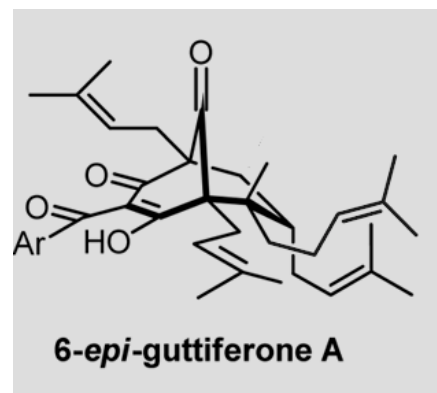
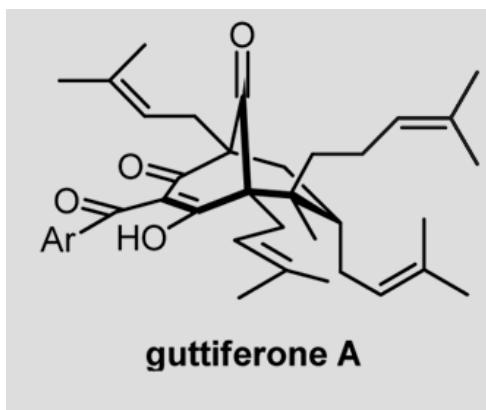


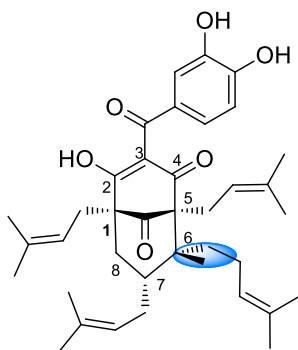
The Total Syntheses of Guttiferone A and 6-*epi*-Guttiferone A

Fiene Horeischi, Nicoles Biber, and Bernd Plietker*

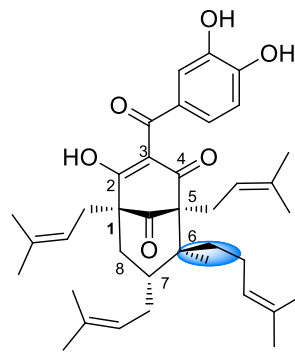
J. Am. Chem. Soc. ASAP



Introduction



6-*epi*-guttiferone A



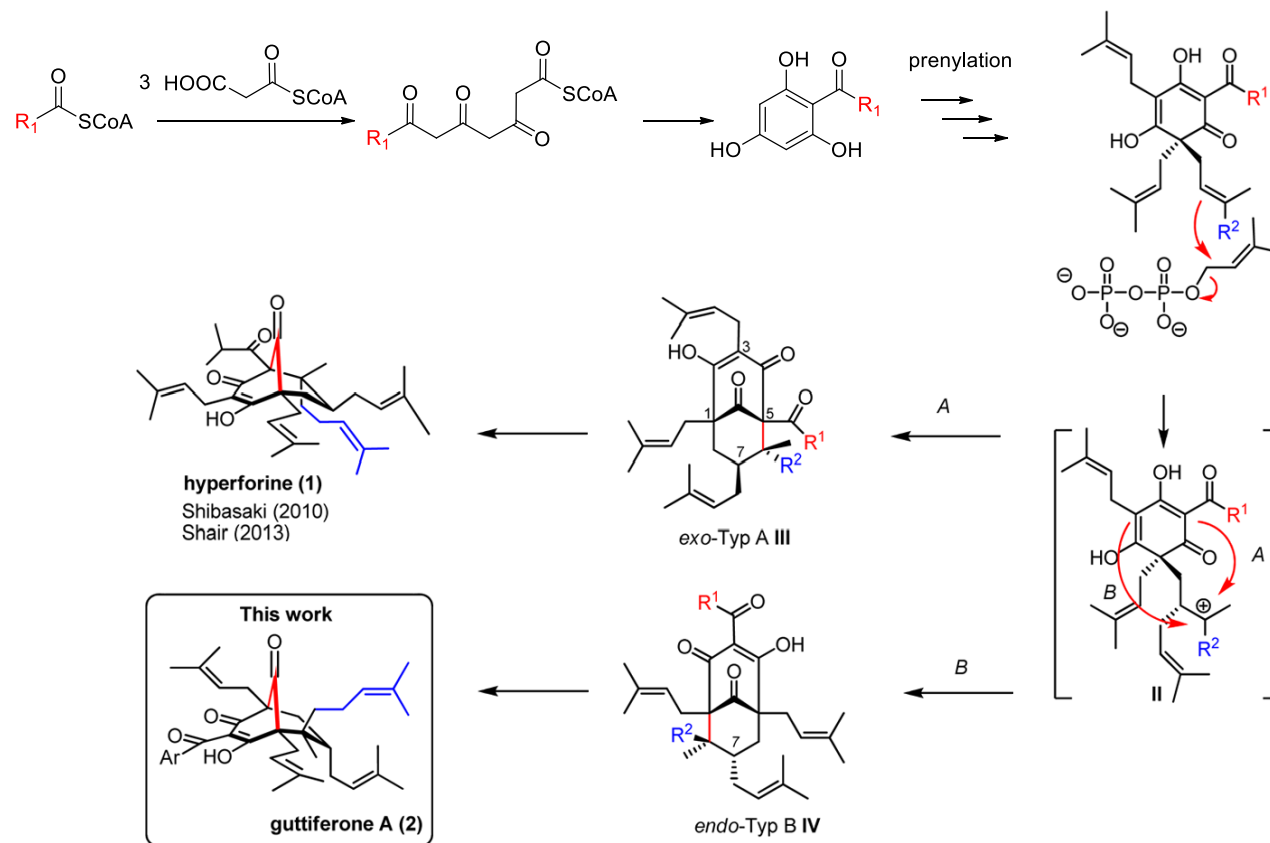
guttiferone A



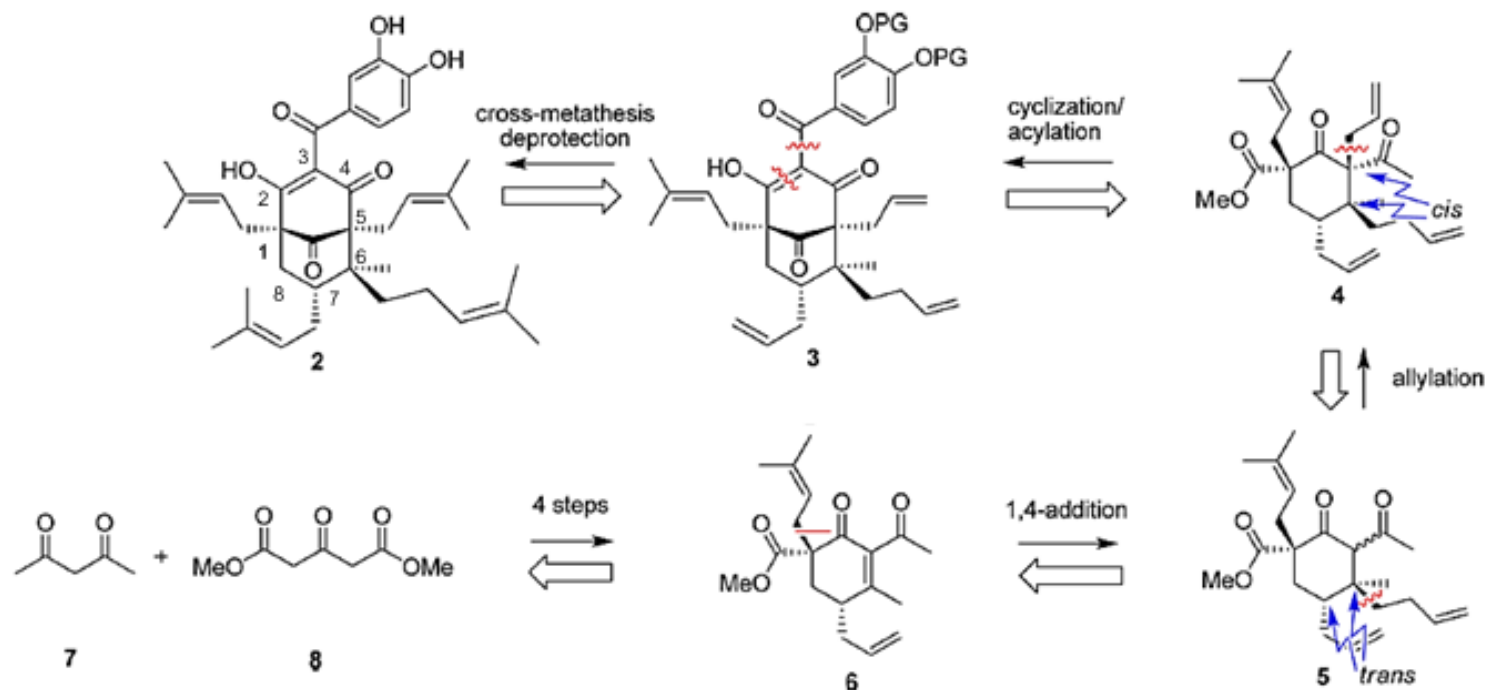
- Isolated from *Guttiferae* (*Clusiaceae*) and *Garcinia*
- Belong to the polyprenylated polycyclic acylphloroglucinols family (PPAP)
Subclassification :
 - Type B: PPAPs has a C3 acyl group
 - Endo: C7 trans to the acyl group
- Structural features : bicyclo[3.3.1]nonatrione core decorated with prenyl side chains
Usually PPAP with C1, C5 and C7 stereocenters, here additional C6
- Bioactivities: human colon and ovarian cancer cells, anti HIV, protection against Iron-induced neuronal cell damage and antimicrobial activities

