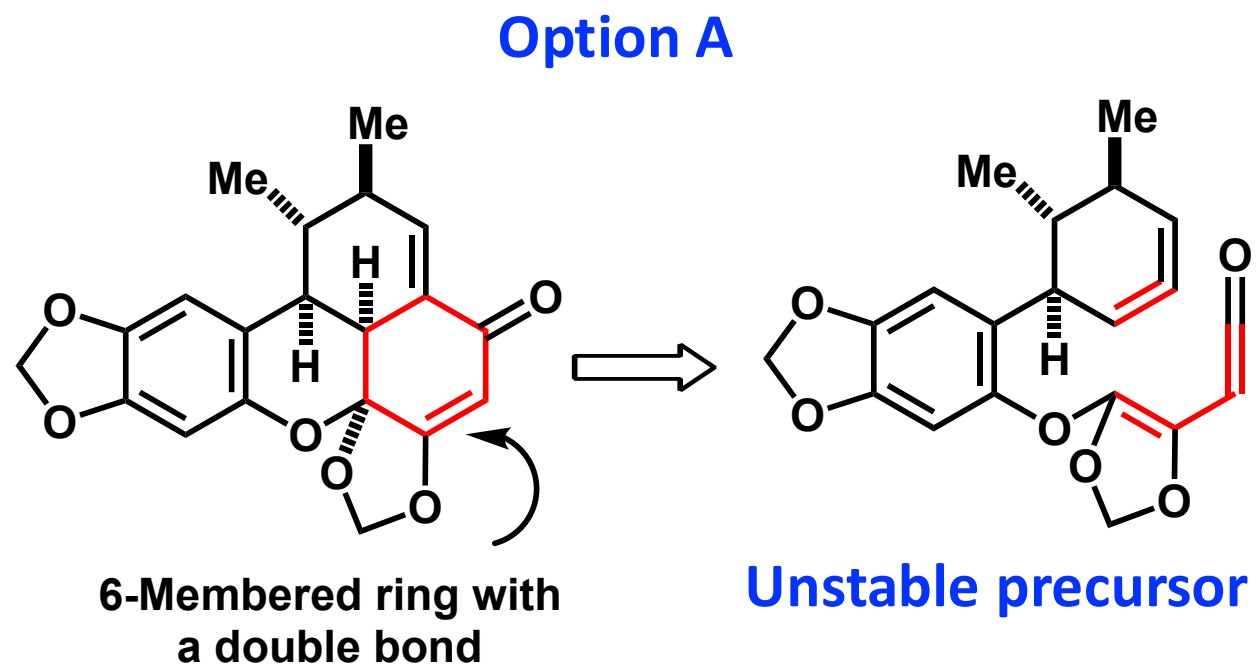
Chapman, O.L.; co-workers. *J. Am. Chem. Soc.* **1971**, 93, 6696

