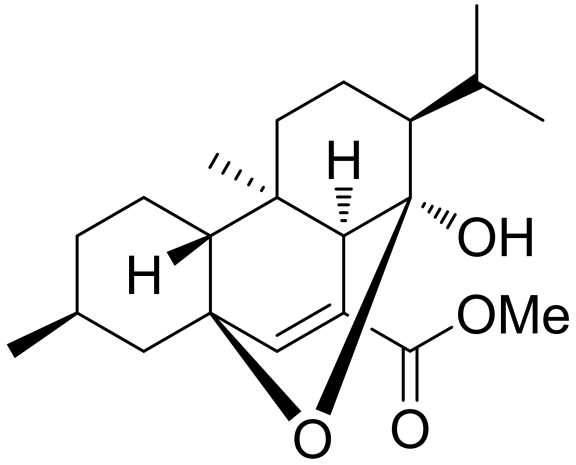
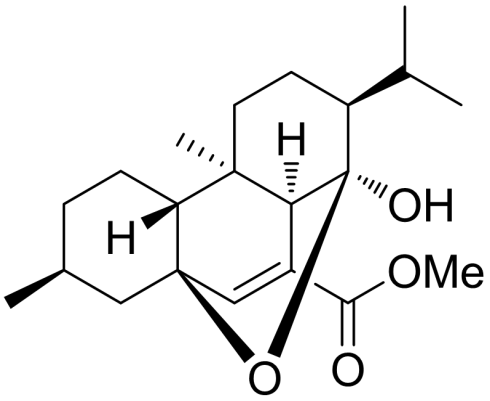
Short, Enantioselective Total Synthesis of Chatancin

Zhao, Y.-M.; Maimone, T. J. *Angew. Chem. Int. Ed.* **2015,** *54,* 1223–1226.

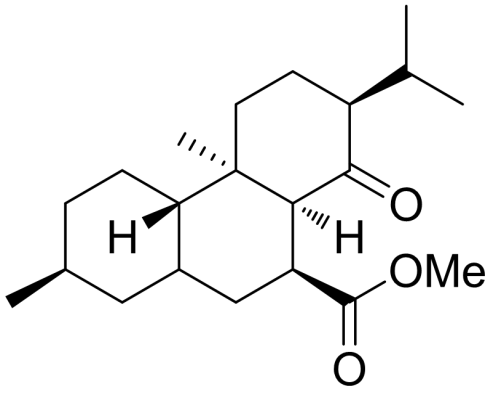


Zachary X. Giustra
Liu Group
January 1, 2016

Previous Isolation and Biological Activity



(+)-chatancin (**1**)
active against PAF

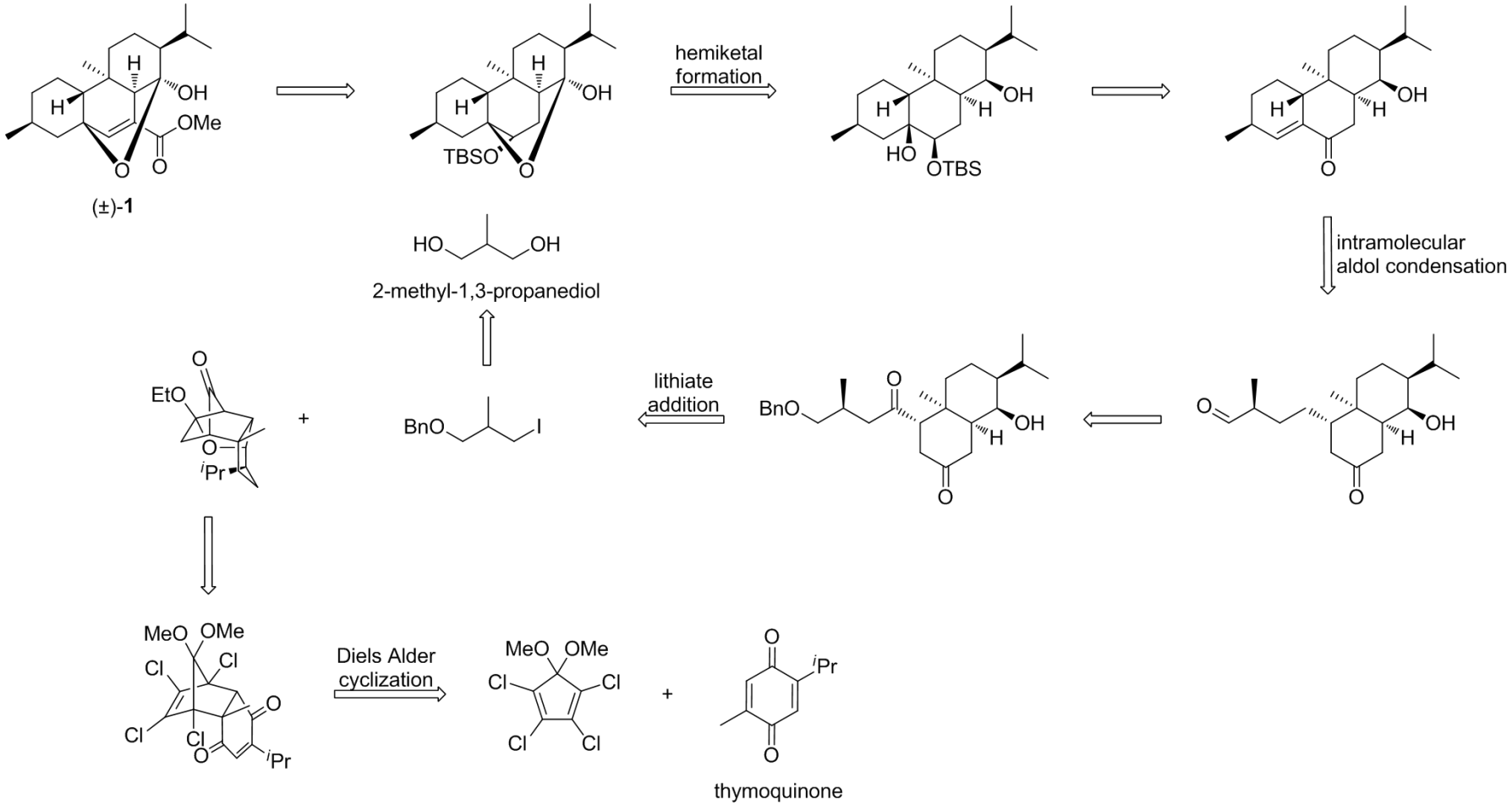


dehydro-**1**
no activity against PAF

- Originally isolated from an Okinawan soft coral*, Sarcophyton* sp.
- Found to inhibit platelet aggregation induced by platelet activation factor (IC_{50} = 2.2 μM).
- Demonstrated no effect on aggregation induced by adenosine diphosphate, arachidonic acid, or collagen (IC_{50} > 300 μM).
- Activity ascribed to the hemiketal moiety (no activity observed for *dehydro* form)

Sugano, M.; Shindo, T.; Sato, A.; Iijima, Y.; Oshima, T.; Kuwano, H.; Hata, T. *J. Org. Chem.* **1990,** *55,* 5803–5805.

