Literature Report 1

Total Synthesis of (+)-3-Deoxyfortalpinoid F, (+)-Fortalpinoid A, and (+)-Cephinoid H

Reporter: Qing-Xian Xie

Checker: Han Wang

Ren, Z.; Hu, X.* *Angew. Chem. Int. Ed.* **2021**, *60*, 18572

2021-12-13

CV of Prof. Xiangdong Hu

Background:

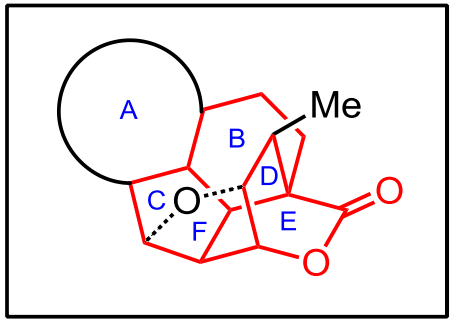
- **1993-1997** B.S., Lanzhou University
- **1998-2006** Ph.D., Lanzhou University
- **2006-2009** Postdoctor, University of South Florida
- **2009-Now** Professor, Northwest University

Research:

- Total Synthesis of Natural Products
- Synthesis-oriented Methodology

Contents

Introduction



Cephalotaxus diterpenoids

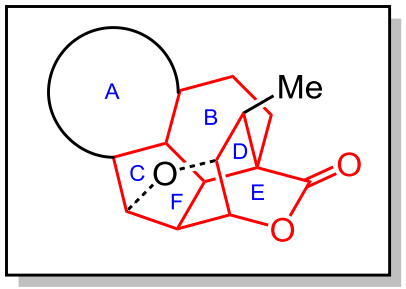
三尖杉二萜

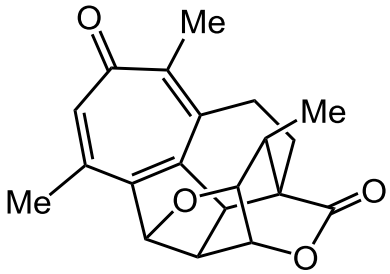
Cephalotaxaceae

三尖杉科植物

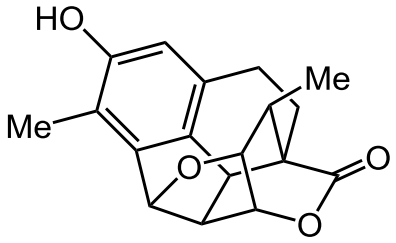
- Containing an identical tetracyclic skeleton (B-C-D-E ring);
- The structural diversity is primarily derived from differences in the A ring;
- Cephalotaxus diterpenoids have shown a broad range of bioactivity that includes plant growth inhibition, antiviral, and antitumor properties.