Key Steps in Total Synthesis

➤ Intramolecular Diels-Alder Reaction

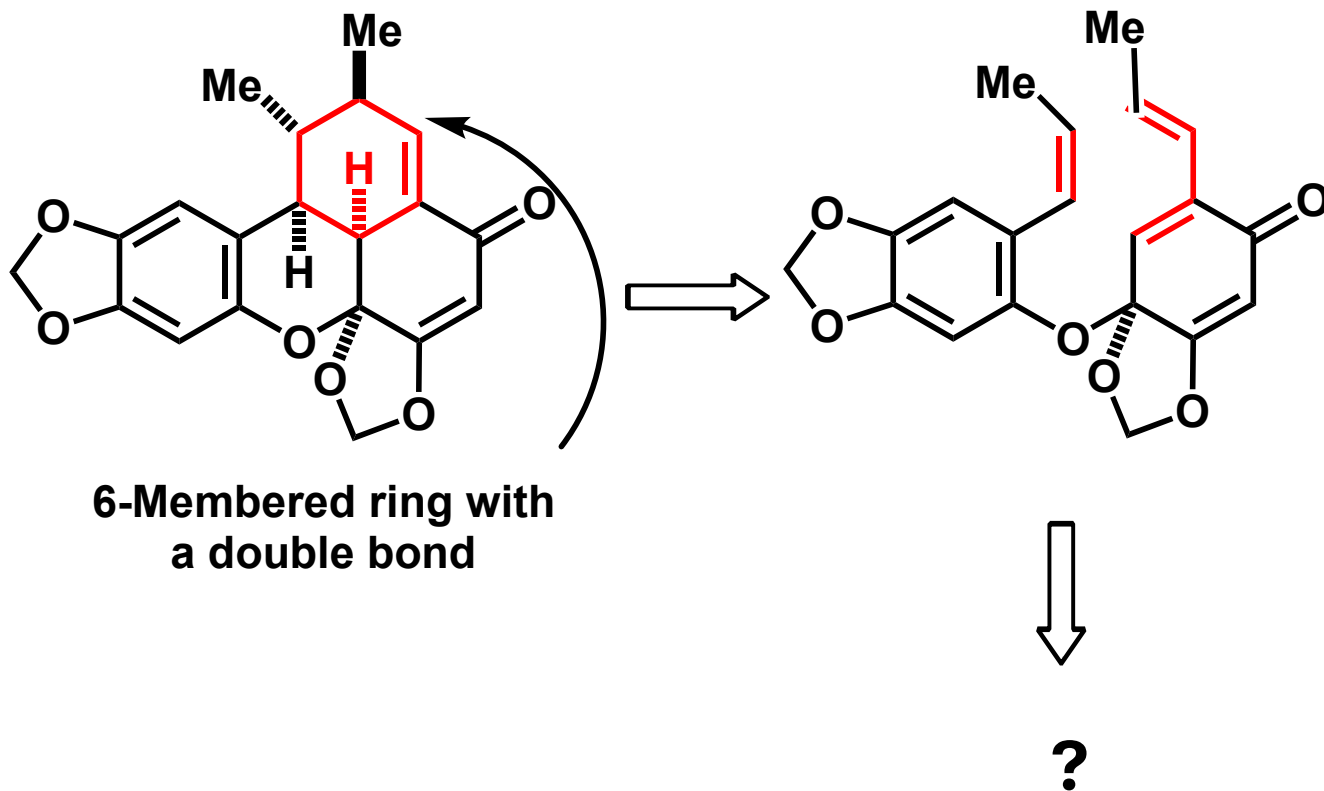


Intramolecular Diels-Alder Reaction

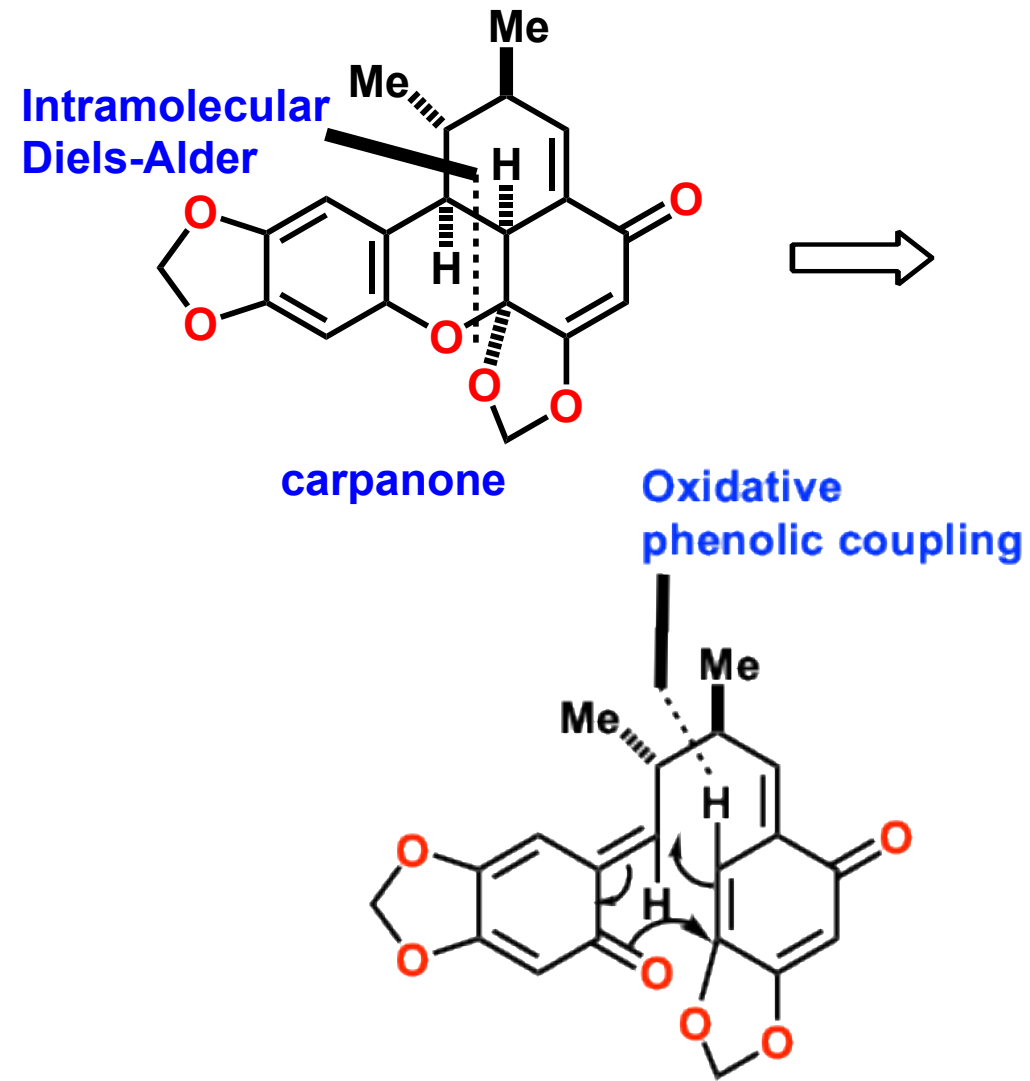


Intramolecular Diels-Alder Reaction