Biosynthesis of guttiferone A

Biosynthetic route from monocyclic polyprenylated acylphloroglucinols (MPAPs)



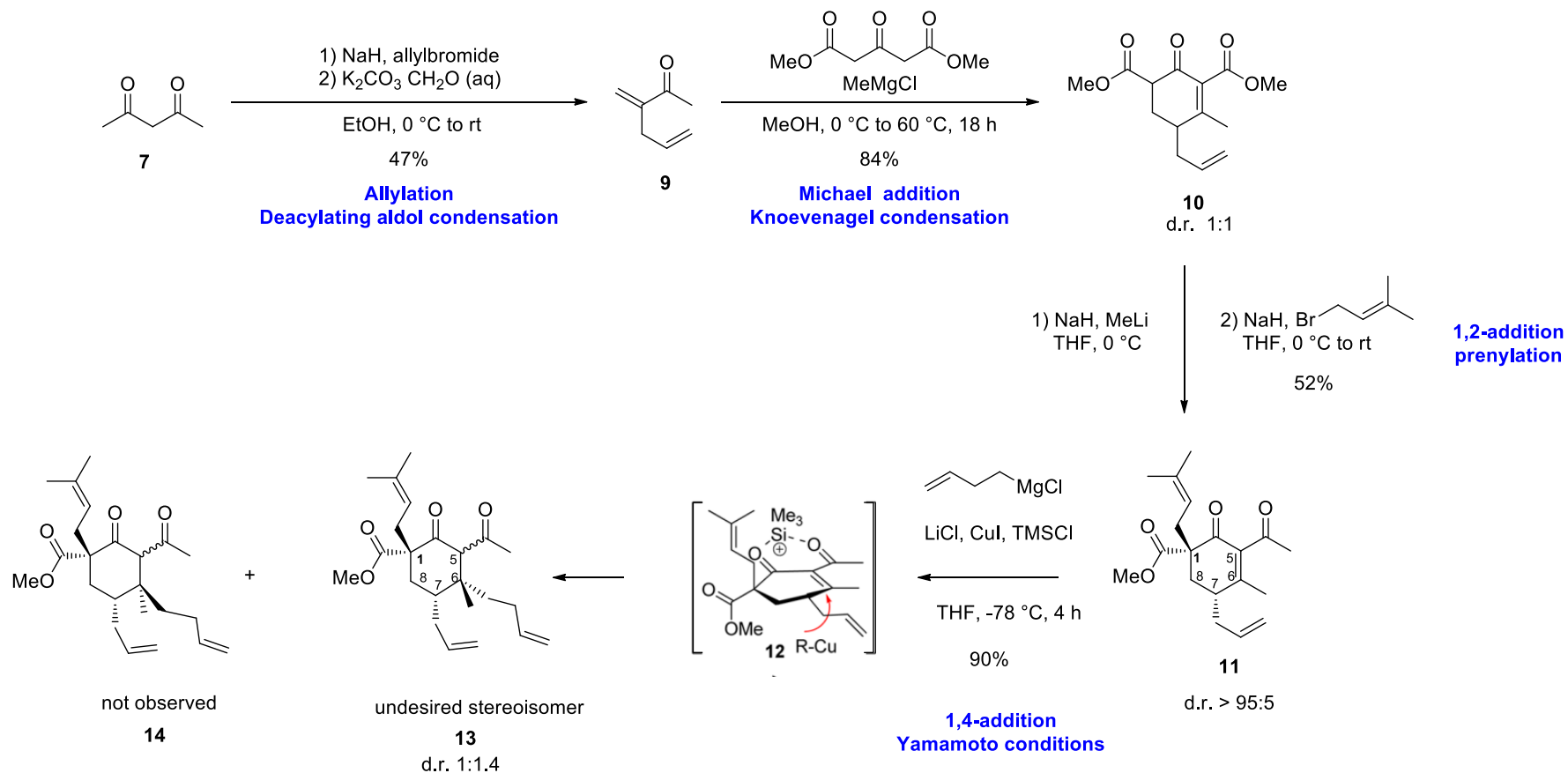
Retrosynthesis of guttiferone A



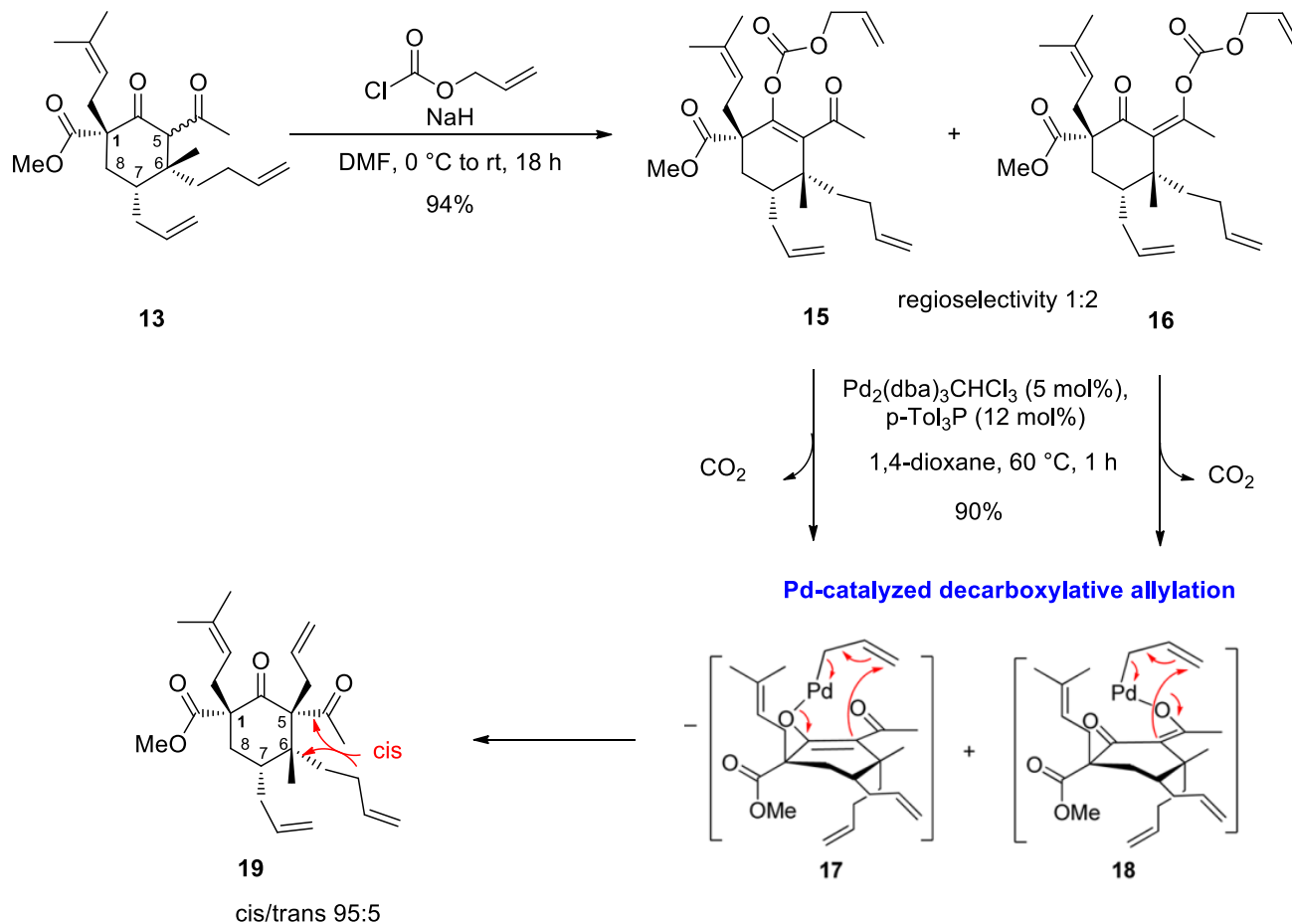
Challenges :