Introduction

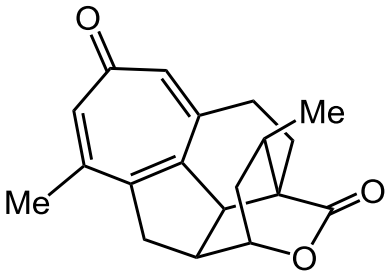




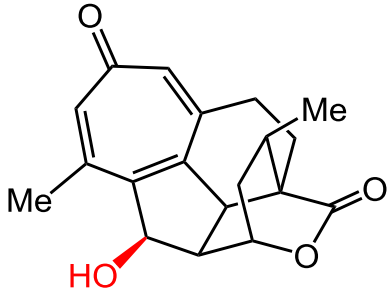
harringtonolide



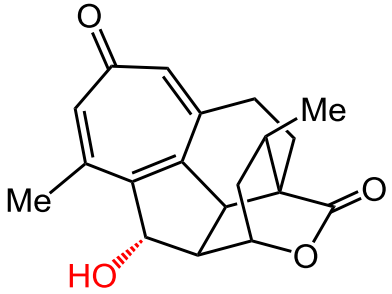
cephanolide A



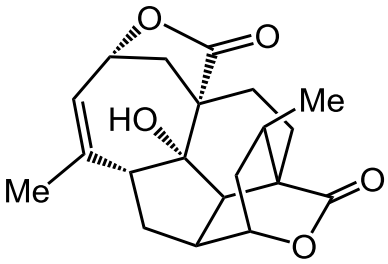
cephinoid H



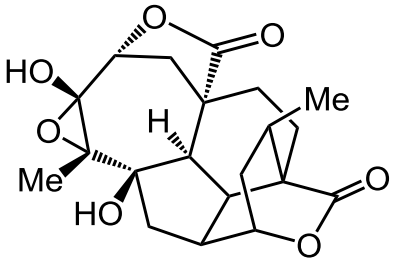
3-deoxyfortalpinoid F



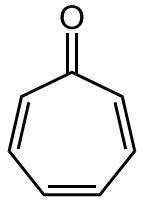
fortalpinoid A



mannolid A



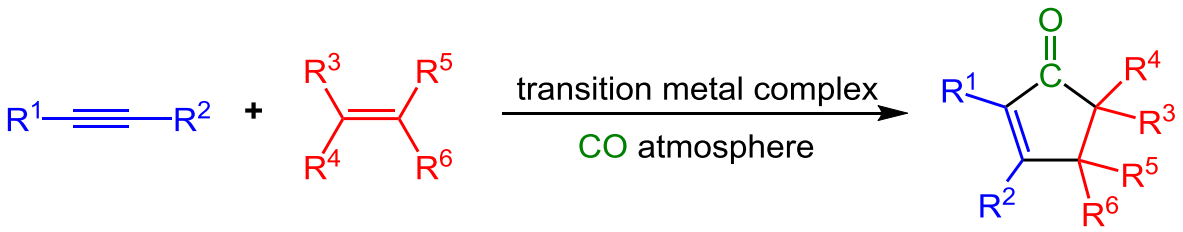
cephafortunoid C



tropone

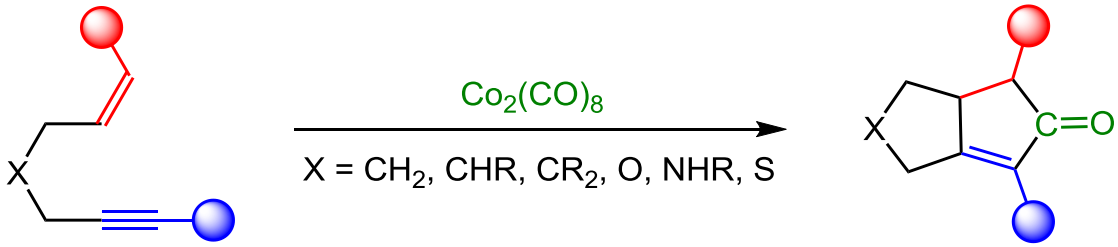
Pauson-Khand Reaction

Modified P-K reaction



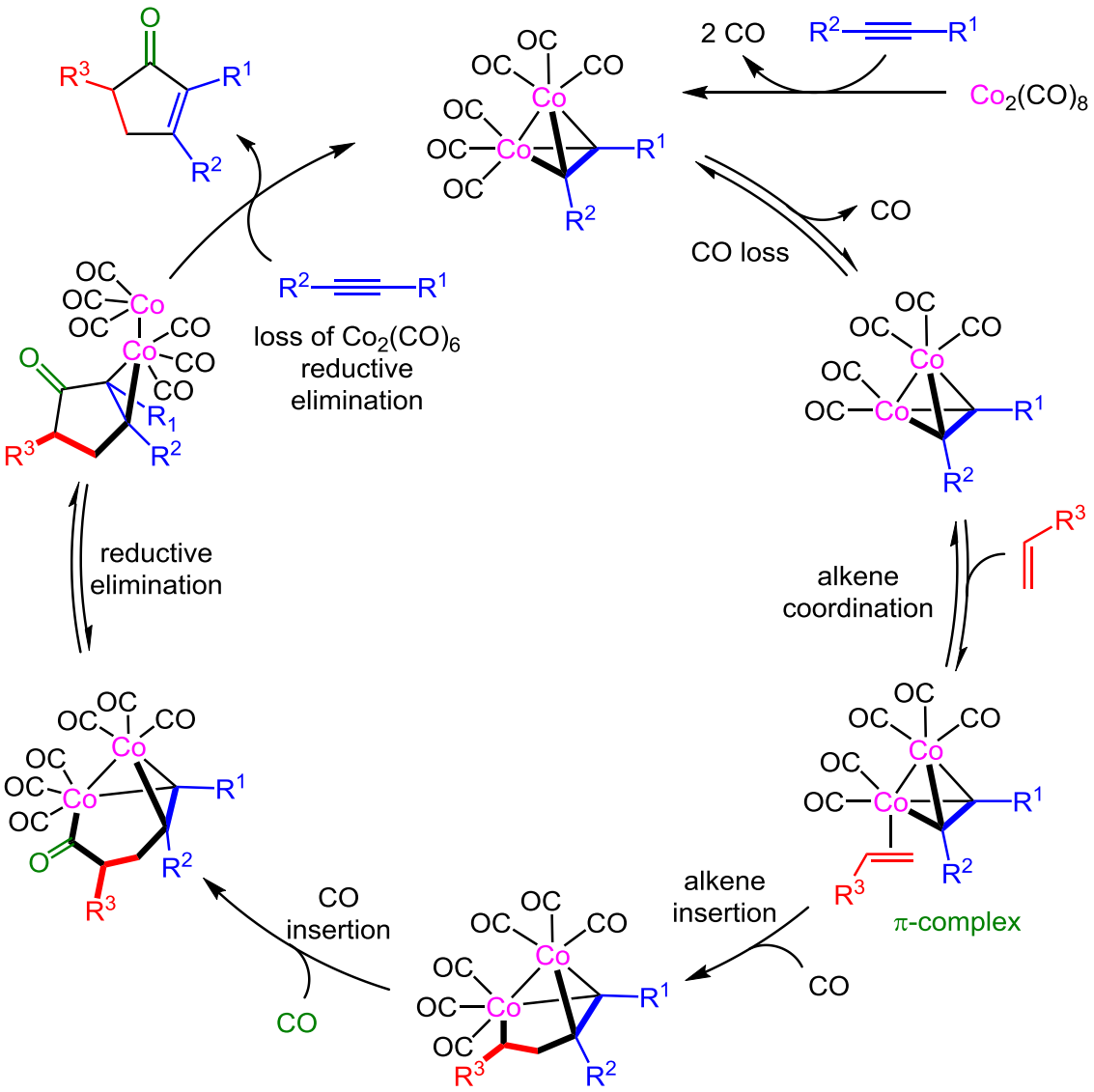
transition metal complex: $Co_2(CO)_8$, $Fe(CO)_5$, $Ru_2(CO)_{12}$, Cp_2TiR_2, $Ni(COD)_2$, $W(CO)_6$, $Mo(CO)_6$, $[RhCl(CO)_2]_2$

Intramolecular variant



Blanco-Urgoiti, J.; Pérez-Castells, J.* *Chem. Soc. Rev.* **2004**, *33*, 32

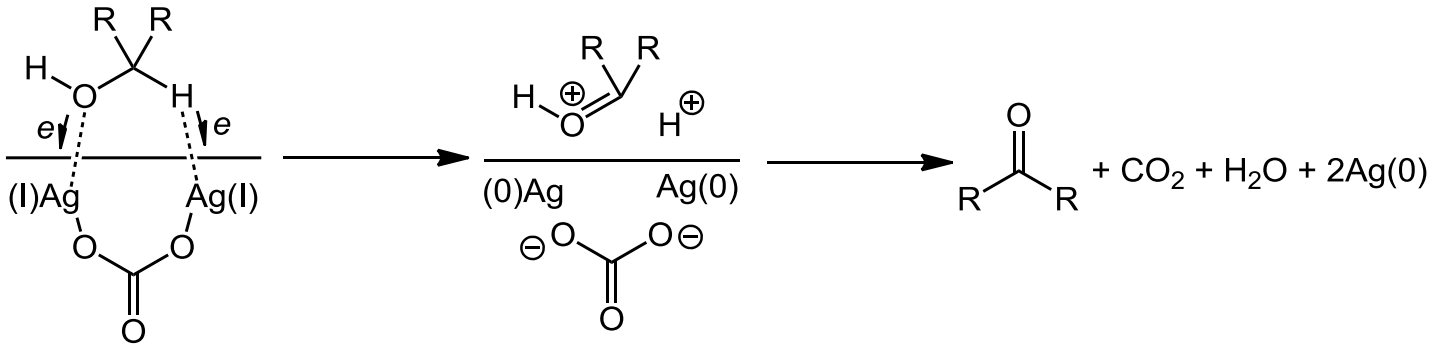
Mechanism on Pauson-Khand Reaction



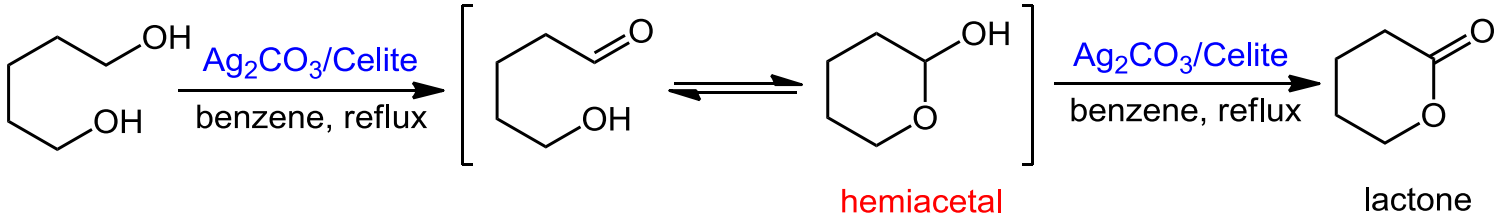
Fetizon's Reagent

Fetizon's Reagent: Ag_2CO_3 on Celite

Reaction Mechanism:



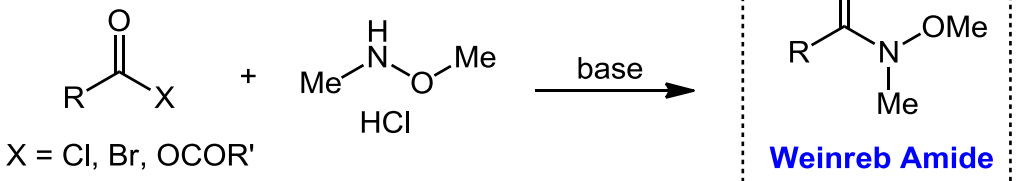
Oxidation of 1,5-pentanediol:



Fetizon, M.; Mourgues, P.* *Tetrahedron Lett.* **1972**, *13*, 4445

Weinreb Amide

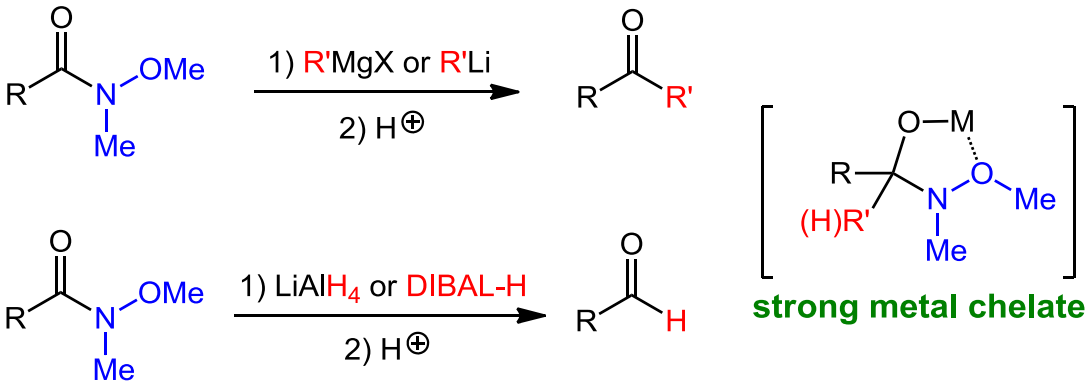
General preparation method:



X = Cl, Br, OCOR'

Weinreb Amide (WAs)

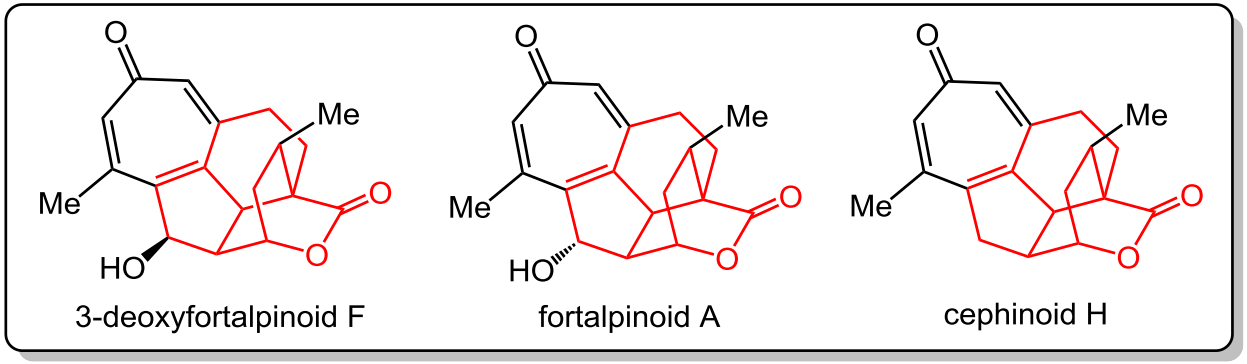
Reactions:

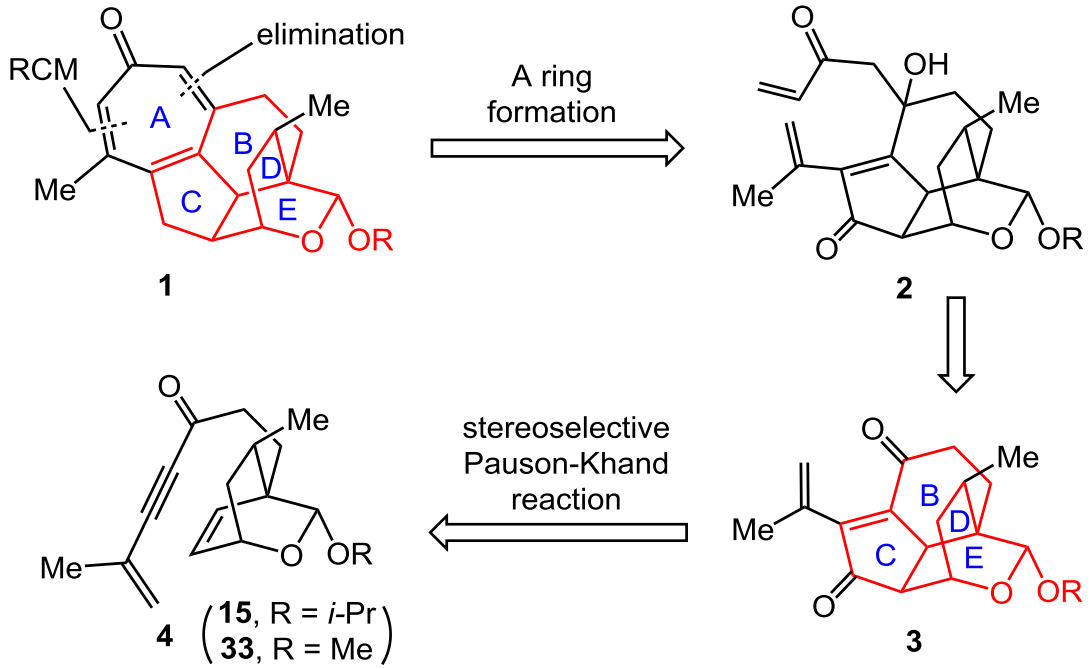


strong metal chelate

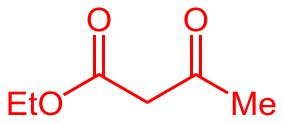
Basha, A.; Weinreb, S. M.* *Tetrahedron Lett.* **1977**, *18*, 4171