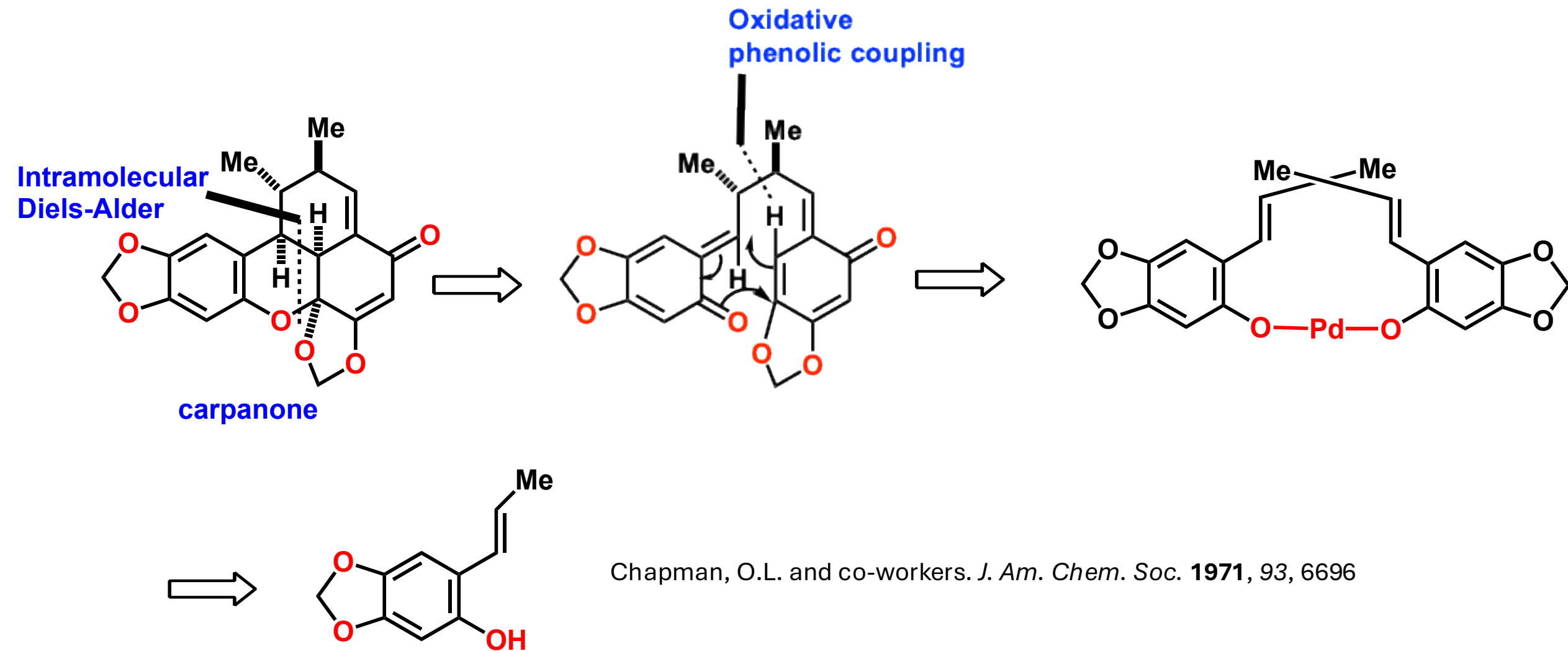
Option B



Option C



Retrosynthesis



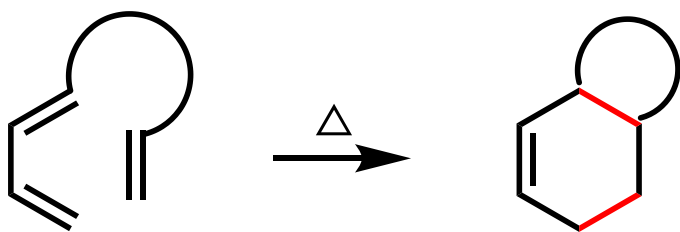
➤ Intermolecular Diels-Alder Reaction

➤ Intramolecular Diels-Alder Reaction

Type I (IMDA):

➤ Results in the formation of **fused bicyclic system**

➤ **Dienophile** is attached to **C-1 atom of diene**

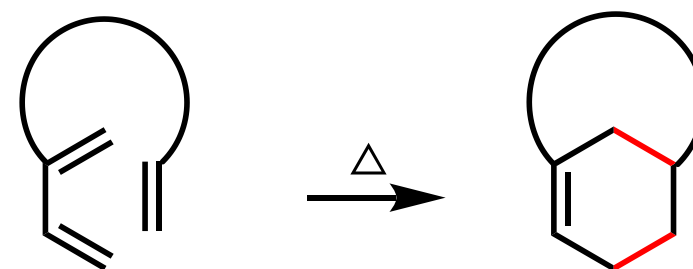


Fused bicyclic system

Type II (IMDA)

