Intramolecular Cyclobutadiene Cycloaddition/Cyclopropanation/Thermal Rearrangement: An Effective Strategy for the Asymmetric Syntheses of Pleocarpenene and Pleocarpenone

Michael J. Williams, Holly L. Deak and Mark L. Snapper

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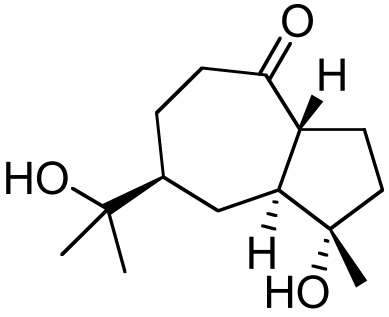
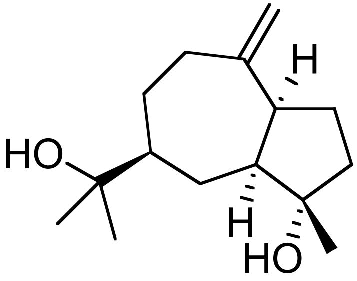




Outline

- Cyclobutadiene introduction
- Cyclobutadiene in synthesis
- Snapper work with cyclobutadiene
- Pleocarpenene and pleocarpenone
- Total syntheses of pleocarpenene and pleocarpenone
- Conclusions

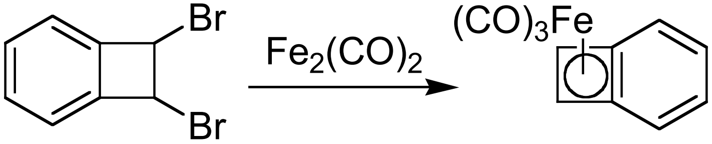
Cyclobutadiene

- Anti-aromatic species that rapidly dimerizes
- Observed at 8 K (*JACS*, **1973**, *95*, 614)
- First synthesized in 1965 by Rowland Pettit

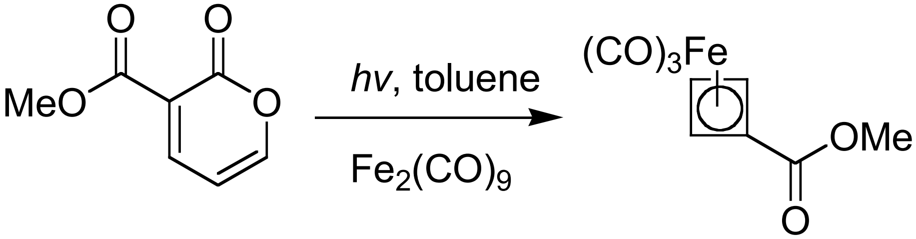
  (*JACS*, **1965**, *87*, 131)
- Reactivity modulated with stabilizing groups
  - Bulky groups
  - Electron withdrawing, donating groups
- Stabilized when complexed to metal
  - As tricarbonylcyclobutadiene iron complex:
    - Stable to Friedel-Crafts conditions, $NaBH_4$, Grignard Reagents, HCl, mild oxidants, etc. (*JACS*, **1965**, *87*, 3254)
    - Iron complex can be readily removed with CAN, $FeCl_3$, $Pb(OAc)_4$ or trimethyl ammonium *N*-oxide

Cyclobutadiene Synthesis

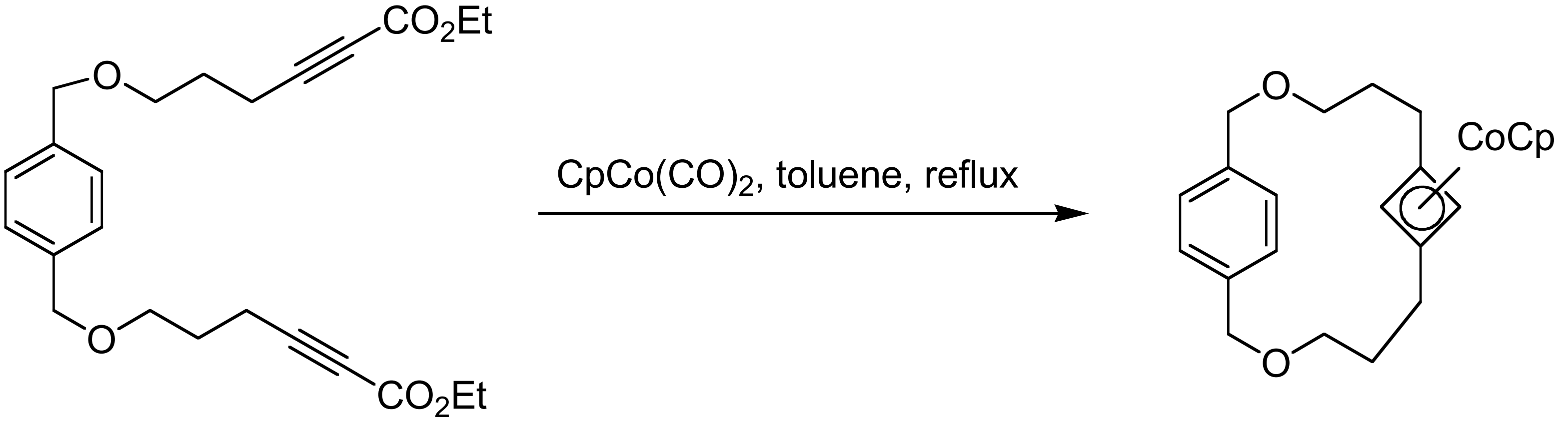
- Synthetic methods:
  - Cyclobutane, (*JACS*, **1965**, *87*, 131)