Retrosynthetic Analysis



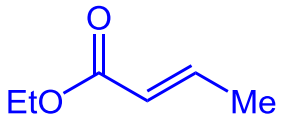


Synthesis of Intermediates 15 and 21



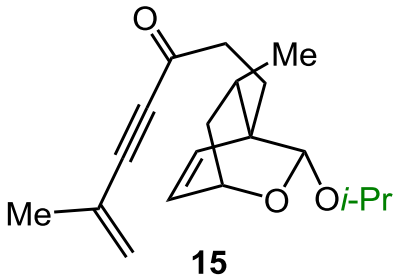
5

+



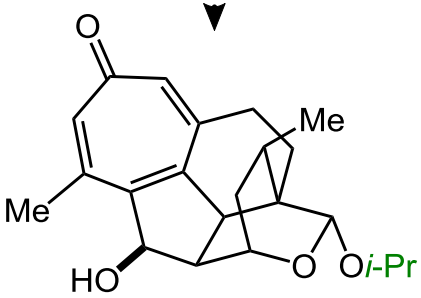
6

13 steps, 5% yield



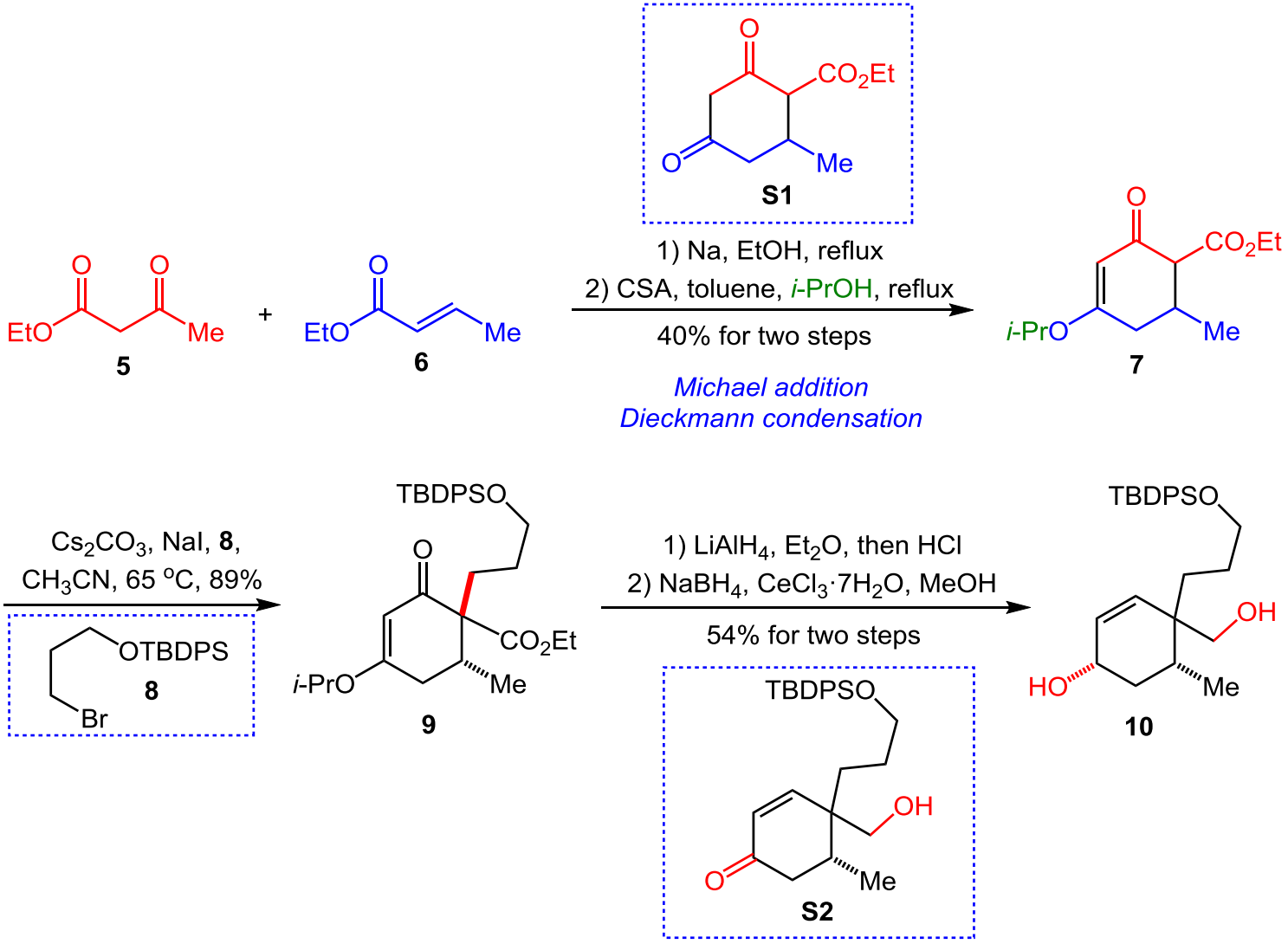
15

9 steps, 11% yield

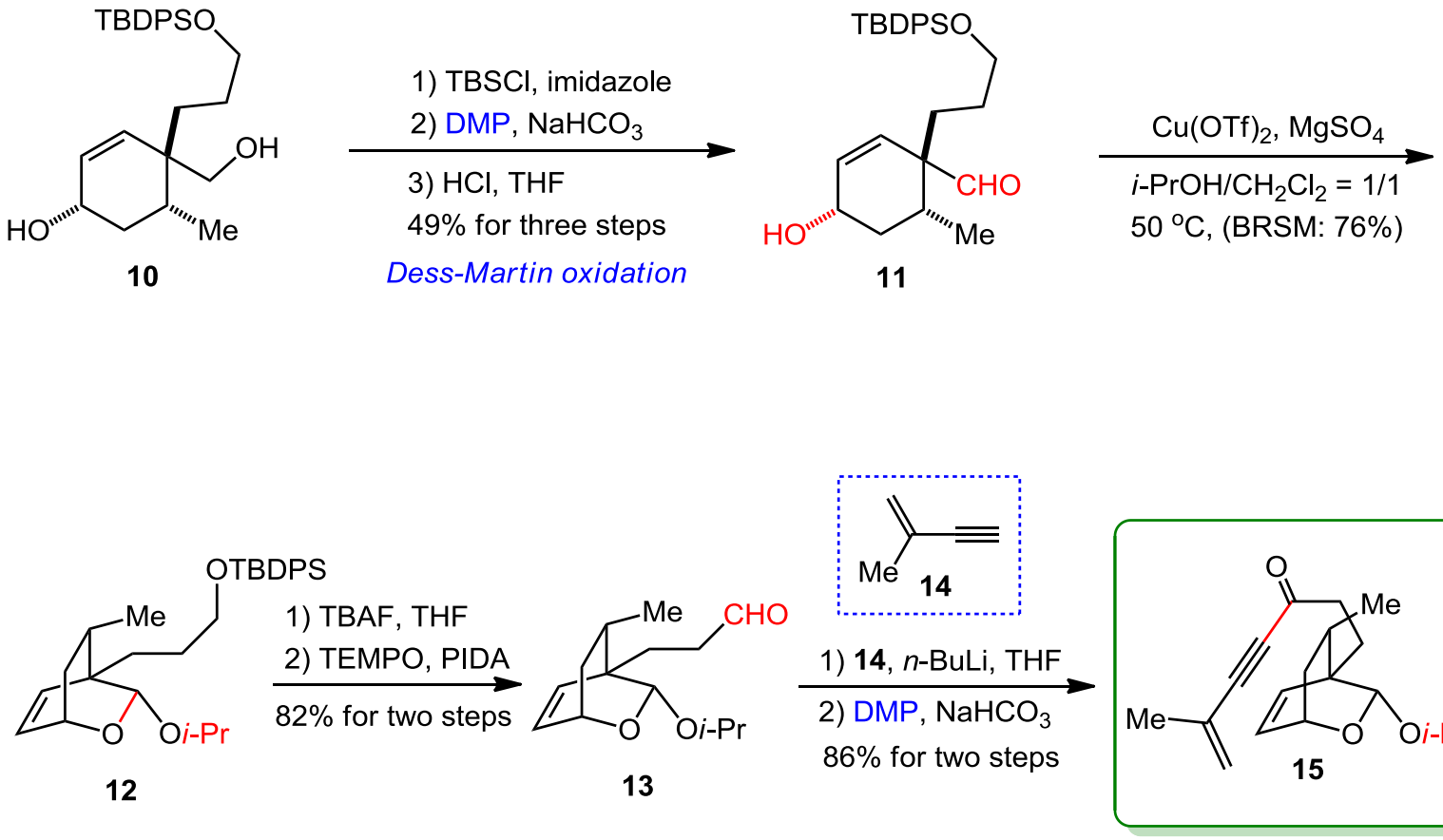


21

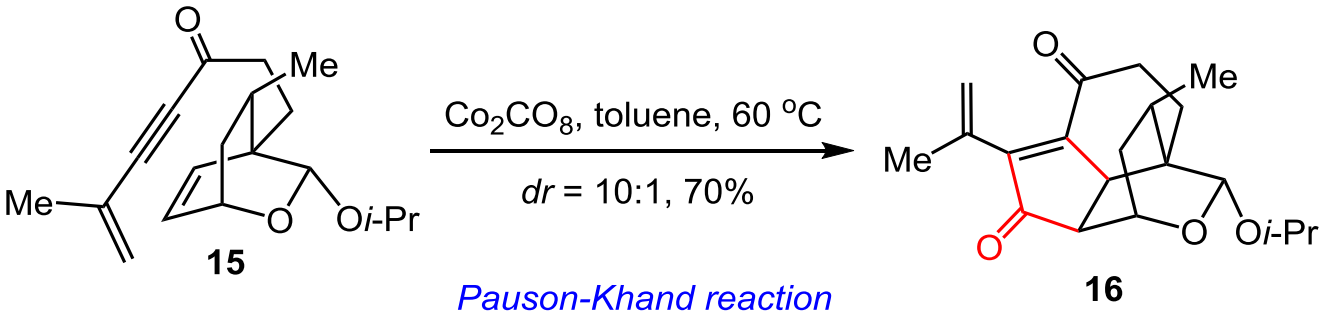
Synthesis of Intermediate 15

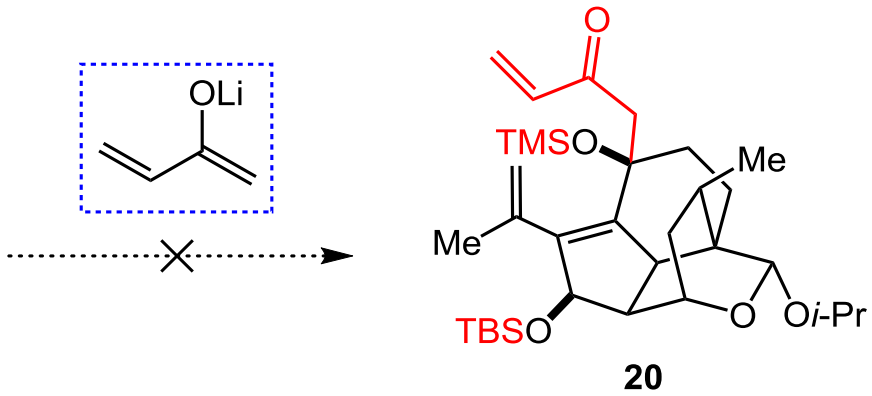


Synthesis of Intermediate 15

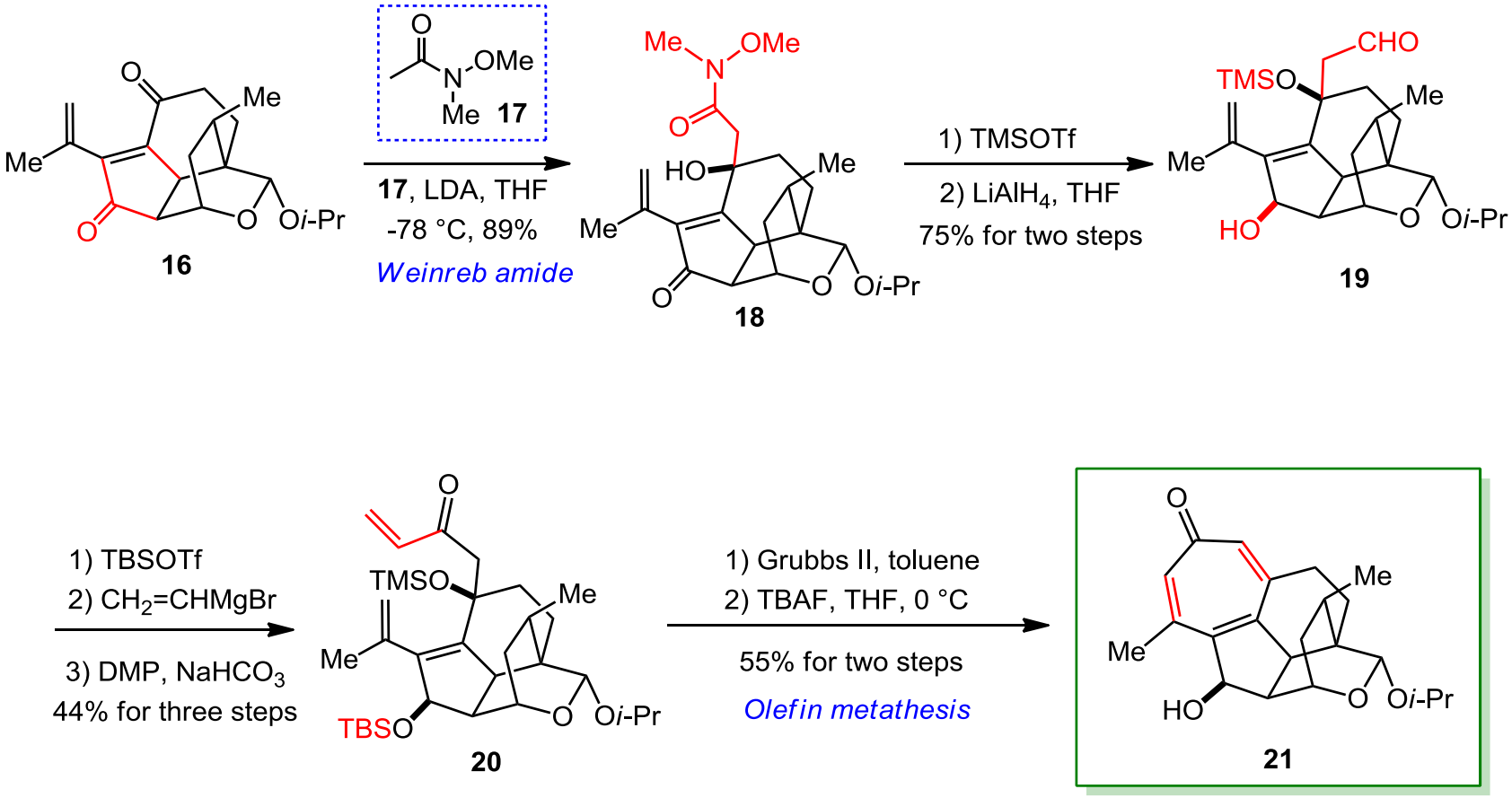