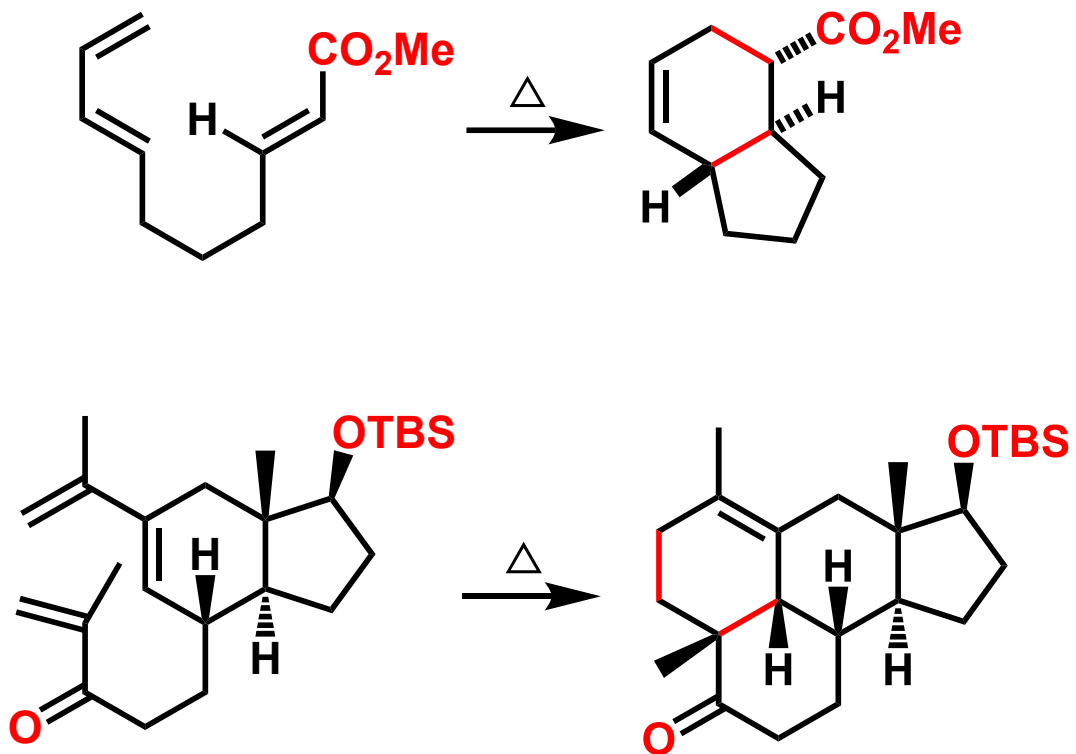
➤ **Dienophile** is attached to **C-2 atom of diene**

➤ **Type II IMDA** generally results in the formation of **bridged bicyclic system**, provided the ring formed should be larger than six membered (should be minimum **seven** membered ring)