- Creation of an additional stereocenter at C6
- Separation of framework construction and functionalization
- Use substrate induction to control all stereocenters

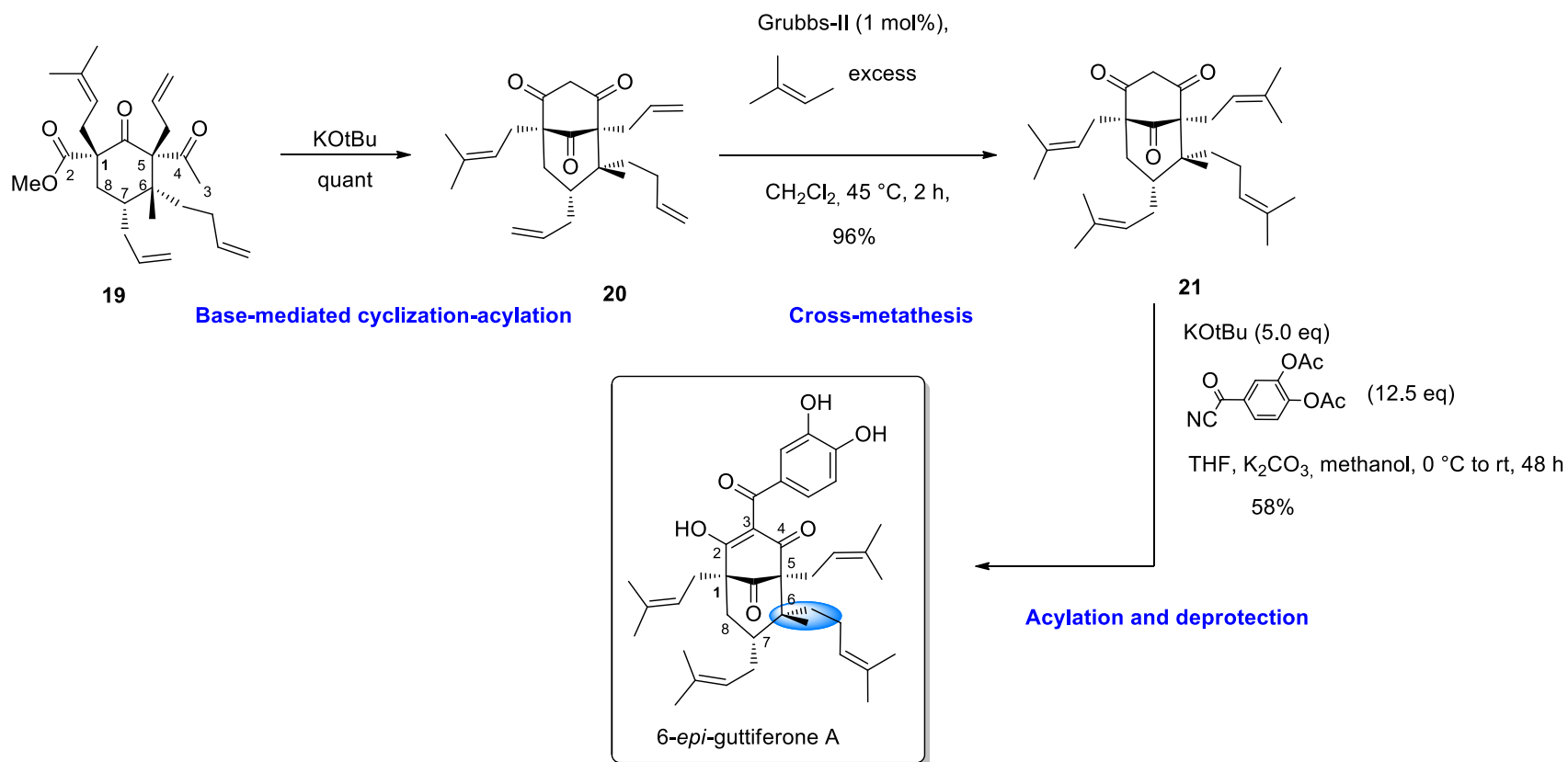
Synthesis of 6-*epi*-guttiferone A



Synthesis of 6-*epi*-guttiferone A

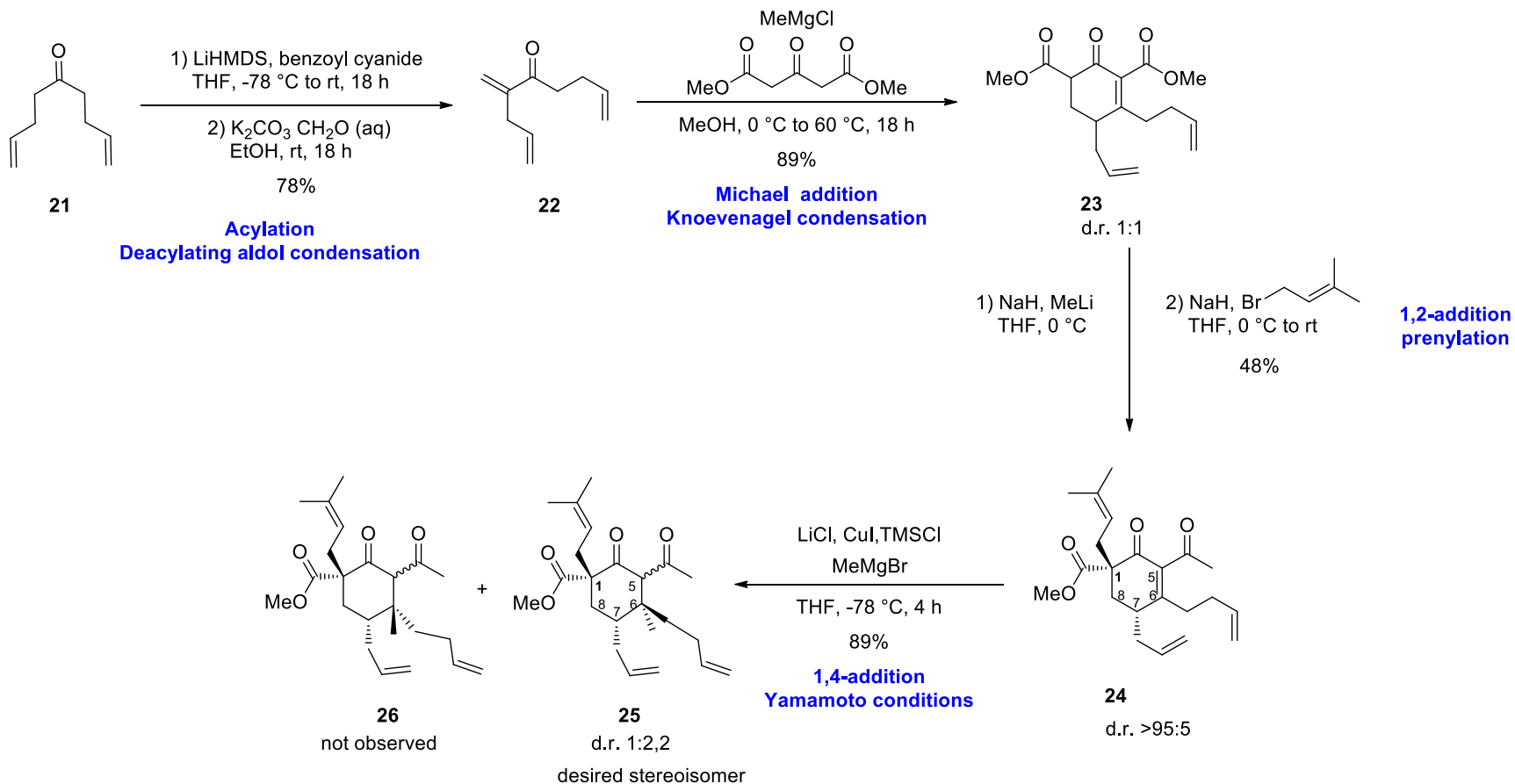


Synthesis of 6-*epi*-guttiferone A

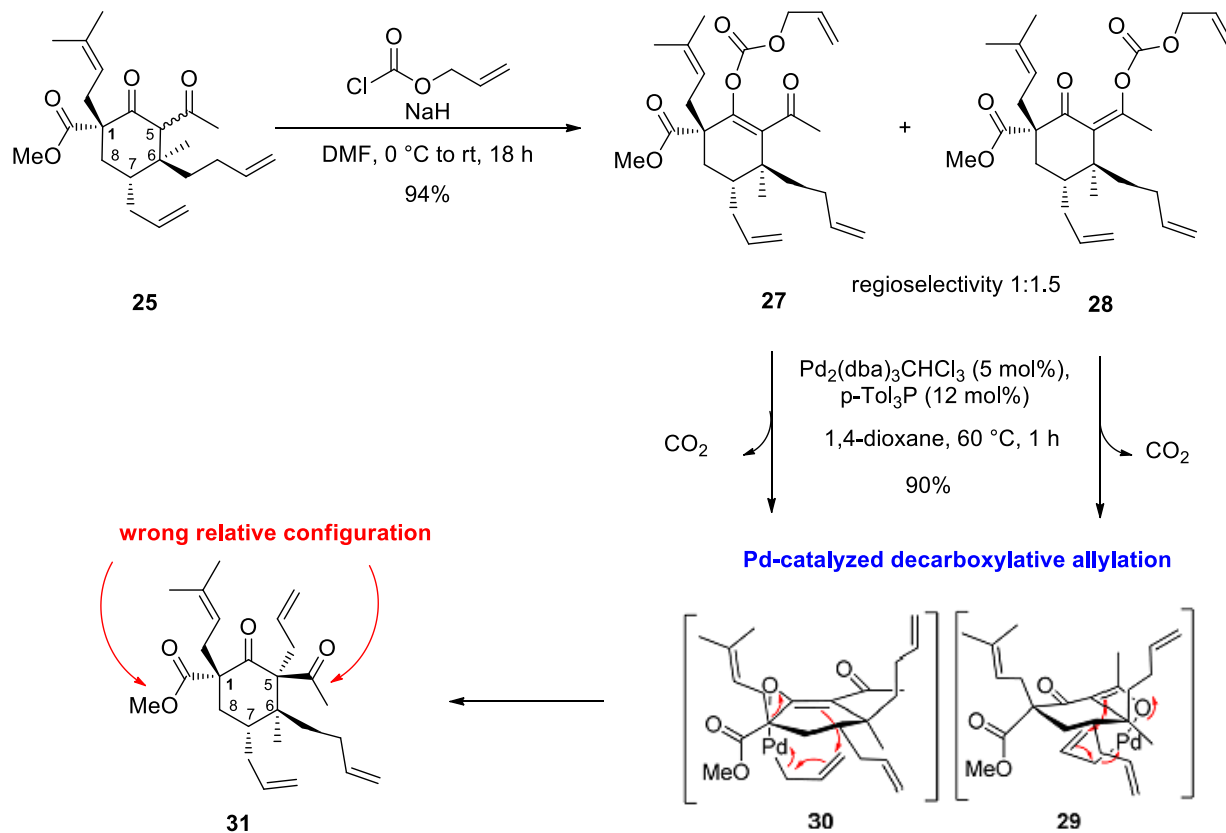


Wrong stereochemistry at C6 during organocopper 1,4-addition ➔ New strategy!