Synthesis of Intermediate 21

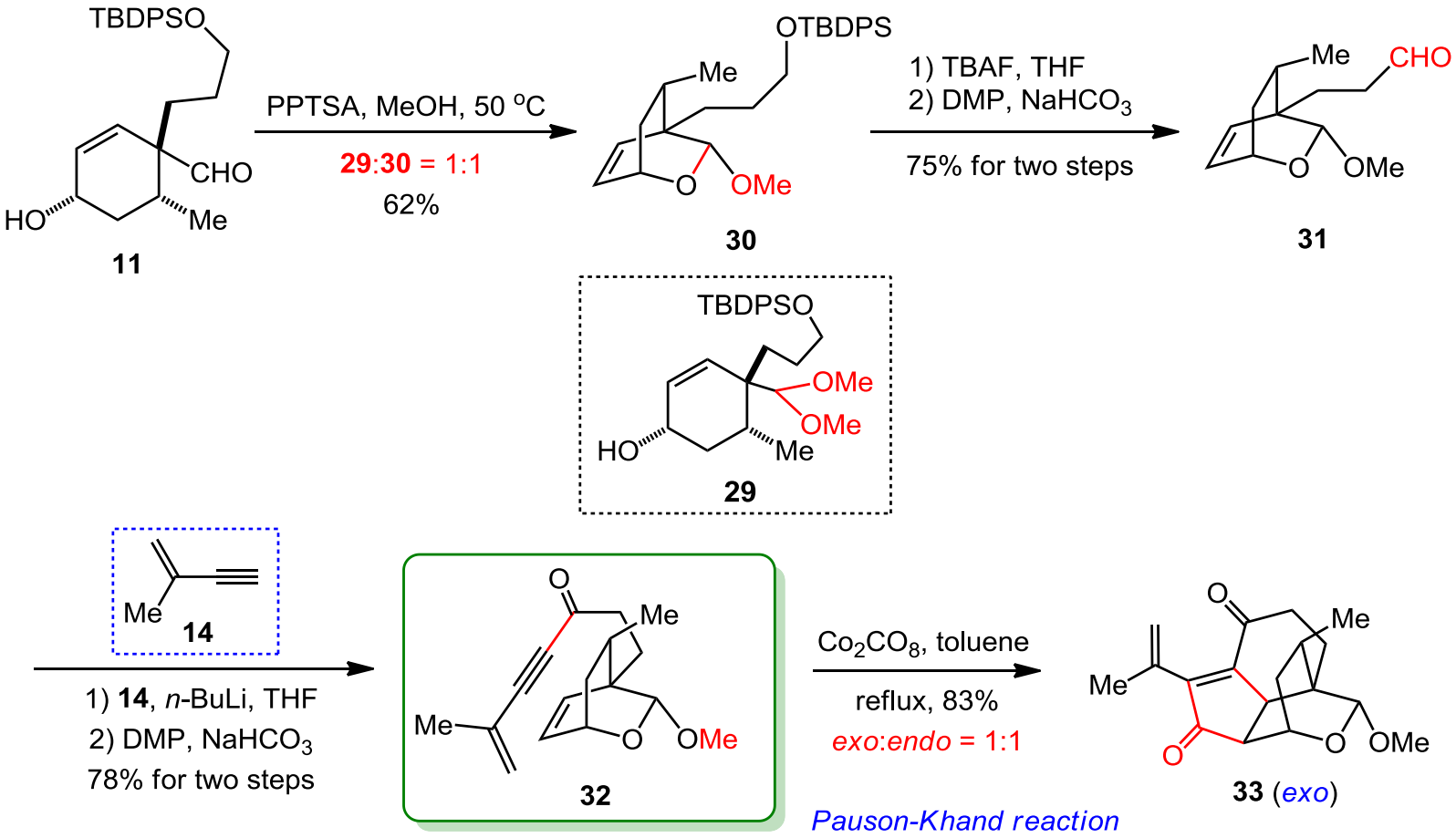




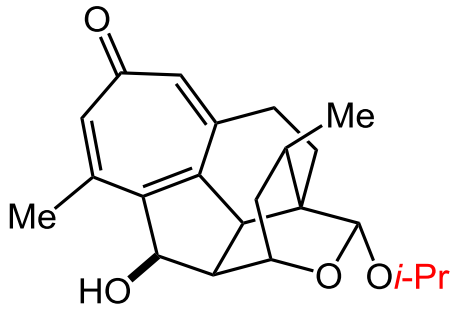
Synthesis of Compound 21



Synthesis of Compound 32



Synthesis of *Cephalotaxus diterpenoids*



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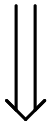
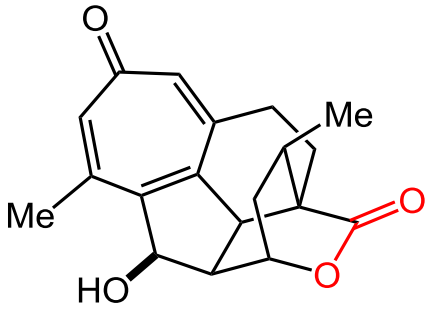
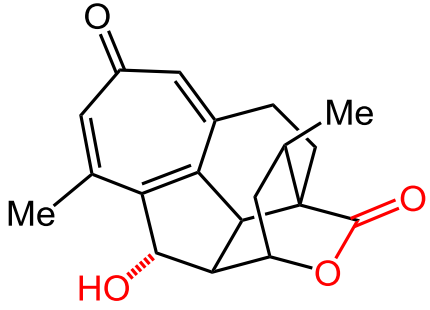
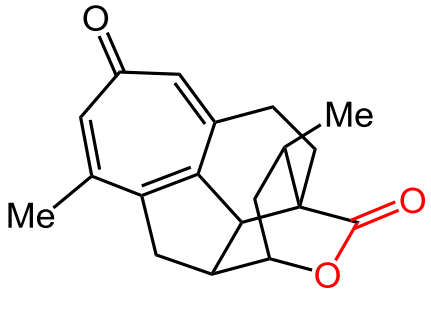




3-deoxyfortalpinoid F

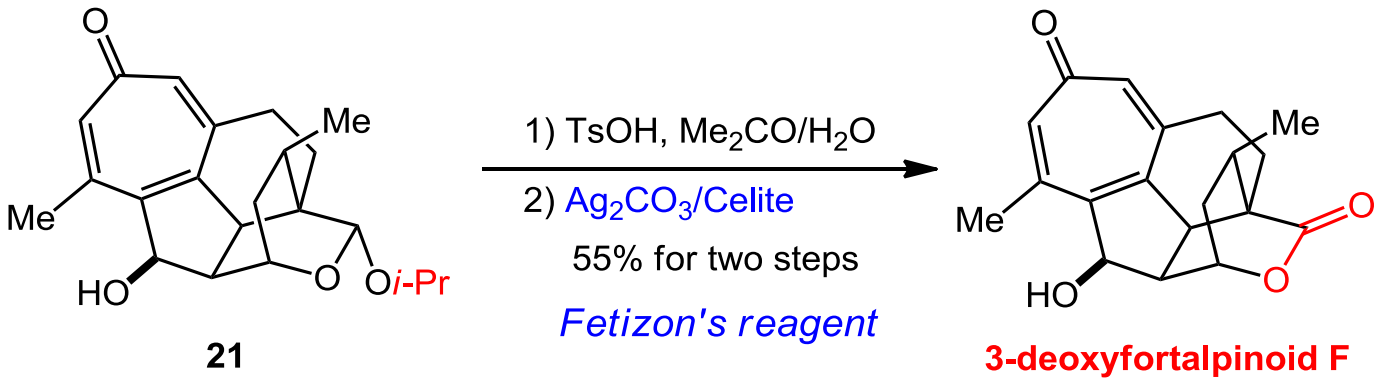


fortalpinoid A