Previous Syntheses

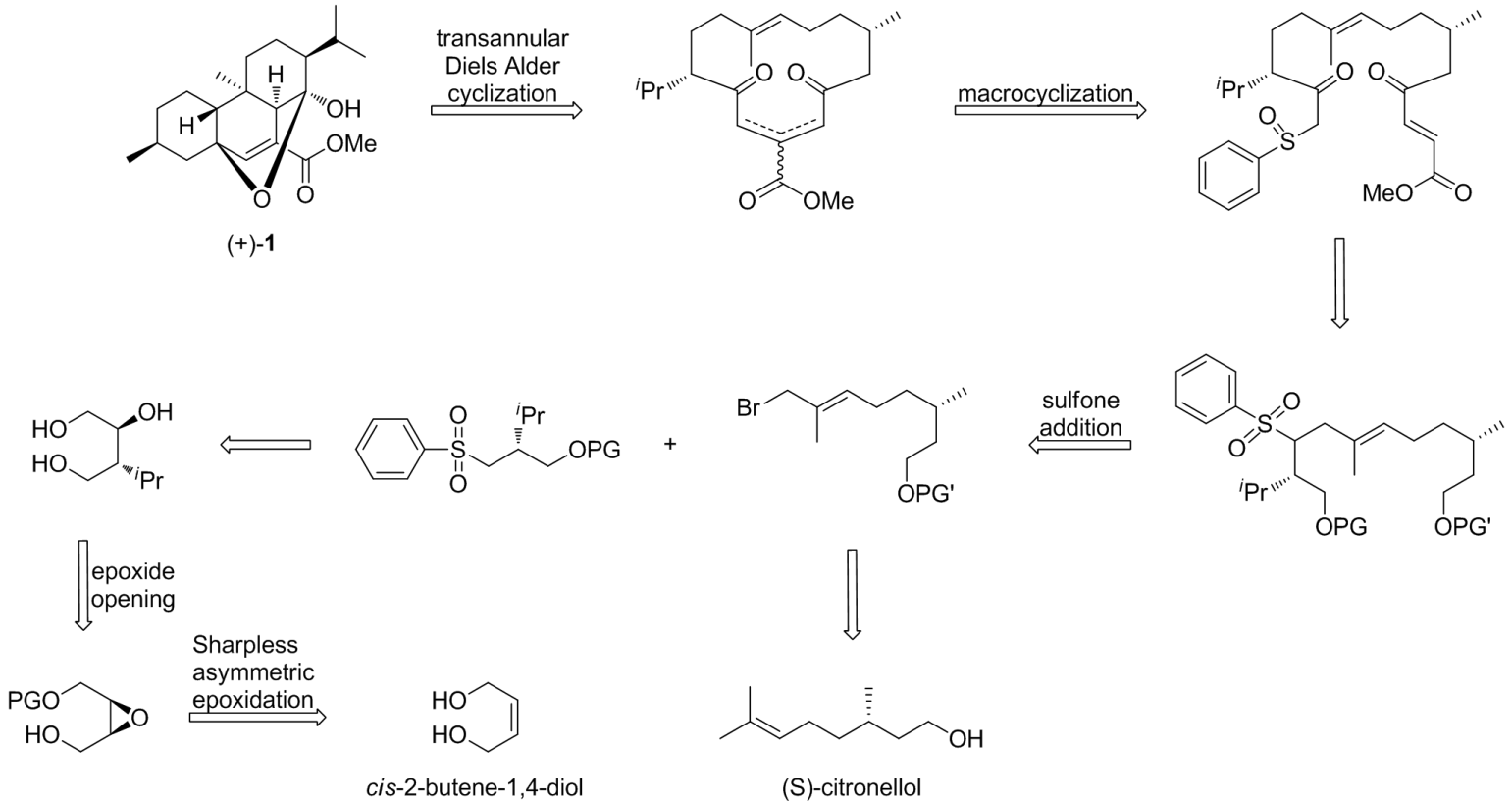


- Racemic synthesis reported by Gössinger in 1998.
- 33 steps longest linear sequence from thymoquinone.

Aichberger, W. D.; Aigner, J.; Gössinger, E.; Gruber, K.; Menz, G. *Monatsh. Chem.* **1994,** *125,* 991–1010. (German language)

Aigner, J.; Gössinger, E.; Kählig, H.; Menz, G.; Pflugseder, K. *Angew. Chem. Int. Ed.* **1998,** *37,* 2226–2228.