  - Pyranone, (*JACS,* **1967**, *89*, 5074)

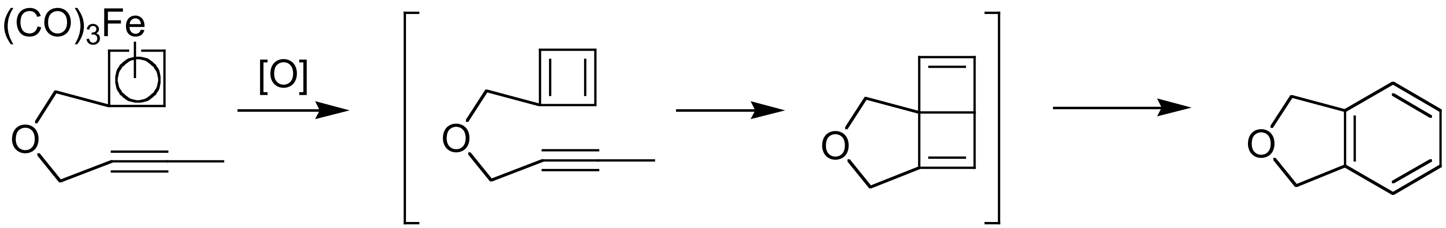


  - Alkyne (*JACS*, **2005**, *127*, 3473)

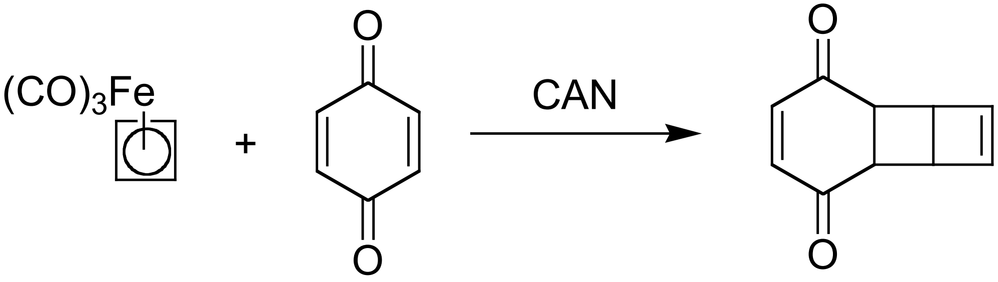


Cyclobutadiene Reactions

- Aromatic Synthesis (Grubbs, *Tet.Lett*, **1974**, 2425)



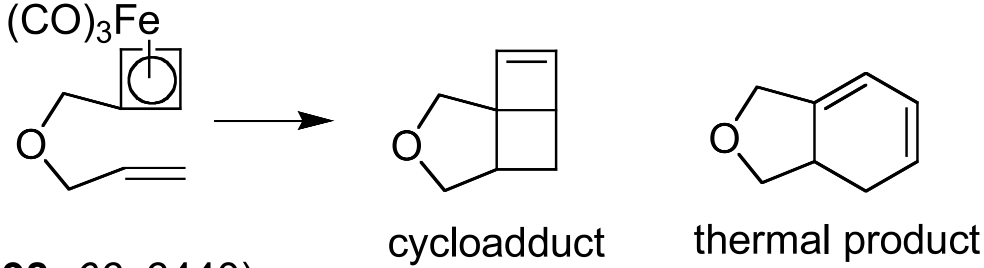
- 2+2 (Pettit, *JACS*, **1966**, 1328)