cephinoid H

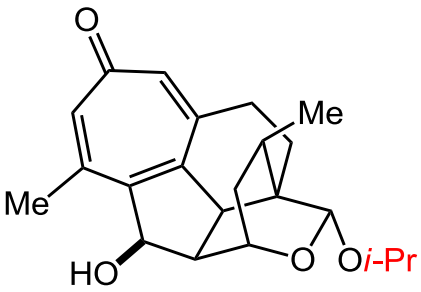
Synthesis of *Cephalotaxus Diterpenoids*



21

3-deoxyfortalpinoid F

Synthesis of *Cephalotaxus Diterpenoids*

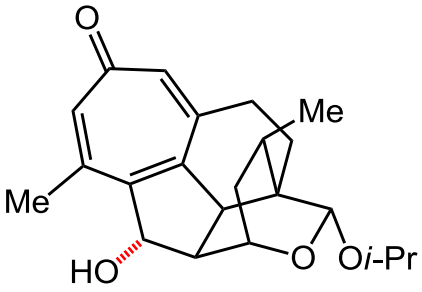


21

1) MsCl, Et_3N, DMAP

2) $AgBF_4$, Me_2CO/H_2O

54% for two steps

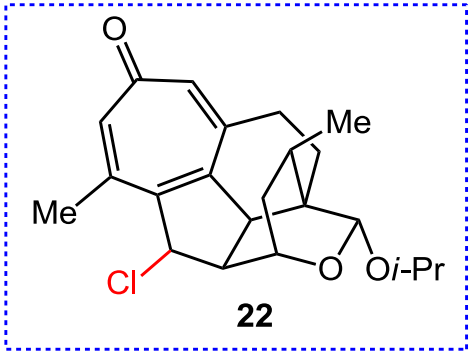


23

1) TsOH, Me_2CO/H_2O

2) Ag_2CO_3/Celite

45% for two steps



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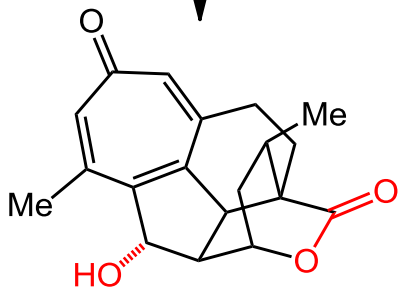
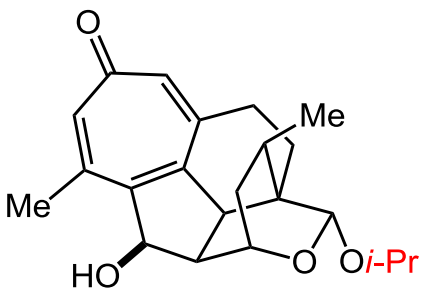