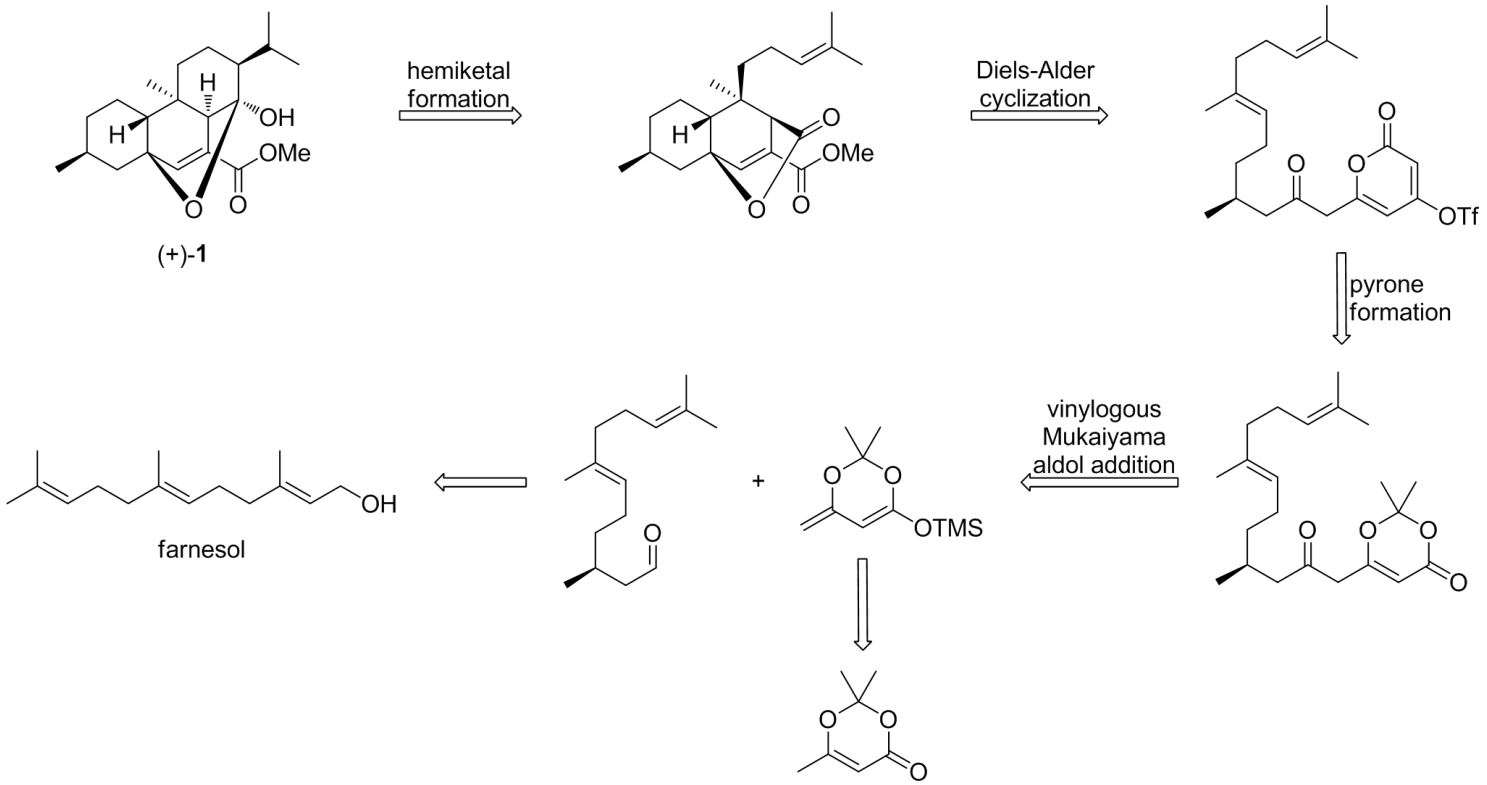
Previous Syntheses



- Enantioselective synthesis achieved by Deslongchamps in 2003.
- 23 steps longest linear sequence from *cis*-2-butene-1,4-diol.

Soucy, P.; L'Heureux, A.; Toró, A.; Deslongchamps, P. *J. Org. Chem.* **2003,** *68,* 9983–9987.
Astles, P. C.; Thomas, E. J. *J. Chem. Soc., Perkin Trans. 1* **1997,** 845–856.

(+)-**1** Retrosynthesis



- Exceedingly acid-sensitive hemiketal moiety formed in the penultimate step.
- Intramolecular Diels-Alder cyclization with pyrone diene to set four of the final product's seven stereocenters.
- Vinylogous Mukaiyama aldol addition to combine two fragments containing all necessary carbon atoms.

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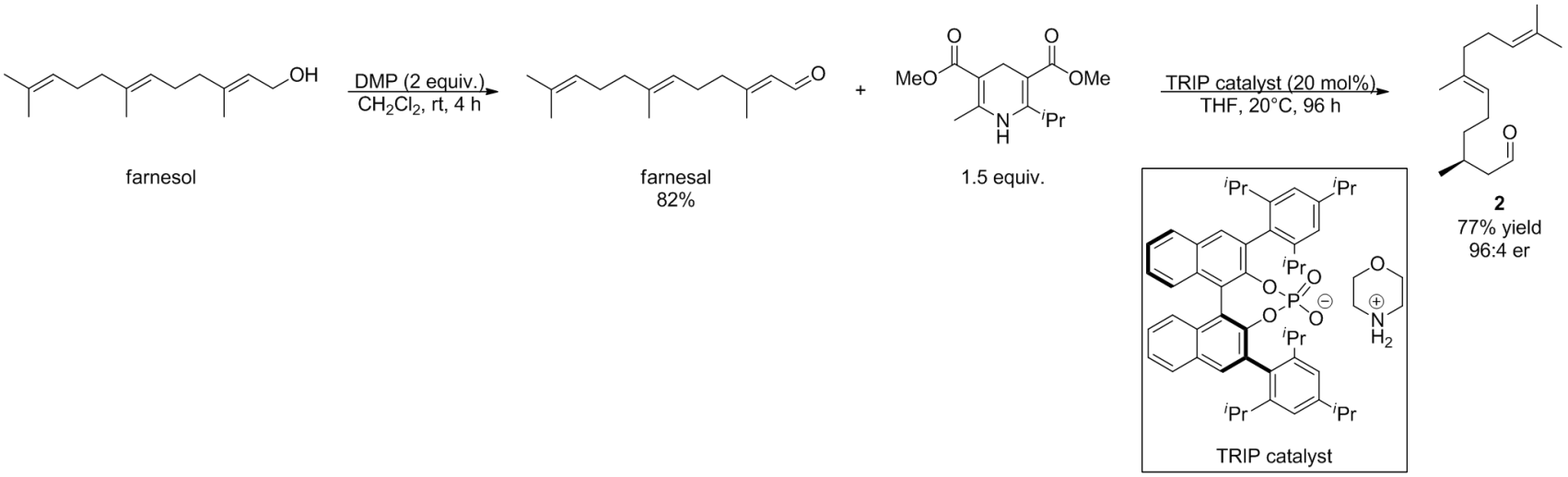
Forward Synthesis



- The authors begin their synthesis with **2** prepared by oxidation of a sample of (*S*)-2,3-dihydrofarnesol received from the Takasago Corporation.