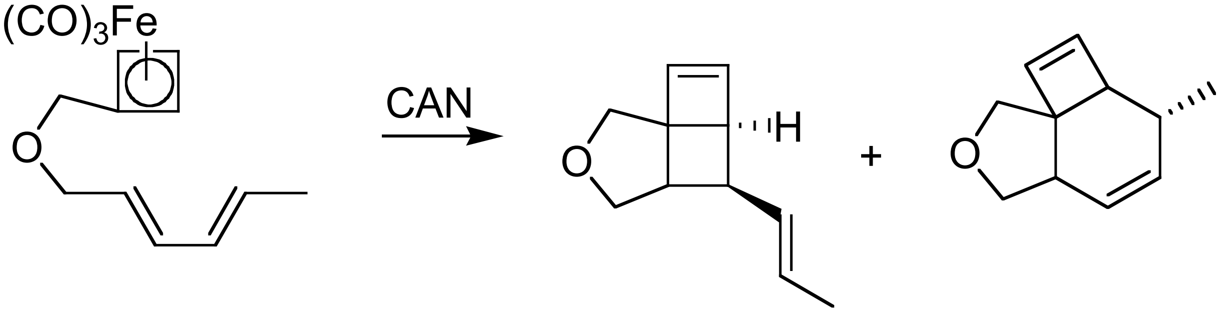
Typically run at 1 mM

Early Snapper Work

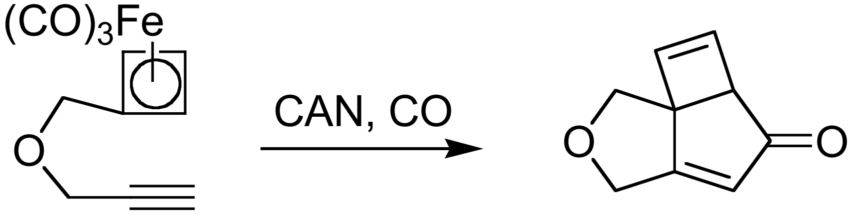
- (2+2) (*JACS*, **1996**, *118*, 9196)



- (4+2) (*JOC*, **1998**, *63*, 6440)



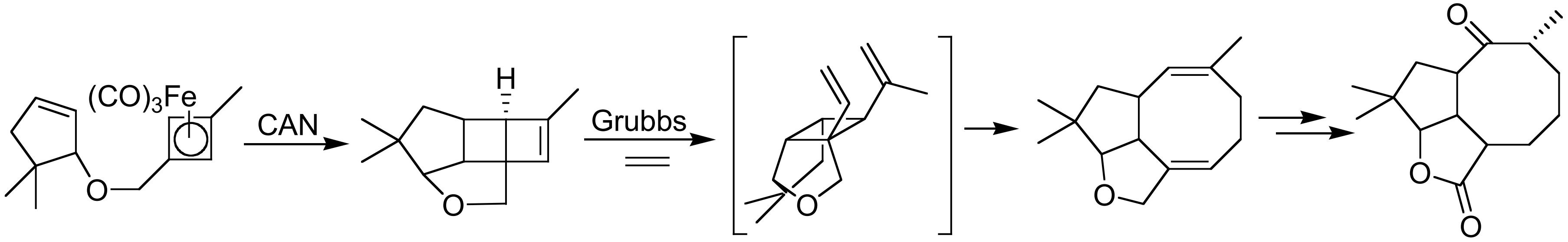
- (2+2+1) (*Angew.Chem.Int.Ed*, **2005**, *44*, 4929)



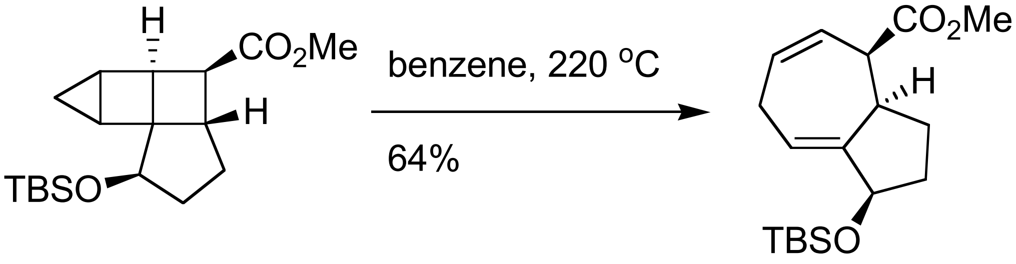
Huisgen Notation

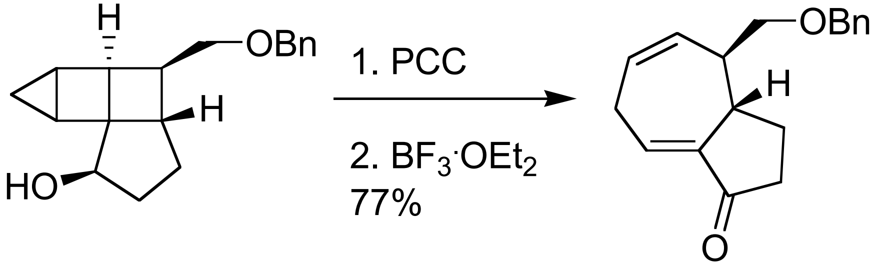
Snapper Work (cont.)