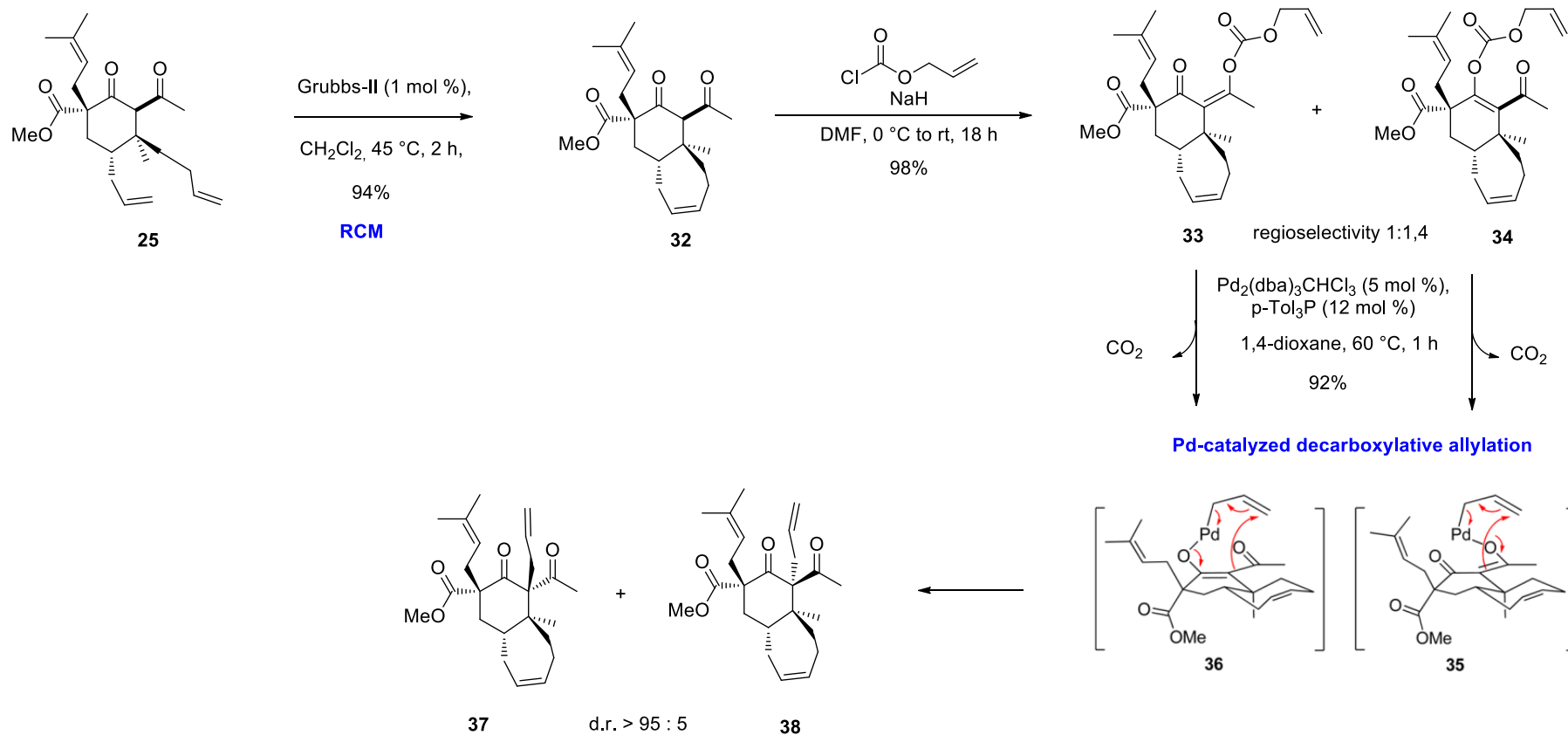
Synthesis of guttiferone A : «frustrating» approach



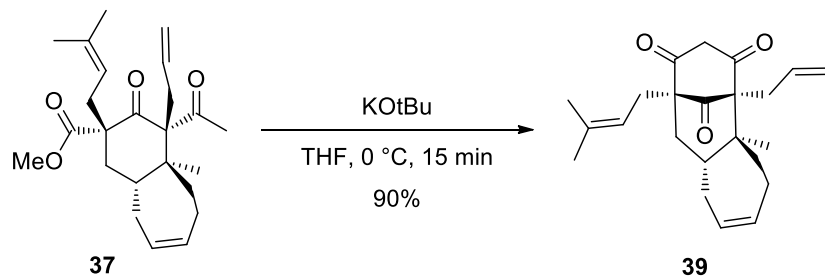
Synthesis of guttiferone A : «frustrating» approach



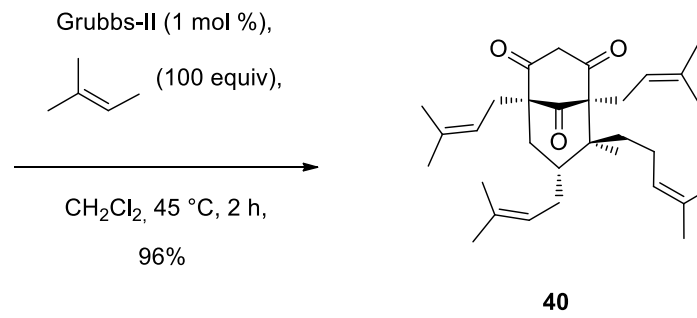
Synthesis of guttiferone A : «successful» approach



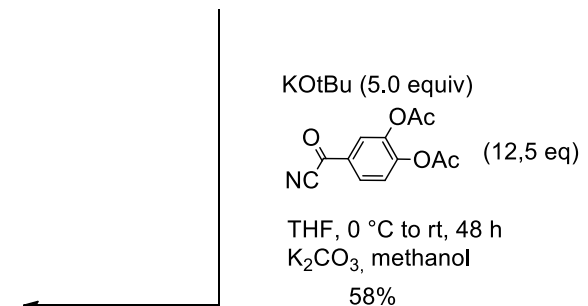
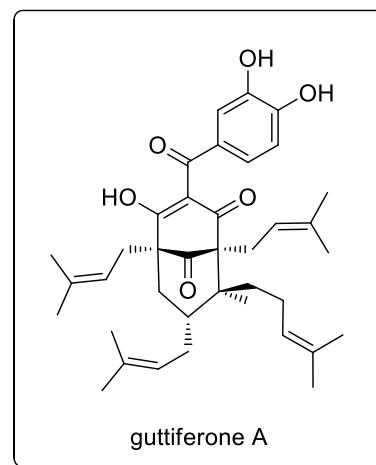
Synthesis of guttiferone A : «successful» approach