- The above scheme shows a potential route to **2** from a more readily available starting material: farnesol.

- Farnesol can be readily oxidized to farnesal using a variety of reagents; conditions for DMP oxidation are shown as an example.

DMP = Dess-Martin periodinane

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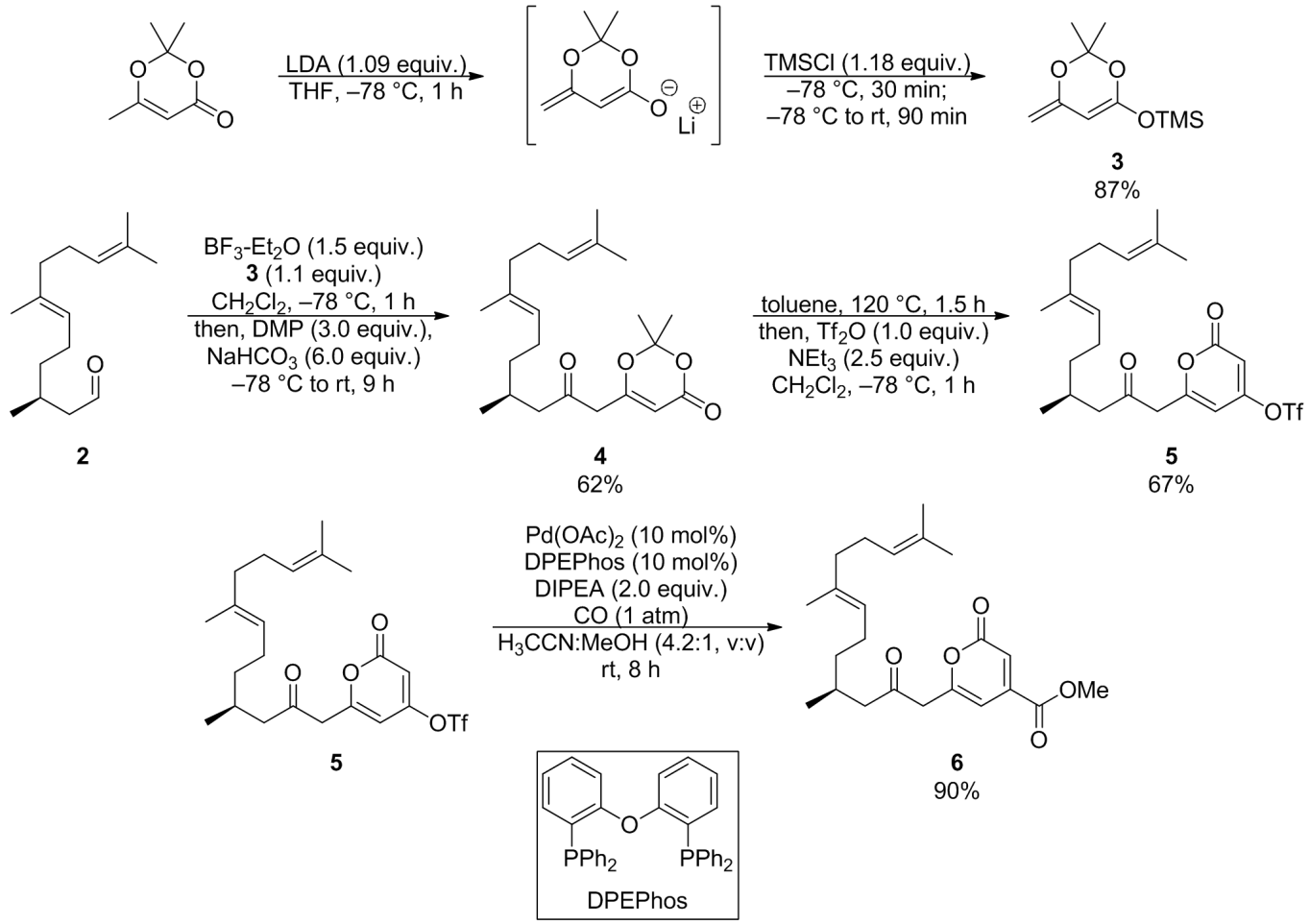
Estévez, R. E.; Justicia, J.; Bazdi, B.; Fuentes, N.; Paradas, M.; Choquesillo-Lazarte, D.; García, J. M.; Robles, R.; Gansäuer, A.; Cuerva, J. M.; Oltra, J. E. *Chem. Eur. J.* **2009,** *15,* 2274–2791.

Mayer, S.; List, B. *Angew. Chem. Int. Ed.* **2006,** *45,* 4193–4195.

Forward Synthesis



LDA = lithium diisopropylamide; DMP = Dess-Martin periodinane; DIPEA = *N*,*N*-diisopropyl-*N*-ethylamine

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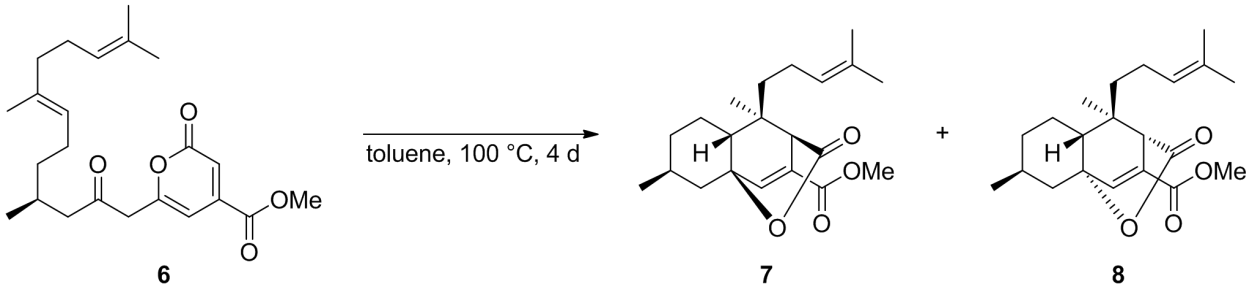
Fettes, A; Carreira, E. M. *J. Org. Chem.* **2003,** *68,* 9274–9283.

Forward Synthesis



6 **7** **8**

90% combined yield
1:1 dr

- Diastereomers **7** and **8** separable by column chromatography.
- Only decarboxylated products obtained when attempted with triflate **5**.
- Significant decarboxylation also observed in more polar solvents (DMF, acetonitrile), and at higher temperatures (120 ºC).
- Cyclization reaction was markedly sluggish at 80 ºC.