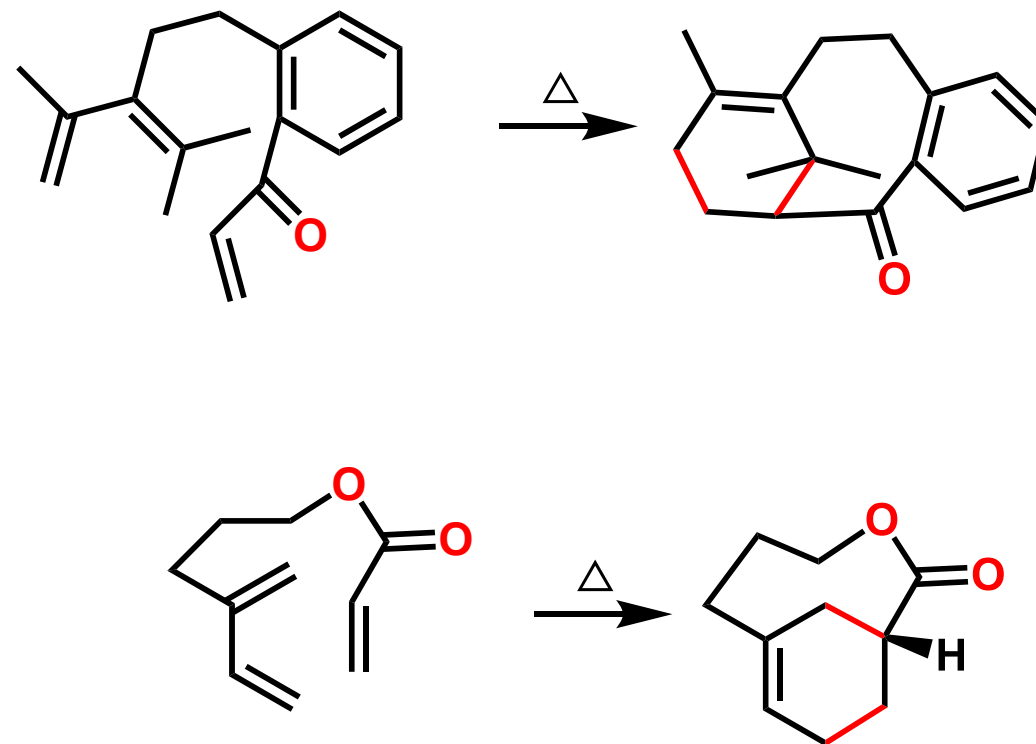


Bridged bicyclic system

Type I (IMDA):

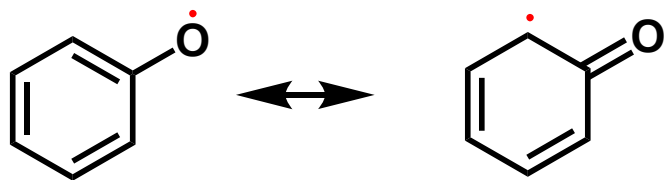


Type II (IMDA):

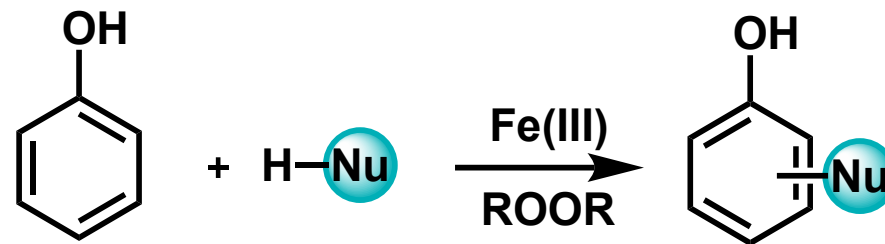


➤ **Oxidative coupling** is an important reaction in the **biosynthesis of secondary plant metabolites**. It was estimated that the biosynthesis of more than **10% of alkaloids** involves one or more oxidative coupling steps

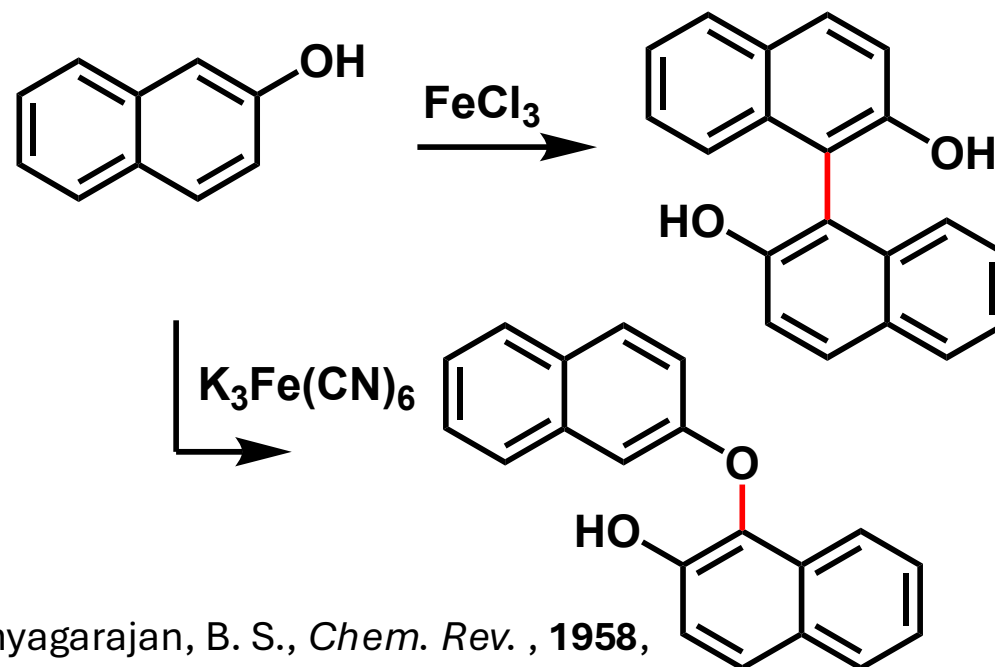
➤ It was **Barton and Cohen** who first suggested that the biotransformation of benzylisoquinolines to morphine alkaloids may involve **phenolic radicals**, which by radical pairing form new C-C and C-O bonds either intra- or intermolecularly