fortalpinoid A

Synthesis of *Cephalotaxus Diterpenoids*

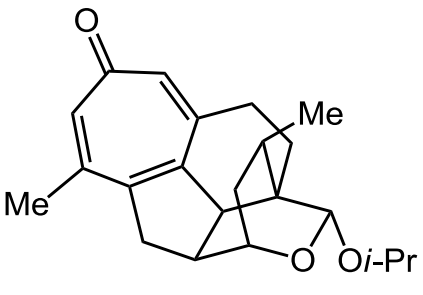


21

1) MsCl, Et_3N, DMAP

2) Bu_3SnH, AIBN

40% for two steps

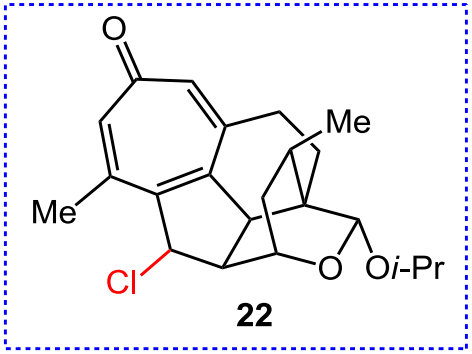


24

1) TsOH, Me_2CO/H_2O

2) Ag_2CO_3/Celite

56% for two steps



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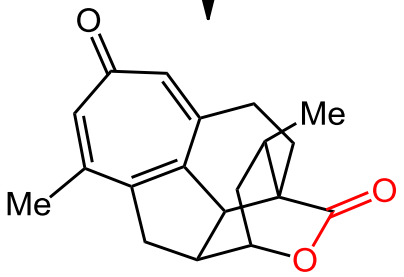
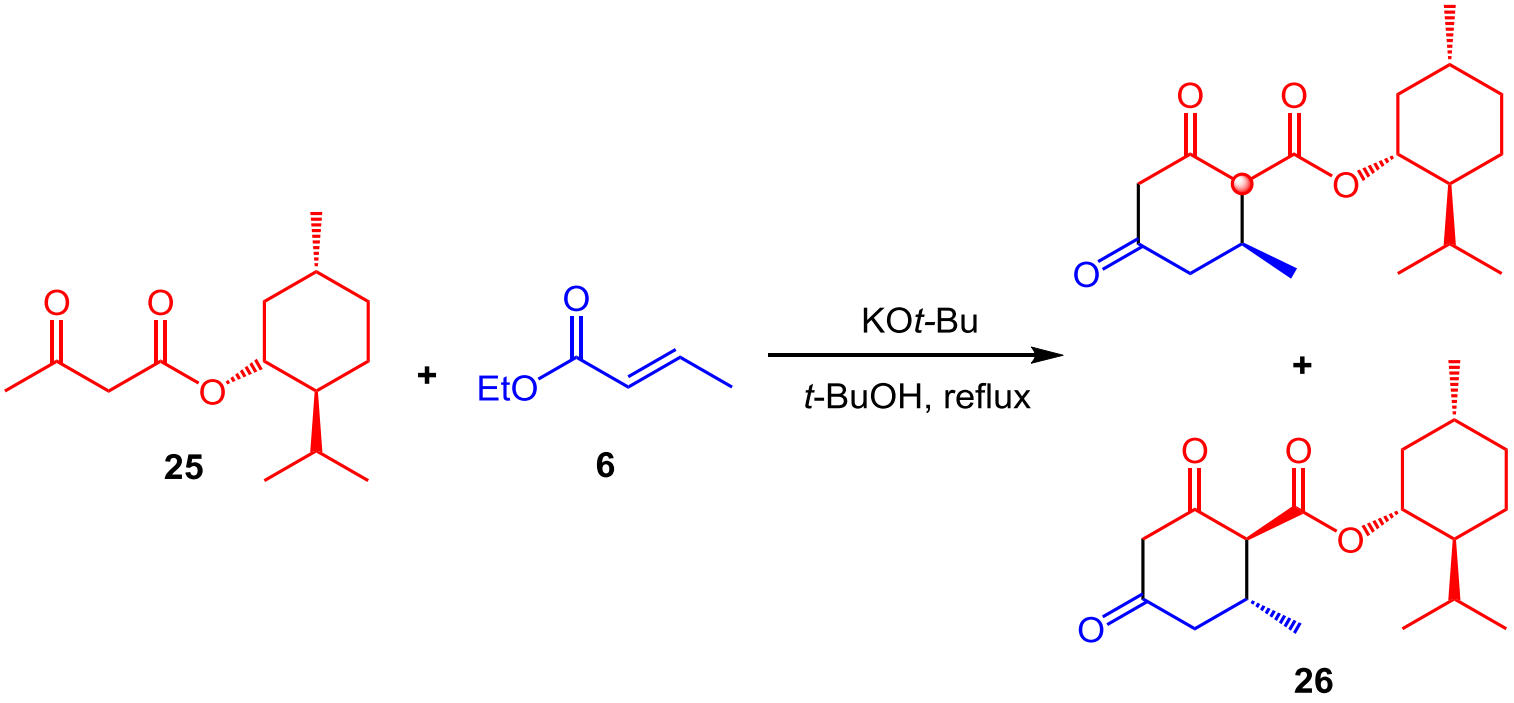