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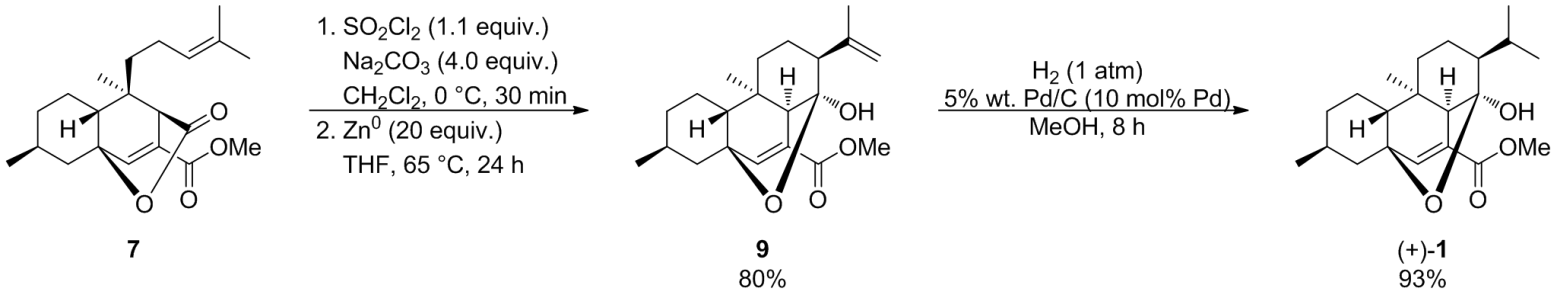
Forward Synthesis



7

9
80%

(+)-**1**
93%

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Summary

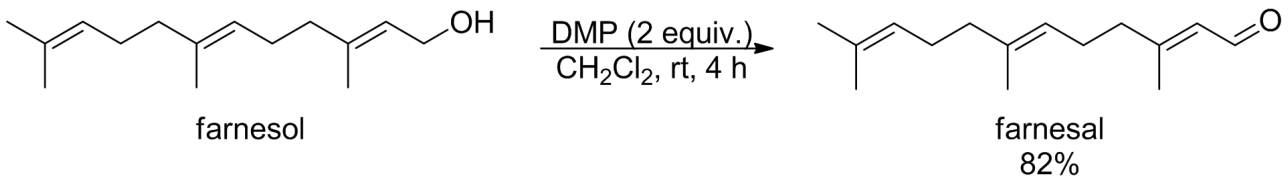
- Asymmetric synthesis of (+)-chatancin in 9 steps longest linear sequence from farnesol; 13% overall yield from **2**.

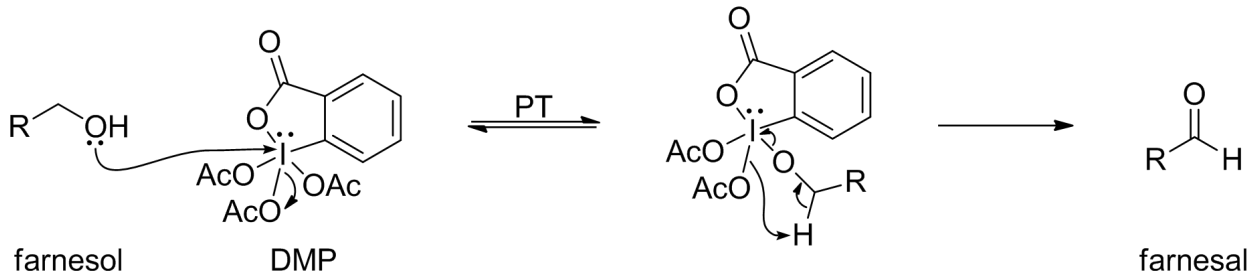
- Synthetic strategy facilitates general avoidance of protecting groups.

- Stereocenters set by asymmetric transfer hydrogenation (alternatively from chiral pool material) and intramolecular pyrone/alkene [4+2] cyclization.

- Sensitive, acid-labile hemiketal moiety formed in penultimate step.

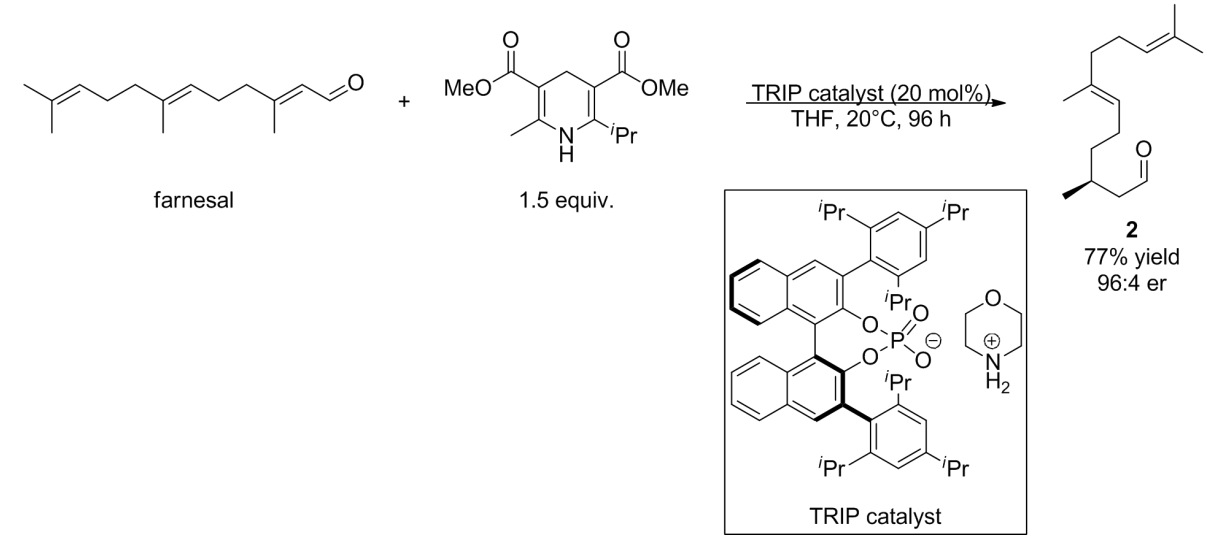
Mechanisms:
Dess-Martin Periodinane Oxidation