Base-mediated cyclization-acylation



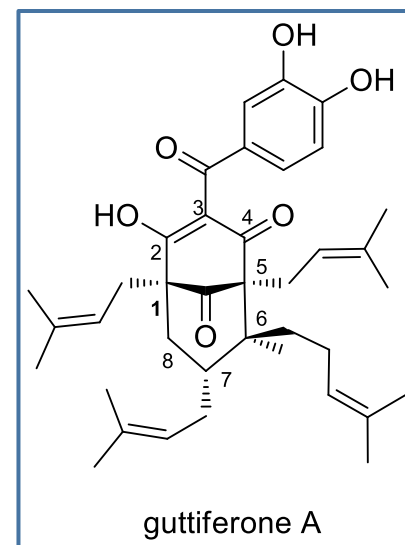
Cross-metathesis



Acylation and deprotection

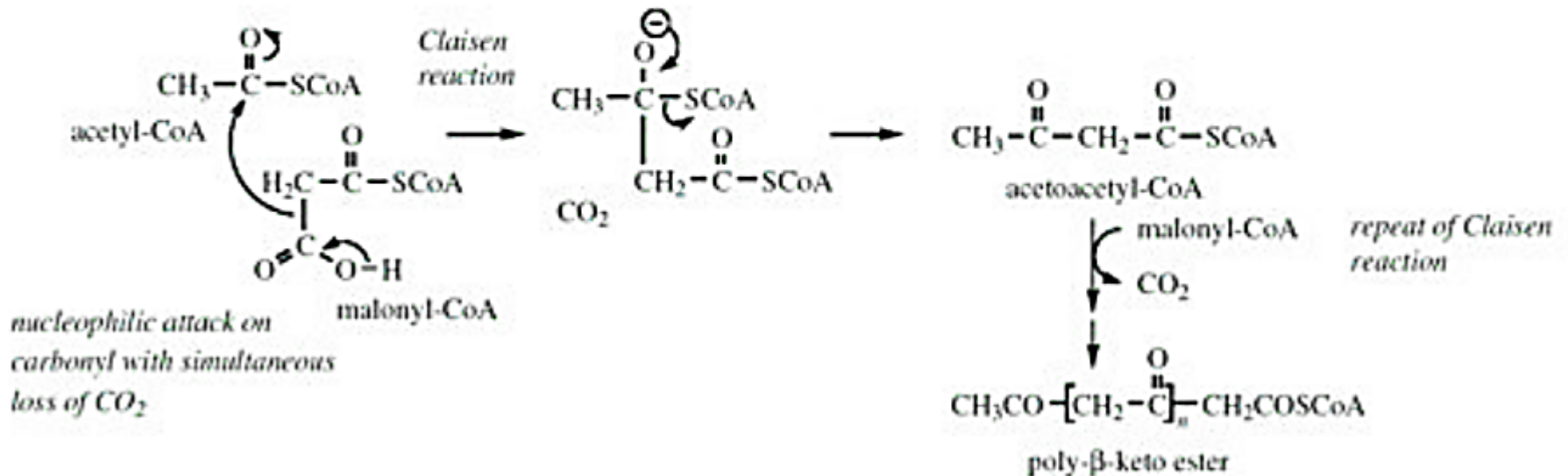
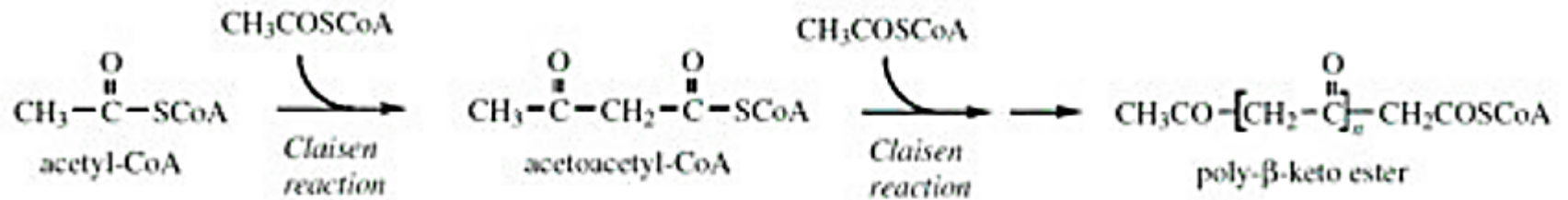
Conclusion

- Synthesis of 6-*epi*-guttiferone A : 10 steps, overall yield 8,7%
- Synthesis of guttiferone A : 13 steps, overall yield 13,4%
- Full control of four adjacent stereocenters (C1, C5, C6, C7)
- Base for further total syntheses of higher prenylated PPAPs
- Extension to synthesis of *exo*-type PPAP (*i.e.* inversion during C1 allylation)

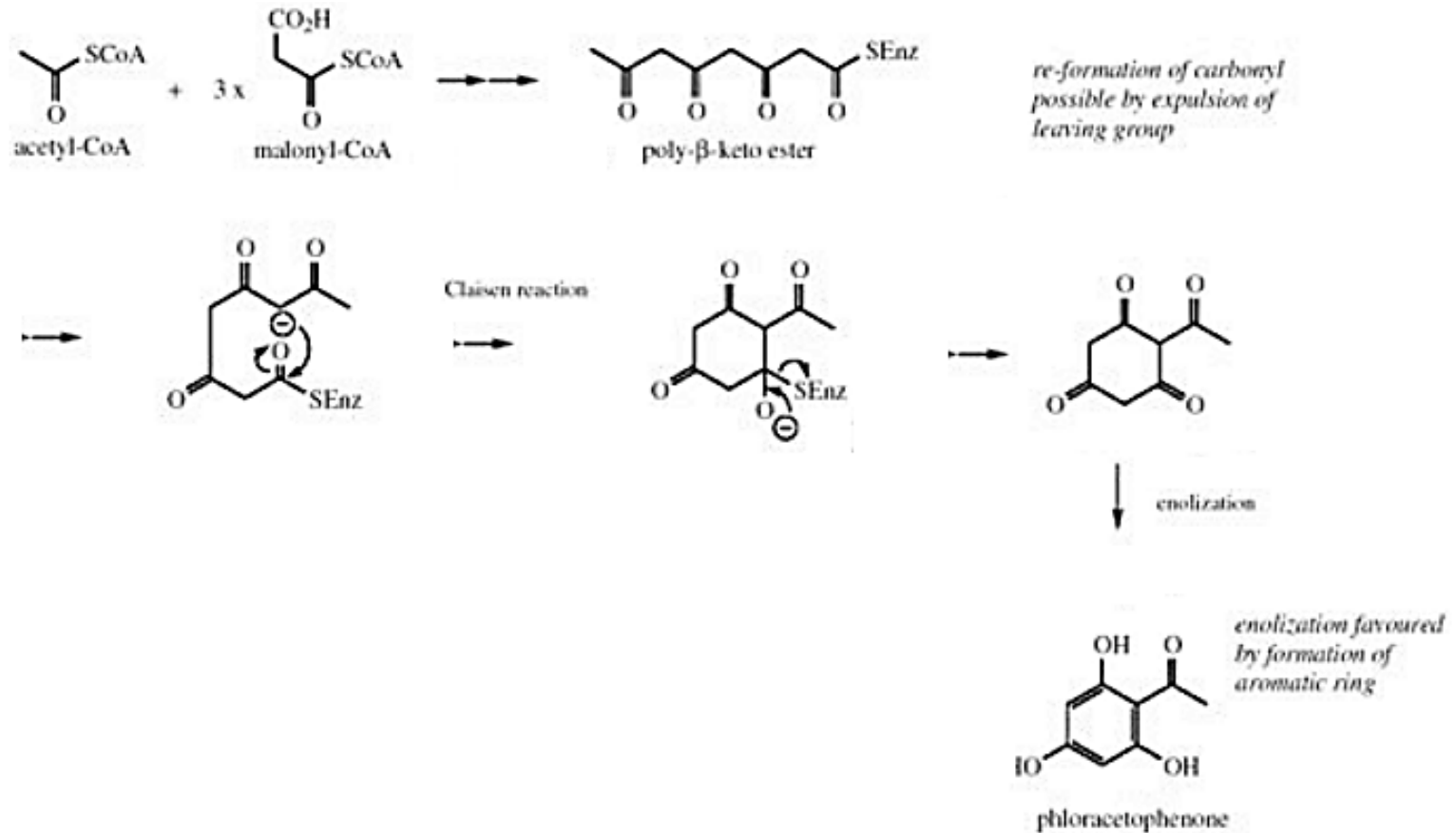


Thank you for your attention!