- Asteriscanolide (*JACS*, **2000**, *122*, 8071)

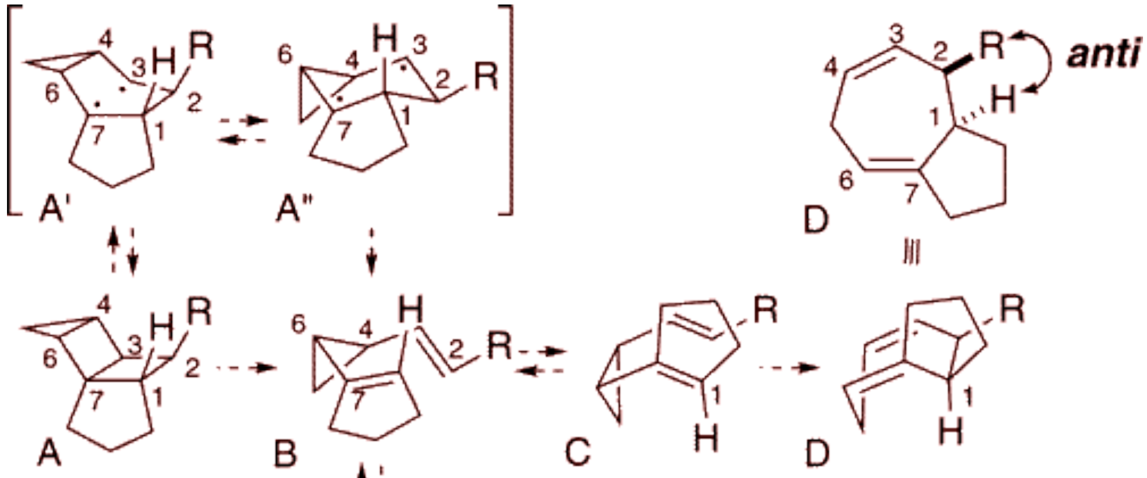


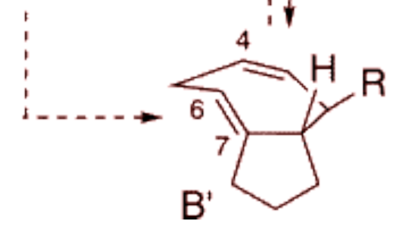
- Cyclopropanation (*Org. Lett*, **2005**, *7*, 5785)