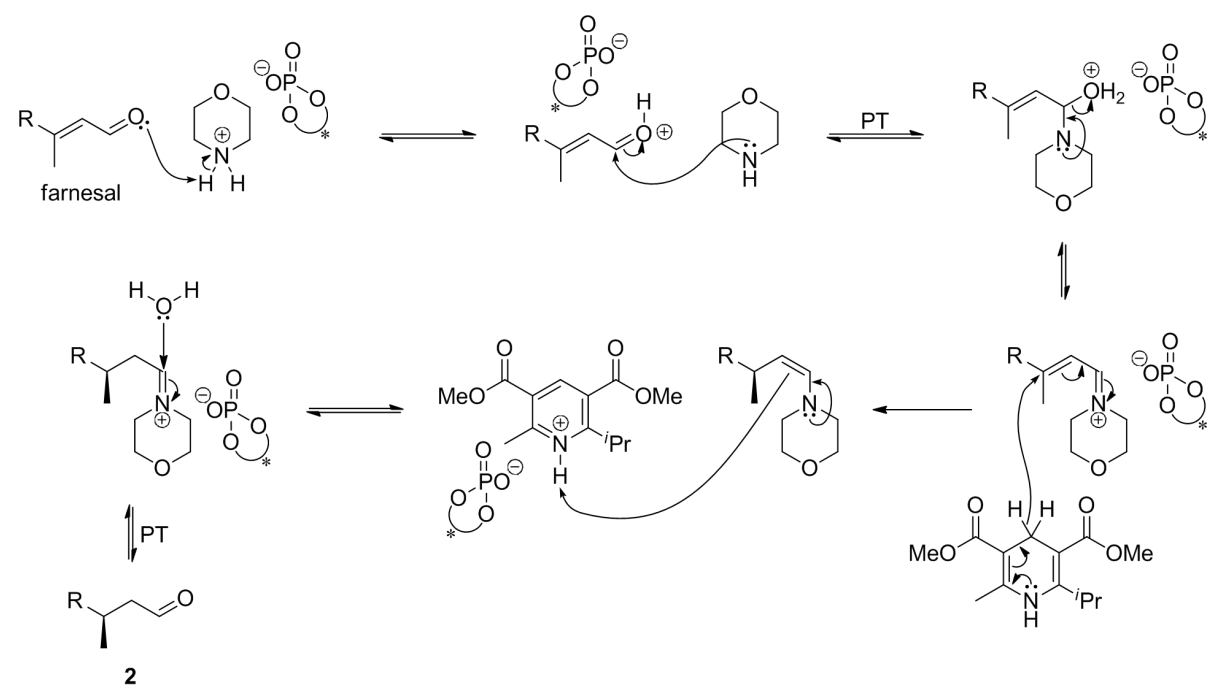




Estévez, R. E.; Justicia, J.; Bazdi, B.; Fuentes, N.; Paradas, M.; Choquesillo-Lazarte, D.; García, J. M.; Robles, R.; Gansäuer, A.; Cuerva, J. M.; Oltra, J. E. *Chem. Eur. J.* **2009,** *15,* 2274–2791.

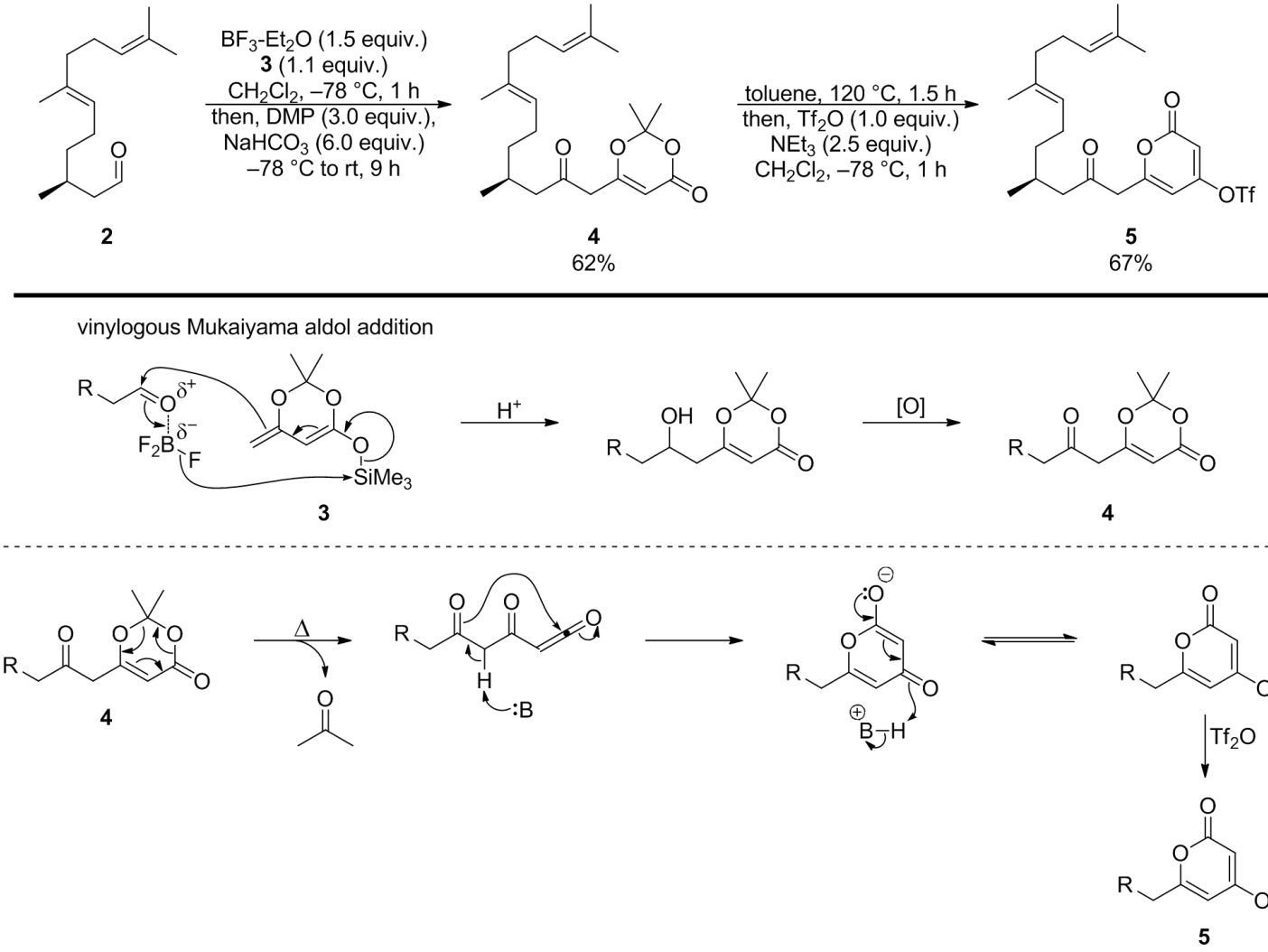
Mechanisms





Mayer, S.; List, B. *Angew. Chem. Int. Ed.* **2006,** *45,* 4193–4195.