Barton, D. H. R.; Cohen, T. *Festschrift Arthur Stoll*, **1957**; p 117

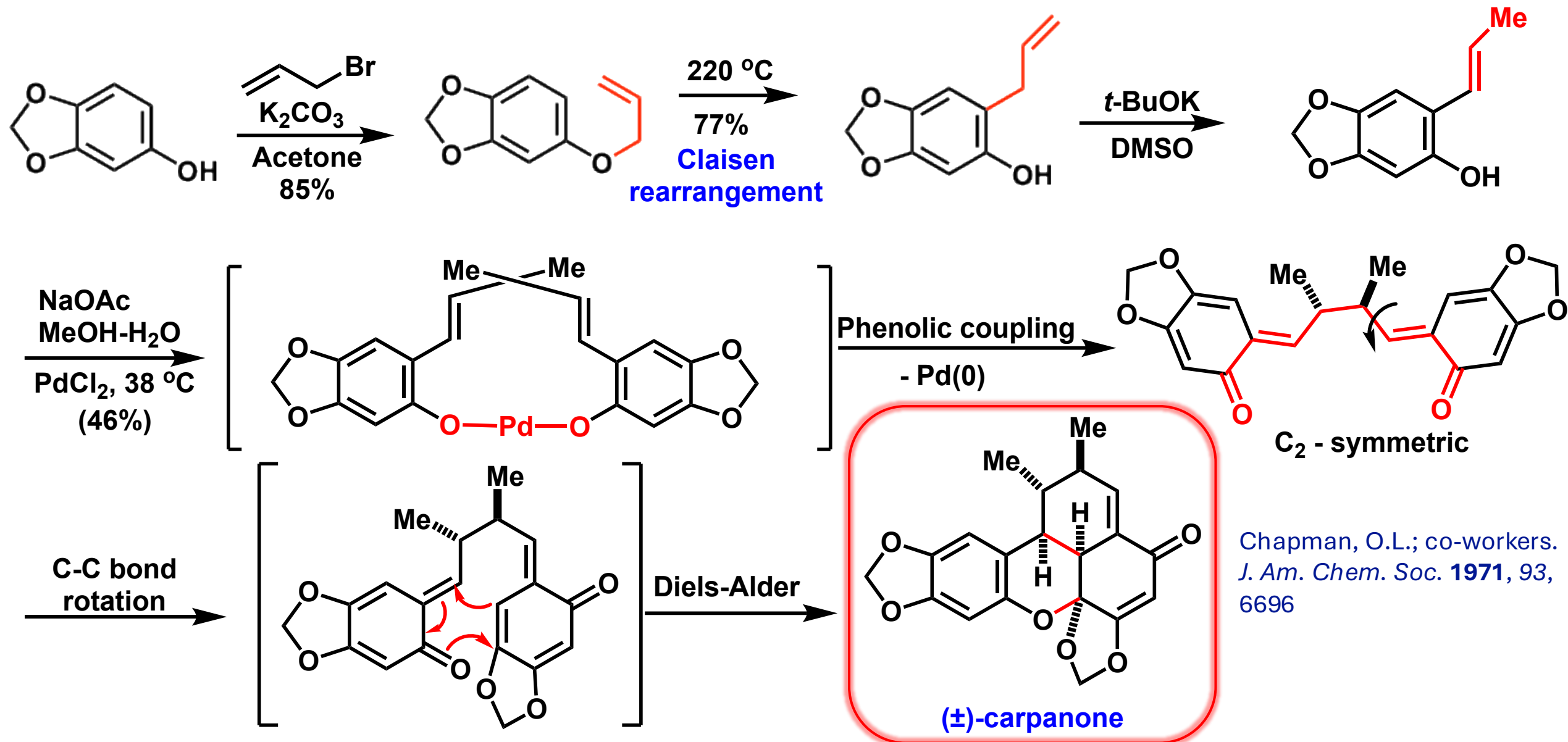


Pappo, D; co-workers. *J. Org. Chem.* **2019**, 84, 4, 1677–1686

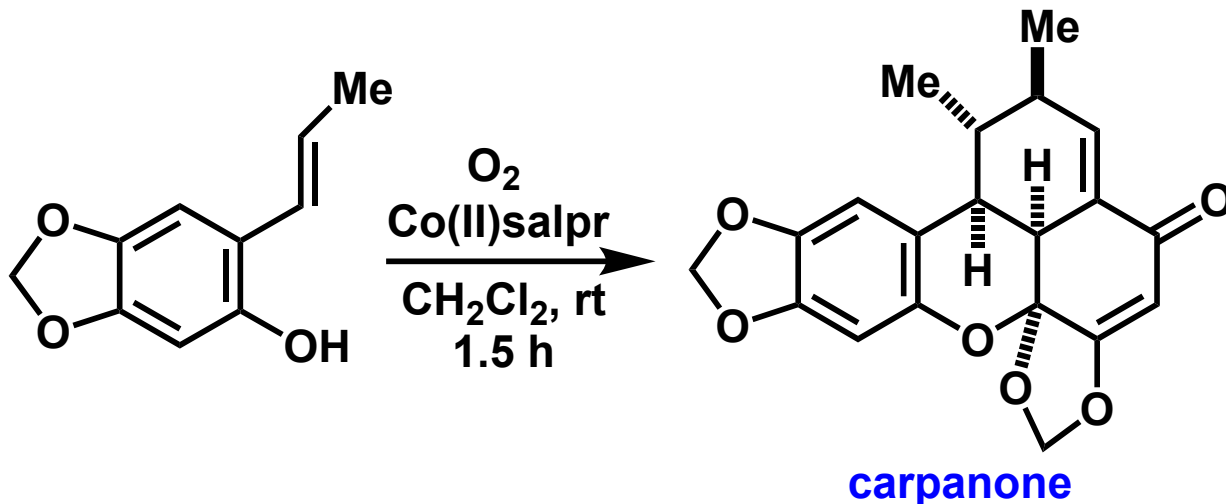


Thyagarajan, B. S., *Chem. Rev.* , **1958**, 58 , 439

Total Synthesis of Carpanone



One step Synthesis



Matsumoto, M.; et al. *Tetrahedron Lett.* **1981**, 22, 4437-4440

- Carpanone was synthesized by Matsumoto in an excellent yield by oxidation of *trans*-2-(1-propenyl)-4,5-methylenedioxyphenol with molecular oxygen in the presence of transition metal complexes

Summary

- An elegant biomimetic synthesis of carpanone was reported by Chapman and coworkers in 1971
- This remarkable synthesis of carpanone involves Diels-Alder cycloaddition and oxidative phenolic coupling as the key reactions
- The total synthesis was accomplished in 4 steps with an overall yield of 46%
- Matsumoto's approach made use of the oxidation of *trans*-2-(1-propenyl)-4,5-methylenedioxyphenol with molecular oxygen in the presence of transition metal complexes to give carpanone in 90% yield in a single step