Biosynthesis of guttiferone A

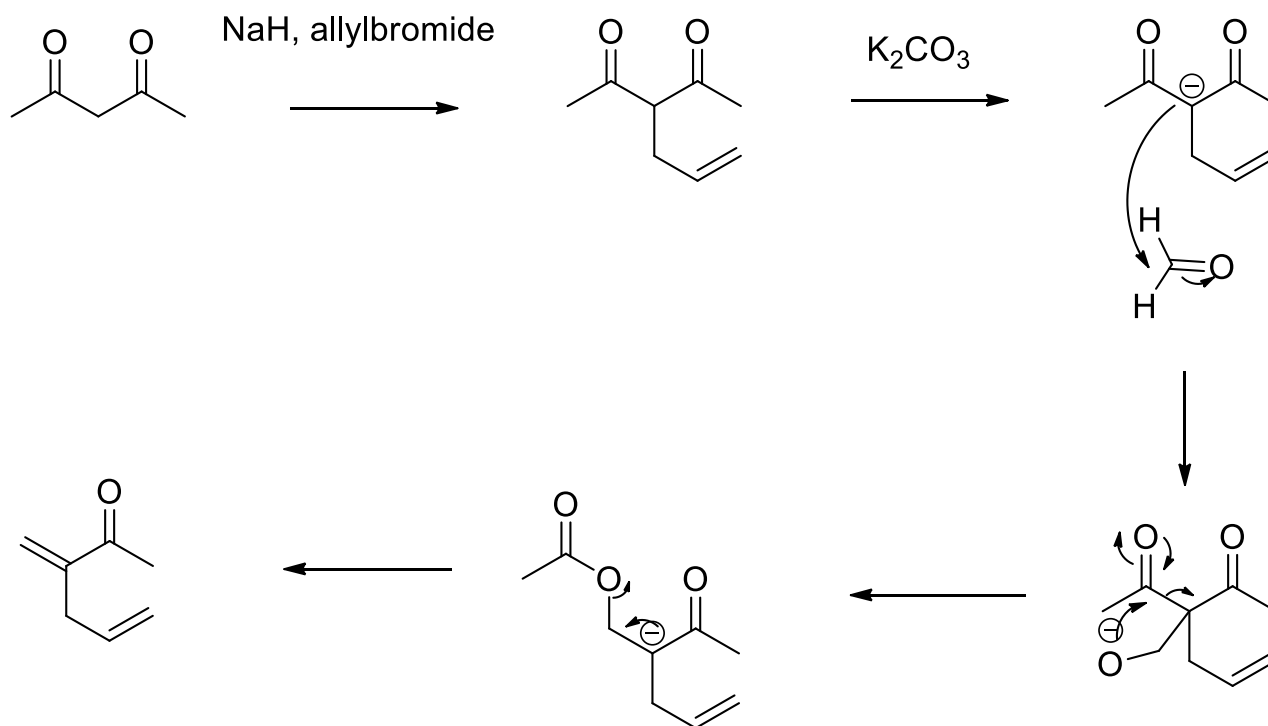


Biosynthesis of guttiferone A



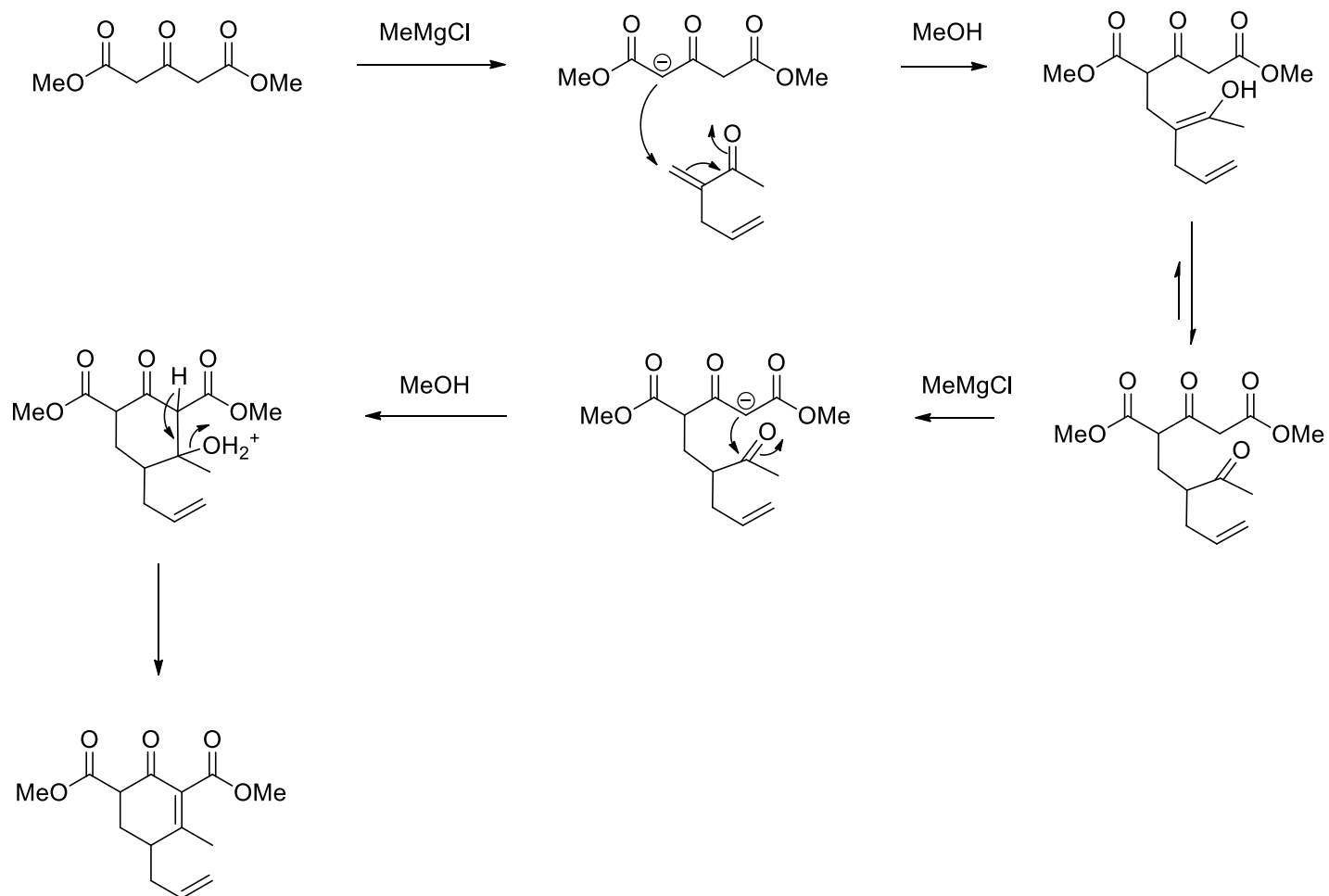
Synthesis of 6-*epi*-guttiferone A

allylation and deacylating aldol condensation



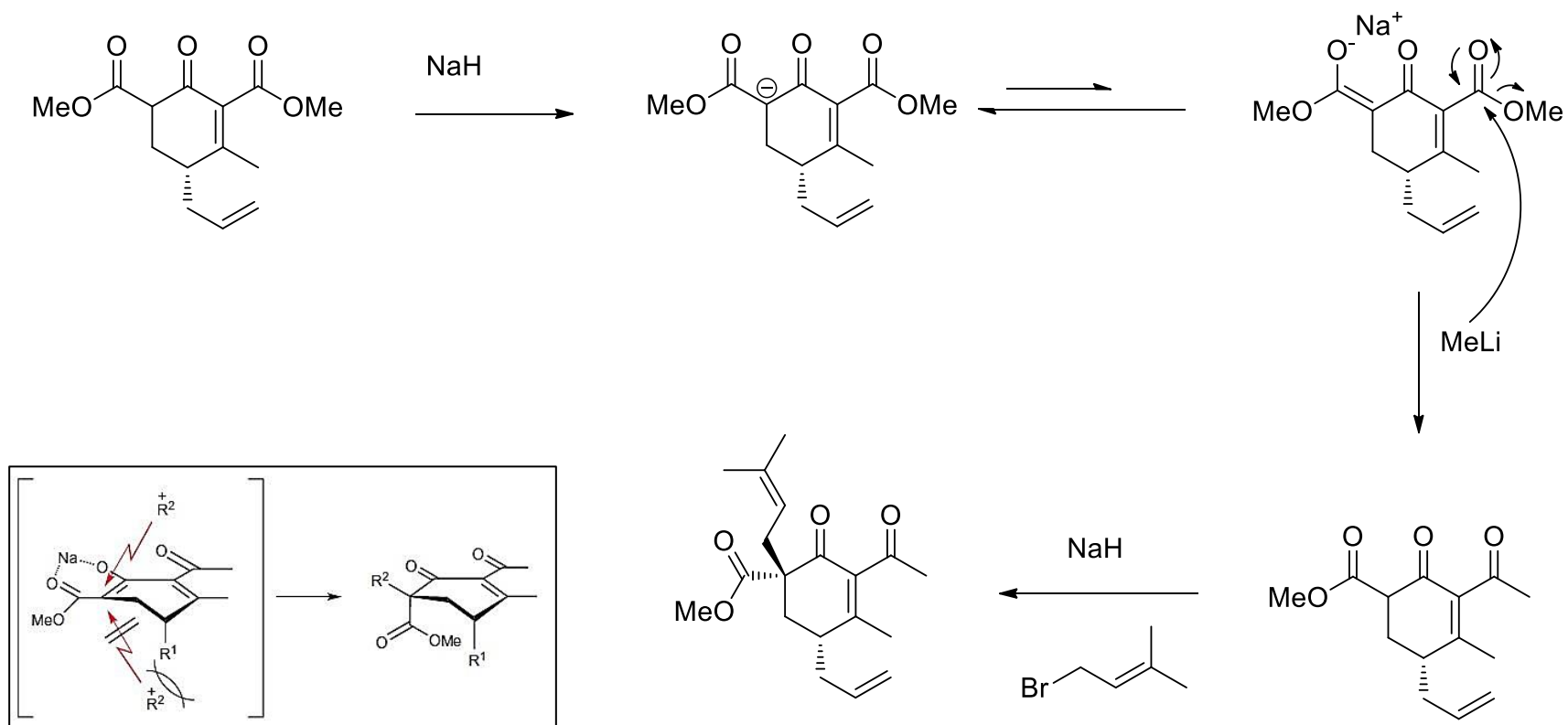
Synthesis of 6-*epi*-guttiferone A