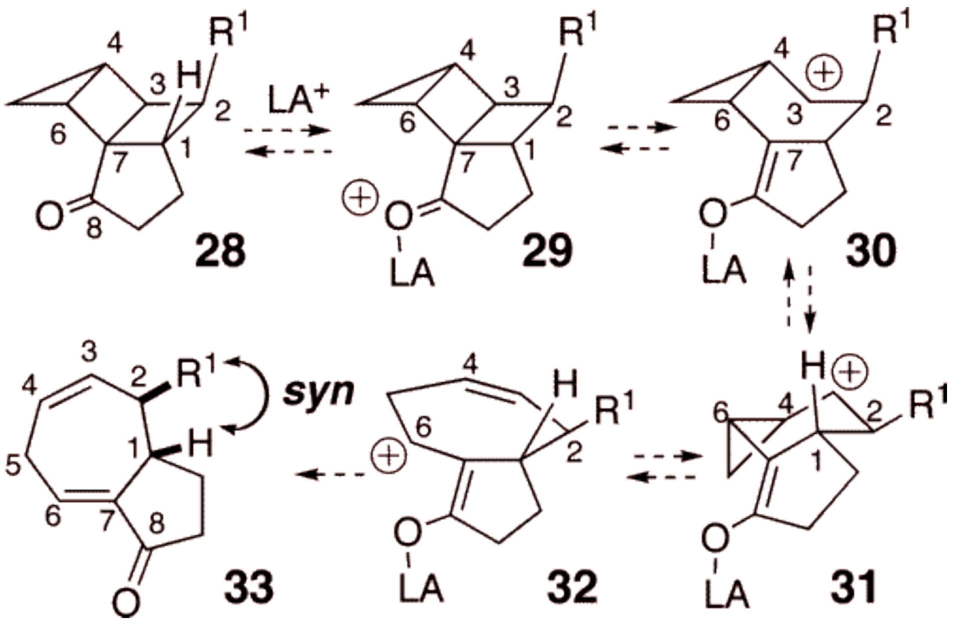
Rearrangement Stereochemistry





Thermal Rearrangement

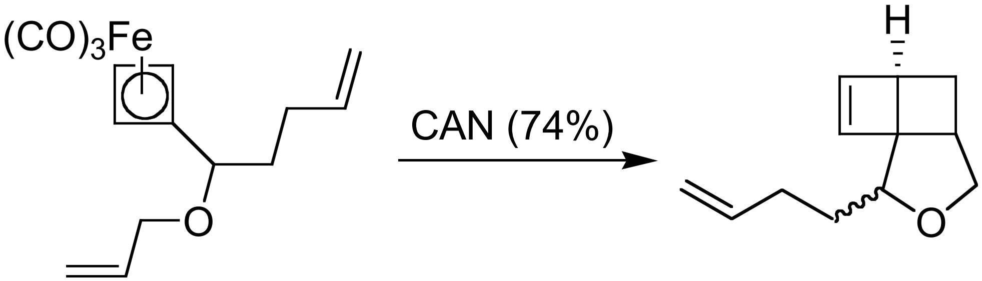
Acid-Mediated Rearrangement



Org. Lett, **2005**, *7*, 5785

Trends

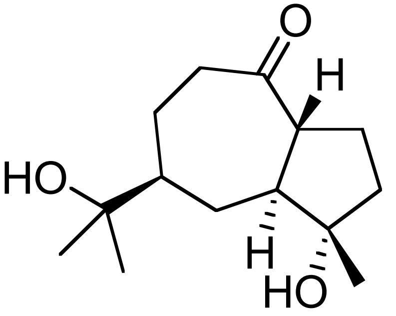
- The activation energy for intramolecular cyclization must be less than 13.5 kcal/mol or dimerization becomes the major competitive pathway (*JACS*, **2003**, *125*, 16310)
- 3 atom heteroatom containing tethers with electronically unactivated olefins yield the best results



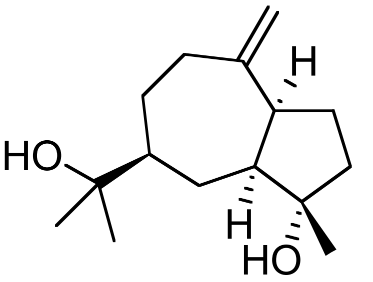
- When there is the possibility of either a 2+2 or 4+2 cyclization, the 2+2 product can be thermally converted to the 4+2 product

Pleocarpenene and Pleocarpenone

- Guaiane natural products isolated in 1976 from *Pleocarphus revolutus* (*Cryst. Struct. Commun.* **1976**, *5*, 601)
- *Pleocarphus revolutus* is a small shrub found in Chile. Powdered extracts showed anti-cancer activity in the Cancer Chemotherapy National Service Center Screen (*Phytochemistry*, **1977**, *16*, 379)
- Also isolated from *Chenopodium botrys, C.* A medicinal plant found in Southern Europe (*Tetrahedron*, **1980**, *36*, 371)