Mechanisms



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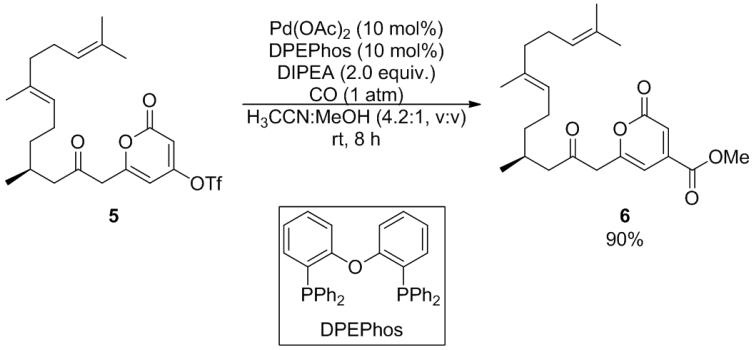
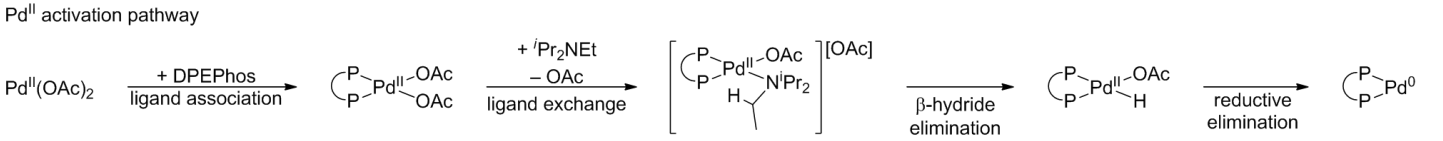
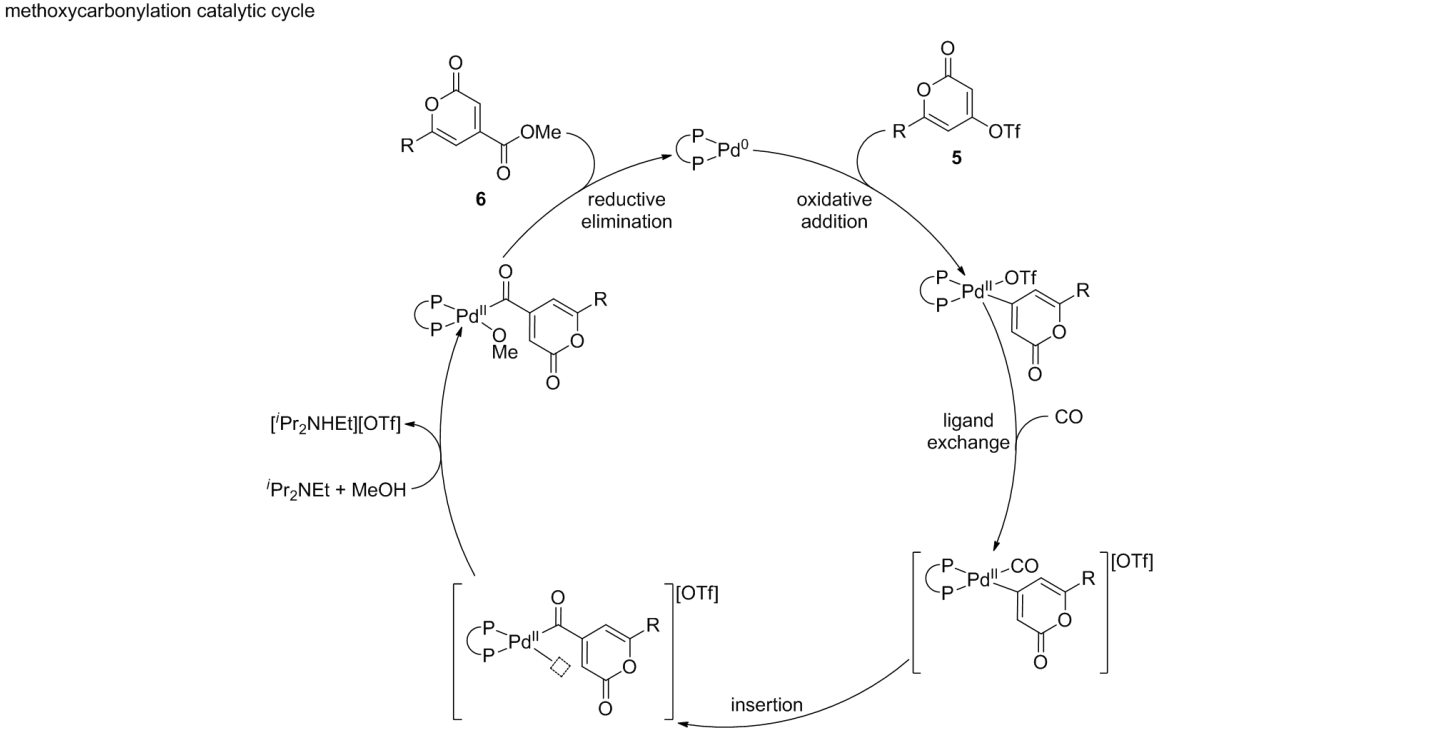
Mechanisms