Tandem Michael addition-Knoevenagel condensation



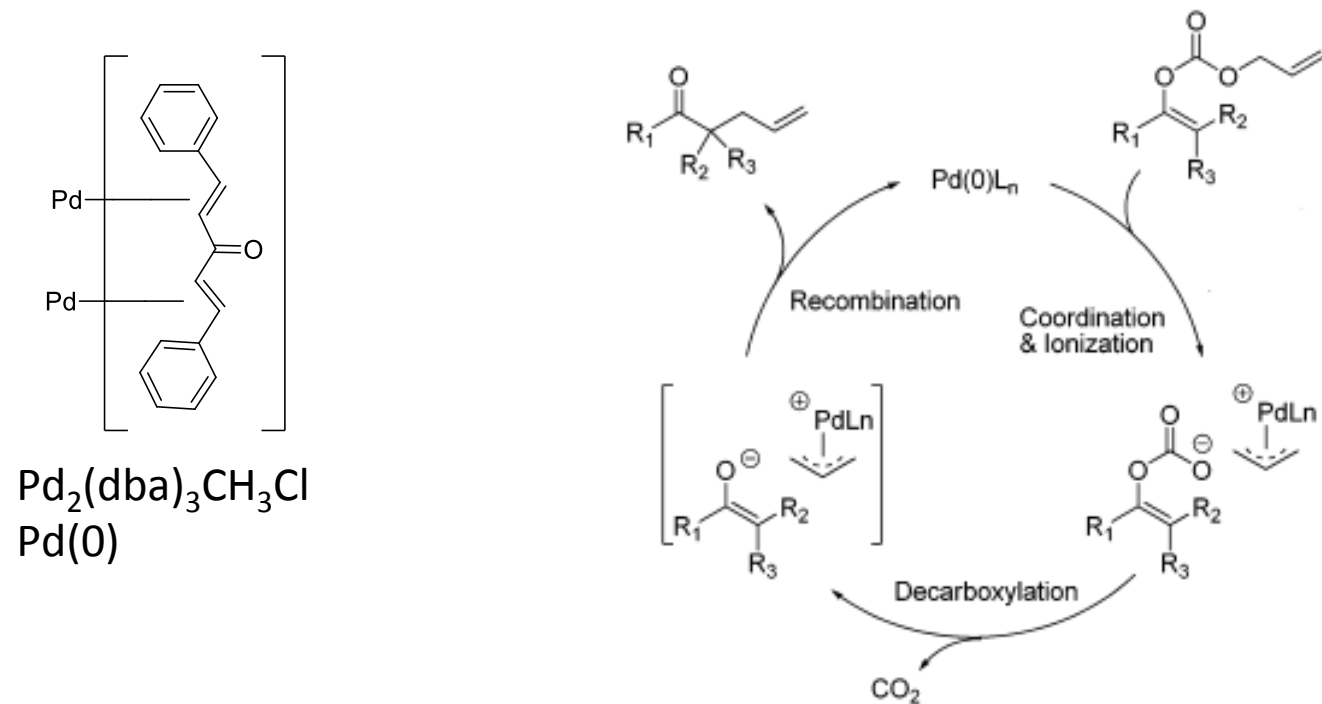
Synthesis of 6-*epi*-guttiferone A

1,2 addition and prenylation

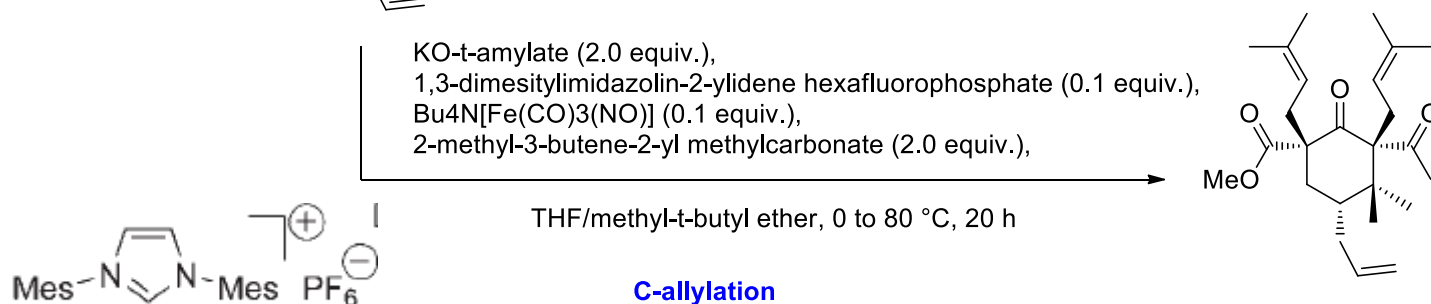
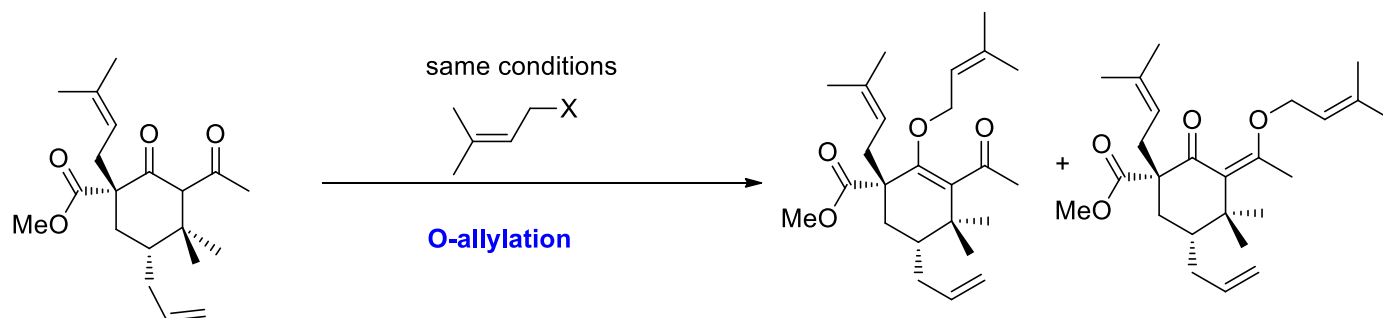
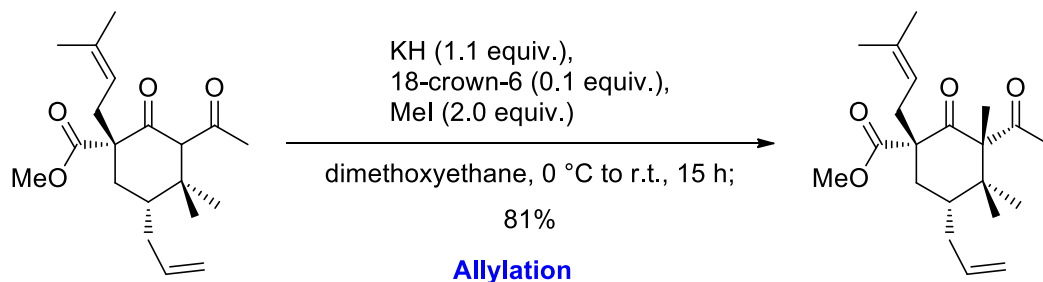