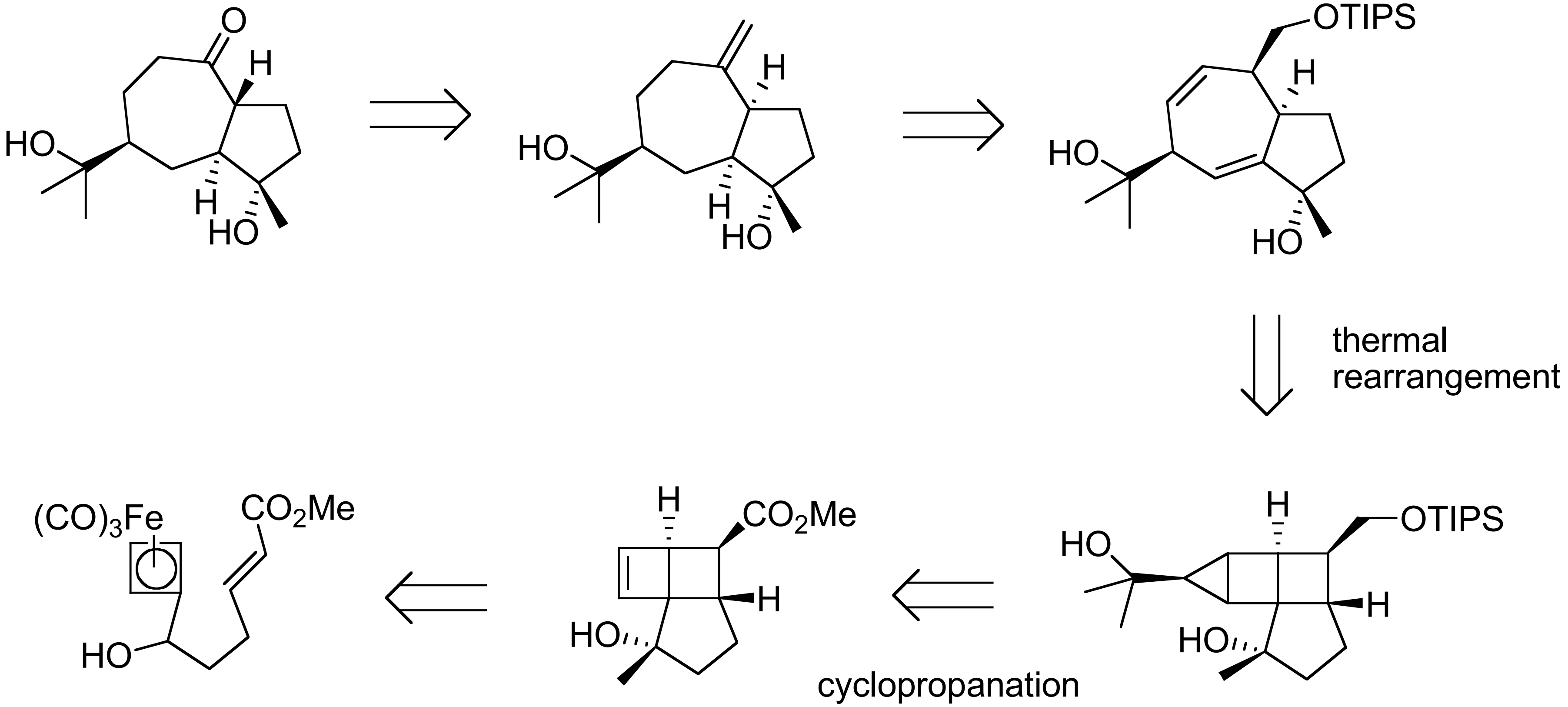


Pleocarpenone



Pleocarpenene

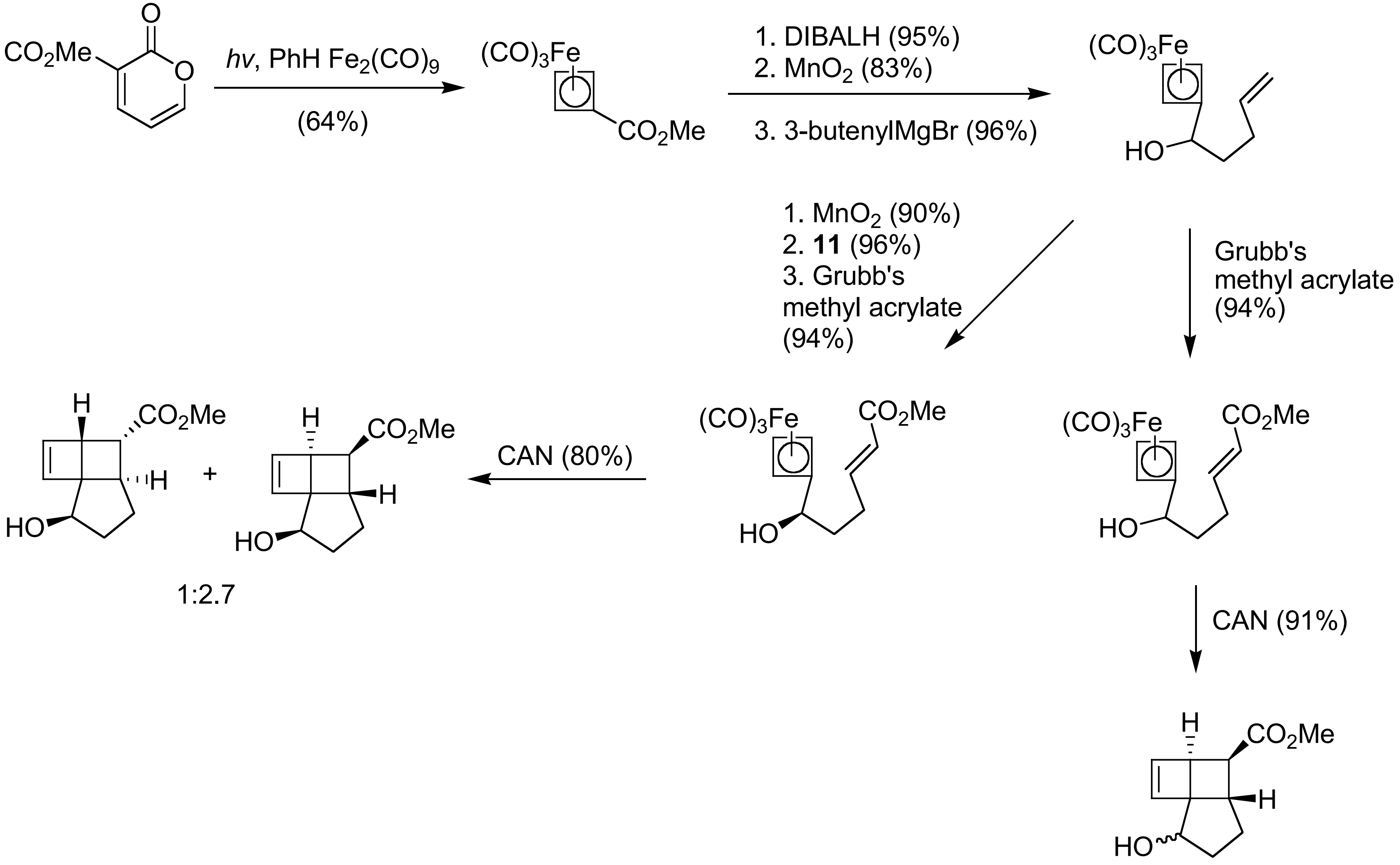
Retrosynthesis



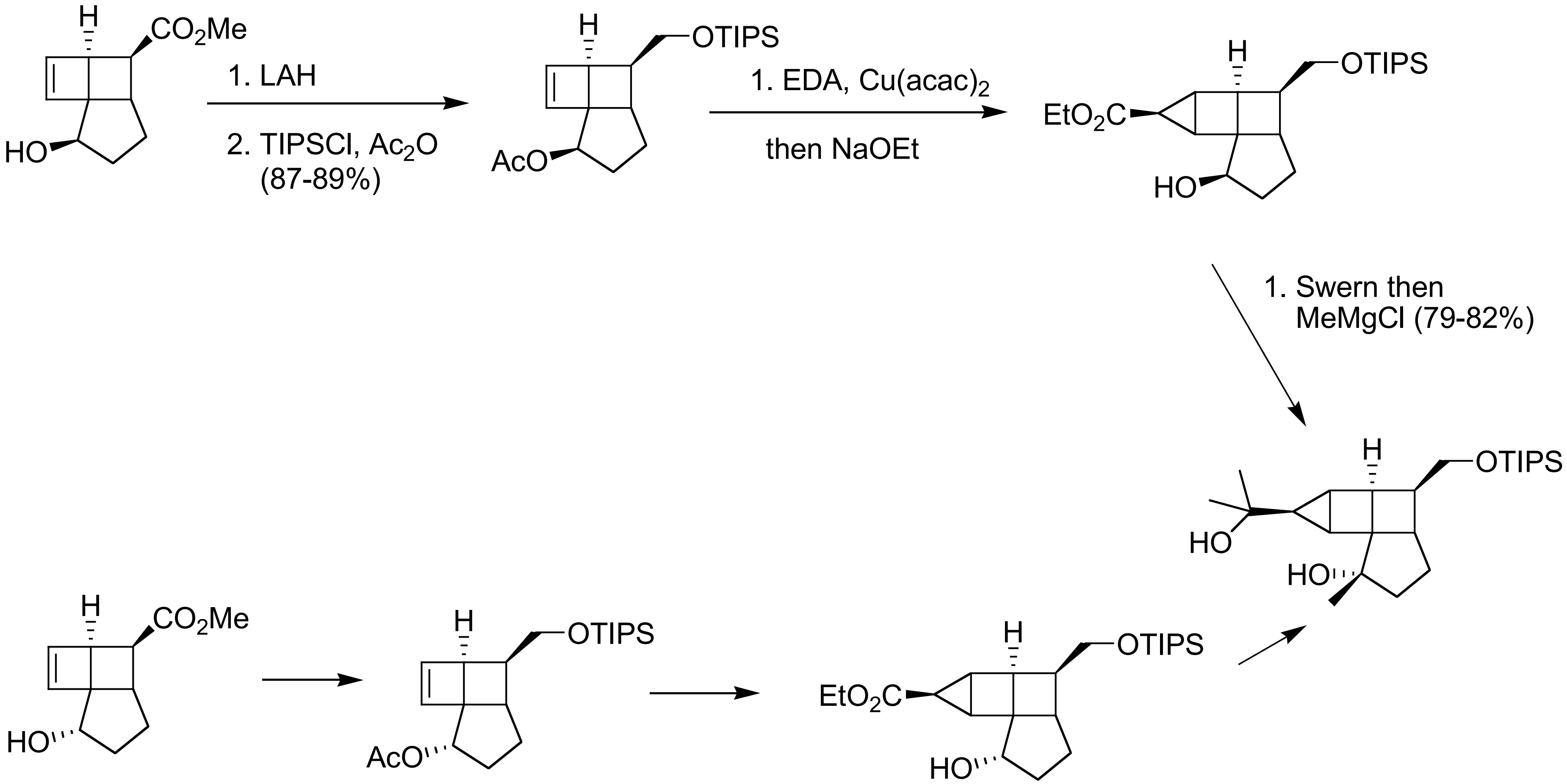
thermal rearrangement

cyclopropanation

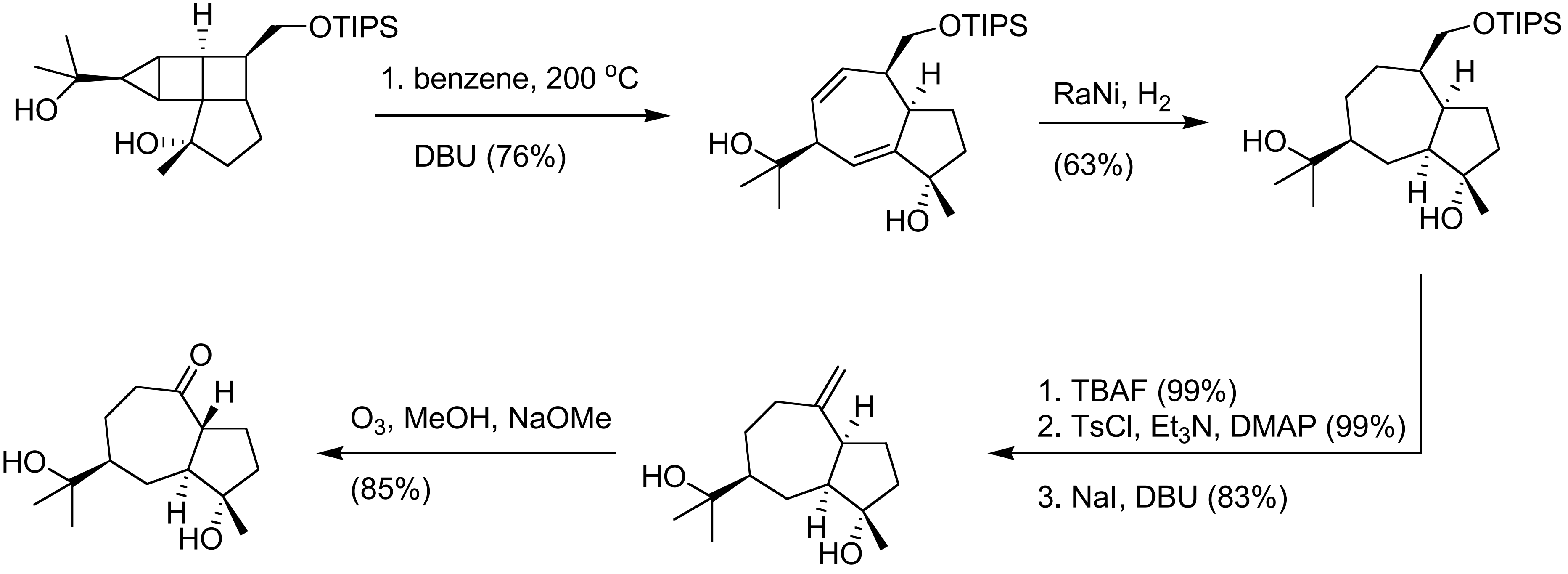
Cyclobutene Synthesis



Cyclopropanation



End Game



1. benzene, 200 ^{o}C

DBU (76%)

RaNi, H_2

(63%)

1. TBAF (99%)
2. TsCl, Et_3N, DMAP (99%)
3. NaI, DBU (83%)

O_3, MeOH, NaOMe

(85%)

Conclusions

- Iron tricarbonyl is a robust protecting group that modifies the reactivity of cylobutadiene so that it can be synthetically useful
- Iron tricarbonylcyclobutadiene is stable to acid, base, mild oxidative and reductive conditions. Treatment with CAN unmasks a highly reactive species that can provide access to structurally interesting intermediates.
- The total syntheses of pleocarpenene and pleocarpenone were accomplished in 16 steps and 8.1% overall yield, and 17 steps and 6.9% overall yield respectively