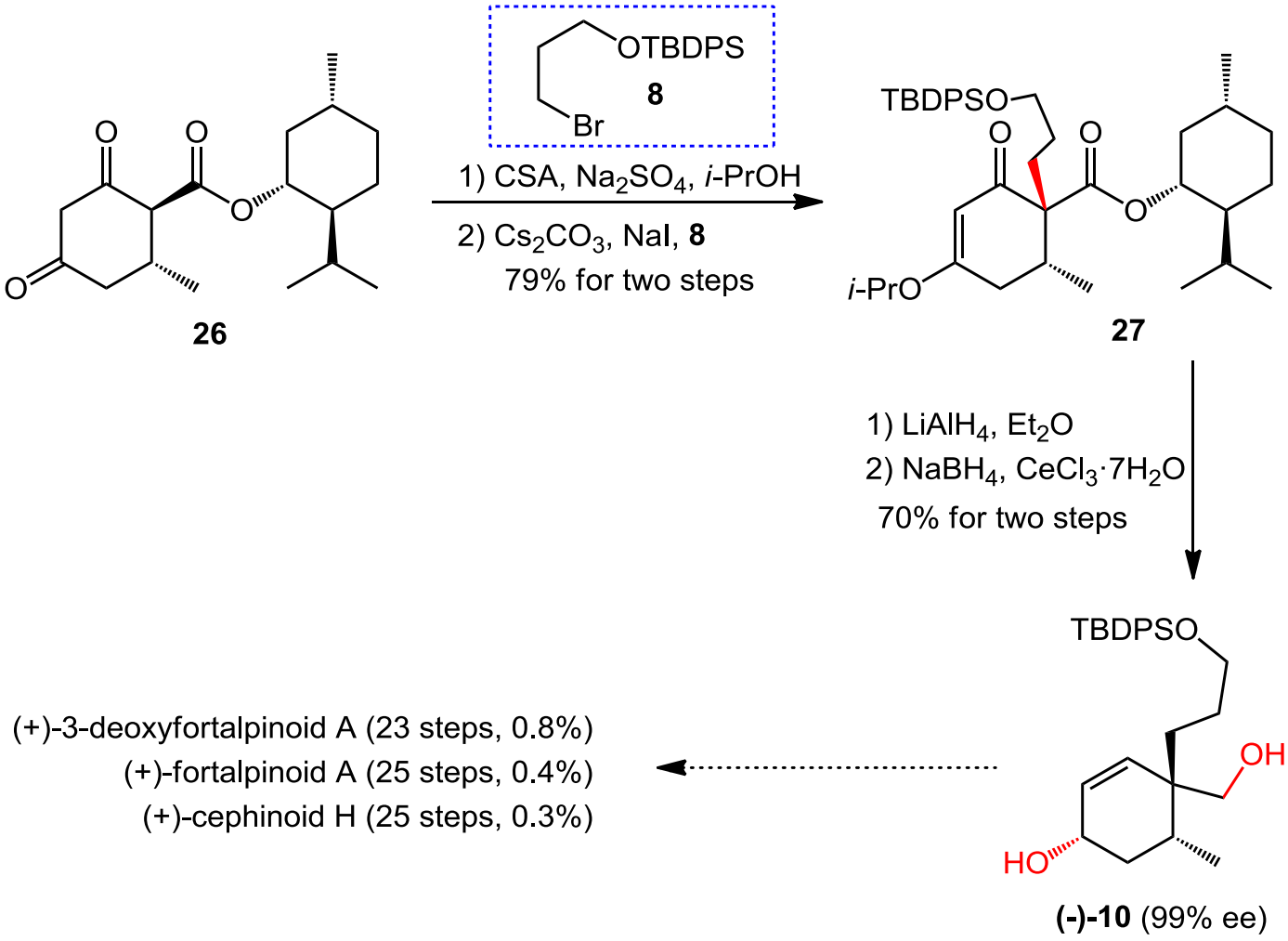
cephinoid H

Asymmetric Synthesis

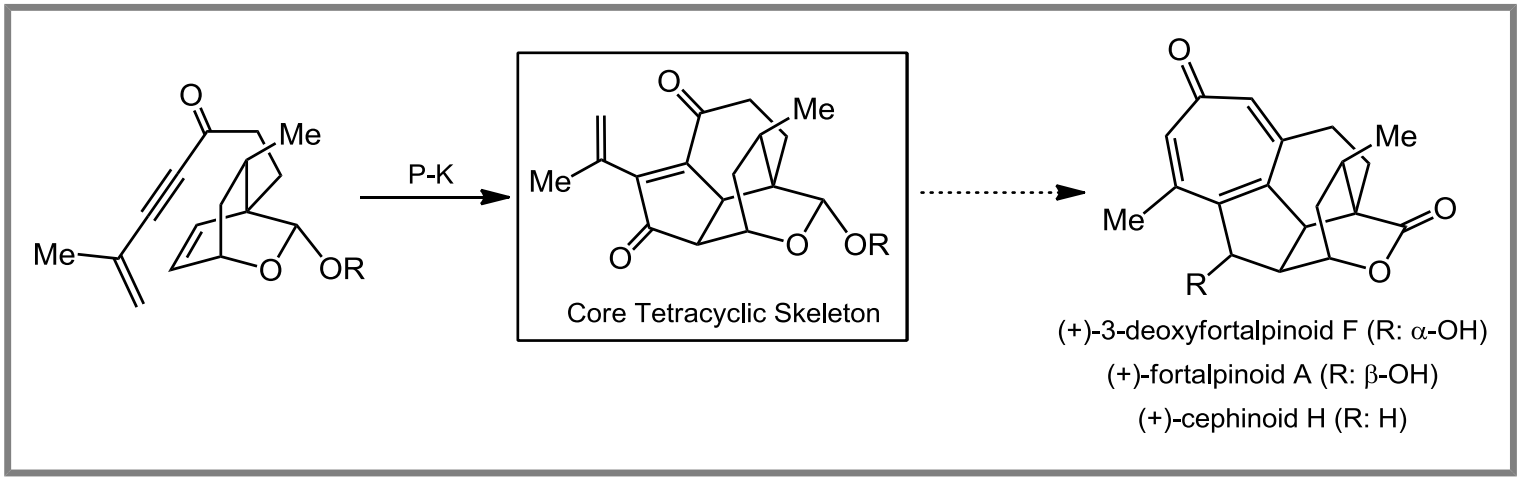


Myers, A. D.; Madar, D. J.* *J. Am. Chem. Soc.* **1997**, *119*, 6072

Asymmetric Synthesis



Summary



- A diastereoselective intramolecular Pauson-Khand was developed as an effective way to the tetracyclic skeleton of Cephalotaxus diterpenoids;
- The key tropone moiety was constructed by a ring-closing metathesis/ elimination protocol;
- Asymmetric total synthesis of (+)-3-deoxyfortalpinoid F, (+)-fortal-pinoid A, and (+)-cephinoid H was accomplished for the first time.

The First Paragraph

Writing Thought

Bioactivities of Cephalotaxus Diterpenoids

↓

Previous Work

↓

Development of Synthesis Strategy

The First Paragraph

Cephalotaxus diterpenoids are a class of natural products isolated from plants of the Cephalotaxaceae family. Their valuable biological properties and interesting structural diversity have attracted considerable attention from the synthetic chemistry community. In 1996, the first total synthesis of a Cephalotaxus diterpenoid was achieved by Mander and co-workers with their elegant synthesis of 3-deoxyfortalpinoid F using an intramolecular arene cyclopropanation-ring expansion strategy during their endeavor to synthesize harringtonolide (also named hainanolide). Notably, 3-deoxy-fortalpinoid F was not identified as a Cephalotaxus diterpenoid until its discovery from a natural source in 2019. Based on the same strategy, Mander and coworkers later achieved the total synthesis of harringtonolide, which possesses remarkably potent and selective anticancer activity (IC50 = 43 nm on KB tumor cells).

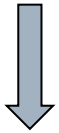
The First Paragraph

Tang and co-workers developed a gentle approach to Harringtonolide through an intramolecular oxidopyrylium-based [5+2] cycloaddition protocol. Employing rhodium-catalyzed intramolecular [3+2] cycloaddition as the key step, Zhai and co-workers reported the first asymmetric total synthesis of harringtonolide. Based on the development of a palladium-catalyzed cascade cyclization, Zhao and co-workers devised an ingeniously concise route to the core skeleton of Cephalotaxus diterpenoids and achieved the total synthesis of cephanolides B and C. Through a mild intramolecular Prins cyclization strategy, Gao and co-workers accomplished the asymmetric total synthesis of cephanolides A and B. Recently, Sarpong and co-workers successfully developed a concise synthetic approach to cephanolides A–D with the artful application of an intramolecular inverse-demand Diels–Alder reaction.

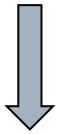
The Last Paragraph

Writing Thought

What Did We Do



Important Steps in Total Synthesis



Significance of This Work

The Last Paragraph

In conclusion, we have developed a diastereoselective Pauson–Khand reaction as an effective route to the core tetracyclic skeleton (B-C-D-E ring), which is present in a broad range of Cephalotaxus diterpenoids. Furthermore, through a RCM/elimination protocol, we enabled the construction of the tropone moiety, the most fundamental structure of the A ring in Cephalotaxus diterpenoids. As the first example of a combination of construction of the core tetracyclic skeleton with the later-stage formation of the A ring, the total synthesis of (+)-3-deoxyfortalpinoid F, (+)-fortalpinoid A, and (+)-cephinoid H was accomplished in a total of 23 to 25 steps from known compound **25**. Based on the strategy developed, synthetic studies on other Cephalotaxus diterpenoids are ongoing in our laboratory.

Representative Examples

- To this point, as the most basic A ring of Cephalotaxus diterpenoids, the tropone moiety was introduced successfully using the RCM/elimination protocol.

  至此（可用于某一部分工作小结）

- Structurally, 3-deoxyfortalpinoid F, fortalpinoid A, and cephinoid H share the same composition of the core tetracyclic skeleton (B-C-D-E ring) and the tropone moiety (A ring).

  从结构上说…

- Gratifyingly, application of Weinreb amide 17 enabled the addition of 16 to proceed smoothly, generating 18 in 89% yield.

  令人欣慰的是…

Acknowledgement

Thanks for Your Attention