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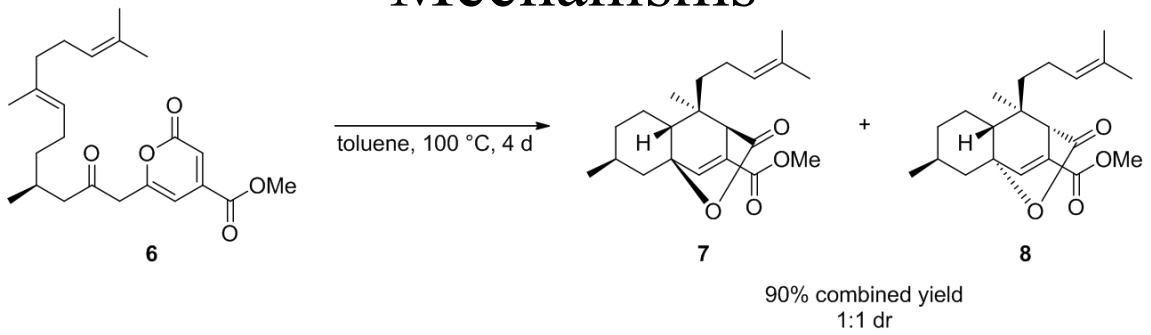
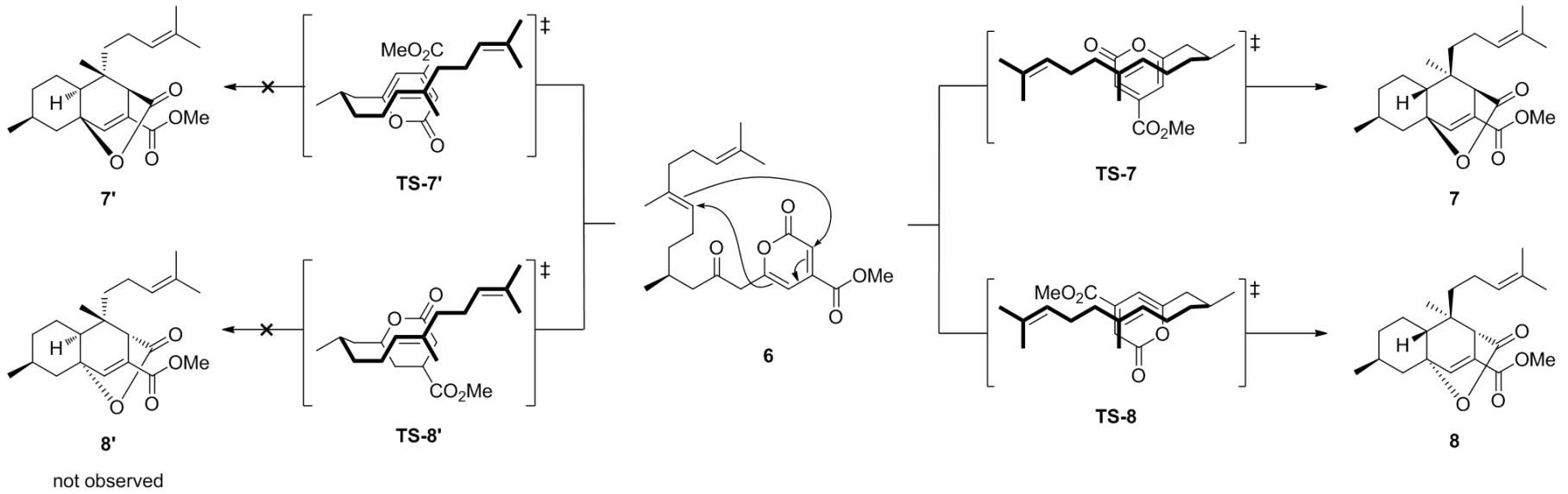
Mechanisms





- Diastereomers **7** and **8** form through the more favorable chair-conformer transition states **TS-7** and **TS-8**.
- Relatively unrestricted rotation of the pyrone group results in a 1:1 mixture.
- Diastereomers **7′** and **8′** resulting from the boat-conformer transition states **TS-7′** and **TS-8′** were not observed.

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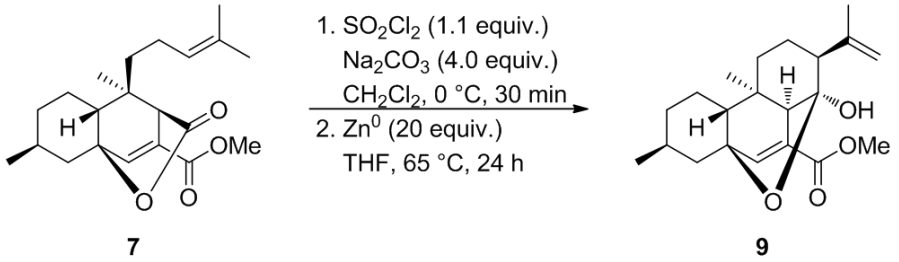
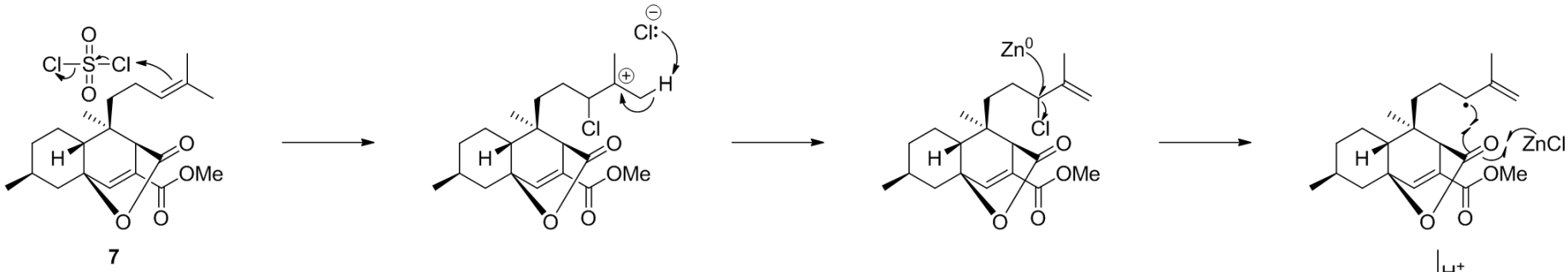
Mechanisms



7 **9**
80%



7 **9**

- A hemiketal formation mechanism involving intramolecular attack of a zincate on the lactone carbonyl is also plausible.

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