Synthesis of 6-*epi*-guttiferone A

Pd-catalyzed decarboxylative allylation



Synthesis of 6-*epi*-guttiferone A

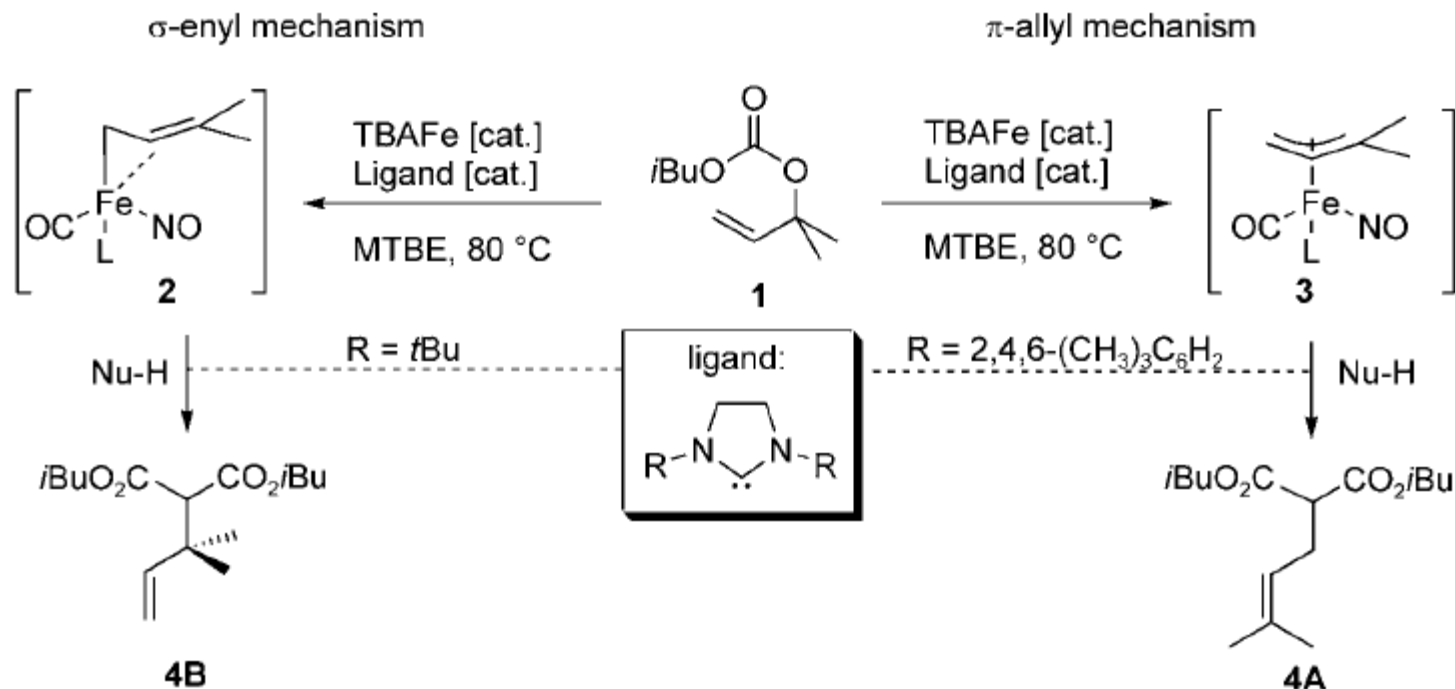


(a) Plietker, B. *Angew. Chem., Int. Ed.* **2006**, *45*, 1469–1473

(b) Plietker, B.; Dieskau, A.; Möws, K.; Jatsch, A.; *Angew. Chem., Int. Ed.* **2008**, *47*, 198–201.

(c) Holzwarth, M.; Dieskau, A.; Tabassam, M.; Plietker, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 7251–7255.

Synthesis of 6-*epi*-guttiferone A

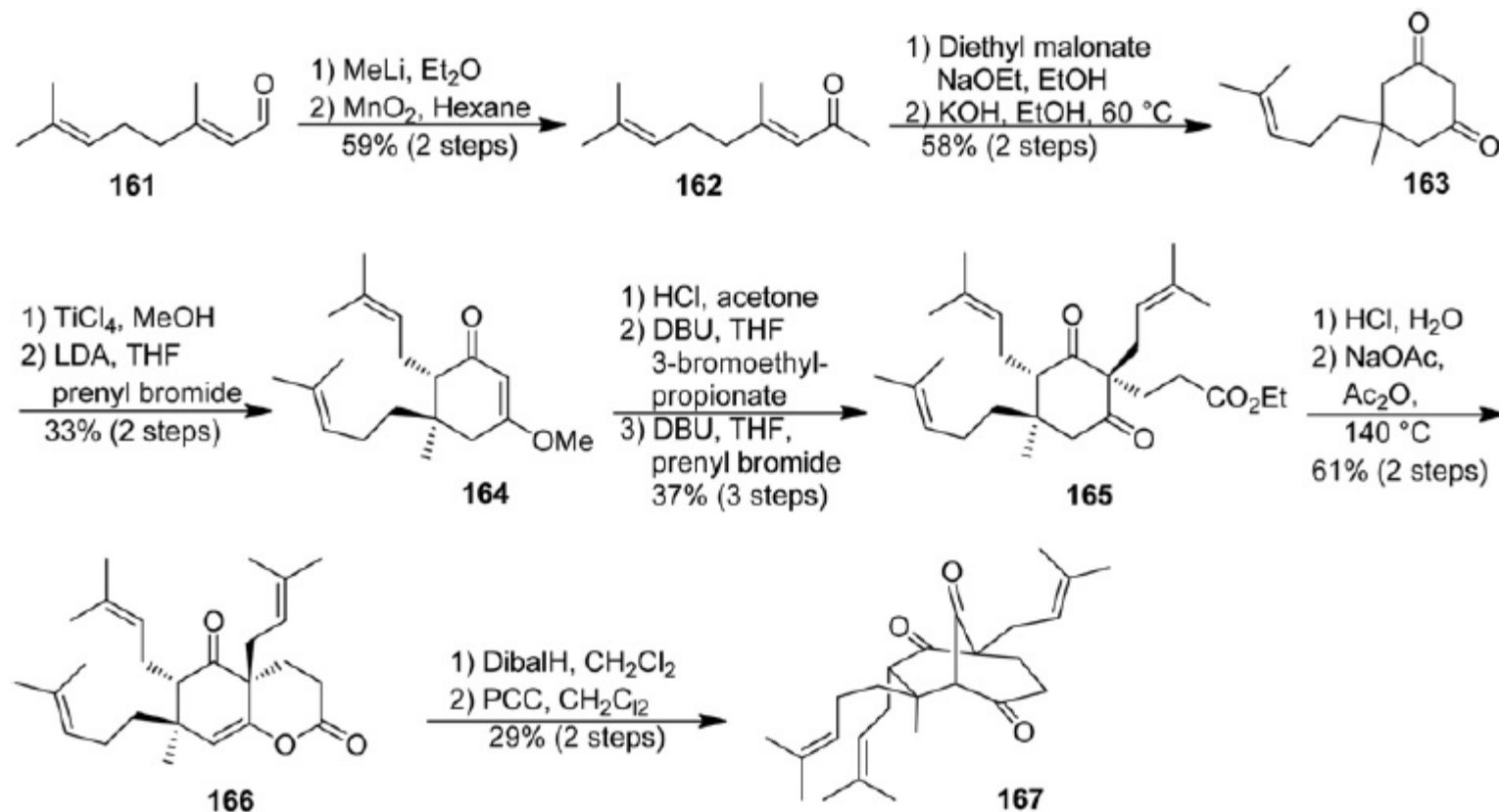


(a) Plietker, B. *Angew. Chem., Int. Ed.* **2006**, *45*, 1469–1473

(b) Plietker, B.; Dieskau, A.; Möws, K.; Jatsch, A.; *Angew. Chem., Int. Ed.* **2008**, *47*, 198–201.

(c) Holzwarth, M.; Dieskau, A.; Tabassam, M.; Plietker, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 7251–7255.

G. Mehta's 2008 synthetic approach toward guttiferone A



Njardarson, J. T. *Tetrahedron* **2011**, *67*, 7631–7666